Toxicological Outbreak Investigation Course

Module Five:
Steps of a Toxicological Outbreak Investigation
This training follows the general steps outlined in CDC’s *Principles of Epidemiology in Public Health Practice, An Introduction to Applied Epidemiology and Biostatistics*.
Module 5 Objectives

- Define the steps for an outbreak investigation
- Recognize factors indicating that a toxic agent may have caused an outbreak
- Apply outbreak investigation steps to a toxic agent outbreak
- Describe the purpose of the materials in the Toxicological Outbreak Tool Kit
Step 1: Establish that an outbreak exists
Step 2: Verify the diagnosis
Step 3: Prepare for field work
Step 4: Construct a working case definition
Step 5: Find cases systematically and record information
Step 6: Perform descriptive epidemiology
Step 7: Develop hypotheses
Step 8: Evaluate the hypotheses
Step 9: Refine hypotheses and perform additional studies
Step 10: Reconcile with lab data
Step 11: Implement control and prevention measures
Step 12: Initiate or maintain surveillance measures
Step 13: Communicate findings
Definition of an Outbreak

What is an outbreak?
Definition of an Outbreak (cont.)

- An increase in the number of people with similar signs or symptoms, above what is expected.
- In some cases (especially for toxicological outbreaks) the exact disease may not be known.
Toxicological Outbreaks

**NEWS**

Nearly 70 die after drinking beer tainted with crocodile bile
By Chris Perez
January 12, 2015 | 4:11pm

Suspected moonshine poisoning leaves 1 man dead

More Kids Accidentally Poisoned by Essential Oils

**Spice outbreak larger than first thought**

Published: Monday, April 6th 2015, 3:54 pm EDT
Updated: Monday, April 6th 2015, 7:52 pm EDT

Posted by David Kenney, Reporter
Whyte and Buckley (1995) first defined toxicoepidemiology as the application of epidemiological methods to the problem of acute poisoning. Toxicological outbreaks often involve cases of acute poisoning resulting from exposure to a toxic agent. Toxicoepidemiology is used to investigate outbreaks of unknown or suspected toxic etiology.
The first step is to learn as much as you can about the patients to determine if this is an outbreak

- Speak to:
  - Physicians
  - Patients
  - Family/friends/community
- Review surveillance data (if available and applicable)
Reasons to Investigate

If you determine it is an outbreak, there are several reasons why you might choose to investigate it:

- To find the cause of the outbreak in order to initiate control measures
- To learn more about the disease to prevent future outbreaks
- To address public concerns
- To address political, legal, or programmatic considerations
- To train public health staff
Identify Possible Toxic Agent

- It is important to consider a possible toxic agent exposure as early as possible
- Some toxic agents have quick elimination periods
- The sooner that an environmental or biological sample is collected, the greater the chances that the sample will still contain the toxic agent

Remember in module 2, we learned elimination period is the time it takes for a toxic agent to be removed from the body.
### Characteristics of a Toxic Agent Outbreak

**What characteristics are associated with toxicological outbreaks? (one per row)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever more likely</td>
<td>Fever less likely</td>
</tr>
<tr>
<td>Long latency</td>
<td>Short latency</td>
</tr>
<tr>
<td>Strong dose-response relationship</td>
<td>Weak dose-response relationship</td>
</tr>
<tr>
<td>May involve animal illness at same time</td>
<td>Unlikely to affect animals</td>
</tr>
<tr>
<td>Similar symptoms across cases</td>
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If you decide to investigate, it is time to prepare for fieldwork.
Prepare for Field Work

- Preparing for field work includes the following:
  - Developing investigation objectives
  - Assembling an investigation team
Typical Objectives

- Typical investigation objectives:
  - Determine extent of the outbreak
  - Describe the illness
  - Identify the etiology
  - Identify the source of exposure

Etiology = Toxic agent that caused the outbreak

Exposure = Method by which patients came into contact with the toxic agent
Assemble an Investigation Team

Most **infectious** investigation teams include:

- Physician
- Epidemiologist
- Lab technician
- Community member
Assemble an Investigation Team (cont.)

Most toxicological investigation teams include:

- Physician
- Epidemiologist
- Lab technician
- Community member
- Toxicologist

- Studies the effects of toxic agents on people
- During an investigation...
  - Can help determine which toxic agents cause illness similar to what you are seeing
  - Can advise on what exposures and clinical signs and symptoms to ask about and what signs to observe
  - Can help interpret laboratory results
Assemble an Investigation Team (cont.)

Core team:
- Physician
- Epidemiologist
- Lab technician
- Community member
- Toxicologist

Other possible team members:
- Veterinarian

Many toxic agents affect humans and animals similarly.

A veterinarian can assist with...

- Collecting biologic specimens from animals
- Performing necropsies
Assemble an Investigation Team (cont.)

