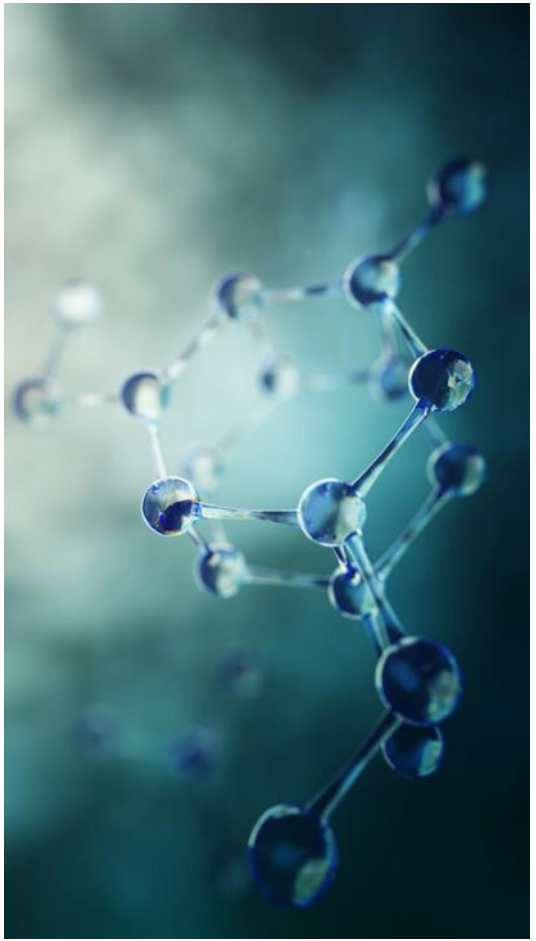
Toxicological Outbreak Investigation

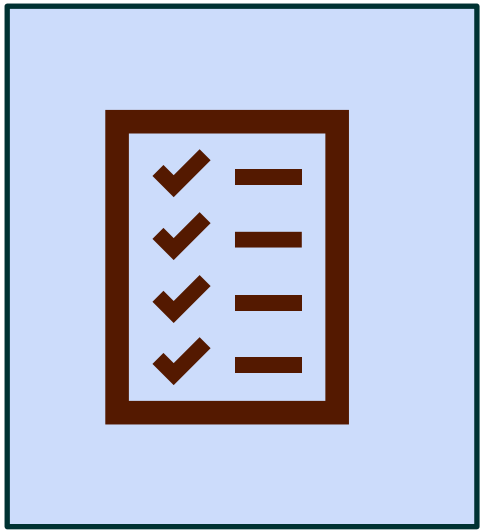
Module 6: Domestic Case Study

Welcome

- Welcome to Module 6 of Toxicological Outbreak Investigation. In this module, you will have the opportunity to practice what you have learned in Modules 1–5 by completing a domestic case study.
- This module should take 45–60 minutes to complete.

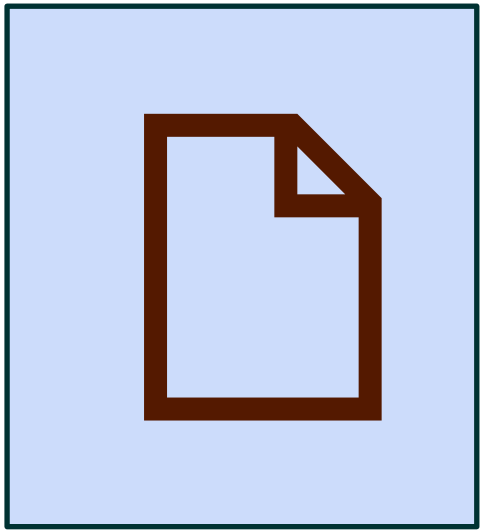


After Completing This Module, You Will Be Able to



Apply toxicological outbreak investigation steps

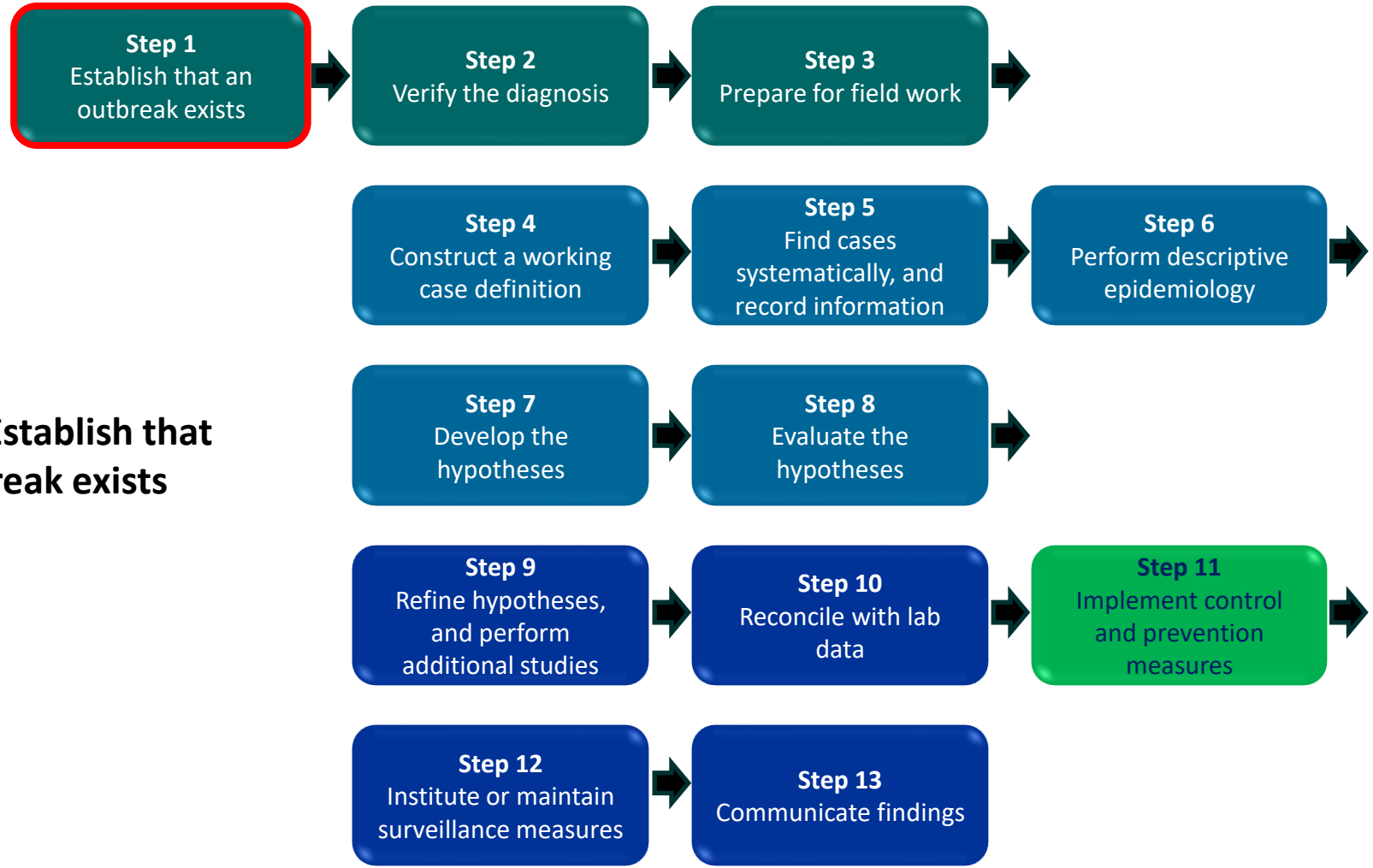
Interpret lab sample results



Describe relevant toolkit resources

Note About Case Study

- **This case study is loosely based on an actual investigation. However, many details have been modified, and in some cases, fictional data are used.**
- **References containing reports on the actual outbreak investigation are provided at the end of the case study.**



Step 1: Establish that an outbreak exists

The Call

- In mid-March, your health department is contacted by three individuals from the same extended family. They all live in different households. All reported hair loss, nail discoloration, and nail brittleness.
- Your health department collected the following information from these individuals

Patient	Age (years)	Sex	Occupation	Reported Symptoms	Comments
1	35	Female	Restaurant worker	Lost her hair, her fingernails turned gray and were brittle, nausea, muscle fatigue, difficulty concentrating, foul breath	Symptoms started in early March, recently began taking a new dietary supplement
2	50	Male	Police officer	Lost all his body hair, his fingernails turned gray and were brittle, his joints were sore, he felt weak and tired, diarrhea	Symptoms started in late February
3	60	Female	Retired	Headaches, grayish and brittle fingernails, nausea, rash, and a bald spot on her head that seemed to be getting bigger	Symptoms started in late February, has a friend with similar symptoms

The Call (cont.)

- All 3 initially affected people lived in County A.
- None had other household members with similar symptoms, but one patient reported having a friend with similar symptoms that developed around the same time as her symptoms.
  - The health department interviews this person and adds them to the line-list.
- One of the individuals reported taking a new dietary supplement recommended by their chiropractor.

Discussion

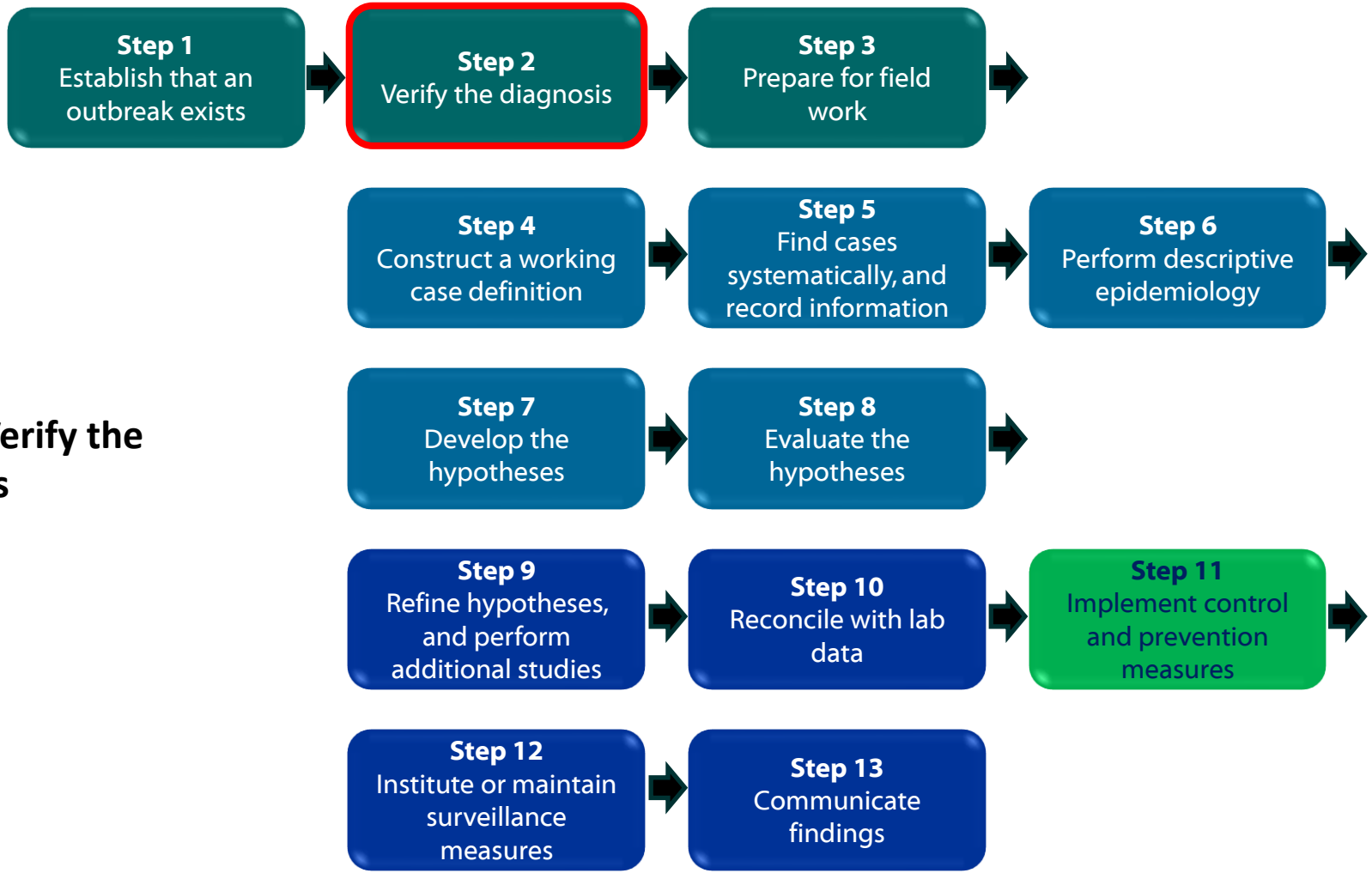
- ***Is this an outbreak?***
- ***Why or why not?***
- ***What else might you want to know before deciding?***

The Call (cont.)

