Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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CHAPTER

Case Detection, Outbreak Detection, and Outbreak Characterization

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1. INTRODUCTION

In Chapter 2, we saw how some well-known outbreaks first came to the attention of investigators and how the investigators proceeded to elucidate the causative biological agent, source, route of transmission, and other characteristics of the outbreaks. In this chapter, we examine in detail how biosurveillance systems detect and characterize outbreaks. We introduce an important distinction between case detection and outbreak detection. We discuss *outbreak characterization,* which is the process by which investigators elucidate characteristics of an outbreak that are important for disease control (e.g., causative biological agent, source, and route of transmission). We break down and analyze biosurveillance in this manner so that it can be modeled more formally, which is a prerequisite to providing computer support. Table 3.1 summarizes the topics of this chapter and links them to examples in Chapter 2 and additional examples introduced in this chapter (marked by bold type). The table serves as both an outline and a summary of the chapter.

2. CASE DETECTION

The objective of *case detection* is to notice the existence of a single individual with a disease. We say that this individual is a *case* of the disease. The importance of case detection is that detection of an outbreak typically depends on detection of individual cases (Figure 3.1).

Many entities are involved in case detection. People (e.g., physicians, veterinarians, nurse practitioners, infection control practitioners, medical examiners, and pathologists) and laboratories detect cases. Biosurveillance organizations detect cases through surveillance systems and screening programs. Increasingly, computers detect cases.

Some methods of case detection use *case definitions,* a written statement of findings both necessary and sufficient to classify a sick individual as having a disease or syndrome (Figure 3.2). More commonly, however, the determination of whether an individual has a disease (or syndrome) is left to the expert judgment of a clinician.

2.1. Case Detection by Clinicians

Case detection by clinicians (physician, veterinarian, nurse practitioner, pathologist) is a by-product of routine medical and veterinary care. It works as follows: A sick individual seeks medical attention or is brought to a clinician, who establishes a diagnosis. If the diagnosis is considered a notifiable disease[1], the clinician reports it (for more information on notifiable diseases, see Chapter 5). If the sick individual is a person, the clinician reports the case to a state or local health department. If the sick individual is an animal, the clinician reports the case to a state department of agriculture (see Chapter 7). This mechanism of case detection played a role in the detection of every outbreak described in Chapter 2, with the exception of cryptosporidiosis.

A clinician establishes a diagnosis by collecting and interpreting diagnostic data, including symptoms, physical observations (e.g., rash or temperature), risk factors for disease (e.g., travel to a foreign country), pre-existing diseases in the individual (e.g., diabetes), results of microbiological tests, radiographic examinations, and autopsy findings. The interpretation of diagnostic data is a complex cognitive activity. The clinician first generates a *differential diagnosis,* which is a list of diseases that the patient could have given the information the clinician has thus far. The clinician then resolves the differential

1 A notifiable disease is a diagnosed condition for which a health statute requires reporting by physicians and laboratories. Health departments decide to make diseases notifiable based on their potential as threats to a community. We discuss notifiable diseases in Chapter 5.

TABLE 3.1 Methods for Detection of Cases, Clusters, Outbreaks, and Methods for Characterization of Outbreaks

Process	Method	Examples
Case detection	Diagnosis by clinician*	SARS, mad cow disease, anthrax, **meningitis, measles**
	Laboratory-based detection	Hepatitis A, **foodborne illness,** influenza
	Sentinel clinician	Influenza, **ILI**
	Drop-in surveillance	**Syndromes**
	Screening	SARS, **meningococcal meningitis**
	Computer detects case	**Hospital acquired illness, syndromes, pneumonia, tuberculosis, foodborne illness, laboratory notifiable diseases**
Outbreak detection	From individual case of unusual disease	Foot and mouth disease, **measles**
	Astute observer notices cluster†	Lyme disease, hepatitis A, AIDS, foot and mouth disease, cryptosporidiosis, SARS, Legionnaire's disease, **foodborne illness**
	Biosurveillance staff notices cluster	**Hospital-acquired illness**
	Computer notices cluster	**Influenza, ILI and other syndromes, listeriosis**
Outbreak characterization		
Biologic agent	Analysis of case data to narrow differential diagnosis, microbiological testing	Legionnaire's disease, AIDS, mad cow disease, Lyme disease and Nipah virus, **foodborne illness**
Disease	Clinical profile, case definition, incubation and infectious periods, attack rate, case mortality	Legionnaire's disease, SARS, Lyme disease, AIDS, Nipah virus, **anthrax 2001**
Source and route of transmission	Spatial analysis	Anthrax,‡ **cholera**
	Cohort or case-control study	Hepatitis A
	Trial of control method (e.g., vector control)	Nipah virus
	Food chain investigation	Hepatitis A
	Vector investigation	Lyme, **West Nile virus, encephalitis, monkeypox**
	Environmental investigation	Legionnaire's disease, **foodborne illness, anthrax 2001**
Number ill, number at risk, spatial distribution	Screening, contact tracing	All
	Spatial and temporal analysis	All
	Mathematical modeling	None

The examples are outbreaks discussed in Chapter 2 and additional examples that we discuss in this chapter (in bold type). SARS indicates severe acute respiratory syndrome; ILI, influenza-like illness.
*Includes physicians, nurse practitioners, veterinarians, and pathologists.
†Astute observer includes clinicians and lay observers.
‡The spatial analysis of the Sverdlovsk outbreak included a meteorological analysis.

diagnosis by ruling in (confirming) or ruling out (excluding) these diseases by further questioning, observation, and testing. The clinician draws on a large set of facts (medical knowledge) about the effects of disease on people or animals to generate and resolve a differential diagnosis. Clinicians acquire this knowledge during professional training and from textbooks of medicine (human or veterinary) and medical journals. The clinician also draws on available information about local disease prevalence, which may come to her attention through health alerts, morbidity and mortality reports, informal collegial consultations, and hospital surveillance information. In Chapter 13, we discuss how researchers have modeled clinical diagnosis mathematically and implemented these models in diagnostic expert systems.

Coroners, medical examiners, hospital pathologists, and veterinarians use a similar reasoning process when performing postmortem examinations to establish the cause of death. We further discuss the role of coroners and medical examiners in biosurveillance in Chapter 11 and the role of veterinarians in biosurveillance in Chapter 7. Postmortem examinations played a role in the detection of mad cow disease and anthrax (1979).

The strength of case detection by clinicians is that sick individuals seek medical care. Furthermore, clinicians are expert at diagnosing illness, which is fundamental to case detection.

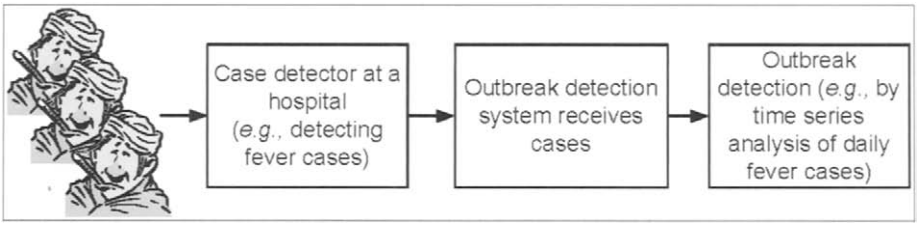


FIGURE 3.1 The relationship between case detection and outbreak detection. After the severe acute respiratory syndrome (SARS) 2003 outbreak, the Beijing center for disease prevention developed a biosurveillance system that comprised 61 "fever clinics" to which city residents were instructed to report if they developed fever (or were referred by emergency departments and physicians). Clinic staff entered the data from each clinic daily into a Web-based interface for central analysis. (Figure courtesy of Fu-Chiang Tsui.)

SARS-CoV disease classification

Probable case of SARS-CoV disease: in a person who meets the clinical criteria for severe respiratory illness and the epidemiologic criteria for likely exposure to SARS-CoV

Confirmed case of SARS-CoV disease: in a person who has a clinically compatible illness (i.e., early, mild-to-moderate, or severe) that is laboratory confirmed

FIGURE 3.2 Rules for classifying a patient as probable or confirmed severe acute respiratory syndrome (SARS). For expositional clarity, we split the Centers for Disease Control and Prevention (CDC) SARS case definition into two figures. Figure 3.3 contains definitions of the clinical, epidemiological, and laboratory criteria. The complete CDC SARS case definition is in Appendix C, which includes four additional rules for classifying patients as *SARS Reports under Investigation.* SARS-CoV refers to the coronavirus that causes the disease SARS. (From *http://www.cdc.gov/ncidod/sars/guidance/b/app1.htm.*)

Some limitations are that not every sick individual sees a clinician, clinicians may not correctly diagnose every individual they see, and clinicians may forget to report cases or fail to report cases in the time frame required by law (Ewert et al., 1994, 1995). Even when a clinician reports a case, the reporting occurs relatively late in the disease process. With some exceptions (e.g., suspected meningococcal meningitis, suspected measles, suspected anthrax) clinicians report cases only after they are certain about the diagnosis.

2.2. Case Detection by Laboratories

Case detection by laboratories is also a by-product of routine laboratory operation. Laboratories perform diagnostic tests. From the results of these tests, they often become aware of cases of notifiable diseases either before or at the same time as the clinician that ordered the test.

Laboratories play an increasing role in the detection of cases (including hepatitis A, cases of foodborne illness and influenza) as rapid, reliable, and specific laboratory tests are increasingly available. (Laboratories did not play a central role in the detection of outbreaks described in Chapter 2 because most of these outbreaks were caused by novel agents with no existing laboratory test.) The strength of laboratories as case detectors is that they are process oriented; therefore, they may report cases more reliably than can busy clinicians. A weakness is that there is not a definitive diagnostic test for every disease. A laboratory cannot detect a case unless a sick individual sees a clinician, who must suspect the disease and order a definitive test. Furthermore, not every individual for whom a test is ordered will comply and have the test done, and for some individuals with an illness, the test can be negative. Lag times for the completion of laboratory work can be substantial.

We further discuss the case detection role (and other roles) of laboratories in biosurveillance in Chapter 8.

2.3. Case Definitions

We next discuss several approaches to case detection that use case definitions. A case definition is a Boolean (logical) combination of patient findings, such as *the patient must have fever AND either cough OR pneumonia.* A case definition contains findings that are both necessary and sufficient for an investigator (or a clinician or research epidemiologist) to conclude that a patient has a disease.

Readers with backgrounds in public health should be quite familiar with case definitions.

Figure 3.2, for example, is the Centers for Disease Control and Prevention (CDC) case definition for both confirmed and probable cases of severe acute respiratory syndrome (SARS). Figure 3.3 contains definitions of the clinical, epidemiological, and laboratory criteria used in the case definitions. You can find additional examples of case definitions at Web sites operated by World Health Organization (WHO), CDC, and state and local departments of health (WHO, 2003; CDC, 2005).

2.4. Case Detection by Sentinel Clinicians

Health departments worldwide organize networks of sentinel clinicians to assist in monitoring influenza (Snacken et al., 1995, 1998; Fleming and Cohen, 1996; Zambon, 1998; Aymard et al., 1999; Manuguerra and Mosnier, 2000; Schoub et al., 2002). A sentinel clinician reports the number of individuals she sees per week who match a case definition for influenza-like illness (ILI). The California Department of Health Services provides school nurses with the following case definition for ILI: *fever (greater than 100.0°F) AND cough and/or sore throat.* The Global Influenza Surveillance Program of the Department of Defense uses a slightly different case definition: *fever (greater than 100.5°F) and either cough or sore throat or clinical radiographic evidence of acute nonbacterial pneumonia.* In some jurisdictions, the health department supplies the sentinel clinicians with rapid diagnostic tests for influenza, the results of which the clinicians also report.

