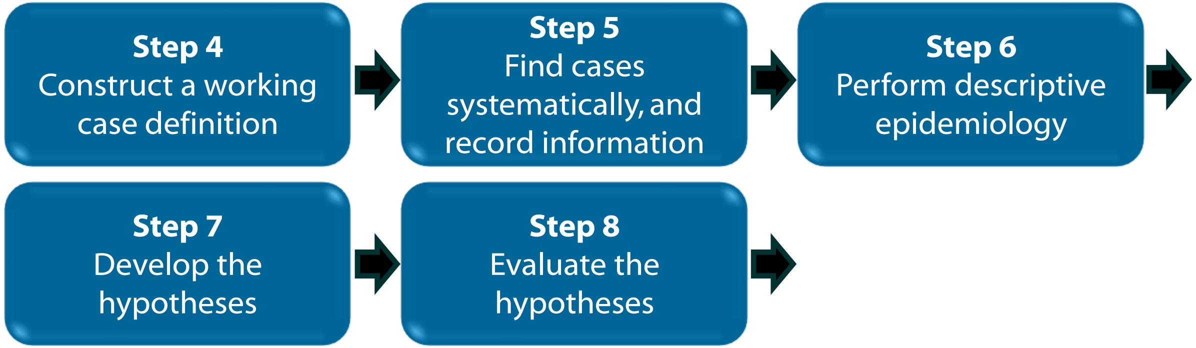
CDC's National Center for Environmental Health

Toxicological Outbreak Investigation

Module 5: Steps of a Toxicological Outbreak Investigation, Part 2

Welcome

- Welcome to Module 5 Part 2 of 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, 3rd edition.
- In this module, we will discuss steps 4–8 in an outbreak investigation.
- This module should take about 90 minutes to complete.



Objectives

- After completing this course, you will be able to
  - Construct a working case definition
  - Find cases systematically and record information
  - Perform descriptive epidemiology
  - Develop a hypothesis
  - Evaluate the hypothesis

Steps in an Outbreak Investigation

Depending on the circumstances, some of these steps might be done in a different order.

Implementing control and prevention measures should be a constant consideration. This should be done as soon as there is information to support such actions.

Step 1
Establish that an outbreak exists

Step 2
Verify the diagnosis

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Step 8
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Step 12
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Communicate findings

Case Definition Components

- In epidemiology, a “case” is an instance of a specified health condition.
- The person who experiences the health condition can be called a case-patient (if they are receiving medical care) or a person with a case.
- In an outbreak setting, it is important to clearly define what will be considered a “case” for the purposes of the investigation.
- ***What should be included in a case definition?***

Case Definition Components (cont.)

- A good case definition answers the questions What? Who? Where? and When?

A good case definition includes:			
What: Clinical signs and symptoms	**Who:** Person characteristics	**Where:** Place characteristics	**When:** Time characteristics

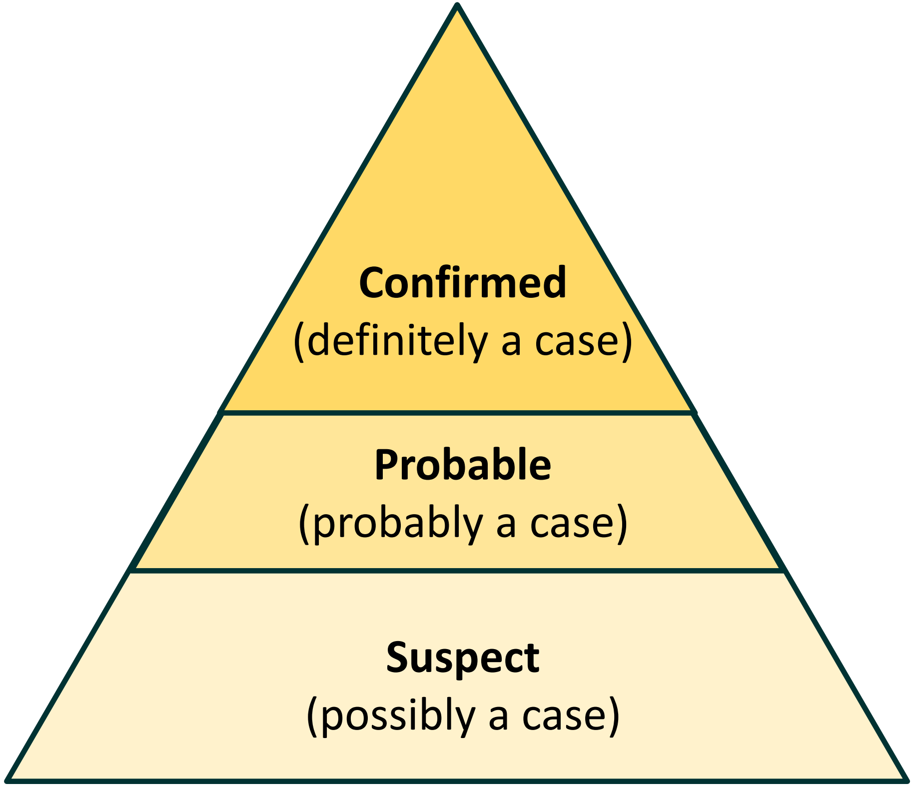
Case Definition Example

Try to have clear definitions for each of these criteria.

	What: Clinical signs and symptoms	Who: Person characteristics	Where: Place characteristics	When: Time characteristics
Okay	Vomiting or diarrhea	Child	Enrolled as a student at School A	Fell ill during the morning of November 9
Better	Vomiting or diarrhea (three or more loose stools within a 24-hour period)	Person aged 15 years or younger	Confirmed attendance as a student at School A during exposure period	Fell ill between 6:00 a.m. and 10:00 a.m. on November 9

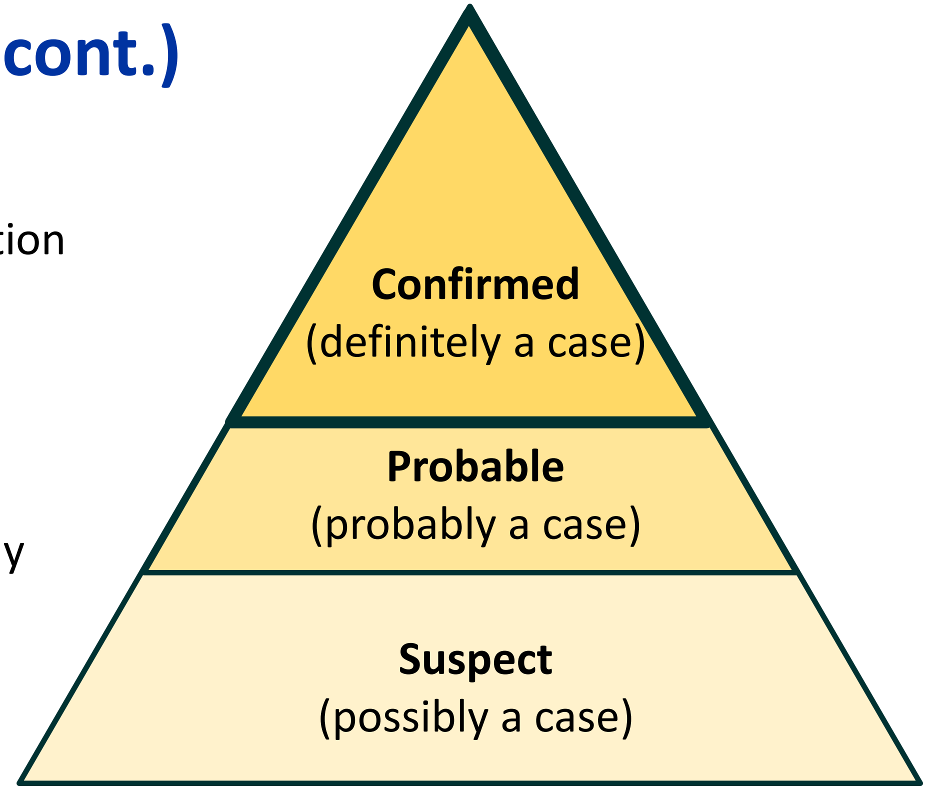
Tiered Case Definition

- Sometimes, a case definition is divided into suspect, probable, and confirmed cases.
- A case must meet more criteria to be a probable case and even more criteria to be a confirmed case.



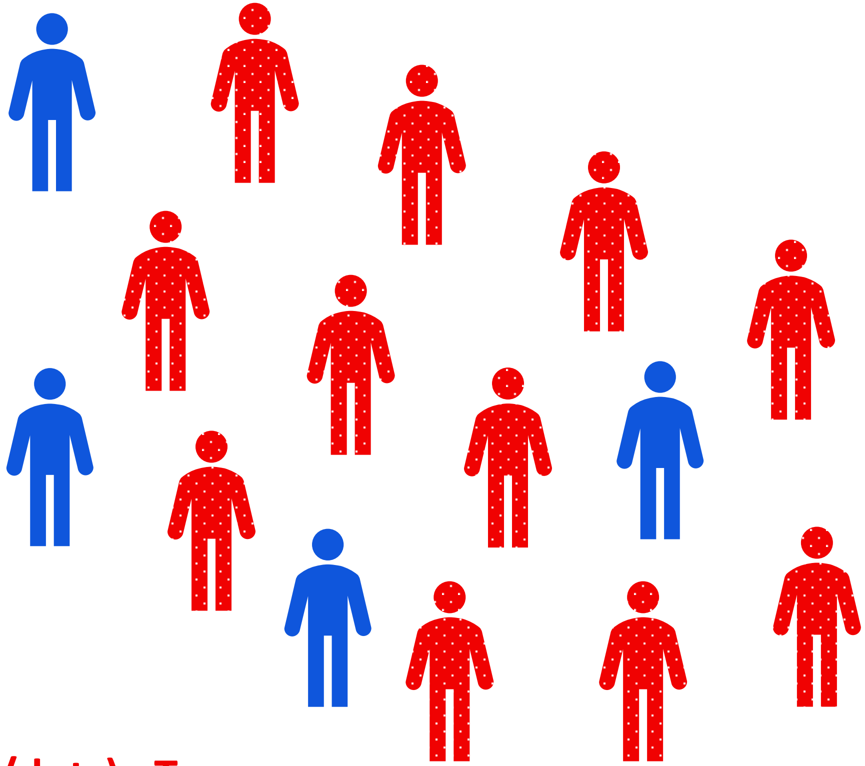
Tiered Case Definition (cont.)

