Investigation of Multistate Foodborne Disease Outbreaks

Jeremy Sobel, MD, MPH[a]
Patricia M. Griffin, MD[a]
Laurence Slutsker, MD, MPH[b]
David L. Swerdlow, MD[c]
Robert V. Tauxe, MD, MPH[a]

SYNOPSIS

The U.S. food supply is characterized increasingly by centralized production and wide distribution of products, and more foodborne disease outbreaks are dispersed over broad geographic areas. Such outbreaks may present as a gradual, diffuse, and initially unapparent increase in sporadic cases. Recognition and reporting by clinicians and local public health officials and the ordering of laboratory tests by clinicians continue to be cornerstones of detecting all outbreaks. New methods—such as active laboratory-based surveillance, automated algorithms for detecting increases in infection rates, and molecular subtyping—facilitate detection of diffuse outbreaks. Routines have evolved for the investigation of multistate outbreaks; they are characterized by rapid communication between local, state, and federal public health officials; timely review of epidemiologic data by expert panels; collaboration on tracebacks with food safety regulatory agencies; and communication with the public and media. Rapid, efficient investigation of multistate outbreaks may result in control of acute public health emergencies, identification and correction of hazardous food production and processing practices, and consequent improvement in food safety.

[a]Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA

[b]Epidemiology Branch, Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA

[c]Surveillance Branch, Division of HIV/AIDS Prevention, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA

Address correspondence to: Jeremy Sobel, MD, MPH, Foodborne and Diarrheal Diseases Branch, Division of Bacterial and Mycotic Diseases, MS-A38, National Center for Infectious Diseases, CDC, 1600 Clifton Rd., Atlanta, GA 30329; e-mail <jsobel@cdc.gov>.

BACKGROUND

Purpose of this article

The nature of foodborne outbreaks has changed in the past decade because of changes in food consumption, production, and distribution patterns, and improved safety in commercial food preparation. At the same time, surveillance and foodborne disease outbreak detection are being improved by new technologies.[1–3] As a result, recognition of diffuse outbreaks spanning several states has become common. This article describes the approach to the investigation of multistate bacterial foodborne disease outbreaks used by the Foodborne and Diarrheal Diseases Branch of the Centers for Disease Control and Prevention (CDC). For brevity, it will be referred to as the CDC approach. The complexity of foodborne disease outbreaks precludes prescription of activities in predetermined sequence; thus, not all steps described in this article are relevant to all outbreaks. In each case, investigators must adapt their approach to circumstances at hand.

Goals and phases of foodborne disease outbreak investigation

Despite changes in the food supply, and consequently in the nature of foodborne disease outbreaks, the objectives and overall structure of foodborne outbreak investigation remain unchanged (Figure 1).[4]

The immediate objective is to identify the contaminated food that is causing disease, remove it from the market, and prevent further consumption and illness. In other words, to "remove the pump handle," as John Snow did during the great cholera outbreak of 1854 in London.[5] Careful investigation can help limit economic loss by targeting for recall only those lots and brands of a product that are likely to contain the pathogen. Such actions also provide reassurance to the public, an important outcome in highly publicized outbreaks.

A second objective is to identify the gap in manufacturing or handling that allowed contamination of the food so that preventive measures to render the food supply safer can be implemented, both in the immediate outbreak and industry-wide. Examples of recent long-term preventive measures propelled by outbreak investigations include pasteurization of commercial juices[6] and rigorous flock-based control programs, including microbiological surveillance of egg-producing poultry farms for *Salmonella enteritidis*.[7]

A third objective is to augment scientific understanding about agent, host, and environment. Most foodborne agents were discovered in the course of outbreak investigations, along with much of what we know about their reservoirs and specific routes of transmission. Outbreak investigations led to the recognition of *Escherichia coli* O157:H7 as a human pathogen, the description of the clinical spectrum of illness,[8] the establishment of an animal reservoir for this organism,[9,10] and its association with ground beef[11]—the latter resulting in the regulatory declaration of *E. coli* O157:H7 as an adulterant if found in raw ground beef, making it unfit for sale or use in commerce.

A new model for multistate outbreak coordination and management is evolving to accomplish the objectives of outbreak investigations in the face of the complexity of contemporary foodborne disease outbreaks and the multiplicity of parties and agencies involved. This model is characterized by flexibility and involvement of officials and researchers from various backgrounds at many different levels. The model uses centralized coordination, compatible epidemiologic and laboratory tools by different groups that permit data aggregation, standardized modes of communication, and rapid, formalized decision-making for public health action. Basing such public health action on strong and well-performed epidemiologic investigations in advance of laboratory confirmation of contamination is critical to rapid control.

Changing nature of the food supply

The U.S. food supply consists of many thousands of different foods, both domestically produced and imported, and it is characterized increasingly by centralized production and wide distribution. For example, in 1969 470,832 layer-hen farms with an average of 632 hens per farm produced 67 billion eggs per year. By 1992, the number of farms dropped by 85% to 70,623, the number of hens per farm increased by 470% to 2,985, and annual production rose to 70 billion eggs.[12] These changes may have influenced the incidence of *Salmonella enteritidis* in humans. Human infection, associated principally with the consumption of raw or undercooked eggs, rose dramatically between 1976 and 1986.[13] *S. enteritidis* colonizes the ovaries of the layer hen, where it can infect the contents of eggs before the shell is formed. After introduction of the pathogen into animal populations, it might have been disseminated more efficiently among fewer and larger layer-hen flocks. Another example is the cattle industry. At present, four firms slaughter 80% of feed cattle, half the number of two decades ago,[14] and the proportion of cattle slaughtered in plants categorized as large has increased from 32% in 1972 to 72% in 1992.[15] This concentration of production and the nature of processing methods result in the commingling of meat from many carcasses and, consequently, increased risk of cross-contamination.[15] Because large volumes of