The motivation for the sentinel clinician ILI system is earlier and more complete case finding of influenza to enable health departments to better control this common yet dangerous epidemic disease. Sentinel systems are not limited to influenza. The International Society of Travel Medicine and the CDC track diseases in patients who present to travel clinics (GeoSentinel, 2005).

2.5. Case Detection by Drop-In Surveillance

In the 1990s, the threat of bioterrorism led to the development of sentinel clinician–like capability for other diseases. This need

A. Clinical Criteria

Early illness: Presence of two or more of the following features: fever (might be subjective), chills, rigors, myalgia, headache, diarrhea, sore throat, rhinorrhea

Mild-to-moderate respiratory illness

Temperature of >100.4° F (>38° C) *and*

One or more clinical findings of lower respiratory illness (e.g., cough, shortness of breath, difficulty breathing)

Severe respiratory illness

Meets clinical criteria of mild-to-moderate respiratory illness, *and*

One or more of the following findings:

Radiographic evidence of pneumonia, *or*

Acute respiratory distress syndrome, *or*

Autopsy findings consistent with pneumonia or acute respiratory distress syndrome without an identifiable cause

B. Epidemiologic Criteria

Possible exposure to SARS-associated coronavirus (SARS-CoV)

One or more of the following exposures in the 10 days before onset of symptoms:

Travel to a foreign or domestic location with documented or suspected recent transmission of SARS-CoV *or*

Close contact with a person with mild-to-moderate or severe respiratory illness and with history of travel in the 10 days before onset of symptoms to a foreign or domestic location with documented or suspected recent transmission of SARS-CoV

Likely exposure to SARS-CoV

One or more of the following exposures in the 10 days before onset of symptoms:

Close contact with a confirmed case of SARS-CoV disease *or*

Close contact with a person with mild-moderate or severe respiratory illness for whom a chain of transmission can be linked to a confirmed case of SARS-CoV disease in the 10 days before onset of symptoms

C. Laboratory Criteria

Tests to detect SARS-CoV are being refined, and their performance characteristics assessed; therefore, criteria for laboratory diagnosis of SARS-CoV are changing. The following are the general criteria for laboratory confirmation of SARS-CoV:

Detection of serum antibody to SARS-CoV by a test validated by CDC (e.g., enzyme immunoassay [EIA]), *or*

Isolation in cell culture of SARS-CoV from a clinical specimen, *or*

Detection of SARS-CoV RNA by a reverse-transcription-polymerase chain reaction (RT-PCR) test validated by CDC and with subsequent confirmation in a reference laboratory (e.g., CDC)

Information regarding the current criteria for laboratory diagnosis of SARS-CoV is available at www.cdc.gov/ncidod/sars/labdiagnosis.htm.

FIGURE 3.3 Definitions of criteria used in severe acute respiratory syndrome (SARS) classification rules in Figure 3.2. (From *http://www.cdc.gov/ncidod/sars/guidance/b/app1.htm.*)

was most acute in cities that were hosting prominent events, such as the Olympic Games.

Drop-in surveillance refers to the practice of asking physicians in emergency departments to complete a form for each patient seen during the two- to six-week period surrounding a special event (County of Los Angeles, 2000; Arizona Department of Health Services, 2002; CDC, 2002b; Das et al., 2003; Moran and Talan, 2003). The clinicians record whether the patient meets the case definition for one or more syndromes of interest (Figure 3.4). Hospital staff, an epidemiologist, or an assistant then transcribes the data from the form into a database.

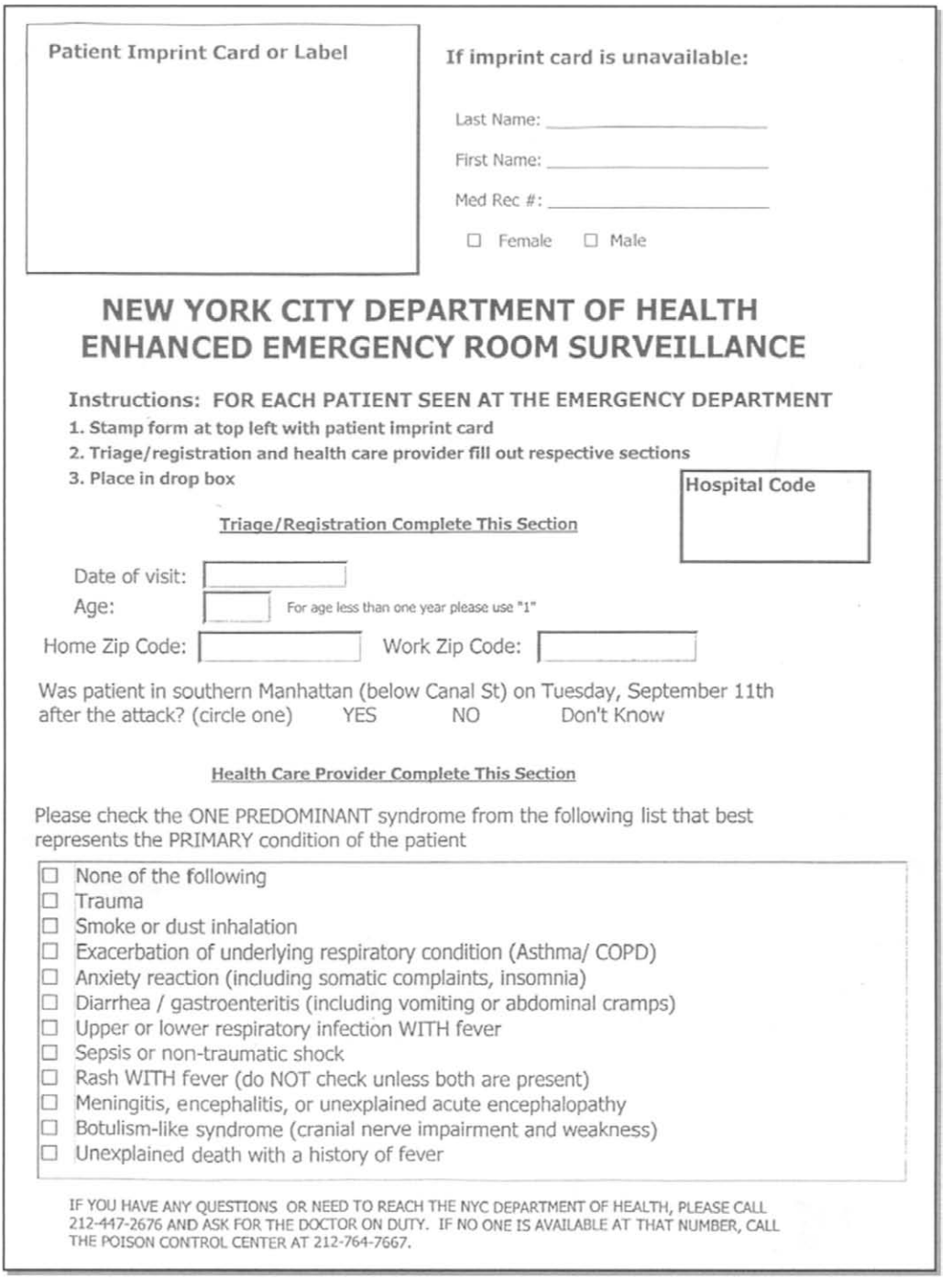
Sydney, Salt Lake City, and Athens used a surveillance variant during their Olympic Games that eliminated the need for physicians to fill out a form for each patient (Meehan et al., 1998; Dafni et al., 2004; Mundorff et al., 2004). Health department personnel visited each emergency department on a daily or more frequent basis and reviewed patient logs (and in some cases charts) to extract the required information.

The strength of drop-in surveillance (and sentinel clinician surveillance) is that it detects sick individuals on the day they first present for medical care; however, it is labor intensive.

Drop-in surveillance is a method of both case detection and outbreak detection. The drop-in surveillance team for the special event analyzes information from many emergency departments in the city on a daily basis for increased numbers of patients suggestive of an outbreak. Drop-in surveillance is initiated at least a week in advance of an event, if possible, so that a baseline rate of patients presenting with respiratory or diarrheal illness can be established.

2.6. Case Detection by Screening

Screening involves interviewing and testing people during a known outbreak to identify additional cases (or carriers of the disease). Screening is most often used for contagious diseases, for which it is important to find infected individuals to prevent further infections. A biosurveillance organization may use



Patient Imprint Card or Label

If imprint card is unavailable:

Last Name: _____

First Name: _____

Med Rec #: _____

☐ Female ☐ Male

NEW YORK CITY DEPARTMENT OF HEALTH
ENHANCED EMERGENCY ROOM SURVEILLANCE

Instructions: FOR EACH PATIENT SEEN AT THE EMERGENCY DEPARTMENT

1. Stamp form at top left with patient imprint card
2. Triage/registration and health care provider fill out respective sections
3. Place in drop box

Hospital Code

Triage/Registration Complete This Section

Date of visit: ____

Age: ____ For age less than one year please use "1"

Home Zip Code: ____ Work Zip Code: ____

Was patient in southern Manhattan (below Canal St) on Tuesday, September 11th after the attack? (circle one) YES NO Don't Know

Health Care Provider Complete This Section

Please check the ONE PREDOMINANT syndrome from the following list that best represents the PRIMARY condition of the patient

- ☐ None of the following
- ☐ Trauma
- ☐ Smoke or dust inhalation
- ☐ Exacerbation of underlying respiratory condition (Asthma/ COPD)
- ☐ Anxiety reaction (including somatic complaints, insomnia)
- ☐ Diarrhea / gastroenteritis (including vomiting or abdominal cramps)
- ☐ Upper or lower respiratory infection WITH fever
- ☐ Sepsis or non-traumatic shock
- ☐ Rash WITH fever (do NOT check unless both are present)
- ☐ Meningitis, encephalitis, or unexplained acute encephalopathy
- ☐ Botulism-like syndrome (cranial nerve impairment and weakness)
- ☐ Unexplained death with a history of fever

IF YOU HAVE ANY QUESTIONS OR NEED TO REACH THE NYC DEPARTMENT OF HEALTH, PLEASE CALL 212-447-2676 AND ASK FOR THE DOCTOR ON DUTY. IF NO ONE IS AVAILABLE AT THAT NUMBER, CALL THE POISON CONTROL CENTER AT 212-764-7667.

FIGURE 3.4 Drop-in surveillance form used in September and October 2001 in New York City. (From the New York City Department of Health and Mental Hygiene, New York, NY.)

screening in a focused manner (e.g., screening of all staff in a hospital), or it may deploy screening on a wide-scale basis. The scope of the screening effort depends on the nature of the outbreak. An outbreak of meningococcal disease in a hospital wing may require screening of only a few staff to find the person harboring the bacteria in their throat or nose. A disease such as SARS may warrant screening of tens of thousands of people.

During the SARS outbreak of 2003, many countries screened arriving and departing air travelers by using infrared thermal imaging devices in airports tuned to detect people with fevers (Figure 3.5). Similarly, hospitals and healthcare

FIGURE 3.5 Thermal screening device at the Chiang Kai-shek Airport, Taipei. Lighter shades of grey correspond to higher temperatures (From Wagner.)

facilities used thermometers and questionnaires to screen people who wished to enter the facility, referring individuals with fever and respiratory illness to an isolation facility for more detailed screening. In Singapore, the government issued an electronic thermometer to every schoolchild; the child then measured his or her own temperature at school in the morning and afternoon.