Core team:
- Physician
- Epidemiologist
- Lab technician
- Community member
- Toxicologist

Other possible team members:
- Botanist

Some toxic agents are plant-based

A botanist can assist with determining...
- What types of toxic trees, plants, and herbs grow in the region
- What types of illness these toxic plants might cause
Some toxicological outbreaks occur at the worksite.

An industrial hygienist can assist with...

- Providing insights on what potential exposures may be present at a particular workplace
- Developing questions for studying workplace exposures

Assemble an Investigation Team (cont.)

Core team:
- Physician
- Epidemiologist
- Lab technician
- Community member
- Toxicologist

Other possible team members:
- Industrial hygienist
The next step is to construct a working case definition.
Case Definition Components

What should be included in a case definition?
What should be included in a case definition?

A good case definition answers:

- What
- Who
- Where
- When
Case Definition Components (cont.)

A good case definition includes:

<table>
<thead>
<tr>
<th>WHAT</th>
<th>WHO</th>
<th>WHERE</th>
<th>WHEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms</td>
<td>Person characteristics</td>
<td>Place characteristics</td>
<td>Time characteristics</td>
</tr>
</tbody>
</table>
## Case Definition Example

It is good to have clear definitions for each of these criteria.

<table>
<thead>
<tr>
<th></th>
<th>What</th>
<th>Who</th>
<th>Where</th>
<th>When</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Okay</strong></td>
<td>Did not have a fever</td>
<td>Child</td>
<td>Spent time at School A</td>
<td>Fell ill during the morning</td>
</tr>
<tr>
<td><strong>Better</strong></td>
<td>Temperature less than 101.5°F by thermometer upon first presentation</td>
<td>15 years of age or younger</td>
<td>Enrolled as a student at School A</td>
<td>Fell ill between 6am and 10am</td>
</tr>
</tbody>
</table>
Sometimes a case definition is divided into suspect, probable, and confirmed cases.

A case has to meet more criteria to be a probable case, and even more criteria to be a confirmed case.
Confirmation usually requires laboratory identification/confirmation of the etiologic agent.
In toxicological outbreaks, we rarely have confirmed cases at the beginning of an outbreak.

In infectious outbreaks, you often have confirmed cases from the beginning.
Sensitive vs. Specific

- When developing a working case definition, there is a delicate balance between increasing sensitivity versus enhancing specificity
Consider a hypothetical group of people who might be included in an outbreak investigation.
Sensitive Case Definition

• More likely to include more true cases
• Might incorrectly include non-cases
Specific Case Definition

- More likely to correctly exclude non-cases
- Risks missing true cases because some of them may not meet the more narrow case definition
Several school children (ages 6–10 years) developed nausea, vomiting, and abdominal pain between the hours of 12pm and 4pm today.

Some developed altered mental status and multi-system organ dysfunction, and one died.

Most of the cases are friends and playmates, and they attend the same school.
## Scenario: Working Case Definition

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<th>What</th>
<th>Who</th>
<th>Where</th>
<th>When</th>
</tr>
</thead>
<tbody>
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<td>Nausea, vomiting, abdominal pain</td>
<td>Child aged 6 to 10 years</td>
<td>Attends School A</td>
<td>Onset between 12pm to 4pm</td>
</tr>
</tbody>
</table>
Scenario: Working Case Definition (cont.)

How might you revise each of these components to make the definition more sensitive?

- What
- Who
- Where
- When

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Scenario: Working Case Definition (cont.)

Answer:

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<th>Who</th>
<th>Where</th>
<th>When</th>
</tr>
</thead>
<tbody>
<tr>
<td>More specific definition</td>
<td>Nausea, vomiting, abdominal pain</td>
<td>Child aged 6 to 10 years</td>
<td>Attends School A</td>
<td>Onset between 12pm to 4pm</td>
</tr>
<tr>
<td>More sensitive definition</td>
<td>Any illness</td>
<td>Children aged ≤12 years</td>
<td>Lives in the city that houses School A</td>
<td>Onset anytime that day</td>
</tr>
</tbody>
</table>

How might you revise each of these components to make the definition more sensitive?
Sensitive vs. Specific

Considerations for deciding on specificity/sensitivity:

- Stage of the investigation
- Resources available for case finding
- Size of outbreak
Once you develop your case definition, the next step is to search for cases and learn more details of the outbreak.
Case Finding

What are some ways to find cases?
Case Finding (cont.)

What are some ways to find cases?

- Speak with physicians
- Review hospital records
- Speak with patients and their families
- Conduct door-to-door interviews
- Publicly announce the outbreak
A line list is a table that summarizes information about persons who may be associated with an outbreak.

What information would you include on a line list?
Line List (cont.)

What information would you include on a line list?

