Accessible version can be found here:
https://www.cdc.gov/nceh/hsb/elearning/toi/Mod6/

Toxicological Outbreak Investigation Course

Module Six (Domestic):

Case Study

Module 6 Objectives

- Apply the steps of an outbreak investigation to a toxicological outbreak case study
- Interpret results of biologic and environmental samples
- Describe the purpose of relevant forms from the Toxicological Investigation Tool Kit

The Call

- In May, a health department is contacted by two individuals
- Both individuals reported having gastrointestinal illness and hair loss
- Upon further questioning, it was discovered that both individuals were taking a specific dietary supplement recommended by their chiropractor

The Call (cont.)

Who at your agency would investigate this type of incident?

The Call (cont.)

Points to Consider

- How would the call get transitioned to the right people?
- Would this be investigated by the same people who do the foodborne outbreaks? Or, would it go to environmental health?
- What is your process for determining whether to investigate a possible outbreak?

Background Information

- A health department staff member spoke with the chiropractor, who noted symptoms of gastrointestinal illness and hair loss in several other patients
- In response to their illness, several patients doubled the dose of a dietary supplement sold at the chiropractor's office
  - This resulted in worsening symptoms

Background Information (cont.)

- The chiropractor describes three patients from the past week

Patient	Clinical Vignette
1	35 year-old female lost her hair; her fingernails turned gray
2	50 year-old male lost all his body hair; his fingernails turned gray; his joints were sore; he felt weak and tired
3	60 year-old female reported headaches, rash, and a bald spot on her head that was getting bigger

Selenium Toxicity

- In consultation with toxicologists at the local poison control center, it is determined that this is suspicious for selenium toxicity
- The health department hypothesizes that the outbreak is selenium toxicity due to a misformulated or contaminated supplement

Contaminated Supplement

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

Contaminated Supplement (cont.)

Points to Consider

- 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 call the CDC or other federal agencies? Why or why not? What would you want/expect from them?

Contaminated Supplement (cont.)

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

- 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

Investigation Objectives

- The health department decides to conduct an investigation
- They develop these objectives:
  - Determine the extent of the outbreak
  - Describe the illness
  - Confirm the etiology and the exposure

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

Case Definition

- They create a case definition for their second two objectives:
  - Hair loss AND
  - Nail discoloration AND
  - Nail brittleness AND
  - 2 or more of the following symptoms:
    - Muscle or joint pains
    - Headache
    - Foul breath
    - Fatigue/weakness
    - Gastrointestinal symptoms
    - Cutaneous eruption

Would you include "use of the supplement A" in your case definition?

Why or why not?

Case Definition (cont.)

Would you include "use of the supplement A" in your case definition?

Why or why not?

Answer:

- It depends if you want the case definition to be more specific or sensitive from the beginning
- If initial information gathering suggests supplement A, you may want to include it. Including supplement A in the case definition allows investigators to study why supplement A made people sick (i.e. cases).
- If you are not sure of the specific supplement, you may want to be general and find out if/what nutritional supplements were taken

Extent of the Outbreak

How would you identify the extent of the outbreak?

Extent of the Outbreak (cont.)

How would you identify the extent of the outbreak?

- Work with FDA to learn how widely the product is distributed
- Other possible methods of case identification would include:
  - CDC's EpiX national notification system
  - FDA's MedWatch reports
  - Press releases

Investigation Design

What type of study would you design to investigate this outbreak?

Investigation Design (cont.)

Points to Consider

- How would you find participants?
- Think about getting representation from sub-groups of the population who are most vulnerable (e.g., children, sick, elderly)
- Would you interview as many people as possible, or develop a sampling plan?
- Would you also interview doctors, go through medical records, visit the distributor or other doctors, etc.?

Data Collection

- The team develops a questionnaire to ask about the following:
  - Demographics (e.g., age, sex, residence)
  - Possible exposures and risk factors (e.g., dietary history, occupation)
  - Clinical information (e.g., presence or absence of specific symptoms, timing of symptom onset, treatment received, recovery)

Exposure to Supplement A

How would you structure a question that asks about exposure to Supplement A?

Exposure to Supplement A (cont.)

