CHAPTER

5

Cluster and Outbreak Investigation

CHAPTER SUMMARY POINTS

- Outbreak investigations are conducted to rapidly identify the source of contamination and take action to prevent additional illnesses. These investigations require effective and timely integration of three types of data:
  - Epidemiologic data that describe illness distributions and reveal common exposures;
  - Informational traceback and environmental assessment data that identify common contamination points and factors in the distribution chain; and
  - Testing data that identify outbreak-associated strains in implicated foods or in environmental samples linked to the foods.
- How a potential outbreak of foodborne illness is initially recognized determines approaches taken to investigate.
  - Complaints identifying multiple illnesses associated with a common event or establishment will lead to an investigation to identify the agent and the mode(s) of transmission. Although most of these investigations will be local, some will be subclusters of larger, multijurisdictional outbreaks.
  - Clusters of cases identified through laboratory-based surveillance at the local or state level will lead to investigations to determine the mode of transmission or source of contamination. Multistate clusters of these cases suggest a commercially distributed food source.
  - Identification of a foodborne pathogen in a commercially distributed food product will lead to a search for illnesses caused by the same organism and an investigation to determine whether the food item was the source of the illness.
- A priority for all investigations is to establish the basis for implementing control measures to stop transmission and prevent additional illnesses.

URLs in this chapter are valid as of July 26, 2019.

5.0 Introduction

5.0.1 Outbreak investigations can help prevent illnesses. This chapter helps investigators quickly and accurately conduct the various steps of an investigation.

These steps are

- Detecting a possible outbreak (Chapter 4).
- Defining and finding cases.
- Generating hypotheses about likely sources.
- Testing hypotheses and evaluating evidence.
- Finding contamination sources.
- Controlling the outbreak (Chapter 6).

Because outbreak investigations are dynamic, multiple steps can occur simultaneously. In addition, as the outbreak investigation progresses, steps might need to be repeated.

When a potential foodborne illness outbreak is first detected or reported, investigators will not know whether the illness is foodborne, waterborne, or attributable to other causes. Investigators must keep an open mind in the early stages of the investigation to ensure that potential causes are not prematurely ruled out. Even though these Guidelines focus on foodborne illness, many of the investigation methods described in this chapter apply to a variety of enteric and other illnesses, regardless of source of contamination.

5.0.2 Recent developments in laboratory and epidemiologic methods impact cluster and outbreak investigation methods.

- Whole-genome sequencing (WGS) used by public health laboratories increases the specificity of pathogen-specific surveillance because case-patients with isolates that have the same DNA fingerprint are more likely to share a common source (Chapter 4). In addition, WGS increases confidence in the relationships between pathogens isolated from food/environments and historical samples, which provides better opportunities to identify outbreaks through food and environmental surveillance sampling. However, WGS may increase the timeline for public health laboratories to characterize foodborne pathogens and thus delay the identification of clusters of cases that warrant investigation.
- Culture-independent diagnostic tests (CIDTs) used by clinical laboratories provide rapid test results but require follow-up culture to produce an isolate for WGS. CIDTs might increase the number of cases reported and decrease the timeline from onset of illness to report but also reduce the proportion of isolates available for WGS and increase the timeline for conducting WGS. CIDTs used by public health agencies may enhance additional case finding in an outbreak investigation by rapidly identifying the agent in fecal samples from suspected case-patients.
- Enhanced use of new exposure assessment methods streamlines epidemiologic investigations to identify common sources for clusters and determine whether they constitute foodborne illness outbreaks.

For purposes of outbreak reporting, the National Outbreak Reporting System (https://www.cdc.gov/nors/downloads/guidance.pdf) distinguishes the definitions of an outbreak and a cluster as follows:

- An *outbreak* is two or more cases of similar illness associated with a common exposure.
- A *cluster* is two or more cases of similar illness that are suspected to be associated with a common exposure, but investigators are unable to identify a shared food, animal, venue, or experience among ill persons.

Outbreak and cluster definitions vary by jurisdiction.

Regardless of how clusters are defined for surveillance purposes, the investigations needed to identify a common exposure include multiple, interrelated epidemiologic, environmental, and laboratory activities (Table 5.1, Figure 5.1).

Table 5.1. Objectives and Investigation Activities that Can Be Conducted During Epidemiologic, Environmental Health, and Public Health Laboratory Investigations of Foodborne Illness Outbreaks*

OBJECTIVE	EPIDEMIOLOGY	ENVIRONMENTAL HEALTH	PUBLIC HEALTH AND/OR FOOD TESTING REGULATORY LABORATORY
Identify etiologic agent.	If outbreak is associated with event or establishment:		
	• Contact healthcare providers of case-patients who have sought medical attention. • Interview case-patients to characterize symptoms, incubation period, and duration of illness. • Obtain fecal specimens from case-patients. • Determine whether symptoms, incubation period, or duration of illness suggest a likely pathogen. • Establish case definition based on confirmed diagnosis or clinical profile of cases.	• Interview management to determine whether it has noticed any ill employees or any circumstances that could cause a foodborne illness. • Interview food workers to determine illness. This activity also could be conducted by nursing/healthcare staff. • Obtain fecal specimens from ill or all food workers. This activity could also be conducted by nursing/healthcare staff. • Obtain and store samples of implicated and suspected food items and ingredients. • Determine whether setting or food item suggests a likely pathogen.	• Contact clinical laboratories that might have performed primary testing on case-patients, and obtain specimens or isolates. • Test fecal samples to identify agent. • Test samples of implicated food items to identify agent. • Subtype all isolates as soon as possible after receipt.
	If outbreak is identified by pathogen-specific surveillance: Agent is known.		

Table 5.1. Objectives and Investigation Activities that Can Be Conducted During Epidemiologic, Environmental Health, and Public Health Laboratory Investigations of Foodborne Illness Outbreaks* *Continued*

OBJECTIVE	EPIDEMIOLOGY	ENVIRONMENTAL HEALTH	PUBLIC HEALTH AND/OR FOOD TESTING REGULATORY LABORATORY
Identify persons at risk, and determine size and scope of outbreak.	If outbreak is associated with event or establishment:		
	• Obtain from event organizer a list of persons attending event or, if possible, list of persons patronizing the establishment during the outbreak period. • Interview persons who attended event or patronized establishment to determine attack rates by time. • Contact healthcare providers to identify additional persons seeking medical care whose illnesses meet the case definition. • If identified agent is reportable, review recently reported cases to identify possible exposures to event or establishment.	• Obtain list of reservations for establishment, credit card receipts, receipts for takeout orders, inventory of foods ordered at establishment, or guest lists for events. Where possible, obtain information electronically.	• Contact clinical laboratories to identify additional fecal specimens being tested.
	If outbreak identified by pathogen-specific surveillance:		
	• Alert healthcare providers of possible outbreak to identify additional persons seeking medical care, and review laboratory reports and medical charts at hospitals or physicians' offices to identify possible cases. • Ask case-patients if they know of others who are similarly ill. • Depending on nature of outbreak, take additional steps as warranted.For example, review employee or school absences, review death certificates, survey population affected, or directly ask members of the public to contact the health department if they have the illness under investigation.	• Review foodborne illness complaints to identify undiagnosed cases that could be linked to outbreak. • Contact restaurants, grocery stores, or other points of final service visited by multiple case-patients to identify employee illnesses or foodborne illness complaints from patrons.	• Contact clinical laboratories to identify additional fecal specimens being tested. • Prioritize referral and subtyping of outbreak pathogen.