- Physicians and others in the community suggested this type of illness is atypical for this community, and they would not generally expect to see this many cases in such a short period of time.
- Your health department decides that this might be an outbreak and decides to investigate the situation further.

- ***Who at your agency would investigate this type of incident?***
- ***How would the call get sent to the right people?***
- ***What is your process for determining whether to investigate a possible outbreak?***
- ***What might be some reasons for investigating this situation?***

Step 2: Verify the diagnosis



What is the Diagnosis?

- ***Based on the information we have so far, what do you think might be causing the outbreak?***
- ***Are there any features of this situation that might favor an infectious versus a toxic cause?***

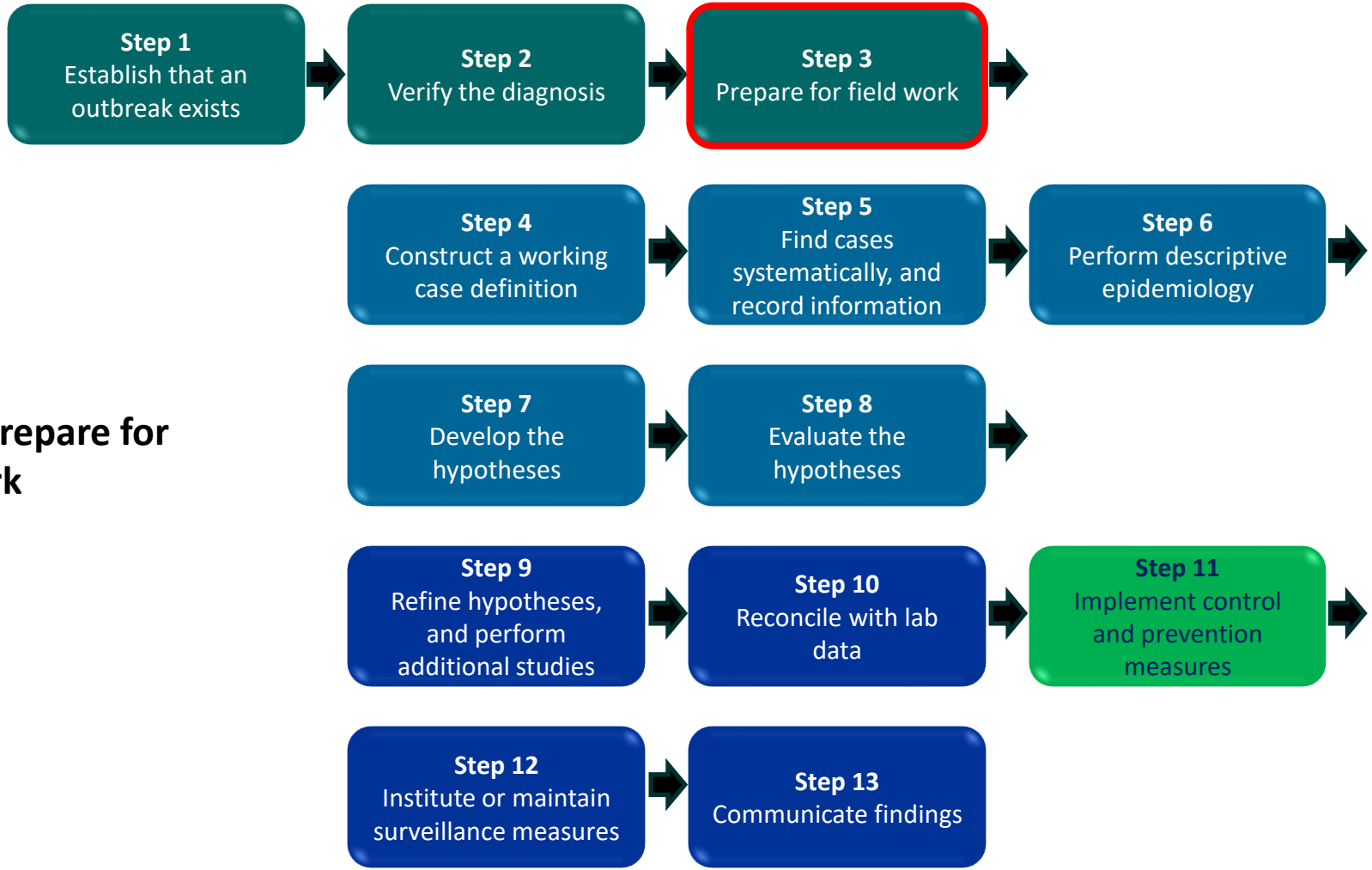
Patient	Age (years)	Sex	Occupation	Reported Symptoms	Comments
1	35	Female	Restaurant worker	Lost her hair, her fingernails turned gray and were brittle, nausea, muscle fatigue, difficulty concentrating, foul breath	Symptoms started in early March; recently began taking a new dietary supplement
2	50	Male	Police officer	Lost all his body hair, his fingernails turned gray and were brittle, his joints were sore, he felt weak and tired, diarrhea	Symptoms started in late February
3	60	Female	Retired	Headaches, grayish and brittle fingernails, nausea, rash, and a bald spot on her head that seemed to be getting bigger	Symptoms started in late February; has a friend with similar symptoms

What is the Diagnosis?

- Note that toxicological outbreaks often start with a group of people who have the same symptoms, but the etiology is still not clearly defined.
- Your health department suspects this might be a toxicological outbreak, for the following reasons:
  - Fever was not mentioned as a prominent symptom.
  - The symptoms of all three patients were similar and might be consistent with the effects of a toxic agent.
  - There was no apparent person-to-person transmission.

What is the Diagnosis?

- After reviewing the reported symptoms and consulting with other clinicians and medical toxicologists, your team has a broad set of differential diagnoses, including
  - Nutritional deficiencies
  - Endocrine disorders
  - Autoimmune conditions
  - Medication adverse effects
  - Toxic metal poisoning
  - Other toxic agents
- Note that sometimes it might not be clear whether everyone who reports having a set of symptoms has the same illness.



Step 3: Prepare for field work

Investigation Objectives

- Your health department develops the following objectives for the investigation:
  - Describe the illness.
  - Determine the extent of the outbreak.
  - Identify the etiology and the exposure.

Are these objectives any different from a typical investigation's objectives?

Would you add any objectives?

Assemble the Field Team

- Your health department also assembles a field team and clearly defines the roles of each team member:
  - Medical toxicologist
  - Laboratorian
  - Epidemiologist
  - Clinician
  - Communications specialist
  - Community member

What would you consider to be the role for each of these team members?

Initial Sample Collection

- The team knows it is important to collect biological samples as soon as possible.
- The toxicologist recommends collecting biological samples from the initial people with potential cases.

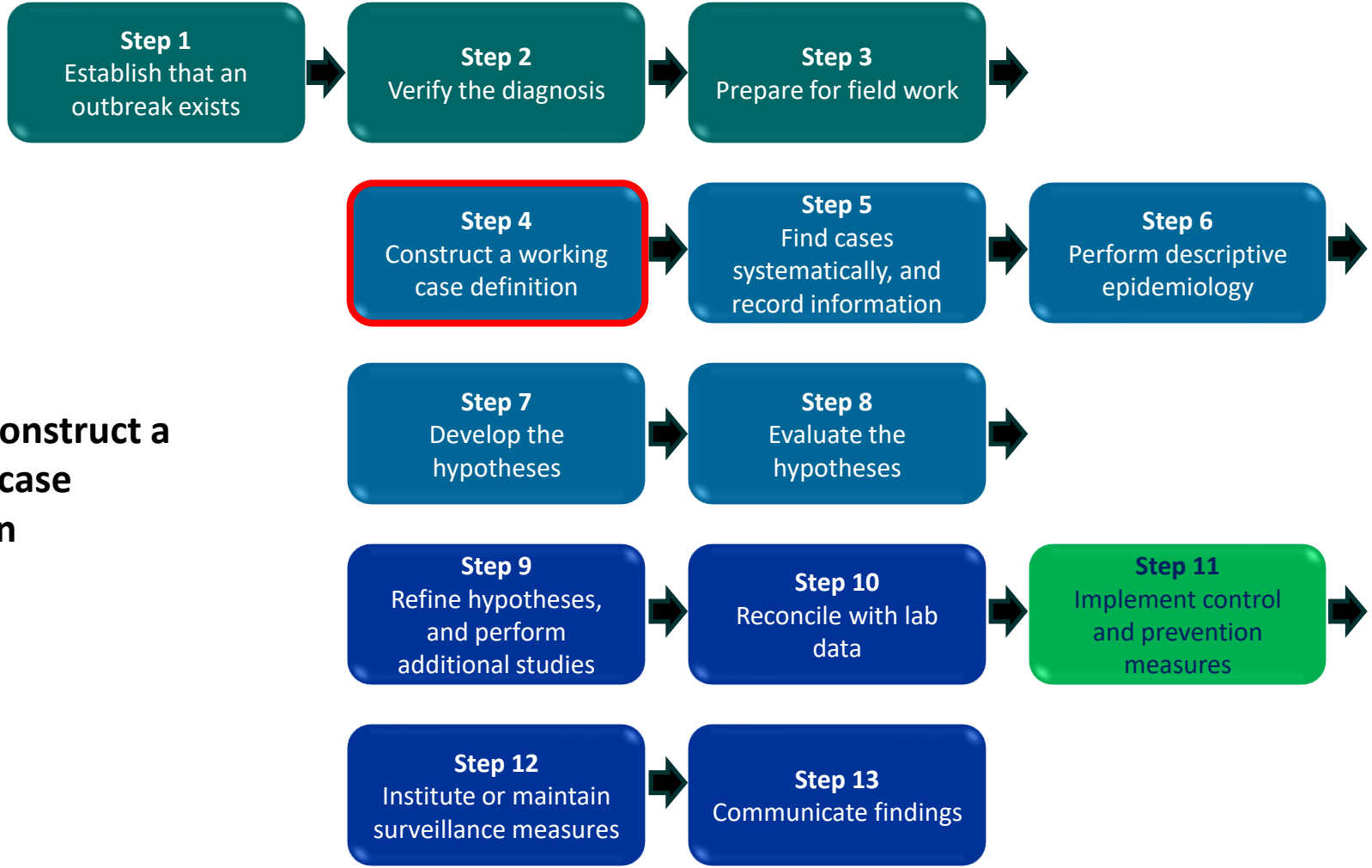
What kinds of samples would you collect?

