Principles of Epidemiology

Second Edition

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Selected Lessons

Lesson 1: Introduction to Epidemiology

Lesson 6: Investigating an Outbreak

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Lesson 1
Introduction to Epidemiology

Epidemiology is considered the basic science of public health, and with good reason. Epidemiology is: a) a quantitative basic science built on a working knowledge of probability, statistics, and sound research methods; b) a method of causal reasoning based on developing and testing hypotheses pertaining to occurrence and prevention of morbidity and mortality; and c) a tool for public health action to promote and protect the public's health based on science, causal reasoning, and a dose of practical common sense (2).

As a public health discipline, epidemiology is instilled with the spirit that epidemiologic information should be used to promote and protect the public's health. Hence, epidemiology involves both science and public health practice. The term ***applied epidemiology*** *is sometimes used to describe the application or practice of epidemiology to address public health issues. Examples of applied epidemiology include the following:*

- *the monitoring of reports of communicable diseases in the community*
- *the study of whether a particular dietary component influences your risk of developing cancer*
- *evaluation of the effectiveness and impact of a cholesterol awareness program*
- *analysis of historical trends and current data to project future public health resource needs*

Objectives

After studying this lesson and answering the questions in the exercises, a student will be able to do the following:

- Define epidemiology
- Summarize the historical evolution of epidemiology
- Describe the elements of a case definition and state the effect of changing the value of any of the elements
- List the key features and uses of descriptive epidemiology
- List the key features and uses of analytic epidemiology
- List the three components of the epidemiologic triad
- List and describe primary applications of epidemiology in public health practice
- List and describe the different modes of transmission of communicable disease in a population

Introduction

The word **epidemiology** comes from the Greek words **epi**, meaning "on or upon," **demos**, meaning "people," and **logos**, meaning "the study of." Many definitions have been proposed, but the following definition captures the underlying principles and the public health spirit of epidemiology:

> "Epidemiology is the **study** of the **distribution** and **determinants of health-related states or events** in **specified populations**, and the **application** of this study to the control of health problems." (17)

This definition of epidemiology includes several terms which reflect some of the important principles of the discipline. As you study this definition, refer to the description of these terms below.

Study. Epidemiology is a scientific discipline, sometimes called "the basic science of public health." It has, at its foundation, sound methods of scientific inquiry.

Distribution. Epidemiology is concerned with the frequency and pattern of health events in a population. Frequency includes not only the number of such events in a population, but also the rate or risk of disease in the population. The rate (number of events divided by size of the population) is critical to epidemiologists because it allows valid comparisons across different populations.

Pattern refers to the occurrence of health-related events by time, place, and personal characteristics.

- Time characteristics include annual occurrence, seasonal occurrence, and daily or even hourly occurrence during an epidemic.
- Place characteristics include geographic variation, urban-rural differences, and location of worksites or schools.
- Personal characteristics include demographic factors such as age, race, sex, marital status, and socioeconomic status, as well as behaviors and environmental exposures.

This characterization of the distribution of health-related states or events is one broad aspect of epidemiology called **descriptive epidemiology**. Descriptive epidemiology provides the *What*, *Who*, *When*, and *Where* of health-related events. It is discussed in more detail beginning on page 16.

Determinants. Epidemiology is also used to search for causes and other factors that influence the occurrence of health-related events. **Analytic epidemiology** attempts to provide the *Why* and *How* of such events by comparing groups with different rates of disease occurrence and with differences in demographic characteristics, genetic or immunologic make-up, behaviors, environmental exposures, and other so-called potential risk factors. Under ideal circumstances, epidemiologic findings provide sufficient evidence to direct swift and effective public health control and prevention measures.

Health-related states or events. Originally, epidemiology was concerned with epidemics of communicable diseases. Then epidemiology was extended to endemic communicable diseases and noncommunicable infectious diseases. More recently, epidemiologic methods have been applied to chronic diseases, injuries, birth defects, maternal-child health, occupational health, and environmental health. Now, even behaviors related to health and well-being (amount of exercise, seat-belt use, etc.) are recognized as valid subjects for applying epidemiologic methods. In these lessons we use the term "disease" to refer to the range of health-related states or events.

Specified populations. Although epidemiologists and physicians in clinical practice are both concerned with disease and the control of disease, they differ greatly in how they view "the patient." **Clinicians are concerned with the health of an individual; epidemiologists are concerned with the collective health of the people in a community or other area.** When faced with a patient with diarrheal disease, for example, the clinician and the epidemiologist have different responsibilities. Although both are interested in establishing the correct diagnosis, the clinician usually focuses on treating and caring for the individual. The epidemiologist focuses on the exposure (action or source that caused the illness), the number of other persons who may have been similarly exposed, the potential for further spread in the community, and interventions to prevent additional cases or recurrences.

Application. Epidemiology is more than "the study of." As a discipline within public health, epidemiology provides data for directing public health action. However, using epidemiologic data is an art as well as a science. Consider again the medical model used above: To treat a patient, a clinician must call upon experience and creativity as well as scientific knowledge. Similarly, an epidemiologist uses the scientific methods of descriptive and analytic epidemiology in "diagnosing" the health of a community, but also must call upon experience and creativity when planning how to control and prevent disease in the community.

Evolution

Although epidemiologic thinking has been traced from Hippocrates (circa 400 B.C.) through Graunt (1662), Farr, Snow (both mid-1800's), and others, the discipline did not blossom until the end of the Second World War. The contributions of some of these early and more recent thinkers are described below.

Hippocrates (circa 400 B.C.) attempted to explain disease occurrence from a rational instead of a supernatural viewpoint. In his essay entitled "On Airs, Waters, and Places," Hippocrates suggested that environmental and host factors such as behaviors might influence the development of disease.

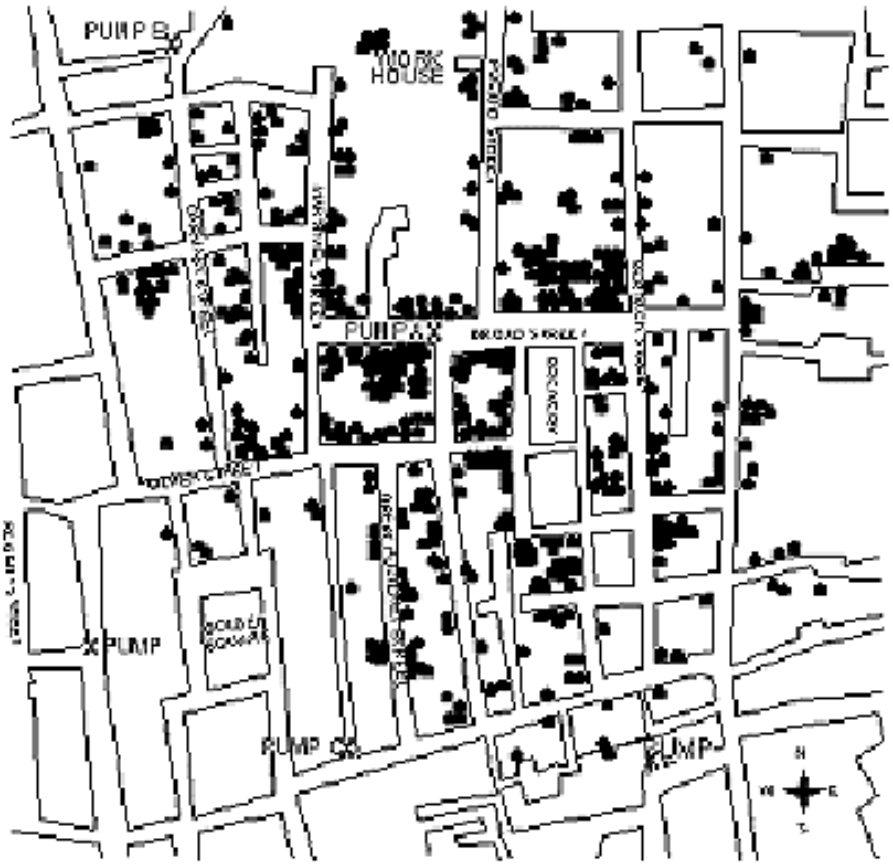
Another early contributor to epidemiology was John Graunt, a London haberdasher who published his landmark analysis of mortality data in 1662. He was the first to quantify patterns of birth, death, and disease occurrence, noting male-female disparities, high infant mortality, urban-rural differences, and seasonal variations. No one built upon Graunt's work until the mid-1800's, when William Farr began to systematically collect and analyze Britain's mortality statistics. Farr, considered the father of modern vital statistics and surveillance, developed many of the basic practices used today in vital statistics and disease classification. He extended the epidemiologic analysis of morbidity and mortality data, looking at the effects of marital status, occupation, and altitude. He also developed many epidemiologic concepts and techniques still in use today.

Meanwhile, an anesthesiologist named John Snow was conducting a series of investigations in London that later earned him the title "the father of field epidemiology." Twenty years before the development of the microscope, Snow conducted studies of cholera outbreaks both to discover the cause of disease and to prevent its recurrence. Because his work classically illustrates the sequence from descriptive epidemiology to hypothesis generation to hypothesis testing (analytic epidemiology) to application, we will consider two of his efforts in detail.

Snow conducted his classic study in 1854 when an epidemic of cholera developed in the Golden Square of London. He began his investigation by determining where in this area persons with cholera lived and worked. He then used this information to map the distribution of cases on what epidemiologists call a spot map. His map in shown in Figure 1.1.

Because Snow believed that water was a source of infection for cholera, he marked the location of water pumps on his spot map, and then looked for a relationship between the distribution of cholera case households and the location of pumps. He noticed that more case households clustered around Pump A, the Broad Street pump, than around Pump B or C, and he concluded that the Broad Street pump was the most likely source of infection. Questioning residents who lived near the other pumps, he found that they avoided Pump B because it was grossly contaminated, and that Pump C was located too inconveniently for most residents of the Golden Square area. From this information, it appeared to Snow that the Broad Street pump was probably the primary source of water for most persons with cholera in the Golden Square area. He realized, however, that it was too soon to draw that conclusion because the map showed no cholera cases in a two-block area to the east of the Broad Street pump. Perhaps no one lived in that area. Or perhaps the residents were somehow protected.

Figure 1.1
Distribution of cholera cases in the Golden Square area of London, August-September 1854



Upon investigating, Snow found that a brewery was located there and that it had a deep well on the premises where brewery workers, who also lived in the area, got their water. In addition, the brewery allotted workers a daily quota of malt liquor. Access to these uncontaminated rations could explain why none of the brewery's employees contracted cholera.

To confirm that the Broad Street pump was the source of the epidemic, Snow gathered information on where persons with cholera had obtained their water. Consumption of water from the Broad Street pump was the one common factor among the cholera patients. According to legend, Snow removed the handle of that pump and aborted the outbreak.

Figure 1.2
Water contaminated with deadly cholera flowed from the Broad Street pump

Figure not shown.

Snow's second major contribution involved another investigation of the same outbreak of cholera that occurred in London in 1854. In a London epidemic in 1849, Snow had noted that districts with the highest mortalities had water supplied by two companies: the Lambeth Company and the Southwark and Vauxhall Company. At that time, both companies obtained water from the Thames River, at intake points that were below London. In 1852, the Lambeth Company moved their water works to above London, thus obtaining water that was free of London sewage. When cholera returned to London in 1853, Snow realized the Lambeth Company's relocation of its intake point would allow him to compare districts that were supplied with water from above London with districts that received water from below London. Table 1.1 shows what Snow found when he made that comparison for cholera mortality over a 7-week period during the summer of 1854.

Table 1.1
Mortality from cholera in the districts of London supplied by the Southwark and Vauxhall and the Lambeth Companies, July 9-August 26, 1854

Districts with Water Supplied by	Population (1851 Census)	Deaths from Cholera	Cholera Death Rate per 1,000 Population
Southwark and Vauxhall Co. only	167,654	844	5.0
Lambeth Co. only	19,133	18	0.9
Both companies	300,149	652	2.2

Source: 27

The data in Table 1.1 show that the risk of death from cholera was more than 5 times higher in districts served only by the Southwark and Vauxhall Company than in those served only by the Lambeth Company. Interestingly, the mortality rate in districts supplied by both companies fell between the rates for districts served exclusively by either company. These data were consistent with the hypothesis that water obtained from the Thames below London was a source of cholera. Alternatively, the populations supplied by the two companies may have differed on a number of other factors which affected their risk of cholera.

To test his water supply hypothesis, Snow focused on the districts served by both companies, because the households within a district were generally comparable except for water supply company. In these districts, Snow identified the water supply company for every house in which a death from cholera had occurred during the 7-week period. Table 1.2 shows his findings.

This further study added support to Snow's hypothesis, and demonstrates the sequence of steps used today to investigate outbreaks of disease. Based on a characterization of the cases and population at risk by time, place, and person, Snow developed a testable hypothesis. He then tested this hypothesis with a more rigorously designed study, ensuring that the groups to be compared were comparable. After this study, efforts to control the epidemic were directed at changing the location of the water intake of the Southwark and Vauxhall Company to avoid sources of contamination. Thus, with no knowledge of the existence of microorganisms, Snow demonstrated through epidemiologic studies that water could serve as a vehicle for transmitting

Table 1.2
Mortality from cholera in London related to the water supply of individual houses in districts served by both the Southwark and Vauxhall Company and the Lambeth Company, July 9-August 26, 1854

Water Supply of Individual House	Population (1851 Census)	Deaths from Cholera	Death Rate per 1,000 Population
Southwark and Vauxhall Co.	98,862	419	4.2
Lambeth Co.	154,615	80	0.5

Source: 27

cholera and that epidemiologic information could be used to direct prompt and appropriate public health action.

In the mid- and late-1800's, many others in Europe and the United States began to apply epidemiologic methods to investigate disease occurrence. At that time, most investigators focused on acute infectious diseases. In the 1900's, epidemiologists extended their methods to noninfectious diseases. The period since the Second World War has seen an explosion in the development of research methods and the theoretical underpinnings of epidemiology, and in the application of epidemiology to the entire range of health-related outcomes, behaviors, and even knowledge and attitudes. The studies by Doll and Hill (13) linking smoking to lung cancer and the study of cardiovascular disease among residents of Framingham, Massachusetts (12), are two examples of how pioneering researchers have applied epidemiologic methods to chronic disease since World War II. Finally, during the 1960's and early 1970's health workers applied epidemiologic methods to eradicate smallpox worldwide. This was an achievement in applied epidemiology of unprecedented proportions.

Today, public health workers throughout the world accept and use epidemiology routinely. Epidemiology is often practiced or used by non-epidemiologists to characterize the health of their communities and to solve day-to-day problems. This landmark in the evolution of the discipline is less dramatic than the eradication of smallpox, but it is no less important in improving the health of people everywhere.

Uses

Epidemiology and the information generated by epidemiologic methods have many uses. These uses are categorized and described below.

Population or community health assessment. To set policy and plan programs, public health officials must assess the health of the population or community they serve and must determine whether health services are available, accessible, effective, and efficient. To do this, they must find answers to many questions: What are the actual and potential health problems in the community? Where are they? Who is at risk? Which problems are declining over time? Which ones are increasing or have the potential to increase? How do these patterns relate to the level and distribution of services available? The methods of descriptive and analytic epidemiology provide ways to answer these and other questions. With answers provided through the application of epidemiology, the officials can make informed decisions that will lead to improved health for the population they serve.

Individual decisions. People may not realize that they use epidemiologic information in their daily decisions. When they decide to stop smoking, take the stairs instead of the elevator, order a salad instead of a cheeseburger with French fries, or choose one method of contraception instead of another, they may be influenced, consciously or unconsciously, by epidemiologists' assessment of risk. Since World War II, epidemiologists have provided information related to all those decisions. In the 1950's, epidemiologists documented the increased risk of lung cancer among smokers; in the 1960's and 1970's, epidemiologists noted a variety of benefits and risks associated with different methods of birth control; in the mid-1980's, epidemiologists identified the increased risk of human immunodeficiency virus (HIV) infection associated with certain sexual and drug-related behaviors; and, more positively, epidemiologists continue to document the role of exercise and proper diet in reducing the risk of heart disease. These and hundreds of other epidemiologic findings are directly relevant to the choices that people make every day, choices that affect their health over a lifetime.

Completing the clinical picture. When studying a disease outbreak, epidemiologists depend on clinical physicians and laboratory scientists for the proper diagnosis of individual patients. But epidemiologists also contribute to physicians' understanding of the clinical picture and natural history of disease. For example, in late 1989 three patients in New Mexico were diagnosed as having myalgias (severe muscle pains in chest or abdomen) and unexplained eosinophilia (an increase in the number of one type of white blood cell). Their physician could not identify the cause of their symptoms, or put a name to the disorder. Epidemiologists began looking for other cases with similar symptoms, and within weeks had found enough additional cases of eosinophilia-myalgia syndrome to describe the illness, its complications, and its rate of mortality. Similarly, epidemiologists have documented the course of HIV infection, from the initial exposure to the development of a wide variety of clinical syndromes that include acquired immunodeficiency syndrome (AIDS). They have also documented the numerous conditions that are associated with cigarette smoking—from pulmonary and heart disease to lung and cervical cancer.

Search for causes. Much of epidemiologic research is devoted to a search for causes, factors which influence one's risk of disease. Sometimes this is an academic pursuit, but more often the goal is to identify a cause so that appropriate public health action might be taken. It has been said that epidemiology can never *prove* a causal relationship between an exposure and a disease. Nevertheless, epidemiology often provides enough information to support effective action. Examples include John Snow's removal of the pump handle and the withdrawal of a specific brand of tampon that was linked by epidemiologists to toxic shock syndrome. Just as often, epidemiology and laboratory science converge to provide the evidence needed to establish causation. For example, a team of epidemiologists were able to identify a variety of risk factors during an outbreak of a pneumonia among persons attending the American Legion Convention in Philadelphia in 1976. However, the outbreak was not "solved" until the Legionnaires' bacillus was identified in the laboratory almost 6 months later.

Exercise 1.1

In the early 1980's, epidemiologists recognized that AIDS occurred most frequently in men who had sex with men and in intravenous drug users.

Describe how this information might be used for each of the following:

a. Population or community health assessment

b. Individual decisions

c. Search for causes

Answers on page 62.

The Epidemiologic Approach

Like a newspaper reporter, an epidemiologist determines *What*, *When*, *Where*, *Who*, and *Why*. However, the epidemiologist is more likely to describe these concepts in slightly different terms: **case definition**, **time**, **place**, **person**, and **causes**.

Case Definition

A **case definition** is a set of standard criteria for deciding whether a person has a particular disease or other health-related condition. By using a standard case definition we ensure that every case is diagnosed in the same way, regardless of when or where it occurred, or who identified it. We can then compare the number of cases of the disease that occurred in one time or place with the number that occurred at another time or another place. For example, with a standard case definition, we can compare the number of cases of hepatitis A that occurred in New York City in 1991 with the number that occurred there in 1990. Or we can compare the number of cases that occurred in New York in 1991 with the number that occurred in San Francisco in 1991. With a standard case definition, when we find a difference in disease occurrence, we know it is likely to be a real difference rather than the result of differences in how cases were diagnosed.

Appendix C shows case definitions for several diseases of public health importance. A case definition consists of clinical criteria and, sometimes, limitations on time, place, and person. The clinical criteria usually include confirmatory laboratory tests, if available, or combinations of symptoms (subjective complaints), signs (objective physical findings), and other findings. For example, on page 13 see the case definition for rabies that has been excerpted from Appendix C; notice that it requires laboratory confirmation.

Compare this with the case definition for Kawasaki syndrome provided in Exercise 1.3 (page 15). Kawasaki syndrome is a childhood illness with fever and rash that has no known cause and no specifically distinctive laboratory findings. Notice that its case definition is based on the presence of fever, at least four of five specified clinical findings, and the lack of a more reasonable explanation.

A case definition may have several sets of criteria, depending on how certain the diagnosis is. For example, during an outbreak of measles, we might classify a person with a fever and rash as having a suspect, probable, or confirmed case of measles, depending on what additional evidence of measles was present. In other situations, we temporarily classify a case as suspect or probable until laboratory results are available. When we receive the laboratory report, we then reclassify the case as either confirmed or “not a case,” depending on the lab results. In the midst of a large outbreak of a disease caused by a known agent, we may permanently classify some cases as suspect or probable, because it is unnecessary and wasteful to run laboratory tests on every patient with a consistent clinical picture and a history of exposure (e.g., chickenpox). Case definitions should not rely on laboratory culture results alone, since organisms are sometimes present without causing disease.

Case definitions may also vary according to the purpose for classifying the occurrences of a disease. For example, health officials need to know as soon as possible if anyone has symptoms of plague or foodborne botulism so that they can begin planning what actions to take. For such rare but potentially severe communicable diseases, where it is important to identify every possible case, health officials use a **sensitive**, or "loose" case definition. On the other hand, investigators of the causes of a disease outbreak want to be certain that any person included in the investigation really had the disease. The investigator will prefer a **specific** or "strict" case definition. For instance, in an outbreak of *Salmonella agona*, the investigators would be more likely to identify the source of the infection if they included only persons who were confirmed to have been infected with that organism, rather than including anyone with acute diarrhea, because some persons may have had diarrhea from a different cause. In this setting, the only disadvantage of a strict case definition is an underestimate of the total number of cases.

Rabies, Human

Clinical description

Rabies is an acute encephalomyelitis that almost always progresses to coma or death within 10 days of the first symptom.

Laboratory criteria for diagnosis

- Detection by direct fluorescent antibody of viral antigens in a clinical specimen (preferably the brain or the nerves surrounding hair follicles in the nape of the neck), or
- Isolation (in cell culture or in a laboratory animal) of rabies virus from saliva, cerebrospinal fluid (CSF), or central nervous system tissue, or
- Identification of a rabies-neutralizing antibody titer greater than or equal to 5 (complete neutralization) in the serum or CSF of an unvaccinated person

Case classification

Confirmed: a clinically compatible illness that is laboratory confirmed

Comment

Laboratory confirmation by all of the above methods is strongly recommended.

Source: 3

Exercise 1.2

In the case definition for an apparent outbreak of trichinosis, investigators used the following classifications:

Clinical criteria

Confirmed case: signs and symptoms plus laboratory confirmation

Probable case: acute onset of at least three of the following four features: myalgia, fever, facial edema, or eosinophil count greater than 500/mm^3

Possible case: acute onset of two of the four features *plus* a physician diagnosis of trichinosis

Suspect case: unexplained eosinophilia

Not a case: failure to fulfill the criteria for a confirmed, probable, possible, or suspect case

Time

Onset after October 26, 1991

Place

Metropolitan Atlanta

Person

Any

Assign the appropriate classification to each of the persons included in the line listing below. (All were residents of Atlanta with acute onset of symptoms in November.)

ID #	Last name	myalgia	fever	facial edema	eosinophil count	Physician diagnosis	Lab confirm	Classification
1	Abels	yes	yes	no	495	trichinosis	yes	----------
2	Baker	yes	yes	yes	pending	trichinosis ?	pending	----------
3	Corey	yes	yes	no	1,100	trichinosis	pending	----------
4	Dale	yes	no	no	2,050	EMS ?	pending	----------
5	Ring	yes	no	no	600	trichinosis	not done	----------

Answers on page 62.

Exercise 1.3

The following is the official case definition for Kawasaki syndrome that is recommended by CDC:

Kawasaki Syndrome

Clinical case definition

A febrile illness of greater than or equal to 5 days' duration, with at least four of the five following physical findings and no other more reasonable explanation for the observed clinical findings:

- Bilateral conjunctival injection
- Oral changes (erythema of lips or oropharynx, strawberry tongue, or fissuring of the lips)
- Peripheral extremity changes (edema, erythema, or generalized or periungual desquamation)
- Rash
- Cervical lymphadenopathy (at least one lymph node greater than or equal to 1.5 cm in diameter)

Laboratory criteria for diagnosis

None

Case classification

Confirmed: a case that meets the clinical case definition

Comment

If fever disappears after intravenous gamma globulin therapy is started, fever may be of less than 5 days' duration, and the clinical case definition may still be met.

Source: 3

Discuss the pros and cons of this case definition for the purposes listed below. (For a brief description of Kawasaki syndrome, see Benenson's *Control of Communicable Diseases in Man*).

a. diagnosing and treating individual patients

b. tracking the occurrence of the disease for public health records

c. doing research to identify the cause of the disease

Answers on page 63.

Numbers and Rates

A basic task of a health department is counting cases in order to measure and describe morbidity. When physicians diagnose a case of a reportable disease they send a report of the case to their local health department. These reports are legally required to contain information on time (when the case occurred), place (where the patient lived), and person (the age, race, and sex of the patient). The health department combines the reports and summarizes the information by time, place, and person. From these summaries, the health department determines the extent and patterns of disease occurrence in the area, and identifies clusters or outbreaks of disease.

A simple count of cases, however, does not provide all the information a health department needs. To compare the occurrence of a disease at different locations or during different times, a health department converts the case counts into **rates**, which relate the number of cases to the size of the population where they occurred.

Rates are useful in many ways. With rates, the health department can identify groups in the community with an elevated risk of disease. These so-called **high-risk groups** can be further assessed and targeted for special intervention; the groups can be studied to identify **risk factors** that are related to the occurrence of disease. Individuals can use knowledge of these risk factors to guide their decisions about behaviors that influence health. (Lesson 2 discusses rates in more detail.)

Descriptive Epidemiology

In descriptive epidemiology, we organize and summarize data according to time, place, and person. These three characteristics are sometimes called the **epidemiologic variables**.

Compiling and analyzing data by time, place, and person is desirable for several reasons. First, the investigator becomes intimately familiar with the data and with the extent of the public health problem being investigated. Second, this provides a detailed description of the health of a population that is easily communicated. Third, such analysis identifies the populations that are at greatest risk of acquiring a particular disease. This information provides important clues to the causes of the disease, and these clues can be turned into testable hypotheses.