OBJECTIVE	EPIDEMIOLOGY	ENVIRONMENTAL HEALTH	PUBLIC HEALTH AND/OR FOOD TESTING REGULATORY LABORATORY
Identify mode of transmission and vehicle.	If outbreak is associated with event or establishment:		
	• Determine appropriate analytical study approach. • Interview identified case-patients and controls or well meal companions about all common exposure sources. • Calculate measures of association for specific exposures, appropriate to study design (i.e., odds ratios for case–control study or attack rates and relative risks for cohort study).	• Obtain menu from establishment or event. • Interview food workers to determine food-preparation responsibilities. • Reconstruct food flow for implicated meal or food item. • Identify contributing factors and environmental antecedents. • Obtain samples of implicated food. • Obtain environmental samples from food contact surfaces or possible environmental reservoirs.	• Test implicated food and environmental samples to confirm presence of agent. • Subtype all isolates as soon as possible after receipt. • Conduct applied food-safety research to determine ability of agent to survive or multiply in implicated vehicle and how vehicle might have become contaminated.
	If outbreak identified by pathogen-specific surveillance:		
	• Interview case-patients as soon as possible with standardized detailed exposure history questionnaire to identify possible common exposures. • Establish case definition on the basis of characteristics of agent that led to detection of outbreak. • Characterize cases by person, place, and time, and evaluate this descriptive epidemiology to identify patterns possibly associated with particular food items or diets. • Compare detailed exposure history questionnaire frequencies against known or estimated background exposure rates, to identify suspected food item. • Interview nonill community controls or nonoutbreak-associated ill persons to obtain detailed exposure information to be used in a case-comparison analysis of exposures.	• Contact restaurants, grocery stores, or other locations identified by multiple case-patients to verify menu choices, identify ingredients, and identify distributors and/or source(s) for ingredients and/or food items of interest. • Obtain samples of suspected food items. Work with appropriate regulatory authority to ensure that food samples are collected and maintained with appropriate chain of custody. This will help the regulatory authority to take appropriate regulatory action. • Conduct an informational traceback to determine whether a suspected food vehicle from multiple case-patientss has a distribution or other point in common.	• Store collected food samples, pending results of epidemiologic analyses. • Culture implicated food samples to confirm presence of agent. • Conduct whole-genome sequencing to further characterize pathogen as necessary for investigation. • Conduct applied food-safety research to determine ability of agent to survive or multiply in implicated vehicle and how vehicle might have become contaminated.

Table 5.1. Objectives and Investigation Activities that Can Be Conducted During Epidemiologic, Environmental Health, and Public Health Laboratory Investigations of Foodborne Illness Outbreaks*
Continued

OBJECTIVE	EPIDEMIOLOGY	ENVIRONMENTAL HEALTH	PUBLIC HEALTH AND/OR FOOD TESTING REGULATORY LABORATORY
Identify mode of transmission and vehicle.	If outbreak identified by pathogen-specific surveillance:		
	• Obtain shopper card information to identify and verify grocery purchases and possibly determine background rates of purchase of item. • Document brand names and product code information for prepackaged food items. • Analyze exposure information comparing cases to relevant comparison groups (e.g., nonill controls or cases not associated with outbreak) to implicate food item or nonfood exposure source.	• If specific food item or ingredient is implicated, conduct formal regulatory traceback.	
Identify source of contamination.	If outbreak is associated with event or establishment:		
	• Combine descriptive and analytical epidemiology results to develop a model for the outbreak.	• Interview food workers to determine food-preparation responsibilities. • Reconstruct food flow for implicated meal or food item. • Evaluate food flow for implicated meal or food item to identify contamination event at point of preparation or service. • If no contamination event identified, trace source of ingredients of implicated food item back through distribution to point where a contamination event can be identified or, if no contamination events can be identified during distribution, to source of production.	• Evaluate results of all outbreak-associated culture subtyping to highlight possible relations among isolates from clinical, food, and environmental samples. • Conduct applied food-safety research to determine how vehicle might have become contaminated.

Identify source of contamination.	If outbreak is identified by pathogen-specific surveillance:		

	• Combine descriptive and analytical epidemiology results to develop a model for outbreak.	• Trace source of implicated food item or ingredients through distribution to point where a contamination event can be identified or to source of production if no contamination events can be identified during distribution.
		• Conduct environmental assessment of likely source of contamination, including
		  ○ Reconstruct food flow for implicated food item.
		  ○ Interview food workers to determine food-preparation responsibilities and practices before exposure.
		  ○ Obtain samples of implicated food or ingredients.
		  ○ Obtain environmental samples from food contact surfaces or potential environmental reservoirs.
			• Evaluate results to highlight possible relations among isolates from clinical, food, and environmental samples.
			• Conduct applied food-safety research to examine likely sources of contamination.
			• Work with appropriate regulatory authority to ensure that food samples are collected and maintained with appropriate chain of custody. This will help the regulatory authority to take appropriate regulatory action.

Identify contributing factors and antecedents (root causes)	If outbreak is associated with event or establishment:		
	• Summarize information to identify confirmed or suspected agent. • Summarize information to identify confirmed or suspected food vehicle.	• Evaluate results of environmental assessment, given identification of agent and results of epidemiologic investigation, to identify factors most likely to have contributed to outbreak and their environmental antecedents.	• Summarize information about testing results from clinical, food, and environmental samples.
	If outbreak is identified by pathogen-specific surveillance:		
	• Summarize information to identify confirmed or suspected food vehicle.	• Evaluate results of environmental assessment, given identification of agent and results of epidemiologic investigation, to identify contributing factors and antecedents.	• Summarize information about testing results from clinical, food, and environmental samples. • Provide background statistics on pathogen prevalence.

Table 5.1. Objectives and Investigation Activities that Can Be Conducted During Epidemiologic, Environmental Health, and Public Health Laboratory Investigations of Foodborne Illness Outbreaks* *Continued*

OBJECTIVE	EPIDEMIOLOGY	ENVIRONMENTAL HEALTH	PUBLIC HEALTH AND/OR FOOD TESTING REGULATORY LABORATORY
Determine potential for ongoing transmission and need for abatement procedures.	If outbreak is associated with event or establishment:		

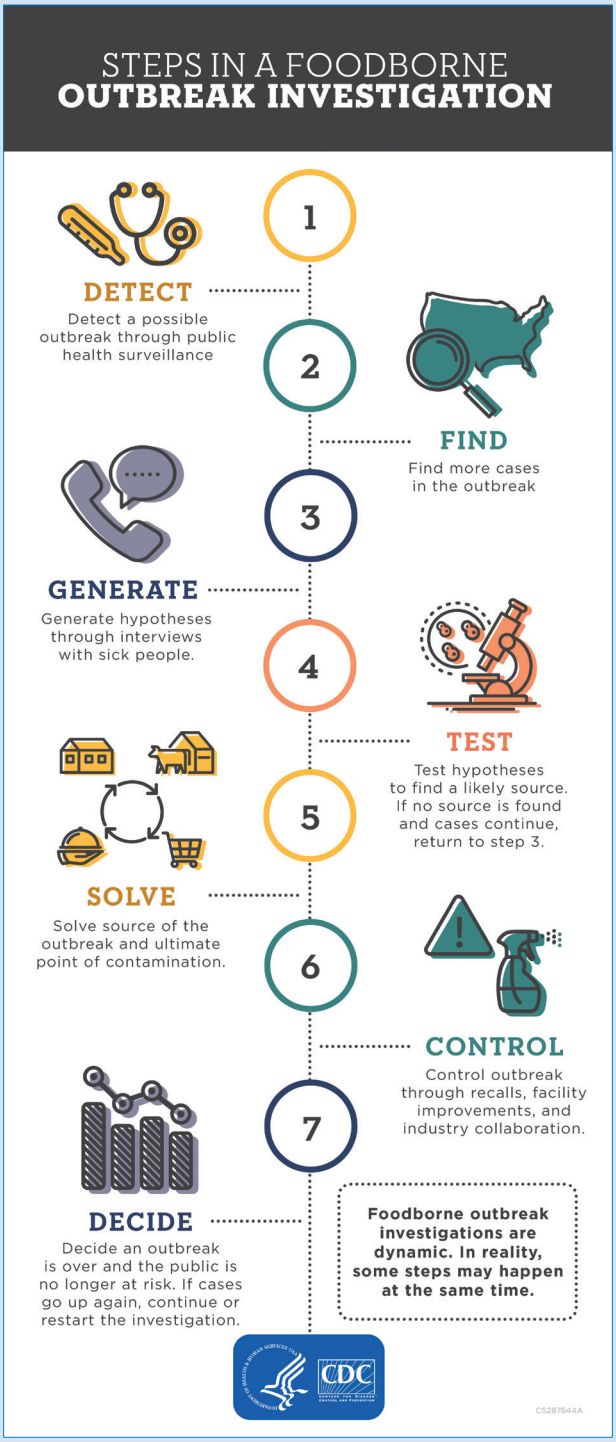
	• On the basis of agent, incubation period, and likelihood of secondary spread, create epidemic curve, and evaluate the course of the outbreak to determine whether additional cases may still be occurring.
	• If outbreak appears to be ongoing, review possible control measures in collaboration with environmental health specialists.
		• Implement control measures to prevent further exposures:
		  ○ Verify that all food workers who pose a risk for transmission have been excluded or restricted, as appropriate.
		  ○ Verify that potentially contaminated foods have been properly disposed of.
		  ○ Verify that food contact surfaces and potential environmental reservoirs have been adequately cleaned and sanitized.
		  ○ Train staff in safe food-preparation practices.
		  ○ Modify food-production and food-preparation processes with appropriate preventive controls.
		  ○ Modify menu.
		• If any of these measures cannot be verified, review additional control measures, or if further exposure appears likely, alert public or close premises.
			• Assess status of completed and pending testing to identify gaps that suggest a potential for ongoing transmission.