- Often, confirmation requires laboratory identification/confirmation of the etiologic agent.
- In infectious outbreaks, you often have confirmed cases from the beginning.
- In toxicological outbreaks, we rarely have confirmed cases at the beginning of an outbreak.



Sensitive vs. Specific

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

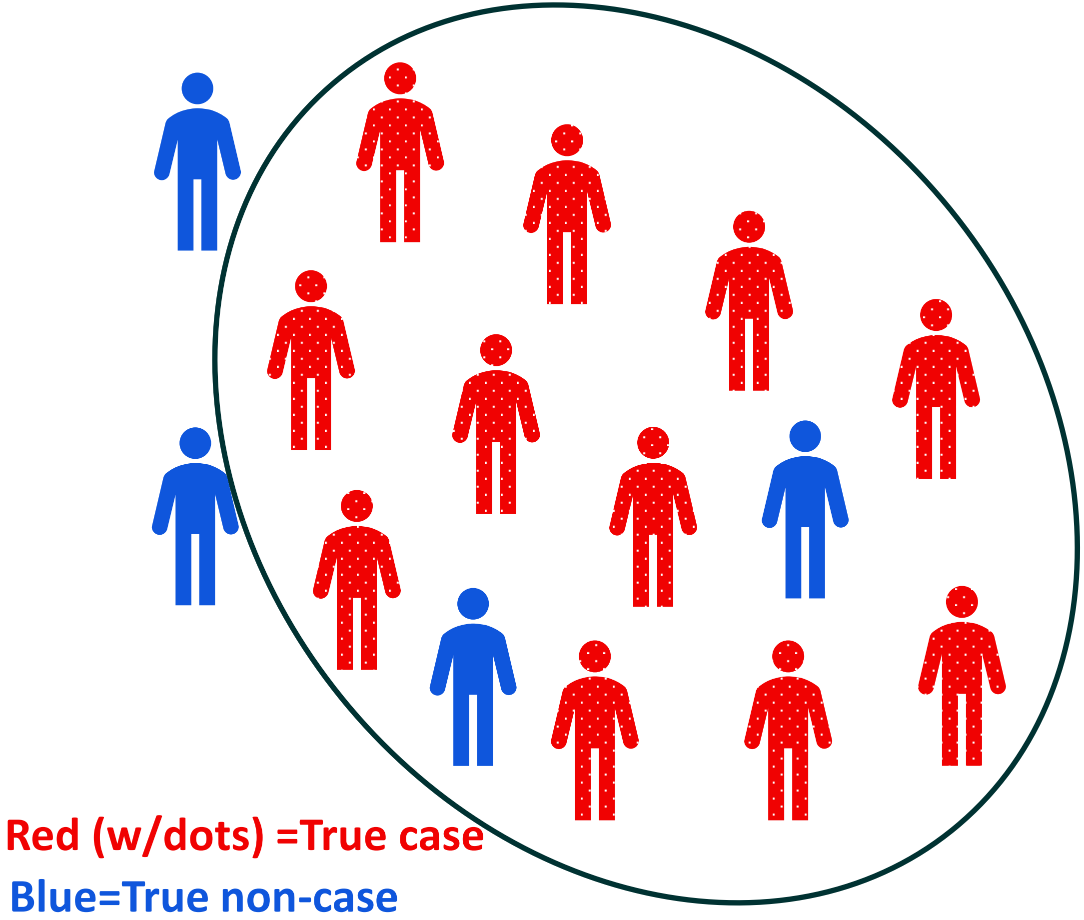


Red (w/dots) =True case

Blue=True non-case

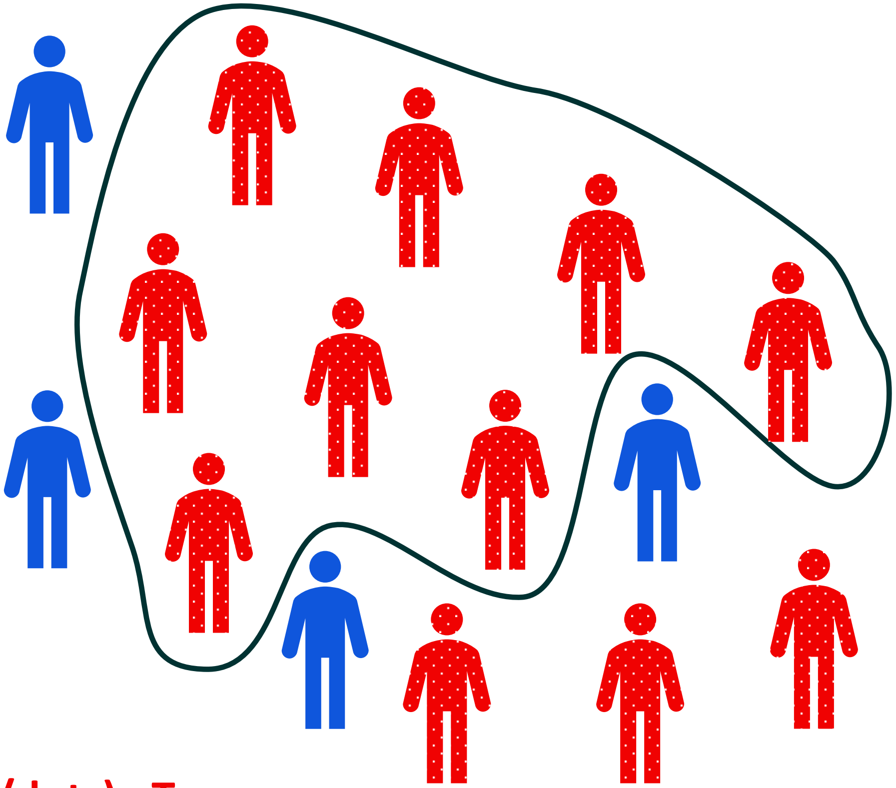
Sensitive

- A sensitive case definition has a high probability of correctly identifying true cases as cases but might incorrectly include some non-cases.



Specific

- A specific case definition has a high probability of correctly identifying true non-cases as non-cases, but risks missing true cases because some of them might not meet the narrower case definition.



Red (w/dots) =True case

Blue=True non-case

Scenario

- Several school children (aged 6–10 years) developed nausea, vomiting, and abdominal pain between the hours of 12 p.m. and 4 p.m. today.
- Some developed altered mental status, respiratory distress, and multi-system organ dysfunction, and one died.
- Most of the affected children are friends and playmates, and they attend the same school.

Scenario: Working Case Definition

- A working case definition might look like this:

	What	Who	Where	When
Working Case Definition	Vomiting and abdominal pain	Child aged 6–10 years	Attends School A	Onset between 12:00 p.m. and 4:00 p.m. today

Scenario: Working Case Definition (cont.)

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

	What	Who	Where	When
Working Case Definition	Vomiting and abdominal pain	Child aged 6–10 years	Attends School A	Onset between 12:00 p.m. and 4:00 p.m. today

Scenario: Working Case Definition (cont.)

- Here are some possible answers:

	What	Who	Where	When
Working Case Definition	Vomiting and abdominal pain	Child aged 6–10 years	Attends School A	Onset between 12:00 p.m. and 4:00 p.m. today
More Sensitive Case Definition	Nausea, vomiting or abdominal pain	Child aged ≤12 years	Attends School A or lives in the neighborhood in which School A is located	Onset any time today

Scenario: Working Case Definition (cont.)

- ***How might you revise each of these components to make the definition more specific?***

	What	Who	Where	When
Working Case Definition	Vomiting and abdominal pain	Child aged 6–10 years	Attends School A	Onset between 12:00 p.m. and 4:00 p.m. today

Scenario: Working Case Definition (cont.)

- Here are some possible answers:

	What	Who	Where	When
Working Case Definition	Vomiting and abdominal pain	Child aged 6–10 years	Attends School A	Onset between 12:00 p.m. and 4:00 p.m. today
More Sensitive Case Definition	Nausea, vomiting or abdominal pain	Child aged ≤12 years	Attends School A or lives in the neighborhood in which School A is located	Onset any time today
More Specific Case Definition	Vomiting, abdominal pain, **and** absence of fever	Child in second grade class	Was present in the School A lunchroom	Onset between 12:00 p.m. and 2:00 p.m. today

Considerations for Balancing Sensitivity and Specificity

- Stage of the investigation
  - Early in the investigation, you might want to use a more sensitive, less specific case definition to get an idea of the extent of the problem and to be sure you do not exclude people you might later want to include.
    - If the condition is not well understood, a more specific case definition might be initially used to only include the cases that you are most confident represent the condition of interest.
  - Later in the investigation you might want to use a more specific case definition when you are evaluating hypotheses and need to be sure only true cases are included as cases.
- Resources available for case finding
  - A more sensitive case definition could require more resources for case finding.
- Size of outbreak
  - In a large outbreak, it might be most efficient to use a more specific case definition.

Steps in an Outbreak Investigation

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Case Finding

- Once you develop your case definition, the next step is to search for cases.
- ***What are some ways to find cases?***

Case Finding (cont.)

- Here 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
  - Review public health surveillance data (if available, for example syndromic surveillance)

Line List

- When recording information about cases (or potential cases) that may be associated with an outbreak, we generally use a line list, which is a table that summarizes specific types of information.

- ***What information would you include on a line list?***

Line List (cont.)