What are some things you should consider before collecting biological samples?

Initial Biological Sample Collection

- Given that a specific hypothesis has not yet been developed, your team decides to collect both urine and blood samples from case-patients.
- The laboratorian on your field team
  - Provides recommendations relating to sample containers
  - Trains relevant staff on sample collection and on recording all relevant information in the specimen log
  - Provides recommendations relating to sample processing and storage

Step 4: Construct a working case definition



Case Definition

- The team reviews the available information about the four individuals and develops an initial case definition.

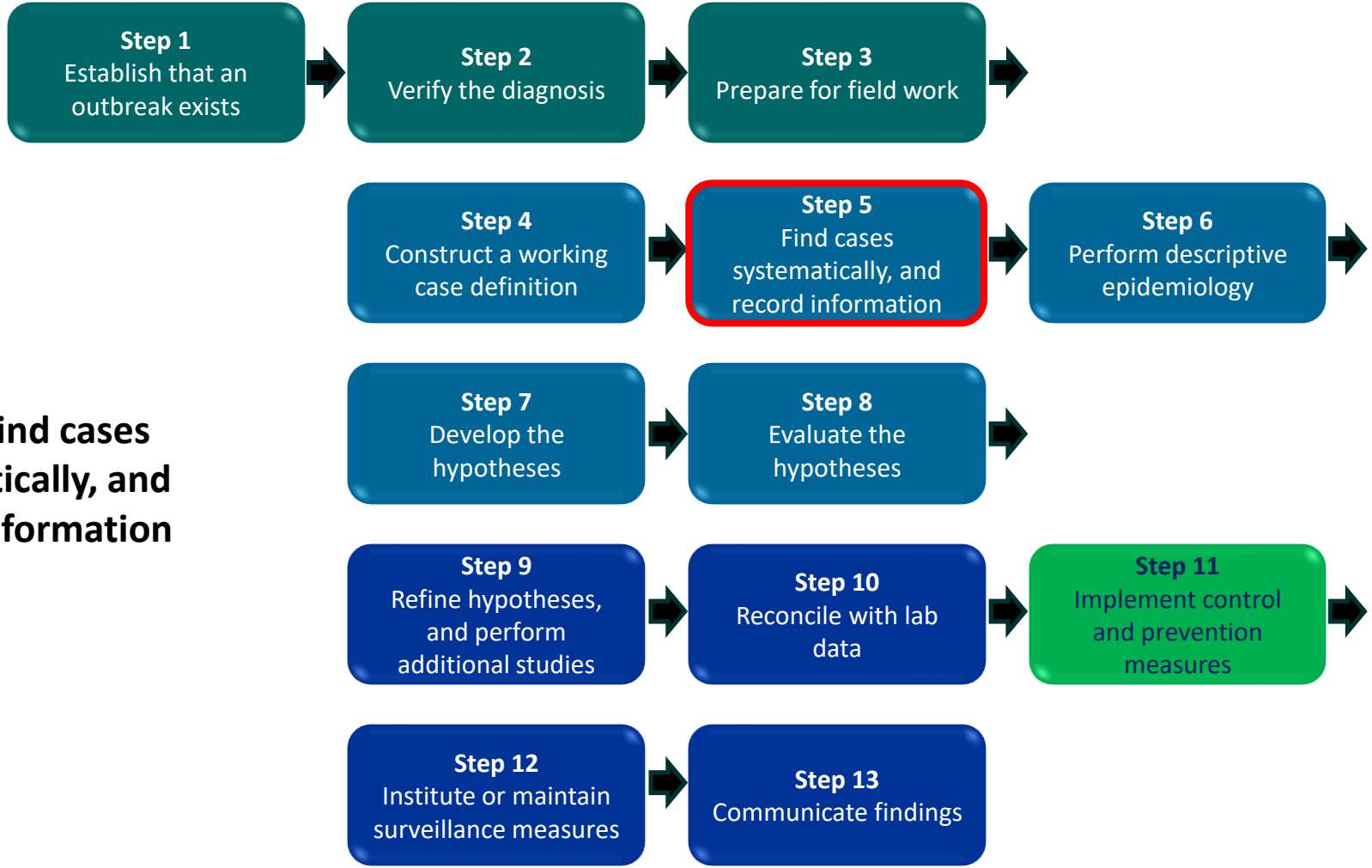
Patient	Age (years)	Sex	Occupation	Reported Symptoms	Comments
1	35	Female	Restaurant worker	Lost her hair, her fingernails turned gray and were brittle, nausea, muscle fatigue, difficulty concentrating, foul breath	Symptoms started in early March, recently began taking a new dietary supplement
2	50	Male	Police officer	Lost all his body hair, his fingernails turned gray and were brittle, his joints were sore, he felt weak and tired, diarrhea	Symptoms started in late February
3	60	Female	Retired	Headaches, grayish and brittle fingernails, nausea, rash, and a bald spot on her head that seemed to be getting bigger	Symptoms started in late February, has a friend with similar symptoms
4	40	Male	Businessman	Hair loss, headache, foul breath, discolored fingernails, nail brittleness, lethargy, nausea, vomiting	N/A

What might you include in a case definition in this situation?

Case Definition (cont.)

- Remember that a case definition should include elements relating to “what?,” “who?,” “where?,” and “when?”.
- The team develops the following initial case definition:
  - Hair loss, nail discoloration, or nail brittleness

    and
  - Two or more of the following symptoms:
    - Muscle or joint pains
    - Headache
    - Foul breath
    - Fatigue/weakness
    - Gastrointestinal symptoms (nausea, vomiting, or diarrhea)
  - In a resident of county A, with onset during January through the present



Step 5: Find cases systematically, and record information

Finding Cases

How would you find additional cases that might be related to the outbreak?

Finding Cases (cont.)

- Possible methods of case identification:
  - Speak with physicians or other healthcare providers in the area.
  - Contact other nearby health departments to find out whether they have been notified of similar cases.
  - Contact your local poison center to find out if they have had people call the poison center reporting similar symptoms.
  - Issue a press release and ask people to notify the health department if they have symptoms meeting the case definition.
  - CDC's *Epi-X* is a secure system for exchanging information about outbreaks and epidemics. It could be used to ask for reports of cases from other states.
- The approach in each outbreak will depend on the situation.

Finding Cases (cont.)

- Several clinicians in the area report seeing patients with illness meeting your case definition, and one reports having several patients with such illness.
- Your team decides to work with local media on a press release to identify possible additional cases and issues an *Epi-X* report to request reports of cases from other states.
- In response, hundreds of people report related symptoms to your health department, of whom 82 report illness meeting your case definition.

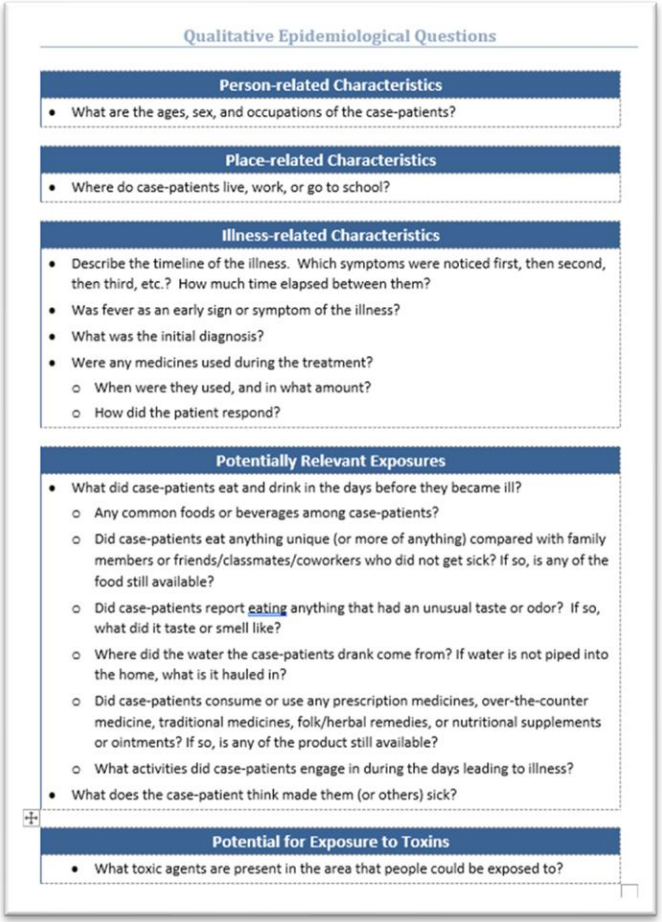
Hypothesis-Generating Interviews

- Your team plans to conduct hypothesis-generating interviews by phone with several people with illness meeting the case definition to
  - Identify potential sources of the outbreak and guide the investigation's next steps
  - Further understand the course of the illness and potential responses to any medical treatments

What kinds of questions would you ask?

Hypothesis-Generating Interviews

- The team develops a hypothesis-generating questionnaire to ask about the following:
  - Demographics (e.g., age, sex, occupation, residence)
  - Clinical information (e.g., presence or absence of specific symptoms, timing of symptom onset, diagnosis, treatment received, recovery)
  - Possible exposures and risk factors (e.g., dietary history, medication/supplement use)
- At this stage, it can be helpful to keep questions broad and open-ended.
- It can be helpful to have the same person speak with as many people as possible.
- Refer to the Qualitative Epidemiological Questions in the Tool Kit.



Qualitative Epidemiological Questions

Person-related Characteristics

- What are the ages, sex, and occupations of the case-patients?

Place-related Characteristics

- Where do case-patients live, work, or go to school?

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?
- Was fever as an early sign or symptom of the illness?
- What was the initial diagnosis?
- Were any medicines used during the treatment?
  - When were they used, and in what amount?
  - How did the patient respond?