2.7. Case Detection by Computers

As a result of the ever-expanding use of computers to collect and store clinical information, it has become possible for computers to detect cases by analyzing these data. Evans and colleagues (Evans, 1991; Evans et al., 1985, 1986, 1992, 1998) used computers to detect patients with infectious diseases in hospitals. Khan et al. (1993, 1995) demonstrated methods for automatic case finding for hospital infection control, and Jain et al. (1996) developed a tuberculosis case detector. Many organizations are creating electronic laboratory reporting systems, which automate case detection by laboratories (Effler et al., 1999; Overhage et al., 2001; Panackal et al., 2001; Hoffman et al., 2003).

Computerized case detection is most widely used at present, however, for detecting syndromes (DoD-GEIS, 2000; Lazarus et al., 2001; Lewis et al., 2002; Gesteland et al., 2003; Lombardo et al., 2003; Platt et al., 2003; Tsui et al., 2003, Espino et al., 2004; Heffernan et al., 2004; Nordin et al., 2004; Wagner et al., 2004; Yih et al., 2004; Chapman et al., 2005). A syndrome is an early presentation of illness. Almost all infectious diseases present initially as one of a small number of syndromes. Current computer-based case detection systems monitor for diarrhea, respiratory, influenza-like, rash, hemorrhagic, and paralytic syndromes.

In part, computers are widely used for detecting syndromes because of technical feasibility. Virtually all hospitals elicit a chief complaint from patients at the time that they register for service. The hospitals collect this information electronically and can provide it to a biosurveillance organization in a relatively uniform format.

Many of the above systems use techniques developed by the field of artificial intelligence to detect cases of disease (Cooper, 1989). We discuss these techniques in detail in Chapter 13.

2.8. Diagnostic Precision of Case Detection

We use the term *diagnostic precision* to refer to the nosological specificity of a diagnosis. For example, a physician may formulate (correctly) a relatively imprecise diagnosis of "pneumonia" after initial evaluation of a patient; subsequently, the physician may establish a more precise diagnosis of tuberculosis based on the results of laboratory testing. Diagnostic precision is not to be confused with diagnostic accuracy, which speaking loosely refers to whether the doctor was "right."

The range of diagnostic precision in medical practice (and biosurveillance) ranges from the very imprecise ("patient or animal is sick or dead") through intermediate levels of

precision ("patient has respiratory illness with fever"), through organism-level diagnostic precision ("patient has *Mycobacterium tuberculosis*"), to the ultimate level, which is quite precise ("patient has *M. tuberculosis*, Beijing genotype, strain W"). As we all know from personal experience with the healthcare system, there may be considerable imprecision early in the course of a diagnostic workup about the diagnosis (and even at its conclusion). In general, the level of diagnostic precision improves over time as results of diagnostic tests become available.

For many decisions about the treatment of individual patients (e.g., surgery), the precision of diagnosis must be relatively high. In biosurveillance, however, the diagnostic precision of case detection can be lower—even as low as "sick" or "dead." As with medical care, the more diagnostic precision the better, although increased precision comes not only at the cost of further testing but also at a time cost due to the delay involved in waiting for results of the testing.[2]

The value of extremely precise case detection is that it can support detection of small or geographically diffuse outbreaks. Pulse-field gel electrophoresis (PFGE) of common pathogens now routinely matches outbreak victims separated by time and place. An outbreak that was not detected by any other method was a 2000 listeriosis outbreak: eight perinatal (three miscarriages/stillbirths) and 21 nonperinatal (median age 65) cases distributed over 10 states and seven months were only linked because of identical PFGE (PulseNet pattern numbers GX6A16.0014 by *Asc*1 and GX6A12.0017 by *Apa*1) and ribotyping (DUP-1053). A case-control study of 17 of the cases evaluating food eaten in the 30 days before illness found an association with consumption of a specific brand of deli turkey (CDC, 2000c).

The CDC National Food Borne Pathogen System serotypes every enteric isolate received to achieve the ultimate in diagnostic precision and the ability to detect very diffuse outbreaks in a nation with a population of 350 million (discussed in Chapters 5, 8).

We discuss the relationship between diagnostic precision and *detectability*—the smallest outbreak that a biosurveillance system can detect—later in this chapter and again in Chapter 20.

2.9. Investigations of Cases of Notifiable Diseases

Health departments investigate individual cases of notifiable diseases for four reasons: (1) to confirm that the case meets the case definition, (2) to determine whether there are environmental or other causes of the illness that can be remediated, (3) to identify other people who may have been exposed for antibiotic prophylaxis or vaccination, and (4) to educate or isolate communicable individuals so that their infection is not transmitted to others. When resources do not allow a case investigation on every notifiable disease, a health department must decide which reported diseases to investigate. Some investigations are so important (sexually transmitted diseases, tuberculosis) that the federal government provides substantial resources to health departments to ensure that sufficient resources are available for investigation.

The investigator may use CDC disease-specific reporting forms, department-generated interview forms, or computer-generated dynamic questionnaires to collect additional disease specific information from clinicians, infection control nurses, and/or patients. The questions explore the more common sources and exposures for the disease. If appropriate, the investigator contacts exposed individuals to provide information, screening, medication, and/or vaccination as appropriate to the disease and circumstances of exposure. Case investigations of notifiable diseases are an example of the feedback loop in Figure 1.1. If an outbreak is identified as a result of the case (or the analysis of subsequent cases), the case data already collected provide investigators a base of information for characterizing the outbreak.

3. OUTBREAK DETECTION

We use the term *outbreak detection* to refer to biosurveillance methods that detect the existence of an outbreak. A clinician may detect an outbreak by diagnosing a highly communicable disease such as measles or a rare disease such as anthrax. (A biosurveillance organization treats a single case of such a disease as evidence of an outbreak until proven otherwise.) An astute clinician may notice a cluster of cases, as happened in the 2003 hepatitis A outbreak, or a biosurveillance organization may detect an outbreak from analysis of surveillance data. Biosurveillance organizations are automating the collection and analysis of surveillance data, so a computer may detect an outbreak.

3.1. Outbreak Detection from an Individual Case of Highly Contagious or Unusual Disease

The 2004 SARS outbreak and the foot-and-mouth disease (FMD) outbreak in the United Kingdom, described in Chapter 2, illustrate a common means by which outbreaks are detected: that is a clinician, veterinarian, or pathologist encounters an individual with a rare disease. Outbreaks of measles, botulism, and tuberculosis often come to attention in this manner.

2 We note that clinicians and especially veterinarians working in agribusiness do not always work-up a case to the highest level of diagnostic precision due to cost-benefit considerations. For example, medical practice guidelines suggest that a clinician treating a woman with uncomplicated urinary tract infection may treat this relatively imprecise diagnosis without obtaining a urine culture (to establish a more precise bacteriological diagnosis) because the probability of curing the condition with a broad-spectrum antibiotic is high.

3.2. Outbreak Detection by an Astute Observer

The outbreaks of Lyme disease, hepatitis A, AIDS, cryptosporidium, SARS (2003), and Legionnaire's disease were detected by an astute observer who noticed a cluster of illness and reported its existence to a health department. Outbreaks caused by contamination of food are often discovered when affected individuals who have dined together phone each other upon waking up sick the next day, and one of them calls the health department.

3.3. Outbreak Detection by Biosurveillance Personnel

There are many examples of outbreaks that biosurveillance organizations detect through analysis of surveillance data. Some notifiable diseases, especially the enteric organisms that cause diarrhea, occur sporadically, and a single case report therefore does not constitute prima facie evidence of an outbreak. The New York State Department of Health detected an outbreak at a county fair after receiving reports of 10 children hospitalized with *Escherichia coli* 0157:H7 in counties near Albany, New York (CDC, 1999e). The Volusia County Health Department detected an outbreak when they received three reports of children with *Shigella sonnei* sharing a common exposure to a water fountain at a beach-side park (CDC, 2000d).

Hospital infection control units conduct similar surveillance of organisms of epidemiologic significance in the healthcare setting, such as antibiotic-resistant organisms, *Clostridium difficile,* and *Legionella pneumophila.* In addition, surveillance is done for hospital-acquired infections followed by trend analysis to access clustering of specific infection types (e.g., central-line associated blood-stream infections) and specific pathogens (e.g, *Klebsiella pneumoniae*).

3.4. Outbreak Detection by Computers

Increasingly, biosurveillance organizations use computers to analyze data to identify clusters of cases. These data may be cases reported by clinicians, veterinarians, or laboratories; aggregate data about the health of the population, such as sales of thermometers or diarrhea remedies; or a clinical data repository set up by a hospital for surveillance of nosocomial infections and levels of antibiotic-resistant organisms.

It is useful to note in the literature describing these approaches that the diagnostic precision of the data that are being analyzed by the detection algorithms can vary from notifiable diseases at the high end of diagnostic precision to "numbers of individuals absent from work" or "unit sales of diarrhea remedies" at the other end of the spectrum.

3.4.1. Automatic Cluster Detection from Notifiable Disease Data

Epidemiologists have long used the Serfling method to identify outbreaks of influenza retrospectively from pneumonia and influenza morbidity and mortality data (Serfling, 1963). But the use of computers to detect clusters in notifiable disease data is uncommon, perhaps because the necessary infrastructure is still being put into place in many jurisdictions. In current practice, epidemiologists use computers primarily to display and manipulate these data. The literature on automatic detection of clusters from notifiable disease data is, perhaps, as a result, relatively sparse at present (Hutwagner et al., 1997; Stern and Lightfoot, 1999; Hashimoto et al., 2000). A noteworthy exception is the use of clustering algorithms to analyze molecular fingerprints of enteric isolates (discussed above and in Chapter 8).

3.4.2. Automatic Cluster Detection from "Syndromic" Data

In contrast, there is a growing literature on the use of algorithms to detect clusters of cases or outbreaks with less diagnostically precise data, such as billing diagnoses.

Quenel and colleagues were the first to study detection of outbreaks from such data. They studied the sensitivity, timeliness, and specificity for detection of influenza outbreaks from 11 types of data (emergency home visits, sick leave reported to national health service, sick leave reported to general practitioners [GPs], sick leave reported by companies, sentinel GP visits, sentinel GP visits due to ILI, sentinel pediatrician visits, hospital fatality, influenza-related drug consumption, sentinel GP overall activity, and sentinel pediatrician overall activity).

Detecting outbreaks through analysis of cases of illness at an early stage is a relatively new approach for governmental public health and has been termed *syndromic surveillance.* Note that some investigators restrict the use of the term *syndromic surveillance* to methods for automatically detecting clusters of illness from case data, whereas other investigators use the term to also refer to monitoring of data aggregated from populations, such as total daily sales of thermometers, which are not case data (Buehler, 2004). Kelly Henning (2004) tabulated the various terms that have been used to refer to biosurveillance systems that provide early warning of disease outbreaks. Of these terms, we prefer "early warning systems" as it is the most descriptive of their functions

The rationale for early warning surveillance is as follows: Although the diagnostic precision of case detection is low, a highly unusual number of individuals with early symptoms consistent with a disease (e.g., 100 individuals from a single zip code presenting in 24 hours with fever and cough) may provide an early warning of an outbreak. The diagnostic precision can then be improved quickly by testing affected individuals to achieve a more precise diagnosis.