- The following are some types of information to record on a line list:
  - Identifiers (name, unique ID number given to the case)
  - Demographics of the person with the case (age, sex, residence)
  - Clinical information (date and time of symptom onset, specific signs and symptoms, treatment received, outcome)
  - Laboratory sample collection (e.g., sample type, collection date) and results
  - Source of the report (how the case was identified)
  - Whether case definition is met and the tier (if applicable)
  - Other information that is important, given the stage of the investigation
    - Information on specific risk factors for the illness (if there are preliminary hypotheses)
    - Other pertinent notes

Line List Template

- **A line list template is available in the Tool Kit.**

Demographic Information					
ID#	First Name	Last Name	Address	Age (years)	Sex (M/F)

Clinical Illness Information					
Date of illness onset	Time of illness onset	Symptom #1 (Y/N)	Symptom #2 (Y/N)	Symptom #3 (Y/N)	Outcome

Record Keeping						
Questionnaire complete (Y/N)	Chart abstraction complete (Y/N)	Biological sample collected (Y/N)	If yes, biological sample results	Environmental sample collected (Y/N)	If yes, environmental sample results	Meets case definition (Y/N)

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
- At this point, you might also want to collect biological or environmental samples (such as samples of foods that were eaten) because those samples might not be available later.

Scenario: Hypothesis-Generating Interviews

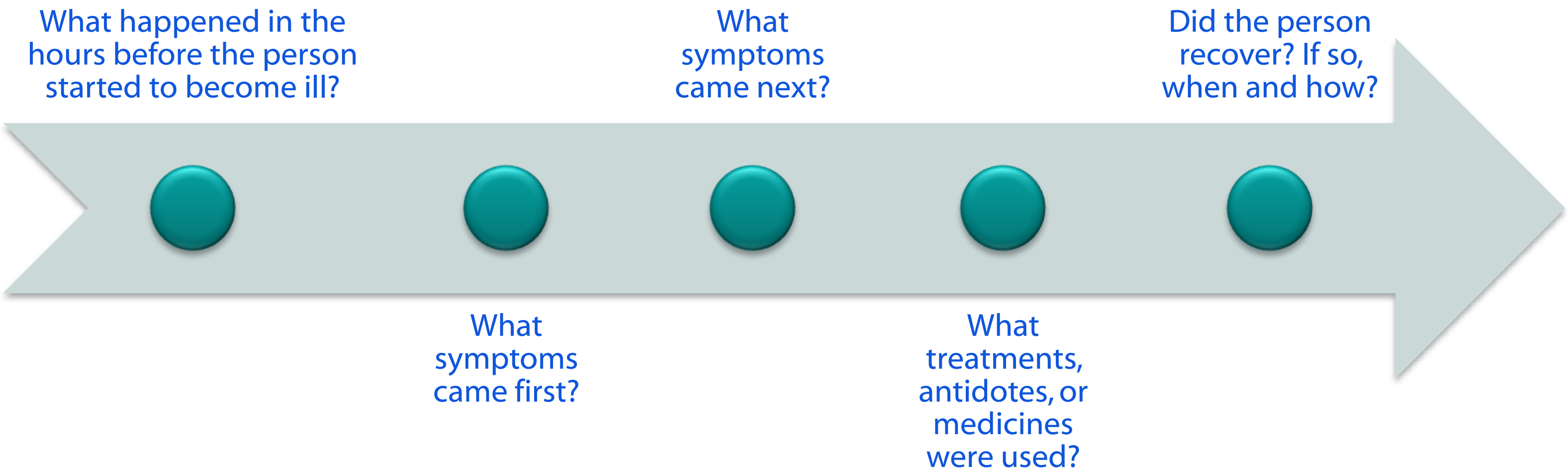
- You have an opportunity to speak with two of the patients from the previous scenario.
- ***What are some questions you might want to ask them and their parents?***

Scenario: Hypothesis-Generating Interviews (cont.)

- Here are some possible questions:
  - What did you eat and drink in the hours before you became sick?
  - Did anything you eat have an unusual taste or smell?
  - Where did you go and what did you do in the hours before you became sick?
  - Please tell me about your illness.
- The questions to ask depend on the situation.

Hypothesis-Generating Interviews: Toxidrome

- Some toxic agents produce a very specific illness progression, which helps determine the toxidrome. The toxidrome helps the toxicologist identify the toxic agent.
- Ask open-ended questions to identify whether there is a common toxidrome.



Hypothesis-Generating Interviews (cont.)

- The Tool Kit includes some examples of qualitative questions that could be asked at this stage of the investigation for people who had illness meeting the case definition.

- Questions can relate to the following:
  - Person-related characteristics
  - Place-related characteristics
  - Time-related characteristics
  - Illness-related characteristics
  - Potentially relevant exposures
  - Potential for exposure to toxins

Hypothesis-Generating Interviews (cont.)

Person-related Characteristics
• What are the ages, sex, and occupations of the affected people?

Place-related Characteristics
• Where did the affected people spend their time in the hours preceding illness? ○ Did the affected people spend time in any areas that were different from other family members/friends/co-workers who did not get sick? • Where do the affected people live, work, or go to school? ○ Any geographic clustering? • Are there any known poisonous animals, insects, reptiles, or plants in the area? • Have there been any unusual animal deaths in the area? *Questions for Farming Regions* • What types of crops are grown in the area? Has that changed recently? • Are there any new plants or weeds growing in the area?

Hypothesis-Generating Interviews (cont.)

Time-related Characteristics

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

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 affected people have the same or similar order of symptom progression?
- Did the affected persons 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 affected person respond?
- Did the affected person experience any lingering 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)?
  - Were any autopsies done? If so, what were the findings?

Hypothesis-Generating Interviews (cont.)

Potentially Relevant Exposures

- What did affected people eat and drink in the hours before they became ill?
  - Any common foods or beverages among affected people?
  - If there were any common foods or beverages, where were they from? For example, were they purchased in a store or home grown?
  - Did the affected people eat anything unique (or more of anything) compared with family members, friends, classmates, or coworkers who did not get sick? If so, is any of the food still available?
  - Were fruits and vegetables washed before being eaten?
  - Did the affected people report eating anything that had an unusual taste or odor? If so, what did it taste or smell like?
  - Where did the water the affected people drank come from? If water is not piped into the home, what is it hauled in?
  - Did the affected people consume or use any prescription medicines, over-the-counter medicine, traditional medicines, folk or herbal remedies, or nutritional supplements or ointments? If so, is any of the product still available?
  - What activities did the affected people engage in during the hours leading to illness?
    - If the cases are primarily in children, where did they play?
    - If the cases are primarily in adults, where do they work?
- Any recollection of bites or stings before illness?
- Did the affected people 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? Are any of the products still available?
- What do you think made you (or others) sick?

Hypothesis-Generating Interviews (cont.)

Potential for Exposure to Toxins
• What toxic agents are present in the area 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.)? ***Questions for Farming Regions*** • What pesticides and other chemicals (such as rodenticides or other agricultural chemicals) are applied in the area? • 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?

Observations

- It might be useful to visit the location of the outbreak to observe these factors:
  - Daily life
  - Cultural habits
  - Typical diet
  - Any recent changes in the community
  - Possible toxic agent exposures

Potential Toxic Agents and Vehicles

- The hypothesis-generating interviews and observations might lead you to suspect possible exposure to specific toxic agents.
- They might also lead you to suspect that a toxic agent might be present in a particular vehicle, such as a food or cosmetic. A **vehicle** is a material or object that is not toxic itself but is the means through which people are exposed to a toxic agent.
- If possible, a sample of the purported toxic agent or vehicle should be collected.
  - Information about the samples that are collected should be systematically recorded in a sample log (discussed in detail in module 3).
- ***What type of information might be collected about a potential toxic agent or vehicle?***

Potential Toxic Agents and Vehicles (cont.)

- Information that might be collected about a potential vehicle or toxic agent includes
  - The name of the vehicle or toxic agent
  - When and where it was purchased or made
  - Who made it (manufacturer's name)
  - Where it is stored
  - Who has access to it
  - When and where it was applied, consumed, or used
  - The amount applied, consumed, or used
  - Any recent changes in application, consumption, or use patterns

Scenario: Additional Information

- As you interview two of the ill children, you learn
  - Both spent time in the school auditorium the morning before they fell ill.
  - Both reported eating a snack in the morning that was brought in by another student.
  - Both rode the bus to school.
- You interview school staff and learn the auditorium had been cleaned that morning.
- *What additional questions might you ask relating to potential toxic agents and vehicles?*

Scenario: Additional Information (cont.)

- Some possible questions might include
  - For children
    - Did you notice anything unusual about the auditorium that morning?
    - Did the snack have an unusual taste?
    - Did you notice anything unusual about the bus that morning?
  - For staff
    - Which cleaning agents were used in the auditorium that morning?
    - Was there anything different about the way the auditorium was cleaned that morning?
    - At what time was the auditorium cleaned?

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Descriptive Epidemiology

- Before you begin a more formal part of the investigation, summarize the data you collected during case finding and hypothesis-generating interviews.
- This usually includes summarizing by person, place, and time:
  - Person: Describes who the case-patients are and who is at risk.
  - Place: Provides information on the geographic extent of the problem and demonstrates clusters or patterns that can provide etiologic clues.
  - Time: Depicts the time course of a spike in the number of cases.

Summarizing Information by Person Characteristics

- When summarizing by person, investigators in our scenario refer to the line list they created.
- ***What can you conclude from this information?***
- ***What other information would you like to have?***

	Number of case-patients (n=12)
Age: 6 years	4
Age: 7 years	5
Age: 8 years	2
Age: 9 years	1
Age: 10 years	0
Sex: Male	11
Sex: Female	1

Summarizing Information by Person Characteristics (cont.)