Potentially Relevant Exposures

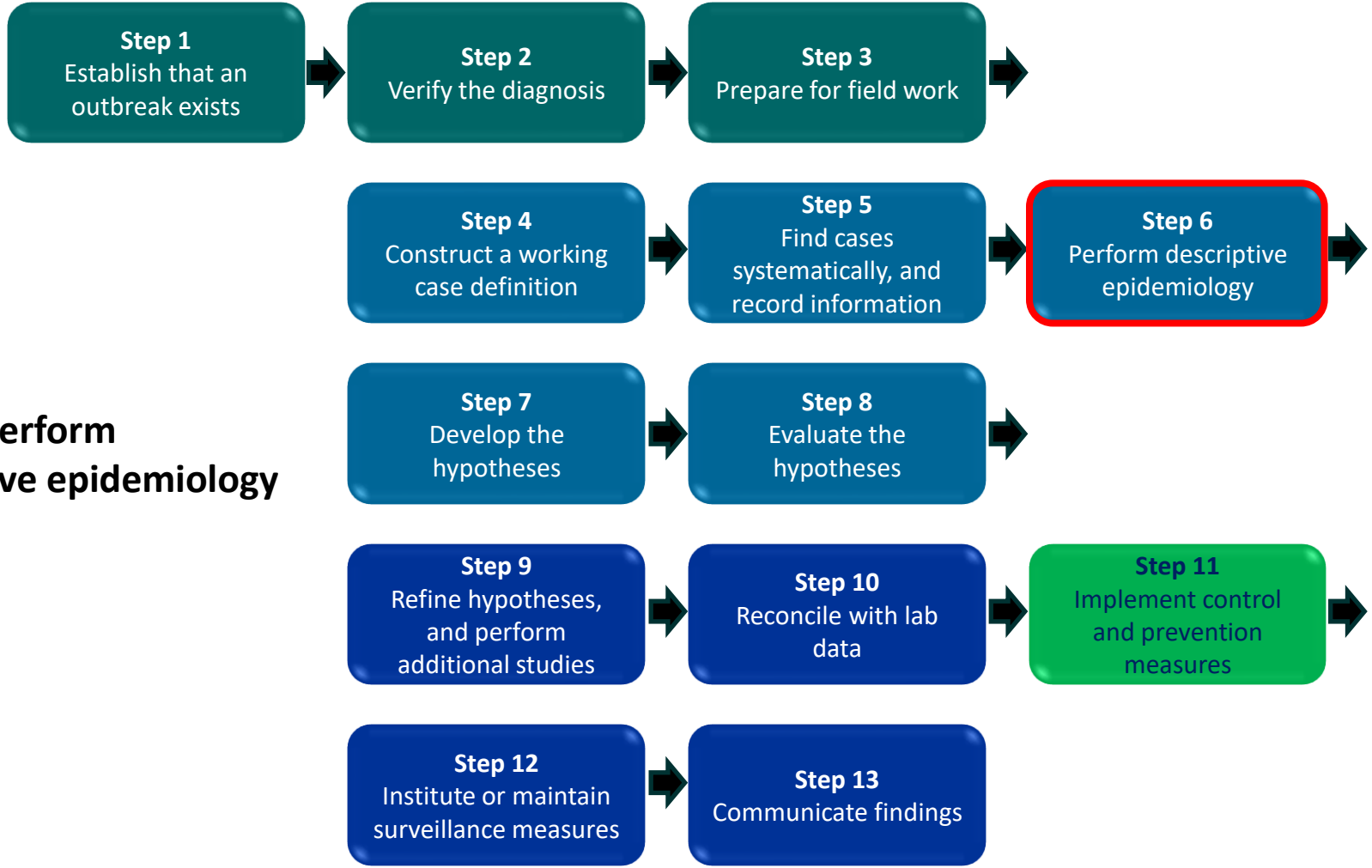
- What did case-patients eat and drink in the days before they became ill?
  - Any common foods or beverages among case-patients?
  - Did case-patients eat anything unique (or more of anything) compared with family members or friends/classmates/coworkers who did not get sick? If so, is any of the food still available?
  - Did case-patients report eating anything that had an unusual taste or odor? If so, what did it taste or smell like?
  - Where did the water the case-patients drank come from? If water is not piped into the home, what is it hauled in?
  - Did case-patients consume or use any prescription medicines, over-the-counter medicine, traditional medicines, folk/herbal remedies, or nutritional supplements or ointments? If so, is any of the product still available?
  - What activities did case-patients engage in during the days leading to illness?
- What does the case-patient think made them (or others) sick?

Potential for Exposure to Toxins

- What toxic agents are present in the area that people could be exposed to?

Biological Sample Collection

- After conducting the hypothesis-generating interviews, your team arranges to collect blood and urine samples from people with illness meeting the case definition.
- Those who are willing are asked to visit their local health department for the specimen collection.
- You make sure all samples are appropriately labeled, logged, processed (e.g., separation of serum), and stored according to the laboratorian's instructions.
- You do not yet have a clear hypothesis about what caused the outbreak, so you do not perform any laboratory testing on the samples at this point.



Step 6: Perform descriptive epidemiology

Findings of Hypothesis-Generating Interviews

- The team conducted hypothesis-generating interviews with the first 20 people who were identified as having an illness that met the case definition.
- The team then organized key information in a line list and conducted descriptive analyses.

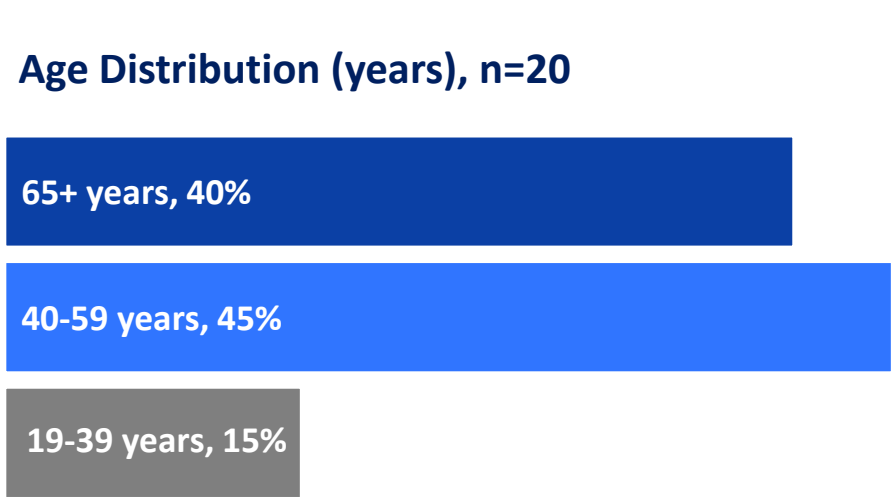
Demographic Information						
ID #	First Name	Last Name	Address	Age (years)	Sex (M/F)	Occupation

Clinical Illness Information												
Approximate date of first symptom onset	Hair loss (Yes/No)	Nail discoloration (Yes/No	Nail brittleness (Yes/No)	Muscle pain (Yes/No)	Joint pain (Yes/No)	Headache (Yes/No)	Foul breath (Yes/No)	Fatigue/ Weakness (Yes/No)	Nausea (Yes/No)	Vomiting (Yes/No)	Diarrhea (Yes/No)	Notes on other symptoms

Exposure Information			**Specimen Collection**			
Medications	Supplements	….	Urine Sample (Yes/No)	Urine Sample Date	Blood Sample (Yes/No)	Blood Sample Date

People with Cases Were Mostly Middle-Aged and Older-Aged Adults.

A slightly higher proportion of people with cases were female than male.



60%
of people with cases were female

A Variety of Occupations Were Reported, Suggesting the Exposure is Likely *Not* Occupation Related.

Reported occupations included

Business/ management, 25%

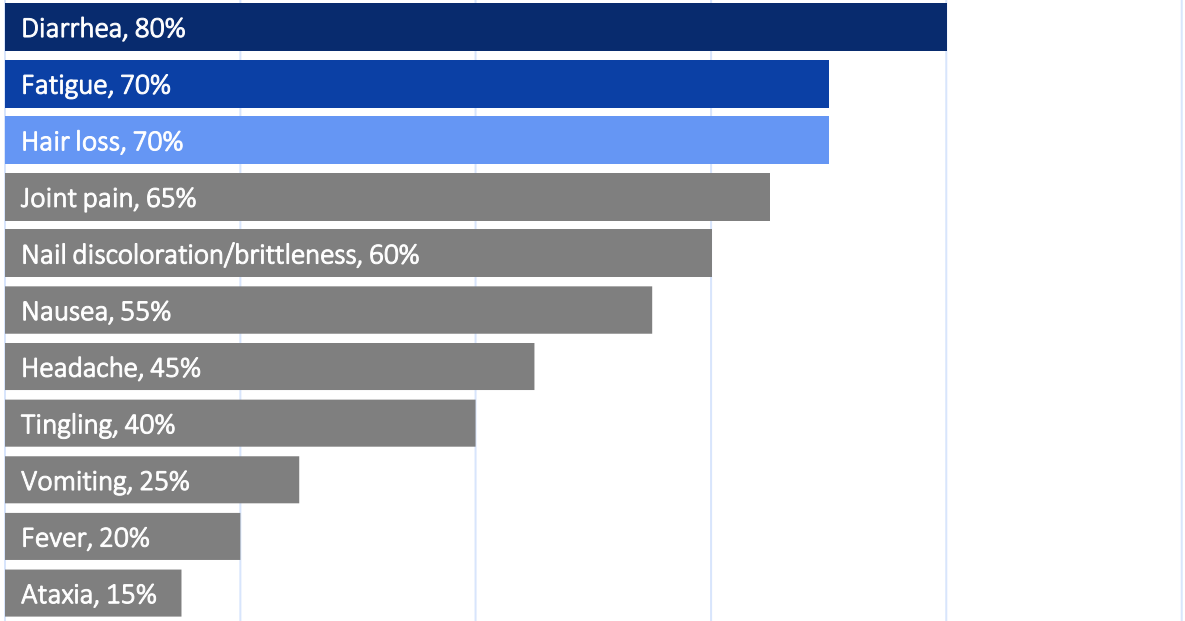
Healthcare, 20%

Service industry, 10%

Farming, 5%

Other, 40%

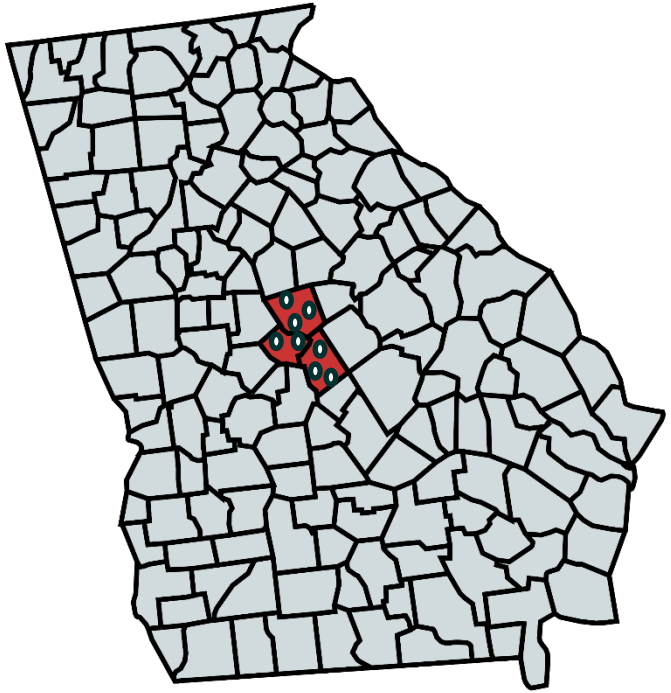
The Most Common Symptoms Reported by People with Cases Included Diarrhea, Fatigue, and Hair Loss.



Clinical Presentation of Cases

- The reported symptom progression varied between patients:
  - Some reported initial symptoms of diarrhea or muscle pain followed by hair loss.
  - Others reported hair loss or nail changes as their initial symptom.
  - Some reported difficulties with memory or concentration, a metallic taste in their mouth, a garlic-like odor to their breath, or skin changes.
  - Most eventually developed hair loss and most reported nail changes. All reported multiple concurrent symptoms.

All People with Cases Resided Within Three Neighboring Counties in Your State.