Sentinel ILI clinicians and drop-in surveillance are simple forms of early warning surveillance. In the past five years, there has been a marked trend to automate these surveillance activities to reduce the cost and possibly improve the performance. Although organizations still conduct drop-in surveillance during special events, the appropriate role for drop-in surveillance is limited to special events in cities that have not created equivalent automated capability or in areas where the

surveillance requires additional data to improve diagnostic precision. Even in those settings, the current trend is to install an automated system in advance of the event and to supplement it with manual data collection from hospitals that cannot participate in the automated process, or to augment the data collected automatically with additional data collected manually to improve diagnostic precision.

3.5. How and How Well Are Outbreaks Detected?

Two studies have analyzed how existing biosurveillance systems have detected outbreaks. Dato et al. (2001, 2004) reviewed 43 well-known outbreaks, finding that 53% of the outbreaks were detected by health department staff through review of case reports from clinicians and laboratories, and 28% were detected by an astute clinician or person with knowledge of an outbreak in a school or work setting. An additional eight outbreaks (19%) were detected by laboratory networks using advanced testing and fingerprinting of specimens (three), by public sexually transmitted disease clinics (two), and by the military, another government, and a university (one each).

Ashford et al. (2003) reviewed 1,099 outbreak investigations conducted in the United States and abroad by the CDC's Epidemic Intelligence Service from 1988 to 1999. Of the 1,099 outbreaks, 399 (36%) were first recognized by healthcare providers or infection control practitioners. Health departments were the first to recognize 31% of the outbreaks. Other entities that recognized outbreaks were surveillance systems (5%), ministries of health (2.7%), nongovernmental organizations (2%), the WHO (1.5%), and the Indian Health Service (1.1%). Forty-nine (4.5%) of outbreaks were reported by other sources such as private clinics, laboratories, or private citizens. The study records were inadequate to establish the recognizing entity for the remaining 17% of outbreaks. The time delay from first case to recognition of the existence of an outbreak ranged from zero to 26 days. This study is also interesting because it analyzed 44 outbreaks caused by biological agents with high potential for use by bioterrorists.

Evidence indicates that some outbreaks are never detected, suggesting that there is room for improvement in current methods of outbreak detection. For example, the study by Dato et al. found multiple reports of outbreaks that involved contamination of nationally distributed products. However, the health departments of only one or two states detected these outbreaks, suggesting that outbreaks occurring in other states went undetected. The multistate outbreaks that were detected by only a few states involved commercially processed deli meat (CDC, 2000c), burritos (CDC, 1999c), orange juice (CDC, 1999b), parsley (CDC, 1999d), and dip (CDC, 2000e).

3.6. Diagnostic Precision and Outbreak Detection

The ability of a human or a computer to notice an anomalous number of cases above the background number of cases depends on the diagnostic precision of the surveillance data. For example, if a biosurveillance organization only collects information about the numbers of "sick" cattle in a feedlot (low diagnostic precision) and there are typically 500 sick cattle on the feedlot, an outbreak of FMD affecting 10 cattle will not stand out against the background level of sick cattle. If, however, the case data are diagnostically precise (e.g., the cases are confirmed diagnoses of FMD), one such animal in a data stream will stand out against the background level of zero. Figure 3.6 illustrates this concept for SARS surveillance,

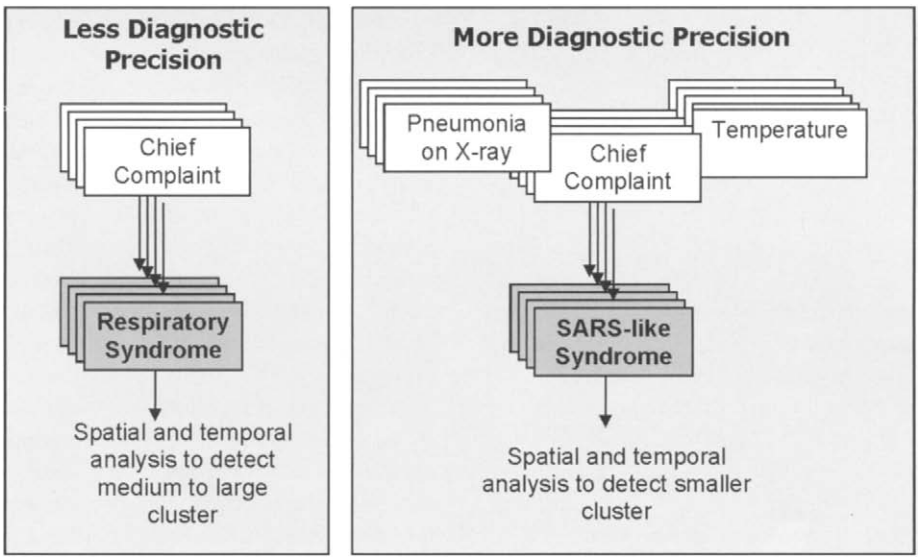


FIGURE 3.6 Diagnostic precision and minimum size of outbreak that can be detected. In this hypothetical example, the multiple boxes represent many cases in a population being detected automatically by computers from data available electronically. If the data available electronically support more diagnostically precise case detection, the size of a cluster that can be noticed above background levels will be smaller.

showing that if the diagnostic data available support a more diagnostically precise case detection (i.e., SARS-like syndrome rather than respiratory syndrome), then subsequent analysis of the case data is expected to detect smaller clusters of disease against the background levels of individuals presenting with respiratory illness.

3.7. Timeliness of Outbreak Detection

We close this section on methods for outbreak detection with a comment on the importance of timely detection of outbreaks. A biosurveillance system must detect an outbreak as quickly as possible to enable treatment of those already sick and to prevent further illness. The required timeliness varies by biological agent and route of transmission. Early detection is usually expensive, so the exact relationship between morbidity and mortality and time of detection for each type of outbreak is important. An outbreak of anthrax due to aerosol release, for example, must be detected within days of release or, ideally, at the moment of release because many people will sicken and die within days of the release. Therefore, significant resources should be expended to accomplish detection as close to day zero as possible. In contrast, detection of some diseases, even those as virulent as smallpox, as late as weeks from the onset of symptoms in the first case is still within the window of opportunity to reduce considerably mortality and morbidity (Meltzer et al., 2001).

4. OUTBREAK CHARACTERIZATION

We use the term *outbreak characterization* to refer to processes that elucidate the causative biological agent, source, route of transmission and other characteristics of an outbreak. These characteristics guide the treatment of victims and the application of control measures to prevent additional cases (e.g., by removing or isolating the source). Table 3.1 includes the complete list of outbreak characteristics and methods for their elucidation that we discuss.

As mentioned in Chapter 1, some outbreak characteristics may already be known at the time that an outbreak is detected. For example, if a biosurveillance organization detects an outbreak from analysis of notifiable disease data (which is largely organism-based reporting), it will already know the causative biological agent. If a participant in a church picnic reports an outbreak to a health department, that person may also report the source as macaroni salad, having "interviewed" most of the picnickers by phone before calling the health department. We expect the number of outbreak characteristics that are known at the time of outbreak detection to increase as biosurveillance systems collect increasing amounts of surveillance data on a continuous basis. The distinction between outbreak detection and characterization will continue to blur.

Nevertheless, a relatively crisp demarcation between the processes of outbreak detection and characterization exists. Health departments conduct disease surveillance to detect outbreaks, and they conduct investigations using different methods to characterize them. At present, the feedback loop in Figure 1.1 (Chapter 1) becomes quite active only after an investigation commences.

4.1. Outbreak Investigations

Outbreak investigations range in size from a small inquiry conducted by a single investigator to a major multinational investigation. A seasoned investigator may need only a 10-minute phone call to determine that a suspected outbreak is small, self-limited, and not worthy of additional investigation. An outbreak that is spreading rapidly and killing many individuals (such as the SARS outbreak in 2003) may warrant deployment of thousands of investigators and researchers.

When a health department suspects an outbreak based on any of the methods described in the previous sections, its staff typically initiates a preliminary inquiry to verify the available information and estimate the severity and scope of the event. The staff reviews notifiable disease records and available medical records and/or conducts open-ended interviews of a small number of individuals, asking questions and listening, quickly obtaining important information on signs/symptoms, source, and those who might have contracted the disease through contact with known cases. At this point, the staff decides if the problem is severe enough to launch a field investigation, a decision that is based on "The severity of the illness, the potential for spread, political considerations, public relations, available resources, and other factors" (CDC, 2002a). The staff also must decide whether to inform superiors and/ or request extra help, resources, or consultation. Extra investigators can divide and complete individual case investigations much more quickly than can one person.

The investigation team (or single investigator) then begins the process of interviewing all available patients and contacts. The investigators review other sources of information such as emergency department logs, pathology specimens, medical examiner records, entomological (insect) data, and animal health data (if they suspect the cause to be exposure to a sick animal). They might issue a health alert to physicians or the public requesting that similar cases be reported by healthcare providers or institutions. The investigators obtain blood, stool, urine or other specimens from affected individuals; collect materials that they suspect may be contaminated (e.g., food, water); and send samples to laboratories to be tested for organisms that may be involved based on the epidemiological information collected to that point.

The initial round of interviews and tests may yield a fairly complete characterization of the outbreak. The investigators may know the causative organism from tests done on the first infected individual, the source of the outbreak from commonalities identified among the cases identified to date, and even the complete set of affected individuals when the outbreak is geographically localized. If they do not, the outbreak

investigation will continue to use many, if not all, of the analytical techniques that we will be discussing.

Throughout this process, investigators continuously formulate and refine hypotheses about outbreak characteristics that are not yet known (e.g., biological agent, source, and route of transmission), and seek to resolve *differential diagnoses* for the unknown characteristics by collecting additional information. As physicians do in clinical diagnosis, the investigators apply their knowledge of epidemiology to generate hypotheses and decide what additional information to collect. They may apply control measures suggested by the most likely and/or the most serious of the possible causes of the outbreak.

Outbreak investigations are labor intensive. Outbreak investigations are sometimes referred to as *shoe leather* epidemiology because investigators must visit numerous hospitals, homes, stores, and morgues during the course of an investigation. There are many opportunities to use information technology to improve the speed of this process and to extend the life of investigators' shoes. Significant portions of the case data that investigators assemble by hand are available electronically in clinical information systems (see Chapter 6). Opportunities also exist to provide cognitive support to investigators with their process of generating and efficiently resolving differential diagnoses of the biological agent as well as other outbreak characteristics.

4.2. General Analytic Techniques

We here provide a brief overview of general analytic techniques that investigators use to analyze case data collected during an investigation. Investigators use these techniques (e.g., spatial analysis) to elucidate outbreak characteristics.

4.2.1. Spatial Distribution of Cases

Investigators examine the spatial (geographic) distribution of cases as soon as possible. The spatial distribution of cases often provides a strong clue about the source of an outbreak. Because of the importance of spatial analysis, one of the first stories told to epidemiologists in training is the John Snow cholera story (Snow, 1855). Dr. John Snow, a London anesthesiologist and pioneer of the science of epidemiology, decided to test his hypothesis that cholera outbreaks were a result of contamination of the water supply, a view contrary to the medical beliefs of the time. He plotted the home address of people who died of cholera on a map of London; he also marked the location of neighborhood water pumps, which were the source of drinking water at the time. The striking cluster he found of cholera deaths centered on water pumps has become legendary. The concentration of cholera deaths around the Broad Street pump was twice the number of deaths in the rest of the city of London, with approximately 500 deaths in the neighborhood in 10 days. Figure 3.7 shows Snow's map with bars denoting people who died from cholera in buildings in the immediate vicinity of the Broad Street pump.