Figure 1. Foodborne disease outbreak investigation and response: stages and overall objectives[a]

Stage and specific tasks	*Overall objectives*
Stage 1. Acute outbreak investigation	Prevent additional cases of illness by identifying and removing contaminated food from circulation.
• Identify pathogen. • Characterize outbreak: time, place, person. • Identify source of food vehicle. • Implement acute control measures.	• Identify food vehicle.
Stage 2. Traceback	
• Identify contamination event and/or practices/ circumstances that allowed contamination event. • "Trace-forward"—determine where contaminated food was sent.	• Prevent further contamination of implicated product.
Stage 3. Long-term prevention	
• Determine frequency of contamination event. • Resolve scientific questions related to outbreak (e.g., biologic plausibility of proposed mode of contamination or transmission). • Identify production/processing/handling changes needed to prevent future occurrences. • Identify methods of instituting required changes (education, regulation). • Implement changes. • Monitor and evaluate effect of changes on food safety.	• Refine understanding of food production process. • Identify and answer unresolved scientific questions about foodborne disease. • Develop long-term prevention programs.

[a]This table encompasses the activities of epidemiologists, food safety regulators, and basic scientists.

ground beef are funneled through a limited number of processing facilities, the introduction of *E. coli* O157:H7 can lead to large volumes of potentially contaminated meat. Centralization also means that introduction of safer meat processing procedures in a relatively small number of plants could have widespread benefits.

The potential for widely distributed processed foods to cause diffuse, widespread outbreaks is illustrated by recent outbreaks traced to widely distributed commercial products such as breakfast cereals, unpasteurized fruit juices, and ice cream. In these instances, breakdowns in safety resulted in intermittent, low-level microbial contamination of products.[6,16–20] Increasing consumption of fresh fruits and vegetables has also been accompanied by a growing number of outbreaks due to contamination of fresh produce from distant national or international sources.[21] Consequently, foodborne disease outbreaks in the past decade have occurred over large, dispersed geographic areas, a situation that may delay recognition of the outbreak and complicate identification of the contaminated food.[1–3] In 1999, the CDC's Foodborne and Diarrheal Diseases Branch participated in the investigation of 18 outbreaks that affected three or more states simultaneously.

Improved surveillance for outbreaks

The classic local "church supper" outbreak, the stuff of epidemiologic and even popular lore,[22,23] has been joined by the diffuse multistate outbreak. Similarly, the traditional means of outbreak detection—depending on calls from affected citizens, notification by astute clinicians and laboratorians, and review of passive surveillance data—have been augmented by new epidemiologic and laboratory techniques. These new surveillance tools have been grafted onto the passive laboratory-based reporting system and, as such, depend on identification of pathogens from clinical samples. The effectiveness of traditional and new surveillance schemes therefore depends on the willingness and ability of clinicians to order stool cultures on patients. One new tool is the *Salmonella* outbreak detection algorithm, which detects increases in *Salmonella* serotypes reported by state health departments to the CDC via the electronic Public Health Laboratory Information System. The Public Health Laboratory Information System is a

pc-based reporting system of electronic entry, analysis, and transmission of reportable disease cases from state public health laboratories.[24] The *Salmonella* outbreak detection algorithm is a computerized algorithm that compares the current weekly count of each *Salmonella* serotype with summary historical data for that serotype by state and region;[25] increases are reported to state epidemiologists. This system has assisted the detection of large, diffuse multistate outbreaks caused by various *Salmonella* serotypes.[26,27]

A second new tool is PulseNet, the national molecular subtyping network for foodborne disease surveillance. PulseNet is a network of public health laboratories that conduct routine molecular subtyping of a panel of foodborne pathogens using highly standardized, uniform protocols. All state health department laboratories participate, as well as laboratories at the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture (USDA) and Food and Drug Administration (FDA). A pulsed-field gel electrophoresis (PFGE) pattern of bacterial DNA, or "genetic fingerprint," is determined for human pathogens obtained from clinical specimens and food products. These patterns can be transmitted electronically for comparison with patterns of isolates in other laboratories in the network and with a national electronic database of patterns obtained from isolates in the past. Frequently PFGE subtyping demonstrates that geographically dispersed isolates, thought to be sporadic, have identical PFGE patterns and are therefore related and possibly originate from a common source. When a cluster of "matching" isolates is identified by public health laboratories, the investigators can target investigations to those cases, looking for the unsuspected common links. This has resulted in the detection and investigation of outbreaks that otherwise would not have been detected,[28] an approach that has proven highly cost-effective.[29]

Hence, diffuse outbreaks spread over several states are not only likely to be more common, but also to be more readily detected. In fact, more and more illnesses initially thought to be "sporadic" (defined as those not related to outbreaks) are being linked to diffuse outbreaks.