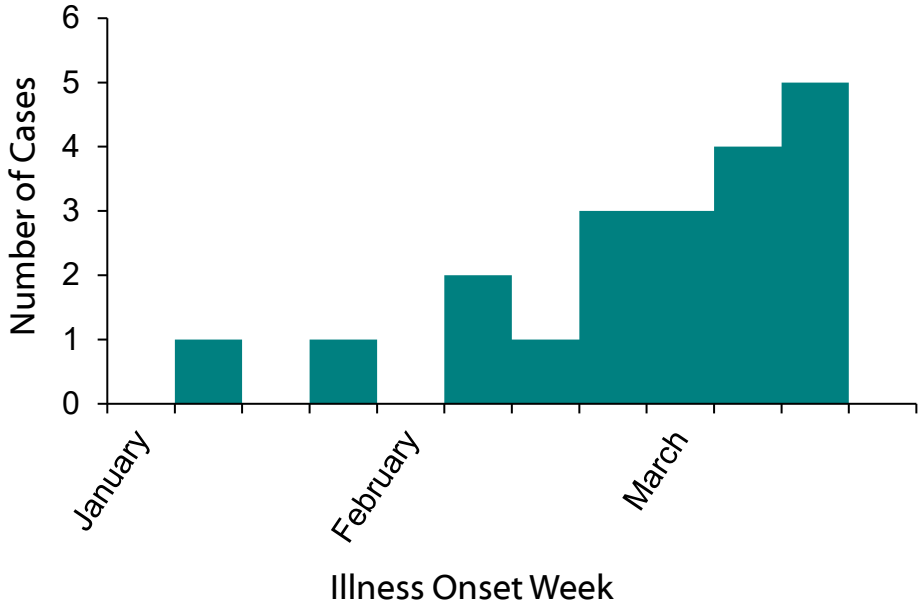


Counties with cases*

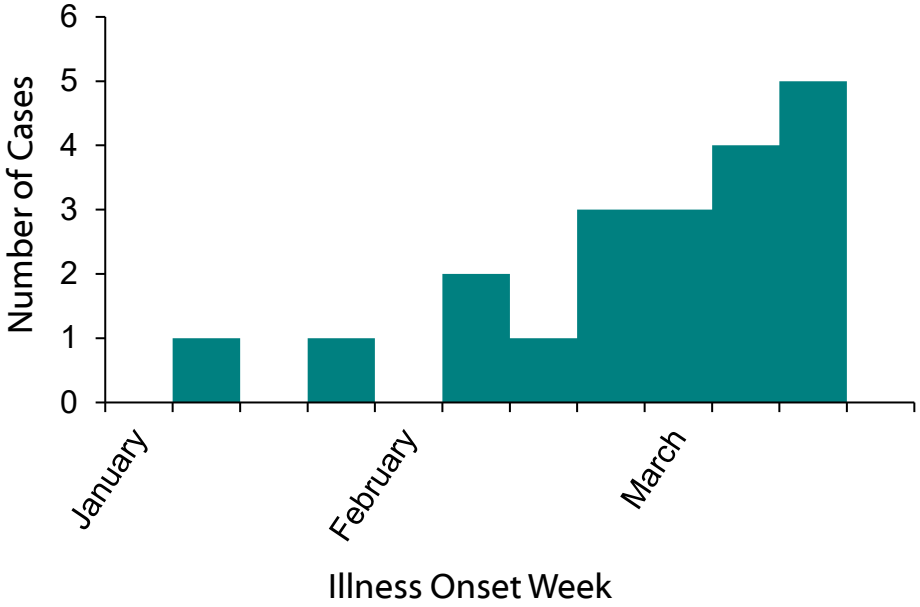
Created with mapchart.net

*Note: This is for instructional purposes only and has no connection with actual cases.

Here Current Epidemic Curve.



What would you conclude from this epidemic curve?



- The epidemic curve suggests that the outbreak may be ongoing.

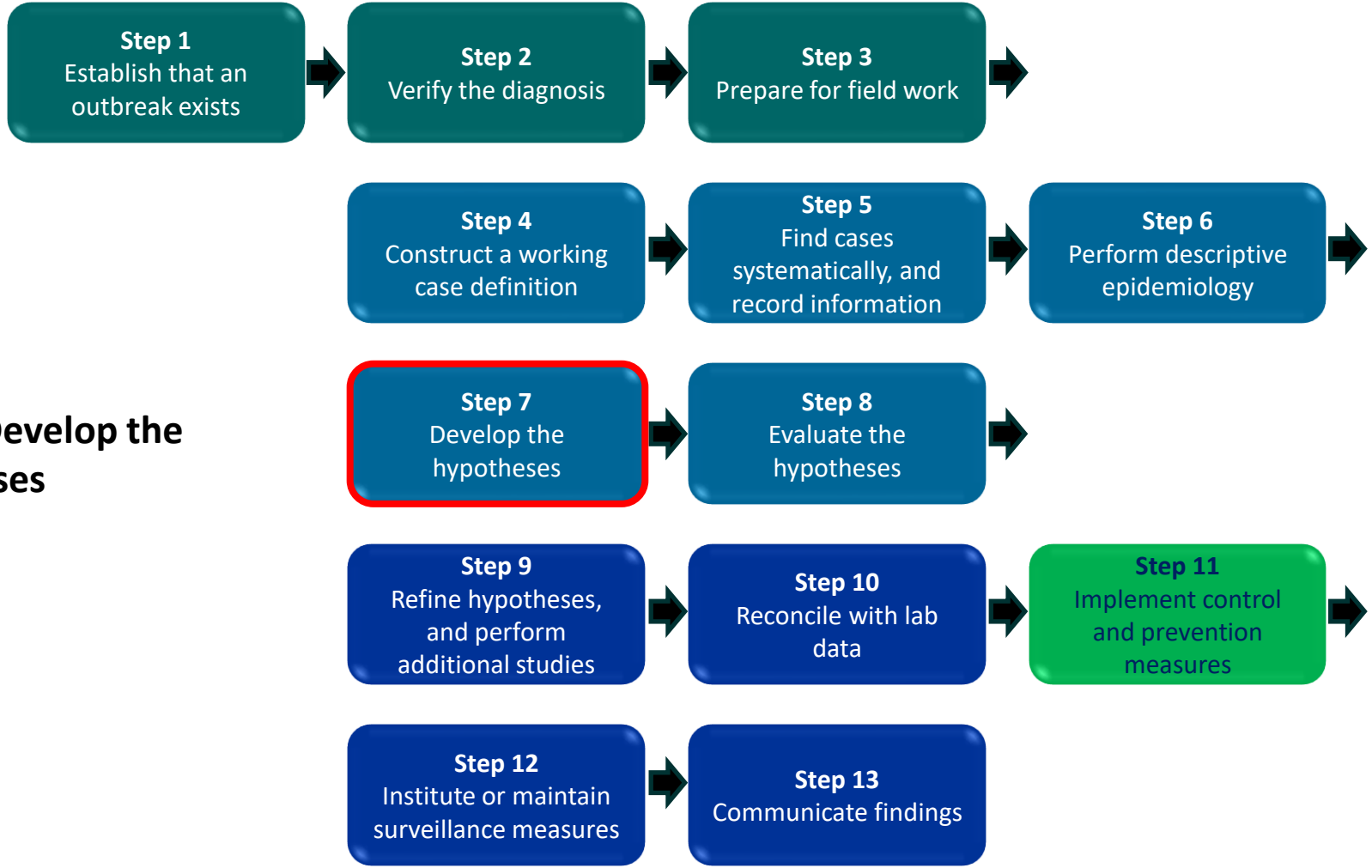
Among the 20 People with Cases Who Completed Hypothesis-Generating Interviews, 80% Reported Consuming a Specific Dietary Supplement, Supplement A (Specific Brand and Type).

Medications/supplements*	N (%)
Consumed Supplement A	16 (80%)
Consumed Supplement B	5 (25%)
Consumed acetaminophen	9 (45%)

***Patients could report multiple medications/supplements.**

- Some people with cases had been consuming supplement A for several months or years but only recently developed symptoms. A few had recently started using supplement A.
- Most obtained the supplement from a chiropractor at clinic A.
- You did not identify any meaningful patterns for other medications and supplements, dietary histories, or water sources.

Based on this descriptive information, what next steps would you consider?



Step 7: Develop the hypotheses

Hypotheses

- You hypothesize that Supplement A might be the source of the outbreak, potentially due to a misformulated or contaminated supplement.

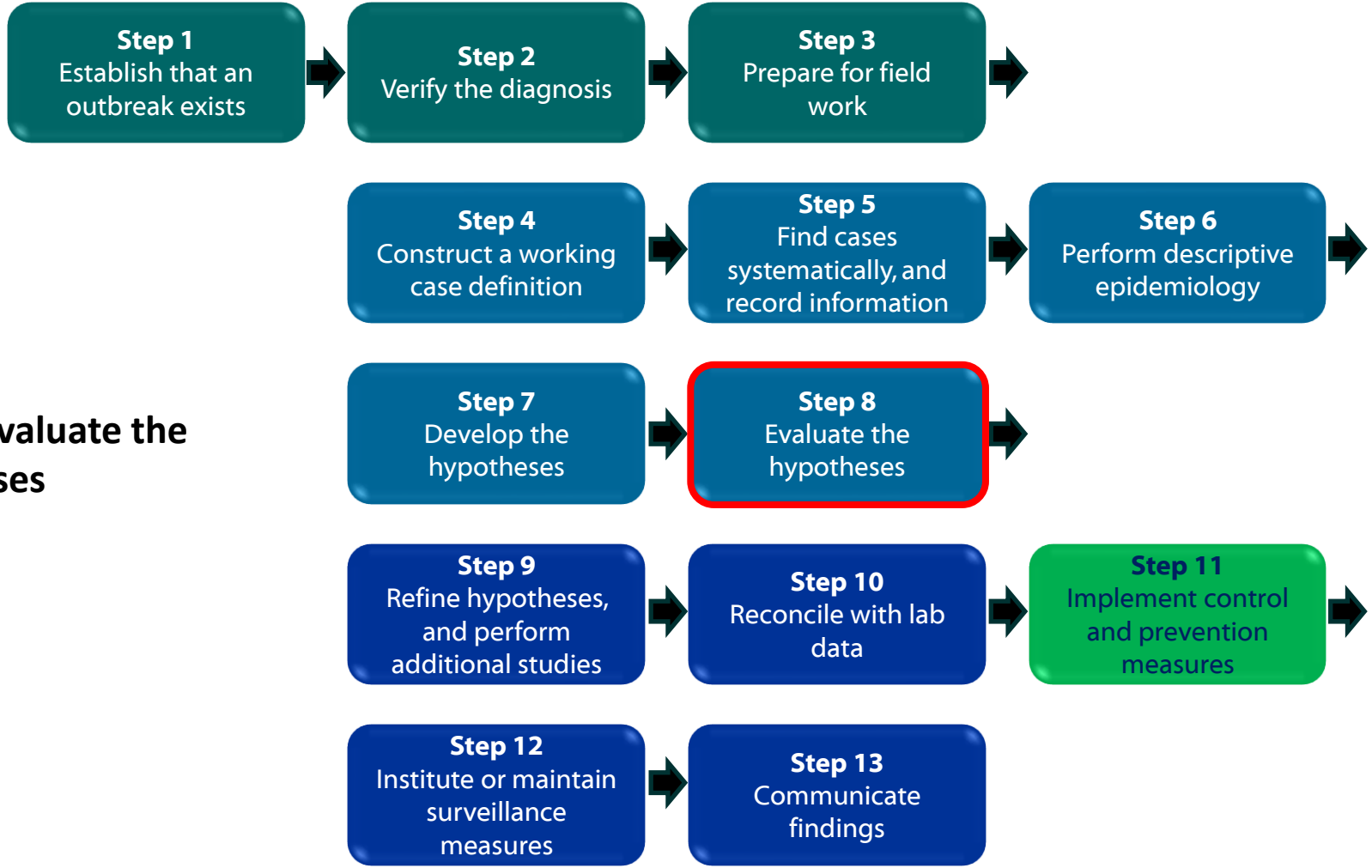
Given that this appears to be possibly caused by a nutritional supplement, what other agencies might become involved?

Hypotheses (cont.)

- Given that this is a dietary supplement, the U.S. Food and Drug Administration (FDA) regulates the product and will take the lead in the product investigation.