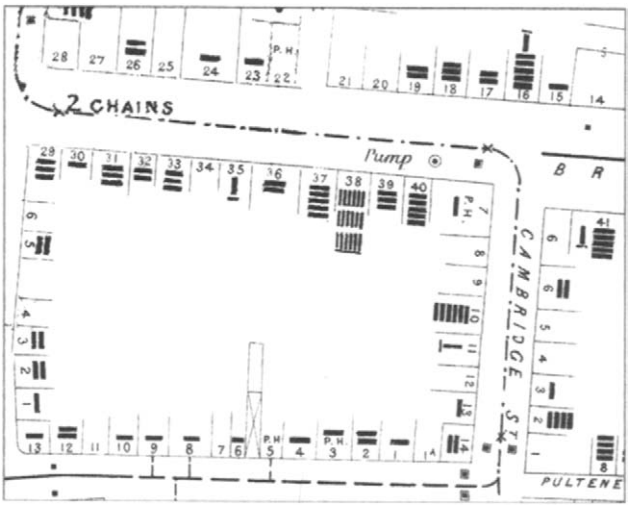


FIGURE 3.7 John Snow's cholera map showing 115 cholera deaths in the immediate vicinity of a pump on the corner of Broad Street and Cambridge Street. According to the legend, Snow advised unbelieving officials simply to remove the pump handle. (From *http://www.ph.ucla.edu/epi/snow.html.*)

At the beginning of an investigation, the investigators may only have the home address of each reported case. Therefore, the map they plot first is typically the home address of each case. During the course of an investigation, they may create many maps as they test hypotheses that the exposures may have occurred at work, school, a restaurant, fruit stand, or events such as conventions, picnics, and sporting events. Investigators may also map the location of individuals not affected. Snow did this and demonstrated that there were no cholera fatalities among brewery workers on Broad Street; these men had an allowance of free beer every day, which they apparently preferred to the water from the Broad Street pump.

Geographic information systems are modern descendants of Snow's painstakingly developed map. These systems partly automate spatial analysis. Spatial scans (see Chapter 16) are computer algorithms that more fully automate spatial analysis; these scans construct and search maps automatically for clusters of disease like that around the Broad Street pump. They can ask and answer questions such as the following: *If I were to map the people in a community who developed pneumonia in the past week by using their work addresses, would the cases cluster in particular hospitals?* This type of analysis would be very useful in SARS surveillance as SARS caused many hospital-based outbreaks in 2003. This type of analysis can be done routinely (e.g., daily or more frequently) even in the absence of a known outbreak as a method of outbreak detection. Spatial scans are an example of how the distinction between outbreak detection and characterization is blurring. When used for outbreak detection, spatial scans both find and spatially characterize outbreaks in one step.

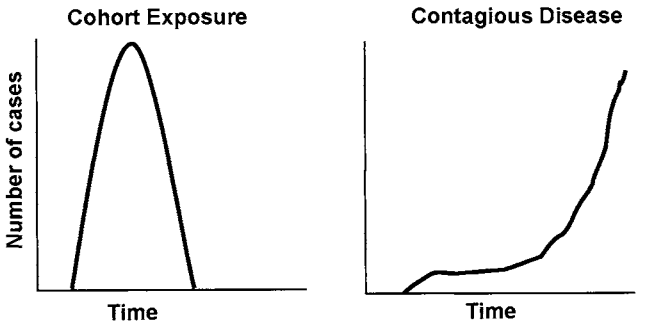


FIGURE 3.8 Hypothetical epidemic curves that would suggest a cohort exposure and a contagious disease.

4.2.2. Temporal Distribution of Cases

Investigators also examine the temporal distribution of cases as soon as possible by plotting an *epidemic curve,* which is a graph of the number of cases by date of onset of illness (Figure 3.8). The epidemic curve can provide a clue to the biological agent, source, and route of transmission. If the epidemic curve, for example, shows a sudden increase in cases, the investigator might suspect that the cause of the outbreak is contamination of food, air, or water and that the causative biological agent is more likely to be an agent with a propensity or ability to be transmitted in one of these ways (Figure 3.8, left) because such contaminations can infect a large cohort of individuals in a short period, producing a steep epidemic curve. If the epidemic curve rises more gradually, an investigator would suspect a communicable disease such as measles, in which the number of cases increases in an exponential fashion owing to successive generations of infection (Figure 3.8, right). A more level epidemic curve would suggest a continuous source of exposure, such as a persistently contaminated swimming pool.

4.2.3. Disease Incidence, Mortality Rates, and Attack Rates

Disease incidence is one measure of the magnitude of an outbreak (as are maps and epidemic curves). Disease incidence is the number of new cases in a population during a defined period such as a week. If disease incidence for every day or week during an outbreak is plotted, the result is an epidemic curve.

For lethal diseases, investigators gauge the severity (virulence) of the disease by the *case fatality rate,* which is the probability of death among diagnosed cases. Recall that investigators observed a 30% case fatality rate for the outbreak that they initially thought was Japanese encephalitis; however, the case fatality rate was highly atypical of Japanese encephalitis and led them to suspect a different disease. Investigators also compute other mortality rates. *Age-specific mortality rates,* for example, can help characterize an outbreak that is poorly understood by revealing that the disease affects the elderly or young with greater frequency or severity.

If investigators suspect an environmental exposure, they will calculate the *attack rate,* which is the fraction of people or animals exposed to a specific factor (e.g., macaroni salad or another infected individual) who subsequently contract the disease. If the attack rate in a population that is exposed to a specific factor is higher than a comparison group that is not exposed to the factor, it suggests a possible link between the factor and illness. If the analysis includes a comparison with a carefully matched control population of individuals known not to have the disease, the analysis is called a case-control study (described below). An investigator would conduct a case-control study if the less formal measurement of attack rate did not produce a definitive answer to the outbreak characteristic in question (e.g., if it did not point to macaroni salad, then the more formal case-control study likely would have).

4.2.4. Cohort and Case-Control Studies

An investigator conducts a *cohort* or a *case-control study* to test one or more hypotheses about some characteristic (oftentimes the source) of the outbreak. A cohort study compares the rate of illness of those exposed to specific factors (e.g., macaroni salad) to the rate of illness among those not exposed. A case-control study compares the frequency of specific factors in affected individuals relative to their frequency in unaffected individuals, controlling for age and other potentially confounding factors that may be correlated with the disease in question but do not cause it.

A cohort study is technically easier to conduct than is a case-control study. It is typically used for those outbreaks in which there is a small well-defined population available for interview. Examples of suitable cohorts are everyone who attended a wedding, a school, a camp, or a business conference or who ate at a specific restaurant on a given day. An investigator designs a form with three main types of questions: (1) contact and demographic information, (2) presence and onset of illness, and (3) specific exposures. For example, for a wedding at which gastrointestinal illness occurred, the questionnaire would include questions about sex, age, vomiting and diarrhea, every food item served or available (identified from menu's and the party coordinator), drinks, ice, and edible party favors. If the biological agent norovirus was suspected, exposure to public vomiting, other events such as the rehearsal dinner, and/or individuals known to be ill might also be asked. (An example of a form from a cohort study of a business conference is included in Appendix D.)

To conduct a case-control study, an investigator develops a questionnaire that covers all of the suspected sources and routes of transmission. Epidemiologists know from experience and knowledge of epidemiological patterns when to include items (e.g., intravenous drug abuse, food and water

consumption, places visited, sexual practices, exposure to sick or dead animals or people, and travel history). Case-control studies invariably include age and sex, markers for socioeconomic status, race/ethnicity, occupation, disease history, and prior immunizations, in addition to questions on the exposures of interest in a specific investigation. The investigator then assembles a set of individuals with disease (cases) and a set without disease (controls). In the design of a case-control study, attention is given to matching controls to cases on known confounding variables such as socioeconomic status, age, and sex to remove these influences from the analysis.

The investigator then administers the questionnaire to each of the cases and controls. Required data may be collected or verified from medical records. The odds ratio (OR) for each factor is calculated, which is the ratio of the incidence rate in exposed individuals relative to that among unexposed individuals (Rothman and Greenland, 1998). If the OR is equal to one, it suggests that the factor is not causing the illness.

The investigation of the hepatitis A outbreak described in Chapter 2 involved a case-control study of food items served in the restaurant. Investigators interviewed individuals with hepatitis A and controls without hepatitis A who either had dined with case patients at Restaurant R or were identified through credit card receipts as having dined at Restaurant R during October 3 through 6. They found an OR of 24.2 for consumption of mild salsa with green onions, and an OR of 5.2 for consumption of chili con queso with green onions (CDC, 2003a). An OR of 24.2 indicated that people who dined at restaurant R and subsequently developed hepatitis A were 24.2 times more likely to have eaten mild salsa with green onions than were people who dined at the same restaurant but did not develop the disease.

Case-control studies depend on the ability of people to remember key historical details accurately such as what they ate. For the outbreak of hepatitis A, the investigators obtained a food history for a period of two to six weeks before onset of symptoms because the incubation period of hepatitis A is long. For this reason, investigators need to move quickly to develop and administer outbreak questionnaires. Investigators follow standard methods of interviewing to minimize bias in how they ask questions and to minimize recall and prevarication bias on the part of the interviewee (Kalter, 1992).

4.3. Outbreak Characteristics

This section discusses how investigators elucidate the following outbreak characteristics: biological agent; source; route of transmission; size; and, when the disease is new or unusual, the disease process itself.

4.3.1. Biological Agent

The causative biological agent is perhaps the single most important characteristic of an outbreak. It has immediate implications for treating the sick and focuses the search for the source and route of transmission as each biological agent has propensities and limitations in the environments in which it can reside and the mechanisms by which it can be transmitted. The investigators of Legionnaire's disease, AIDS, mad cow disease, Lyme disease, and Nipah virus did not know the causative biological agent and had great difficulty finding the sources and routes of transmission.

Although the biological agent is often known at the time that an outbreak is detected, for diseases that have recently crossed species or for rare diseases that clinicians do not routinely test for, it may not be known. Importantly, the recent trend toward monitoring surveillance data of lower diagnostic precision (e.g., sales of diarrhea remedies or numbers of individuals with flulike symptoms) has increased the number of situations in which the biological agent is not known when an outbreak is detected. In these situations, the differential diagnosis may be large (Table 3.2). When the biological agent is not known, investigators use the clinical symptoms of affected individuals to select laboratory tests to narrow down and ultimately identify the biological agent.

A significant amount of laboratory work may be required to identify the biological agent. As in the case of Legionnaire's disease, Lyme disease, and Nipah virus in which the organism was previously unknown, it may take considerable time to isolate the organism. Identification of a difficult-to-identify organism is largely a process of elimination. Laboratories use cultures, serological tests, immunohistochemistry, and nucleic acid probes to search for known organisms that are most

TABLE 3.2 Biological Agents and Toxins of Concern for a Large-Scale Aerosol Release

Biological Agent	Treatable?	Early Clinical Presentation
Bacteria		
Bacillus anthracis	Yes	Flulike
Brucella sp.	Yes	Flulike
Coxiella burnetti (Q fever)	Yes	Flulike
Francisella tularensis (Tularemia)	Yes	Flulike
Burkholderia mallei (Glanders)	Yes	Flulike
Histoplasmosis/coccidiomycosis	Yes	Flulike
Pseudomonas mallei	Yes	Flulike
Yersinia pestis	Yes	Flulike
Viruses		
Smallpox (aerosol release)	Yes (early vaccination)	Flulike, rash
Venezuelan equine encephalitis	No	Flulike, headache
Biological toxins		
Staph enterotoxin B	No	Flulike
Clostridium perfringens toxin	No	Respiratory distress/failure
Botulinum toxin	Yes	Double vision and paralysis
Ricin toxin	No	Cough, difficulty breathing

The differential diagnosis of a sudden, large increase in flulike illness includes the first 11 agents.

likely epidemiologically to be causing the illness. We discuss the full range of laboratory tests in Chapter 8.