Finally, FoodNet—a collaborative undertaking by the CDC, FSIS, FDA, and selected state health departments—is the foodborne disease component of the CDC's Emerging Infections Program. FoodNet was established to determine the burden of foodborne illness using population-based active surveillance and related studies. In 1999, eight FoodNet sites (four metropolitan areas and four states with a total population of 33 million) conducted population-based active surveillance for laboratory-diagnosed cases of seven enteric bacterial and two parasitic infections, and one clinical syndrome—the hemolytic uremic syndrome. Active surveillance within FoodNet sites may enhance outbreak detection in those populations.[30–32]

Agencies involved in foodborne disease outbreak investigations

The principal agencies involved in the detection and epidemiologic investigation of foodborne disease outbreaks include local and state health departments, public health laboratories at the local and state level, the Council of State and Territorial Epidemiologists, the Association of Public Health Laboratories, and the CDC. Agencies that have regulatory authority over foods and may participate in food-specific aspects of outbreak investigation, especially those related to the traceback of suspected foods, include state departments of agriculture or food safety divisions and the federal food safety regulatory agencies, principally FDA and the FSIS. In the case of international outbreaks, foreign governments and international organizations may also play a role.

Individual food producers or processors involved in an outbreak, as well as their trade groups, can be approached for collaboration in outbreak investigations. Academic food microbiology laboratories and hygiene consultants contracted by the food industry are also important partners in devising and implementing improvements in food safety suggested by outbreak investigations.

Optimizing the response to multistate foodborne disease outbreaks is being addressed at the national level. An interagency Foodborne Outbreak Response Coordinating Group has been formed, consisting of Department under secretary and agency director-level officials from the USDA, the Department of Health and Human Services, the FDA, and the Environmental Protection Agency, as well as representatives from organizations representing state and local public health associations. This group is charged with improving the approach to multistate outbreaks by reviewing and evaluating responses by federal agencies, developing standard operating procedures, assessing available resources, and developing procedures for improved interagency coordination.[33]

EXAMPLES OF MULTISTATE OUTBREAK INVESTIGATIONS

A multistate foodborne disease outbreak may present in one of two basic forms: one or more local outbreaks that in fact herald a single larger event, or a diffuse

increase in sporadic cases apparently unrelated to each other that is detected through national surveillance.

The first scenario is likely to be detected and investigated by local or state public health officials. The possibility that it heralds a wider event means that other states and the CDC should be notified to help determine if the outbreak is affecting other areas; the investigative approach may be one of local or state leadership with state or CDC support. In the second scenario, a state health department or the CDC will most likely coordinate a single investigation using uniform methodology in multiple states.

Certain features should prompt investigators to suspect and report an outbreak that may cross jurisdictional lines. These include knowledge that a suspected food vehicle is marketed or consumed beyond the jurisdiction of the agency investigating the outbreak or that persons have contracted the same infection in another jurisdiction or country, the identification of a new or rare pathogen, the involvement of a tourist facility, the occurrence of many cases, a new or unusual food vehicle, or high media interest. In these cases, notification means an alert soon after first learning about the outbreak, such as an e-mail, listserve posting, telephone call, or fax, rather than "reporting" in the traditional sense of a conventional surveillance report.

Example: Multistate outbreak of *E. coli* O157:H7 from commercial unpasteurized apple juice[6]

In October 1996, a state department of health identified 16 *E. coli* O157:H7 infections during one week, including three cases of the hemolytic uremic syndrome, a known complication of infection with *E. coli* O157:H7. The CDC was informed on October 29. On October 30, a case-control study conducted by the county health department implicated a specific brand of unpasteurized apple juice; the FDA provided the CDC with a list of four states and two Canadian provinces to which the apple juice was shipped, all but one of which the CDC was able to inform immediately by telephone. Three additional states that received the apple juice were not on the list and were therefore not notified at that time. Shortly before midnight the same evening, a conference call was held with the FDA Commissioner, state public health officials, and the CDC, with the Foodborne and Diarrheal Diseases Branch staff participating. The juice manufacturer had already issued a press notice. CDC epidemiologists were asked to make a recommendation to the FDA based on the strength of the evidence generated by the county health department study. CDC epidemiologists examined the raw data while the conference call was in process and found that they justified vigorous action to ensure complete removal of the product from the market. The FDA issued a press release on October 31. Also on October 31, the CDC recommended to the company that other products produced on the same line as the implicated apple juice be recalled (the company agreed). The CDC arranged for an epidemiologist from the state department of health to accompany FDA inspectors to the plant that produced the implicated juice. The CDC also sent a communication to all 50 states informing them of the outbreak, and produced a standardized questionnaire for interviewing patients. On the following day, November 1, a conference call with all states involved in the outbreak was conducted to agree on case definitions, establish case count methodologies, define contacts and plan communications, and plan coordinated dissemination of information to the press. By the following day, CDC epidemiologists produced draft case definitions, a line listing of patients and exposures, questionnaires, and a list of contacts in each state. This information was updated regularly as the investigation proceeded.

Ultimately investigators identified 70 cases in three states and in British Columbia. More than half of the infected persons were 5 years of age or younger, 14 developed the hemolytic uremic syndrome, and one died. On November 7, FDA isolated *E. coli* O157:H7 from an unopened container of the implicated juice produced on October 7. The juice isolate had a PFGE pattern indistinguishable from that of isolates from patients. Almost all infected persons had consumed apple juice produced on this date. Traceback of the apples used in juice production suggested that any one of three lots of apples could have contaminated the juice. Two lots originated from orchards frequented by deer, which can carry *E. coli* O157:H7,[34] and a third lot was said to have contained decayed apples.

The findings of this investigation and others resulted in an FDA regulation requiring a warning label to be placed on most unpasteurized apple juice, and a second proposed regulation that would mandate the application of Hazard Analysis and Critical Control Point (HACCP) practices to fruit and vegetable juice processing.[6,35]

In this example, the outbreak was detected and investigated by a county health department, whose data prompted a nationwide recall of the product by the company. The FDA requested the CDC to review the data immediately and advise the FDA on the strength of the epidemiologic association. This resulted in public health action by the regulatory agency many days before laboratory identification of the pathogen in the implicated juice.