Time

Disease rates change over time. Some of these changes occur regularly and can be predicted. For example, the seasonal increase of influenza cases with the onset of cold weather is a pattern that is familiar to everyone. By knowing when flu outbreaks will occur, health departments can time their flu shot campaigns effectively. Other disease rates make unpredictable changes. By examining events that precede a disease rate increase or decrease, we may identify causes and appropriate actions to control or prevent further occurrence of the disease.

We usually show time data as a graph. We put the number or rate of cases or deaths on the vertical, *y-axis*; we put the time periods along the horizontal, *x-axis*. We often indicate on a graph when events occurred that we believe are related to the particular health problem described in the graph. For example, we may indicate the period of exposure or the date control measures were implemented. Such a graph provides a simple visual depiction of the relative size of a problem, its past trend and potential future course, as well as how other events may have affected the problem. Studying such a graph often gives us insights into what may have caused the problem.

Depending on what event we are describing, we may be interested in a period of years or decades, or we may limit the period to days, weeks, or months when the number of cases reported is greater than normal (an **epidemic period**). For some conditions—for many chronic diseases, for example—we are interested in long-term changes in the number of cases or rate of the condition. For other conditions, we may find it more revealing to look at the occurrence of the condition by season, month, day of the week, or even time of day. For a newly recognized problem, we need to assess the occurrence of the problem over time in a variety of ways until we discover the most appropriate and revealing time period to use. Some of the common types of time-related graphs are further described below.

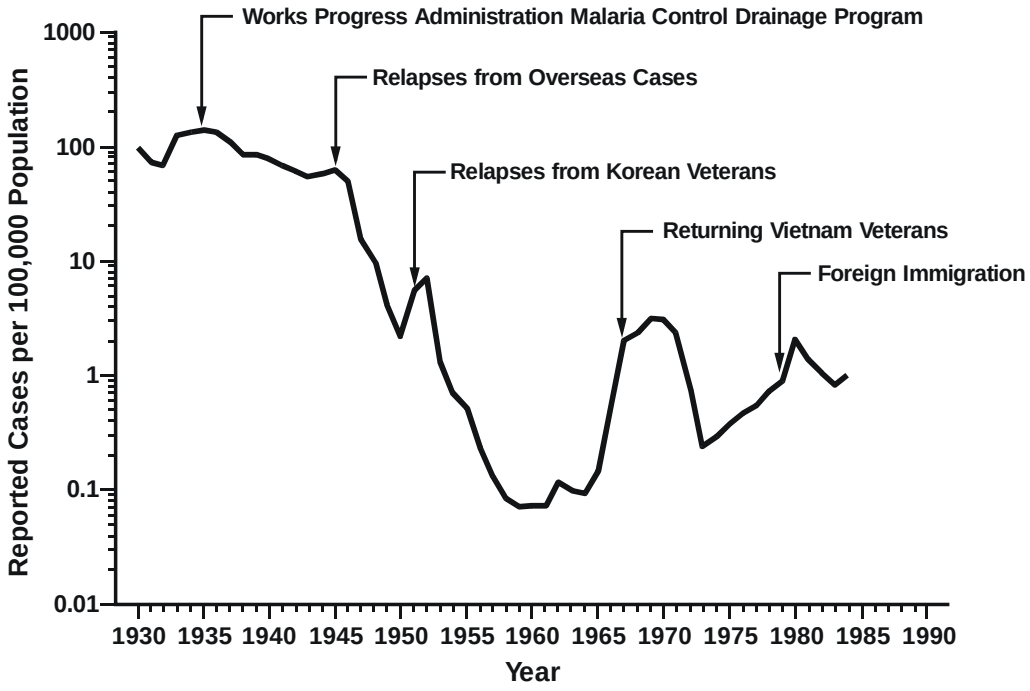
Secular (long-term) trends. Graphing the annual cases or rate of a disease over a period of years shows long-term or **secular trends** in the occurrence of the disease. We commonly use these trends to suggest or predict the future incidence of a disease. We also use them in some instances to evaluate programs or policy decisions, or to suggest what caused an increase or decrease in the occurrence of a disease, particularly if the graph indicates when related events took place, as Figure 1.3 does. (NOTE: If you have difficulty understanding the graphs in this lesson, refer to Lesson 4 for information on Tables, Graphs, and Charts.)

Seasonality. By graphing the occurrence of a disease by week or month over the course of a year or more we can show its seasonal pattern, if any. Some diseases are known to have characteristic seasonal distributions; for example, as mentioned earlier, the number of reported cases of influenza typically increases in winter. Seasonal patterns may suggest hypotheses about how the infection is transmitted, what behavioral factors increase risk, and other possible contributors to the disease or condition. The seasonal pattern of farm tractor fatalities is shown in Figure 1.4. What factors might contribute to its seasonal pattern?

Notice that Figure 1.5 shows the occurrence of a disease event over the course of a year. Before reading further, examine the pattern of cases in this graph and decide whether you can conclude from this graph that the disease will have this same pattern every year.

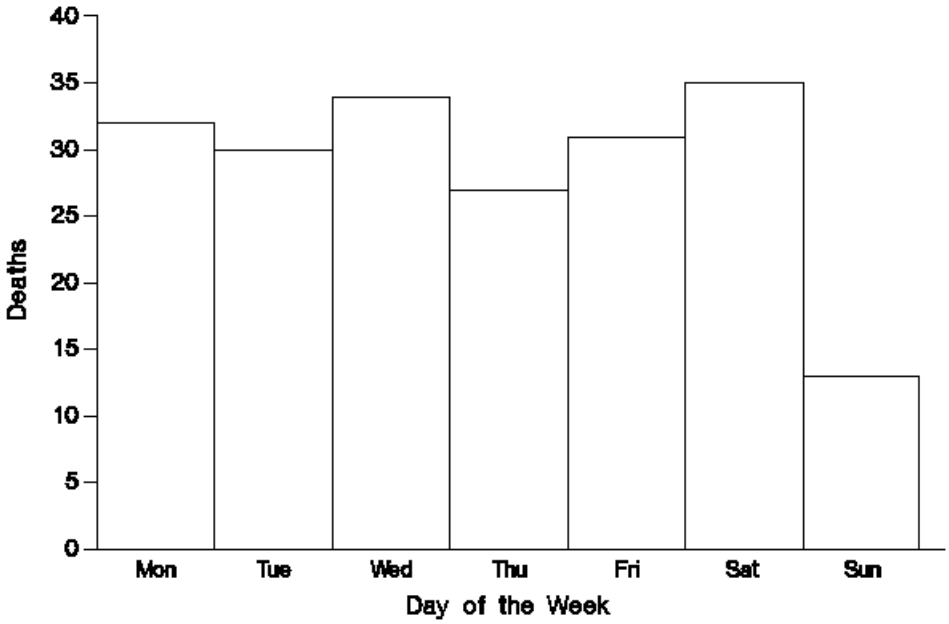
From only the single year’s data in Figure 1.5, it is difficult to conclude whether the peak in June represents a characteristic seasonal pattern that would be repeated yearly, or whether it is simply an epidemic that occurred in the spring and summer of that particular year. You would need more than one year’s data before you could conclude that the pattern shown there represents the seasonal variation in this disease.

Figure 1.3
Malaria by year, United States, 1930-1990



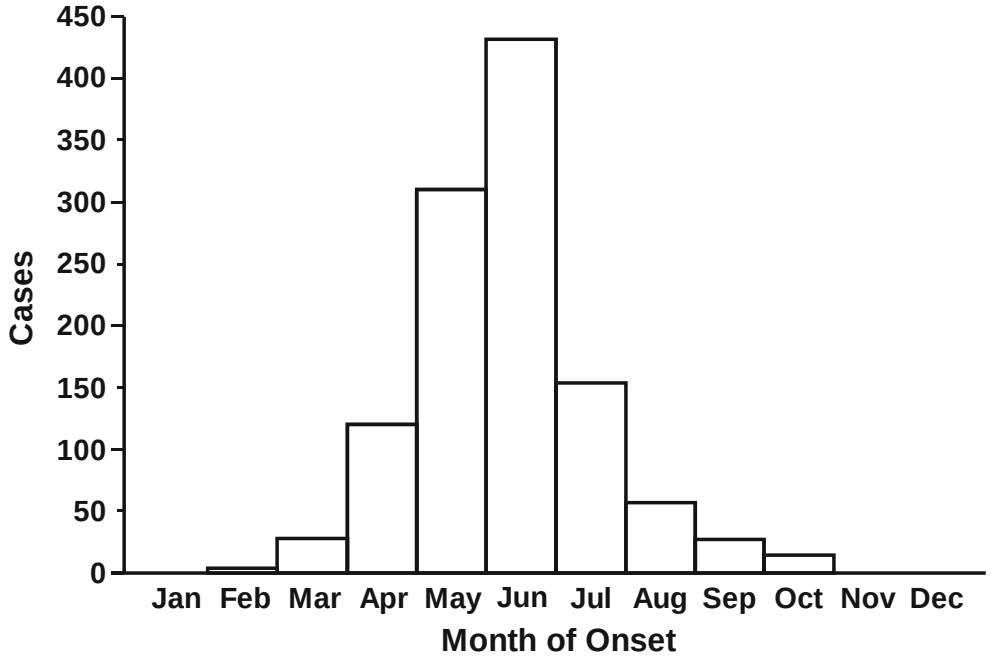
Source: 9

Figure 1.4
Fatalities associated with farm tractor injuries by month of death, Georgia, 1971-1981



Source: 15

Figure 1.5
Cases of an unknown disease by month of onset



Source: 14

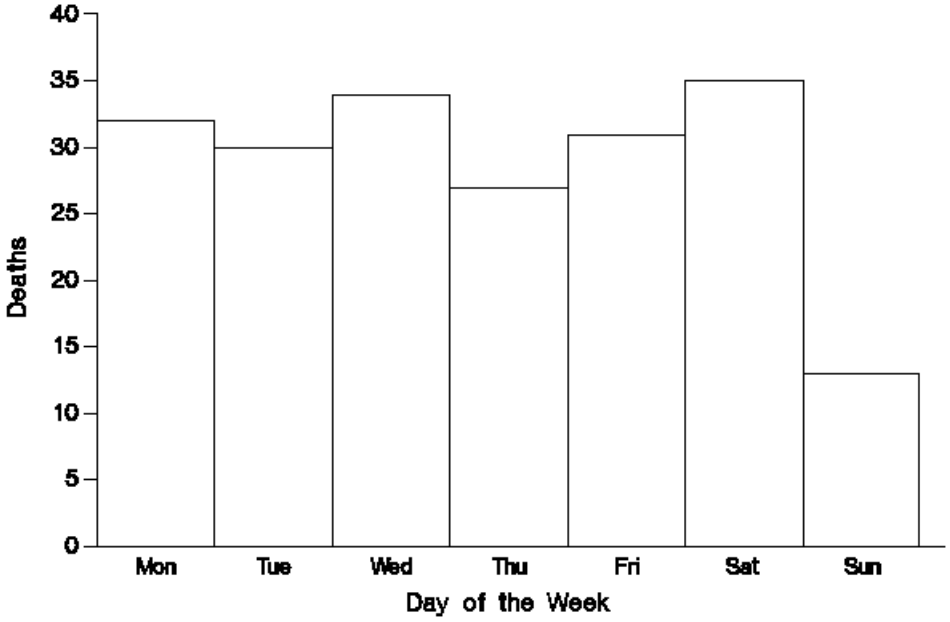
Day of week and time of day. Displaying data by days of the week or time of day may also be informative. Analysis at these shorter time periods is especially important for conditions that are potentially related to occupational or environmental exposures, which may occur at regularly scheduled intervals. In Figure 1.6, farm tractor fatalities are displayed by days of the week. Does this analysis at shorter time periods suggest any hypothesis?

In Figure 1.6 the number of farm tractor fatalities on Sundays is about half the number on the other days. We can only speculate why this is. One reasonable hypothesis is that farmers spend fewer hours on their tractors on Sundays than on the other days.

Examine the pattern of fatalities associated with farm tractor injuries by hour in Figure 1.7. How might you explain the morning peak at 11:00 AM, the dip at noon, and the afternoon peak at 4:00 PM?

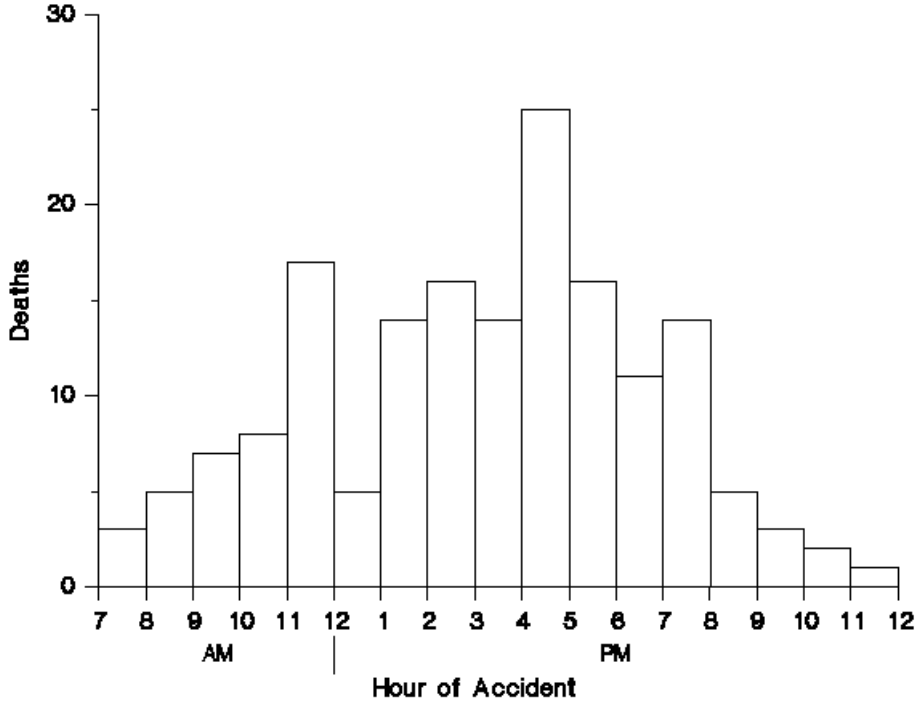
Epidemic period. To show the time course of a disease outbreak or epidemic, we use a specialized graph called an **epidemic curve**. As with the other graphs you have seen in this section, we place the number of cases on the vertical axis and time on the horizontal axis. For time, we use either the time of onset of symptoms or the date of diagnosis. For very acute diseases with short incubation periods (i.e., time period between exposure and onset of symptoms is short), we may show time as the hour of onset. For diseases with longer incubation periods, we might show time in 1-day, 2-day, 3-day, 1-week, or other appropriate intervals. Figure 1.8 shows an epidemic curve that uses a 3-day interval for a foodborne disease outbreak. Notice how the cases are stacked in adjoining columns. By convention, we use this format, called a **histogram**, for epidemic curves. The shape and other features of an epidemic curve can suggest hypotheses about the time and source of exposure, the mode of transmission, and the causative agent. Epidemic curves are discussed in more detail in Lessons 4 and 6.

Figure 1.6
Fatalities associated with farm tractor injuries
by day of death, Georgia, 1971-1981



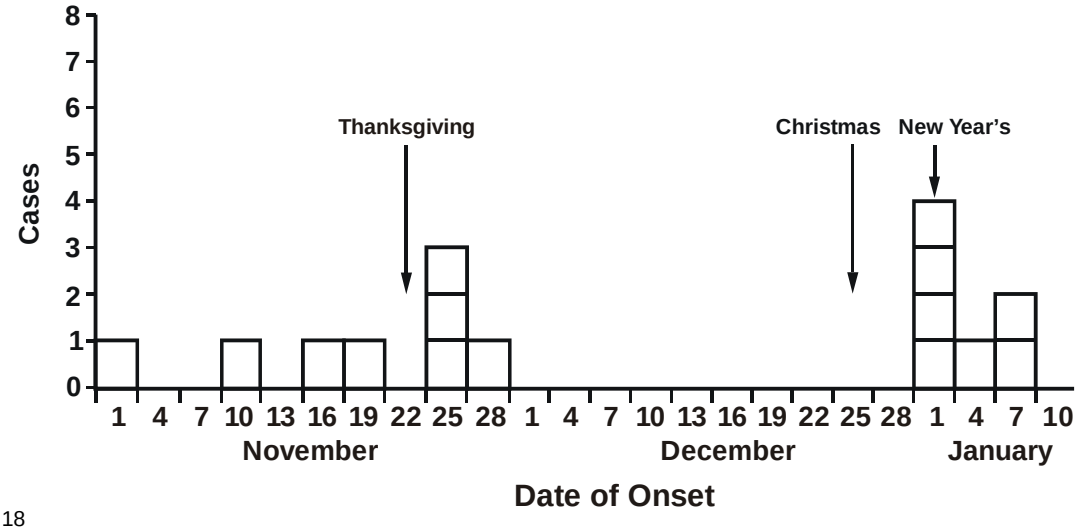
Source: 15

Figure 1.7
Fatalities associated with farm tractor injuries
by time of day, Georgia, 1971-1981



Source: 15

Figure 1.8
Date of onset of illness in patients with culture-confirmed *Yersinia enterocolitica* infections, Atlanta, November 1, 1988-January 10, 1989



Source: 18

Place

We describe a health event by place to gain insight into the geographical extent of the problem. For place, we may use place of residence, birthplace, place of employment, school district, hospital unit, etc., depending on which may be related to the occurrence of the health event. Similarly, we may use large or small geographic units: country, state, county, census tract, street address, map coordinates, or some other standard geographical designation. Sometimes, we may find it useful to analyze data according to place categories such as urban or rural, domestic or foreign, and institutional or noninstitutional.

Not all analyses by place will be equally informative. For example, examine the data shown in Table 1.3. Where were the malaria cases diagnosed? What "place" does the table break the data down by? Would it have been more or less useful to analyze the data according to the "state of residence" of the cases?

We believe that it provides more useful information to show the data in Table 1.3 by where the infection was acquired than it would have to show where the case-patients lived. By analyzing the malaria cases by place of acquisition, we can see where the risk of acquiring malaria is high.

By analyzing data by place, we can also get an idea of where the agent that causes a disease normally lives and multiplies, what may carry or transmit it, and how it spreads. When we find that the occurrence of a disease is associated with a place, we can infer that factors that increase the risk of the disease are present either in the persons living there (**host factors**) or in the environment, or both. For example, diseases that are passed from one person to another spread more rapidly in urban areas than in rural ones, mainly because the greater crowding in urban areas provides more opportunities for susceptible people to come into contact with someone who

Table 1.3
Malaria cases by distribution of Plasmodium species and area of acquisition, United States, 1989

	Species			
Area of Acquisition	**Vivax**	**Falciparum**	**Other**	**Total**
Africa	52	382	64	498
Asia	207	44	29	280
Central America & Caribbean	107	14	9	130
North America	131	3	13	147
(United States)	(5)	(0)	(0)	(5)
South America	10	1	2	13
Oceania	19	2	5	26
Unknown	6	2	0	8
Total	**532**	**448**	**122**	**1,102**

Source: 6

is infected. On the other hand, diseases that are passed from animals to humans often occur in greater numbers in rural and suburban areas because people in those areas are more likely to come into contact with disease-carrying animals, ticks, and the like. For example, perhaps Lyme disease has become more common because people have moved to wooded areas where they come into contact with infected deer ticks.

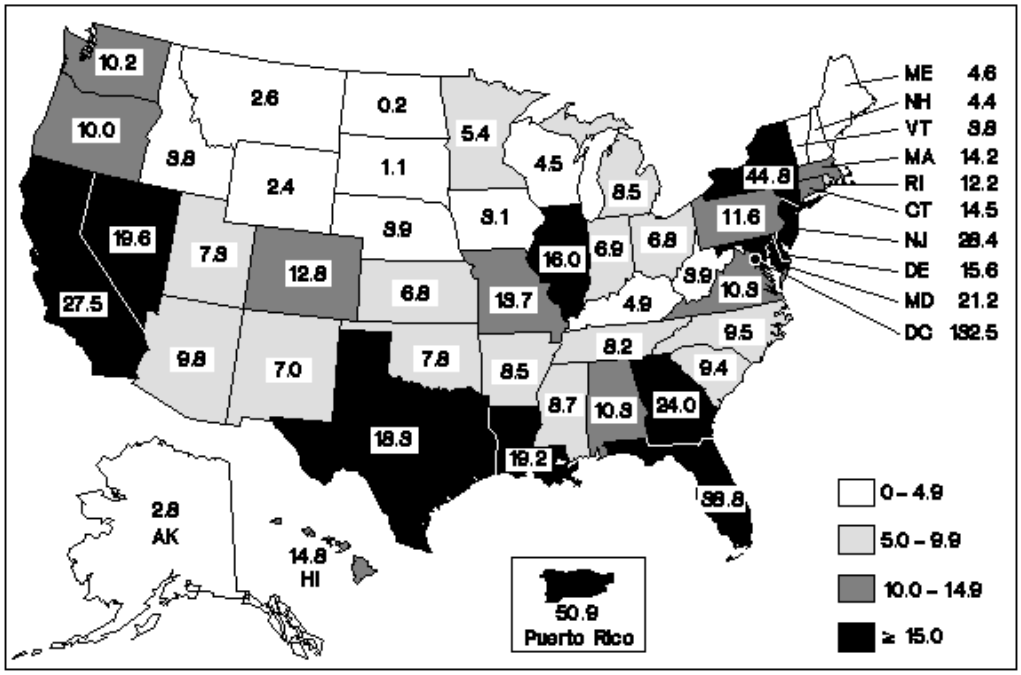
Although we can show data by place in a table—as Table 1.3 does—it is often better to show it pictorially in a map. On a map, we can use different shadings, color, or line patterns to indicate how a disease or health event has different numbers or rates of occurrence in different areas, as in Figure 1.9.

For a rare disease or outbreak, we often find it useful to prepare a **spot map**, like Snow's map of the Golden Square of London (Figure 1.1, page 5), in which we mark with a dot or an X the relation of each case to a place that is potentially relevant to the health event being investigated—such as where each case lived or worked. We may also label other sites on a spot map, such as where we believe cases may have been exposed, to show the orientation of cases within the area mapped.

Figure 1.10 is a spot map for an outbreak of mumps that occurred among employees of the Chicago futures exchanges. Study the location of each case in relation to other cases and to the trading pits. The four numbered areas delineated with heavy lines are the trading pits. Do the location of cases on the spot map lead you to any hypothesis about the source of infection?

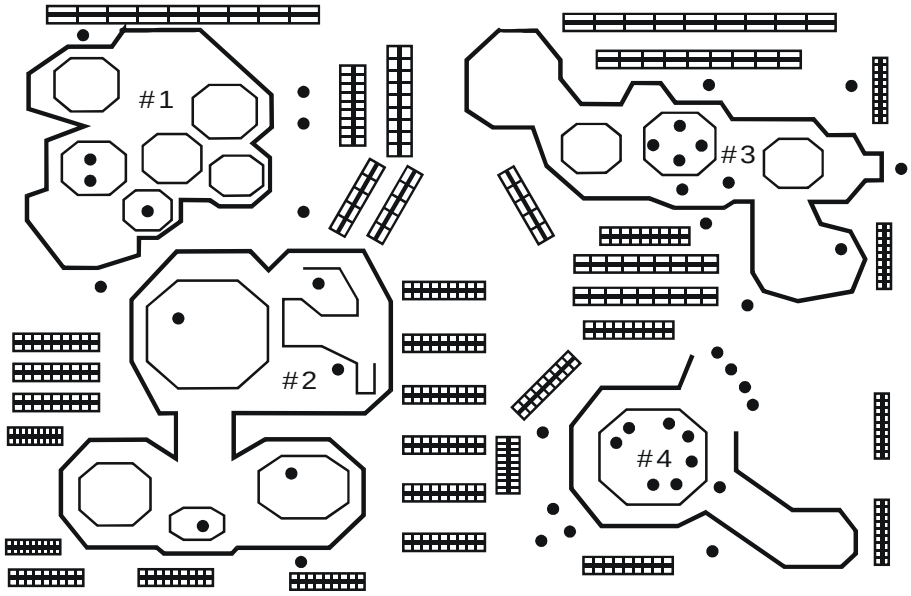
You probably observed that the cases occurred primarily among those working in trading pits #3 and #4. This clustering of illness within trading pits provides indirect evidence that the mumps was transmitted person-to person.

Figure 1.9
AIDS cases per 100,000 population,
United States, July 1991-June 1992



Source: 4

Figure 1.10
Mumps cases in trading pits of exchange A, Chicago, Illinois,
August 18-December 25, 1987



Pit areas are numbered and delineated by heavy lines.
Individual trading pits within pit areas are outlined by light lines.

Source: CDC, unpublished data, 1988

Person

In descriptive epidemiology, when we organize or analyze data by "person" there are several person categories available to us. We may use inherent characteristics of people (for example, age, race, sex), their acquired characteristics (immune or marital status), their activities (occupation, leisure activities, use of medications/tobacco/drugs), or the conditions under which they live (socioeconomic status, access to medical care). These categories determine to a large degree who is at greatest risk of experiencing some undesirable health condition, such as becoming infected with a particular disease organism. We may show person data in either tables or graphs.

In analyzing data by person, we often must try a number of different person categories before we find which are the most useful and enlightening. Age and sex are most critical; we almost always analyze data according to these. Depending on what health event we are studying, we may or may not break the data down by the other attributes. Often we analyze data into more than one category simultaneously; for example, we may look at age and sex simultaneously to see if the sexes differ in how they develop a condition that increases with age—as they do for heart disease.