Points for Further Discussion:

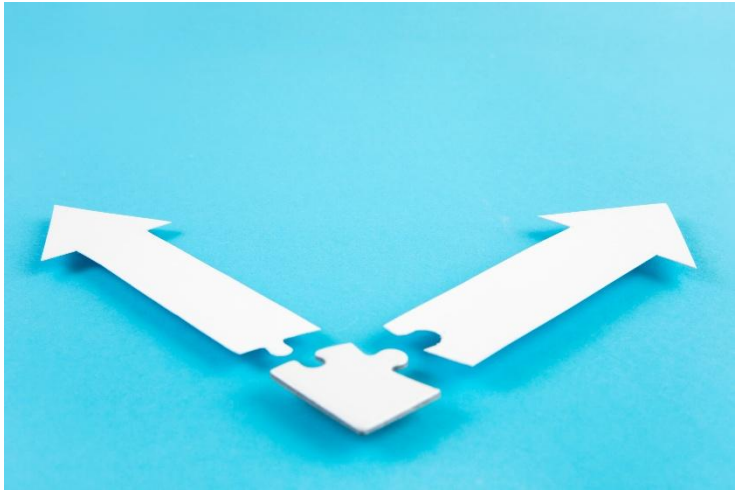
- ***What would the role of other agencies be?***
- ***Who would take the lead?***
- ***Would there be turf issues? How would these be worked out?***
- ***How would information be shared between agencies?***
- ***Would you contact CDC or other federal agencies? Why or why not? If yes, whom would you contact? What would you want/expect from them?***



Step 8: Evaluate the hypotheses

Two Scenarios

- Every investigation proceeds differently.
- Here we will consider two possible scenarios to illustrate some common directions investigations can take.



Scenario 1

Scenario 1

- After consulting with FDA, you find out they are not aware of additional cases.
- Your local poison center has also not received calls from people reporting similar symptoms.
- Your *Epi-X* notice did not result in any notifications of additional cases from other states.

Scenario 1

What type of study would you design to evaluate your hypothesis?

Study Design?

Scenario 1

Investigation Design

- You decide on a case-control study for the following reasons:
  - The source population is not well defined.
  - This is a rare outcome.
  - The outbreak seems to be on-going, and you need results quickly.

Points for Discussion:

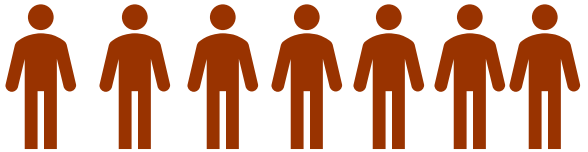
- ***How would you find case-patients?***
- ***How would you find control participants?***
- ***Would you use any matching? Why or why not?***

Scenario 1

Case-Control Study Design

- You decide to use your previous case-finding efforts as a source of people with cases, and you include everyone you identified who met the case definition (including the 20 you already interviewed).
- Earlier in this course, the definition of a case focused on the occurrence of illness that met the case definition. However, in the context of a case-control study, cases are people.

Cases: people with illness meeting the case definition who were identified through case finding



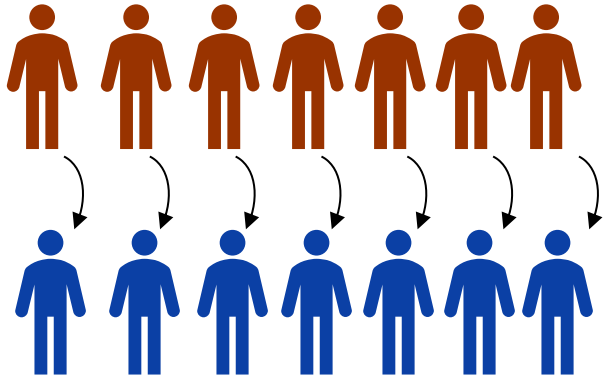
Matched Case-Control Study Design

Scenario 1

- To identify controls, you ask each case to refer you to a neighbor of the same sex whose age is in the same 10-year age category as their own age (e.g., 20–29, 30–39). You ask them to identify two neighbors to allow for non-response and because you will need to exclude anyone with illness meeting the case definition. You enroll one control per case (randomly selecting one to invite and inviting the other if you cannot enroll the first one).

Cases: **patients with illness meeting the case definition who were identified through case finding**

Controls: **age and sex-matched neighbors**



Scenario 1

Questions About Illness

In developing the questionnaire for your case-control study, how would you ask about symptoms of illness?

Questions About Illness

- Closed-ended questions about specific symptoms are best at this stage.
  - Be sure to include specific questions about all the symptoms included in the case definition.
  - You might want to also include specific questions about other symptoms, especially other unique symptoms reported by the initial cases.
- For both cases and controls, you will need to determine the period to ask about (e.g., since February 1).
- Ask when symptoms started (either symptom-by-symptom or when the first symptoms started).

Scenario 1

Exposure to Supplement A

In developing the questionnaire for your case-control study, how would you structure questions that ask about exposure to Supplement A?

Exposure to Supplement A (cont.)

Scenario 1

- Some aspects to consider including in your questions about Supplement A might include the following:
  - Have they ever used Supplement A? If yes
    - When did they first take Supplement A?
    - How frequently did they take Supplement A? (e.g., daily, weekly, etc.)
    - When they took Supplement A, how much did they usually take?
    - When did they last take Supplement A?
    - When did they last obtain a new supply of Supplement A?
    - How was Supplement A obtained?(e.g., where it was purchased)

Scenario 1

Supplement Exposure

The investigators decide to use this format

	What month, day, and year did you first start taking the supplement?	Approximately how often did you take the supplement? (every X days)	On days when you took the supplement, how many tablets, on average, did you take?	What month, day, and year did you stop taking the supplement?	When did you last obtain a new supply of the supplement (month, day, and year)?
Supplement A? •(Yes complete row) •No (skip to next row) •Don't know/refused (skip to next row)	•MM: _____ •DD: _____ •YYYY: _____ •Don't know/refused	•Number: _____ •Don't know/refused	•Number: _____ •Don't know/refused	•MM: _____ •DD: _____ •YYYY: _____ •Still taking •Don't know/refused	•MM: _____ •DD: _____ •YYYY: _____ •Don't know/refused
Supplement B? •(Yes complete row) •No (skip to next row) •Don't know/Refused (skip to next row)	•MM: _____ •DD: _____ •YYYY: _____ •Don't know/refused	•Number: _____ •Don't know/refused	•Number: _____ •Don't know/refused	•MM: _____ •DD: _____ •YYYY: _____ •Still taking •Don't know/refused	•MM: _____ •DD: _____ •YYYY: _____ •Don't know/refused

Scenario 1

Questionnaire

What other questions would you consider adding to the questionnaire?

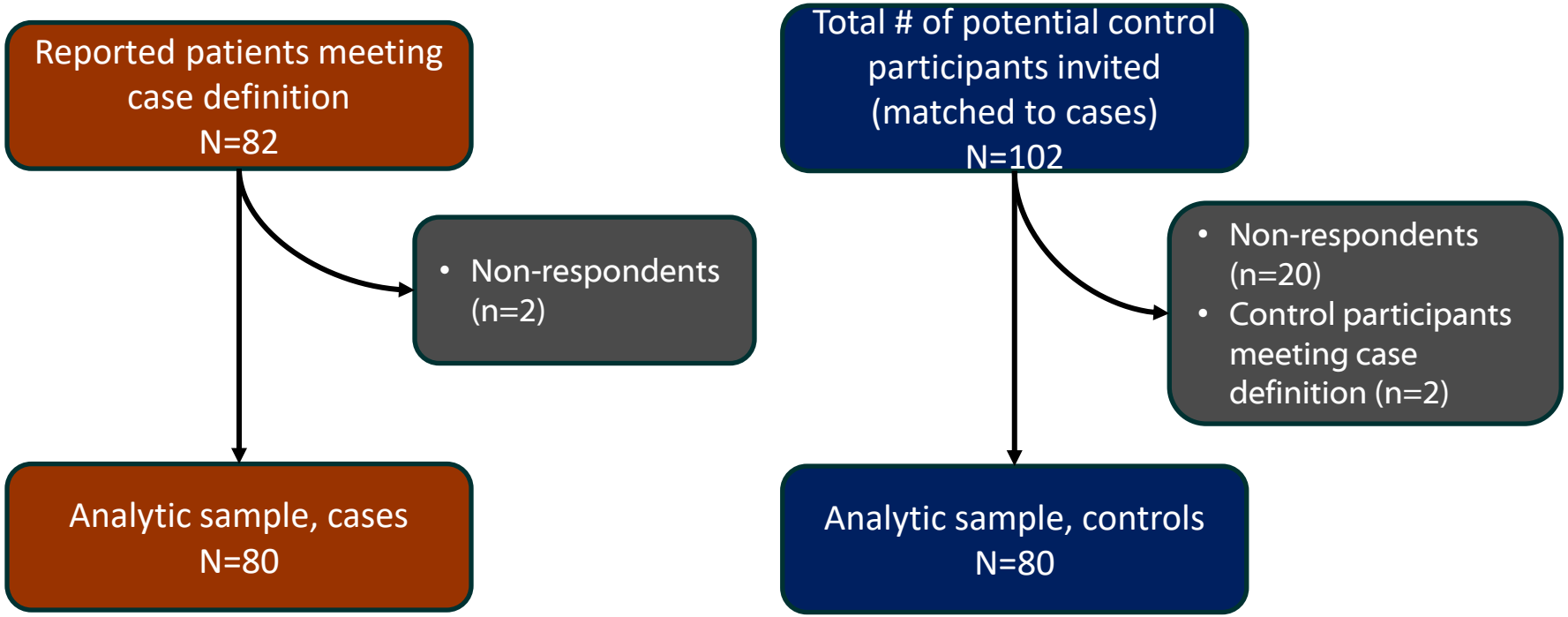
Scenario 1

Questionnaire (cont.)

- You could consider asking the following types of questions:
  - Demographics (e.g., age, sex, occupation, residence address)
  - Medical history
  - Other exposures that could be of interest or that could act as confounders, such as other supplements, medications, chiropractor visits, etc.
  - For cases: diagnoses, treatment received, recovery

Scenario 1

Case-Control Study Results



Data Analysis

How would you analyze the data from your case-control study?

Data Analysis

- Descriptive analyses, separating cases from controls
  - Demographics
  - Exposures
  - Symptoms
- Analyses of associations between exposures and illness meeting the case definition
  - Because this was a matched study, you will need to do a matched analysis.
  - If it appears that cases are different from controls in important ways, or if you are concerned about potential confounding by other exposures, you could consider analyses that control for those factors (e.g., using logistic regression models).

Scenario 1

Case-Control Study Results

- **Cases**
  - 65% female (52/80)
  - Age category:
    - 30–39: 10
    - 40–49: 21
    - 50–59: 36
    - 60–69: 10
    - 70–79: 3
  - Occupation: …
- **Controls**
  - 65% female (n=52/80)
  - Age category:
    - 30–39: 10
    - 40–49: 21
    - 50–59: 36
    - 60–69: 10
    - 70–79: 3
  - Occupation: …

Calculating Odds Ratios for Pair-Matched Case-Control Data

- Data from a matched case-control study should be analyzed using a matched analysis.
- The typical format for presenting those data is as follows:

Exposure X		Control pair member: Exposed	Control pair member: Unexposed
Case pair member	Exposed	e	f
	Unexposed	g	h

- The table cells (e, f, g, and h) show the number of pairs with each possible combination of case and control exposure status.
- The matched odds ratio is calculated as follows: mOR=f/g
- The 95% confidence interval (CI) can be calculated as: $\exp[\ln(mOR) \pm 1.96\left(\sqrt{\frac{1}{f}+\frac{1}{g}}\right)]$
- Note that the odds ratio only uses the numbers of discordant pairs (f and g).