Because the outbreak involved a product shipped widely, CDC moved rapidly to coordinate a multistate outbreak investigation by alerting all states to the outbreak, standardizing investigational instruments, and setting up systems to receive case reports and disseminate updates of case counts and exposures. Notification of public health officials in all 50 states was important because the distribution of the juice was still uncertain, the juice was known to be sold in airports, and uninvolved states also needed to be able to respond to public and press inquiries. Additionally, the CDC assisted state health departments and the FDA in traceback investigation. Later, the CDC participated in the discussion and public meetings with industry, consumer groups, and regulatory agencies. These discussions led to the adoption of FDA regulations aimed at reducing the risk of infection from unpasteurized fruit juices. It must be emphasized that the timely, coordinated multistate response would not have been possible without the initial identification of the outbreak and its immediate and effective investigation by local and state health authorities.[36]

When diffuse increases in apparently sporadic cases are detected through surveillance data, the key to rapid identification of the etiologic agent, vehicle of transmission, and manner of contamination is a uniform method of generating comparable epidemiologic data from multiple sites. This can be accomplished by a uniform study using agreed-upon data collection instruments directed and coordinated at the national level.

Some features of this approach are listed in Figure 2, although not all outbreak investigations will necessarily use each feature.

This approach can draw on the expertise of many experienced investigators for study design, can yield results more rapidly than would small independent studies in various states, and will have the statistical power of a large sample size. In most outbreaks investigated in this manner, study designs and methods are agreed upon by consensus.

Outbreak investigations may identify vehicles that may cause an ongoing risk to the public health should they remain on the market. In this case, decisions about the need for a recall must be made before all the data have been gathered and analyzed. To decide when sufficient data have been accumulated to take action, it is sometimes helpful to present the data to an ad hoc group of state epidemiologists who were not involved in the investigation, particularly if the decisions or data are controversial. This objective review can lend weight to conclusions about the source of the outbreak or to encourage voluntary recalls by industry.

As in multistate outbreaks in which studies are conducted independently by local or state health officials, an important feature of the centrally coordinated outbreak investigation is frequent, regular feedback to states of case counts, isolate subtyping information, and completion rates of interviews. Regulatory agencies may be limited by law and protocol from sharing all traceback findings. Some of this information is also shared with states not affected by the outbreak, as their health officials may use it for public education, enhanced surveillance, and response to public and press inquiries.

Example: Multistate outbreak of *Salmonella* serotype Agona associated with toasted oats cereal

On May 28, 1998, the state of Pennsylvania reported nine cases of *Salmonella* Agona infection; two weeks earlier, the state of Illinois had reported 23 cases. This represented an increase above historical baselines in both states. The CDC contacted neighboring states by telephone, and 10 were found to have an increased number of cases compared with baseline. On Friday, May 29, at the request of the Illinois State Department of Public Health, a three-person CDC field team departed to assist the investigation in Illinois. At the same time, an outbreak-response team formed at CDC, consisting of an overall supervising medical epidemiologist and an investigation coordinator data manager.

Figure 2. Features of a single, centrally coordinated, multistate foodborne disease outbreak investigation

- Input of experienced investigators from states and CDC into design
- Logistic support from CDC (faxes, conference calls, database creation, data entry)
- Rapid administration of telephone questionnaires by the state and CDC staff
- Comparable data, rapid analysis
- Statistical power of single study with large population
- Validity for all areas in study
- Efficient presentation and interpretation of results to regulatory agencies
- Follow-up by state health departments and the CDC with regulatory agencies and industry for long-term action

CDC = Centers for Disease Control and Prevention

Support was provided by CDC epidemiologic and administrative staff, statisticians, and media relations personnel.

Also on May 29, the CDC notified all state and territorial epidemiologists of the outbreak, and a conference call was held with the states involved in the outbreak and FSIS and FDA personnel. Patient interviews in several states conducted to generate hypotheses indicated consumption of toasted oats cereal purchased from a specific supermarket chain as a possible vehicle. The following day, a second conference call was convened to discuss study methodology. By consensus, a case-control study was designed, and a standard questionnaire was developed and administered by investigators in state health departments and at the CDC. On June 3, the study implicated a specific brand of toasted oats cereal purchased at a particular supermarket chain. The FDA liaison stationed at the CDC called the supermarket chain for distribution data; upon learning of the outbreak, the chain voluntarily withdrew the cereal from its shelves immediately. On June 4, a panel of senior epidemiologists of several disciplines from the CDC and Council of State and Territorial Epidemiologists who were not part of the outbreak investigation team considered the evidence and concluded that the data supported the association between food product and illness. At a conference call the same day with states and regulatory authorities, a decision was made to inform the public by means of a press release. Also, on June 4 the manufacturer was advised, and the company responded by immediately recalling all brands of the product made on the same production line. An environmental investigation of the plant by FSIS identified a postheating processing step as an uncontrolled processing step. Fifty-three patients still had the food product in their homes, and lot numbers corresponded to production on a single line during a four-day period. On June 7, *Salmonella* Agona was isolated from an open package of the product, and it was subsequently isolated from the manufacturing facility's floor, production line, and exhaust system; the production line was permanently dismantled. The investigation identified 215 laboratory-confirmed illnesses and one death.[16]

This outbreak was identified by reports of increases in a specific serotype of *Salmonella* in two states. Neither state had identified a suspected vehicle, and there was no evidence that a widely distributed product was contaminated. The sequence described above illustrates the value of routine reporting of possible outbreaks due to undetermined vehicles to federal health authorities. A state CDC field team collaborated to generate hypotheses, whereas the CDC coordinated the simultaneous multistate investigation by directing communications between states, producing standardized questionnaires, receiving and analyzing the uniform data, and providing feedback and updates. FDA, state authorities, and the CDC worked on the traceback, using data on the implicated product line to guide the in-plant investigation.