Tool Kit: Qualitative Epidemiological Questions

Points to Consider

- Open-ended versus closed-ended questions?
- You might want to know:
  - How much was ingested to get at dose quantification (dose-response curve)
  - The timing of supplement consumption in relation to symptom onset
  - If it is still being ingested

Supplement Exposure

- The investigators decide to use this format:

	What was the brand name of the supplement that you took?	What month and year did you first start taking the supplement?	How many tablets per day on average did you take?	What month and year did you stop taking the supplement?
Supplement A? ☐ Yes *(complete row)* ☐ No *(skip to next row)* ☐ Don't know/Refused *(skip to next row)*	☐ Company 123 ☐ Other _____ _____ ☐ Don't know/Refused	MM: _____ YYYY: _____ ☐ Don't know/Refused	Number: _____ ☐ Don't know/Refused	MM: _____ YYYY: _____ ☐ Currently still taking ☐ Don't know/Refused
Supplement B? ☐ Yes *(complete row)* ☐ No *(skip to next row)* ☐ Don't know/Refused *(skip to next row)*	☐ Company 123 ☐ Other _____ _____ ☐ Don't know/Refused	MM: _____ YYYY: _____ ☐ Don't know/Refused	Number: _____ ☐ Don't know/Refused	MM: _____ YYYY: _____ ☐ Currently still taking ☐ Don't know/Refused