Case-Control Study: Analyzing Supplement Data

Scenario 1

You collect the following data about dietary supplement use (displayed in the matched-pair format):

Supplement A

		Control pair member	
		Exposed	Unexposed
Case pair member	Exposed	4	60
	Unexposed	2	14

Supplement B

		Control pair member	
		Exposed	Unexposed
Case pair member	Exposed	8	11
	Unexposed	10	51

Calculate matched ORs and 95% CIs for exposure to Supplement A and Supplement B.

Case-Control Study: Analyzing Supplement Data

Scenario 1

Supplement A

Case pair member	Control pair member: Exposed	Control pair member: Unexposed
Exposed	4	60
Unexposed	2	14

Matched OR = 60/2 = 30
95% CI = 7.33-122.74

Supplement B

Case pair member	Control pair member: Exposed	Control pair member: Unexposed
Exposed	8	11
Unexposed	10	51

Matched OR = 11/10 = 1.1
95% CI = 0.47-2.59

Dose-Response Relationship

Scenario 1

You might also want to assess a possible dose-response relationship for Supplement A. You could classify exposures as “high” or “low” based on the duration of use and dose.

		Control pair member		
		High exposure	Low exposure	Unexposed
Case pair member	High exposure	1	1	50
	Low exposure	1	1	10
	Unexposed	1	1	14

OR for High exposure vs Unexposed = 50/1 = 50

OR for Low exposure vs Unexposed = 10/1 = 10

Scenario 2

Scenario 2

- FDA informs you that they have received several consumer complaints associated with Supplement A. The people who filed the complaints reported symptoms similar to those of your cases.
- Your local poison center has also received several calls from patients who reported similar symptoms and reported taking Supplement A.
- In response to your *EPI-X* posting, three other states let you know that their poison centers notified them of calls from clinicians whose patients reported experiencing similar symptoms after taking Supplement A.

Scenario 2

Would your approach be different in this scenario than in scenario 1?

Points for Further Discussion:

- ***Would this information change the objectives of your ongoing investigation?***
- ***Would this information change the agencies or organizations that you would contact?***
- ***Would this information lead you to use a different case definition in any additional studies?***

Scenario 2

Possible Multistate Investigation with a Highly Suspected Toxic Agent

- You might still want to do a case-control study as in Scenario 1, but this information (possibly along with information from laboratory testing) might lead you to already be confident that the illness was caused by supplement A, making that study less of a priority.
- Because it appears that this might be a multistate outbreak, it would be important to contact CDC (specifically, NCEH for a suspected toxicological outbreak). CDC might coordinate a multistate investigation.
- Objectives of a multistate investigation might include the following:
  - Document the magnitude and extent of the outbreak and determine whether it is ongoing.
  - Collect clinical information about cases to support investigation into the causative agent (i.e., the substance in Supplement A that caused illness) and provide an understanding of the severity and spectrum of disease.
  - Collect additional specimens (e.g., blood, urine, and samples of left over supplement A) for laboratory testing from exposed cases to help identify the causative agent.
  - Collect more complete exposure data to understand how the product is used and potential risk factors for more severe outcomes.

Scenario 2

Scenario 2 Case Definition

In this scenario, should consumption of Supplement A be included in the case definition for the national investigation? Why or why not?

Scenario 2 Case Definition

- Whether or not you would include exposure to Supplement A in the case definition for the national investigation would depend on the objectives of the investigation.
  - If one investigation objective was to epidemiologically examine the association between use of Supplement A and the illness of interest, then you would **NOT** include exposure to Supplement A in the case definition.
  - If the objectives were limited to documenting the magnitude of the outbreak and learning more about the exposure and the outcome **among exposed persons**, then it might be more efficient to include exposure to Supplement A in the case definition than to also include cases among people who did not have the exposure.
  - Including exposure to Supplement A in the case definition could help you find outbreak-related cases by using information about who purchased the product.
  - The decision might also depend on the details of the situation, such as how common the exposure is, how specific the symptoms of the illness are, and whether there is a well-defined source population that could allow a cohort study.

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Step 2
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Step 3
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Step 4
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Step 5
Find cases systematically, and record information

Step 6
Perform descriptive epidemiology

Step 7
Develop the 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

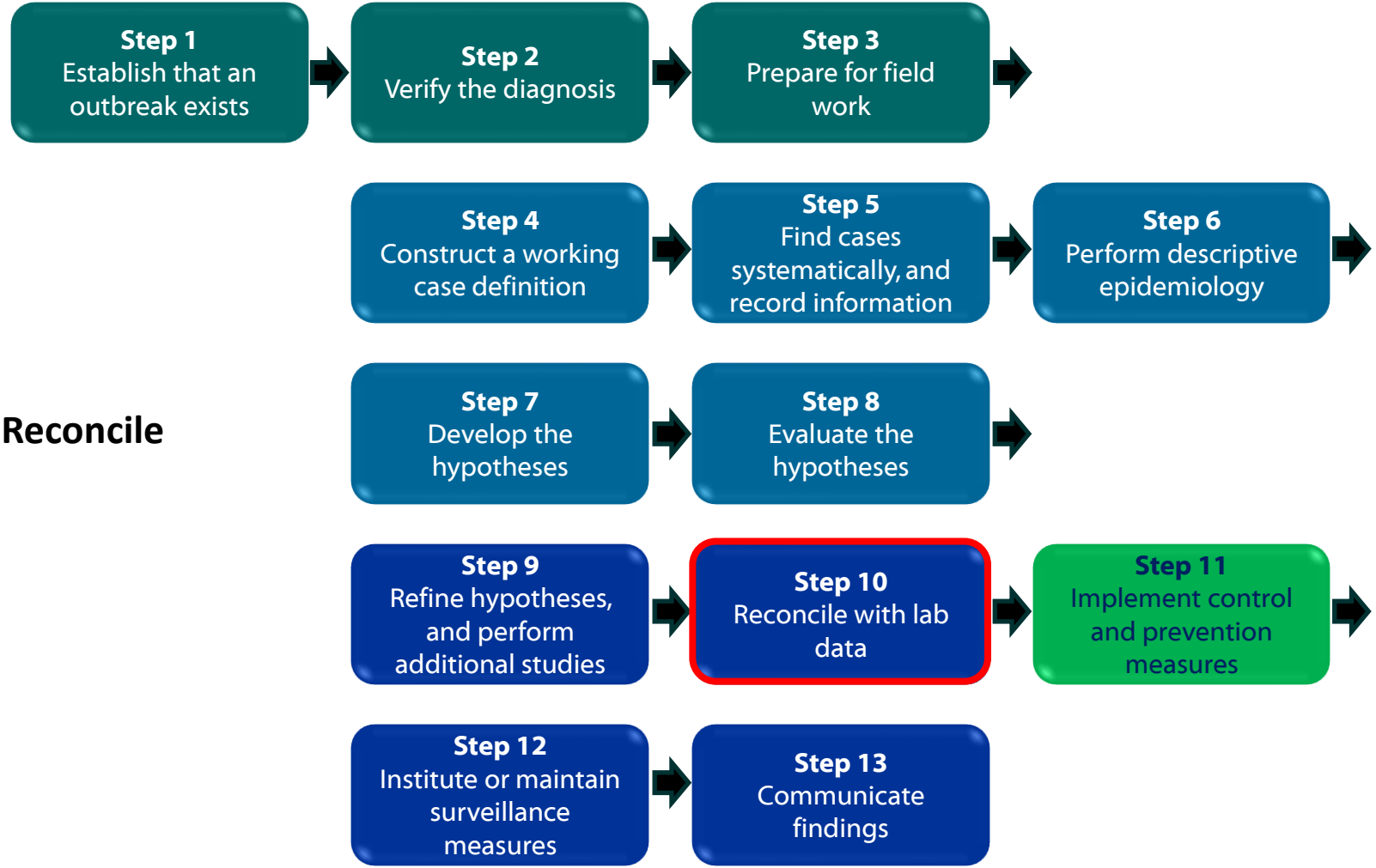
Step 12
Institute or maintain surveillance measures

Step 13
Communicate findings

Step 9: Refine hypotheses and perform additional studies

Refining Hypotheses

- You work with medical toxicologists to review the clinical presentation of the cases more thoroughly and identify potential etiologic agents.
- Based on the clinical information collected from all the cases, toxicologists suspect selenium poisoning, but they also think that the symptoms of some patients might be consistent with mercury or arsenic poisoning.
- Note that the recommendations relating to testing of collected specimens may depend on several factors, including whether the testing is likely to be informative given when the samples were collected in relation to symptom onset and the toxicokinetic properties of the toxic agent of interest.
- Toxicologists recommend testing the collected serum and urine specimens for selenium, mercury, and arsenic.



Step 10: Reconcile with lab

Laboratory Data

The health department receives the laboratory data from the blood specimen (serum) testing:

ID	Selenium (µg/L)	Mercury (µg/L)	Arsenic (µg/L)
1	321	Not detected	4.9
2	55	0.8	10.4
3	227	1.2	5.6
4	1,500	Not detected	7.6
5	761	1.8	51.8
6	664	1.3	Not detected
7	166	4.9	21.7
8	179	0.6	8.9
9	281	0.5	5.7
10	947	0.8	Not detected
…			

How are these results different from typical laboratory results for an infectious disease outbreak?

What do you need to consider when analyzing and interpreting these data?

Laboratory Data: Analysis

- In an infectious disease outbreak, test results are often reported as present/absent, while in an outbreak that involves testing samples for toxic agents, the test results are usually continuous.
- These data are usually not normally distributed, so you will need to use analytic approaches that are appropriate for non-normally distributed data (e.g., calculate medians rather than means). If the data are approximately log-normally distributed, you can log-transform the data and calculate geometric means.
- You will have to appropriately handle values of “not detected” (sometimes reported as “below the limit of detection” or “<LOD”). They should not be ignored or treated as missing. Sometimes values such as LOD/$\sqrt{2}$ are substituted for those values.

Laboratory Data: Interpretation

- Laboratory values need to be interpreted with consideration of levels that might be expected in the source population.
- If specimens were collected in a case-control study, control specimens can serve as comparison values that hopefully reflect levels in the source population.
- Other sources of comparison values could come from known levels associated with illness or measurements from general-population surveys.
- Laboratory values also need to be interpreted with consideration of the timing of specimen collection relative to the time of last exposure and the toxicokinetic properties of the toxic agent of interest.
- If you suspect a particular toxic agent but don’t find it in a particular individual, it could be that their exposure was lower than that of others or that their body eliminated it more quickly.