- Identifiers (name, unique number given to the person or ID number)
- Demographics (age, sex, residence)
- Clinical information (date/time of symptom onset, specific signs and symptoms, treatment received, outcome)
- Laboratory results
A line list template is available in the Tool Kit.
Hypothesis-Generating Interviews

- Informal interviewing allows you to collect information to generate hypotheses about...
  - The etiologic agent
  - The source of exposure
- Format
  - One-on-one discussions or group discussions
  - Open-ended questions
Scenario: Hypothesis-Generating Interviews

You have an opportunity to speak with two of the patients from the previous scenario.

What are some questions you might want to ask them?
Scenario: Hypothesis-Generating Interviews

Scenario ...

What are some questions you might want to ask them?

Possible questions:

- What did you eat and drink in the hours before you became sick?
- Did anything you eat taste or smell funny?
- Where did you go and what did you do in the hours before you became sick?
Some toxic agents produce a very specific illness progression, called a toxidrome, which can help the toxicologist identify the toxic agent.

Ask open-ended questions to identify whether there is a common toxidrome.
Hypothesis-Generating Interviews

### Person-related Characteristics

- What are the cases’ age, sex, and occupation?
- What did cases eat and drink in the hours before they became ill?
  - Any common foods or beverages among cases?
  - If there were any common foods or beverages, where are they from? For example, were they purchased in a store or home grown?
  - Did cases eat anything (or more of anything) compared to family members or friends/classmates/coworkers? If so, is any of the food still available?
  - Were fruits and vegetables washed before eaten?
  - Did cases report eating anything that had an unusual taste or odor? If so, what did it taste or smell like?
  - Where did the water the cases drank come from? If water is not piped into the home, what is it hauled in?
  - Did cases consume or use any traditional medicines, folk/herbal remedies, or nutritional supplements or ointments? If so, is any of the product still available?
  - What activities did cases do in the hours leading to illness?
    - If the cases are primarily children, where did they play?
    - If the cases are primarily adults, where do they work?
## Person-related Characteristics

- Any recollection of bites or stings before illness?
  - Did cases use insect repellents lotions/sprays/ointment in the hours preceding illness? If yes, what type, and how much was applied?
  - Where were these products purchased?
  - Is any of the product still available?
- What do you think made you (or others) sick?
Hypothesis-Generating Interviews (cont.)

**Place-related Characteristics**

- Where did cases spend their time in the hours preceding illness?
  - Did the cases spend time in any areas that were different from other family members/ friends/ co-workers?
- Where do cases live?
  - Any geographic clustering?
- Are there any known poisonous animals, insects, reptiles, plants in the area?
- Have there been any unusual animal deaths in the area?

**Questions for Farming Region**

- Are there any new plants or weeds growing in the area?
- What pesticides and other chemicals (such as rodenticides or other agricultural chemicals) are applied here?
- When are these pesticides applied?
- How are pesticides applied? For example, are they sprayed, applied by hand, etc. Can you show me how you apply the pesticide?
- Who applies the pesticides?
- Where are the pesticides purchased?
- How are pesticides stored?
- Have any new pesticides or chemicals been applied recently?
Hypothesis-Generating Interviews (cont.)

**Time-related Characteristics**

- What day and time did the case become ill?
  - Is there any clustering by time?
- Was there anything unusual about the day when the case became ill? If the case became ill in the morning, was there anything unusual about the previous day?

Tool Kit: Qualitative Epidemiological Questions
Hypothesis-Generating Interviews (cont.)

Illness-related Characteristics

- Describe the timeline of the illness. Which symptoms were noticed first, then second, then third, etc.? How much time elapsed between them? Did all cases have the same or similar order of symptom progression?
- Did the cases have fever as an early sign or symptom of the illness?
- Were any medicines used during the treatment?
  - When were they used, and in what amount?
  - How did the patient respond?
- Any preeminent or long term health effects after recovery or hospital discharge (such as numbness or rashes)?
- For fatal cases, what was the exact cause of death (cardiac arrest, respiratory failure, brain death, cerebral herniation, sepsis)?
Hypothesis-Generating Interviews (cont.)

Tool Kit: Qualitative Epidemiological Questions

Toxic Agent-related Questions

- What toxic agents are here that people could be exposed to?
- How might people come into contact with these toxic agents (food, water, etc.)?
- What are potential routes of exposure (ingestion, inhalation, etc.)?
Observations

It can be useful to visit the location of the outbreak to observe the following:

- Daily life
- Cultural habits
- Typical diet
- Any recent changes in the community
- Possible toxic agent exposures
Potential Toxic Agents

- If the hypothesis-generating interviews and/or observations lead you to suspect possible exposures to specific toxic agents, then information about these toxic agents should be collected systematically onto a sample log.
  - If possible, a sample of the purported toxic agent should also be collected.

What type of information might be collected on the sample log?
Potential Toxic Agents (cont.)