The causative biological agent for some outbreaks is never found. Causative agents were not identifed for 16 outbreaks associated with burritos that affected approximately 1,700 individuals (CDC, 1999c). These outbreaks were eventually (epidemiologically) traced to two companies, resulting in the recall of two million pounds of burritos. In the study by Ashford et al. (2003), the causative biological agent was not found in 41 of the 1,099 (3.7%) investigations studied.

4.3.2. Characterizing the Disease

If the biological agent is unknown or if the disease itself is unusual in its presentation or severity, then characterizing the disease process becomes a priority for investigators. They will develop a working case definition, as was done by CDC and WHO for both AIDS and SARS, to enable additional case finding and to use in case-control studies. They will measure the incubation and infectious periods of the disease to bracket the period in which to search for causative factors and contacts.

Incubation Period. The *incubation period* is the time from infection of an individual to onset of clinical illness (Figure 3.9). The incubation period may vary from individual to individual based on health status and the dose of the biological agent to which the individual was exposed; therefore, investigators measure the average and range of the incubation period.

If the source or route of transmission of the infection is known, investigators measure the incubation period as the time from exposure to onset of symptoms. For contagious diseases, the time of exposure is the date at which an individual was exposed to an index case. For infections caused by contaminated materials, the time of exposure is the date that the contaminated material was ingested or otherwise entered the body of the victim.

The incubation period may provide a weak clue to the identity of the organism. Some classes of organisms such as HIV have long incubation periods.

Infectious Period. The *infectious period* is the time during the course of an individual's illness when he or she can transmit the disease to another individual. It usually does not provide a clue to the biological agent. Its importance is as a basis for developing guidelines for isolating infected individuals to prevent further infections. The beginning of the infectious period usually coincides with onset of symptoms because many diseases are transmitted by coughing, sneezing, diarrhea, or weeping skin lesions. There are exceptions, however, and the infectious period may begin before or after the onset of symptoms.

Investigators establish the beginning of the infectious period by analysis of dates of contact between infected individuals. In particular, investigators compare the dates of contact between an index case and the secondary cases that likely resulted from

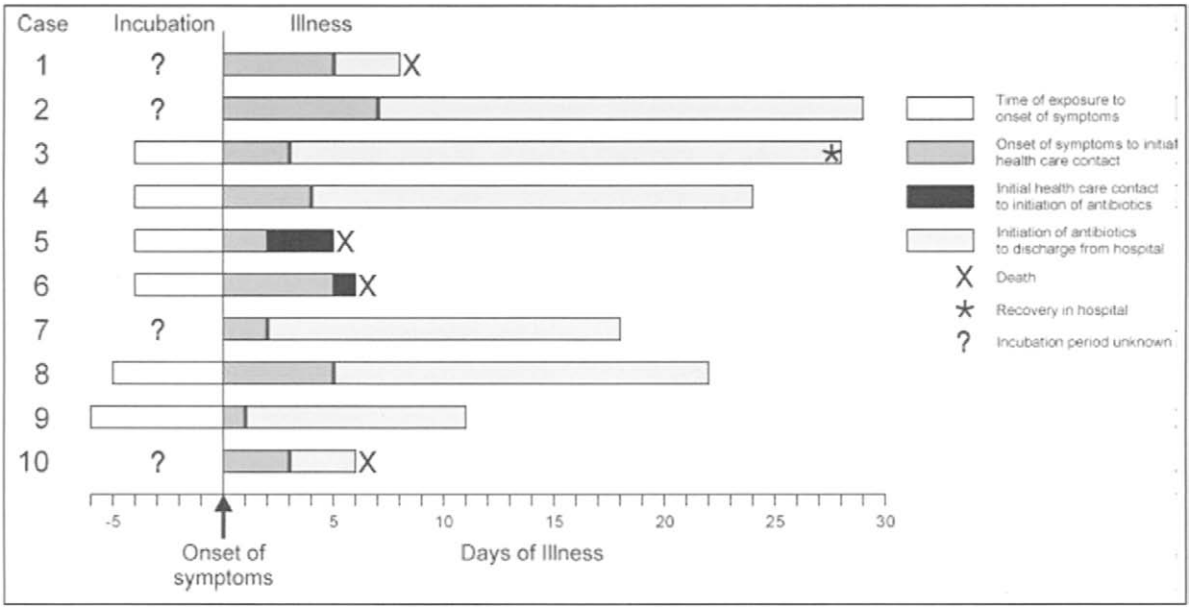


FIGURE 3.9 Incubation and symptomatic periods for 10 cases of inhalational anthrax. The *incubation period* is the time from infection or exposure to onset of symptoms (white bars to the left of the vertical line denoting day of onset of symptoms). The *symptomatic period* is the time from onset of symptoms to recovery or death (bars to the right of the vertical line). The infectious period may begin before of after the onset of symptoms. The infectious period for anthrax ends when the host develops sufficient antibodies to clear the infection, when the infection is eradicated through treatment, or when the body is cremated (Jernigan et al., 2001).

contact with that index case. The beginning and end of the infectious period for an index case are roughly the dates when that individual starts and stops infecting other individuals, respectively. As with the incubation period, investigators compute the average and range of the infectious period over many cases.

Another method of establishing the end of the infectious period is laboratory testing for agent-specific antibodies. When antibodies appear, the person is usually no longer infectious.

4.3.3. Source

The term *source* refers to the starting point in the path via which a biological agent is eventually conveyed into the body of a victim (Table 3.2). The source is critically important because removal or isolation of a source prevents further infections. In Hong Kong in 1997, an outbreak of avian influenza due to the H5N1 strain led to a small number of human cases with a high fatality rate. Fearing that the avian influenza would lead to a human pandemic, authorities sacrificed millions of chickens harboring the H5N1 strain (Sims et al., 2003).

There are many possible sources for outbreaks. The most common sources are food, water, other people, and animals.[3] We note that the source is simply the starting point in a path of transmission. Investigations seek to understand the entire path because it may contain many points at which they can apply disease control measures. We also note that the source attributed to an outbreak may not be the ultimate source. For example, the nominal source of the hepatitis A outbreak described in Chapter 2 was green onions from farms in Mexico. The source of contamination of the green onions is unknown. Operationally, the search for a source ends when a common early point in the path of transmission of the disease is found at which control measures can be applied to halt the outbreak.

Sometimes a source is never identified. The source was never identified for three outbreaks involving group A rotavirus (CDC, 2000b), *E. coli* O111:H8 (CDC, 2000a), and Norwalk-like virus (CDC, 2000f). Table 3.3 provides examples of potential sources and routes of transmission for microbes.

4.3.4. Route of Transmission

The term *route of transmission* refers to the path that connects a source of biological agent to sick individuals.[4] The route of transmission for the U.S. 2001 postal anthrax attack, for example, started in an unknown facility or facilities that manufactured the anthrax powder (the source) (Jernigan et al., 2002). Unknown individuals then transferred the powder into envelops and deposited them in mailboxes in or around Trenton, New Jersey. Mail sorting machines in postal processing and distribution centers compressed the envelops, thus expressing spores, which were sufficiently light to float in the air. The air carried the spores into the lungs of individuals working in the processing centers. After an incubation period, some of these individuals developed the disease inhalational anthrax. Postal workers delivered the envelopes to the addressees, who opened them, allowing the spores to float into the air in buildings. The addressees and other occupants of the buildings inhaled spores, and some developed inhalational anthrax. The spores infected the skin of other individuals, who developed the disease cutaneous anthrax. Investigators believe that cross-contamination of bulk mail resulted in a case of inhalational anthrax in a woman in rural Connecticut (Griffith et al., 2003). Figure 3.10 shows the route of transmission identified by investigators for the 2001 postal attack.

TABLE 3.3 Examples of Sources and Routes of Transmission

Source	Route of Transmission (Path)	Hosts
→ Terrorist	→ envelop → mail system → air	Postal workers, recipients of mail, people in buildings in which envelops were opened
→ Green onions	→ food → system → restaurant	Restaurant patrons
→ Contaminated source water (reservoir)	→ water *treatment plant* → water distribution system	Consumers of tap water
Poultry	→ air → persons → air	Close contacts of infected individuals

An arrow before the source means that there may be more proximate sources that remain unknown.

The final step in a route of transmission is always the point of entry into the host, which is biologically possible through only a finite number of entry points. Biological agents can enter humans (and other animals) through the respiratory tract (breathing or sniffing), the gastrointestinal tract (eating or per rectum), the skin, the eyes, sexual contact, medical procedures (surgical incision, transfusion, intubation), and nonmedical intravenous injections.

In contrast, the paths by which a biological agent can arrive at an entry point of an individual are virtually infinite. They include the air, any water (bottled water, city water supply, temporary water supplies at public events, swimming pools, hot tubs, dental office water), any food, the mail, manufactured products,

3 The term *reservoir* is somewhat synonymous with source, although it only refers to sources in which an organism lives and multiplies. The human body is a reservoir for many viruses and bacteria as are animals. Bats are a reservoir for rabies, and sheep a reservoir for anthrax. Human diseases that have an animal reservoir are called *zoonotic* diseases.

4 Epidemiologists use the term 'route of transmission' or 'mode of transmission' to refer to generic transmission patterns such as airborne, sexual, person-to-person, and food borne. When characterizing an outbreak, however, the goal is to elucidate in detail the particular path by which biological agents 'travel' from a source to a host (host is the term for an individual who is sick).

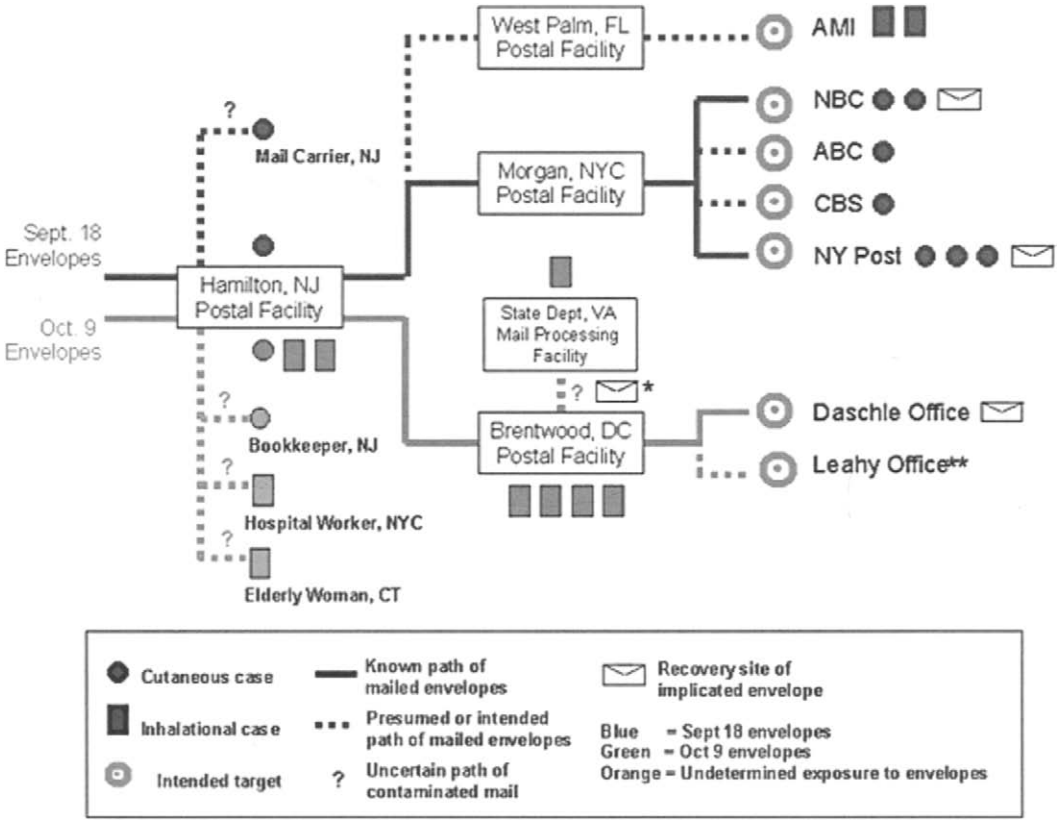


FIGURE 3.10 Cases of anthrax associated with mailed paths of implicated envelopes and intended target sites. NY indicates New York; NBC, National Broadcasting Company; AMI, American Media; USPS, United States Postal Service; and CBS, Columbia Broadcasting System. *Envelope addressed to Senator Leahy, found unopened on November 16, 2001, in a barrel of unopened mail sent to Capitol Hill. **Dotted line indicates intended path of envelope addressed to Senator Leahy. (From Jernigan et al., 2002.)