- At this stage of the investigation, you might only have information about case-patients and not the larger population. That can still tentatively point you in specific directions.
- If you have information about the larger population, you can calculate attack rates.

$$Attack\ rate = \frac{\#\ of\ \ cases\ with\ characteristic}{\#\ in\ population\ with\ charactersitic}$$

(Attack rates are usually presented as percentages)

What might you conclude based on this information?

	Number of case-patients (n=12)	Total Number of Children in School (n=120)	Attack Rate
Age: 6 years	4	24	17%
Age: 7 years	5	24	21%
Age: 8 years	2	24	8%
Age: 9 years	1	24	4%
Age: 10 years	0	24	0%
Sex: Male	11	60	18%
Sex: Female	1	60	2%

Summarizing Information by Person Characteristics (cont.)

- The attack rate was highest among
  - 6- and 7-year-old children
  - Males
- Based on these findings, you might do further informal data collection to determine what these groups had in common.

	Number of case-patients (n=12)	Total Number of Children in School (n=120)	Attack Rate
Age: 6 years	4	24	17%
Age: 7 years	5	24	21%
Age: 8 years	2	24	8%
Age: 9 years	1	24	4%
Age: 10 years	0	24	0%
Sex: Male	11	60	18%
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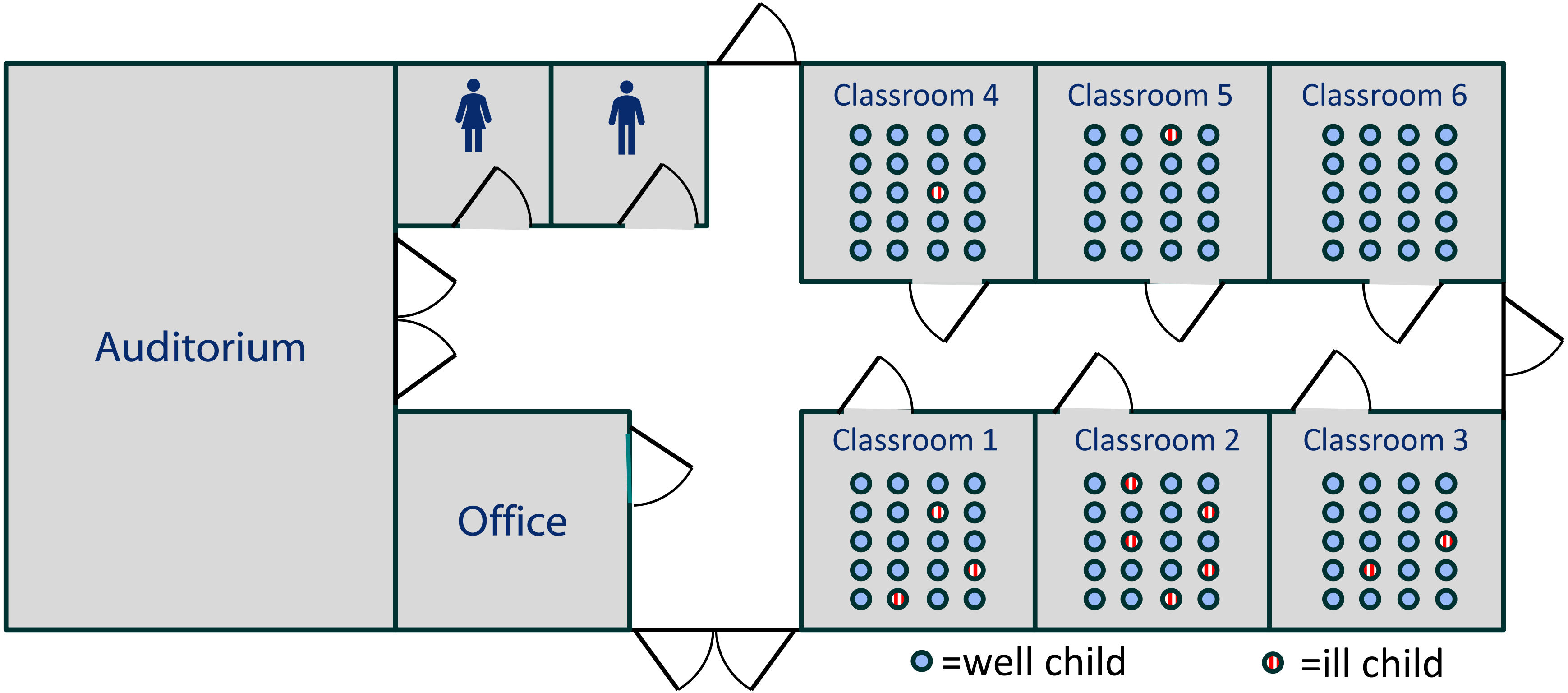
Summarizing by Place: Spot Maps

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

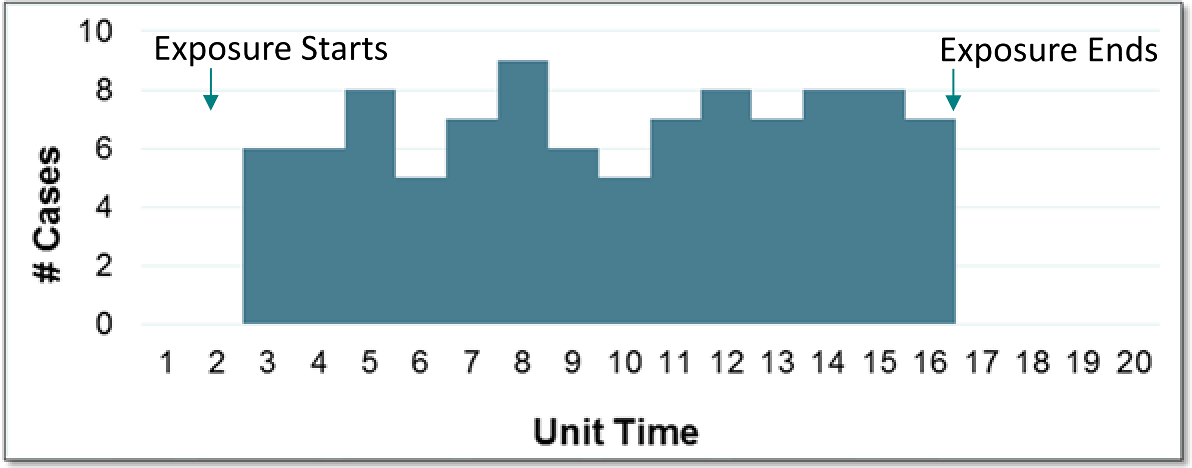


Summarizing by Time: Epi Curves

- A special type of histogram, called an epi curve, is used to depict the time course of when the cases occurred (distribution of cases across time).
- An epi curve shows the number of cases by unit of time, typically by the date or time of illness onset or the diagnosis date.
- Examining the shape of an epi curve can provide clues about the exposure.
- We will consider four main epi curve shapes:
  - Continuing source
  - Point source
  - Intermittent outbreak
  - Propagated

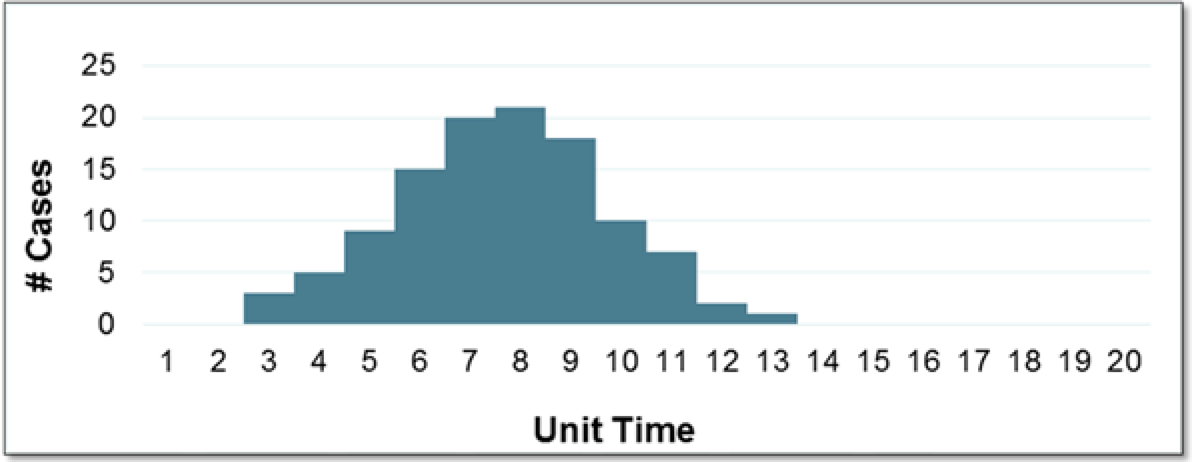
Continuing Source Outbreak Epi Curve

- An epi curve for a continuing source outbreak shows that the illnesses continue to occur until the exposure ceases.
- Examples include a contaminated drinking water supply or a contaminated food or supplement with national distribution.



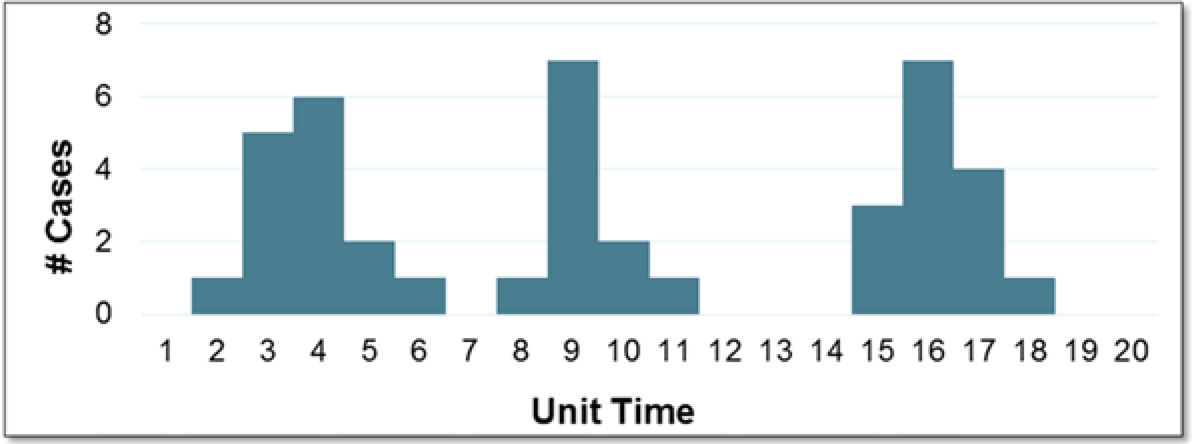
Point Source Outbreak Epi Curve

- An epi curve for a point source outbreak shows that the group is exposed over a brief period. The number of cases rises rapidly to a peak and falls gradually.
- The cases are somewhat spread out in time because the time between exposure and symptom onset can vary between people.
- Examples include contaminated food served at a party or a one-time spraying of harmful pesticide indoors.