COORDINATION AND COMMUNICATION IN A MULTISTATE OUTBREAK

The National Food Safety System's Outbreak Coordination Workgroup has prepared a document entitled "Multistate Foodborne Outbreak Investigations: Guidelines for Improving Coordination and Communication" (available at: http://www.fda.gov/ora/fed_state/NFSS/Default.htm). This is a standard reference on interagency collaboration in multistate outbreak investigations, including traceback activities and the various state and federal food regulatory agencies. The workgroup is comprised of representatives from federal, state, and local environmental, health, agricultural, and regulatory agencies, including experts in epidemiology, laboratory, and environmental aspects of investigations. In this article we limit ourselves to presenting comments on principles and practices of selected aspects of multistate outbreak investigations. As noted previously, no two outbreaks are completely alike, and investigators adapt the general protocol to circumstances, altering, omitting or adding steps.[37]

How the CDC communicates with state health departments

As soon as possible, that is, early in Stage 1 of the investigation (Figure 1), a conference call including all states involved in an investigation and the CDC is arranged. During the early stages of the investigation, as case finding is conducted, hypotheses are generated, and study instruments developed; the group holds frequent conference calls, usually at least twice weekly. As the routines of the investigation become better defined, a weekly conference call of all parties may suffice, while issues related to events in one or a few states can be discussed in smaller calls or by e-mail. Depending on the agenda, regulatory agency representatives may be invited to participate early on. Inclusion of regulatory agency representatives at this point allows these officials to respond to public inquiries and optimally prepare to respond should a specific food vehicle be identified.

Further regular communication with federal and state partners in the investigation can be maintained through additional conference calls; the Foodborne

Diseases Listserve (an electronic communications board); the *Morbidity and Mortality Weekly Report*, a widely read weekly CDC publication; and the CDC website. In the future, a dedicated web page may serve as a tool for updating information on ongoing outbreaks. A secure site could serve as a forum for communication between the states, regulatory agencies, and the CDC, whereas an unencrypted area could be used to update the public and media.

Communication between the CDC and federal food safety regulatory agencies

The interaction between the CDC and federal food safety regulatory agencies may occur principally in Stage 2 of the outbreak investigation (Figure 1), but notification of the outbreak should take place as early as possible in Stage 1 when foodborne transmission is suspected. Many foodborne pathogens can also be transmitted via other routes; early in an outbreak investigation, it may not be apparent that the source is foodborne at all. Once a likely food hypothesis emerges, it is important to notify the relevant regulatory agency. To this end, the FDA and USDA station personnel at the CDC to serve as liaisons with these agencies; additionally, the CDC has liaisons at the FDA's Center for Food Safety and Applied Nutrition and at the USDA's Food Safety Inspection Service. Through these liaisons, the food safety regulatory agencies are alerted when outbreaks occur that may be related to a product under their jurisdiction. A joint investigation may follow once a food has been implicated.

Communication with the press and public

The press is an important resource in multistate foodborne outbreak investigations. Through the press, potential cases can be identified and the public can be informed about the outbreak and, when necessary, protective measures it can adopt. This aspect of communication should be addressed throughout all stages of the investigation, especially the initial ones (Figure 1). Two principles guide interactions with the media. First, all press inquiries about outbreaks go through the Office of Communications, Division of Media Relations. Inquiries are best handled by these professionals, who are accustomed to answering inquiries and developing messages for this medium. Some inquiries are referred by this office to a designated CDC epidemiologist or to the appropriate regulatory agency. Second, the many investigators in a multistate outbreak must articulate a consistent interpretation of the same data; otherwise, the accuracy of the seemingly conflicting messages and the adequacy of the response will be justly questioned.

One useful approach is to establish, at the outset of an investigation, a regular schedule to provide media updates, with a frequency proportional to the urgency of the investigation. This establishes public health agencies' availability and openness, and makes the communications process orderly. Special attention should be devoted in advance to coordinating information updates for the press between the media relations offices of government agencies to ensure message consistency and advance awareness of their content by all investigators.

Communications with industry

Clear communication of the objectives of the outbreak investigation and an understanding of industries' concerns may facilitate collaboration in the acute outbreak setting and provide opportunities for long-term positive impact on food safety. In the long run, collaboration between investigators and industry can result in the identification and correction of systematic errors of food production or processing, improving food safety and public confidence. Working with regulatory agencies, investigators should update implicated companies about the number of cases, deaths, and states involved, as appropriate. In past outbreaks, sharing of information has helped the company arrive at a decision to recall the product as soon as, or even before, conclusive epidemiologic data implicating the product were available, potentially preventing illnesses.[6,16]

An epidemiologic association is much more difficult to understand than a laboratory finding of contamination in a product; therefore, explaining epidemiologic methods to industry is often necessary. If industry representatives wish to engage in extensive discussions of methodology or data interpretation, they should be encouraged to consult reputable academic or private sector epidemiologists.

Contact with a company can be most effective by interacting with the appropriate level of management, preferably with a person responsible for overseeing quality control. Working with executives authorized to make speedy decisions without lengthy consultations may facilitate quick access to information needed for the investigation and prompt action in response to investigation findings.