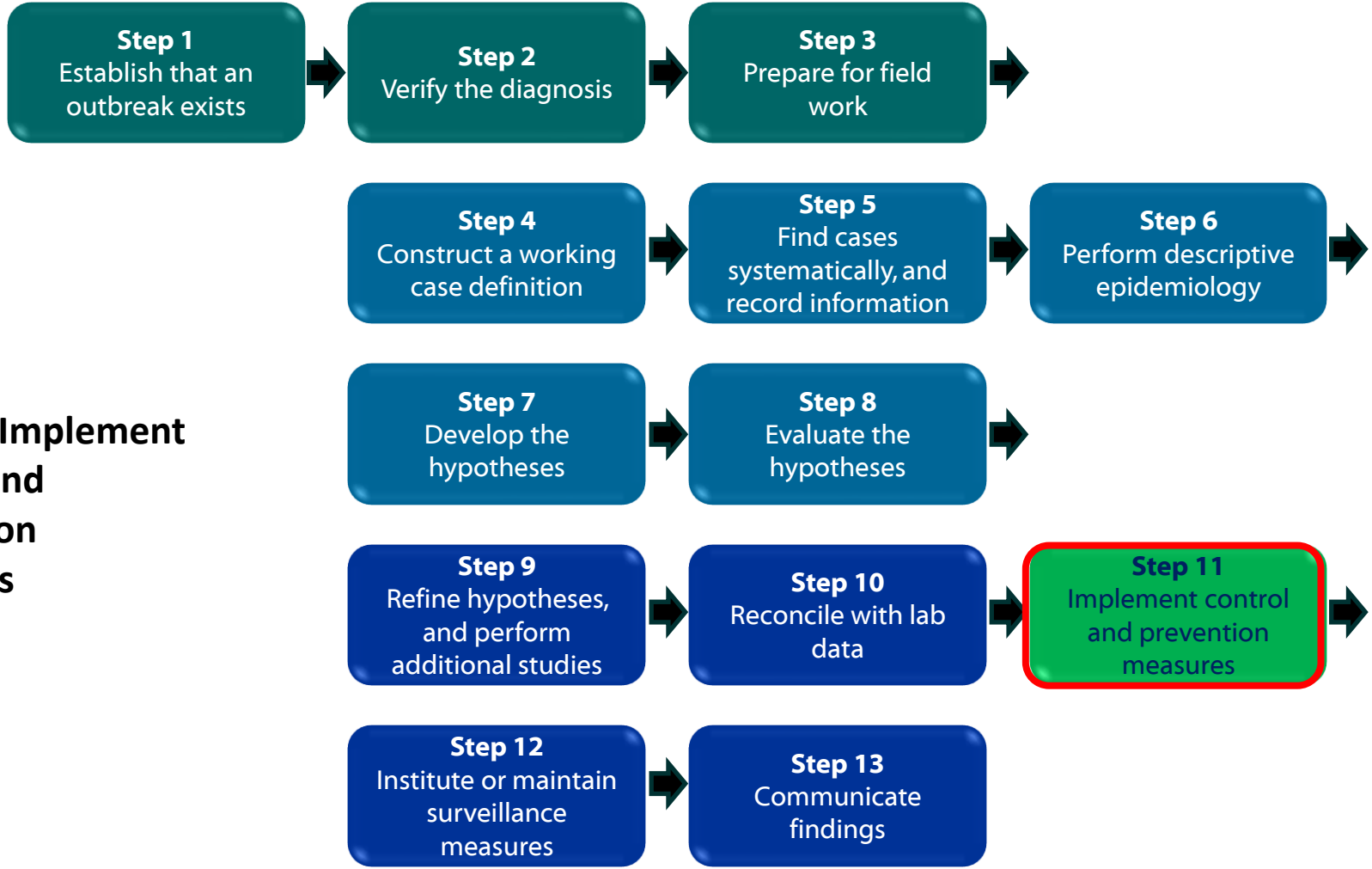
Laboratory Data

- The geometric mean serum selenium level found in participants was 751 µg/L. This value is
  - Consistent with serum selenium concentrations identified during previous toxic events (~400 to 30,000 µg/L)
  - Much higher than levels typically seen in the U.S. population, based on NHANES (median 127 µg/L)
- Based on the signs, symptoms, and these serum concentrations in case-patients, the health department concludes that the illness was due to selenium toxicity.

FDA Investigation

- You work with FDA to learn more about the product distribution and manufacturing.
  - The product was distributed by a company in Georgia but was also available in other states.
  - The product had been available for 12 years, but the company that distributed Supplement A recently switched to a new manufacturer for the product.
  - An investigation at the manufacturer revealed that a recent lot had been misformulated due to an error.
- FDA tested samples from the misformulated lot and found a selenium concentration of 40,800 µg/fl oz, although it was labeled as containing 200 µg/fl oz.

Step 11: Implement control and prevention measures



What possible control and prevention methods could be considered?

Implementing Control and Prevention Measures

- Some prevention and control measures to consider might include the following:
  - Short term measures
    - FDA could work with the manufacturer to issue a nationwide press release and recall all lots of dietary supplement A that were purchased during January through the present.
    - Investigators could determine where the product is left on the market and ensure that it is removed.
    - Responding agencies could work to ensure that the public gets the message not to consume the product.
  - Longer-term measures
    - Educate the public regarding the limitations of regulation of dietary supplements
    - Work towards improving the regulation of dietary supplements

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Step 12: Institute or maintain surveillance measures

Institute or Maintain Surveillance Measures

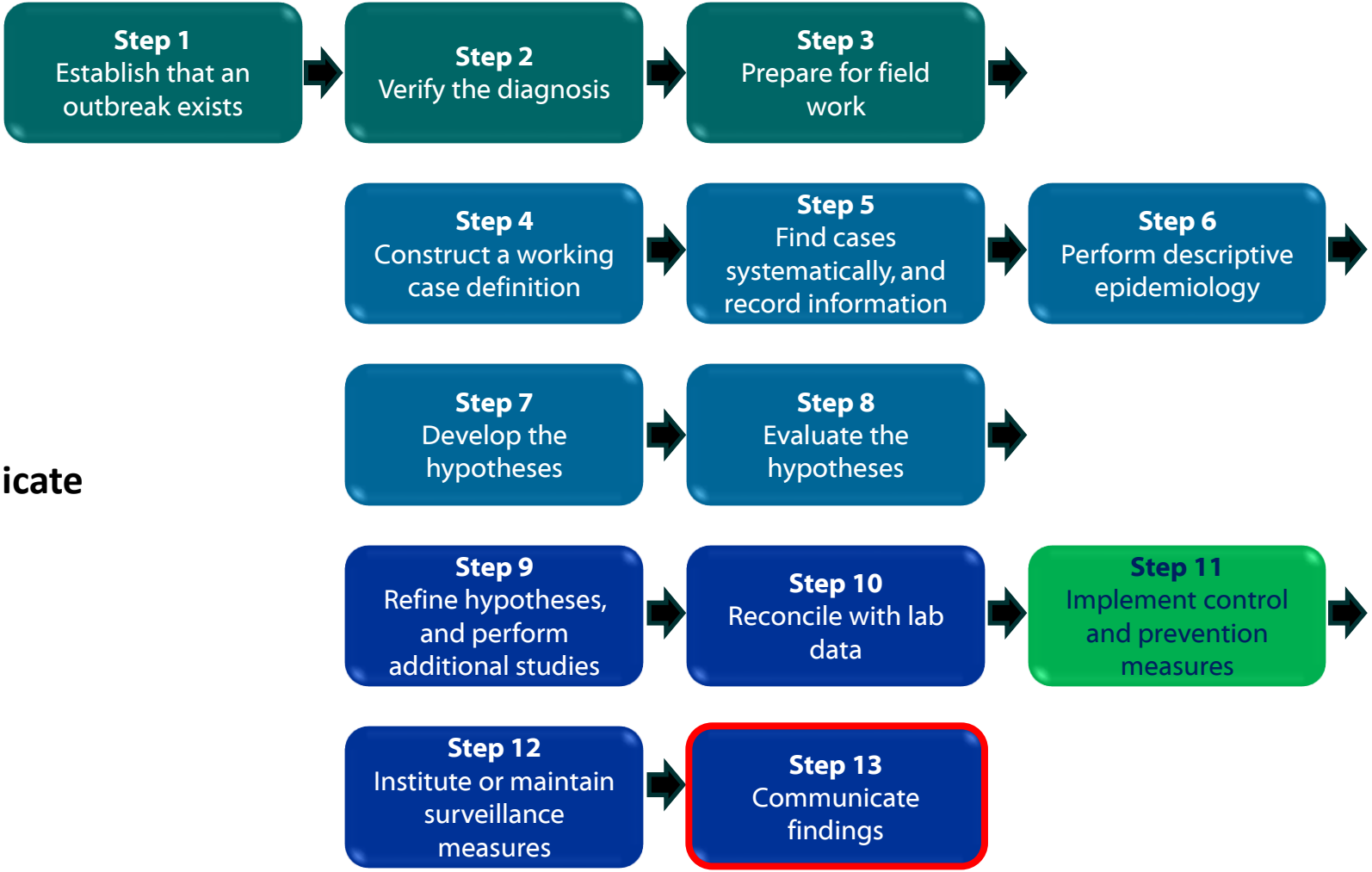
- It is important to establish surveillance measures to identify additional people with cases following the conclusion of the investigation.

How would you monitor for possible future cases associated with this product or similar products?

Institute or Maintain Surveillance Measures (cont.)

- Some possible surveillance measures could include the following:
  - Inform healthcare practitioners regarding the symptoms of selenium intoxication and ask them to report cases associated with use of Supplement A to local and state health departments (active surveillance).
    - Some possible ways to get the message to healthcare practitioners could include
      - EpiX
      - State distribution lists for healthcare practitioners
      - Health Alert Network
    - Some possible ways of collecting reports from healthcare practitioners could include
      - Direct reports to the health department (could be labor and time intensive)
      - Notification of poison centers of cases, and coordination with America's Poison Centers for monitoring the data
  - Monitor data from the National Poison Data System (even in the absence of a request for reporting) as a means of more passive surveillance.
  - FDA: Conduct recall effectiveness checks on the misformulated product.

Step 13: Communicate findings



Communicate Findings

- Now that your team concluded the outbreak investigation, you must inform the public of your findings and address any concerns.

What talking points would you develop to inform the community about the conclusions of this outbreak investigation?

Will you publish your findings? Why or why not?

Communicate Findings (cont.)

- Some talking points could include the following:
  - Explain that a high concentration of selenium in a misformulated lot of Supplement A was identified as the cause of the outbreak.
  - Advise people to immediately stop consuming Supplement A products from the misformulated lot.
  - Discuss the symptoms of selenium poisoning.
  - Discuss the potential risks involved with taking supplements that are unregulated by FDA.
- You might need to be prepared to address questions related to laboratory testing results. For example, you might need to explain why a high blood concentration of selenium might not have been found in some people with cases or why finding other specific toxic agents in tested samples does not mean that those agents caused the outbreak.
- Publication of the findings of the investigation can help disseminate findings to clinicians and public health professionals and can help them be prepared to identify and investigate future outbreaks.

Resources

- The following resources may be helpful in further explaining the contents of this module:
  - CDC, Principles of Epidemiology in Public Health Practice: An Introduction to Applied Epidemiology and Biostatistics, Third Edition. 2006
  - CDC Field Epidemiology Manual. 2019
  - PH 101 Series: Introduction to Epidemiology
  - Manual for investigating suspected outbreaks of illnesses of possible chemical etiology: guidance for investigation and control. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
- The following publications report the findings of the actual investigation on which this case study was loosely based:
  - MacFarquhar JK, Broussard DL, Melstrom P, Hutchinson R, Wolkin A, Martin C, Burk RF, Dunn JR, Green AL, Hammond R, Schaffner W, Jones TF. Acute Selenium Toxicity Associated With a Dietary Supplement. Archives of Internal Medicine. 2010;170(3):256–261.
  - Aldosary BM, Sutter ME, Schwartz M, Morgan BW. Case series of selenium toxicity from a nutritional supplement. Clinical Toxicology. 2021;50(1):57–64.
  - Melstrom P. Investigation of selenosis associated with a dietary supplement. Georgia Epidemiology Report. 2008;24(12):1–3.

Questions?

For more information, contact NCEH
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