	If outbreak is identified by pathogen-specific surveillance:		
	• Create and evaluate epidemic curve to determine whether additional cases might still be occurring. • If outbreak appears to be ongoing, continue surveillance, and review potential abatement procedures.	• Verify that food workers who might have been infected during outbreak and who pose a risk for transmission have been excluded or restricted, as appropriate. • Verify that potentially contaminated foods have been removed from distribution. • Train staff on safe food-preparation practices. • Modify food-production and food-preparation processes by implementing appropriate preventive controls. • Modify menu.	• Assess status of completed and pending testing to identify gaps that may suggest a potential for ongoing transmission.

*The table format highlights the major objectives of the investigation to help ensure coordination among epidemiologists, environmental health specialists, and laboratorians in meeting each objective. The assignment of investigation responsibilities to a particular discipline within each table is not intended to be prescriptive. The actual responsibilities for an individual vary by the practices of the jurisdiction responsible for the investigation, roles defined in the outbreak investigation and control team, and resources.

5.0 Introduction

Figure 5.1. Steps in a Foodborne Illness Outbreak Investigation



5.1 Outbreak Investigation Initiation

5.1.1 Alert outbreak investigation and control team leaders as soon as a possible outbreak is identified. Outbreaks are detected in several principle ways (Chapter 4). However, a common initial approach is to review descriptive features of the outbreak setting and relevant background information about the etiologic agent, establishment, or event:

- Most local investigations require coordination between epidemiologists, environmental health specialists, and public health laboratorians within the jurisdiction of the cases, event, or establishment.
- Multistate clusters also require communication and coordination of activities between local, state, and federal agencies to rapidly investigate a suspected vehicle (Chapter 7).

5.1.2 Assess the priority of the outbreak investigation. Although any outbreak might warrant investigation, give highest priority for investigation to outbreaks that

- Have a high public health impact:
  - Cause severe or life-threatening illness, such as infection with *Escherichia coli* O157:H7, Listeria *monocytogenes*, or botulism;
  - Affect populations at high risk for complications of the illness (e.g., infants, elderly persons, immunocompromised persons); or
  - Affect a large number of persons.
- Appear to be ongoing:
  - May be associated with food-service establishment in which ill food workers provide a continuing source of infection.
  - May be associated with a commercially distributed food product that is still being consumed.

If the scale or complexity of an outbreak investigation is likely to overwhelm agency resources, the agency should request assistance as soon as possible for the additional resources and expertise required to respond to it (Chapter 3).

5.1.3 Assemble and brief the outbreak investigation and control team. Open communication between investigation members to plan, conduct, and evaluate outbreak investigation activities is critical to the success of the investigation.

- Investigation and control team leaders should assess the availability of staff to conduct the investigation. In particular, the team leader should ensure the presence of adequate staffing to interview case-patients within 24–48 hours. If sufficient staff are not available, request external assistance to conduct interviews.
- Outbreak investigation and control staff should be briefed on the outbreak, and their individual roles in the investigation. Ensure that all members of the investigation team—epidemiologists, laboratorians, and environmental health specialists—are familiar with and follow relevant state and federal laws and data handling practices.
- For outbreaks involving multiple jurisdictions, the outbreak investigation and control team should include members from all agencies participating in the investigation (Chapter 7).

5.1.4 Ensure that leadership of the investigation reflects the focus of investigation activities, which may change over time. During an investigation, the focus of activities may shift among the following:

- Laboratory studies to identify an agent, including microbiologic studies and applied food-safety research.
- Epidemiologic studies to identify transmission routes, exposure sources, or food vehicles and risk factors for illness.
- Regulatory investigations of food-production sources and distribution chains to identify

5.1 Outbreak Investigation Initiation

where, during production or distribution of the food, contamination occurred and facilitate recall of food items.

- Environmental assessments of food production, processing, and service facilities to identify routes of contamination, contributing factors, and environmental antecedents;
- Communication of investigation findings to the public and the food industry to support control and prevention measures.

5.1.5 Coordinate activities and set up good lines of communication between individuals and agencies involved in the investigation (Chapter 3, Chapter 7).

Investigations are rarely linear (Figure 5.1). Although the steps for investigating outbreaks follow a logical process—from determining whether an outbreak is occurring to identifying and controlling the source—most investigations feature multiple concurrent steps. Maintaining close communication and coordination among members of the outbreak investigation team is the best way to ensure that concurrent activities do not interfere with each other and important investigation steps are not forgotten.

5.1.6 Establish goals and objectives for the investigation. The primary goal for most investigations is to obtain enough information to implement specific interventions to stop the outbreak. The results of the investigation also should provide information to prevent a similar outbreak from occurring in the future. Secondary goals are to increase knowledge of the epidemiology and control of foodborne illnesses. Unanswered questions about the etiologic agent, the mode of transmission, or contributing factors should be identified and included in the investigation to add to the public health knowledge base.

Objectives for meeting these goals vary by type of outbreak.

- **Complaints identifying multiple illnesses associated with a common event or establishment** will lead to an investigation to identify the agent and the mode(s) of transmission. Most of these investigations will be local and require coordination between epidemiologists, environmental health specialists, and public health laboratorians within the jurisdiction of the event or establishment. Case-patients need to be rapidly interviewed to confirm illness and exposure details that may suggest a likely etiology and potential source of exposure. Environmental health specialists, guided by descriptive epidemiology, need to assess food-handling practices and food worker health and hygiene habits at the establishment. Public health laboratories need to test clinical specimens to confirm the etiology of the outbreak based on the description of signs, symptoms, and incubation periods (CIFOR Outbreaks of Undetermined Etiology Guidelines [*1*]). If the source of contamination was determined to be upstream from the establishment, the outbreak could involve multiple locations and require a multijurisdictional investigation (Chapter 7).
- **Clusters of cases identified through laboratory-based surveillance** at the local or state level will lead to investigations to determine the mode of transmission or source of contamination. Case-patients need to be rapidly interviewed with a thorough exposure assessment questionnaire to identify potentially common exposures or likely routes of transmission. Environmental health specialists and food regulators need to be prepared to help investigate subclusters associated with food establishments and to initiate product tracing for suspected food exposures. Public health laboratories need to rapidly confirm additional cases, and food-regulatory laboratories need to prepare to rapidly test suspected food products.

5.1 Outbreak Investigation Initiation

- **Multistate clusters of cases** suggest a commercially distributed food source (Chapter 7). Product tracing may be needed for successful exposure assessment. Communication and coordination of activities between local, state, and federal agencies must be established at the onset of the investigation.
- **Identification of a foodborne pathogen in a commercially distributed food product** will lead to a search for illnesses caused by the same organism and an investigation to determine whether the food item was the source of the illness. This type of outbreak presentation will most likely increase with the use of WGS to link isolates from food or environmental samples with cases identified through pathogen-specific surveillance. In all instances, investigating the possible link between contaminated food product and illnesses requires multijurisdictional investigation to assess the likelihood the cases are attributable to the suspected food exposure.