legal drugs, illegal drugs, medical instruments (surgery, endoscopic examinations, intravenous lines), blood products, another person, or an animal (including insects, snakes, and fish). With the advent of bioterrorism, the path is limited only by the ingeniousness of man, as evidenced by the murder of the expatriate Bulgarian writer and broadcaster Georgi Ivanov Markov by the Bulgarian secret police, who used an umbrella tip to inject a tiny platinum ball filled with the toxin ricin (http://en.wikipedia.org/wiki/Georgi_Markov).

4.3.5. Methods to Elucidate Source and Route of Transmission

Elucidating the source and route of transmission may be labor and time intensive. For example, the investigation that elucidated the source of the listeriosis outbreak described earlier involved a case-control study of 17 cases conducted by five states, two local health departments, and the CDC to identify potential common sources. The root source—a supplier of processed deli meat—was identified by visiting 13 stores to identify the supplier that they had in common (CDC, 2000c).

Environmental Investigations. Much of the dramatic decrease in U.S. crude death rate in the early part of the 20th century can be attributed to sanitary improvements in water, food, and sewage management (CDC, 1999a). Outbreaks may result when these practices break down or are not adhered to.

An environmental investigation may examine water and food sanitation, underground water, surface water, agriculture, and domestic or wild animals. When there is reasonable possibility that a facility may be involved in an outbreak, investigators request that sanitarians conduct an inspection or review of a facility. Sanitarians (also known as environmental health specialists), using a body of science developed through the past century, routinely inspect and advise food service facilities and recreational and potable water facilities to ensure that environmental safeguards are in place to prevent outbreaks and a return to 19th-century rates of infectious diseases. The sanitarian can quickly determine whether the facility is operating with no violations or practices that would cause an outbreak. If stronger evidence becomes available that a facility or

specific environment is involved, the investigators may initiate a more extensive environmental investigation (Massachusetts Department of Public Health, 2005a,b).

More generally, an environmental investigation, depending on the problem at hand, explores the environments that provide reservoirs where agents can reside and multiply. When the causative biological agent and the source are unknown, as was the case during the 1976 Legionnaire's outbreak, an environmental investigation can be far-ranging.

Food service inspection and investigation methods are well developed as the result of accumulated experience with thousands of foodborne outbreaks. Hazard analysis critical control point (HACCP) is a "science based method to identify or prevent hazards which contribute to foodborne disease" (Massachusetts Department of Public Health, 2005a). *Critical control points* include the appropriate heating and cooling of food. The value of the HACCP method is that it can identify likely points in a path of transmission well in advance of full characterization of an outbreak. A malfunctioning refrigerator, for example, is both a clue to the potential source of an outbreak (staphylococcus can elaborate a toxin, which is heat stable and therefore not neutralized by subsequent cooking) as well as a point for immediate correction to prevent future problems. If a specific food is implicated by survey methods or microbiological analysis, the sanitarian will look very carefully at food preparation steps.

The investigators of the 2001 anthrax outbreak conducted environmental investigations in postal processing and distribution centers, offices, and homes to determine the presence of *Bacillus anthracis* and the paths by which it spread. For the environmental investigation related to the most unusual case–the 94-year-old woman in Connecticut discussed earlier–specialists assessed the patient's activities in her home and searched for letters she received in the prior two months, in addition to conducting sampling in and on the periphery of her home by using swabs on surfaces and high-efficiency particulate air vacuums (Griffith et al., 2003). Molecular subtyping identified the isolate from the 94-year-old woman as matching the isolates from the other anthrax patients infected through mail. The investigators did not find matching isolates in the woman's home or in any of the places she regularly visited. They did learn by going through her garbage that she regularly tore her bulk mail in half before discarding. And they found that bulk mail that was processed and delivered by her local mail distribution center had been processed in another post office in the 24 hours after heavily contaminated letters. Evidence that at least some of that bulk mail was cross-contaminated came when matching isolates were found on her local bulk mail processing machines. Investigators believe this woman's advanced age, medical condition, and habit of ripping junk mail in half before discarding it contributed to infection from a very low level of contamination of the mail she received. This explanation was the simplest and most biologically plausible.

The anthrax environmental investigations led to routine use of biohazard detection systems (BDSs) (Military Postal Service Agency, 2004) to identify mail contamination before mail distribution to the public.

Food Chain Investigation (Trace-Back and Trace-Forward). When investigators suspect or find a contaminated food item (based on microbiological analysis of a sample of the food or as the result of a case-control study), they trace backward through the food supply to identify the root source of the contamination. The trace-back begins when a sanitarian collects information about a product or food item from the restaurant, consumer, or retail seller. The necessary information includes brand name, product name, code/lot number, expiration/sell by/use by date, size/weight, package type, date of purchase, manufacturer and address, distributor name and address, and retail food establishment where purchased or consumed (Massachusetts Department of Public Health, 2005).

The U.S. Food and Drug Administration (FDA) conducted a trace-back study that led to green onions grown on farms in Mexico as the source of the hepatitis A outbreak in Pennsylvania (CDC, 2003a). The FDA then conducted an environmental investigation at the farms: "The investigation team identified issues of concern from interviews and observations at all four firms visited including items such as poor sanitation, inadequate hand washing facilities, questions about worker health and hygiene, the quality of water used in the fields, packing sheds, and the making of ice, any of which can have a role in the spread of infectious diseases such as hepatitis A" (FDA, 2003).

The complexity of a trace-back is evident from Figure 3.11. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (FDA, 2004) requires that food producers, retailers, and restaurants maintain records to facilitate trace-back investigations. We discuss these regulations in more detail in Chapter 10.

Trace-forward investigations similarly track a product through the supply chain, but they do so in the forward direction; that is, from a starting point that may have been discovered by the trace-back process through the distribution system to the consumer. U.S. Department of Agriculture (USDA) and other entities conduct trace-forward investigations to find and remove contaminated products before they are distributed to consumers. Trace-forward can also identify people who have already been exposed, who are sick, or who may already have recovered or died from the illness.

Readers interested in more details about food-chain investigation should consult *The Guide to Trace Back of Fresh Fruits and Vegetables Implicated in Epidemiological Investigations* at *http://www.fda.gov/ora/inspect_ref/igs/epigde/epigde.html.* An example of a trace-forward protocol used by the USDA (for a plant disease) is at *http://www.aphis.usda.gov/ppq/ispm/pramorum/pdf_files/traceforwardprotocol.pdf.*

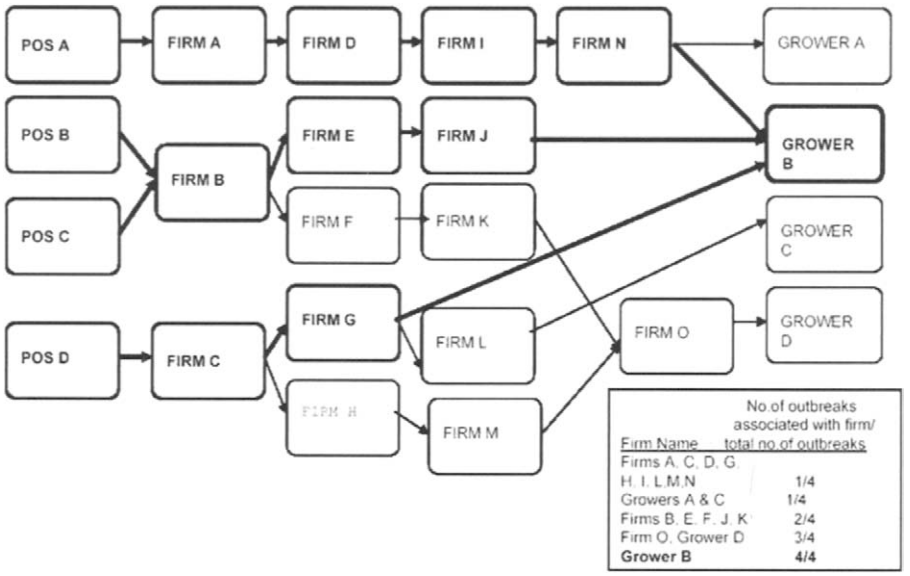


FIGURE 3.11 A hypothetical trace-back investigation involving four different points of service (POSs). POSs are restaurants or other retail stores (e.g., produce store) that sell or serve food or products believed to have caused an outbreak. In this example grower B was the ultimate source of produce for all four points of services. (From *The Guide to Trace Back of Fresh Fruits and Vegetables Implicated in Epidemiological Investigations http://www.fda.gov/ora/inspect_ref/igs/epigde/epigde.html.*)

Vector Investigation. A vector is an animal that can transmit a disease to humans. Many vectors are insects that depend on specific ecological conditions for survival. If the biological agent causing an outbreak is known and if it is known to be associated with vector-based transmission, an investigator will interview the patients and ask questions related to exposure to vectors, insect bites, animal bites, use of prophylaxis such as antimalarial drugs, and travel history before onset of illness. If travel is involved, the investigator may consult CDC travel advisory documents for current information on levels of vector-borne disease around the world.