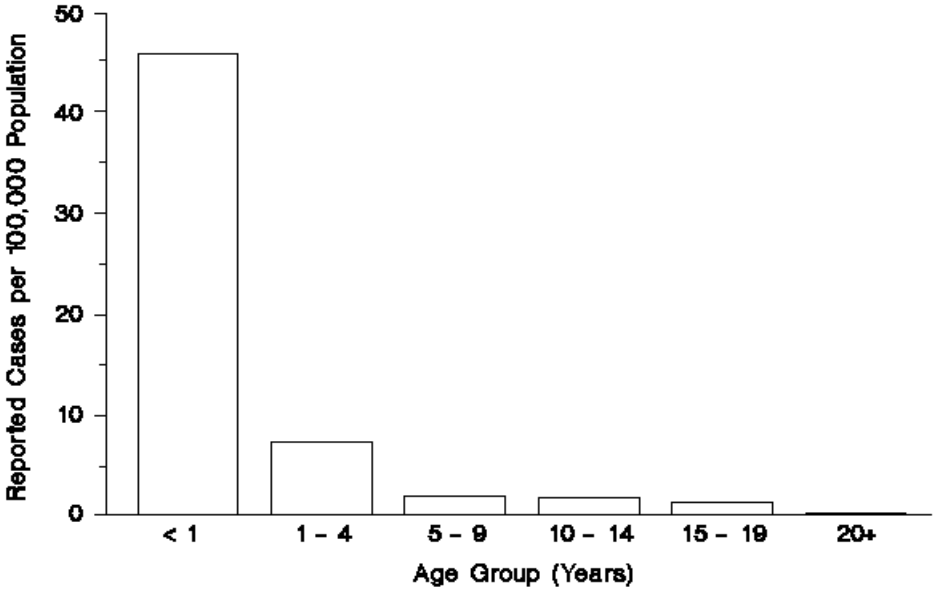
Age. Age is probably the single most important "person" attribute, because almost every health-related event or state varies with age. A number of factors that also vary with age are behind this association: susceptibility, opportunity for exposure, latency or incubation period of the disease, and physiologic response (which affects, among other things, disease development).

When we analyze data by age, we try to use age groups that are narrow enough to detect any age-related patterns that may be present in the data. In an initial breakdown by age, we commonly use 5-year age intervals: 0 to 4 years, 5 to 9, 10 to 14, and so on. Larger intervals, such as 0 to 19 years, 20 to 39, etc., can conceal variations related to age which we need to know to identify the true population at risk. Sometimes, even the commonly used 5-year age groups can hide important differences. Take time to examine Figure 1.11a, for example, before you read ahead. What does the information in this figure suggest health authorities should do to reduce the number of cases of whooping cough? Where should health authorities focus their efforts?

You probably said that health authorities should focus on immunizing infants against whooping cough during the first year of life. Now, examine Figure 1.11b. This figure shows the same data but they are presented in the usual 5-year intervals. Based on Figure 1.11b where would you have suggested that health authorities focus their efforts? Would this recommendation have been as effective and efficient in reducing cases of whooping cough?

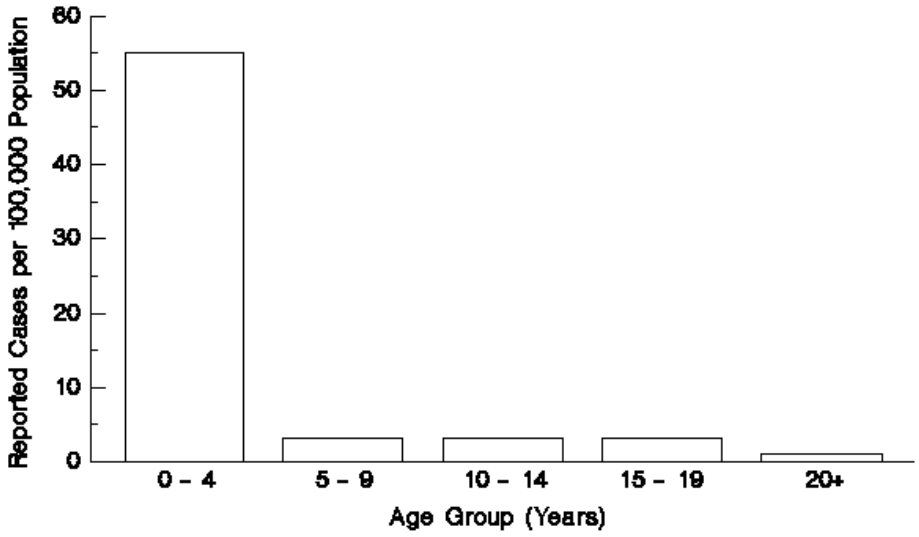
You probably said that health authorities should immunize infants and children before the age of 5. That recommendation would be effective, but it would not be efficient. You would be immunizing more children than actually necessary and wasting resources.

Figure 1.11a
Pertussis (whooping cough) incidence by age group, United States, 1989



Source: 9

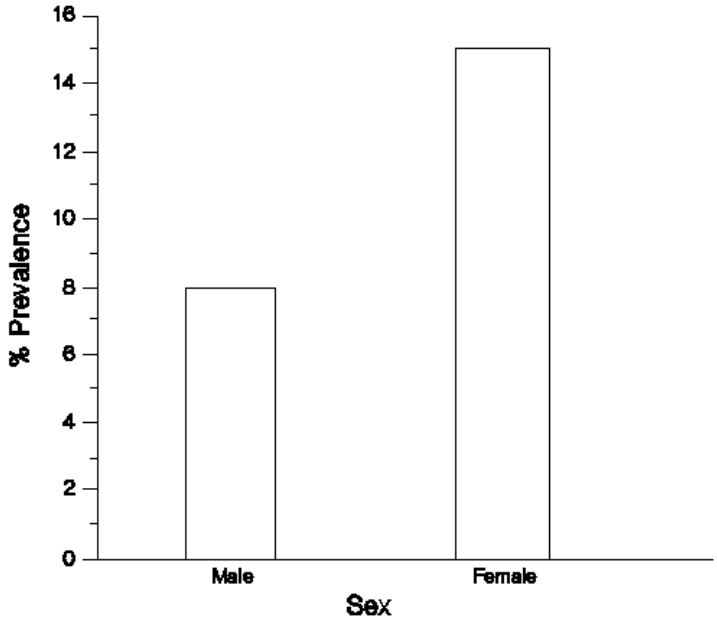
Figure 1.11b
Pertussis (whooping cough) incidence by age group, United States, 1989



Source: 9

Sex. In general, males have higher rates of illness and death than females do for a wide range of diseases. For some diseases, this sex-related difference is because of genetic, hormonal, anatomic, or other inherent differences between the sexes. These inherent differences affect their susceptibility or physiologic responses. For example, premenopausal women have a lower risk of heart disease than men of the same age. This difference is attributed to higher estrogen levels in women. On the other hand, the sex-related differences in the occurrence of many diseases reflect differences in opportunity or levels of exposure. For example, Figure 1.12 shows that hand/wrist disorders occur almost twice as often in females than in males. What are some sex-related differences that would cause a higher level of this disorder in females?

Figure 1.12
Prevalence of hand/wrist cumulative trauma disorder by sex, Newspaper Company A, 1990



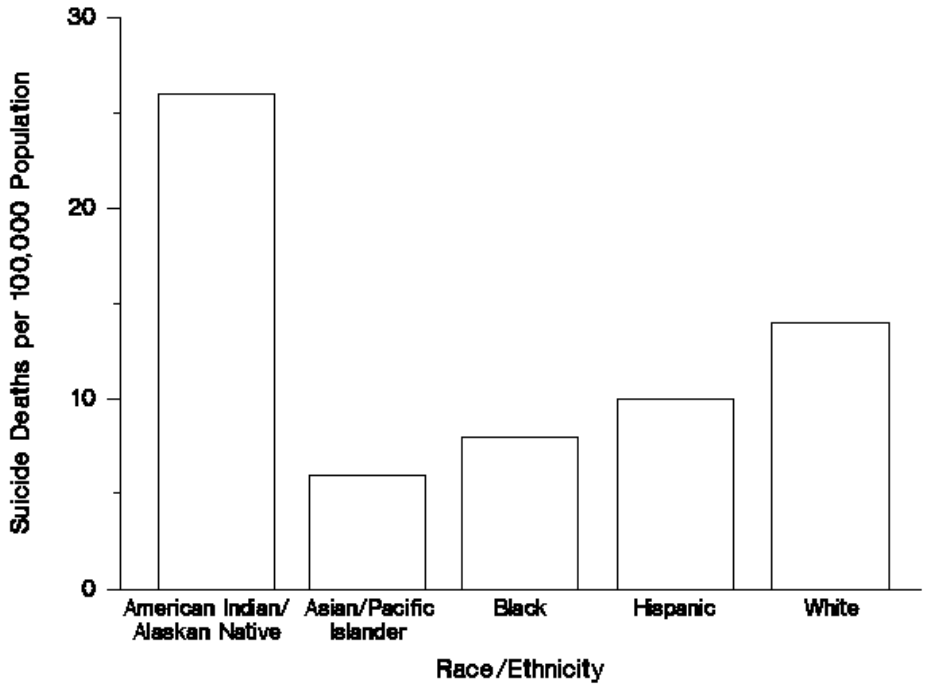
Source: NIOSH, unpublished data, 1991

You may have attributed the higher level of disorders in females to their higher level of exposure to occupational activities that require repetitive hand/wrist motion such as typing or keyboard entry. With occupationally-related illness, we usually find that sex differences reflect the number of workers in those occupations. You may also have attributed the higher level of disorders in females to anatomical differences; perhaps women's wrists are more susceptible to hand/wrist disorders.

Ethnic and racial groups. In examining epidemiologic data, we are interested in any group of people who have lived together long enough to acquire common characteristics, either biologically or socially. Several terms are commonly used to identify such groups: race, nationality, religion, or local reproductive or social groups, such as tribes and other geographically or socially isolated groups.

Differences that we observe in racial, ethnic, or other groups may reflect differences in their susceptibility or in their exposure, or they may reflect differences in other factors that bear more directly on the risk of disease, such as socioeconomic status and access to health care. In Figure 1.13, the rates of suicide for five groups of people are displayed.

Figure 1.13
Suicide death rates for persons 15 to 24 years of age according to race/ethnicity, United States, 1988



Source: 22

Clearly this graph displays a range of suicide death rates for the five groups of people. These data provide direction for prevention programs and for future studies to explain the differences.

Socioeconomic status. Socioeconomic status is difficult to quantify. It is made up of many variables such as occupation, family income, educational achievement, living conditions, and social standing. The variables that are easiest to measure may not reflect the overall concept. Nevertheless, we commonly use occupation, family income, and educational achievement, while recognizing that these do not measure socioeconomic status precisely.

The frequency of many adverse health conditions increases with decreasing socioeconomic status. For example, tuberculosis is more common among persons in lower socioeconomic strata. Infant mortality and time lost from work due to disability are both associated with lower income. These patterns may reflect more harmful exposures, lower resistance, and less access to health

care. Or they may in part reflect an interdependent relationship which is impossible to untangle—does low socioeconomic status contribute to disability or does disability contribute to lower socioeconomic status?

Some adverse health conditions are more frequent among persons of higher socioeconomic status. These conditions include breast cancer, Kawasaki syndrome, and tennis elbow. Again, differences in exposure account for at least some of the differences in the frequency of these conditions.

Exercise 1.4

The following series of tables show person information about cases of the unknown disease described in Figure 1.5. Look again at Figure 1.5 (page 19), study the information in the exercise tables, and then describe in words how the disease outbreak is distributed by time and person. Write your description below.

Answers on page 63.

Exercise 1.4 — continued

Exercise 1.4, Table 1
Incidence of the disease by age and sex
in 24 villages surveyed for one year

Age Group (years)	Males			Females		
	Population*	# Cases	Rate per 1,000	Population*	# Cases	Rate per 1,000
<1	327	0	0	365	0	0
1	233	2	8.6	205	1	4.9
2	408	30	73.5	365	16	43.8
3	368	26	70.7	331	28	84.6
4	348	33	94.8	321	32	99.7
5-9	1,574	193	122.6	1,531	174	113.7
10-14	1,329	131	98.6	1,276	95	74.5
15-19	1,212	4	3.3	1,510	17	11.3
20-24	1,055	1	.9	1,280	51	39.8
25-29	882	1	1.1	997	75	75.2
30-34	779	4	5.1	720	47	65.3
35-39	639	4	6.3	646	51	78.9
40-44	469	10	21.3	485	34	70.1
45-49	372	7	18.8	343	18	52.5
50-54	263	13	49.4	263	12	45.6
55-59	200	5	25.0	228	6	26.3
60-64	164	9	53.6	153	3	19.6
65-69	106	4	37.7	105	2	19.1
≥70	80	6	75.0	114	2	17.5
Total	**10,812**	**483**	**44.7**	**11,238**	**664**	**59.1**

*As enumerated between May 1 and July 15.

Exercise 1.4, Table 2
Incidence of the disease in women
by marital status and age

Age Group (years)	Married Women			Single Women		
	Population	#Cases	Rate per 1,000	Population	# Cases	Rate per 1,000
16-29	1,905	89	46.7	1,487	16	10.7
30-49	1,684	98	58.2	141	4	28.4
≥50	387	4	10.3	26	0	0
Total	**3,976**	**191**	**48.0**	**1,654**	**20**	**12.1**

Exercise 1.4 — continued

Exercise 1.4, Table 3
Incidence of the disease by occupation, age, and sex

Sex	Mill Worker?	Age Group	Ill	Well	Total	Percent Ill
Female	Yes	<10	0	0	0	—
		10-19	2	330	332	0.6
		20-29	4	194	198	2.0
		30-44	2	93	95	2.1
		45-54	0	9	9	0
		≥55	0	5	5	0
Female	No	<10	28	577	605	4.6
		10-19	5	200	205	2.4
		20-29	12	204	216	5.6
		30-44	16	220	236	6.8
		45-54	4	91	95	4.2
		≥55	1	92	93	1.1
Male	Yes	<10	0	0	0	—
		10-19	3	355	358	0.8
		20-29	1	361	362	0.3
		30-44	3	318	321	0.9
		45-54	0	93	93	0
		≥55	1	51	52	1.9
Male	No	<10	23	629	652	3.5
		10-19	4	161	165	2.4
		20-29	1	12	13	7.7
		30-44	0	10	10	0
		45-54	1	14	15	6.7
		≥55	4	26	30	13.3

Exercise 1.4, Table 4
Incidence of the disease by socioeconomic status in 24 villages* surveyed for one year

Family Socioeconomic Status	Cases	Population	Rate per 1,000
Stratum 1 (Lowest)	99	796	124.4
Stratum 2	240	2,888	83.1
Stratum 3	260	4,868	53.4
Stratum 4	177	5,035	35.2
Stratum 5	132	5,549	23.8
Stratum 6	23	1,832	12.6
Stratum 7 (Highest)	2	769	2.6
Total	**933**	**21,737**	**42.9**

*Restricted to cases developing after 30 day's residence.

Analytic Epidemiology

As you have seen, with descriptive epidemiology we can identify several characteristics of persons with disease, and we may question whether these features are really unusual, but descriptive epidemiology does not answer that question. Analytic epidemiology provides a way to find the answer: the comparison group. Comparison groups, which provide baseline data, are a key feature of analytic epidemiology.

For example, in one outbreak of hepatitis A, it was found that almost all of those infected ate pastries from a particular bakery and drank city water (26). However, without knowing the habits of persons without hepatitis, it was not possible to conclude that pastries, city water, or both were risk factors for hepatitis. Therefore, a comparison group of healthy persons from the same population were questioned. Among the comparison group without hepatitis, almost all drank city water but few were exposed to the pastries. This finding indicated that pastries from the particular bakery were a risk factor for hepatitis A.

When—as in the example above—we find that persons with a particular characteristic are more likely than those without the characteristic to develop a certain disease, then the characteristic is said to be **associated with** the disease. The characteristic may be a demographic factor such as age, race, or sex; a constitutional factor such as blood group or immune status; a behavior or act such as smoking or having eaten a specific food such as potato salad; or a circumstance such as living near a toxic waste site. Identifying factors that are associated with disease helps us identify populations at increased risk of disease; we can then target public health prevention and control activities. Identifying risk factors also provides clues to direct research activities into the causes of a disease.

Thus, analytic epidemiology is concerned with the search for causes and effects, or the *why* and the *how*. We use analytic epidemiology to quantify the association between exposures and outcomes and to test hypotheses about causal relationships. It is sometimes said that epidemiology can never *prove* that a particular exposure caused a particular outcome. Epidemiology may, however, provide sufficient evidence for us to take appropriate control and prevention measures.

Epidemiologic studies fall into two categories: **experimental** and **observational**. In an experimental study, we determine the exposure status for each individual (clinical trial) or community (community trial); we then follow the individuals or communities to detect the effects of the exposure. In an observational study, which is more common, we simply observe the exposure and outcome status of each study participant. The study of hepatitis A cases described above was an observational study.

Two types of observational studies are the **cohort study** and the **case-control study**. A **cohort** study is similar in concept to the experimental study. We categorize subjects on the basis of their exposure and then observe them to see if they develop the health conditions we are studying. This differs from an experimental study in that, in a cohort study, we observe the exposure status rather than determine it. After a period of time, we compare the disease rate in the exposed group with the disease rate in the unexposed group. The length of follow-up varies, ranging from a few days for acute diseases to several decades for cancer, cardiovascular disease, and other chronic diseases. The Framingham study is a well-known cohort study which has followed over 5,000 residents of Framingham, Massachusetts, since the early 1950's to establish the rates and risk factors for heart disease (12).

The **case-control** study—the other type of observational study—is more common than the **cohort** study. In a case-control study, we enroll a group of people with disease ("cases") and a group without disease ("controls") and compare their patterns of previous exposures. The study of hepatitis A described above is an example of a case-control study. The key in a case-control study is to identify an appropriate control, or comparison, group, because it provides our measure of the expected amount of exposure.

In summary, the purpose of an epidemiologic study is to quantify the relationship between an exposure and a health outcome. The hallmark of an epidemiologic study is the presence of at least two groups, one of which serves as a comparison group. In an experimental study, the investigator determines the exposure for the study subjects; in an observational study, the subjects determine their own exposure. In an observational cohort study, subjects first are enrolled on the basis of their exposure, then are followed to document occurrence of disease. In an observational case-control study, subjects first are enrolled according to whether they have the disease or not, then are questioned or tested to determine their prior exposure.

Exercise 1.5

Classify each of the following studies as experimental, observational/cohort, observational/case-control, or not an epidemiologic study.

_____ a. Vietnam Experience Study: Subjects were several thousand soldiers stationed in Vietnam from 1969-1971 and several thousand soldiers stationed in Europe from 1969-1971. In the mid-1980's, investigators determined and compared the death rate and prevalence of illness in both groups.

_____ b. Subjects were 59 patients with end-stage cancer. All were given a new treatment. The monthly survival was charted over 2 years.

_____ c. Subjects were persons with laboratory-confirmed trichinosis, and one healthy friend of each. All subjects were asked about their consumption of pork and other meat products.

_____ d. Subjects were children enrolled in a health maintenance organization. At 18 months, each child was randomly given one of two types of vaccine against *Haemophilus influenzae*. Parents were asked to record any side effects on a card, and mail it back after 2 weeks.

Answers on page 64.

Causation

Although we use analytic epidemiology to search for causes of disease, this is not a straightforward matter. First, not all associations between exposures and disease are causal relations. In addition, the accepted models of disease causation all require the precise interaction of factors and conditions before a disease will occur. Finally, the concept of cause itself continues to be debated as a philosophical matter in the scientific literature. Nonetheless, the following models and guidelines provide a framework for considering causation at a practical level.

For purposes of this course, we will define a **cause** of disease as a factor (characteristic, behavior, event, etc.) that influences the occurrence of disease. An increase in the factor leads to an increase in disease. Reduction in the factor leads to a reduction in disease. If disease does not develop without the factor being present, then we term the causative factor "**necessary**." If the disease always results from the factor, then we term the causative factor "**sufficient**." Exposure to *Mycobacterium tuberculosis* is necessary for tuberculosis to develop, but it is not sufficient, because not everyone infected develops disease. On the other hand, exposure to a large inoculum of rabies virus is a sufficient cause in a susceptible person, since clinical rabies and death will almost inevitably occur.

A variety of models of disease causation have been proposed. Models are purposely simplified representations. In this instance, the purpose of the model is to facilitate the understanding of nature, which is complex. Two of these models are discussed below.

The Epidemiologic Triad: Agent, Host, and Environment

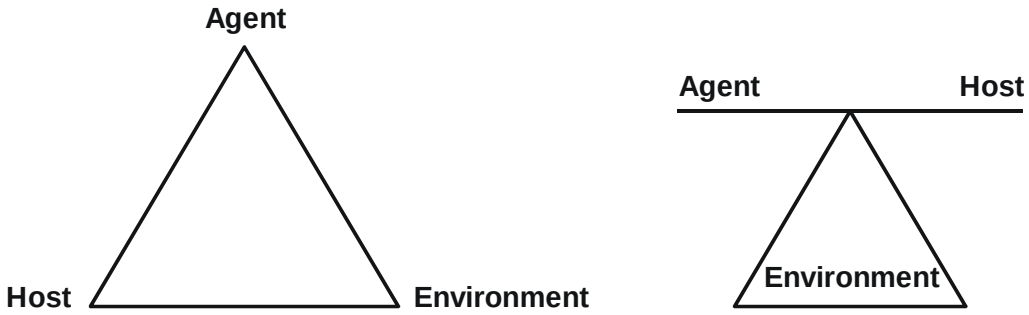
The **epidemiologic triangle** or **triad** is the traditional model of infectious disease causation. It has three components: an external agent, a susceptible host, and an environment that brings the host and agent together. In this model, the environment influences the agent, the host, and the route of transmission of the agent from a source to the host. Figure 1.14 shows two versions of this model in diagram form.

Agent factors

Agent originally referred to an infectious microorganism—virus, bacterium, parasite, or other microbe. Generally, these agents must be present for disease to occur. That is, they are necessary but not always sufficient to cause disease.

As epidemiology has been applied to noninfectious conditions, the concept of agent in this model has been broadened to include chemical and physical causes of disease. These include chemical contaminants, such as the l-tryptophan contaminant responsible for eosinophilia-myalgia syndrome, and physical forces, such as repetitive mechanical forces associated with carpal tunnel syndrome. This model does not work well for some noninfectious diseases, because it is not always clear whether a particular factor should be classified as an agent or as an environmental factor.

Figure 1.14
Epidemiologic triangle and triad (balance beam)



Host factors

Host factors are intrinsic factors that influence an individual's exposure, susceptibility, or response to a causative agent. Age, race, sex, socioeconomic status, and behaviors (smoking, drug abuse, lifestyle, sexual practices and contraception, eating habits) are just some of the many host factors which affect a person's likelihood of exposure. Age, genetic composition, nutritional and immunologic status, anatomic structure, presence of disease or medications, and psychological makeup are some of the host factors which affect a person's susceptibility and response to an agent.

Environmental factors

Environmental factors are extrinsic factors which affect the agent and the opportunity for exposure. Generally, environmental factors include physical factors such as geology, climate, and physical surroundings (e.g., a nursing home, hospital); biologic factors such as insects that transmit the agent; and socioeconomic factors such as crowding, sanitation, and the availability of health services.

Agent, host, and environmental factors interrelate in a variety of complex ways to produce disease in humans. Their balance and interactions are different for different diseases. When we search for causal relationships, we must look at all three components and analyze their interactions to find practical and effective prevention and control measures.

Component Causes and Causal Pies

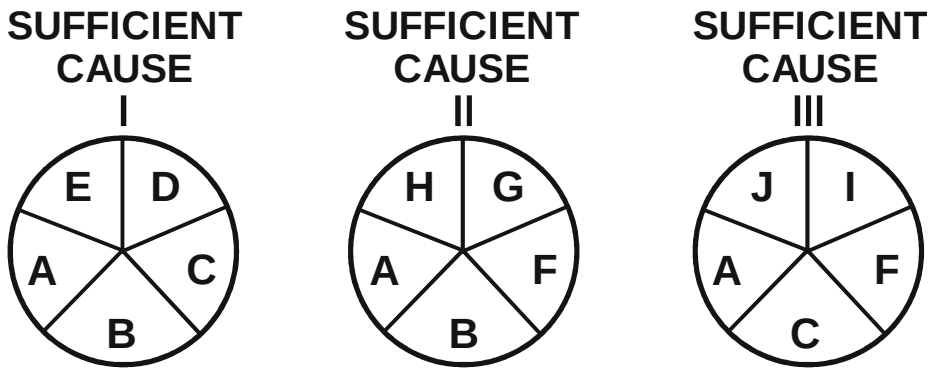
Because the agent-host-environment model does not work well for some noninfectious diseases, several other models have been proposed. One of the newer models is based on the multifactorial nature of causation in many diseases. This model is shown in Figure 1.15. It illustrates the factors that act to cause disease as pieces of a pie, the whole pie making up the sufficient cause for a disease. Notice that it shows that a disease may have more than one sufficient cause, with each sufficient cause being composed of several factors. What is the letter of the **necessary** cause shown for the hypothetical disease illustrated by this model?

The factors represented by the pieces of the pie in this model are called **component causes**. They include intrinsic host factors, as well as the agent and the environmental factors of the agent-host-environment model. A single component cause is rarely a sufficient cause by itself. For example, even exposure to a highly infectious agent such as measles virus does not invariably result in measles disease—the host must be susceptible; other host factors may also play a role.

At the other extreme, an agent which rarely causes disease in healthy persons may be pathogenic when other conditions are right. *Pneumocystis carinii* is one such organism, harmlessly colonizing some healthy persons but causing potentially lethal pneumonia in persons whose immune systems have been weakened by human immunodeficiency virus (HIV). Presence of *Pneumocystis carinii* organisms is therefore a necessary but not sufficient cause of pneumocystis pneumonia. In Figure 1.15 it would be represented by component A in each "pie."