Public health investigators should be aware that companies may be in possession of "libraries" of product samples, foods returned by consumers who became ill, and quality-control and environmental testing samples. A written request from a government agency early in the investigation to preserve such materials for subsequent laboratory analysis should be

issued whenever relevant. Such a request may prevent these product samples from being discarded.

Investigators and regulators should discuss their findings with the affected company at the earliest appropriate time. The general results of an investigation may have important implications for the entire industry. When industry-wide issues are raised, the outcome of the investigation can promote the search for long-term control measures. Discussing them with both industry and regulatory agencies is an important long-term goal.

COMMENTS ON SELECTED ASPECTS OF MULTISTATE OUTBREAK INVESTIGATIONS

Traceback investigation

A traceback investigation is often an integral part of the epidemiologic investigation. The traceback tracks the food vehicle implicated by epidemiologic studies or laboratory tests to its origin to determine its source. At the source, the epidemiologic data, combined with the results of an environmental investigation, can lead to an understanding of where contamination is likely to have occurred—at the caterer, factory, or farm, for example. Information gathered in the course of a traceback investigation includes the volume of food produced and the area in which it was distributed; for multi-ingredient foods, other foods that might contain the contaminated ingredient; the stage of growth, production, or transportation at which contamination may have occurred; and the specific practice or circumstance that allowed contamination. These findings are relevant both to controlling the acute outbreak, and to identifying and ultimately changing farming, production, or transport processes that allowed food contamination.[38,39]

Tracebacks provide important information for the epidemiologic investigation. Epidemiologists who conducted the study of human cases of illness should participate with regulatory agencies in traceback investigation activities to relate epidemiologic and laboratory data to production dates, distribution patterns, environmental investigation results, and manufacturing process deficiencies.

Using epidemiologic data generated in outbreak investigation to take preventive action

In some outbreak investigations, cases may still be occurring at the time a food is implicated, and public health action to end the outbreak is needed. This may be issuing a press release warning the public to avoid consuming a specific food, issuing a product recall, or shutting down a production facility. Strong epidemiologic data implicating a contaminated food vehicle can be the basis for rapid, targeted, and carefully applied control measures to prevent illness and death even without laboratory confirmation. Recall of the unpasteurized apple juice in the above example preceded isolation of *E. coli* O157:H7 from the juice by weeks. The pathogen responsible for an outbreak may never be isolated from the implicated food, for several reasons: (*a*) bacteria that are difficult to identify may not be detected, and many viruses and parasites simply cannot be detected in food using available methods; (*b*) pathogens may have been reduced or eliminated from food samples by freezing, temperature abuse, or overgrowth by other microorganisms; and (*c*) in many outbreaks, samples of implicated foods no longer exist.

The precise weight of evidence sufficient to trigger public health action requires judgment in each case. In the balance is the risk of not acting and allowing additional illnesses to occur while gathering more data versus acting precipitously; identifying the wrong food and thereby leaving the public exposed to the actually contaminated food vehicle; and losing public confidence and causing financial losses to industry.

Follow-up after control of the acute outbreak

Once an outbreak has been controlled, the epidemiologic investigation shifts to addressing underlying causes of contamination, such as manufacturing process defects, environmental change, and microbial adaptation. An important objective at this stage is to understand the event that allowed food contamination so that it may be prevented throughout the industry (Figure 1). The approach often includes post-intervention monitoring and basic science studies to establish the plausibility of growth or survival of specific pathogens in specific food vehicles. Ideally, follow-up studies with industry, regulators, and academic researchers may further characterize gaps and breakdowns, and find appropriate preventive measures. Hazard Analysis and Critical Control Point (HACCP) assessment is a process and pathogen control approach to food safety that seeks to identify points of risk for contamination of food products and systematically control these risks. HACCP has been adopted as a central aspect of food safety assurance by both the FDA and FSIS, and it is gaining wide acceptance in the food industry in general.[15] Epidemiologic data are useful in the identification of critical points where safety failures occurred. A foodborne outbreak may instigate additional research to determine how to control a hazard. An outbreak should lead to the revalidation of a company's HACCP plan, as well as an industry evalu-

ation of control measures for appropriate hazard control.

For example, after the 1995 investigation of a large multistate outbreak of *Salmonella* serotype Stanley infections associated with consumption of alfalfa sprouts,[26] research initiated by the investigating epidemiologists, in collaboration with university food safety scientists and the sprouting industry, explored the nature of *Salmonella* contamination of sprout seeds, the effects of the various stages of the commercial sprouting process on microbial growth, and effectiveness of disinfection methods.[38] The FDA established a consortium of industry, government, and academic research, and produced guidance for the sprout industry. These efforts, however, established that at present no specific intervention can render sprouts completely safe. Similarly, collaboration between epidemiologists who investigated the first outbreak of *E. coli* O157:H7 infections from apple cider, the FDA, and other researchers demonstrated the plausibility of this association;[40,41] this and subsequent investigations contributed to changes in microbiological safety standards and in labeling requirements for unpasteurized juices.[6] Similarly, following an investigation of a multistate outbreak of *Shigella sonnei* infections traced to parsley imported from Mexico,[42] the Mexican Ministry of Agriculture implemented a distance-learning course on farm safety for 5,000 produce farmers (Personal communication, J. Guzewich; 2001).

CHALLENGES FOR THE FUTURE: MULTISTATE OUTBREAK INVESTIGATION AS AN EVOLVING ART FORM

As surveillance methods improve, we can expect to find more dispersed outbreaks and be able to link together simultaneous outbreaks occurring in multiple jurisdictions. One challenge will be to manage a more rapid flow of information about outbreaks so that such multistate events can be identified and investigated.