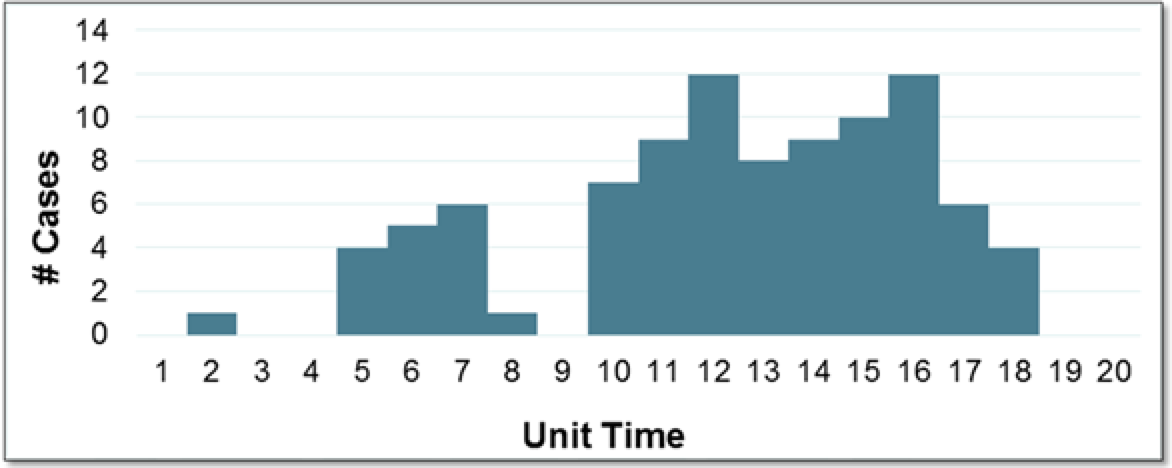
Intermittent Outbreak Epi Curve

- An epi curve for an intermittent outbreak has a pattern reflecting the intermittent nature of the exposure.
- Examples include periodic spraying of a harmful pesticide or seasonal lead exposure.



Propagated Outbreak Epi Curve

- An epi curve for a propagated outbreak shows that there is no single common source responsible for the agent. The causative agent is associated with person-to-person transmission.
- Examples include syphilis or hepatitis B.



Challenge

- **Which epi curve are you less likely to see during a toxicological outbreak? Select the best response.**

A. Continuing source epi curve

B. Point source epi curve

C. Intermittent outbreak epi curve

D. Propagated epi curve

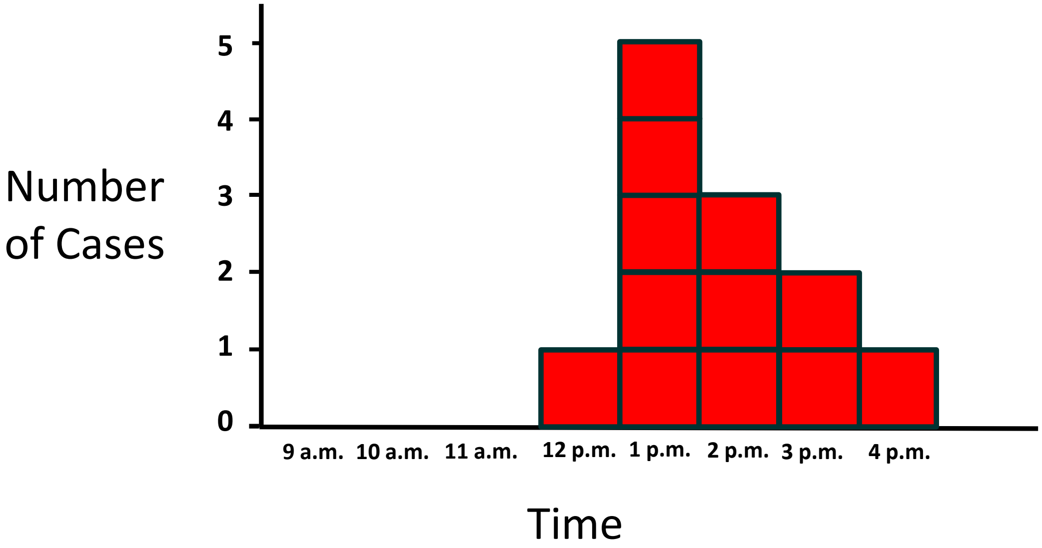
Challenge Answer

- **The correct answer is D.**

  You are less likely to see a propagated epi curve during a toxicological outbreak.

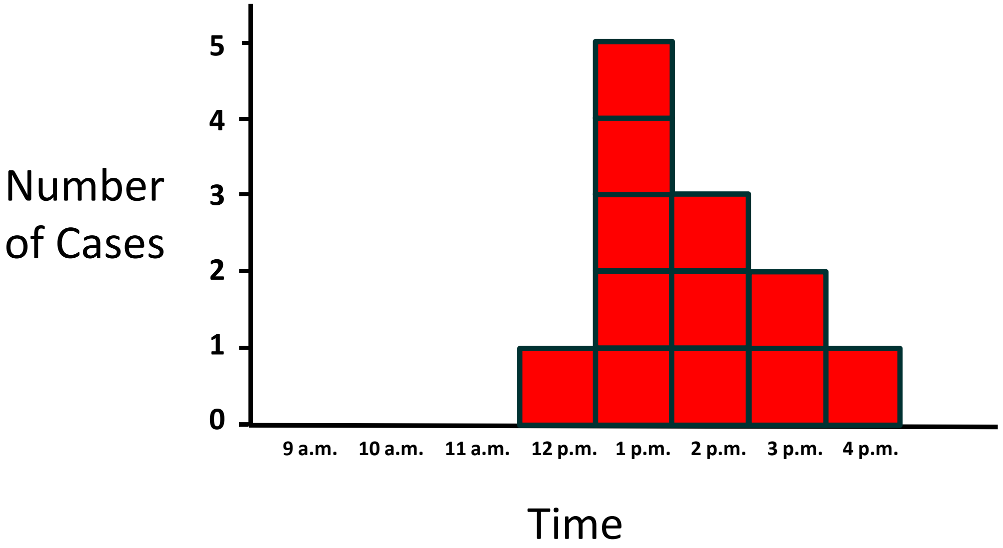
Scenario: Epi Curve

- Returning to the scenario, the epi curve looks like this.
- ***What might you deduce based on this epi curve?***



Scenario: Epi Curve (cont.)

- This is a point source epi curve. Thus, it is likely the exposure occurred during a single, one-time event.
- The latency period was relatively short and did not vary a lot, given the condensed epi curve.



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Generating Hypotheses

- Generally, this step has been happening throughout the investigation.
- These are some considerations in generating hypotheses:
  - Known causes of the type of illness that is occurring and causes of similar outbreaks in the past
  - Ideas about possible causes from case-patients, the community, and clinicians
  - Unique aspects of descriptive epidemiology in terms of person, time, and place
  - Outliers (e.g., in time or space) that might provide clues

Two General Types of Hypotheses

- Two types of hypotheses need to be considered in toxicological outbreak investigations, relating to the etiologic agent and exposure (or vehicle).

- **Etiologic Agent**
  - How do you figure it out?
    - Signs and symptoms: a toxicologist can help identify a toxidrome (see toxidromes chart in Tool Kit).
    - Biologic or environmental lab testing can help.
    - Sometimes, questionnaires and environmental testing could also help.
  - Why do we need to know this?
    - It can help you treat patients.
    - It could help stop the outbreak.

- **Exposure or Vehicle**
  - How do you figure it out?
    - Questionnaires
    - Environmental lab testing
  - Why do we need to know this?
    - It will help stop the outbreak.

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Refine hypotheses, and perform additional studies

Step 10
Reconcile with lab data

Step 11
Implement control and prevention measures

Step 12
Institute or maintain surveillance measures

Step 13
Communicate findings

Evaluating Hypotheses

- Once you have developed hypotheses, the next step may be to conduct an epidemiologic study to evaluate these hypotheses.
- One consideration in planning a study relates to selecting an epidemiologic **study design**. Two commonly used study designs include cohort studies and case-control studies, although other study designs can be used.

Cohort Study

Case-Control Study

- Another consideration in planning a study relates to **data sources**. Investigations may involve collecting questionnaires, medical records, and laboratory data.