What type of information might be collected?

- The toxic agent’s name
- When and where it was purchased or made
- Who was it made by – manufacturer’s name
- Where it is stored
- Who has access to it
- When and where it was applied/consumed
- The amount applied/consumed
- Any recent changes in application or consumption patterns

The “toxic agent” could be an item that is not typically considered toxic, such as a contaminated food product or cosmetics.
As you interview the two ill children, you learn both had spent time in the school hall the morning before they fell ill

- You interview school staff and learn the auditorium had been cleaned that morning
- Both children reported eating a snack in the morning that was brought in by another student
- Both children also rode the bus to school
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Step 13: Communicate findings
Descriptive Epidemiology

- Before you begin your formal investigation, summarize the data you collected during case finding and hypothesis-generating interviews.
- This usually includes summarizing by...
  - Person
  - Place
  - Time

Person – describes who the cases are and who is at risk.

Place – provides information on geographic extent of the problem and demonstrates clusters or patterns that provide etiologic clues.

Time – depicts the time course of a spike in cases.
### Scenario: Attack Rates

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases (n=50)</th>
<th>Total number of children (n=500)</th>
<th>Attack rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 years</td>
<td>18</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>7 years</td>
<td>22</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>8 years</td>
<td>5</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>9 years</td>
<td>3</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>10 years</td>
<td>2</td>
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<table>
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<tr>
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<th>Cases (n=50)</th>
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</tr>
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<tbody>
<tr>
<td>Male</td>
<td>45</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>250</td>
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<table>
<thead>
<tr>
<th>Classroom</th>
<th>Cases (n=50)</th>
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<tbody>
<tr>
<td>A</td>
<td>16</td>
<td>125</td>
<td></td>
</tr>
<tr>
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<td>24</td>
<td>125</td>
<td></td>
</tr>
<tr>
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<td>125</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>2</td>
<td>125</td>
<td></td>
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**Summarizing by person...**

Investigators refer to the line list they created and calculate attack rates...

**How do you calculate an attack rate?**
### Scenario: Attack Rates (cont.)

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<td>2</td>
<td>125</td>
<td>2%</td>
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*Note: attack rate is presented as a percentage.*
The attack rate was highest among:
- 6- and 7-year old children
- Males
- Children in classrooms A and B

Based on these findings, you might do further informal data collection to determine what these groups had in common.

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A spot map is a simple and useful technique for illustrating where cases may have been exposed, including where they live, work, or play.

Example of a spot map showing cases by room

Summarizing by place...

Returning to the scenario...

What place would you consider drawing a spot map for and what would you include on the map?

Epi Curve

- An epi curve depicts the distribution of cases across time
- Examining the shape of an epi curve can provide clues about the exposure

Summarizing by time...

A special type of histogram is used to depict the time course of when the cases occurred.
We will consider these four main types of epi curves:

- Continuing source
- Point source
- Intermittent outbreak
- Propagated
A **continuing source** epi curve shows that the illnesses continue to occur until the exposure ceases.

Examples:
- Contaminated drinking water supply
- Contaminated food or supplement with national distribution
A **point source** epi curve shows that the group is exposed over a brief period of time and that the number of cases rises rapidly to a peak and falls gradually.

Examples:
- Contaminated food is served at a party
- One-time spraying of harmful pesticide indoors
An intermittent outbreak epi curve often has a pattern reflecting the intermittent nature of the exposure.

Examples:
- Periodic spraying of a harmful pesticide
- Seasonal lead exposure
Propagated epi curves show that there is not one common source responsible for the agent. The causative agent is associated with person-to-person transmission.

Examples:
- Syphilis
- Hepatitis B
Activity: Epi Curve

Which epi curve are you less likely to see during a toxicological outbreak?

a. 

b. 

c. 

d.
Activity: Epi Curve (cont.)

Which epi curve are you less likely to see during a toxicological outbreak?

a.  

b.  

c.  

d.
Returning to the scenario, the epi curve looks like this.

What might you deduce based on this epi curve?
Scenario: Epi Curve (cont.)

What might you deduce based on this epi curve?

It is a point source epi curve. Thus, it is likely that the exposure occurred during a single, one-time event.

The latency period (or time between when the exposure occurred to when symptoms appeared) was relatively short, given the condensed epi curve.
There are two types of hypotheses that you need to consider in toxicological outbreak investigations:

- Etiologic Agent
- Exposure
### Tool Kit: Toxidromes Chart

A toxicologist can help you identify the toxic agent based on the toxidrome.