A standard methodology for assessing the impact of outbreak investigations has yet to be developed. Impact evaluations in the past have often centered on estimating the number of illnesses prevented by a food recall action. Recalls may not prevent all subsequent infections from the implicated vehicle—recalls may be incomplete, the public may not be aware of the consequences of consuming the implicated product, or the pathogen may spread from one person to another.[43] Often, several outbreaks due to the same food type must be identified and investigated before regulatory agencies and industry are ready to discuss long-term changes in production methods. The greatest public health impact may result from follow-up studies and regulatory changes that induce systematic changes in food production and processing.

Finally, the process of investigating multistate outbreaks will be facilitated by having available "on-the-shelf" standardized instruments that can be adapted with minimal effort to specific outbreaks. These instruments, currently being developed, include draft case definitions, clinical and environmental microbiological sampling protocols, and general and pathogen-specific and food vehicle-specific questionnaires. Such instruments, however, may need to be adapted to specific outbreak situations, optimally with the generation of hypotheses through open-ended interviews with a small number of patients.

The detection and response to multistate foodborne outbreaks are increasingly rapid and efficient. Established protocols of communication, standardized investigational instruments, electronic data transfer, rapid formal review of data by uninvolved experts, and coordinated effort by public health and regulatory agencies while engaging industry are facilitating this work. Although complex, these outbreak investigations are yielding data that are being used to render the food supply safer.

The authors wish to thank LeeAnne Jackson, PhD, of the U.S. Food and Drug Administration and Noreen Hynes, MD, of the Food Safety and Inspection Service for their review of the manuscript and helpful comments.

REFERENCES

1. Swerdlow D, Altekruse SF. Food-borne diseases in the global village: what's on the plate for the 21st century. In: WM Scheld, WA Craig, JM Hughes, editors. Emerging infections 2. Washington: ASM Press; 1998.
2. Hedberg CW, MacDonald KL, Osterholm MT. Changing epidemiology of food-borne disease: a Minnesota perspective. Clin Infect Dis 1994;18:671-82.
3. Tauxe RV. New approaches to surveillance and control of emerging foodborne infectious diseases. Emerg Infect Dis 1998;4:455-6.
4. Goodman RA, Gregg MB, Gunn RA, Sacks JJ. Operational aspects of epidemiologic investigations. In: Gregg MA, editor. Field epidemiology. New York: Oxford University Press; 1996.
5. Snow J. On the mode of communication of cholera. In: Frost WH, editor. Snow on cholera. New York: The Commonwealth Fund; 1936.
6. Cody SH, Glynn MK, Farrar JA, Cairns KL, Griffin PM, Kobayashi J, et al. An outbreak of *Escherichia coli* O157:H7 infection from unpasteurized commercial apple juice. Ann Intern Med 1999;130:202-9.
7. Hogue A, White P, Guard-Petter J, Schlosser W, Gast R,