If the three pies in the model represented all the sufficient causes for a particular disease, component A would be considered a necessary cause for the disease, as *P. carinii* is for pneumocystis pneumonia. Because component A is included in all sufficient causes for the disease, it would have to be present, usually with various combinations of other factors, for disease to occur. Infectious agents are likely to be represented by component A. Did you recognize earlier that "A" was the necessary cause for the hypothetical disease shown in each pie?

Figure 1.15
Rothman's causal pies: conceptual scheme for the causes of a hypothetical disease



Source: 25

As the model indicates, a particular disease may result from a variety of different sufficient causes. They are different pathways leading to the same end. For example, lung cancer may result from a sufficient cause which includes smoking as a component cause. Smoking is not a sufficient cause by itself, however, since not all smokers develop lung cancer. Neither is smoking a necessary cause, because lung cancer may occur in persons who never smoked. Thus smoking may be represented by component B, which is present in sufficient causes I and II but not in III. Asbestos exposure may be represented by component C, present in causes I and III but not in II. Indeed, since lung cancer may develop in persons with neither smoking or asbestos exposure, there would have to be at least one other sufficient cause pie that did not include components B and C.

To apply this model, we do not have to identify every component of a sufficient cause before we can take preventive action. We can prevent disease by blocking any single component of a sufficient cause, at least through that pathway. For example, eliminating smoking (component B) would prevent lung cancer from sufficient causes I and II, although some lung cancer would still occur through sufficient cause III.

Exercise 1.6

Use the two models (Agent-Host-Environment and Causal Pies) to describe the following:

a. Use the Agent-Host-Environment model to describe the role of the human immunodeficiency virus (HIV) in AIDS.

Agent:

Host:

Environment:

b. Some of the risk factors for heart disease are smoking, hypertension, obesity, diabetes, high cholesterol, inactivity, stress, and type A personality. Are these risk factors necessary causes, sufficient causes, or component causes?

Answers on page 64.

Epidemiology in Public Health Practice

Epidemiology is a tool that is essential for carrying out four fundamental functions: public health surveillance, disease investigation, analytic studies, and program evaluation. Although an active epidemiology unit will do other things as well, these are the key areas through which epidemiology contributes to the promotion of the public's health.

Public Health Surveillance

Through **public health surveillance**, a health department systematically collects, analyzes, interprets, and disseminates health data on an ongoing basis (28). Public health surveillance, which has been called "information for action" (23), is how a health department takes the pulse of its community. By knowing the ongoing pattern of disease occurrence and disease potential, a health department can effectively and efficiently investigate, prevent, and control disease in the community.

At the local level, the most common source of surveillance data is reports of disease cases received from health-care providers, who are required to report patients with certain "reportable" diseases, such as cholera or measles or syphilis. In addition, surveillance data may come from laboratory reports, surveys, disease registries, death certificates, and public health program data such as immunization coverage. It may also come from investigations by the health department of cases or clusters of cases reported to it.

Most health departments use simple surveillance systems. They monitor individual morbidity and mortality case reports, record a limited amount of information on each case, and look for patterns by time, place, and person. Unfortunately, with some reportable diseases, a health department may receive reports of only 10% to 25% of the cases that actually occur (20). Nevertheless, health departments have found that even a simple surveillance system can be invaluable in detecting problems and guiding public health action. The principal epidemiologist of a large county health department has said that "surveillance is the practicing epidemiologist's primary occupation; it pervades and keynotes all his activities" (24). We will discuss surveillance in more detail in Lesson 5.

Disease Investigation

As noted above, surveillance is considered information for action. The first action of a health department when it receives a report of a case or a cluster of cases of a disease is to investigate. The investigation may be as limited as a telephone call to the health-care provider to confirm or clarify the circumstances of the reported case, or it may be as extensive as a field investigation coordinating the efforts of dozens of people to determine the extent and cause of a large outbreak.

The objectives of such investigations vary. With a communicable disease, one objective may be to identify additional unreported or unrecognized cases in order to control spread of the disease. For example, one of the hallmarks of sexually transmitted disease investigations is the identification of sexual contacts of cases. When these contacts are interviewed and tested they are often found to have asymptomatic infections. By providing treatment that these contacts had not realized they needed, the health department prevents them from spreading the disease further.

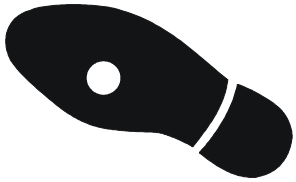
For other diseases, the objective of an investigation may be to identify a source or vehicle of infection which can be controlled or eliminated. For example, the investigation of a case of botulism usually focuses on trying to identify the vehicle contaminated with botulinum toxin, such as a food that was improperly canned. Once they have identified the vehicle, the investigators can establish how many other people may have been exposed and how many continue to be at risk, and take action to prevent their exposure. In Taiwan, investigators of a cluster of botulism cases implicated consumption of canned peanuts prepared by a single manufacturer (10). They then initiated a nationwide recall of that product from warehouses, stores, and homes to reduce the risk of exposure for others.

For some diseases, the objective of an investigation may be simply to learn more about the disease itself—its natural history, clinical spectrum, descriptive epidemiology, and risk factors. In the nationwide outbreak of toxic shock syndrome in 1980, early investigations focused on establishing a case definition based on the clinical symptoms, and on describing the populations at risk by time, place, and person. From the descriptive epidemiology, investigators were able to develop hypotheses which they could test with analytic studies. They conducted a series of increasingly specific studies which narrowed specific risk factors down from menstruating women to tampon users to users of a specific brand of tampon. This information prompted the withdrawal of that brand from the market, and subsequent research to identify what factors in the composition and use of the tampon were necessary for the syndrome to develop (8).

Field investigations of the type described above are sometimes referred to as “shoe-leather epidemiology,” conjuring images of dedicated if haggard epidemiologists beating the pavement in search of additional cases to interview and clues to identify the source and mode of transmission. This approach is commemorated in the symbol of the Epidemic Intelligence Service, CDC’s cadre of disease detectives—a shoe with a hole in the sole.

We will discuss disease investigation in more detail in Lesson 6.

Figure 1.16
Epidemic Intelligence Service (EIS) shoe



Analytic Studies

Surveillance and case investigation sometimes are sufficient to identify causes, modes of transmission, and appropriate control and prevention measures. Sometimes they provide clues or hypotheses which must be assessed with appropriate analytic techniques.

Investigators initially use descriptive epidemiology to examine clusters of cases or outbreaks of disease. They examine incidence of the disease and its distribution by time, place, and person. They calculate rates and identify parts of the population that are at higher risk than others. When they find a strong association between exposure and disease, the investigators may implement control measures immediately. More often, investigators find that descriptive studies, like case investigations, generate hypotheses which they can then test with analytic studies.

Epidemiologists must be familiar with all aspects of the analytic study, including its design, conduct, analysis, and interpretation. In addition, the epidemiologist must be able to communicate the findings as well.

- Study **design** includes determining the appropriate study design, writing justifications and protocols, calculating sample sizes, deciding on criteria for subject selection (e.g., choosing controls), designing questionnaires, and numerous other tasks that are part of the study plan.
- To **conduct** a study requires securing appropriate clearances and approvals, abstracting records, tracking down and interviewing subjects, collecting and handling specimens, and managing the data.
- **Analysis** begins with describing the characteristics of the subjects and progresses to calculating rates, creating comparative tables (e.g., two-by-two tables), and computing measures of association (e.g., risk ratios and odds ratios), tests of statistical significance (e.g., chi-square), confidence intervals, and the like. These techniques will be discussed in Lessons 2 and 6. Many epidemiologic studies require more advanced analytic techniques such as stratified analysis, regression, and modeling.
- Finally, **interpretation** involves putting the findings of the study into perspective and making appropriate recommendations.

Evaluation

Evaluation of control and prevention measures is another responsibility of epidemiologists. Evaluation often addresses both **effectiveness** and **efficiency**. **Effectiveness** refers to the ability of a program to produce the intended or expected results in the field. Effectiveness differs from **efficacy**, which is the ability to produce results under *ideal* conditions. Finally, **efficiency** refers to the ability of the program to produce the intended results with a minimum expenditure of time and resources. Evaluation of an immunization program, for example, might compare the stated efficacy with the field effectiveness of the program, and might assess the efficiency with which the acceptable results are achieved.

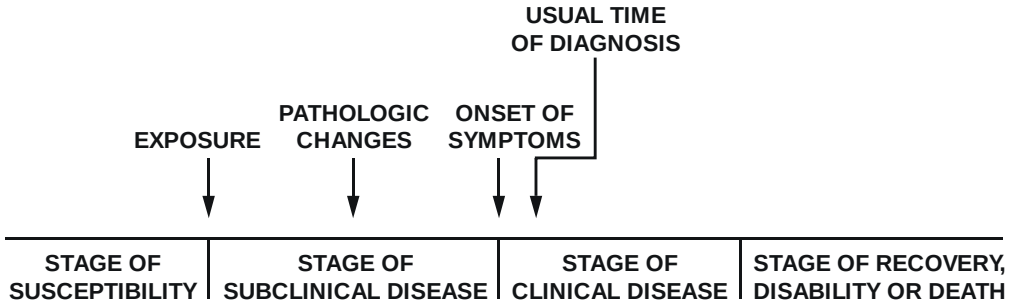
Selected Topics in Epidemiology and Disease

Although epidemiologic approaches can be applied to all types of disease, injury, and health conditions, the chain of infection for infectious diseases is better understood. In addition, infectious diseases remain an important focus of state and local public health department activities. Therefore, a description of some of the key concepts of infectious disease epidemiology are presented below. These concepts are rooted in infectious disease, but are also relevant to noninfectious diseases.

Natural History and Spectrum of Disease

Natural history of disease refers to the progress of a disease process in an individual over time, in the absence of intervention. The process begins with exposure to or accumulation of factors capable of causing disease. Without medical intervention, the process ends with recovery, disability, or death. The stages in the natural history of disease are shown in Figure 1.17. Most diseases have a characteristic natural history (which is poorly understood for many diseases), although the time frame and specific manifestations of disease may vary from individual to individual. With a particular individual, the usual course of a disease may be halted at any point in the progression by preventive and therapeutic measures, host factors, and other influences.

Figure 1.17
Natural history of disease



As shown in Figure 1.17, the natural history begins with the appropriate exposure to or accumulation of factors sufficient to begin the disease process in a susceptible host. For infectious disease, the exposure usually is a microorganism. For cancers, the critical factors may require both **cancer initiators**, such as asbestos fibers or components in tobacco smoke (for lung cancer), and **cancer promoters**, such as estrogens (for endometrial cancer).

Usually, a period of subclinical or inapparent pathologic changes follows exposure, ending with the onset of symptoms. For infectious diseases, this period is usually called the **incubation period**; for chronic diseases, this period is usually called the **latency period**. This period may be as brief as seconds for hypersensitivity and toxic reactions to as long as decades for certain chronic diseases. Even for a single disease, the characteristic incubation period has a range. For example, for hepatitis A, this range is about 2 to 6 weeks. For leukemia associated with exposure to the atomic bomb blast in Hiroshima, the range was 2 to 12 years with a peak at 6 to 7 years

(11). Although disease is inapparent during the incubation period, some pathologic changes may be detectable with laboratory, radiographic, or other screening methods. Most screening programs attempt to identify the disease process during this phase of its natural history, since early intervention may be more effective than treatment at a later stage of disease progression.

The onset of symptoms marks the transition from subclinical to clinical disease. Most diagnoses are made during the stage of clinical disease. In some people, however, the disease process may never progress to clinically apparent illness. In others, the disease process may result in a wide spectrum of clinical illness, ranging from mild to severe or fatal.

Three terms are used to describe an infectious disease according to the various outcomes that may occur after exposure to its causative agent.

- **Infectivity** refers to the proportion of exposed persons who become infected.
- **Pathogenicity** refers to the proportion of infected persons who develop clinical disease.
- **Virulence** refers to the proportion of persons with clinical disease who become severely ill or die.

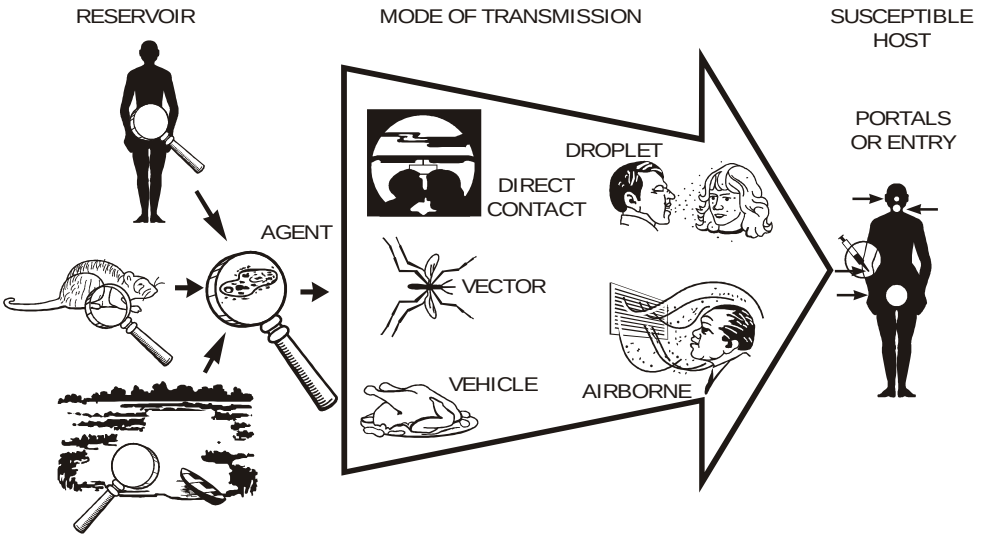
For example, hepatitis A virus in children has low pathogenicity and low virulence, since many infected children remain asymptomatic and few develop severe illness. In persons with good nutrition and health, measles virus has high pathogenicity but low virulence, since almost all infected persons develop the characteristic rash illness but few develop the life-threatening presentations of measles, pneumonia, or encephalitis. In persons with poorer nutrition and health, measles is a more virulent disease, with mortality as high as 5-10%. Finally, rabies virus is both highly pathogenic and virulent, since virtually 100% of all infected persons (who do not receive treatment) progress to clinical disease and death.

The natural history and spectrum of disease presents challenges to the clinician and to the public health worker. Because of the clinical spectrum, cases of illness diagnosed by clinicians in the community often represent only the “tip of the iceberg.” Many additional cases may be too early to diagnose or may remain asymptomatic. For the public health worker, the challenge is that persons with inapparent or undiagnosed infections may nonetheless be able to transmit them to others. Such persons who are infectious but have subclinical disease are called **carriers**. Frequently, carriers are persons with incubating disease or inapparent infection. Persons with measles, hepatitis A, and several other diseases become infectious a few days before the onset of symptoms. On the other hand, carriers may also be persons who appear to have recovered from their clinical illness, such as chronic carriers of hepatitis B virus.

Chain of Infection

As described on page 35 of this lesson, the traditional model (epi triad) illustrates that infectious diseases result from the interaction of agent, host, and environment. More specifically, transmission occurs when the **agent** leaves its **reservoir** or host through a **portal of exit**, and is conveyed by some **mode of transmission**, and enters through an appropriate **portal of entry** to infect a susceptible **host**. This is sometimes called the chain of infection and is illustrated in Figure 1.18.

Figure 1.18
Chain of infection



Reservoir

The **reservoir** of an agent is the habitat in which an infectious agent normally lives, grows, and multiplies. Reservoirs include humans, animals, and the environment. The reservoir may or may not be the source from which an agent is transferred to a host. For example, the reservoir of *Clostridium botulinum* is soil, but the source of most botulism infections is improperly canned food containing *C. botulinum* spores.

Human reservoirs. Many of the common infectious diseases have human reservoirs. Diseases which are transmitted from person to person without intermediaries include the sexually transmitted diseases, measles, mumps, streptococcal infection, most respiratory pathogens, and many others. Smallpox was eradicated after the last human case was identified and isolated because humans were the only reservoir for the smallpox virus. Two types of human reservoir exist:

- persons with symptomatic illness
- carriers

A **carrier** is a person without apparent disease who is nonetheless capable of transmitting the agent to others. Carriers may be **asymptomatic carriers**, who never show symptoms during the time they are infected, or may be **incubatory** or **convalescent carriers**, who are capable of transmission before or after they are clinically ill. A **chronic carrier** is one who continues to harbor an agent (such as hepatitis B virus or *Salmonella typhi*—the agent of typhoid fever) for an extended time (months or years) following the initial infection. Carriers commonly transmit disease because they do not recognize they are infected and consequently take no special precautions to prevent transmission. Symptomatic persons, on the other hand, are usually less likely to transmit infection widely because their symptoms increase their likelihood of being diagnosed and treated, thereby reducing their opportunity for contact with others.

Animal reservoirs. Infectious diseases that are transmissible under normal conditions from animals to humans are called **zoonoses** (ZOH-uh-NOH-seez). In general, these diseases are transmitted from animal to animal, with humans as incidental hosts. Such diseases include brucellosis (cows and pigs), anthrax (sheep), plague (rodents), trichinosis (swine), and rabies (bats, raccoons, dogs, and other mammals).

Another group of diseases with animal reservoirs are those caused by viruses transmitted by insects and caused by parasites that have complex life cycles, with different reservoirs at different stages of development. Such diseases include St. Louis encephalitis and malaria (both requiring mosquitos) and schistosomiasis (requiring fresh water snails). Lyme disease is a zoonotic disease of deer incidentally transmitted to humans by the deer tick.

Environmental reservoirs. Plants, soil, and water in the environment are also reservoirs for some infectious agents. Many fungal agents, such as those causing histoplasmosis, live and multiply in the soil. The primary reservoir of Legionnaires' bacillus appears to be pools of water, including those produced by cooling towers and evaporative condensers.

Portal of exit

Portal of exit is the path by which an agent leaves the source host. The portal of exit usually corresponds to the site at which the agent is localized. Thus, tubercle bacilli and influenza viruses exit the respiratory tract, schistosomes through urine, cholera vibrios in feces, *Sarcoptes scabiei* in scabies skin lesions, and enterovirus 70, an agent of hemorrhagic conjunctivitis, in conjunctival secretions. Some bloodborne agents can exit by crossing the placenta (rubella, syphilis, toxoplasmosis), while others exit by way of the skin (percutaneously) through cuts or needles (hepatitis B) or blood-sucking arthropods (malaria).

Modes of transmission

After an agent exits its natural reservoir, it may be transmitted to a susceptible host in numerous ways. These modes of transmission are classified as:

- Direct
  - — Direct contact
  - — Droplet spread
- Indirect
  - — Airborne
  - — Vehicleborne
  - — Vectorborne
    - Mechanical
    - Biologic

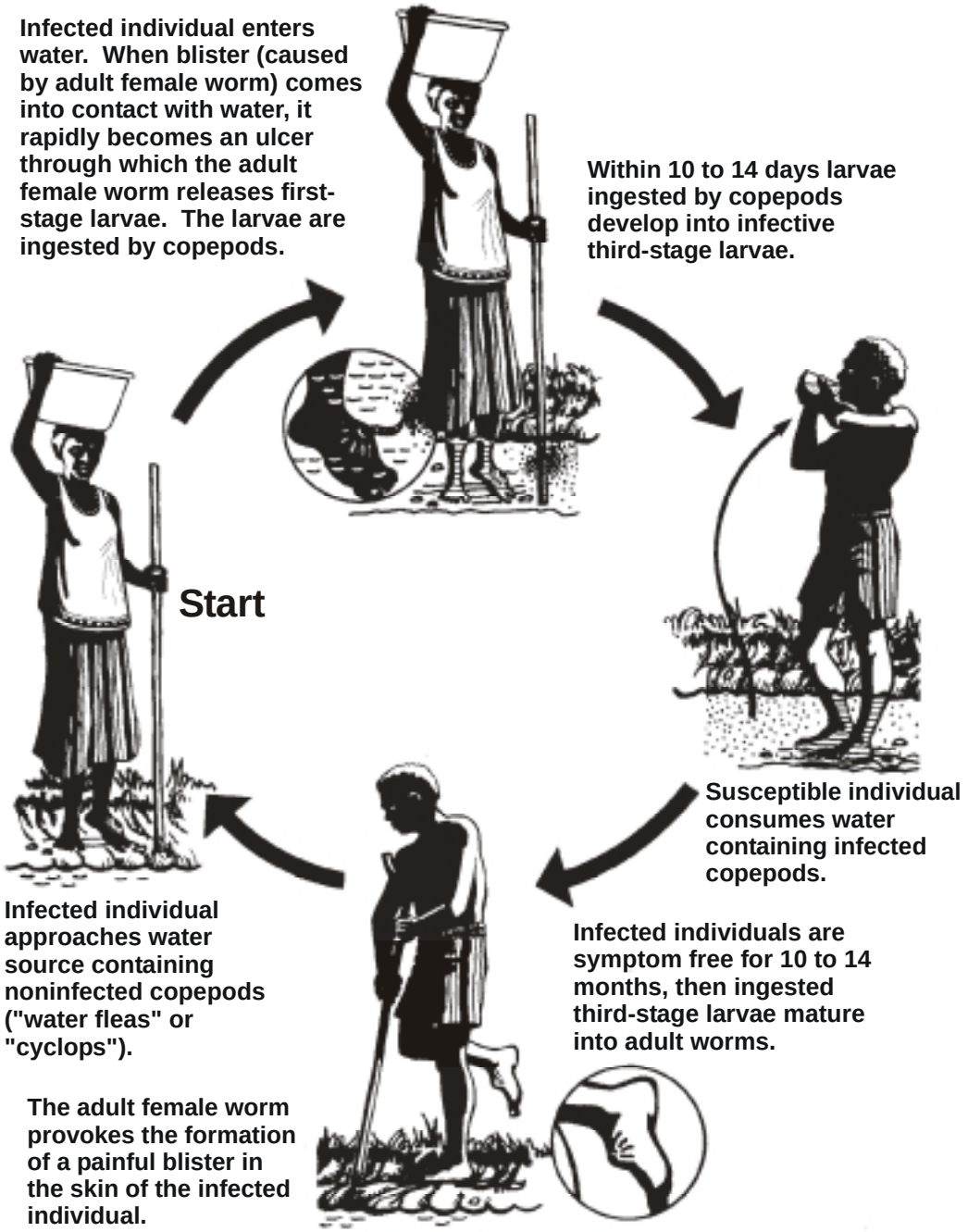
In **direct transmission**, there is essentially immediate transfer of the agent from a reservoir to a susceptible host by direct contact or droplet spread. **Direct contact** occurs through kissing, skin-to-skin contact, and sexual intercourse. Direct contact refers also to contact with soil or vegetation harboring infectious organisms. Thus, infectious mononucleosis ("kissing disease") and gonorrhea are spread from person-to-person by direct contact. Hookworm is spread by direct contact with contaminated soil. Droplet spread refers to spray with relatively large, short-range aerosols produced by sneezing, coughing, or even talking. **Droplet spread** is classified as direct because transmission is by direct spray over a few feet, before the droplets fall to the ground.

In **indirect transmission**, an agent is carried from a reservoir to a susceptible host by suspended air particles or by animate (**vector**) or inanimate (**vehicle**) intermediaries. Most **vectors** are arthropods such as mosquitoes, fleas, and ticks. These may carry the agent through purely mechanical means. For example, flies carry *Shigella* on appendages; fleas carry *Yersinia pestis* (agent that causes plague) in the gut and deposit the agent on the skin of a new host. In mechanical transmission, the agent does not multiply or undergo physiologic changes in the vector. This is in contrast to instances in which an agent undergoes part of its life cycle inside a vector before being transmitted to a new host. When the agent undergoes changes within the vector, the vector is serving as both an intermediate host and a mode of transmission. This type of indirect transmission is a **biologic transmission**.

Guinea worm disease and many other vectorborne diseases have complex life cycles which require an intermediate host. Follow the life cycle of *Dracunculus medinensis* (Guinea worm) illustrated in Figure 1.19 on page 48. What type of transmission does this illustrate?

Since the agent undergoes part of its life cycle in the intermediate host, the agent cannot be transmitted by the intermediate host until the agent has completed that part of its life cycle. Therefore, this is an indirect, vectorborne, biologic transmission.

Figure 1.19
The complex life cycle of *Dracunculus medinensis* (Guinea worm)



The agent, *Dracunculus*, develops in the intermediate host (fresh water copepod). Man acquires the infection by ingesting infected copepods in drinking water.

Vehicles that may indirectly transmit an agent include food, water, biologic products (blood), and fomites (inanimate objects such as handkerchiefs, bedding, or surgical scalpels). As with vectors, vehicles may passively carry an agent—as food or water may carry hepatitis A virus—or may provide an environment in which the agent grows, multiplies, or produces toxin—as improperly canned foods may provide an environment in which *C. botulinum* produces toxin.

Airborne transmission is by particles that are suspended in air. There are two types of these particles: **dust** and **droplet nuclei**. Airborne **dust** includes infectious particles blown from the soil by the wind as well as material that has settled on surfaces and become resuspended by air currents. **Droplet nuclei** are the residue of dried droplets. The nuclei are less than 5 μ (microns) in size and may remain suspended in the air for long periods, may be blown over great distances, and are easily inhaled into the lungs and exhaled. This makes them an important means of transmission for some diseases. Tuberculosis, for example, is believed to be transmitted more often indirectly, through droplet nuclei, than directly, through droplet spread. Legionnaires' disease and histoplasmosis are also spread through airborne transmission.