5.2 Define and Find Cases

5.2.1 Developing case definitions. Initially, case definitions reflect the cluster recognition methods.

- A cluster of illnesses linked to foodborne illness complaints most likely will be defined by similar features of the illness and by common suspected source of exposure, such as time, place, or person. As case-patients are interviewed, a distinctive clinical profile may emerge that suggests an etiology. If testing of clinical specimens confirms an agent, the features of that agent can be used to establish a clinical case definition.
- Clusters of cases identified by pathogen-specific surveillance are usually defined by common phenotypic or molecular characteristics (serotype, pulsed-field gel electrophoresis [PFGE] pattern, WGS), time frame when the cases occurred, and geographic distribution of the cases. CIDTs are a challenge to this approach. Although the initial CIDT-positive result may be available within a few days after onset of illness, the need to perform culture and then subtype the isolate means that some cases will not be subtyped, and the timeline will be longer for those that are cultured and subtyped.
- **During the early stages of the investigation, case definitions should be made specific to increase the likelihood that the detected cases share a common exposure.** Including unrelated cases in an outbreak investigation makes recognizing a common exposure more difficult and dilutes observed measures of association in analytic studies. For example, in an outbreak of salmonellosis, case-patients may share common symptoms of diarrhea and fever and all their illnesses might be caused by isolates with the same serotype that have a distinctive PFGE pattern and are closely related by WGS. Each of these additional points of identity increases the likelihood that the cases are related and the source may be identified.
- **After a common source has been identified, changing the case definition might be necessary or desirable to better assess the magnitude of the outbreak.** A change might be needed when additional pathogens, or strains of a pathogen, are linked to the same source. Although outbreaks are detected through monoclonal surveillance for highly defined clusters, many food-contamination events are polyclonal, i.e., involve multiple strains of pathogenic bacteria. The true

5.2 Define and Find Cases

nature of these events is usually not discovered until late in the investigation. In addition, after a common source has been identified, accounting for illnesses that occurred after exposure to the source that were not confirmed but had similar clinical characteristics to the confirmed cases can help provide a better estimate of the size, scope, and public health impact of the outbreak.

5.2.2 Reviewing current surveillance systems for illnesses that meet the case definition. Once a case definition has been established, investigators should search for more illnesses related to the outbreak.

- **For clusters of illnesses reported through complaints, review complaint logs or databases to find other complaints that identify exposure to the suspected event or establishment.** Although many complainants focus on their most recent exposure, reviewing all exposures in a 3-day food history could link unrecognized cases to the outbreak. A 3-day history may not cover the exposure window for all cases, but it covers the most common foodborne illness incubation periods and saves resources.

  In addition, if the confirmed etiology of the complaint-based outbreak is *Salmonella*, Shiga toxin–producing *E. coli*, or other foodborne pathogen for which case-patients are routinely interviewed, reviewing all exposures for case-patients interviewed during the likely outbreak period could link unrecognized cases to the outbreak.
- **For clusters identified through laboratory-based surveillance, review regular surveillance reports and laboratory reports.** In addition, for restaurants and retailers identified in the relevant exposure window, review the complaint database to identify potential subclusters of cases.

5.2.3 Supplement case-finding activities. Ask local clinical and laboratory professionals to report cases as soon as they suspect the diagnosis, alert health officials in surrounding areas to watch for illnesses that might be related, and survey groups that may have been exposed.

5.2.4 Plot Cases on an Epidemic Curve to Track Illnesses Over Time. The epidemic curve (epi curve) shows progression of an active outbreak over time. The horizontal axis (x-axis) is the date a person became ill (date of onset). The vertical axis (y-axis) is the number of persons who became ill on each date. These numbers are updated as new data come in and thus are subject to change. The epi curve is complex and incomplete. Several issues are important in understanding it:

- An inherent delay exists between the date of illness onset and the date the case is reported to public health authorities. For example, for *Salmonella* infections, this delay is typically is 2–3 weeks. Therefore, a person who became ill last week is unlikely to have been reported yet, and a person who became ill 3 weeks ago might just now be reported. (See *Salmonella* Outbreak Investigations: Timeline for Reporting Cases [Chapter 4, Figure 4.1].)
- Some cases are background cases of illness that most likely would have occurred even without an outbreak; therefore, determining exactly which case is the first in an outbreak is difficult. Epidemiologists typically focus on the first recognized cluster or group of cases rather than on the first case. Because of the inherent reporting delay, a cluster sometimes is not detected until several weeks after people became ill.
- For some cases, date of illness onset is not known because of the delay between reporting and case-patient interview. Sometimes an interview never occurs. If the date an ill person brought his or her specimen to the

5.2 Define and Find Cases

laboratory for testing is known, date of illness onset can be estimated as 3 days before that.

- Determining when cases start to decline can be difficult because of the reporting delay but becomes clearer as time passes.
- Because of the reporting delay, determining the end of an outbreak can be difficult. The curve for the most recent 3 weeks always makes the outbreak appear to be ending, even it is ongoing. The full shape of the curve is clear only after the outbreak ends.

5.3 Generate Hypotheses about Likely Sources

To narrow the focus of an investigation and most effectively use time and resources, investigators should begin to generate hypotheses about potential sources of the outbreak during the earliest stages of the investigation and refine them as they receive information. Hypotheses may emerge from common case characteristics, shared exposures, or historical information about the agent. The process comprises several key steps.

5.3.1 Review demographic information, including age, sex, and geographic and temporal distributions of case-patients. The Centers for Disease Control and Prevention (CDC) developed the System for Enteric Disease Response, Investigation, and Coordination to help organize and visualize cluster-associated data (*2*). Patterns in the distributions of these characteristics may suggest possible sources. On a local level, case surveillance data should be reviewed with data from foodborne illness complaints.

5.3.2 Review previous exposure sources linked to the agent. Identify previous vehicles associated with outbreaks and isolation of the agent from food items or food-production environments. However, avoid focusing only on historic sources because they could miss a new or previously unknown source.

5.3.3 Use standardized data collection forms, and compile data from case-patient interviews. CDC, in collaboration with states, developed a National Hypothesis Generating Questionnaire (NHGQ) to collect information on a broad range of food and nonfood exposures (http://cifor.us/downloads/clearinghouse/NHGQ_v2_OMB0920_0997.pdf).

The NHGQ contains a mix of closed- and open-ended questions designed to elicit likely exposure sources. However, the NHGQ cannot capture detailed source information about all possible exposures, and supplemental approaches may be needed. A key to identifying the source of an outbreak is to collect detailed information on both the food item and its source for as many cases as possible as early in the process as possible.

When conducting hypothesis-generating interviews, use the following interview techniques to improve food recall:

- Question case-patients as soon as possible after their illnesses are reported.
- Encourage them to remember information by asking them to elaborate on where they ate, with whom they ate, and events associated with the meals. Ask them to look at a calendar from the appropriate time periods to jog their memory.
- Interview persons who prepared meals during the period of interest.
- Ask case-patients whether they keep cash register or credit card receipts, or review online banking or bank statements to indicate where or what they ate. Purchase receipts can often be reproduced if the case-patient paid with a credit card.