Ebel E, et al. Epidemiology and control of egg-associated *Salmonella enteritidis* in the United States of America. Rev Sci Technol 1997;16:542-53.
8. Griffin PM, Ostroff SM, Tauxe RV, Greene KD, Wells JG, Lewis JH et al. Illnesses associated with *Escherichia coli* O157:H7 infections: a broad clinical spectrum. Ann Intern Med 1988;109:705-12.
9. Martin ML, Shipman LD, Wells JG, Potter ME, Hedberg K, Wachsmuth IK, et al. Isolation of *Escherichia coli* O157:H7 from dairy cattle associated with two cases of haemolytic uraemic syndrome [letter]. Lancet 1986; ii:1043.
10. Ostroff SM, Griffin PM, Tauxe RV, Shipman LD, Greene KD, Wells JG, et al. A statewide outbreak of *Escherichia coli* O157:H7 infections in Washington State. Am J Epidemiol 1990;132:239-47.
11. Riley LW, Remis RS, Helgerson SD, McGee HB, Wells JG, Davis BR, et al. Hemorrhagic colitis associated with a rare *Escherichia coli* serotype. N Engl J Med 1983;308:681-5.
12. Department of Agriculture, Animal and Plant Health Inspection Service (US). Current trends and uncertainties for the future of agriculture. Available from: URL: http://www.aphis.usda.gov/vs/ceah/cei/market.htm
13. St. Louis ME, Morse DL, Potter ME, DeMelfi TM, Guzewich JJ, Tauxe RV, et al. The emergence of grade A eggs as a major source of *Salmonella enteritidis* infections: new implications for the control of salmonellosis. JAMA 1988;259:2103-7.
14. Department of Agriculture (US), Economic Research Service. Consolidation in U.S. meatpacking. Agricultural Economic Report No. 785 (AER-785). 2000 Feb.
15. MacDonald JM, Ollinger ME, Nelson KE, Handy CR. Structural change in meat industries: implications for food safety regulation. Am J Agr Econ 1996;78:780-5.
16. Multistate outbreak of *Salmonella* serotype Agona infections linked to toasted oats cereal—United States, April–May, 1998. MMWR Morb Mortal Wkly Rep 1998;47: 462-4.
17. Cook KA, Dobbs TE, Hlady WG, Wells JG, Barrett TJ, Puhr ND, et al. Outbreak of *Salmonella* serotype Hartford infections associated with unpasteurized orange juice. JAMA 1998;280:1504-9.
18. Hennessy TW, Hedberg CW, Slutsker L, White KE, Besser-Wiek JM, Moen ME, et al. A national outbreak of *Salmonella enteritidis* infections from ice cream. N Engl J Med 1996;334:1281-6.
19. Ryan CA, Nickels MK, Hargrett-Bean NT, Potter ME, Endo T, Mayer L, et al. Massive outbreak of antimicrobial-resistant salmonellosis traced to pasteurized milk. JAMA 1987;258:3269-74.
20. Outbreak of *Salmonella* serotype Muenchen infections associated with unpasteurized orange juice—United States and Canada, June 1999. MMWR Morb Mortal Wkly Rep 1999;48:582-5.
21. Tauxe R, Kruse H, Hedberg C, Potter M, Madden J, Wachsmuth K. Microbial hazards and emerging issues associated with produce. A preliminary report to the national advisory committee on microbiologic criteria for food. J Food Prot 1997;60:1400-3.
22. Gross M. Oswego county revisited. Public Health Rep 1976;91:168-70.
23. Roueche B. Eleven blue men. New York: Berkley Medallion Books; 1968.
24. Bean MH, Martin SM, Bradford H. PHLIS: an electronic system for reporting public health data from remote sites. Am J Public Health 1992;82:1273-6.
25. Hutwagner LC, Maloney EK, Bean NH, Slutsker L, Martin SM. Using laboratory-based surveillance data for prevention: an algorithm for detecting *Salmonella* outbreaks. Emerg Infect Dis 1997;3:395-400.
26. Mahon B, Ponka A, Hall W, Komatsu K, Dietrich SE, Siitonen A, et al. An international outbreak of *Salmonella* infections caused by alfalfa sprouts grown from contaminated seeds. J Infect Dis 1997;175:876-82.
27. Sivapalasingam S, Kimura A, Ying M, Frisch A, et al. A multistate outbreak of *Salmonella* Newport infections linked to mango consumption, November–December 1999. Latebreaker Abstract. 49th Annual Epidemic Intelligence Service (EIS) Conference, Centers for Disease Control and Prevention. Atlanta, GA. Schedule Addendum, Latebreaker Abstracts; 2000.
28. Swaminathan B, Barrett TJ, CDC PulseNet Task Force. A national molecular subtyping network for food-borne bacterial disease surveillance in the United States. In: Nachamkin I, Blaser MJ, editors. Campylobacter. Washington, DC: American Society for Microbiology; 2000.
29. Elbasha EH, Fitzsimmons TD, Meltzer MI. Costs and benefits of a subtype-specific surveillance system for identifying *Escherichia coli* O157:H7 outbreaks. Emerg Infect Dis 2000;6:293-7.
30. Preliminary data on the incidence of foodborne illnesses—selected sites, United States, 1999. MMWR Morb Mortal Wkly Rep 2000;49:201-5.
31. Yang S. FoodNet and Enter-net: emerging surveillance programs for foodborne diseases. Emerg Infect Dis 1998;4:457-8.
32. Stephenson J. New approaches for detecting and curtailing foodborne microbial infections. JAMA 1997;277: 1339-40.
33. FDA/CFSAN. Foodborne Outbreak Response Coordinating Group Memorandum of Understanding among United States Department of Agriculture and United States Department of Health and Human Services and Environmental Protection Agency. May, 1998. Available from: URL: http://www.foodsafety.gov/~dms/forcgmou.html
34. Sargeant JM, Hafer DJ, Gillepsie JR, Oberst RD, Flood SJA. Prevalence of *Escherichia coli* O157:H7 in white-tailed deer sharing rangeland with cattle. J Am Vet Med Assoc 1999;215:792-4.
35. Outbreak of *Escherichia coli* O157:H7 infections associated with drinking unpasteurized commercial apple juice—British Columbia, California, Colorado, and Washington, October 1996. MMWR Morb Mortal Wkly Rep 1996;45;975.

36. *Escherichia coli* O111:H8 outbreak among teenage campers—Texas, 1999. MMWR Morb Mortal Wkly Rep 2000;49:321-4.
37. Centers for Disease Control and Prevention. Update: leptospirosis and unexplained acute febrile illness among athletes participating in triathlons—Illinois and Wisconsin, 1998. JAMA 1998;280:1474-5.
38. Toarmina PJ, Beuchat LR, Slutsker L. Infections associated with eating seed sprouts: an international concern. Emerg Infect Dis 1999;5:626-34.
39. Villar RG, Macek MD, Simons S, Hayes PS, Goldoft MJ, Lewis JH, et al. Investigation of multidrug-resistant *Salmonella* serotype *typhimurium* DT104 infections linked to raw-milk cheese in Washington state. JAMA 1999;281: 1811-6.
40. Besser RE, Lett SM, Weber JT, Doyle MP, Barrett T, Wells JG, Griffin PM. An outbreak of diarrhea and hemolytic uremic syndrome from *Escherichia coli* O157:H7 in fresh-pressed apple cider. JAMA 1993;269: 2217-20.
41. Zhao T, Doyle MP, Besser RE. Fate of enterohemorrhagic *Escherichia coli* O157:H7 in apple cider with and without preservatives. Appl Environ Microbiol 1993;59:2526-30.
42. Outbreaks of *Shigella sonnei* infection associated with eating fresh parsley—United States and Canada, July–August 1998. MMWR Morb Mortal Wkly Rep 1999;48: 285-9.
43. Mahon BE, Slutsker L, Hutwagner L, Drenzek C, Maloney K, Toomey K, Griffin PM. Consequences in Georgia of a nationwide outbreak of *Salmonella* infections: what you don't know might hurt you. Am J Public Health 1999;89:31-5.