Portal of entry

An agent enters a susceptible host through a portal of entry. The portal of entry must provide access to tissues in which the agent can multiply or a toxin can act. Often, organisms use the same portal to enter a new host that they use to exit the source host. For example, influenza virus must exit the respiratory tract of the source host and enter the respiratory tract of the new host. The route of transmission of many enteric (intestinal) pathogenic agents is described as "fecal-oral" because the organisms are shed in feces, carried on inadequately washed hands, and then transferred through a vehicle (such as food, water, or cooking utensil) to the mouth of a new host. Other portals of entry include the skin (hookworm), mucous membranes (syphilis, trachoma), and blood (hepatitis B).

Host

The final link in the chain of infection is a susceptible host. Susceptibility of a host depends on genetic factors, specified acquired immunity, and other general factors which alter an individual's ability to resist infection or to limit pathogenicity. An individual's genetic makeup may either increase or decrease susceptibility. General factors which defend against infection include the skin, mucous membranes, gastric acidity, cilia in the respiratory tract, the cough reflex, and nonspecific immune response. General factors that may increase susceptibility are malnutrition, alcoholism, and disease or therapy which impairs the nonspecific immune response. Specific acquired immunity refers to protective antibodies that are directed against a specific agent. Individuals gain protective antibodies in two ways: 1) They develop antibodies in response to infection, vaccine, or toxoid; immunity developed in these ways is called **active immunity**. 2) They acquire their mothers' antibodies before birth through the placenta or they receive injections of antitoxins or immune globulin; immunity that is acquired in these ways is called **passive immunity**.

Note that the chain of infection may be interrupted when an agent does not find a susceptible host. This may occur if a high proportion of individuals in a population is resistant to an agent. These persons limit spread to the relatively few who are susceptible by reducing the probability of contact between infected and susceptible persons. This concept is called **herd immunity**. The degree of herd immunity necessary to prevent or abort an outbreak varies by disease. In theory, herd immunity means that not everyone in a community needs to be resistant (immune) to prevent disease spread and occurrence of an outbreak. In practice, herd immunity has not prevented outbreaks of measles and rubella in populations with immunity levels as high as 85 to 90%. One problem is that, in highly immunized populations, the relatively few susceptible persons are often clustered in population subgroups, usually defined by socioeconomic or cultural factors. If the agent is introduced into one of these subgroups, an outbreak may occur.

Implications for public health

By knowing how an agent exits and enters a host, and what its modes of transmission are, we can determine appropriate control measures. In general, we should direct control measures against the link in the infection chain that is most susceptible to interference, unless practical issues dictate otherwise.

For some diseases, the most appropriate intervention may be directed at controlling or eliminating the agent at its source. In the hospital setting, patients may be treated and/or isolated, with appropriate “enteric precautions,” “respiratory precautions,” “universal precautions,” and the like for different exit pathways. In the community, soil may be decontaminated or covered to prevent escape of the agent.

Sometimes, we direct interventions at the mode of transmission. For direct transmission, we may provide treatment to the source host or educate the source host to avoid the specific type of contact associated with transmission. In the hospital setting, since most infections are transmitted by direct contact, handwashing is the single most important way to prevent diseases from spreading. For vehicleborne transmission, we may decontaminate or eliminate the vehicle. For fecal-oral transmission, we may also try to reduce the risk of contamination in the future by rearranging the environment and educating the persons involved in better personal hygiene. For airborne transmission, we may modify ventilation or air pressure, and filter or treat the air. For vectorborne transmission, we usually attempt to control (i.e., reduce or eradicate) the vector population.

Finally, we may apply measures that protect portals of entry of a susceptible potential host or reduce the susceptibility of the potential host. For example, a dentist’s mask and gloves are intended to protect the dentist from a patient’s blood, secretions, and droplets, as well to protect the patient from the dentist. Prophylactic antibiotics and vaccination are strategies to improve a potential host’s defenses.

Exercise 1.7

Information describing viral hepatitis A and yellow fever is provided on the following pages. After you study this information, outline the chain of infection of each disease by identifying the reservoirs, portals of exit, modes of transmission, portals of entry, and factors in host susceptibility.

Yellow Fever

Reservoirs:

Portals of exit:

Modes of transmission:

Portals of entry:

Factors in host susceptibility:

Answers on page 65.

Viral Hepatitis A

Reservoirs:

Portals of exit:

Modes of transmission:

Portals of entry:

Factors in host susceptibility:

Answers on page 65.

YELLOW FEVER[1] ICD-9 060

1. Identification — An acute infectious viral disease of short duration and varying severity. The mildest cases are clinically indeterminate; typical attacks are characterized by a dengue-like illness, i.e., sudden onset, fever, chills, headache, backache, generalized muscle pain, prostration, nausea and vomiting. As the disease progresses, the pulse slows and weakens, even though the temperature may be elevated (Faget's sign); albuminuria (sometimes pronounced) and anuria may occur. A saddle-back fever curve is common. Leukopenia appears early and is most pronounced about the fifth day. Common hemorrhagic symptoms include epistaxis, buccal bleeding, hematemesis (coffee-ground or black), and melena. Jaundice is moderate early in the disease and is intensified later. The case fatality rate among indigenous populations of endemic regions is <5%, but may exceed 50% among nonindigenous groups and in epidemics.

Laboratory diagnosis is made by isolation of virus from blood by inoculation of suckling mice, mosquitoes or cell cultures (especially those of mosquito cells); by demonstration of viral antigen in the blood or liver tissue by ELISA or FA and in tissues by use of labeled specific antibodies; and by demonstration of viral genome in liver tissue by hybridization probes. Serologic diagnosis is made by demonstrating specific IgM in early sera or a rise in titer of specific antibodies in paired acute-phase and convalescent sera. Serologic cross-reactions occur with other flaviviruses and vaccine-derived antibodies cannot be distinguished from natural immunity. The diagnosis is suggested but not proven by demonstration of typical lesions in the liver.

2. Infectious agent — The virus of yellow fever, a flavivirus.

* * *

4. Reservoir — In urban areas, man and *Aedes aegypti* mosquitoes; in forest areas, vertebrates other than man, mainly monkeys and possibly marsupials, and forest mosquitoes. Transovarian transmission in mosquitoes may contribute to maintenance of infection. Man has no essential role in transmission of jungle yellow fever or in maintaining the virus.

5. Mode of transmission — In urban and certain rural areas, by the bite of infective *Aedes aegypti* mosquitoes. In forests of S America, by the bite of several species of forest mosquitoes of the genus *Haemagogus*. In East Africa, *Ae. africanus* is the vector in the monkey population, while semidomestic *Ae. bromeliae* and *Ae. simpsoni*, and probably other *Aedes species*, transmit the virus from monkey to man. In large epidemics in Ethiopia, good epidemiologic evidence incriminated *Ae. simpsoni* as a person-to-person vector. In West Africa, *Ae. furcifer-taylori*, *Ae. luteocephalus* and other species are responsible for spread between monkey and man. *Ae. albopictus* has been introduced into Brazil and the USA from Asia and has the potential for bridging the sylvatic and urban cycles of yellow fever in the Western Hemisphere. However, no instance of involvement of this species in transmission of yellow fever has been documented.

* * *

8. Susceptibility and resistance — Recovery from yellow fever is followed by lasting immunity; second attacks are unknown. Mild inapparent infections are common in endemic areas. Transient passive immunity in infants born to immune mothers may persist for up to 6 months. In natural infections, antibodies appear in the blood within the first week.

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[1]This material is from *Control of Communicable Diseases in Man*, Fifteenth Edition, Abram S. Benenson (ed), 1990. Reprinted by permission of American Public Health Association.

I. VIRAL HEPATITIS A[2] ICD-9 070.1

(Infectious hepatitis, Epidemic hepatitis, Epidemic jaundice, Catarrhal jaundice, Type A hepatitis, HA)

1. Identification — Onset is usually abrupt with fever, malaise, anorexia, nausea and abdominal discomfort, followed within a few days by jaundice. The disease varies in clinical severity from a mild illness lasting 1-2 weeks, to a severely disabling disease lasting several months (rare). Convalescence often is prolonged. In general, severity increases with age, but complete recovery without sequelae or recurrences is the rule. Many infections are asymptomatic; many are mild and without jaundice, especially in children, and recognizable only by liver function tests. The case fatality rate is low (about 0.6%); the rare death usually occurs in an older patient in whom the disease has a fulminant course.

Diagnosis is established by the demonstration of IgM antibodies against hepatitis A virus in the serum of acutely or recently ill patients; IgM may remain detectable for 4-6 months after onset. Diagnosis may also be made by a fourfold or greater rise in specific antibodies in paired sera; virus and antibody can be detected by RIA or ELISA. (Assay kits for the detection of IgM and total antibodies to the virus are available commercially.) If laboratory tests are not available, epidemiologic evidence can provide support for the diagnosis. However, HA cannot be distinguished epidemiologically from hepatitis E, in areas where the latter is endemic.

2. Infectious agent — Hepatitis A virus (HAV), a 27-nm picornavirus (i.e., a positive-strand RNA virus). It has been classified as *Enterovirus* type 72, a member of the family Picornaviridae.

* * *

4. Reservoir — Man, and rarely captive chimpanzees; less frequently, certain other nonhuman primates. An enzootic focus has been identified in Malaysia, but there is no suggestion of transmission to man.

5. Mode of transmission — Person-to-person by the fecal-oral route. The infectious agent is found in feces, reaching peak levels the week or two before onset of symptoms, and diminishing rapidly after liver dysfunction or symptoms appear, which is concurrent with the appearance of circulating antibodies to HAV. Direct transmission occurs among male homosexuals. Common-source outbreaks have been related to contaminated water; food contaminated by infected foodhandlers, including sandwiches and salads which are not cooked or are handled after cooking; and raw or undercooked molluscs harvested from contaminated waters. Although rare, instances have been reported of transmission by transfusion of blood from a donor during the incubation period.

* * *

8. Susceptibility and resistance — Susceptibility is general. Low incidence of manifest disease in infants and preschool children suggests that mild and anicteric infections are common. Homologous immunity after attack probably lasts for life.

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[2]This material is from *Control of Communicable Diseases in Man*, Fifteenth Edition, Abram S. Beneson (ed), 1990. Reprinted by permission of American Public Health Association.

Epidemic Disease Occurrence

Level of disease

The amount of a particular disease that is usually present in a community is the baseline level of the disease. This level is not necessarily the preferred level, which should in fact be zero; rather it is the observed level. Theoretically, if no intervention occurred and if the level is low enough not to deplete the pool of susceptible persons, the disease occurrence should continue at the baseline level indefinitely. Thus, the baseline level is often considered the **expected** level of the disease. For example, over the past 4 years the number of reported cases of poliomyelitis has ranged from 5 to 9. Therefore, assuming there is no change in population, we would expect to see approximately 7 reported cases next year.

Different diseases, in different communities, show different patterns of expected occurrence: 1) a persistent level of occurrence with a low to moderate disease level is referred to as an **endemic** level; 2) a persistently high level of occurrence is called a **hyperendemic** level; 3) an irregular pattern of occurrence, with occasional cases occurring at irregular intervals is called **sporadic**.

Occasionally, the level of disease rises above the expected level. When the occurrence of a disease within an area is clearly in excess of the expected level for a given time period, it is called an **epidemic**. Public health officials often use the term **outbreak**, which means the same thing, because it is less provocative to the public. When an epidemic spreads over several countries or continents, affecting a large number of people, it is called a **pandemic**.

Epidemics occur when an agent and susceptible hosts are present in adequate numbers, and the agent can effectively be conveyed from a source to the susceptible hosts. More specifically, an epidemic may result from the following:

- a recent increase in amount or virulence of the agent
- the recent introduction of the agent into a setting where it has not been before
- an enhanced mode of transmission so that more susceptibles are exposed
- some change in the susceptibility of the host response to the agent
- factors that increase host exposure or involve introduction through new portals of entry (16)

Epidemic patterns

We sometimes classify epidemics by how they spread through a population, as shown below:

- Common source
  — Point
  — Intermittent
  — Continuous
- Propagated
- Mixed
- Other

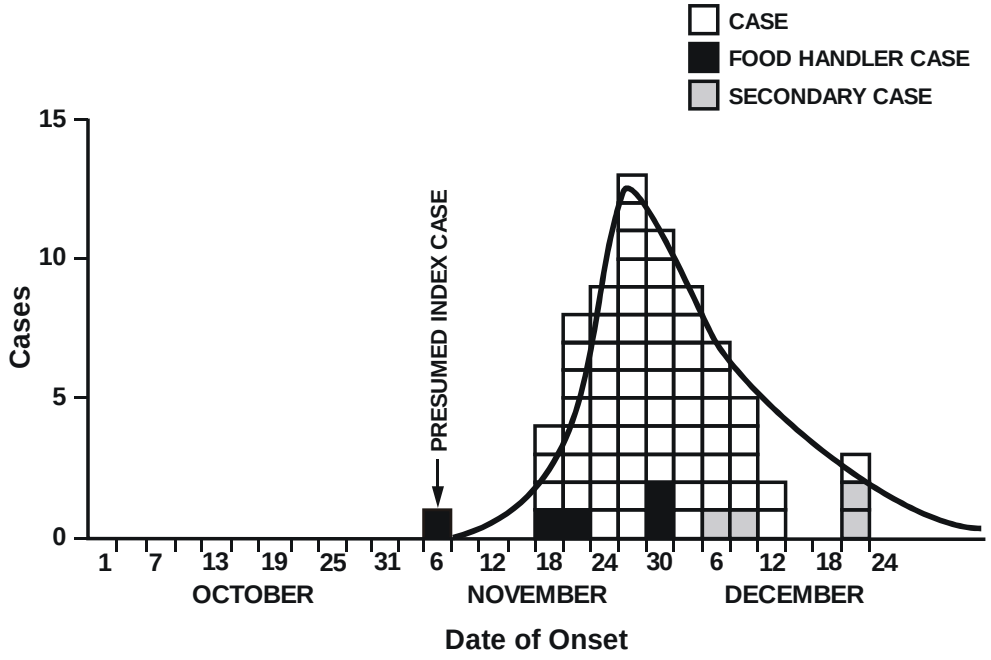
A **common source outbreak** is one in which a group of persons is exposed to a common noxious influence, such as an infectious agent or a toxin. If the group is exposed over a relatively brief period, so that everyone who becomes ill develops disease at the end of one incubation period, then the common source outbreak is further classified as a **point source outbreak**. The epidemic of leukemia cases in Hiroshima following the atomic bomb blast and the epidemic of hepatitis A among college football players who unknowingly drank contaminated water after practice one day each had a point source of exposure (11, 21). When the number of cases in a point source epidemic is plotted over time, the resulting epidemic curve classically has a steep upslope and a more gradual downslope (a so-called "log-normal distribution"). Figure 1.20 is an example of the typical log-normal distribution of a point source outbreak.

In some common source outbreaks, cases may be exposed over a period of days, weeks, or longer, with the exposure being either **intermittent** or **continuous**. Figure 1.21 is an epidemic curve of a common source outbreak with continuous exposure. When we plot the cases of a continuous common source outbreak over time, the range of exposures and range of incubation periods tend to dampen and widen the peaks of the epidemic curve. Similarly, when we plot an intermittent common source outbreak we often find an irregular pattern that reflects the intermittent nature of the exposure.

An outbreak that does not have a common source, but instead spreads gradually from person to person—usually growing as it spreads—is called a **propagated** outbreak. Usually transmission is by direct person-to-person contact, as with syphilis. Transmission may also be vehicleborne, as the transmission of hepatitis B or HIV by sharing needles, or vectorborne, as the transmission of yellow fever by mosquitoes.

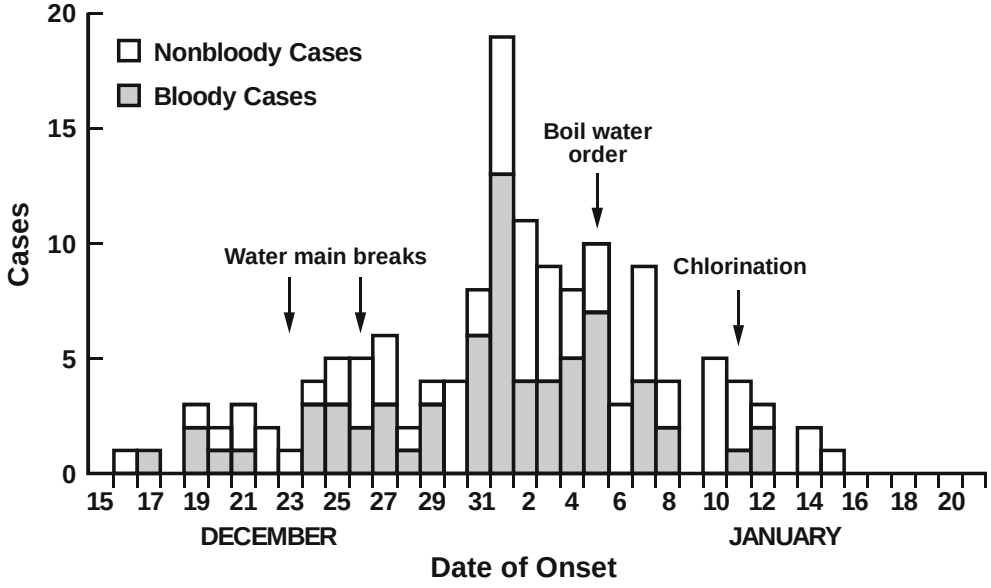
In a propagated epidemic, cases occur over more than one incubation period. In theory, the epidemic curve of a propagated epidemic would have a successive series of peaks reflecting increasing numbers of cases in each generation. The epidemic usually wanes after a few generations, either because the number of susceptibles falls below some critical level, or because intervention measures become effective. Figure 1.22 shows such an epidemic curve.

Figure 1.20
Example of common source outbreak with point source exposure: Hepatitis A cases by date of onset, Fayetteville, Arkansas, November-December 1978, with log-normal curve superimposed



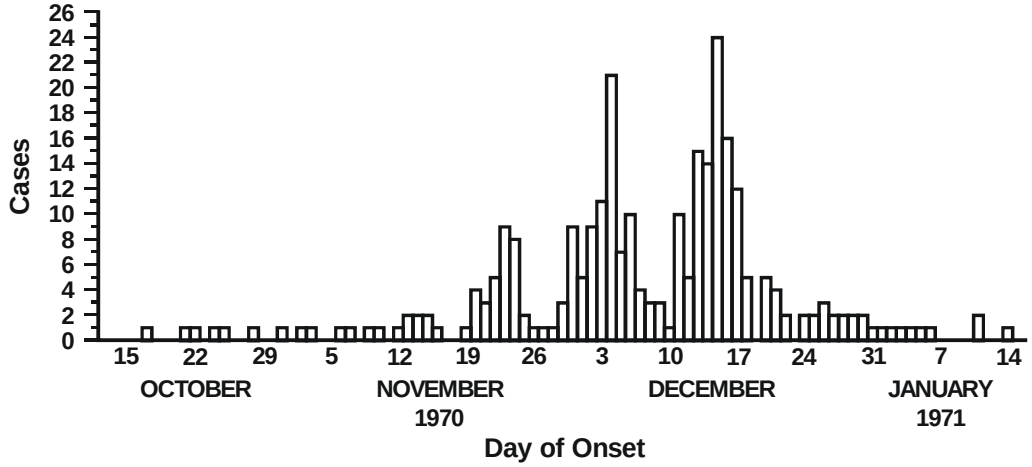
Source: CDC, unpublished data, 1979

Figure 1.21
Example of common source outbreak with continuous exposure: Diarrheal illness in city residents by date of onset and character of stool, Cabool, Missouri, December 1989-January 1990



Source: CDC, unpublished data, 1990

Figure 1.22
Example of the classic epidemic curve of a propagated epidemic: Measles cases by date of onset, Aberdeen, South Dakota, October 15, 1970-January 16, 1971



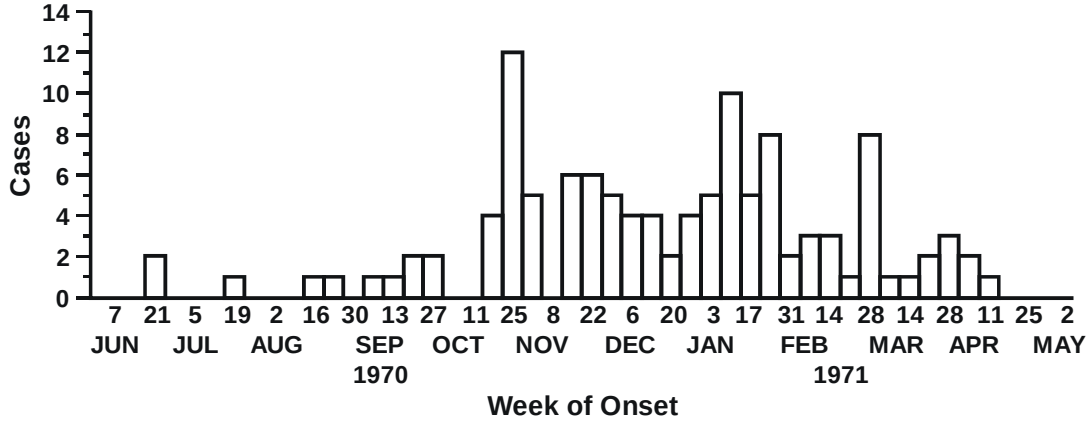
Source: 7

In reality, few propagated outbreaks provide as classic a pattern as that shown in Figure 1.22. For many diseases, the variability of time of exposure and range of incubation periods tend to smooth out the peaks and valleys, as shown in Figure 1.23. For influenza, the incubation period is so short and transmission is so effective that its epidemic curve can look like that of a point source epidemic.

Some epidemics may have features of both common source epidemics and propagated epidemics. The pattern of a common source outbreak followed by secondary person-to-person spread is not uncommon. These are called **mixed** epidemics. For example, Figure 1.24 illustrates a common source epidemic of shigellosis that occurred among a group of 3,000 women attending a national music festival. Many developed symptoms after returning home. Over the next few weeks, several state health departments detected subsequent generations of shigella cases spread by person-to-person transmission from festival attendees (19).

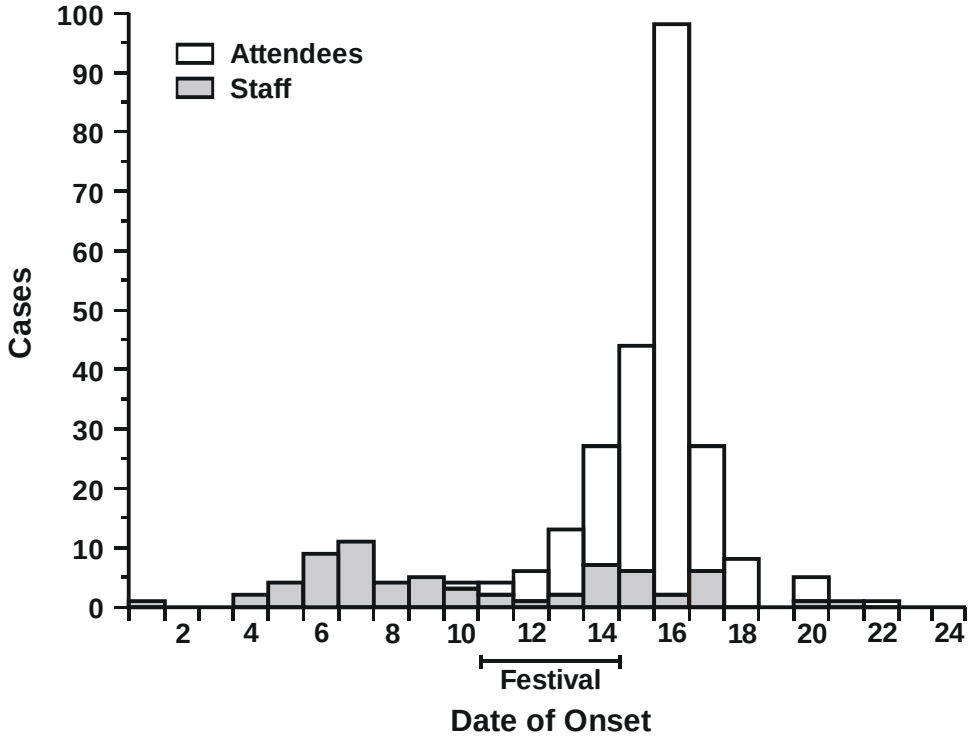
Finally, some epidemics are neither common source in its usual sense nor propagated from person-to-person. Outbreaks of zoonotic or vectorborne disease may result from sufficient prevalence of infection in host species, sufficient presence of vectors, and sufficient human-vector interaction. Examples include the epidemic of Lyme disease which affected several states in the northeastern United States in the late 1980's and the large epidemic of St. Louis encephalitis in Florida in 1990.

Figure 1.23
Example of a propagated epidemic that does not show the classic pattern: Infectious hepatitis cases by week of onset, Barren County, Kentucky, June 1970-April 1971



Source: 5

Figure 1.24
Example of a mixed epidemic: Shigella cases at a music festival by day of onset, Michigan, August 1988



Source: 19

Exercise 1.8

You have just studied about three epidemic patterns:

1) point source, 2) intermittent or continuous, and 3) propagated. For each of the following outbreak settings, choose the most likely epidemic pattern.

Pattern **Outbreak Setting**

_____ a. Outbreak of salmonellosis traced to turkey cooked and held at an improper temperature and served at a pot-luck supper.

_____ b. Outbreak of influenza among nursing home residents, new cases occurring over a 3-week period (Hint: incubation period for influenza is less than 5 days.)

_____ c. Episodic cases of Legionnaires' disease in hospitalized patients traced to showers and the hospital's water supply.

Answers on page 72.

Summary

As a discipline within public health, epidemiology includes the study of the frequency, patterns, and causes of health-related states or events in populations, and the application of the information gained to public health issues. In epidemiology, our "patient" is the public at large—the community—and in "treating" our patient we perform several tasks, including public health surveillance, disease investigation, analytic epidemiology, and evaluation.