5.3 Generate Hypotheses about Likely Sources

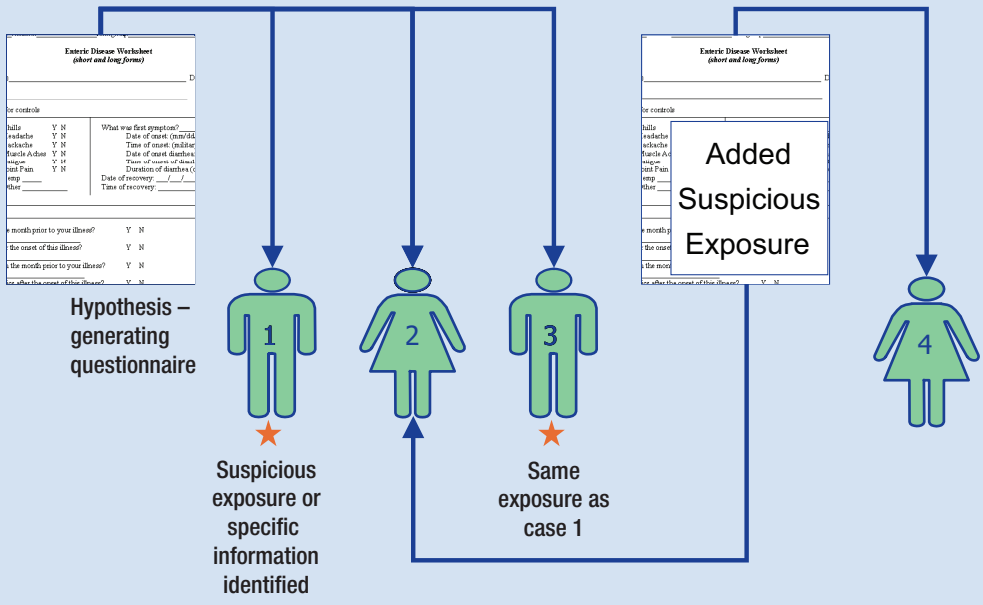
- If the case-patient uses a grocery store shopper card, ask permission to obtain purchase records for a specified time period. Some grocery chains readily cooperate with these requests; others require additional documentation, which delays investigation.
- Use a structured list of the places where people might get food to encourage case-patients to think about possible exposures other than restaurants and grocery stores. The list could include food pantries, farmers markets, conferences and meetings, caterers, and meal delivery services.

5.3.4 Use a dynamic cluster investigation process to generate and develop hypotheses. In the dynamic cluster investigation model, initial case-patients within a recognized cluster are interviewed with a detailed exposure history questionnaire. As suspicious exposures are identified during interviews, the initial case-patients are systematically reinterviewed to uniformly assess these suspicious exposures. Newly reported case-patients also will be asked specifically about these exposures (Figure 5.2).

On the basis of this information, investigators can identify possible exposures for further evaluation by epidemiologic, laboratory, or environmental studies. These should include the review of specific information about establishments/products of interest:

- Guest lists for common events reported by case-patients.
- Historical information on firms or food items of interest.
- Recipe and ingredient lists for common menu items.

Figure 5.2. Dynamic cluster investigation



In this model, case-patients are interviewed with a detailed hypothesis-generating questionnaire. Specific exposures shared by multiple cases might surface that are suspicious because they involve commodities not commonly eaten, or involve specific brands of a commonly eaten food item. Because the original questionnaire might not have captured these exposures, specific questions should be added to the questionnaire for future use, and to systematically re-interview cases to assess the suspicious sources discovered during the investigation process.

5.3 Generate Hypotheses about Likely Sources

- Shopper card data or reproduced receipts from credit card purchases to compare grocery store or online meal purchases

In practice, the generation and testing of hypotheses is an iterative process, and the hypothesis is modified as more information is obtained.

5.3.5 Investigate subclusters. When a group of case-patients within a cluster identifies exposure to the same individual point of service, such as a restaurant, cafeteria, grocery store, or institution, this group of cases is termed a subcluster and represents an invaluable opportunity to solve the outbreak because the outbreak vehicle was most likely served or sold by the common establishment. Thus, subcluster investigations represent a hybrid of hypothesis-generating and hypothesis-testing approaches and are a useful model of the general approach to outbreak investigations.

- **Commit all available resources to rapidly and comprehensively investigate such a subcluster to increase the investigation's likelihood of success.** If resources are not available to conduct an investigation fully and rapidly, seek assistance from other agencies.
- **Ascertain additional cases associated with subcluster locations.** In their initial interview, ask all newly identified case-patients within a cluster to identify all dining locations at which they ate during the exposure period. Case-patients often do not recall eating at some locations outside the home when asked open ended questions on initial interview (e.g., "What restaurants did you eat at?"). Ask all newly identified case-patients in a cluster specifically about the list of dining locations named by previously interviewed persons. Ascertain additional subcluster cases by contacting additional patrons of the subcluster establishment (e.g., through credit card receipts, online orders, or reservations).
- **Once a subcluster is identified, reinterview previously interviewed case-patients and ask specifically about the subcluster establishment.** Ask all newly identified cluster case-patients specifically about the subcluster establishment during their first interview. Ask them to check credit/debit card statements to improve recall. Obtain and analyze shopper card records for cases linked to common grocery store chains; grocery store receipts also can often be reproduced if the purchase was made with a credit card, even for a store without a shopper card program. Pinpointing the purchase date and meal date to the extent feasible is important. (If a receipt or credit card statement is not available, record the case-patient's level of confidence about the purchase or meal date.)
- **Gather detailed food-consumption data for subcluster cases.** Interview case-patients using the subcluster establishment's menu or, if an event cohort with a limited discrete menu is identified, a more defined menu.
  - Ask case-patients about additions or subtractions to the menu item(s) they ordered.
  - Interview the establishment manager and/or chef to obtain ingredient lists for menu items.
  - Compile a frequency distribution of ingredients consumed by case-patients. Include every ingredient consumed by at least one case-patient.
- **Conduct an analytical study at the subcluster establishment.** Conduct an ingredient-specific case–control study. There is no rule as to a minimum number of cases necessary to initiate such a study, but it is reasonable to do so with as few as three cases.
  - Identify additional cases and enroll controls by
    - Asking case-patients for meal companions;

5.3 Generate Hypotheses about Likely Sources

- Obtaining credit card receipts, reservation lists, takeout orders, and/or lists of workers or students (if a school cafeteria) for patrons who dined at the establishment on the implicated meal dates.
  - Ascertain additional cases (and increase the number of controls) to increase the likelihood of meaningful results and your confidence in those results.
  - Make the clinical case definition specific for the pathogen of interest (e.g., for Salmonella use "fever and diarrhea" or "diarrhea duration >3 days") to minimize the likelihood that unrelated illness will dilute associations.
  - **Include every plausible ingredient** in the study. Be systematic—do not focus solely on one or two ingredients case-patients commonly reported. Some ingredients (e.g., spices, garnishes) may be used in multiple menu items and thus could be overlooked.
  - **Trace back suspected vehicle(s).** If there are multiple subclusters (i.e., multiple points of service), trace back ingredients implicated in analytic studies or, if analytic studies cannot be done, ingredients that case-patients most frequently consumed. Do not exclude food ingredients from an analytic study based on apparent differences in distributors for ingredients used by the subcluster establishments because commonalities in the source of food items might not occur until farther back in the distribution chain.
- **Link subclusters in multistate outbreak to look for common distribution links between establishments** (possible even if there are too few cases for a case–control study). Traceback of individual cases also can provide important information to corroborate subcluster data.

5.3.6 Maintain open, regular communication between public health and regulatory partners to discuss new or updated information about the epidemiologic investigation and food/establishment findings.

5.4 Test Hypotheses

Much of the work of outbreak investigations involves developing sound hypotheses that explain the patterns of illnesses observed. Testing these hypotheses requires epidemiologic analysis of common exposures, typically combined with informational traceback and environmental assessment data that identify common contamination points in the distribution chain and testing data that identify outbreak-associated strains in implicated foods or in environmental samples linked to the foods.

5.4.1 Analytic studies: characteristics, use, and limitations. Epidemiologic studies to analyze the association between illness and exposures take different forms depending on the setting of the outbreak, number of cases reported, and public health resources available. In recent years, approaches to using these study methods have evolved that have resulted in fewer large community case–control studies. Instead, investigators now often use case-aggregation methods with comparisons to reference data or, for very specific product identification (e.g., brand names and lot numbers), direct intervention with no analytic study whatsoever.

- **Cohort study.** Cohort studies are limited to outbreaks with defined exposure settings in which exposed persons can be identified without respect to illness status, e.g,, a banquet with a defined guest list.

5.4 Test Hypotheses

Interviewing persons without respect to their illness status enables determination of attack rates to assess the magnitude of the outbreak and calculation of relative risks for individual exposures. Because many of these settings involve a defined menu and guest list, developing an online survey to rapidly collect illness and exposure information might be possible.