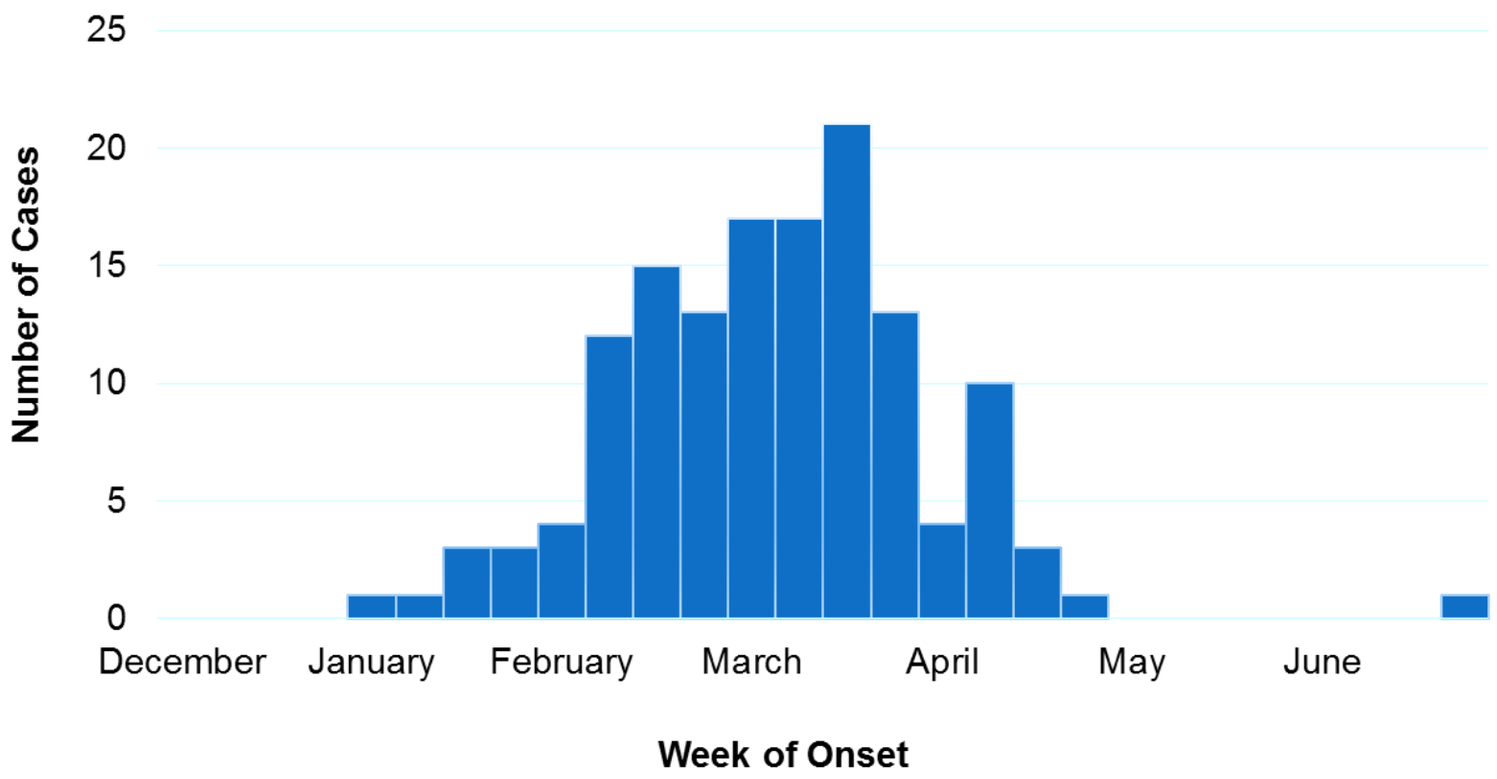
Tool Kit: Sample Questionnaire

Supplement Exposure Questionnaire Results

Of 227 patients interviewed who reported consuming Supplement A:

- 201 (89%) met the case definition
- Ages ranged from 4-92 years with a median of 54
- 121 were female

Results: Epi Curve



Results: Symptom Frequency

Symptom	n	%
Diarrhea	156	78
Fatigue	144	72
Hair loss	140	70
Joint pain	135	67
Nail discoloration/ brittleness	122	61
Nausea	115	67
Headache	90	45
Tingling	78	39
Vomiting	52	26
Fever	43	21
Ataxia	27	31

Laboratory Data

- The health department receives the laboratory data

ID	Selenium (µg/L)	Mercury (µg/L)	Arsenic (µg/L)	Etc.
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 compared to results from an infectious disease outbreak?

Laboratory Data (cont.)

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…				

How are these results different compared to results from an infectious disease outbreak?

- In an infectious disease outbreak, tests results are usually reported as present/absent.
- In an outbreak that involves testing samples for toxic agents, the test results are usually continuous.

Laboratory Data (cont.)

Points to Consider

- These data are usually not normally distributed; how will that affect your analysis?
- What would you do with samples with a level <LOD?

Laboratory Data (cont.)

Points to Consider (continued)

- What does the “not detected” mean?
  - It doesn’t necessarily mean the individual does not come into contact with the toxic agent -- just that their levels are below the LOD
- If you suspect a particular toxic agent but don’t find it, what are some possible reasons why?
  - Their recent exposure is likely lower than the LOD
  - Or, their body metabolized it faster

Laboratory Data (cont.)

- The geometric mean serum selenium level found in participants (751 µg/L) was:
  - Consistent with levels identified during previous toxic events (400 to 30,000 µg/L)
  - Much higher than levels typically seen in the U.S. population [13 µg/L]
- Based on the signs, symptoms, and serum level, the health department concludes that the illness was due to selenium toxicity

FDA Findings

- The supplement was distributed by a small company
  - It had been on the market for 12 years without any reported problems
- The distributor received the finished product from an out-of-state manufacturer who received ingredients from a different supplier

FDA Findings (cont.)

- Inspections revealed that:
  - The distributor had recently changed manufacturers
  - Misformulated lots were the first lots produced after this change
- An employee error at an ingredient supplier was found to be the cause of increased selenium in the product

Conclusions

The team reviewed the data, noting:

- The most prevalent signs and symptoms (e.g., nail discoloration/brittleness, hair loss) are consistent with what would be expected from consumption of excessive levels of selenium
- FDA discovered that a misformulation of the product occurred during manufacture due to human error
- Many cases continued to take the supplement; some increased their dose, thinking it would make them feel better

Communicating Findings

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

Communicating Findings

- A parent of a child who was in the investigation is concerned that her child had arsenic exposure
- She wants to know how that occurred and what the health department will do about it

What would you tell her?

Control and Prevention Measures

What possible control and prevention measures could be considered?

Control and Prevention Measures (cont.)

- Determine where the product is left on the market
- Short term: Work with FDA and the company to encourage a voluntary recall of the product
- A voluntary recall would include a press release to the public to cease ingestion of this product
- Educate the public regarding the limitations of regulation of dietary supplements
- Long term: Work towards improving the regulation of dietary supplements

What possible control and prevention measures could be considered?

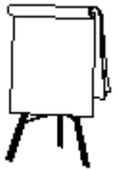
Surveillance Measures

How would you monitor for possible future cases?

Surveillance Measures (cont.)

How would you monitor for possible future cases?

- Inform health care practitioners regarding the symptoms of selenium intoxication
  - Use EpiX
  - State lists of health care practitioners
  - HAN – Health Alert Network
- FDA: Conduct recall effectiveness checks on the misformulated product



Module Conclusion

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

Thank you for your participation!