#### Table 1. Classic Toxidromes

<table>
<thead>
<tr>
<th>Toxidrome</th>
<th>Signs and Symptoms</th>
<th>Potential Toxic Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic crisis</td>
<td>Salivation, diarrhea, lacrimation, bronchorrhea, diaphoresis, urination, Miosis, fasciculations, weakness, bradycardia or tachycardia, hypotension or hypertension, altered mental status, seizures</td>
<td>Nicotine, Organophosphate insecticides, Carbamate insecticides, Medicinal carbamates (e.g., physostigmine)</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Cutaneous flushing, hyperthermia, dry skin, mydriasis, dry mucous membranes, disorientation, hallucination, seizures, tachycardia, hypertension, urinary retention</td>
<td>Belladonna alkaloids, Jimson Weed/Datura, Brugmansia, Diphenhydramine</td>
</tr>
<tr>
<td>Hallucinogen</td>
<td>Disorientation, hallucination, panic</td>
<td>Peyote, Psilocybin mushrooms, LSD, PCP, Lysergic acid containing plants: morning glory, Hawaiian woodrose</td>
</tr>
</tbody>
</table>
Once you have developed hypotheses, the next step is to conduct a study to evaluate these hypotheses.
Types of Data Collected

A typical investigation involves collecting:

- Epidemiologic data
- Clinical data
- Laboratory data
Evaluate Hypotheses Using Analytic Epidemiology

- To quantify relationships between exposures and outcomes
- To test hypotheses about causal relationships
- Key feature is a *comparison group*
Types of Analytic Epidemiology Studies

- Case-control studies
  - Compares patients who have a disease or outcome of interest (cases) with patients who do not have the disease or outcome (controls) to describe the relationship between exposure and outcome.
  - Measures of associations between exposures and outcomes are measured using the odds ratio. The odds ratio compares the odds of a health event (e.g., disease) of those exposed to the odds of a disease to those unexposed.

One kind of comparison group used in case control studies is a group of people with the exposure but may not have the disease.

Case control studies useful when population is not well defined and speed of investigation is important
Types of Analytic Epidemiology Studies

- Retrospective cohort studies
  - Investigators contact each member of a defined population, determine each person’s past exposure to possible sources, and note whether they have disease.
  - Measures of associations between exposures and outcomes are measured using relative risk. The relative risk compares the risk of a health event (e.g., disease) among one group with the risk among another group.

Two common types of analytic epidemiology studies used in outbreak scenarios: Retrospective cohort studies and case control studies

Retrospective cohort studies feasible when the population is small and well defined and can be followed over time
Types of Analytic Epidemiology Studies

- **Retrospective cohort studies** useful when the population is small and well defined

- **Case control studies** useful when population is not well defined and speed of investigation is important
Epidemiologic Data: Questionnaires

Questionnaires:
1. Demographics
2. Potential risk factors for illness
3. Self-reported health information
4. Possible toxic agents and exposures
5. Quantification of exposure to toxic agent
6. Timeline of toxic agent exposure
Epidemiologic Data: Questionnaires (cont.)

Questionnaires:

1. Demographics
2. Potential risk factors for illness
3. Self-reported health information
4. Possible toxic agents and exposures
5. Quantification of exposure to toxic agent
6. Timeline of toxic agent exposure

Similar to infectious outbreak investigation
Epidemiologic Data: Questionnaires (cont.)

Questionnaires:
1. Demographics
2. Potential risk factors for illness
3. Self-reported health information
4. Possible toxic agents and exposures
5. Quantification of exposure to toxic agent
6. Timeline of toxic agent exposure

Toxicological outbreak investigations have a strong emphasis on timing of self-reported health information.
Epidemiologic Data: Questionnaires (cont.)

Questionnaires:
1. Demographics
2. Potential risk factors for illness
3. Self-reported health information
4. Possible toxic agents and exposures
5. Quantification of exposure to toxic agent
6. Timeline of toxic agent exposure
Questions about Exposures

- Questions about exposures can be asked in a yes/no format, or a quantified format

<table>
<thead>
<tr>
<th>Yes/No Format</th>
<th>Quantified Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Often used when there is a large number of possible exposures</td>
<td>• Often asked when there is a small number of possible exposures</td>
</tr>
<tr>
<td>• Easier for participants to answer</td>
<td>• Harder for participants to answer</td>
</tr>
<tr>
<td>• Takes less time</td>
<td>• Takes more time</td>
</tr>
<tr>
<td>• Less informative</td>
<td>• More informative</td>
</tr>
</tbody>
</table>
### Activity: Questions about Exposures

**How would you ask these questions in a quantified format?**

<table>
<thead>
<tr>
<th>Yes/No Format</th>
<th>Quantified Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you eat a banana?</td>
<td></td>
</tr>
<tr>
<td>Did you spray pesticides?</td>
<td></td>
</tr>
</tbody>
</table>
To ask about an exposure in a quantified format, think about...

- Frequency
- Duration
- Dose/Amount

### Activity: Questions about Exposures (cont.)

How would you ask these questions in a quantified format?