With surveillance, we constantly monitor the health of a community to detect any changes in disease occurrence. This requires us to regularly collect, analyze, interpret, and disseminate data, with the intention of taking prompt and appropriate public health action should we identify a problem.

Epidemiology provides us with a systematic approach for determining *What*, *Who*, *Where*, *When*, and *Why/How*. We rely on standard case definitions to determine *What*, that is, whether a specific person has a particular disease. We use descriptive epidemiology to describe disease occurrence by person (*Who*), place (*Where*), and time (*When*). We also use descriptive epidemiology to portray the characteristics and public health of a population or community.

Two essential concepts in this systematic approach are population and rates. We identify the populations in which cases occur, and calculate rates of disease for different populations. We use differences in disease rates to target disease intervention activities and to generate hypotheses about possible risk factors and causes of disease. We then use analytic epidemiology to sort out and quantify potential risk factors and causes (*Why*).

As epidemiologists carrying out these tasks, we must be part of a larger team of institutions and individuals, including health-care providers, government leaders and workers, laboratorians, and others dedicated to promoting and protecting the public's health.

Answers To Exercises

Answer—Exercise 1.1 (page 11)

a. Two high-risk behaviors have been identified. If either of these behaviors is common in the community, public health officials can expect a substantial number of AIDS cases over time. Therefore, public health officials need to ask, How common are these behaviors in our community? (Another way of phrasing this question is, How large are the groups of persons in our community who engage in these behaviors?) Where are they located? What types of public health programs might be most effective in reaching these groups? Answers to these questions should help officials develop appropriate policies and programs.

b. The individual can use this information to make individual choices regarding sexual behavior and use of intravenous drugs. For example, the findings might convince someone who uses intravenous drugs only occasionally to abandon them altogether.

c. The researcher asks, What specifically about these behaviors might be associated with disease? Are people who engage in the behaviors more frequently at greater risk of the disease? What other risk factors can we identify? What common pathway might there be? Could AIDS be caused by some toxic agent (chemical) used by both groups? Could it be caused by an infectious agent transmitted by exchange of blood, like hepatitis B? Could it be caused by sheer immunologic overload? By addressing these questions and hypotheses with epidemiologic and laboratory methods, researchers identified the modes of transmission (and prevention strategies) and, eventually, the causative virus.

Answer—Exercise 1.2 (page 14)

ID #	Last name	myalgia	fever	facial edema	eosinophil count	Physician diagnosis	Lab confirm	Classification
1	Abels	yes	yes	no	495	trichinosis	yes	CONFIRMED
2	Baker	yes	yes	yes	pending	trichinosis ?	pending	PROBABLE
3	Corey	yes	yes	no	1,100	trichinosis	pending	PROBABLE
4	Dale	yes	no	no	2,050	EMS ?	pending	SUSPECT
5	Ring	yes	no	no	600	trichinosis	not done	POSSIBLE

Answer—Exercise 1.3 (page 15)

Note that the cause of Kawasaki syndrome is unknown and no definitive laboratory test is available. Many other childhood illnesses cause fever, rash and/or swollen glands, but none usually causes the entire constellation of findings listed under the case definition. Therefore, the case definition is necessarily strict to exclude those other childhood diseases. However, the case definition describes a fairly serious illness lasting at least 5 days. In all likelihood, there is a spectrum of disease ranging from mild or even asymptomatic (certainly not captured by the current case definition) to severe (captured by the case definition).

a. The case definition is useful in excluding other febrile rash illnesses, but it might be a little too strict to guide therapy. Consider a child who has fever of at least 5 days' duration, three of the first four clinical findings, and cervical lymphadenopathy with the largest lymph node measuring about 1.0 cm in diameter (not 1.5 cm, as required). If a safe, effective, and convenient treatment were available for Kawasaki syndrome, would you treat the child who misses the case definition by ½ cm (1/4 inch)? Many would, indicating that the case definition may be too strict for treatment purposes.

b. For surveillance purposes, a case definition should be consistent over time and across space. It should also be easy to use. By promoting a standard case definition, CDC hopes that it will be used consistently. Unfortunately, it is a bit cumbersome, so the number of reported cases will underrepresent the true total number of cases.

c. As noted on page 13, investigators searching for causes prefer strict case definitions. To identify exposures associated with disease, investigators must be sure that "cases" have the disease under study, and that "non-cases" (controls) do not have the disease. Thus this definition is appropriate if it satisfactorily excludes the other febrile rash illnesses.

Answer—Exercise 1.4 (page 29)

Time

- seasonal variation with spring/early summer peak

Person

- age distribution
  — no cases among infants (less than 1-year-olds)
  — increased incidence among children to 14 years of age
  — increased incidence among females ages 2 to 50 years.
  — low incidence among males ages 15 to 40 years
  — increased incidence among males greater than 50 years of age.
- married women at greater risk than unmarried women at every age
- incidence inversely related to socioeconomic level
- mill workers at lower risk than non-mill workers

Answer—Exercise 1.5 (page 34)

a. Observational cohort study, because subjects were enrolled on the basis of their exposure (Vietnam or Europe)

b. Not an epidemiologic study, because there is no comparison group

c. Observational case-control study, because subjects were enrolled on the basis of whether they had trichinosis or not

d. Experimental study because the investigators rather than the subjects themselves controlled the exposure

Answer—Exercise 1.6 (page 39)

a. Role of human immunodeficiency virus in AIDS:

Agent

human immunodeficiency virus

Host

- behavioral factors which increase likelihood of exposure, such as intravenous drug use, men who have sex with men, etc.
- biologic factors which determine whether an exposed person becomes infected, such as presence of genital ulcers
- biologic factors, largely unknown at present, which determine whether (or when) an infected person develops clinical AIDS

Environment

- biologic factors, such as infected persons to transmit the infection
- physical factors, such as inconvenient bedside position and needle design which contribute to needlestick injuries among health care workers
- socioeconomic and societal factors, such as those that contribute to drug use

b. Classification of risk factors for heart disease

All are component causes.

Answer—Exercise 1.7 (page 51)

Yellow Fever

Reservoirs: humans, *Aedes aegypti* mosquitoes, monkeys, possibly marsupials, forest mosquitoes, and other vertebrates

Portals of exit: by way of skin

Modes of transmission: indirect transmission to humans by mosquito vector

Portals of entry: blood

Factors in host susceptibility: lack of active immunity (1)

Viral Hepatitis A

Reservoirs: humans and certain nonhuman primates

Portals of exit: feces

Modes of transmission: indirect transmission through contaminated vector (e.g., unwashed hands) to vehicle (e.g., food, water); direct transmission occurs among homosexuals and through blood transfusions.

Portals of entry: mouth; blood

Factors in host susceptibility: lack of active immunity or passive immunity (1)

Answer—Exercise 1.8 (page 60)

a. point source

b. propagated

c. intermittent or continuous

Self-Assessment Quiz 1

Now that you have read Lesson 1 and have completed the exercises, you should be ready to take the self-assessment quiz. This quiz is designed to help you assess how well you have learned the content of this lesson. You may refer to the lesson text whenever you are unsure of the answer, but keep in mind that the final will be a closed book examination. Circle ALL correct choices in each question.

1. In the definition of epidemiology, the terms “distribution” and “determinants” taken together refer to:
   A. frequency, pattern, and causes of health events
   B. dissemination of information to those who need to know
   C. knowledge, attitudes, and practices related to health
   D. public health services and resources

2. **Descriptive epidemiology** includes all EXCEPT:
   A. what
   B. who
   C. when
   D. where
   E. why

3. The London cholera epidemic of 1848 was traced to the Broad Street pump by whom?
   A. Graunt
   B. Farr
   C. Snow
   D. Doll
   E. Hill

4. The four components of a case definition are:
   _____
   _____
   _____
   _____

5. The time course of a disease outbreak is usually displayed as a/an:
   A. secular trend
   B. seasonal trend
   C. epidemic curve
   D. endemic curve

For questions 6-12: Each week, each state health department sends to CDC a computerized line listing of persons diagnosed with a reportable disease (for example, measles or hepatitis A). The variables included in the line listing are shown in questions 6-12. Identify which of the following categories (A-F) describes each variable.

   A. What (clinical information)
   B. When (time)
   C. Where (place)
   D. Who (person)
   E. Why (cause or risk factor)
   F. Other

6. ____ ID number
7. ____ Disease code
8. ____ Race
9. ____ County
10. ____ Date of onset
11. ____ Date of report
12. ____ Outcome (alive or dead)

13. When analyzing data by age the categories should be:
   A. the same for all diseases
   B. <1 year, 1 to 4 years, 5 to 9 years, 10 to 14 years, 15 to 19 years, and 20 years for communicable diseases, but not necessarily for chronic diseases
   C. appropriate for each condition and narrow enough to detect any age-related patterns present in the data
   D. 5-year age groups for all diseases unless the data suggest the need for narrower categories to find a pattern or aberrancy

14. Because socioeconomic status is difficult to quantify, we commonly use all of the following substitute measures EXCEPT:
    A. educational achievement
    B. family income
    C. occupation
    D. social standing

15. The Framingham study, in which a group of residents have been followed since the 1950's to identify occurrence and risk factors for heart disease, is an example of which type(s) of study? (Circle ALL that apply.)
    A. Experimental
    B. Observational
    C. Cohort
    D. Case-control
    E. Clinical trial

16. The Cancer and Steroid Hormone (CASH) study, in which women with breast cancer and a comparable group of women without breast cancer were asked about their prior use of oral contraceptives ("the Pill"), is an example of which type of study? (Circle ALL that apply.)
    A. Experimental
    B. Observational
    C. Cohort
    D. Case-control
    E. Clinical trial

17. The primary difference between an experimental and observational study is:
    A. the investigator is "blinded" (prevented from knowing the subjects' true exposure status until the end of the study) in an experimental study but not in an observational study
    B. the investigator controls the subject's exposure in an experimental study but not in an observational study
    C. the investigator controls the subject's outcome in an experimental study but not in an observational study
    D. experimental studies are conducted with animals; observational studies are conducted with humans

18. If a particular disease is caused by any of the three sufficient causes diagrammed in Figure 1.25 (but only these three), which components, if any, are a necessary cause? (Circle ALL that apply.)

    A. A

    B. B

    C. C

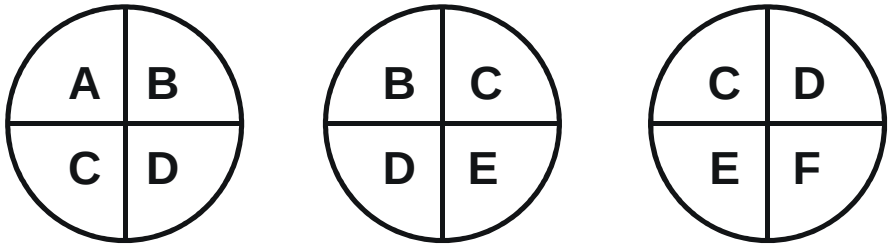
    D. D

    E. E

    F. F

    G. None

Figure 1.25
Causal pies representing all sufficient causes of a particular disease



19. The functions of public health surveillance include which of the following? (Circle ALL that apply.)

    A. Collection of health data

    B. Analysis of health data

    C. Interpretation of health data

    D. Dissemination of health data

    E. Disease control actions developed from the collection, analysis, and interpretation of health data

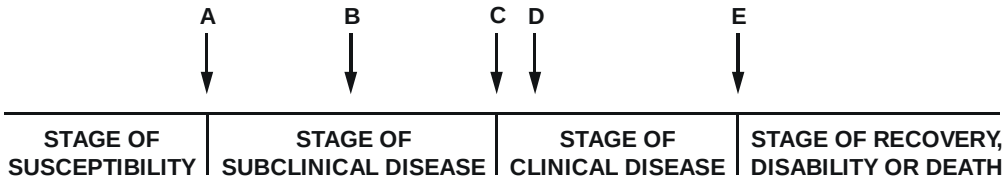
20. For each of the following, identify the appropriate letter from the time line in Figure 1.26 representing the natural history of disease.

    ____ Onset of symptoms

    ____ Usual time of diagnosis

    ____ Exposure

Figure 1.26
Natural history of disease timeline



21. **Direct transmission** includes which of the following modes of transmission? (Circle ALL that apply.)

    A. Droplet spread

    B. Vehicleborne transmission

    C. Vectorborne transmission

    D. Airborne transmission

Questions 22-24 describe the case-report pattern of disease X for three communities. The communities have the same size population. Identify which term A-D below best describes the occurrence of disease X.

A. Endemic

B. Epidemic

C. Hyperendemic

D. Pandemic

22. ____ Community A: usually 10 cases/week; last week, 28 cases
23. ____ Community B: 50-70 cases/week; last week, 55 cases
24. ____ Community C: usually 25 cases/week; last week, 28 cases

25. An epidemic curve which follows the classic log-normal pattern of sharp rise and more gradual decline is most consistent with which manner of spread?

    A. Continuous source

    B. Intermittent source

    C. Point source

    D. Propagated

    E. Mixed

Answers are in Appendix J.
If you answered at least 20 questions correctly, you understand Lesson 1 well enough to go to Lesson 2.

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Lesson 6
Investigating an Outbreak

One of the most exciting and challenging tasks facing an epidemiologist working in a public health department is investigating an outbreak. Frequently, the cause and source of the outbreak are unknown. Sometimes large numbers of people are affected. Often, the people in the community are concerned because they fear more people, including themselves, may be stricken unless the cause is found soon. There may be hostilities and defensiveness if an individual, product, or company has been accused of being the cause. Into this pressure-packed situation comes the epidemiologist, sometimes from the local health department, more often from "the outside." In this setting the epidemiologist must remain calm, professional, and scientifically objective. Fortunately, epidemiology provides the scientific basis, the systematic approach, and the population and prevention orientations that are needed.

Objectives

After studying this lesson and answering the questions in the exercises, a student will be able to do the following:

- List the reasons that health agencies investigate reported outbreaks
- List the steps in the investigation of an outbreak
- Define the terms **cluster, outbreak, epidemic**
- Given the initial information of a possible disease outbreak, describe how to determine whether an epidemic exists
- State what a line listing is and what it is used for
- Given information about a community outbreak of disease, execute the initial steps of an investigation and develop biologically plausible hypotheses
- Draw a traditional epidemic curve
- Given data in a two-by-two table, calculate the appropriate measure of association and chi-square test

Introduction to Investigating an Outbreak

Uncovering Outbreaks

One of the uses of surveillance--covered in Lesson 5--is the detection of outbreaks. Outbreaks may be detected when routine, timely analysis of surveillance data reveals an increase in reported cases or an unusual clustering of cases. In a health department, we may detect increases in or unusual patterns of disease from the weekly tabulations of case reports by time and place or from the examination of the exposure information on the case reports themselves. For example, health department staff detected an outbreak of hepatitis B that was transmitted by a dentist because they regularly reviewed and compared the dental exposures reported for hepatitis B cases (19). Similarly, in a hospital, weekly analysis of microbiologic isolates from patients by organism and ward may reveal an increased number of apparent nosocomial (hospital-acquired) infections in one part of the hospital.

Nonetheless, most outbreaks come to the attention of health authorities because an alert clinician is concerned enough to call the health department. The nationwide epidemic of eosinophilia-myalgia syndrome (EMS) was first detected when a physician in New Mexico called a consultant in Minnesota and realized that, together, they had seen three patients with a highly unusual clinical presentation. All three patients said they used L-tryptophan. The local physician promptly called the New Mexico State Health and Environment Department, which set into motion a chain of public health actions leading to the recall of L-tryptophan throughout the country (14,23).

Members of affected groups are another important reporting source for apparent clusters of both infectious and noninfectious disease. For example, someone may call a health department and report that he and several co-workers came down with severe gastroenteritis after attending a banquet several nights earlier. Similarly, a local citizen may call about several cases of cancer diagnosed among his neighbors and express concern that these are more than coincidental. Most health departments have routine procedures for handling calls from the public regarding potential communicable disease outbreaks, and a few states have developed guidelines for how to respond to noninfectious disease cluster reports (2,8,9).

Why Investigate Possible Outbreaks

Health departments investigate suspected outbreaks for a variety of reasons. These include the need to institute control and prevention measures; the opportunity for research and training; program considerations; and public relations, political concerns, and legal obligations.

Control/prevention

The primary public health reason to investigate an outbreak is to control and prevent further disease. Before we can develop control strategies for an outbreak, however, we must identify where the outbreak is in its natural course: Are cases occurring in increasing numbers or is the outbreak just about over? Our goal will be different depending on the answers to these questions.

If cases are continuing to occur in an outbreak, our goal may be to prevent additional cases. Therefore, the objective of our investigation would be to assess the extent of the outbreak and the size and characteristics of the population at risk in order to design and implement appropriate control measures.

On the other hand, if an outbreak appears to be almost over, our goal may be to prevent outbreaks in the future. In that case, the objective of our investigation is more likely to be to identify factors which contributed to the outbreak in order to design and implement measures that would prevent similar outbreaks in the future.

The balance between control measures versus further investigation depends on how much is known about the cause, the source, and the mode of transmission of the agent (11). Table 6.1 illustrates the relative emphasis as influenced by how much we know about these factors.

Table 6.1
Relative priority of investigative and control efforts during an outbreak, based on level of knowledge of the source, mode of transmission, and causative agent

		Source/Mode of Transmission: Known	Source/Mode of Transmission: Unknown
Causative Agent: Known		Investigation + Control +++	Investigation +++ Control +
Causative Agent: Unknown		Investigation +++ Control +++	Investigation +++ Control +

+++ = highest priority
+ = lower priority
Source: 11

If we know little about the source and mode of transmission, as indicated in the right-hand column of the table, we must investigate further before we can design appropriate control measures. In contrast, if we know the source and mode of transmission, as indicated in the left-hand column, control measures can be implemented immediately. However, if we don't know what the agent is, as indicated in the bottom row of the table, we must investigate further to identify the agent.

The public health response to the outbreak of EMS described earlier illustrates this point. Since investigators quickly determined that EMS was associated with the ingestion of L-tryptophan, that product was immediately withdrawn from the market, and persons were warned to avoid taking any they had on hand. However, officials continued the investigation for quite some time until they were certain they had identified the specific contaminant and reason that contamination occurred.

The decisions regarding whether and how extensively to investigate an outbreak are influenced by characteristics of the problem itself: the severity of the illness, the source or mode of transmission, and the availability of prevention and control measures. It is particularly urgent to investigate an outbreak when the disease is severe (serious illness with high risk of hospitalization, complications, or death) and has the potential to affect others unless prompt control measures are taken. For example, in the United States, every case of plague and botulism is investigated immediately to identify and eradicate the source. Cases of syphilis, tuberculosis, and measles are investigated promptly to identify contacts and interrupt further transmission.

Research opportunities

Another important objective of outbreak investigations is, simply, to gain additional knowledge. Each outbreak may be viewed as an experiment of nature waiting to be analyzed and exploited. Each presents a unique opportunity to study the natural history of the disease in question. For a newly recognized disease, field investigation provides an opportunity to define the natural history--including agent, mode of transmission, and incubation period--and the clinical spectrum of disease. Investigators also attempt to characterize the populations at greatest risk and to identify specific risk factors. Acquiring such information was an important motivation for investigators studying such newly recognized diseases as Legionnaires' disease in Philadelphia in 1976, toxic shock syndrome in 1980, acquired immunodeficiency syndrome in the early 1980's, and EMS in 1989.

Even for diseases that are well characterized, an outbreak may provide opportunities to gain additional knowledge by assessing the impact of control measures and the usefulness of new epidemiology and laboratory techniques. For example, an outbreak of measles in a highly immunized community provides a setting for investigators to study vaccine efficacy, the effect of age at vaccination, and the duration of vaccine-induced protection (16). An outbreak of giardiasis was used to study the appropriateness of a new clinical case definition (15), while an outbreak of pertussis was used to study the performance of a new culture medium (7).

Training

Investigating an outbreak requires a combination of diplomacy, logical thinking, problem-solving ability, quantitative skills, epidemiologic know-how, and judgment. These skills improve with practice and experience. Thus many investigative teams pair a seasoned epidemiologist with an epidemiologist-in-training. The latter gains valuable on-the-job training and experience while providing assistance in the investigation and control of the outbreak.

Public, political, or legal concerns

Public, political, or legal concerns sometimes override scientific concerns in the decision to conduct an investigation. Increasingly, the public has taken an interest in disease clusters and potential environmental exposures, and has called upon health departments to investigate. Such investigations almost never identify a causal link between exposure and disease (4,22). Nevertheless, many health departments have learned that it is essential to be "responsibly responsive" to public concerns, even if the concern has little scientific basis (9,2,18). Thus several states, recognizing their need to be responsive and an opportunity to educate the public, have adopted protocols for investigating disease clusters reported by its citizens. Some investigations are conducted because the law requires an agency to do so. For example, CDC's National Institute of Occupational Safety and Health (NIOSH) is required to evaluate the risks to health and safety in a workplace if requested to do so by three or more workers.

Program considerations

Many health departments routinely offer a variety of programs to control and prevent illnesses such as tuberculosis, vaccine-preventable diseases, and sexually transmitted diseases. An outbreak of a disease targeted by a public health program may reveal a weakness in that program and an opportunity to change or strengthen the program's efforts. Investigating the causes of an outbreak may identify populations which have been overlooked, failures in the intervention strategy, changes in the agent, or events beyond the scope of the program. By using an outbreak to evaluate the program's effectiveness, program directors can improve the program's future directions and strategies.

Exercise 6.1

During the previous year, nine residents of a community died from the same type of cancer. List some reasons that might justify an investigation.

Answers on page 398.

Steps of an Outbreak Investigation

In the investigation of an ongoing outbreak, working quickly is essential. Getting the right answer is essential, too. Under such circumstances, epidemiologists find it useful to have a systematic approach to follow, such as the sequence listed in Table 6.2. This approach ensures that the investigation proceeds forward without missing important steps along the way.

Table 6.2
Steps of an outbreak investigation

1. Prepare for field work
2. Establish the existence of an outbreak
3. Verify the diagnosis
4. Define and identify cases
   a. establish a case definition
   b. identify and count cases
5. Perform descriptive epidemiology
6. Develop hypotheses
7. Evaluate hypotheses
8. As necessary, reconsider/refine hypotheses and execute additional studies
   a. additional epidemiologic studies
   b. other types of studies – laboratory, environmental
9. Implement control and prevention measures
10. Communicate findings

The steps described in Table 6.2 are in conceptual order. In practice, however, several steps may be done at the same time, or the circumstances of the outbreak may dictate that a different order be followed. For example, control measures should be implemented as soon as the source and mode of transmission are known, which may be early or late in any particular outbreak investigation.

Step 1: Preparing for Field Work

Anyone about to embark on an outbreak investigation should be well prepared before leaving for the field. Preparations can be grouped into three categories: (a) investigation, (b) administration, and (c) consultation. Good preparation in all three categories will facilitate a smooth field experience.

(a) *Investigation*

First, as a field investigator, you must have the appropriate scientific knowledge, supplies, and equipment to carry out the investigation. You should discuss the situation with someone knowledgeable about the disease and about field investigations, and review the applicable literature. You should assemble useful references such as journal articles

and sample questionnaires.

Before leaving for a field investigation, consult laboratory staff to ensure that you take the proper laboratory material and know the proper collection, storage, and transportation techniques. Arrange for a portable computer, dictaphone, camera, and other supplies.

(b) *Administration*
Second, as an investigator, you must pay attention to administrative procedures. In a health agency, you must make travel and other arrangements and get them approved. You may also need to take care of personal matters before you leave, especially if the investigation is likely to be lengthy.

(c) *Consultation*
Third, as an investigator, you must know your expected role in the field. Before departure, all parties should agree on your role, particularly if you are coming from "outside" the local area. For example, are you expected to lead the investigation, provide consultation to the local staff who will conduct the investigation, or simply lend a hand to the local staff? In addition, you should know who your local contacts will be. Before leaving, you should know when and where you are to meet with local officials and contacts when you arrive in the field.

Step 2: Establishing the Existence of an Outbreak

An **outbreak** or an **epidemic** is the occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time. In contrast, a **cluster** is an aggregation of cases in a given area over a particular period without regard to whether the number of cases is more than expected. In an outbreak or epidemic, we usually presume that the cases are related to one another or that they have a common cause.

Many epidemiologists use the terms "outbreak" and "epidemic" interchangeably, but the public is more likely to think that "epidemic" implies a crisis situation. Some epidemiologists restrict the use of the term "epidemic" to situations involving larger numbers of people over a wide geographic area.

Most outbreaks come to the attention of health departments in one of two ways. One way is by regular analysis of surveillance data. As noted in Lesson 5, unusual rises or patterns of disease occurrence can be detected promptly if surveillance data collection and analysis are timely. The second, and probably more common, way is through calls from a health care provider or citizen who knows of "several cases." For example, a member of the public may report three infants born with birth defects within a 1-month period in the same community. This aggregation of cases *seems* to be unusual, but frequently the public does not know the denominator--e.g., the total number of births--or the expected incidence of birth defects.

One of your first tasks as a field investigator is to verify that a purported outbreak is indeed an outbreak. Some will turn out to be true outbreaks with a common cause, some will be sporadic and unrelated cases of the same disease, and others will turn out to be unrelated cases of similar

but unrelated diseases. Often, you must first determine the expected number of cases before deciding whether the observed number exceeds the expected number, i.e., whether a cluster is indeed an outbreak.

Thus, as in other areas of epidemiology, you compare the **observed with the expected**. How then, do you determine what's expected? Usually we compare the current number of cases with the number from the previous few weeks or months, or from a comparable period during the previous few years.