- **Establishment-specific case–control study.** In defined setting outbreaks where it is more feasible to identify individual cases than groups of exposed persons, conduct an establishment-specific case–control study (similar to a subcluster study).
- **Community case–control study.** Community case–control studies are a staple of outbreak investigations. Comparing food exposures among case-patients in an outbreak with food exposures among healthy controls has great power to identify foods associated with the illnesses. For example, in a nationwide outbreak of Salmonella associated with commercially distributed ice cream, the source was identified based on interviews of 15 case-patients and 15 community controls (3). Although results of the case–control study implicated an exposure source within 3 days after initiating the case–control study, regulatory testing to confirm the source of contamination required an additional 10 days.
    - Having a stringent case definition is important to reduce the likelihood of including unrelated cases in the study. Because unrelated cases would not share the same exposure source, they would reduce the apparent odds ratio, and make it difficult to implicate the exposure source. WGS subtyping enables stringent case definitions. Along with specific case definitions, having detailed exposure source information is critical.

    Despite their empirical usefulness, large community-based case–control studies are no longer routinely conducted in outbreak investigations. Recruiting suitable controls because of the changing demographics of telephone use is increasingly difficult. Thus, they have become too expensive to conduct and can be too slow to produce actionable results.
- **Case–case comparison studies.** Case–case comparison studies provide many of the same benefits as community case–control studies but are logistically easier to conduct. Molecular subtype–specific surveillance based on PFGE or WGS makes it possible to compare cases caused by an outbreak-associated strain with cases caused by unrelated strains. Because cases caused by unrelated strains have many different sources of exposure, they make an efficient control group. When persons with sporadic cases are routinely interviewed with detailed food-exposure questionnaires, case–case comparison studies can be conducted. For example, in the 2011 outbreak of listeriosis identified by the Colorado Department of Public Health and Environment, cantaloupe was implicated by comparing exposures from reported outbreak-associated case-patients to aggregated exposures of nationally reported cases collected by CDC's *Listeria* Initiative (4).
    - Case–case comparisons produce the same measures of association as case–control studies and are interpreted the same way. The increased stringency of WGS to discriminate outbreak-associated from unrelated cases makes case–case comparisons a desirable alternative to case–control studies when aggregate case exposure data are available.
- **Case series with binomial exposure assessments.** The use of case series with binomial exposure assessments was pioneered by the late Bill Keene at the Oregon Health Authority, who also

5.4 Test Hypotheses

developed a simple binomial calculator to test the significance of differences between case and population exposure proportions. Like the other analytic study methods, it requires that outbreak-associated case-patients to be systematically interviewed using a detailed exposure questionnaire. However, instead of comparing case exposure histories with community controls or unrelated cases, the case exposures are compared with an expected value based on population survey data. FoodNet's Atlas of Exposures (*5*) has been the most commonly used source of population exposure data. However, changing food consumption patterns limit the usefulness of 2006 Atlas data for some exposures. A survey to collect updated population exposure data was conducted in December 2017 through July 2019. Identifying current, local population exposure data is preferred. The Oregon Health Authority is compiling multistate sporadic *Salmonella* case exposure data known as Project Hg, for case–case binomial comparisons (*6*).

- The binomial comparison functions as advanced hypothesis generation. It identifies associations that must be confirmed by product source tracing and corroborated by other investigation findings. Statistically, binomial comparisons emulate very large case–control studies. Results must be cautiously interpreted to avoid spuriously significant results that could lead to errors in identifying the source of an outbreak.

For all analytical studies the significance of results depends on the strength of the association and the size of the study. Thus, studies with large numbers of cases are more likely than studies with few cases to yield statistically significant results. However, the goal of outbreak investigations is to rapidly identify the source to prevent additional cases. In this regard, WGS will improve the efficiency of these studies by providing precise case definitions. Increasing the specificity of food exposures will similarly increase the efficiency of the study. However, with WGS, the expected increase in small cluster investigations limits the usefulness of any of these study designs to produce "significant" results. For clusters involving fewer than five cases, product source tracing and corroborating evidence are needed to confirm the source.

5.4.2 Product tracing. Tracing the source of food items or ingredients through distribution to source of production can be critical to identifying epidemiologic links among cases or ruling them out. For nonbranded commodities, such as produce items, the identification of a common point in multiple distribution pathways that provided a suspected product to case-patients may identify the point where the food(s) became contaminated (Figure 5.3). An onsite environmental assessment of this point (farm, ingredient supplier, processor, restaurant) can then be conducted to identify the contributing factors and environmental antecedents that caused the outbreak. Once the source is identified, tracing products forward through distribution can help identify additional cases or help remove contaminated product from the marketplace. Product tracing is an important tool to inform the epidemiologic investigation, test the hypothesis, and control the outbreak.

Two types of product tracing tools can be used to investigate outbreaks. **Traceback** investigations are used to trace a product suspected to cause the outbreak through the supply chain to determine whether it converges on a common source or supplier. Once a common source or supplier of the contaminated product is identified, **traceforward** investigations are used to determine other locations that received the contaminated product. Both traceback and traceforward activities can be conducted

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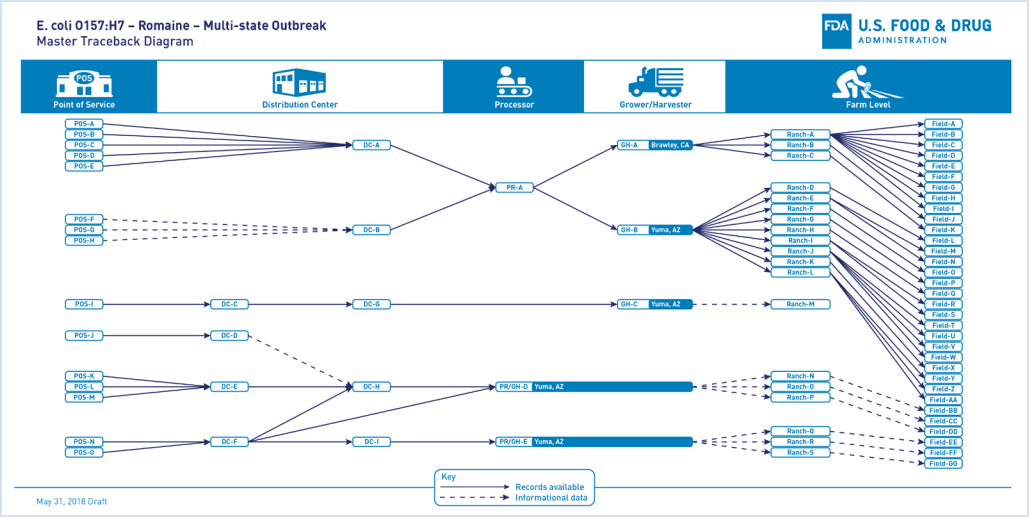
Figure 5.3. Exposure Distribution Pathways Documented During Informational Traceback of Romaine Lettuce during an *Escherichia coli* O157:H7 Outbreak.

Romaine lettuce from multiple growers in the Yuma, Arizona, growing region were implicated as the source of the outbreak. The lack of association with a single grower ultimately reflected the use of contaminated surface water by multiple growers (7).



as informational or regulatory endeavors. Informational product tracing needs to be conducted quickly to be incorporated into the epidemiologic studies. Formal regulatory product tracing may be subsequently needed to confirm the distribution of implicated products.

Traceback Investigations. Traceback investigations begin at the point of service where a case-patient was exposed to the product. Informational, traceback investigations are conducted to help inform the epidemiologic investigation and can be the final step in confirming the outbreak vehicle (http://mnfoodsafetycoe.umn.edu/wp-content/uploads/2015/10/Product-Tracing-in-Epidemiologic-Investigations.pdf).

- If two or more case-patients report the same point of service, specific information must be collected from this subcluster so a traceback investigation can be initiated.
  - Ideal subclusters contain case-patients who can provide the following information: precise illness onset dates, exposure dates to the product of interest, and relative certainty about what foods they ate before illness onset.
  - Traceback of individual cases can provide important information to corroborate subcluster data.
- As informational tracebacks progress and a single product of interest is identified, regulatory traceback can be performed if necessary to assist in confirming the vehicle. These regulatory tracebacks enable detailed record collection and documentation of the product of interest through the supply chain.
- Once an informational traceback is initiated, specific information is necessary from the case-patients within the subcluster and from the point of sale. As the traceback continues, establishment types will change and questions about the handling of the product of interest, time frames, and available record need to be amended accordingly.