Questionnaire Data

Medical Records Data

Laboratory Data

Epidemiologic Study Design

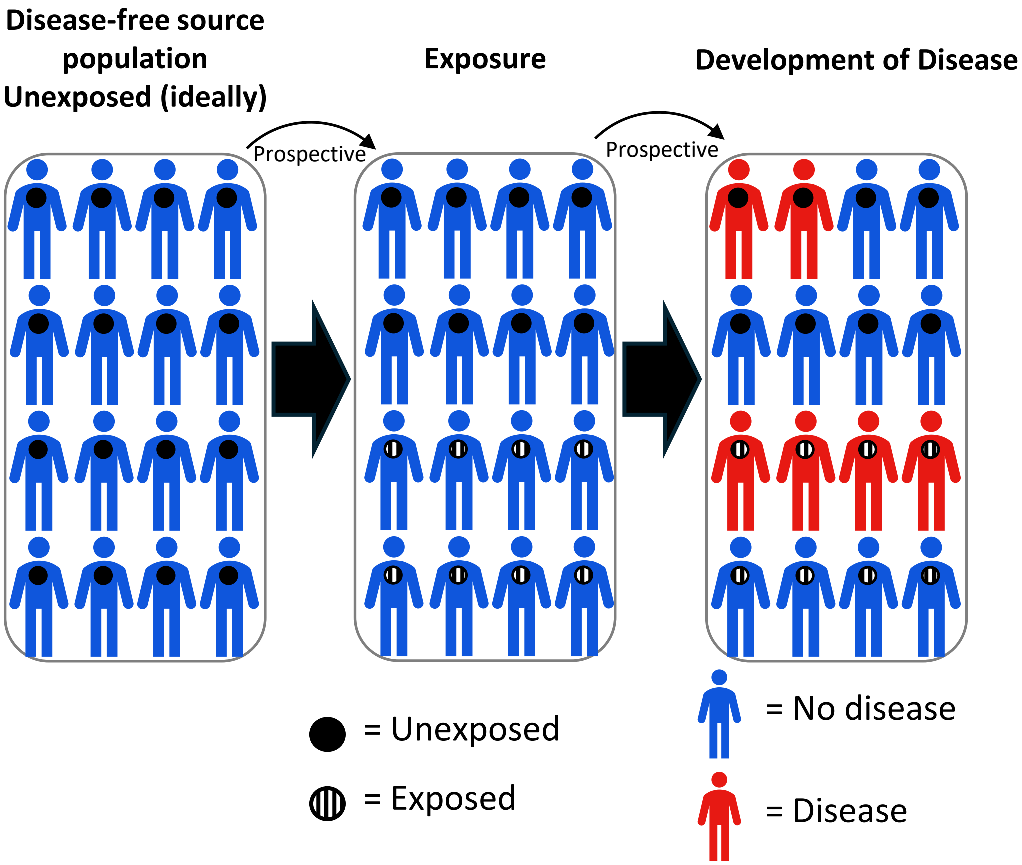
- Two types of epidemiologic studies are commonly used in outbreak scenarios:
  - Cohort studies
  - Case control studies
- The goal of an epidemiologic study is typically to assess associations between exposures and outcomes.
- A key feature of an epidemiologic study is the inclusion of an appropriate comparison group.

Cohort Study

Case-Control Study

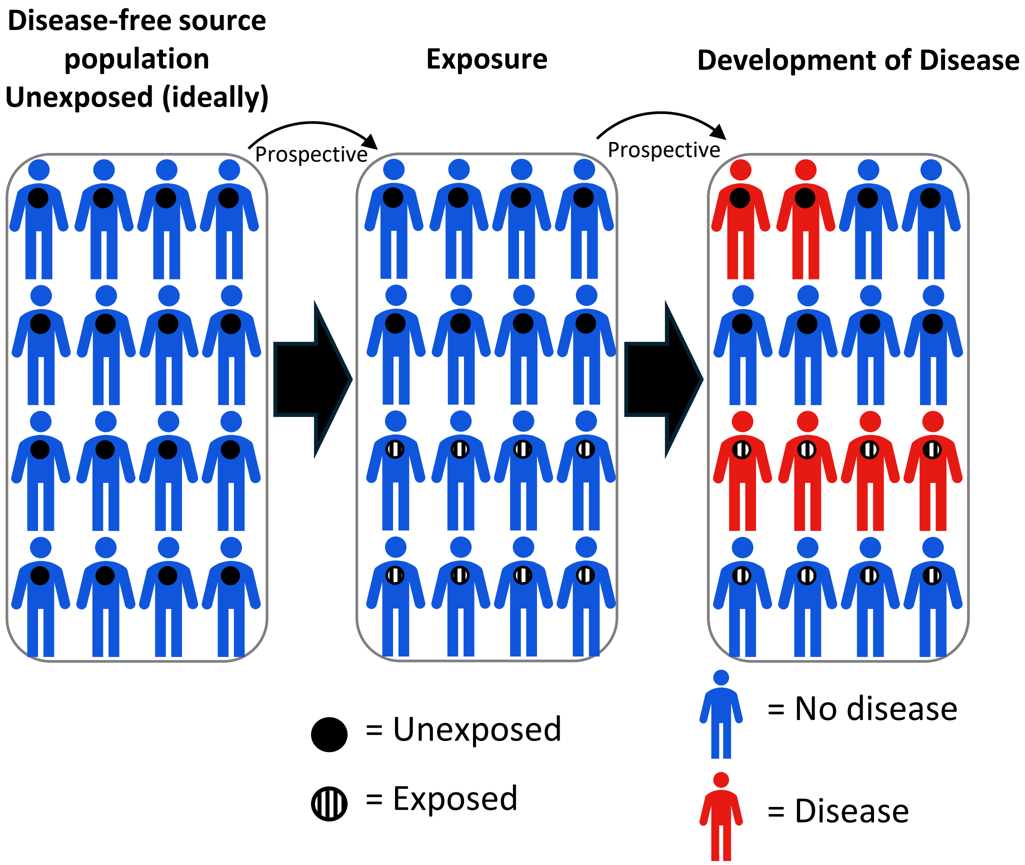
Underlying Conceptual Epidemiologic Cohort

- When an exposure causes a disease in an outbreak, there was an initial population at risk for the disease (the source population) before that exposure occurred.
- At some point, some of those people were exposed, and, **after** exposure, some developed disease.
- Conceptually, the ideal study would be a prospective cohort study:
  - Identify a defined group of people at risk for the outcome (i.e., the source population).
  - Assess exposure prior to disease development.
  - Follow the source population over time to see who develops disease.
  - Compare rates of disease onset in groups defined by exposure status.



Epidemiologic Studies

- In outbreak situations, prospective cohort studies are generally not possible for several reasons:
  - Outbreak investigations generally start after people have already been exposed and have developed disease.
  - Historical information on exposures assessed prior to disease development is rarely available.
  - You do not want to wait for more people to get sick.
  - It might not be clear how to identify the source population.



Cohort Studies

- In a cohort study, investigators either identify all members of a defined population and seek to determine each person's exposures, or they identify an exposed group and an unexposed group (both from the same source population).
- They then determine who among the exposed and unexposed develop the disease.
- Such studies are feasible when:
  - The population at risk is well defined and is either small or can be sampled.
  - The outcome is relatively common.
  - Information can be collected relating to exposures and subsequent disease onset.
    - Exposures would be assessed prior to disease onset (e.g., documentation in existing records, previously collected data, stored specimens)
    - It is important to collect information about the **timing** of exposure and disease onset to make sure that exposure was assessed before disease onset.

Risk Ratio

- In cohort studies, the relevant measure of association between an exposure and an outcome is either the **risk ratio** (also called relative risk) or the **rate ratio**.
- **Risk** is calculated as the probability of disease over some specified follow-up period among everyone in a defined group. Risks are sometimes called "attack rates."
- A **rate** is calculated as the number of cases that occur in a defined group per some unit of time. Rates account for varying lengths of follow up time for different people.
- Risks are often calculated in acute outbreaks, because the follow-up period is typically short and consistent across all study participants.
- The **risk ratio** (ratio of two risks), or **rate ratio** (ratio of two rates), compares the risk or rate of a disease or other health event in one group (such as a group with an exposure) with the risk or rate in another group (such as a group without that exposure).

Risk Ratio Calculation

		Outcome Yes	Outcome No	
Exposure	Yes	a	b	a+b
	No	c	d	c+d

Risk of outcome among exposed = $\boldsymbol{a/(a+b)}$

Risk of outcome among unexposed = $\boldsymbol{c/(c+d)}$

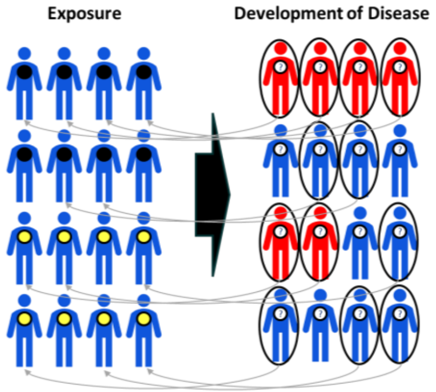
Risk Ratio = $\boldsymbol{\frac{a/(a+b)}{c/(c+d)}}$

Important Study Design Considerations for Cohort Studies

- Selecting participants:
  - Try to include as many people as possible from the source population (e.g., everyone who attended a particular event, everyone in a particular school).
  - It is also possible to enroll people in the study based on their known exposures (e.g., workers who performed a specific task and a random sample of workers at the same company who did not perform that task), but both groups should be from the same source population.
  - If sampling is used, make sure it is done in a way that will not lead to bias.
  - Make sure that the probability of someone being included in the study is not related both to their exposures and to them developing the disease of interest (i.e., study selection is not related to both the exposure and outcome of interest).

Case-Control Studies

- Case-control studies are useful when the population at risk is not well defined and speed of investigation is important.
- Case-control studies compare the previous exposures of people who have a disease (preferably incident rather than prevalent cases) or outcome of interest (case-patients or case-participants) and people from the same source population who do not have the disease or outcome (controls).
- People are enrolled based on whether they developed the disease/outcome of interest, not based on their exposure status.



Odds Ratio

- In a case-control study, you cannot directly calculate rates or risks.
- The relevant measure of association between an exposure and an outcome in a case-control study is the odds ratio.
- **Odds** refers to the probability of something happening divided by the probability of it not happening in some group (i.e., the probability of exposure among people with the disease divided by the probability of no exposure among people with disease).
- The **odds ratio** (ratio of two odds) compares the odds of having had the exposure among people with the disease or outcome of interest and people without the disease or outcome of interest.