- For a notifiable disease, you can use health department surveillance records.
- For other diseases and conditions, you can usually find existing data locally--hospital discharge records, mortality statistics, cancer or birth defect registries.
- If local data are not available, you can apply rates from neighboring states or national data, or, alternatively, you may conduct a telephone survey of physicians to determine whether they have seen more cases of the disease than usual.
- Finally, you may conduct a survey of the community to establish the background or historical level of disease.

Even if the current number of reported cases exceeds the expected number, the excess may not necessarily indicate an outbreak. Reporting may rise because of changes in local reporting procedures, changes in the case definition, increased interest because of local or national awareness, or improvements in diagnostic procedures. A new physician, infection control nurse, or health care facility may see referred cases and more consistently report cases, when in fact there has been no change in the actual occurrence of the disease. Finally, particularly in areas with sudden changes in population size such as resort areas, college towns, and migrant farming areas, changes in the numerator (number of reported cases) may simply reflect changes in the denominator (size of the population).

Whether you should investigate an apparent problem further is not strictly tied to your verifying that an epidemic exists (observed numbers greater than expected). As noted earlier, the severity of the illness, the potential for spread, political considerations, public relations, available resources, and other factors all influence the decision to launch a field investigation.

Exercise 6.2

For the month of August, 12 new cases of tuberculosis and 12 new cases of aseptic meningitis were reported to a county health department. Would you call either group of cases a cluster? Would you call either group of cases an outbreak? What additional information might be helpful in answering these questions?

Answers on page 398.

Step 3: Verifying the Diagnosis

Closely linked to verifying the existence of an outbreak is establishing what disease is occurring. In fact, as an investigator, you frequently will be able to address these two steps at the same time. Your goals in verifying the diagnosis are (a) to ensure that the problem has been properly diagnosed and (b) to rule out laboratory error as the basis for the increase in diagnosed cases.

In verifying the diagnosis you should review the clinical findings and laboratory results. If you have any question about the laboratory findings, i.e., if the laboratory tests are inconsistent with the clinical and epidemiologic findings, you should have a qualified laboratorian review the laboratory techniques being used. If you plan specialized laboratory work such as confirmation in a reference laboratory, DNA or other chemical or biological fingerprinting, or polymerase chain reaction, you must secure the appropriate specimens, isolates, and other laboratory material as soon as possible, and from a sufficient number of patients.

You should always summarize the clinical findings with frequency distributions (see Lessons 2 and 3 for a discussion of frequency distributions). Such frequency distributions are useful in characterizing the spectrum of illness, verifying the diagnosis, and developing case definitions. Many investigators consider these clinical frequency distributions so important that they routinely present these findings in the first table of their report or manuscript.

Finally, you should visit several patients with the disease. If you do not have the clinical background to verify the diagnosis, a qualified clinician should do so. Nevertheless, regardless of background, you should see and talk to some patients to gain a better understanding of the clinical features, and to develop a mental image of the disease and the patients affected by it. In addition, you may be able to gather critical information from these patients: What were their exposures before becoming ill? What do *they* think caused their illness? Do they know anyone else with the disease? Do they have anything in common with others who have the disease? Conversations with patients are very helpful in generating hypotheses about disease etiology and spread.

Step 4a: Establishing a Case Definition

Your next task as an investigator is to establish a case definition. A case definition is a standard set of criteria for deciding whether an individual should be classified as having the health condition of interest. A case definition includes clinical criteria and--particularly in the setting of an outbreak investigation--restrictions by time, place, and person. You should base the clinical criteria on simple and objective measures such as elevated antibody titers, fever $\geq 101°F$, three or more loose bowel movements per day, or myalgias severe enough to limit the patient's usual activities. You may restrict the case definition by time (for example, to persons with onset of illness within the past 2 months), by place (for example, to residents of the nine-county area or to employees of a particular plant) and by person (for example, to persons with no previous history of musculo-skeletal disease, or to pre-menopausal women). Whatever your criteria, you must apply them consistently and without bias to all persons under investigation.

Be careful that the case definition does not include an exposure or risk factor you want to test. This is a common mistake. For example, do not define a case as "illness X among persons who were in homeless shelter Y" if one of the goals of the investigation is to determine whether the shelter is associated with illness.

Ideally, your case definition will include most if not all of the actual cases, but very few or none of what are called "false-positive" cases (persons who actually do not have the disease in question but nonetheless meet the case definition). Recognizing the uncertainty of some diagnoses, investigators often classify cases as confirmed, probable, or possible.

To be classified as confirmed, a case usually must have laboratory verification. A case classified as probable usually has typical clinical features of the disease without laboratory confirmation. A case classified as possible usually has fewer of the typical clinical features. For example, in an outbreak of bloody diarrhea and hemolytic-uremic syndrome caused by infection with *E. coli* O157:H7, investigators defined cases in the following three classes:

- **Definite** case: *E. coli* O157:H7 isolated from a stool culture or development of hemolytic-uremic syndrome in a school-age child resident of the county with gastrointestinal symptoms beginning between November 3 and November 8, 1990
- **Probable** case: Bloody diarrhea, with the same person, place, and time restrictions
- **Possible** case: Abdominal cramps and diarrhea (at least three stools in a 24-hour period) in a school-age child with onset during the same period (CDC, unpublished data, 1991).

As an investigator, you will find such classifications useful in several situations. First, they will allow you to keep track of a case even if the diagnosis is not confirmed. For example, you might temporarily classify a case as probable or possible while laboratory results are pending. Alternatively, the patient's physician or you may have decided not to order the laboratory test required to confirm the diagnosis because the test is expensive, difficult to obtain, or unnecessary. For example, during a community outbreak of measles, which has a characteristic clinical picture, investigators might follow the usual practice of confirming only a few cases and then relying on clinical features to identify the rest of the cases. Similarly, while investigating an outbreak of diarrhea on a cruise ship, investigators usually try to identify an agent from stool samples from a few afflicted persons. If those few cases are confirmed to be infected with the same agent, the other persons with compatible clinical illness are all presumed to be part of the same outbreak.

Early in an investigation, investigators often use a sensitive or "loose" case definition which includes confirmed, probable, and even possible cases. Later on, when hypotheses have come into sharper focus, the investigator may "tighten" the case definition by dropping the possible category. You will find this a useful strategy in investigations that require you to travel to different hospitals, homes, or other sites to gather information, because it is better to collect extra

data while you're there than to have to go back. This illustrates an important axiom of field epidemiology: "Get it while you can."

A "loose" case definition is used early in the investigation to identify the extent of the problem and the populations affected. Important hypotheses may arise from this process. However, in analytic epidemiology, inclusion of false-positive cases can produce misleading results. Therefore, to test these hypotheses using analytic epidemiology (see page 375), specific or "tight" case definitions must be used.

Step 4b: Identifying and Counting Cases

As noted earlier, many outbreaks are brought to the attention of health authorities by concerned health care providers or citizens. However, the cases which prompted the concern are often only a small and nonrepresentative fraction of the total number of cases. Public health workers must therefore "cast the net wide" to determine the geographic extent of the problem and the populations affected by it.

When you need to identify cases, use as many sources as you can. You may have to be creative, aggressive, and diligent in identifying these sources. Your methods for identifying cases must be appropriate for the setting and disease in question.

First, direct your case finding at health care facilities where the diagnosis is likely to be made: physicians' offices, clinics, hospitals, and laboratories. If you send out a letter describing the situation and asking for reports, that is called "stimulated or enhanced passive surveillance." Alternatively, if you telephone or visit the facilities to collect information on cases, that is called "active surveillance."

In some outbreaks, public health officials may decide to alert the public directly, usually through the local media. For example, in outbreaks caused by a contaminated food product such as salmonellosis caused by contaminated milk (21) or L-tryptophan-induced EMS (14), announcements in the media alerted the public to avoid the implicated product and to see a physician if they had symptoms compatible with the disease in question.

If an outbreak affects a restricted population, such as on a cruise ship, in a school, or at a worksite, and if a high proportion of cases are unlikely to be diagnosed (if, for example, many cases are mild or asymptomatic), you may want to conduct a survey of the entire population. You could administer a questionnaire to determine the true occurrence of clinical symptoms, or you could collect laboratory specimens to determine the number of asymptomatic cases.

Finally, you can ask case-patients if they know anyone else with the same condition. Frequently, one person with an illness knows or hears of others with the same illness.

Regardless of the particular disease you are investigating, you should collect the following types of information about every case:

- identifying information
- demographic information
- clinical information
- risk factor information
- reporter information

Identifying information–name, address, and telephone number–allows you and other investigators to contact patients for additional questions, and to notify them of laboratory results and the outcome of the investigation. Names will help you in checking for duplicate records, while the addresses allow you to map the geographic extent of the problem.

Demographic information–age, sex, race, and occupation–provides the "person" characteristics of descriptive epidemiology you need to characterize the populations at risk.

Clinical information allows you to verify that the case definition has been met. Date of onset allows you to chart the time course of the outbreak. Supplementary clinical information, including whether hospitalization or death occurred, will help you describe the spectrum of illness.

You must tailor risk factor information to the specific disease in question. For example, in an investigation of hepatitis A, you would ascertain exposure to food and water sources.

Finally, by identifying the person who provided the case report, you will be able to seek additional clinical information or report back the results of your investigation.

Traditionally, we collect the information described above on a standard case report form, questionnaire, or data abstraction form. We then abstract selected critical items on a form called a line listing. An example of a line listing is shown in Figure 6.1.

In a line listing, each column represents an important variable, such as name or identification number, age, sex, case classification, etc., while each row represents a different case. New cases are added to a line listing as they are identified. Thus, a line listing contains key information on every case, and can be scanned and updated as necessary. Even in the era of microcomputers, many epidemiologists still maintain a hand-written line listing of key data items, and turn to their computers for more complex manipulations, cross-tabulations, and the like.

Figure 6.1
Example of line listing for an outbreak of hepatits A

Line Listing of reported suspect cases, page 1

Case #	Initials	Date of Report	Date of Onset	Diagnostic								Lab		Age	Sex
				MD Dx	Signs and Symptoms							HA IgM	Other		
					N	V	A	F	DU	J					
1	JG	10/12	10/6	Hep A	+	+	+	+	+	+		+	SGOT ↑	37	M
2	BC	10/12	10/5	Hep A	+	–	+	+	+	+		+	ALT ↑	62	F
3	HP	10/13	10/4	Hep A	±	–	+	+	+	S*		+	SGOT ↑	30	F
4	MC	10/15	10/4	Hep A	–	–	+	+	?	–		+	HBs Ag -	17	F
5	NG	10/15	10/9	NA	–	–	+	–	+	+		NA	NA	32	F
6	RD	10/15	10/8	Hep A	+	+	+	+	+	+		+		38	M
7	KR	10/16	10/13	Hep A	±	–	+	+	+	+		+	SGOT = 240	43	M
8	DM	10/16	10/12	Hep A	–	–	+	+	+	–		+		57	M
9	PA	10/18	10/7	Hep A	±	–	+	±	+	+		+		52	F
10	SS	10/11	10/11	R/o Hep A Hep	+	+	+		+	–		pending	HBsAg pending	31	M

S* = scleral
N = nausea
V = vomiting
A = anorexia
F = fever
DU = dark urine
J = jaundice
HA IgM = hepatitis A IgM antibody test

Exercise 6.3

Review the six case report forms in Appendix G. Create a line listing based on this information.

Answers on page 399.

Step 5: Performing Descriptive Epidemiology

Once you have collected some data, you can begin to characterize an outbreak by time, place, and person. In fact, you may wind up performing this step several times during the course of an outbreak. Characterizing an outbreak by these variables is called **descriptive epidemiology**, because you describe what has occurred in the population under study. This step is critical for several reasons. First, by looking at the data carefully, you become familiar with them. You can learn what information is reliable and informative (such as if many cases report the same unusual exposure) and learn what may not be as reliable (for example, many missing or "don't know" responses to a particular question). Second, you provide a comprehensive description of an outbreak by portraying its trend over time, its geographic extent (place), and the populations (persons) affected by the disease. You can assess your description of the outbreak in light of what is known about the disease (usual source, mode of transmission, risk factors and populations affected, etc.) to develop causal hypotheses. You can, in turn, test these hypotheses using the techniques of analytic epidemiology, described under Step 7.

Note that you should begin descriptive epidemiology early, and should update it as you collect additional data. To keep an investigation moving quickly and in the right direction, you must discover both errors and clues in the data as early as possible.

Time

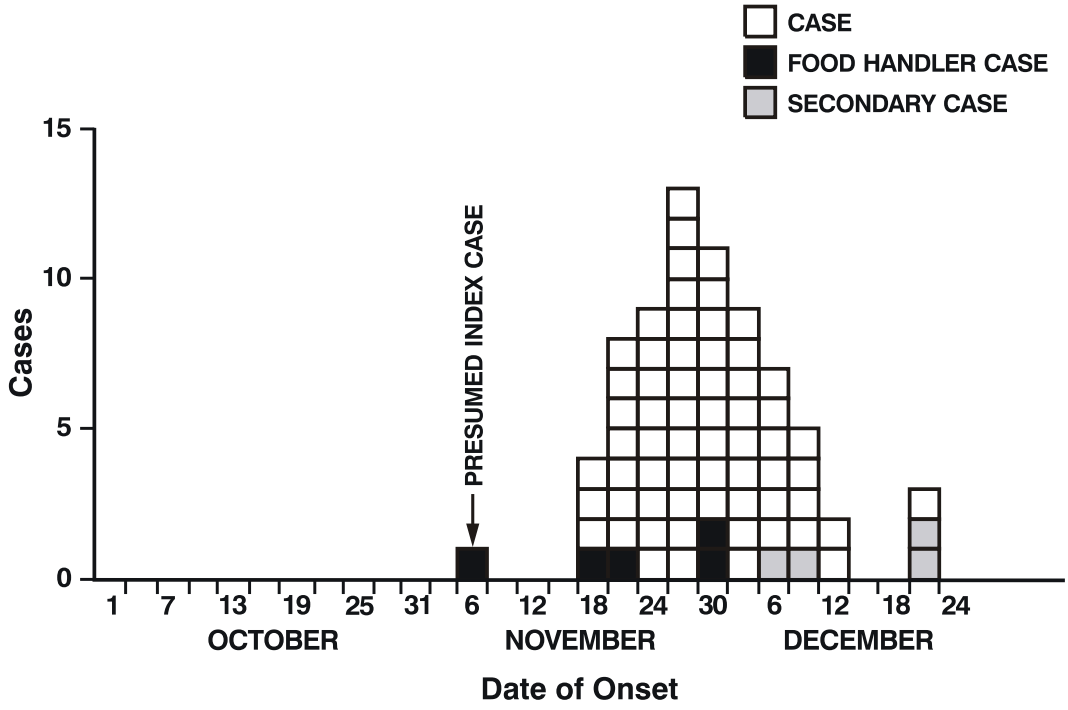
Traditionally, we depict the time course of an epidemic by drawing a histogram of the number of cases by their date of onset. This graph, called an **epidemic curve**, or **epi curve** for short, gives us a simple visual display of the outbreak's magnitude and time trend. Figure 6.2 shows a typical epidemic curve. This visual display can be understood by both epidemiologists and non-epidemiologists alike.

An epidemic curve will provide you with a great deal of information about an epidemic. First, you will usually be able to tell where you are in the time course of an epidemic, and what the future course might be. Second, if you have identified the disease and know its usual incubation period, you usually can deduce a probable time period of exposure and can develop a questionnaire focusing on that time period. Finally, you may be able to draw inferences about the epidemic pattern--whether it is common source or propagated, or both. For a review of epidemic patterns see Lesson 1.

How To Draw an Epidemic Curve. To draw an epidemic curve, you first must know the time of onset of illness for each case. For most diseases, date of onset is sufficient; for a disease with a very short incubation period, hours of onset may be more suitable.

Next, select the unit of time on the *x*-axis. We usually base these units on the incubation period of the disease (if known) and the length of time over which cases are distributed. As a rule of thumb, select a unit that is one-eighth to one-third, i.e., roughly one-quarter as long as the incubation period. Thus, for an outbreak of *Clostridium perfringens* food poisoning (usual incubation period 10-12 hours), with cases confined to a few days, you could use an *x*-axis unit of 2 or 3 hours. Unfortunately, we often need to draw an epidemic curve when we don't know the

Figure 6.2
Typical epidemic curve: Hepatitis A cases by date of onset, Fayetteville, Arkansas, November-December 1978



Source: CDC, unpublished data, 1978

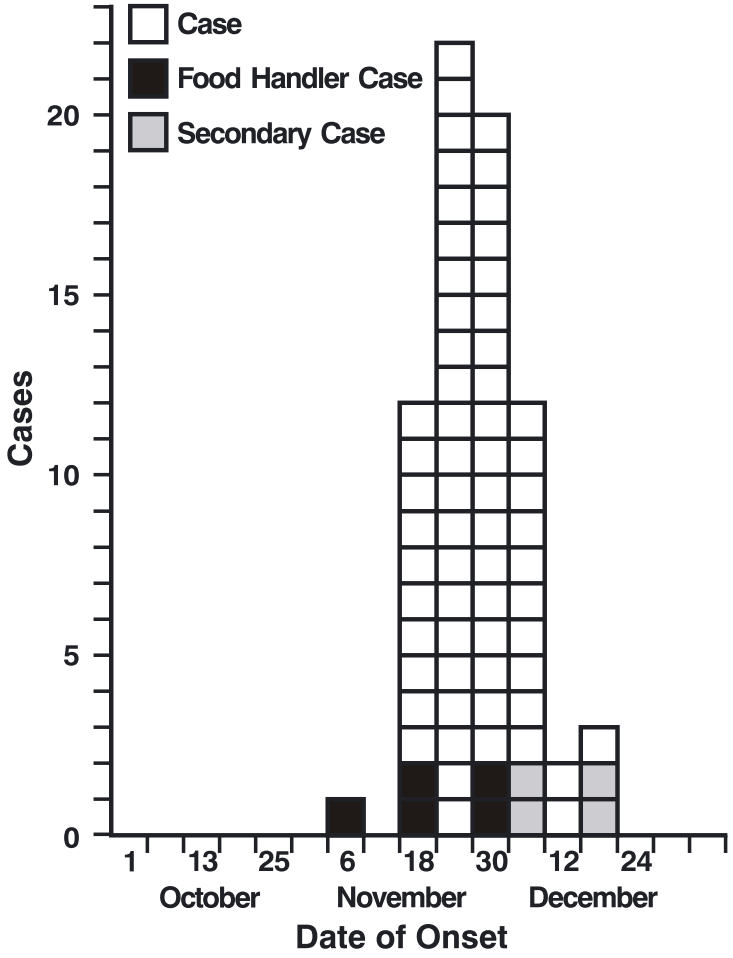
disease and/or its incubation time. In that circumstance, it is useful to draw several epidemic curves with different units on the *x*-axis to find one that seems to portray the data best. For example, Figure 6.3 shows an epidemic curve of the same data as in Figure 6.2; in Figure 6.2 the *x*-axis unit is 3 days and in Figure 6.3 the *x*-axis unit is 6 days. Which unit seems to provide the most useful information about the course of the epidemic?

The units used for the *x*-axis in Figures 6.2 and 6.3 are both useful. They both demonstrate a point-source epidemic. The unit selected for Figure 6.2 is preferred because (1) it distributes the cases more clearly, and (2) it separates out the presumed index case more clearly.

Finally, show the pre-epidemic period on your graph to illustrate the background or "expected" number of cases. (Remember, an epidemic is defined as more cases than expected.) For a disease with a human host, such as hepatitis A, one of the early cases may be a foodhandler who is the source of the epidemic! Notice that both Figure 6.2 and 6.3 show a relatively long pre-epidemic period.

Interpreting an Epidemic Curve. The first step in interpreting an epidemic curve is to consider its overall shape. The shape of the epidemic curve is determined by the epidemic pattern (common source versus propagated), the period of time over which susceptible persons are exposed, and the minimum, average, and maximum incubation periods for the disease.

Figure 6.3
Epidemic curve with different units on *x*-axis:
Hepatitis A cases by date of onset, Fayetteville, Arkansas,
November-December 1978



Source: CDC, unpublished data, 1978

An epidemic curve which has a steep upslope and a more gradual downslope (a log-normal curve) indicates a **point source** epidemic in which persons are exposed to the same source over a relative brief period. In fact, any sudden rise in the number of cases suggests sudden exposure to a common source.

In a point source epidemic, all the cases occur within one incubation period. If the duration of exposure was prolonged, the epidemic is called a **continuous common source** epidemic, and the epidemic curve will have a plateau instead of a peak. Intermittent common source epidemics produce irregularly jagged epidemic curves which reflect the intermittency and duration of

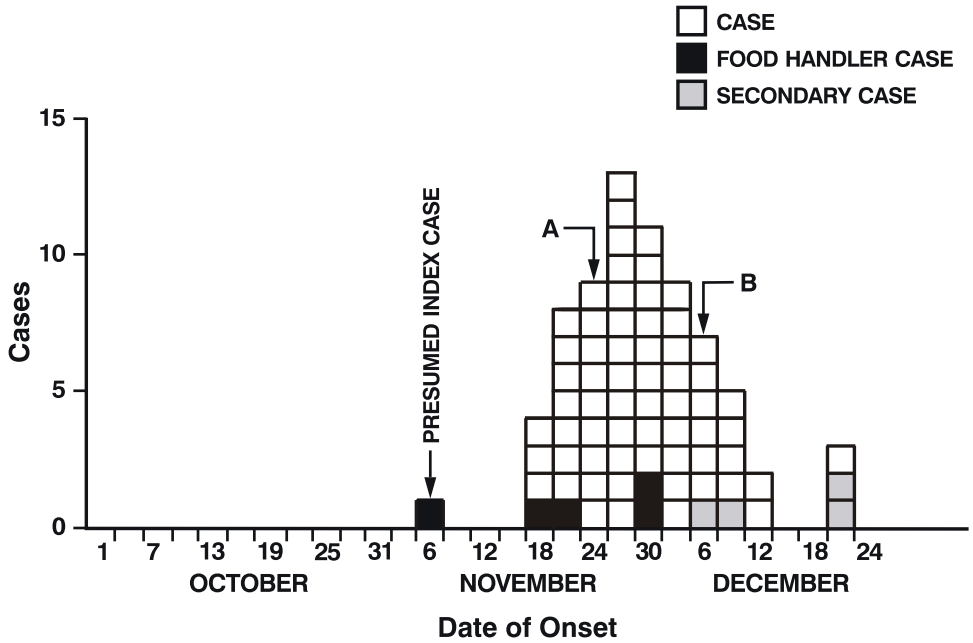
exposure, and the number of persons exposed. Person-to-person spread – a **propagated** epidemic – should have a series of progressively taller peaks one incubation period apart, but in reality few produce this classic pattern.

When you examine an epidemic curve, you should determine where you are in the epidemic. For example, suppose you plotted an epidemic curve of the data in Figure 6.4 when you had only data through November 26 – that is, only through point A. At that point, it should seem clear to you that the outbreak is still on the upswing, and you could safely predict that new cases would continue to occur. On the other hand, if you plotted an epidemic curve using the data through point B, you should realize that the outbreak has peaked and may soon be over, although, depending on the disease, a few late or secondary cases might still occur.

The cases that stand apart may be just as informative as the overall pattern. An early case may represent a background or unrelated case, a source of the epidemic, or a person who was exposed earlier than most of the cases (the cook who tasted her dish hours before bringing it to the big picnic!). Similarly, late cases may represent unrelated cases, long-incubation-period cases, secondary cases, or persons exposed later than most of the cases. On the other hand, these outliers sometimes represent miscoded or erroneous data. All outliers are worth examining carefully because if they are part of the outbreak, their unusual exposures may point directly to the source.

In a point-source epidemic of a known disease with a known incubation period, you can use the epidemic curve to identify a likely period of exposure. This is critical to asking the right questions to identify the source of the epidemic.

Figure 6.4
Typical epidemic curve with point A on upslope and point B on downslope



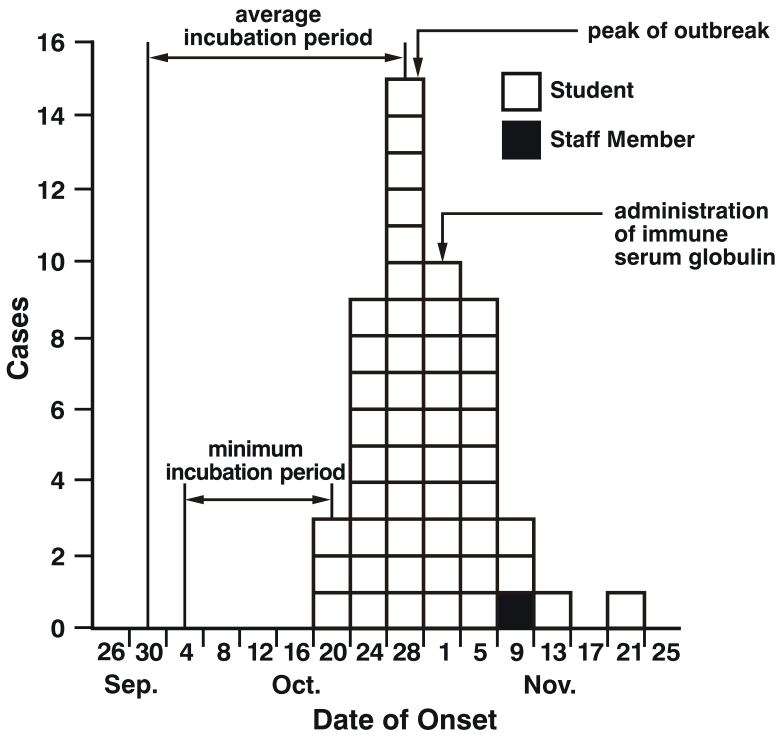
To identify the likely period of exposure from an epidemic curve,

1. Look up the average and minimum incubation periods of the disease. This information can be found in *Control of Communicable Diseases in Man* (3).
2. Identify the peak of the outbreak or the median case and count back on the *x*-axis one average incubation period. Note the date.
3. Start at the earliest case of the epidemic and count back the minimum incubation period, and note this date as well.