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Information collected from each subcluster serves as one leg of the overall traceback investigation. Distribution chains from multiple traceback legs are documented and compared to identify commonalities. Convergence of multiple legs of a traceback on a specific facility assists in targeting resources for environmental assessments, inspections, and/or sampling. In addition, information from the traceback is continuously evaluated as part of the evidence for the overall outbreak investigation; convergence reinforces the hypothesis generated by the epidemiologic investigation.

Informational traceback investigations continue until the product of interest is followed as far back through the supply chain as possible. Interpretation of the traceback can be challenging and should not be done without consideration of the epidemiologic, laboratory, and environmental information collected during the investigation. If no convergence on a single supplier is identified, reevaluate the hypothesis. Informational tracebacks are challenging and can be limited by a case-patient's ability to accurately remember his or her food history, poor record-keeping, lack of common product identifiers through the supply chain, co-mingling, and many other factors. Therefore, lack of convergence of a traceback does not necessarily rule out a vehicle as the source of the outbreak.

Important information for initiation of informational tracebacks:

- **Subcluster information**
  - Exposure dates to product at point of sale (including location name and address).
  - Identification of specific menu items or purchases.
  - Documentation of purchase of product (e.g., credit card, shopper card).
- **Point-of-sale information**
  - List of ingredients in menu items or purchases of interest.
  - Time frame of interest for distribution record collection (determined by considering case-patient exposure dates, product shelf life, shipment frequency, and other pertinent factors).
  - Identity of all suppliers of the product of interest to the point of sale.
  - Frequency the product of interest is ordered by the point of sale.
  - Product handling and inventory management in the facility (example: First in First Out).
  - Point of sale handling of shipments and documentation of receipt of the product of interest.
  - Storage and transportation practices, potential cross contamination; products with common source materials.
  - Distribution records (e.g., invoices, order forms, bills-of-lading) for the time frame of interest that are available at the point of service/sale. Note gaps in or concerns about record keeping.

Traceforward investigations. Tracing products forward in the supply chain can determine where contaminated products were distributed and enable their removal from the supply chain (Chapter 6). Traceforward investigations also are an important tool to identify additional case-patients who were exposed to contaminated products. In the hypothesis-testing phase of an outbreak investigation, tracing a suspected product forward can identify additional points of sale that received the suspected product. Enhanced surveillance efforts in areas where suspected products were distributed can be an effective way of identifying new clinical cases. Linking points of sale of suspected products with

5.4 Test Hypotheses

additional clinical cases provides additional evidence about the outbreak source.

Communication of product tracing information. Product tracing is always multijurisdictional and requires strong collaboration between public health and regulatory agencies. Predetermined lines of communication should be in place to effectively move information between the necessary parties. Updates on the epidemiologic investigation being conducted by the public health agency may greatly impact the traceback being conducted by the regulatory agency and vice versa.

Special considerations need to be given to distribution information collected by regulatory agencies because it may be protected from disclosure by confidentiality agreements. Investigational partners should have agreements in place to allow for the lawful exchange of the information (Chapters 3 and 7).

5.4.2 Environmental assessments. When a food-production, food-processing, or food-service establishment is identified as being associated with a foodborne illness outbreak, environmental health and/or regulatory officials should conduct an environmental assessment. To stop the current outbreak and prevent future ones, investigators must identify both how (contributing factors) and why (environmental antecedents/root causes) the food became contaminated so effective controls can be put in place (Table 5.2).

Goals of an environmental assessment:

- **Identify contributing factors**
  - Factors that introduce or otherwise permit contamination and relate to how the agent got onto or into the food vehicle.
  - Factors that enable proliferation or growth of the agent and relate to how the bacterial agent could increase in numbers and/or produce toxins before the vehicle was ingested.
  - Factors that enable survival or fail to inactivate the contaminants and refer to processes or steps that should have eliminated or reduced the microbial agent.
- **Identify environmental antecedents (root causes) that enabled the system failure**
  - Assessing the internal system components (e.g., people, equipment, processes, foods, and economics) and their effect on allowing the system failure to occur

Table 5.2. Differences between Routine Inspections and Environmental Assessments

ROUTINE INSPECTION	COMMENT
• Nontargeted • Regularly scheduled • Snapshot of current day • Code/regulation-based • Assessment of current conditions • Identification of violations	• Targeted • Response to an outbreak • Focus on the past • Outbreak information-based • Examination of processes and problems during outbreak • Identification of system failures • Identification of underlying factors that enable the system failure

An environmental assessment is a systematic, detailed, science-based evaluation of environmental factors that contributed to the introduction and/or transmission of agents that cause an illness in an outbreak. Environmental assessments are conducted in response to an outbreak and address specific food and process(es) to identify the outbreak's cause. The environmental assessment is guided by epidemiologic and laboratory information and examines how the causative agent, host factors, and environmental conditions interacted to result in the system failure and people becoming ill.

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- Identifying and address root causes of outbreaks that appear to be part of a pattern.

Five main steps in conducting an environmental assessment:

- **Plan and prepare:** Members of the outbreak investigation team review epidemiologic information, product tracing information, laboratory results, and food facility information. Roles and responsibilities, intended outcomes, sampling plans, and ways the team will communicate during the site visit should be determined at this step.
- **Visit the site:** Observe the facility, and evaluate its practices. Collect records and samples pertinent to the investigation. Information that can be collected as part of the visit includes
  - How food moves through the establishment (physical flow diagram).
  - How food is processed and handled within the establishment (process flow diagram).
  - Policy and procedures in place at the establishments and interviews with responsible parties about the execution of policies and procedures.
  - Ill employee records.
  - Sales records for the suspected food item.
  - Employee interviews.
  - Product coding and distribution information if food is suspected to have arrived at the facility contaminated.
- **Assess information:** Review information to identify the outbreak's contributing factors and environmental antecedents.
- **Recommend prevention and control strategies:** Control strategies reflect steps that should be taken immediately to stop the outbreak and prevent further spread of the agent. Longer term strategies reduce the likelihood of future outbreaks at this type of establishment (Chapter 6).
- **Complete the report:** Prepare a summary of the findings that includes detailed diagrams, descriptions, and results. Incorporate this report into the outbreak investigation report.

The timing of an environmental assessment depends largely on the specifics of the outbreak and available information but should be initiated as soon as possible (ideally an initial site visit within 24–48 hours after identification of the establishment). Early investigation and collection of food and environmental specimens will best reflect the conditions at the time of the outbreak. In addition, possible food vehicles can be discarded or grow old, and persons involved in the production, processing, storage, transportation, or preparation of the item can change their practices and procedures. If investigators have identified a common location and a profile of symptoms among ill persons that indicates whether the illness agent is likely to be viral, bacterial, toxic, or chemical, they often can begin an environmental assessment based on possible factors more likely to be associated with that illness-causing agent. As more information becomes available, investigators may need to make additional trips to the establishment to investigate the additional lines of inquiry.

Communication of environmental assessment findings is vital. Share results of the environmental assessments with the outbreak investigation team as soon as possible. This information may change the course of the investigation or confirm the suspected food item causing the outbreak. Sharing findings with industry partners on the contributing factors and environmental antecedents that led to contamination is key to improving hazard identification and implementing control measures (*8*).

5.4.4 Laboratory testing of food products and environments. Targeted sampling of food items and environments of interest in the outbreak investigation can help confirm the

5.4 Test Hypotheses

food causing illness. Targeted sampling occurs when partners working on the epidemiologic and traceback investigations share information about products and establishments of interest. Coordinate with the testing laboratory and consider sampling products and storing appropriately for potential future testing to reduce the chance the product of interest will be unavailable for sampling later.