<table>
<thead>
<tr>
<th>Yes/No Format</th>
<th>Quantified Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you eat a banana?</td>
<td>How many bananas did you eat in the last 24 hours?</td>
</tr>
<tr>
<td>Did you spray pesticides?</td>
<td>How many times did you spray pesticides in the past 36 hours?</td>
</tr>
<tr>
<td></td>
<td>How many minutes did you spend spraying pesticides in the past 36 hours?</td>
</tr>
<tr>
<td></td>
<td>How much pesticide did you spray in the past 36 hours?</td>
</tr>
</tbody>
</table>
Quantifying Exposure

- Quantifying exposure allows you to better assess a dose-response relationship with illness.

<table>
<thead>
<tr>
<th># Times Spraying Pesticide</th>
<th>Attack rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 times</td>
<td>5%</td>
</tr>
<tr>
<td>1 to 2 times</td>
<td>40%</td>
</tr>
<tr>
<td>3 or more times</td>
<td>95%</td>
</tr>
</tbody>
</table>

Calculate attack rates for each of the strata.

If the attack rate increases with increasing exposure, then that suggest that it might be the implicated exposure.
Timeline

- Illness often occurs quickly (minutes to hours) after exposure to a toxic agent
- When asking about possible exposures, the timeframe is usually limited to the hours preceding the event
The Sample Questionnaire can be modified for your investigation.
Clinical Data

Sources of clinical data
- Epidemiologic questionnaire
- Medical chart abstraction

Types of clinical data
- Vital signs
- Clinical laboratory test results
- Presence/absence/timing of specific signs and symptoms
- Sign or symptom severity and frequency
- Medications provided as part of treatment
- Response to treatment/outcome
- Medical history
Questionnaires often include specific questions to determine the timing and order of symptom onset. Questionnaires can be self-administered or done via interview.

The Sample Questionnaire in the Tool Kit contains clinical questions.
Clinical Data (cont.)

Tool Kit: Sample Medical Record Abstraction Form

The Medical Record Abstraction Form template can be modified for your investigation.

Participant ID#: ___________

IV. Medical Record Abstraction
Please use the patient’s medical record to abstract the information requested below for their visit related to this specific outbreak.

Date of abstraction (mm/dd/yyyy): __________
Name of abstractor: ________________________________

Last   First   MI

1. General Information Questions:
2. First Name: ________________
3. Last Name: ________________
4. Medical Record #: __________
5. Phone Number: __________
6. Address/House description: __________
7. Village/District/Province: __________
8. Sex: _______ Male _______ Female
9. Age: __________ (years) if less than 1 year of age ________ (months)
Toxicological Laboratory Data

- It can be useful to collect biological and/or environmental samples for laboratory testing.
- Their utility will depend on:
  - What toxic agent caused the illness (and its biological elimination or environmental half-life)
  - How much time has passed since exposure
  - Whether it is a toxic agent that can be measured in the laboratory
  - Availability of comparison data
Early Sample Collection

- During a toxicological outbreak investigation, collecting biological specimens and/or environmental samples as early as possible is key.
- Some toxic agents may be eliminated from the body or broken down in the environment within minutes to hours after exposure.
- The sooner that a sample is collected, the greater the chances that the sample will still contain the toxic agent.
Data Analysis

- In toxicological outbreaks, epidemiologic and clinical data typically help guide laboratory testing

First stage:
- Clinical data
- Epidemiologic data

Second stage:
- Laboratory data
Data Analysis Steps

1. Look for exposures that are related to case status

2. If common exposures are identified, examine dose-response relationships
   - Compare attack rates by amount of exposure
   - Compare illness severity by amount of exposure
Scenario: Data Analyses

- Recall previous scenario:
  - Illness involving nausea, vomiting, abdominal pain, altered mental status, multi-system organ dysfunction, and death
  - Affected children aged 6–10 years who attended the same school
  - The investigators conducted an investigation.
**Scenario: Identify Common Exposures**

<table>
<thead>
<tr>
<th>Exposures</th>
<th># Cases</th>
<th># Children Exposed</th>
<th>Attack Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riding bus to school</td>
<td>32</td>
<td>245</td>
<td>13%</td>
</tr>
<tr>
<td>Eating breakfast in cafeteria</td>
<td>38</td>
<td>346</td>
<td>11%</td>
</tr>
<tr>
<td>Eating morning snack</td>
<td>45</td>
<td>123</td>
<td>37%</td>
</tr>
<tr>
<td>Spending time in school hall</td>
<td>41</td>
<td>267</td>
<td>15%</td>
</tr>
</tbody>
</table>

Step 1: Look for exposures that are related to case status.

Note: This approach, including calculating attack rates is typically used in a cohort study design.
Step 2: Look for a dose-response relationship

Main findings:
- The attack rate increases as the number of servings of the snack eaten increases.
- Almost all individuals who got sick ate the snack.