Odds Ratio Calculation

		Outcome	
		Yes (case-patient)	No (control)
Exposure	Yes	a	b
	No	c	d
		a+c	b+d

Odds of exposure among case-patients =

$$\frac{Probability\ of\ exposure\ among\ case-patients}{Probability\ of\ no\ exposure\ among\ case-patients} = \frac{a/(a+c)}{c/(a+c)} = \frac{a}{c}$$

Odds of exposure among controls =

$$\frac{Probability\ of\ exposure\ among\ controls}{Probability\ of\ no\ exposure\ among\ controls} = \frac{b/(b+d)}{d/(b+d)} = \frac{b}{d}$$

Odds Ratio =

$$\frac{Odds\ of\ exposure\ among\ patients}{Odds\ of\ exposure\ among\ controls} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

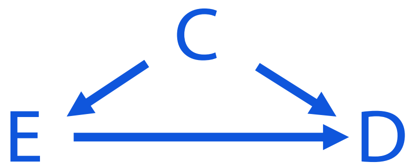
Important Study Design Considerations for Case-Control Studies

- Generally, in an outbreak investigation, the aim is to include all known cases.
- Controls need to be carefully selected.
  - The distribution of exposure among control participants should represent the distribution of exposure in the source population from which the cases came.
  - Selection as a control participant should be independent of exposure status. This can require careful thought.
- Sources of control participants will vary depending on the situation.
- Sometimes matching is used.
  - The purpose of matching is to allow more efficient control for confounding.
  - You cannot assess associations with any matching variable.
  - Be sure not to match on the exposure of interest (intentionally or unintentionally).
  - Special kinds of analysis are needed if matching is used.

Confounding and Effect Modification

- Remember, in an epidemiologic study, exposure and outcome might not be the only variables you need to consider.
- In both cohort studies and case-control studies, you may need to consider confounding and effect modification.
- Both concepts involve variables other than the exposure and the outcome of interest.
- Confounding is a source of bias that we need to try to eliminate.
- Effect modification is of interest, not something to try to eliminate.

Confounding: “Confusion of Effects”



- Confounding occurs when an association between an exposure and a disease is **not causal** but reflects the effects of another associated variable (a “confounder”).
- Confounding can lead to the false conclusion that an exposure caused disease when something else caused them both.
- One simple definition is that a confounder (C) is a factor that is:

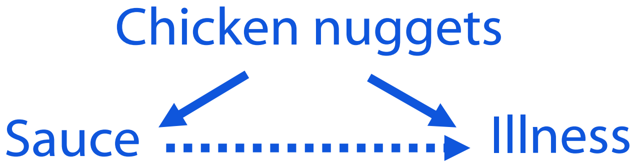
  1) Associated with the exposure (E) or stands in for something else that causes the exposure; **and**

  2) Causally related to the outcome (O) or stands in for something that causes the outcome; **and**

  3) Is not in the causal pathway between the exposure and the outcome
- There are situations in which this definition does not fully capture the complexities of confounding, but this definition gives the general idea.
- Confounding is a source of bias that we need to try to eliminate, by controlling for the confounding variable (e.g., stratifying by the confounder, modeling).

Confounding: Example

- Suppose you are investigating an outbreak of gastrointestinal illness among people who attended a pot-luck dinner.
- You find out that illness was more common among people who said they ate a particular sauce that was intended for use with chicken nuggets than among people who said they did not eat the sauce.
- You might suspect the sauce as the cause of the illness because of the observed association, but the chicken nuggets might be the real cause of the illness, and the association between eating the sauce and illness might reflect **confounding** by eating the chicken nuggets.



Remember: Association does not necessarily indicate causation!

Association ≠ Causation

Effect Modification: "Different Effects in Different Groups"

- Effect modification is present when the measure of association between an exposure and a disease (e.g., risk ratio or odds ratio) depends on the level of a third variable (e.g., age, sex).
- Effect modification is not something you want to eliminate, but something that can tell you something important about the relationship between the exposure and the outcome.
- For example, suppose that you are investigating a large outbreak of illness among workers on a farm that was caused by exposure to a pesticide.
  - You find that the degree to which illness risk increased with increasing duration of exposure (i.e., RRs comparing groups of workers with different exposure durations to unexposed workers) is different for groups of workers who used different protective equipment.
  - You might want to explore differences between the protective equipment in the two groups to figure out the reasons for the observed differences in the RRs.

Study Protocol

- Before starting any study, at a minimum, a brief study protocol should be written that includes the following (to the extent that each of these are applicable):
  - Clear statement of study objectives
  - Study design (e.g., case-control study, retrospective cohort study)
  - Study population, selection procedures, sample size (if applicable)
  - Case definition
  - Data sources
  - Data collection procedures and mode of data collection
  - Questionnaires and medical record abstraction forms
  - Procedures for collection, labeling, and storage of any samples to be collected
  - Data security, privacy, and confidentiality protections
  - Analysis plan
  - Logistics (e.g., budget, personnel, timeline)
  - Any legal considerations

Data Collection for Epidemiologic Studies

- Types of data—epidemiologic studies use several types of data:
  - General descriptive information (e.g., demographics)
  - Data relating to exposures
  - Data relating to disease outcomes
  - Data relating to potential confounders and effect modifiers
- Data sources—data for epidemiologic studies can be collected through these methods:
  - Questionnaires, which can be self-administered or administered through interviews
  - Review of existing records, such as medical records
  - Laboratory testing done on existing or newly collected environmental or biological samples

Questionnaire Data

- When designing questionnaires to collect epidemiologic data, the following types of questions may be considered:
  - Demographics
  - Self-reported health information
    - Symptoms and signs associated with the illness of interest
    - **Time** of onset and **severity**
    - Potential medical risk factors for the illness of interest
  - Exposures, including information about **time** and **quantity** of exposure
    - Possible exposures to toxic agents
    - Exposures to materials that might be vehicles for toxic agents
  - Potential confounders or effect modifiers (if applicable)
- Questionnaires should also include information for participants about the purpose of the study, whom to contact with questions, and a request for consent.
- Questionnaires can be self-administered or done via interview.

Outcome-Related Questions

- Questionnaires often include specific questions to determine the timing and order of symptom onset.
- In an analytic study, asking separate questions about specific symptoms will yield more useful data than asking open-ended questions about symptoms.

Questions About Exposures

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

Yes/No	Quantified
Often used when there is a large number of possible exposures	Often used when there is a small number of possible exposures
Easier for participants to answer	Harder for participants to answer
Takes less time	Takes more time
Less informative	More informative

Activity: Questions About Exposures

- ***How would you ask the questions from the following table in a quantified format?***

Yes/No	Quantified
Did you eat a banana?	
Did you spray pesticides?	

Activity: Questions About Exposures (cont.)

- To ask about an exposure in a quantified format, think about
  - Frequency
  - Duration
  - Dose/amount

Yes/No	Quantified
Did you eat a banana?	• How many bananas did you eat in the last 24 hours?
Did you spray pesticides?	• How many times did you spray pesticides in the past 36 hours? • How many minutes did you spend spraying pesticides in the past 36 hours? • How much pesticide did you spray in the past 36 hours?

Quantifying Exposure

- Quantifying exposure allows you to assess a dose-response relationship with illness.
- If it is a cohort study, you can calculate attack rates (risks) for various exposure strata.
- If the attack rate increases with increasing exposure, that provides support for the hypothesis that it might be the implicated exposure.

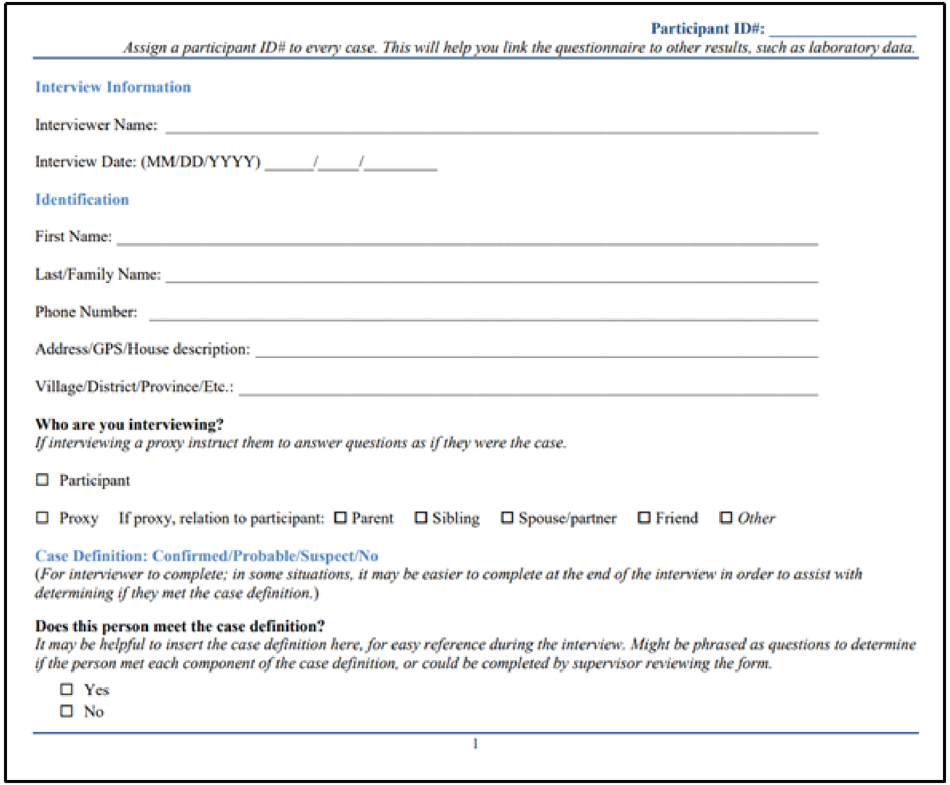
# of Times Spraying Pesticide	Attack Rate
0 times	5%
1–2 times	40%
≥3 times	95%

Timeline

- To determine whether the exposure preceded the illness, it is important to collect information about the timing of both exposure and illness onset.
- In the setting of acute outbreaks, illness often occurs quickly (minutes to hours) after exposure to a toxic agent.
- When asking about possible exposures in acute outbreak investigations, the timeframe of interest is often limited to the hours preceding the event, but this depends on the suspected agent.