- Sampling products of interest early in the epidemiologic investigation can help quickly bring an investigation together, especially if the products of interest are shelf stable. In 2017, state and local authorities sampled soy nut butter reported by case-patients associated with an outbreak of *E. coli* O157:H7 (*9*). The positive samples generated by that early sampling was used as evidence to suspend the registration of the facility manufacturing the product. Not all product sampling occurs at the outset of an investigation. Traceback investigations can identify locations along the supply chain to collect samples.
- Food and environmental sampling enables investigators to directly test hypotheses generated during an investigation, often picking up where analytic studies leave off. By gathering information about items of interest (such as food items or ingredients commonly consumed at a restaurant in question; animals to which case-patients were exposed before illness; or other less common environmental exposures, such as contaminated milk crates), investigators can target very specific items or areas to sample for microbiologic testing. When combined with the case series with binomial exposure assessments, such testing can quickly hone a list of suspected products to a single source.
- Sampling also can be used to illuminate the root cause of product contamination, especially when done in partnership with the grower or product manufacturer. Pathogens such as *Salmonella* and *L. monocytogenes* are known to persist in manufacturing and processing environments. Identification of a pathogen in a processing environment that was linked by epidemiologic and traceback information to clinical cases supports confirmation of the outbreak vehicle.
- WGS is being used to perform molecular subtyping on pathogens recovered from foods and environments impacting foods. The high resolution of WGS increases confidence in the relatedness of pathogens from products and environments to clinical samples. Food or environmental samples that are closely related by WGS can launch retrospective outbreak investigations, in which laboratory evidence from the products or environments drives the epidemiologic investigation. Retrospective outbreak investigations often lead to the swift identification of the outbreak source.

5.4.5 Coordination of epidemiologic, traceback, and sampling activities. Whether the outbreak is restricted to one jurisdiction or involves multiple jurisdictions, notification and updates should be provided to other interested agencies following the Special Considerations for Multijurisdictional Investigations (Chapter 7).

- Arrange for the outbreak investigation and control team to meet daily and to regularly update the entire outbreak control team. In particular, if the outbreak has gained public attention, the public information officer needs to prepare a daily update for the media.
- During investigation of outbreaks involving events or establishments, maintaining close collaboration between epidemiology and environmental health is particularly important. Interview results from persons who attended the event or patronized the establishment will help environmental health specialists focus their environmental assessments by identifying likely agents and food vehicles. Similarly, results of

5.4 Test Hypotheses

interviews of food workers and reviews of food preparation can identify important differences in exposure potential that should be distinguished in interviews of persons attending the event or patronizing the establishment. For example, environmental health investigators might determine that food items prepared only on certain days or by certain food workers are likely to be risky. These refinements also can help establish the need for or advisability of collecting fecal samples from food workers or food and environmental samples from the establishment.

- During the earliest stages of the investigation, patrons need to be interviewed rapidly. However, the focus of outbreak activities is likely to shift to interviews of food workers, environmental assessments of the establishment, and review of food-preparation procedures as the investigation progresses.
- During investigation of outbreaks detected by pathogen-specific surveillance, the public health laboratory needs to immediately forward case information to epidemiologists for every new potentially outbreak-associated case they receive. Doing so ensures rapid enrollment of new cases in the outbreak investigation studies. Similarly, as investigators acquire information from case-patients about exposures in restaurants and other licensed facilities, they should rapidly forward that information to environmental health specialists to ensure rapid identification of commodity ingredients and their distribution sources.
- During the early stages of an investigation, efforts to identify mode of transmission and food vehicle require close coordination of the outbreak team under the leadership of epidemiology. After identification of a likely food vehicle, efforts to identify the source of contamination and contributing factors require engagement of local, state, or federal food-regulatory programs. As the investigation proceeds, the outbreak investigation and control team should always consider whether any information indicates the outbreak might be multijurisdictional (Chapter 7).

5.5 Evaluate Evidence to Solve Point of Contamination and Source of the Food

5.5.1 Evaluate evidence. Identifying the source of contamination and taking action to prevent additional illnesses requires effective and timely integration of three types of data:

- Epidemiologic data that describe illness distributions and enable analysis of common exposures.
- Traceback and environmental assessment data that identify common contamination points in the distribution chain.
- Testing data that identify outbreak-associated strains in implicated foods or in environmental samples linked to the foods.

Evidence from each of these pillars of the outbreak investigation is evaluated in concert to determine whether the data support the conclusion that a suspected food or other exposure caused the outbreak. Investigators typically determine that they have identified the likely source of the outbreak when they have clear and convincing evidence from two pillars. In rare instances, data from one pillar alone might be sufficient to determine the likely source of an outbreak (e.g., complaints or point source clusters linked to a meal or single event). In investigations of products with a short shelf life (e.g., unpasteurized milk or leafy greens), conducting testing on products

5.5 Evaluate Evidence to Solve Point of Contamination and Source of the Food

during the likely period of contamination might be impossible and investigators must rely on evidence from the other pillars to determine the likely source of the outbreak.

5.5.2 Solve point of contamination and source of the food. The outbreak investigator's job is to use all available information to construct a coherent narrative

Box 5.1. Questions to Consider When Associating an Exposure with an Outbreak

Strength of association

- How strong was the association between illness and the implicated item? (The strength of the association increases with the size of the odds ratio or relative risk: 1 = no association; <5 = relatively weak association; 5–10 = relatively strong association; >10 = very strong association.)
- Was the finding statistically significant? (<0.05 is a traditional cutoff p value, but in small studies, even relatively strong associations might not reach this level of significance. Conversely, in large studies examining many exposures, relatively weak associations might reach this level of significance by chance or as an effect of confounding.)
- Were most ill persons exposed to the implicated item? "Yes" is desirable but might not always be apparent if the implicated item is an ingredient in multiple food items.)

Timing

- Did the exposure to the implicated item precede illness by enough time for a reasonable incubation period?
- Do the time windows obtained during traceback and traceforward investigations correlate with reported dates of production, distribution, and purchase of the implicated item?

Dose–response effects

- If assessed, were persons with greater exposure to the implicated item more likely to become ill or have more severe clinical manifestations?

Plausibility

- Is the association consistent with historical experience with this or similar pathogens? Can investigators develop a rational explanation for opportunities for contamination, survival, and proliferation of the pathogen in the implicated item? (If otherwise strong and consistent results cannot be readily explained, the outbreak might herald emergence of a new hazard, which will require additional studies to confirm.)
- Is the geographic location of ill persons consistent with the distribution of the implicated item? (Discrepancies might be explained by gaps in surveillance, product distribution data, or involvement of additional food products.)

Consistency with other studies

- Studies associated with current investigation
  - Do the results of traceback and traceforward investigations suggest a common source?
  - Have environmental health assessments identified problems in the production, transport, storage, or preparation of the implicated item that would enable contamination, survival, and proliferation of the pathogen in that item?
  - If the pathogen was isolated from ill persons and from the implicated item, do subtyping results (e.g., WGS analysis) confirm the association?
- Studies not associated with current investigation
  - Is the association between the pathogen and the implicated item consistent with other investigations of this pathogen?

5.5 Evaluate Evidence to Solve Point of Contamination and Source of the Food

of what happened and why. This begins with the initial detection of the outbreak and formation of hypotheses based on the agent's ecology, microbiology, and mechanisms of transmission in addition to the descriptive epidemiology of reported cases. Results of subsequent analytic studies (e.g., cohort or case–control study results) must be integrated with results of product tracing, food worker interviews, environmental assessments, and food-product and environmental testing. When all of these data elements support and explain the primary hypothesis, investigations can draw very strong conclusions (Box 5.1).

Outbreak investigators should be open to new developments and new twists to old problems. New hazards are frequently identified through outbreak investigations. However, they should be wary of explanations that depend on implausible scenarios.

5.6 Implement Control Measures, Investigation Closeout, and Reporting

5.6.1 Deciding an outbreak is over (Chapter 6). Outbreaks end when cases are no longer detected or reported. Outbreak investigations can continue after the outbreak ends, given product tracing and observations on practices at suspected firms may take longer to obtain. In addition, control measures need to be evaluated if the source of the outbreak was identified. For outbreaks where the source has not been identified, consideration to the prioritization of resources and expected outcome of the investigation should be considered before continuing investigational activities. Experience reminds us—again and again, unfortunately—that even seemingly well-executed investigations can be inconclusive. Small sample sizes, multivehicle situations, "stealth" food items that may not be recognized, and foods with high background rates of consumption are only some of the factors that can reduce the effectiveness of standard epidemiologic methods and make investigations extremely difficult.

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