### Scenario: Dose-Response, Attack Rate

- The team identifies a dose-response relationship with the amount of snack eaten

<table>
<thead>
<tr>
<th>Amount of Snack Eaten</th>
<th># Cases</th>
<th># Children Exposed</th>
<th>Attack Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 servings</td>
<td>2</td>
<td>432</td>
<td>0%</td>
</tr>
<tr>
<td>1 serving</td>
<td>6</td>
<td>26</td>
<td>23%</td>
</tr>
<tr>
<td>2 servings</td>
<td>30</td>
<td>30</td>
<td>100%</td>
</tr>
<tr>
<td>3 servings</td>
<td>12</td>
<td>12</td>
<td>100%</td>
</tr>
</tbody>
</table>
The team decides to look at the relationship between dose and illness severity.

They first need to categorize illness severity:
- Not sick: No symptoms
- Mild sickness: Reported one or more symptoms, but no altered mental status, organ dysfunction, or death
- Severe sickness: Altered mental status, organ dysfunction, or death
Scenario: Dose-Response, Illness Severity

- The team compares the amount of snack eaten by these three illness severity categories

<table>
<thead>
<tr>
<th>Amount of Snack Eaten</th>
<th>Not sick (n=450)</th>
<th>Mild Sickness (n=35)</th>
<th>Severe Sickness (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 servings (n=432)</td>
<td>430 (96%)</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1 serving (n=26)</td>
<td>20 (4%)</td>
<td>5 (14%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>2 servings (n=30)</td>
<td>0 (0%)</td>
<td>25 (71%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>3 servings (n=12)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
<td>9 (60%)</td>
</tr>
</tbody>
</table>

Main findings:
- Most children who were not sick did not eat any snack.
- Everyone with severe sickness ate at least 1 serving of snack.
- Everyone who ate 2 or 3 servings became sick.
Dose-Response

What are some reasons why you might not see a dose-response relationship?
Dose-Response (cont.)

What are some reasons why you might not see a dose-response relationship?

- Some toxic agents cause illness at such a low dose that anyone who is exposed is already above the threshold
- Differences in metabolism and susceptibility
- Mis-classification of exposure or case status
Scenario: Data Analyses

- Based on these findings, the team advises the laboratory to analyze samples of the snack.
- Toxic agents that meet the differential include:
  - Heavy metals (e.g. mercury)
  - Herbicides (e.g. paraquat)
  - Metabolic poisons (e.g. cyanide)
Evaluating Laboratory Results

Four considerations need to be kept in mind when analyzing laboratory data:

- Limit of Detection
- Making Adjustments
- Examining Distribution
- Finding Comparison Values

Refer to Module 4: Analyzing and Interpreting Laboratory Results
Scenario: Laboratory Data Results

- Continuing with the scenario presented earlier, the investigators receive laboratory data on the urine specimens.
- They receive data on cyanide first.
Scenario: Biologic Laboratory Data

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% above Limit of Detection</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Range</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Median</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
</tr>
</tbody>
</table>

Could cyanide have been the culprit?
Could cyanide have been the culprit?

Although it seems unlikely because no cases had detectable levels, it is theoretically possible that it could have been cyanide.

Reasons why it is non-detect:
- The specimens could have been collected after cyanide was metabolized.
- The toxic threshold might be lower than the limit of detection.

### Scenario: Biologic Laboratory Data (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% above Limit of Detection</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Range</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Median</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
</tr>
</tbody>
</table>
Mercury is present in relatively high levels in cases and controls. Does this mean it is causing illness?

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury (µg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% above LOD</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>Range</td>
<td>&lt;LOD to 3.66</td>
<td>&lt;LOD to 2.97</td>
</tr>
<tr>
<td>Median</td>
<td>2.93</td>
<td>1.96</td>
</tr>
<tr>
<td>Paraquat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% above LOD</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Range</td>
<td>&lt;LOD to 41</td>
<td>&lt;LOD to 1.1</td>
</tr>
<tr>
<td>Median</td>
<td>23.5</td>
<td>&lt;LOD</td>
</tr>
</tbody>
</table>
Mercury is present in relatively high levels in cases and controls.

**Does this mean it is causing illness?**

No. The fact that the median level is similar between cases and controls suggests it did not cause the outbreak.

### Scenario: Biologic Laboratory Data (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mercury (μg/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% above LOD</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>Range</td>
<td>&lt;LOD to 3.66</td>
<td>&lt;LOD to 2.97</td>
</tr>
<tr>
<td>Median</td>
<td>2.93</td>
<td>1.96</td>
</tr>
<tr>
<td><strong>Paraquat</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% above LOD</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Range</td>
<td>&lt;LOD to 41</td>
<td>&lt;LOD to 1.1</td>
</tr>
<tr>
<td>Median</td>
<td>23.5</td>
<td>&lt;LOD</td>
</tr>
</tbody>
</table>
Paraquat is detected in a higher proportion of cases compared to controls, and the median is higher in cases than controls.