Sample Questionnaire

- When designing questionnaires, it is helpful to review previous questionnaires from similar outbreaks.
- Questionnaires must be tailored to the specific situation.
- A Sample Questionnaire can be found in the Tool Kit and modified for your investigation.



Participant ID#: ______________

Assign a participant ID# to every case. This will help you link the questionnaire to other results, such as laboratory data.

Interview Information

Interviewer Name: ______________________________

Interview Date: (MM/DD/YYYY) _____/_____/________

Identification

First Name: ______________________________

Last/Family Name: ______________________________

Phone Number: ______________________________

Address/GPS/House description: ______________________________

Village/District/Province/Etc.: ______________________________

Who are you interviewing?
If interviewing a proxy instruct them to answer questions as if they were the case.

☐ Participant

☐ Proxy If proxy, relation to participant: ☐ Parent ☐ Sibling ☐ Spouse/partner ☐ Friend ☐ *Other*

Case Definition: Confirmed/Probable/Suspect/No
(For interviewer to complete; in some situations, it may be easier to complete at the end of the interview in order to assist with determining if they met the case definition.)

Does this person meet the case definition?
It may be helpful to insert the case definition here, for easy reference during the interview. Might be phrased as questions to determine if the person met each component of the case definition, or could be completed by supervisor reviewing the form.

☐ Yes
☐ No

1

Sample Questionnaire (cont.)

- The Sample Questionnaire in the Tool Kit includes a section with sample questions related to symptoms.

Participant ID#: ______________

Assign a participant ID# to every case. This will help you link the questionnaire to other results, such as laboratory data.

This section only to be completed by cases (or their proxy)

Symptoms

When did you first feel sick? Date: ___/____/________ Time: ___ ___:___ ___(24-hour clock)

Specify a time period for "XX" that makes sense based on your investigation.
If appropriate, create answer choices for the questions below. Or, they can remain as open-ended questions.

Symptom	Did you have (*symptom below*) during XX time period?	If yes, date of onset	If yes, time of onset	If yes, has the symptom resolved? 1 = No 2 = Yes 3 = Do not know	If resolved, date resolved	Notes
Symptom 1						
Symptom 2						
Symptom 3						
Symptom 4						

Medical Records Data

- Medical records can be an important additional source of information for an epidemiologic study.
- When collecting information from medical records, use an abstraction form to ensure that the same information is collected for all patients.
- Types of information that might be collected from the medical record include the following:
  - Presence/absence/timing of specific signs and symptoms
  - Sign or symptom severity
  - Medical history, including history of any medications previously taken
  - Vital signs
  - Clinical laboratory test results
  - Medications provided as part of treatment
  - Response to treatment/outcome

Clinical Data (cont.)

- The Tool Kit also contains a sample Medical Record Abstraction Form template which can be modified for your investigation.

Participant ID#: ___________

Attach ID label here

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)

Laboratory Data

Laboratory Data

- It can be useful to collect biological and/or environmental samples for laboratory testing as part of an epidemiologic study.
- The utility of laboratory data will depend on
  - Which toxic agent caused the illness (and its biological elimination or environmental half-life)
  - How much time has passed since exposure
  - Whether the toxic agent of interest can be measured in the laboratory
  - Availability of comparison data (see Module 3 for more details)

Early Sample Collection

- During a toxicological outbreak investigation, collecting biological specimens and/or environmental samples as early as possible can be important.
  - 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.
- However, in toxicological outbreaks, epidemiologic and clinical data often help guide laboratory testing, so decisions about specific tests to be done might be made sometime after sample collection.
- Therefore, samples might or might not be collected at the time of a more detailed broader epidemiologic study.
- Whenever samples are collected, a sound study design should be used for sample collection.

Data Analysis

- Summarize data descriptively.
- Assess associations between exposures and the outcome of interest.
  - Address potential confounding, if needed.
  - Assess effect modification, if needed.
- If possible, examine dose response relationships.
  - Compare attack rates by extent of exposure (for cohort studies).
  - Compare illness severity by extent of exposure.

Scenario: Data Analyses

- Recall the scenario discussed previously:
  - Several school children (aged 6–10 years) who attend the same school became ill between the hours of 12 p.m. and 4 p.m.
  - Their symptoms included nausea, vomiting, abdominal pain, altered mental status, multi-system organ dysfunction, and death.
  - In this case, the investigators conducted a retrospective cohort study because the population at risk was well-defined.

Scenario: Assess Associations Between Exposures and Outcome

- When analyzing data from a cohort study, it is possible to calculate attack rates (risk of the outcome) in groups defined by whether people had particular exposures.
- An example from the scenario is shown below.
- ***Calculate attack rates among the exposed children for each of these exposures.***
- ***What can you conclude from those calculations?***

Exposure	Number of Exposed Case-Patients	Total Number of Exposed Children in School	Attack Rate among Exposed Children
Rode bus to school	10	58	
Ate breakfast in cafeteria	7	113	
Ate a morning snack	11	30	
Spent time in school hall	3	64	

Scenario: Assess Associations Between Exposures and Outcome

- Note that the highest attack rate was among those who ate the morning snack, followed by those who rode the bus.
- That might lead you to suspect those exposures as possibly being associated with the cause of the illness.
- You would also want to calculate attack rates among children who did not have each of the exposures to determine whether attack rates differed between those who did and did not have each exposure.

Exposure	Number of Exposed Case-Patients	Total Number of Exposed Children in School	Attack Rate among Exposed Children
Rode bus to school	10	58	17%
Ate breakfast in cafeteria	7	113	6%
Ate a morning snack	11	30	37%
Spent time in school hall	3	64	5%

Scenario: Assess Associations Between Exposures and Outcome

- A column for the unexposed group for each exposure has been added below.
- ***To assess the associations between these exposures and the outcome, calculate the attack rates (risks) in each group and the risk ratio for each exposure.***

	Number Exposed		Attack Rate (Risk) Among Exposed	Number Not Exposed		Attack Rate (Risk) Among Nonexposed	Risk Ratio
Exposure	Ill	Total		Ill	Total		
Rode bus to school	10	58		2	62		
Ate breakfast in cafeteria	7	113		5	7		
Ate a morning snack	11	30		1	90		
Spent time in school hall	3	64		9	56		

Scenario: Assess Associations Between Exposures and Outcome

- Here are the attack rates and risk ratios.
- The 95% confidence interval for the risk ratio can be calculated using statistical software and is also listed here. That gives you an idea of the degree of uncertainty in the risk ratio estimate

	Number Exposed		**Attack Rate (Risk) Among Exposed**	**Number Not Exposed**		**Attack Rate (Risk) Among Nonexposed**	**Risk Ratio (95% Confidence Interval)**
Exposure	Ill	Total		Ill	Total		
Rode bus to school	10	58	0.172	2	62	0.032	5.3 (1.2–23.4)
Ate breakfast in cafeteria	7	113	0.062	5	7	0.714	0.09 (0.04–0.20)
Ate a morning snack	11	30	0.367	1	90	0.011	33.0 (4.4–245)
Spent time in school hall	3	64	0.047	9	56	0.161	0.29 (0.08–1.02)

Scenario: Dose-Response Relationship

- ***How might you assess a dose-response relationship between the morning snack and the illness?***

Scenario: Dose-Response Relationship—Attack Rate

- The team examined the dose-response relationship for the morning snack by comparing attack rates for various categories of the amount consumed.
- The attack rate increased as the number of servings of the snack increased.

Amount of snack eaten	Total Number of Case-Patients (n=12)	Total Number of Children in School (n=120)	Attack Rate
0 servings	1	90	1%
1 serving	2	11	18%
2 servings	5	14	35%
3 servings	4	5	80%

Scenario: Dose-Response Relationship—Severity

- The team also looked at the relationship between dose and illness severity.
- They first categorized illness severity as follows:
  - **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, respiratory distress, organ dysfunction, or death

Scenario: Dose-Response Relationship—Severity

- For each category of the amount of snack eaten, the team compared the percentage of people who had illness in each severity category.
- Severe illness only occurred among people who ate two or more servings of the snack, and the percentage with severe illness was higher among those who ate three servings than among those who ate two servings.

Amount of snack eaten	Not sick (n=108)	Mild sickness (n=7)	Severe Sickness (n=5)
0 servings (n=90)	89 (99%)	1 (1%)	0 (0%)
1 serving (n=11)	9 (82%)	2 (18%)	0 (0%)
2 servings (n=14)	9 (64%)	3 (21%)	2 (14%)
3 servings (n=5)	1 (20%)	1 (20%)	3 (60%)

Dose-Response

- ***What are some reasons why you might not see a dose response relationship, even if the exposure caused the disease?***

Dose-Response (cont.)

- Some reasons why you might not observe a dose-response relationship, even if the exposure caused the disease, include the following:
  - Some toxic agents cause illness at such a low dose that anyone who is exposed experiences symptoms
  - Differences between people in metabolism and susceptibility
  - Misclassification of exposure or case status

Module Summary

- This concludes Module 5 Part 2.
- In this module, we discussed steps 4–8 of a toxicological outbreak investigation:
  - Construct a working case definition.
  - Find cases systematically and record information.
  - Perform descriptive epidemiology.
  - Develop a hypothesis.
  - Evaluate the hypothesis.

- You should now be able to
  - Apply outbreak investigation steps 4–8 to a toxic agent outbreak
  - Describe the purpose of the materials in the Toxicological Outbreak Tool Kit

For more information, contact NCEH
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