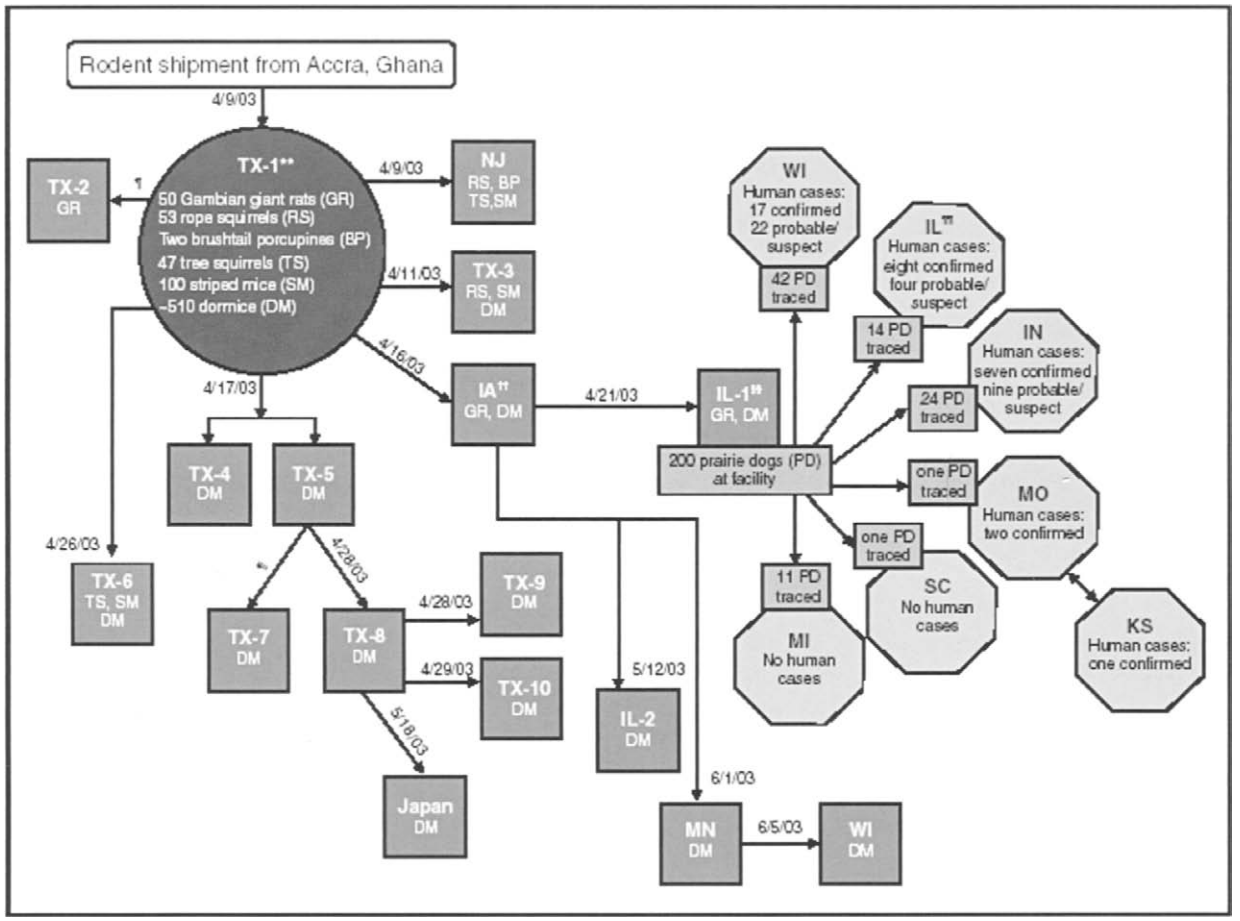
If investigators suspect an exposure to a vector as responsible for disease, they will consult with environmental health specialists to discuss methods to identify the vector habitat and control the vector, especially for prevalent vector-borne diseases such as malaria that have no vaccine. A full investigation of a vector-borne disease normally requires rapid exchange of data and information among a multidisciplinary team of environmental health specialists, veterinarians, and epidemiologists. Environmental health expertise is needed to understand the complex transmission cycles involving a number of vectors (and usually reservoir hosts) and complex environmental controls (World Resources Institute, 1998).

In the spring of 2002, an outbreak of monkeypox in humans produced 71 cases (Ashford et al., 2003). The investigation was initiated based on the report of a three-year-old girl with a history of a prairie dog bite. Investigators used sales invoices to link all cases to a shipment of 38 prairie dogs sold at pet stores or at a swap meet (it is often difficult for investigators to obtain invoices transacted at venues such as a swap meet). A trace-back investigation (Figure 3.12) elucidated the path by which monkeypox was introduced into the United States. A shipment of exotic rodents from Africa made its way via an importer in Texas to its final destination in the midwest. The rodents were colocated temporarily with a colony of prairie dogs. Once the original shipment was identified, trace-forward investigations identified additional animal vendors and owners who purchased prairie dogs during the time frame of the suspect shipment.

4.3.6. Number of People Ill and Number of Persons at Risk

Early during an investigation, the investigators have considerable uncertainty about the number of sick individuals in the population and the number that are infected but not yet symptomatic. The investigators may have very worrisome questions about whether they have enough investigators, vaccine, or antibiotics on hand to manage the outbreak, and they may worry whether their control measures are sufficiently aggressive.

They must estimate the true spatial distribution and true epidemic curve, based on the information available (current set of cases identified, contacts, and known outbreak characteristics). To do this, they must understand the limitations of the biosurveillance systems in place (e.g., the notifiable



* Illinois (IL), Indiana (IN), Iowa (IA), Kansas (KS), Michigan (MI), Minnesota (MN), Missouri (MO), New Jersey (NJ), South Carolina (SC), Texas (TX), and Wisconsin (WI). Japan is included among sites having received shipment of rodents implicated in this outbreak.
† As of July 8, 2003.
§ Does not include one probable human case from Ohio; investigation is ongoing.
¶ Date of shipment unknown.
** Identified as distributor C in *MMWR* 2003;52:561–4.
†† Identified as distributor D in *MMWR* 2003;52:561–4.
§§ Identified as distributor B in *MMWR* 2003;52:561–4.
¶¶ Includes two persons who were employees at IL-1.

FIGURE 3.12 Result of a trace-back and trace-forward investigation of the 2003 Monkeypox outbreak. (From CDC, 2003b.)

disease system, any electronic laboratory reporting systems, and their screening procedures) and of their investigation. In particular, they must understand what fraction of cases their methods detect and what time delay may be present from date of infection. Their decision making related to logistics and control measures depends on an accurate assessment of both the state of the outbreak at the moment as well as projections of the future number of cases and their geographic distribution.

At present, the state of the art in real-time estimation of the magnitude and geographic scope of an outbreak is primitive. In current practice, investigators simply do their best to intensify surveillance to identify all cases so that the observed number of cases is as close to the real number of cases as possible. Any delays in case detection in the biosurveillance system compound the estimation problem. Mathematical models that can estimate the true parameters from observed parameters and knowledge of the delays and sampling efficiency of surveillance methods would likely be very useful, but this topic is an open area of research.

5. LEGAL, ETHICAL, AND PUBLIC RELATIONS ISSUES

Although the immediate purpose of a field investigation is to characterize and control an outbreak, investigators are

cognizant that outbreaks often generate legal proceedings (Gregg, 2002).[5] Outbreak investigators and police investigators often talk to the same individuals and visit the same locations. They may even come into conflict over who gets to speak to an individual first or who has authority over a contaminated building. Police investigators depend on outbreak investigators for many of the clues that they need to identify and successfully prosecute the culprit. Biosurveillance systems must track chain of custody of evidence, especially in the laboratory. For these reasons, the public health workforce receives training in forensic epidemiology to handle legal issues that arise in the setting of joint investigations.

Investigators also must disclose information to the public about outbreaks. Ethical conduct of investigations includes the protection of individual information and confidentiality against disclosure of information (Coughlin and Beauchamp, 1996). Investigators understand that they depend on the public's trust to obtain cooperation and truthful answers to sensitive medical and behavioral questions in future investigations.

The public, politicians, and lawyers can influence the conduct of an investigation, especially investigations of outbreaks of a large number of people or in connection with sudden, mysterious illness with high mortality. The early HIV epidemic highlighted the complex bureaucracy and social agendas that come into play when an epidemic is investigated in an atmosphere charged with fear and prejudice (Shilts and Greider, 1987).

6. SUMMARY

In this chapter, we examined in detail how biosurveillance systems detect and characterize outbreaks. We described the overall process as comprising three distinct subprocesses—case detection, outbreak detection, and *outbreak characterization.* Although we described them as separate steps, one triggering the other, we expect that these processes will become more tightly integrated in the future and that the distinctions between these processes will blur.

Case detection is a front-line activity in biosurveillance, which is accomplished by diverse methods, including detection by clinicians, laboratories, screening programs, and, increasingly, computers. Outbreak detection and characterization depend on case detection. Outbreak detection is based on continuous analysis of human and animal data by people working in health departments, the animal healthcare system, and hospital infection control, as well as by astute citizens. *Outbreak characterization* is an intermittent process that is triggered by outbreak detection. It is the process by which investigators elucidate characteristics of an outbreak that are important for disease control (e.g., causative biological agent, source, and route of transmission). Characterization is based on intensive collection of additional data when an outbreak is suspected or confirmed. Outbreak characterization is the least automated process in biosurveillance at present, but the future role of automation is already recognized (e.g., a recent report from the National Defense University identifies *integrated automated event characterization system based on epidemiological, biological, and chemical models and artificial intelligence* as a key element in an advanced biosurveillance system (Thompson et al., 2005).

Each of these processes involves many individuals with different skills and many organizations with diverse and sometimes overlapping responsibilities. This situation is unlikely to change anytime in the near future, which is why we consider *multiorganizational* and *multidisciplinary* to be fundamental properties of biosurveillance that we must respect when designing biosurveillance systems.

Each of these processes is also data and knowledge intensive (also fundamental properties of biosurveillance). The processes depend not only on substantial data collection but also on mechanisms for the storage, distribution, and presentation of these data. When analyzing these data, people and, increasingly, computers, must bring enormous amounts of knowledge to bear. As in Chapter 1, the analytic processes can perhaps best be summarized by an analogy. The very best outbreak investigators have minds like the great Sherlock Holmes. They are capable of great leaps of insight that appear "elementary" only in retrospect. They arrive at the scene of an outbreak, assimilate the information available from patients and other observers, collect clues, and generate hypotheses about the culprit (the biological agent) and his accomplices (food, water, mail). Their secret: exhaustive knowledge about the modus operandi of hundreds of biological agents produced by scientific studies of past outbreaks. The very best investigators use this knowledge in a way that the clues that they receive and the evidence they collect (e.g., symptoms, test results, and epidemiological patterns) ultimately lead them to

5 The word forensics is derived from the Latin *forensis* meaning legal affairs. *Forensic attribution* assigns responsibility to an individual for an act (but not necessarily to a level required by a specific court as connoted by the term *forensic science*). Forensic attribution can be difficult as demonstrated by the two bioterrorist events that occurred in the U.S. Investigators did not identify the party responsible for the Salmonella outbreak in The Dulles, Oregon—the Bhagwan Shree Rajneesh cult. Although they considered intentional contamination as the source of the outbreak during their investigation, they rejected this idea because there were other plausible theories and no claims of responsibility, no motive, and no observed unusual behavior. Ultimately, an unrelated criminal investigation of the Bhagwan Shree Rajneesh cult uncovered the fact that the cult was responsible for the Salmonella outbreak. The party or parties responsible for the 2001 anthrax letters were never identified.

the biological agent and its source. The deductive techniques they use are numerous, and the selection is dictated by the problem at hand. The potential for formalizing and encoding this knowledge in computer-supported biosurveillance systems is significant.

ADDITIONAL RESOURCES

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Rothman, K. and Greenland, S., eds. (1998). *Modern Epidemiology.* Philadelphia: Lippincott-Raven Publishers. This work describes types of epidemiological studies such as case-control studies and field methods.

U.S. Department of Health and Human Services and Centers for Disease Control. Principles of Epidemiology: An Introduction to Applied Epidemiology and Biostatistics, 2nd ed. Atlanta: Epidemiology Program Office, CDC. *http://www.phppo.cdc.gov/PHTN/catalog/pdf-file/Epi_Course.pdf.* Readers with no formal training in epidemiology will find this an excellent basic introduction. Chapter 6 covers outbreak investigations.

Working Group on Foodborne Illness Control, *Foodborne Illness Investigation and Control Reference Manual.* Boston: Massachusetts Department of Public Health. *http://www.mass.gov/dph/pdf.* This is a comprehensive discussion of foodborne outbreaks, with chapter 7 examining environmental investigations in detail.

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