Does this mean it is causing illness?

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine mercury (μg/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% above LOD</td>
<td>80%</td>
<td>60%</td>
</tr>
<tr>
<td>Range</td>
<td>&lt;LOD to 3.66</td>
<td>&lt;LOD to 2.97</td>
</tr>
<tr>
<td>Median</td>
<td>2.93</td>
<td>1.96</td>
</tr>
<tr>
<td><strong>Paraquat</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% above LOD</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Range</td>
<td>&lt;LOD to 41</td>
<td>&lt;LOD to 11</td>
</tr>
<tr>
<td>Median</td>
<td>23.5</td>
<td>&lt;LOD</td>
</tr>
</tbody>
</table>
Scenario: Biologic Laboratory Data (cont.)

Is Paraquat causing illness?

Based on these data, it would be reasonable to assume that Paraquat likely caused the outbreak.

It is not a substance that would typically be expected to be found in biologic specimens, so its presence would indicate that it likely caused the illness.
Comparing to Reference and Control Values

- IF cases have levels that are higher than the toxic threshold
- AND if their clinical pictures resemble what would be expected following exposure to that toxic agent
- THEN you might conclude that the toxic agent caused the outbreak
Comparing to Comparison Values

- If cases have levels that are lower than the toxic threshold, but their symptoms match the clinical picture, it might mean that:
  - The toxic agent did not cause the outbreak, or
  - The specimens were not collected soon enough following exposure and perhaps the toxic agent was already partly eliminated from the body.
Sources of Comparison Values

- In the United States, the National Health and Nutrition Examination Survey (NHANES) provides a wealth of information for biomonitoring levels:

  https://www.cdc.gov/exposurerreport/
Scenario: Environmental Laboratory Data

- Investigators also receive data from the snack sample
**Scenario: Environmental Laboratory Data**

**Why was paraquat not detected in one of the snack samples?**

<table>
<thead>
<tr>
<th>Toxic Agent</th>
<th>Piece #1</th>
<th>Piece #2</th>
<th>Piece #3</th>
<th>Piece #4</th>
<th>Piece #5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanide</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>13</td>
<td>&lt;LOD</td>
</tr>
<tr>
<td>Mercury</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>5</td>
</tr>
<tr>
<td>Paraquat</td>
<td>331</td>
<td>20</td>
<td>&lt;LOD</td>
<td>648</td>
<td>394</td>
</tr>
</tbody>
</table>
Scenario: Environmental Laboratory Data

Why was one of the snack samples non-detect for Paraquat?

This is probably a result of the heterogeneous distribution of Paraquat in the snack.

This is a good example of why it is important to take more than one sample of an environmental media.
Control Measures

- Every outbreak investigation is unique; therefore, so are the control measures
- Example: Following this investigation, the snack was recalled
Identifying Additional Cases

- Depending on the situation and resources, you may or may not decide to implement a surveillance system.
- Example: Following the investigation, a campaign was started to inform the public, school officials, and healthcare providers to report food poisoning to public health officials.
Step 1: Establish that an outbreak exists

Step 2: Verify the diagnosis

Step 3: Prepare for field work

Step 4: Construct a working case definition

Step 5: Find cases systematically and record information

Step 6: Perform descriptive epidemiology

Step 7: Develop hypotheses

Step 8: Evaluate the hypotheses

Step 9: Refine hypotheses and perform additional studies

Step 10: Reconcile with lab data

Step 11: Implement control and prevention measures

Step 12: Initiate or maintain surveillance measures

Step 13: Communicate findings
Communicating Findings

- Toxicological laboratory results can sometimes be difficult to explain to stakeholders
- Two key issues:
  - Explaining why a specific toxic agent was not found, particularly if it is believed to have caused the outbreak
  - Explaining why finding specific toxic agents in samples does not necessarily mean they caused the outbreak
False Negative Result

- It is not always possible to identify the etiologic agent in an environmental or biologic sample

- Reasons for a false negative:
  - Toxic threshold is lower than the Limit of Detection
  - Toxic agent had a short half-life, and metabolized or degraded before the sample was collected
  - Inadequate sample quality or quantity
Scenario: Explaining Positive Results

What are some possible talking points for describing why mercury was detected in some biologic specimens in the previous scenario?
What are some possible talking points for describing why mercury was detected in some biologic specimens?

- Mercury was detected in a majority of students who had urine specimens collected. Although mercury is a neurotoxin, it is unlikely that mercury contributed to the outbreak.
- The levels of mercury are within the range of levels typically found in the U.S. population.
- There are many possible sources of mercury exposure, including fish.
Module Conclusion

What questions do you have about the information presented in this module?