Ideally, the two dates are similar, and represent the probable period of exposure. This technique is not precise, however, and you usually should widen the period of exposure by 10-20% on either side of these dates. You should then ask about exposures during the wider period in an attempt to identify the source.

For example, consider the outbreak of hepatitis A illustrated by the epidemic curve in Figure 6.5. The incubation period for hepatitis A ranges from 15 to 50 days, with an average incubation period of 28-30 days (roughly one month). First, is this epidemic curve consistent with a point source? That is, do all 48 cases fall within one incubation period?

Figure 6.5
Hepatitis A cases in Colbert County, Alabama, October-November 1972



The epidemic is consistent with a point source because the last case is within 35 days (50 - 15) of the first case. Therefore, we can use the epidemic curve to identify the likely period of exposure by making the following determinations:

1. What is the peak of the outbreak or the median date of onset?

   The peak of the outbreak occurred during the 4-day interval beginning on October 28. The median date of onset of the 48 cases lies between the 24th and 25th case. Both of these occurred during the same 4-day period.

2. What would be the beginning of one average incubation period prior to the peak (median date) of the outbreak?

   Since the interval containing both the peak and the median of the outbreak includes the last four days of October, one month earlier would fall during the last few days of September.

3. What would be the beginning of one minimum incubation period before the first case?

   The earliest case occurred on October 20. Subtracting 15 days from October 20 points us to October 5.

Thus we would look for exposures around the end of September and the beginning of October. This turned out to be the exact period during which there had been a temporary lapse in chlorination of the school's water supply (4)!

Exercise 6.4

Using the data from a hepatitis A outbreak, draw an epidemic curve. From your epidemic curve and your knowledge of the average and minimum incubation periods for hepatitis A, identify the likely exposure period. Work space provided on page 368.

Case #	Age	Sex	Date of Onset	Case #	Age	Sex	Date of Onset
2	16	F	4-3	41	37	F	5-9
3	34	M	4-6	43	16	M	5-10
6	15	M	4-28	45	29	F	5-10
7	46	M	4-30	46	5	M	5-10
8	21	F	5-1	47	8	F	5-11
9	14	M	5-1	48	15	F	5-11
11	13	M	5-2	49	14	M	5-11
12	43	M	5-2	50	16	M	5-11
13	14	M	5-3	52	16	M	5-12
15	37	M	5-3	53	19	M	5-12
16	5	F	5-3	54	15	M	5-12
17	11	F	5-3	55	10	F	5-12
18	19	M	5-4	56	6	M	5-12
19	14	F	5-4	57	20	M	5-12
20	35	F	5-4	58	43	M	5-12
21	11	F	5-4	59	15	F	5-12
22	14	M	5-4	60	12	F	5-12
23	14	M	5-4	61	14	M	5-13
25	15	M	5-5	62	34	M	5-13
26	12	M	5-5	63	15	F	5-13
27	50	M	5-5	64	30	M	5-13
29	50	M	5-6	65	16	M	5-13
31	11	M	5-7	66	15	M	5-14
32	15	M	5-7	67	15	M	5-14
33	18	F	5-7	68	16	M	5-14
34	14	M	5-7	69	16	M	5-14
35	15	M	5-8	70	18	F	5-15
36	30	M	5-8	72	12	M	5-18
37	20	F	5-9	74	22	F	5-20
38	14	F	5-9	75	15	F	5-24
39	17	M	5-9	76	14	M	5-26
40	15	M	5-9				

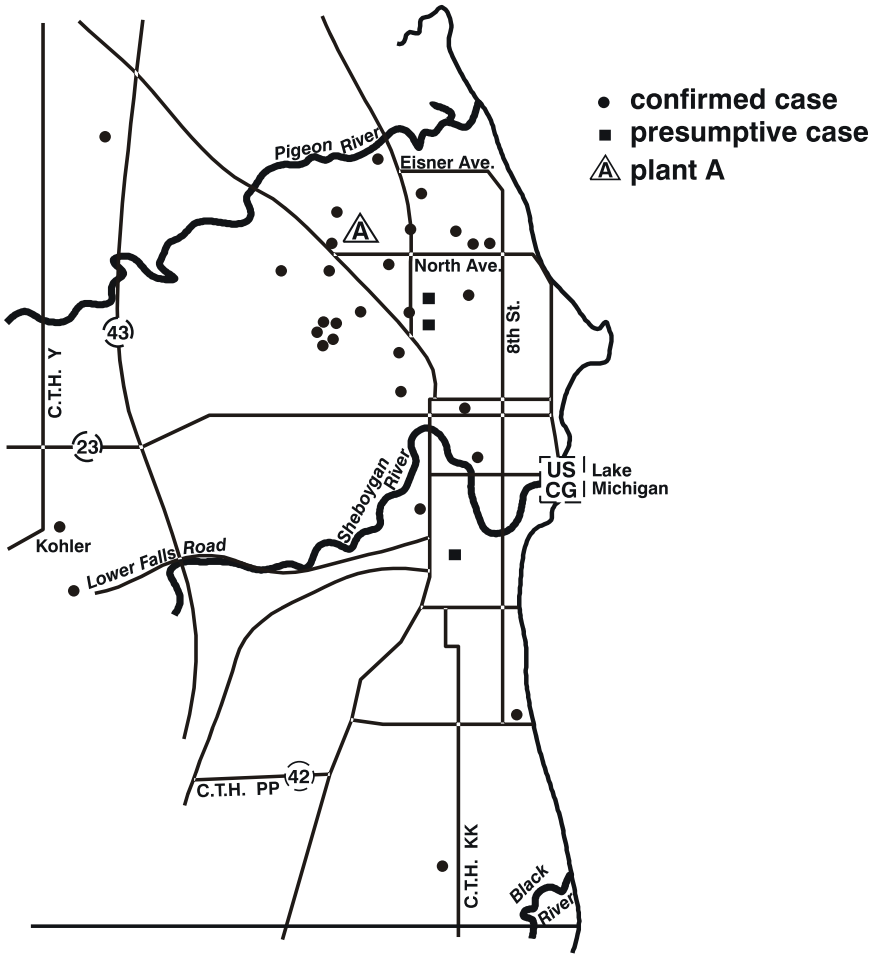
Answers on page 400.

Place

Assessment of an outbreak by place not only provides information on the geographic extent of a problem, but may also demonstrate clusters or patterns that provide important etiologic clues. A spot map is a simple and useful technique for illustrating where cases live, work, or may have been exposed.

On a spot map of a community, clusters or patterns may reflect water supplies, wind currents, or proximity to a restaurant or grocery. In Figure 6.6, for example, the homes of patients with Legionnaires' disease is shown in relation to the cooling tower at plant A (1).

Figure 6.6
Residence of patients with Legionnaires' disease, Sheboygan, Wisconsin, 1986

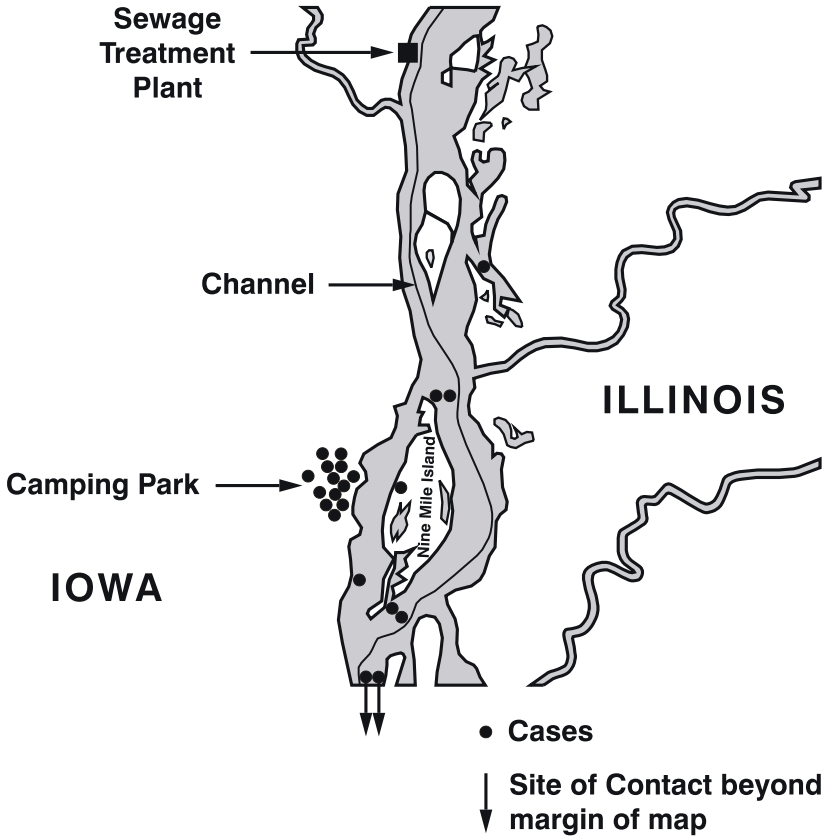


Source: 1

On a spot map of a hospital, nursing home, or other such facility, clustering is consistent with either a focal source or person-to-person spread, while scattering of cases throughout the facility is more consistent with a widely disseminated vehicle or a source common to the residents that is not associated with room assignment, such as a common dining hall.

Although we often use spot maps to plot location of residence, place of work is sometimes more revealing. Certainly, place of work is important in assessing "sick building syndrome" and other disorders related to air-flow patterns in buildings. In studying an outbreak of surgical wound infections in a hospital, we might plot cases by operating room, recovery room, and ward room to look for clustering. We can even use maps to plot recreational opportunities. For example, Figure 6.7 shows persons with shigellosis plotted by where they swam in the Mississippi River (20).

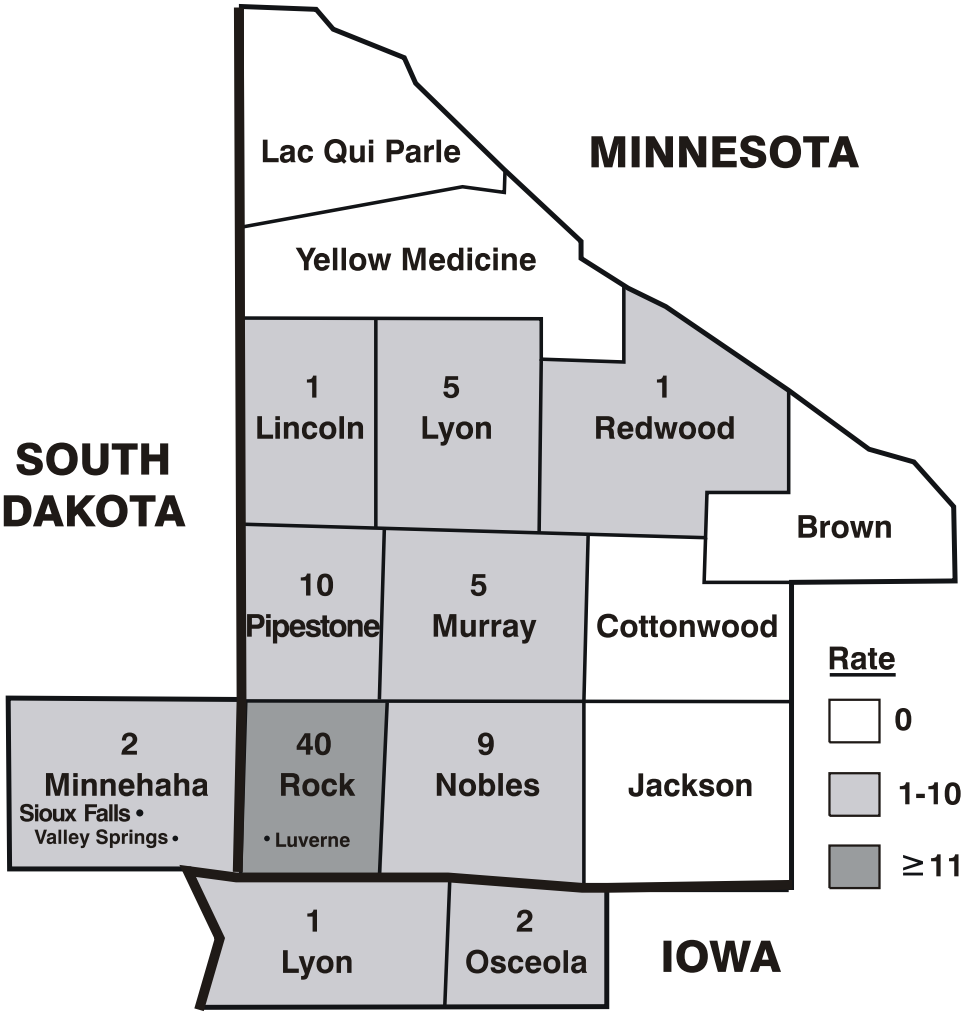
Figure 6.7
Mississippi River sites where 22 culture-positive cases swam within three days of onset of illness



Source: 20

If the size of the population varies between the areas you are comparing, a spot map--which shows numbers of cases–can be misleading. This is a weakness of spot maps. In such an instance, you should show area-specific attack rates with an area map. For example, Figure 6.8 is an area map that shows county-specific attack rates of thyrotoxicosis in 15 counties near the junction of Minnesota, South Dakota, and Iowa (13). If we had used a spot map to plot cases rather than rates, we might have misinterpreted the risk among Minnehaha residents. Seventeen residents of that county were affected, exceeded only by Rock County (43) and Nobles County (20). But because the population of Minnehaha is much larger than the population of the other counties, the risk was actually fairly low. Since this outbreak crosses state lines, it alerts us to maintain broad perspective and not restrict our thinking to artificial geopolitical boundaries.

Figure 6.8
Rate per 10,000 persons of thyrotoxicosis by county, Minnesota, South Dakota, and Iowa, February 1984-August 1985



Source: 13

Person

Characterizing an outbreak by person is how we determine what populations are at risk for the disease. We usually define such populations by host characteristics (age, race, sex, or medical status) or by exposures (occupation, leisure activities, use of medications, tobacco, drugs). Both of these influence susceptibility to disease and opportunities for exposure. As described in Lesson 2, we use rates to identify high-risk groups. In order to calculate rates, we must first have both numerators (numbers of cases) and denominators (number of people at risk).

Usually, age and sex are the two host factors we assess first, because they are often the person characteristics most strongly related to exposure and to the risk of disease. The categories used for age and sex in a frequency distribution should be appropriate for the particular disease and should match the available denominator data.

In many outbreaks, occupation is another important person characteristic. Although we like to calculate rates, it may be difficult to get denominator data for occupation. Nonetheless, the distribution of the cases themselves may suggest hypotheses worth pursuing.

Other person characteristics to analyze will be more specific to the disease under investigation and the setting of the outbreak. For example, if you were investigating an outbreak of hepatitis B, you should consider the usual high-risk exposures for that infection, such as intravenous drug use, sexual contacts, and health care employment. You might characterize an outbreak centered in a school by grade or classroom, and by student versus teacher or other staff.

Summarizing by Time, Place, and Person

After characterizing an outbreak by time, place, and person, it is useful to summarize what you know. For example, during an investigation of a different outbreak of Legionnaires' disease, this time in Louisiana, members of the investigative team discussed what they knew based on the descriptive epidemiology (6). Specifically, the epidemic curve indicated that the outbreak was basically over; no new case had been reported in the last two weeks. The affected population had a greater proportion of persons who were black, female, young, and less likely to smoke than persons in the usual Legionnaires' outbreak. There appeared to be no clustering by either residence or worksite, and no connection with exposure to the town's cooling towers. Thus the investigators were forced to develop new hypotheses about a source of Legionnaires' disease to explain this outbreak.

Step 6: Developing Hypotheses

The next conceptual step in an investigation is formulating hypotheses. However, in reality we usually begin to generate hypotheses with the first phone call. But at this point in an investigation, after talking with some case-patients and with local public health officials, and having characterized the outbreak by time, place, and person, our hypotheses will be sharpened and more accurately focused. The hypotheses should address the source of the agent, the mode (and vehicle or vector) of transmission, and the exposures that caused the disease. Also, the

hypotheses should be testable, since evaluating hypotheses is one of the goals of the next step in an investigation.

You can generate hypotheses in a variety of ways. First, consider what you know about the disease itself: What is the agent's usual reservoir? How is it usually transmitted? What vehicles are commonly implicated? What are the known risk factors? In other words, simply by becoming familiar with the disease, you can, at the very least, "round up the usual suspects."

Another useful way you can generate hypotheses is to talk to a few of the case-patients, as discussed under "Step 3: Verifying the Diagnosis." Your conversations about possible exposures should be open-ended and wide-ranging, not necessarily confined to the known sources and vehicles. In some difficult investigations which yielded few clues, investigators have convened a meeting of several case-patients to search for common exposures. In addition,investigators have sometimes found it useful to visit the homes of case-patientsand look through their refrigerators and shelves for clues.

Just as case-patients may have important insights into causes, so too may the local health department staff. The local staff know the people in the community and their practices, and often have hypotheses based on their knowledge.

The descriptive epidemiology often provides some hypotheses. If the epidemic curve points to a narrow period of exposure, what events occurred around that time? Why do the people living in a particular area have the highest attack rates? Why are some groups with particular age, sex, or other person characteristics, at greater risk than other groups with different person characteristics? Such questions about the data should lead to hypotheses which can be tested by appropriate analytic techniques.

As noted earlier, outliers also can provide important clues. In the outbreak of thyrotoxicosis presented in Figure 6.8, most cases came from Luverne, Minnesota, and the surrounding areas. Only one case was identified in Sioux Falls, South Dakota, 60 miles away. Did this person ever go to Luverne? *Yes.* Was she a friend or acquaintance of any of the Luverne cases? *Not really.* What does she do when she goes to Luverne? *Visit my father and buy the locally-produced ground beef that he sells in his store.* Aha! The hypothesis that the locally-produced ground beef was the vehicle could easily be tested by asking cases and noncases whether they ate ground beef from the same source. Cases did, noncases didn't (13).

Step 7: Evaluating Hypotheses

The step after developing hypotheses to explain an outbreak is evaluating the credibility of those hypotheses. In a field investigation, you can evaluate hypotheses in one of two ways: either by comparing the hypotheses with the established facts, or by using analytic epidemiology to quantify relationshipsand explore the role of chance.

You would use the first method when the clinical, laboratory, environmental, and/or epidemiologic evidence so obviously supports the hypotheses that formal hypothesis testing is unnecessarily. For example, in an outbreak of hypervitaminosis D that occurred in Massachusetts

in 1991 it was found that all of the case-patients drank milk delivered to their homes by a local dairy. Therefore, investigators hypothesized that the dairy was the source and the milk was the vehicle. When they visited the dairy, they quickly recognized that the dairy was inadvertently adding far more than the recommended dose of vitamin D to the milk. No analytic epidemiology was really necessary to evaluate the basic hypotheses in this setting (CDC, unpublished data, 1991).

In many other settings, however, the circumstances are not as straightforward. In those instances, you should use analytic epidemiology to test your hypotheses. The key feature of **analytic epidemiology** is a comparison group. With a comparison group, you are able to quantify relationships between exposures and disease, and to test hypotheses about causal relationships. Careful analysis of the series of cases is insufficient for these purposes; a comparison group is essential. You can use comparison groups in two types of studies: cohort and case-control.

Cohort studies

A cohort study is the best technique for an outbreak in a small, well-defined population. For example, you would use a cohort study if an outbreak of gastroenteritis occurred among persons who attended a wedding and a complete list of wedding guests was available.

In this situation, you would contact each attendee and ask a series of questions. You would determine not only whether the attendee had become ill (and met whatever case definition you had developed), but also what foods and drinks he/she had consumed. You might even try to quantify how much of each item he/she had consumed.

After collecting similar information from each attendee, you would be able to calculate an attack rate for those who ate a particular item and an attack rate for those who did not eat that item. Generally, you should look for three characteristics:

1. The attack rate is high among those exposed to the item
2. The attack rate is low among those not exposed, so the difference or ratio between attack rates is high
3. Most of the cases were exposed, so that the exposure could "explain" most, if not all, of the cases

You could, in addition, compute the ratio of these attack rates. Such a ratio is called a **relative risk**, and is a measure of the association between exposure (the food item) and disease. You could also compute a chi-square or other test of statistical significance to determine the likelihood of finding an association as large or larger on the basis of chance alone.

Table 6.3, which is based on a famous outbreak of gastroenteritis following a church supper in Oswego, New York in 1940, illustrates the use of a cohort study in an outbreak investigation (12). Of 80 persons who attended the supper, 75 were interviewed. Forty-six persons met the case definition. Attack rates for those who did and did not eat each of 14 items are presented in Table 6.3.

Table 6.3
Attack rates by items served at the church supper,
Oswego, New York, April 1940

	Number of persons who ate specified item				Number of persons who did not eat specified item			
	Ill	Well	Total	Attack Rate (%)	Ill	Well	Total	Attack Rate (%)
Baked ham	29	17	46	63	17	12	29	59
Spinach	26	17	43	60	20	12	32	62
Mashed Potato*	23	14	37	62	23	14	37	62
Cabbage salad	18	10	28	64	28	19	47	60
Jello	16	7	23	70	30	22	52	58
Rolls	21	16	37	57	25	13	38	66
Brown bread	18	9	27	67	28	20	48	58
Milk	2	2	4	50	44	27	71	62
Coffee	19	12	31	61	27	17	44	61
Water	13	11	24	54	33	18	51	65
Cakes	27	13	40	67	19	16	35	54
Ice cream (van.)	43	11	54	80	3	18	21	14
Ice cream (choc.)*	25	22	47	53	20	7	27	74
Fruit salad	4	2	6	67	42	27	69	61

*Excludes 1 person with indefinite history of consumption of that food.
Source: 12

Scan the column of attack rates among those who ate the specified items. Which item shows the highest attack rate? Were most of the 46 cases exposed to that food item? Is the attack rate low among persons not exposed to that item?

You should have identified vanilla ice cream as the implicated vehicle. The data for an individual item are often presented in a two-by-two table. The following two-by-two table shows the data on vanilla ice cream.

Table 6.4
Attack rate by consumption of vanilla ice cream,
Oswego, New York, April 1940

		Ill	Well	Total	Attack Rate (%)
Ate vanilla ice cream?	Yes	43	11	54	79.6
	No	3	18	21	14.3
	Total	46	29	75	61.3

The relative risk is calculated as 79.6 / 14.3, or 5.6. The relative risk indicates that persons who ate the vanilla ice cream were 5.6 times more likely to become ill than those who did not eat the vanilla ice cream. Sometimes, attack rate tables such as Table 6.3 include an additional column on the far right for relative risks.

Statistical significance testing. We use tests of statistical significance to determine how likely it is that our results could have occurred by chance alone, if exposure was not actually related to disease. We are not able to cover this broad topic in detail in this course. Instead, we will present only the key features and formulas. For more information, we suggest that you consult one of the many statistics texts that cover the subject well.

The first step in testing for statistical significance is to assume that the exposure is not related to disease. This assumption is known as the **null hypothesis**. (The **alternative hypothesis**, which may be adopted if the null hypothesis proves to be implausible, is that exposure is associated with disease.) Next, you should compute a measure of association, such as a relative risk or odds ratio. Then, you calculate a chi-square or other statistical test. This test tells you the probability of finding an association as strong as, or stronger than, the one you have observed if the null hypothesis is really true. This probability is called the **p-value**. A very small p-value means that you are very unlikely to observe such an association if the null hypothesis is true. If you find a p-value smaller than some cutoff that you have decided on in advance, such as 5%, you may discard or reject the null hypothesis in favor of the alternative hypothesis.

Recall the notation of the two-by-two table described in Lesson 4:

Table 6.5
Standard notation of a two-by-two table

	Ill	Well	Total
Exposed	a	b	H1
Unexposed	c	d	H2
Total	V1	V2	T

The most common statistical test in the outbreak setting is the chi-square test. For a two-by-two table, the chi-square formula is:

$$\text{Chi-square} = \frac{T[|ad - bc| - (T/2)]^2}{V1 \times V2 \times H1 \times H2}$$

Once you have a value for chi-square, you look up its corresponding p-value in a table of chi-squares, such as Table 6.6. Since a two-by-two table has 1 degree of freedom, a chi-square larger than 3.84 corresponds to a p-value smaller than 0.05. This means that if you have planned to reject the null hypothesis when the p-value is less than 0.05, you can do so if your value for chi-square is greater than 3.84.

Table 6.6
Table of Chi Squares

Degree of Freedom	Probability						
	.50	.20	.10	.05	.02	.01	.001
1	.455	1.642	2.706	3.841	5.412	6.635	10.827
2	1.386	3.219	4.605	5.991	7.824	9.210	13.815
3	2.366	4.642	6.251	7.815	9.837	11.345	16.268
4	3.357	5.989	7.779	9.488	11.668	13.277	18.465
5	4.351	7.289	9.236	11.070	13.388	15.086	20.517
10	9.342	13.442	15.987	18.307	21.161	23.209	29.588
15	14.339	19.311	22.307	24.996	28.259	30.578	37.697
20	19.337	25.038	28.412	31.410	35.020	37.566	43.315
25	24.337	30.675	34.382	37.652	41.566	44.314	52.620
30	29.336	36.250	40.256	43.773	47.962	50.892	59.703

The chi-square test works well if the number of people in the study is greater than about 30. For smaller studies, a test called the **Fisher Exact Test** may be more appropriate. Again, we refer you to any statistics book for further discussion of this topic.

Case-control studies

In many outbreak settings, the population is not well defined. Therefore, cohort studies are not feasible. However, since cases have been identified in an earlier step of the investigation, the case-control study is ideal. Indeed, case-control studies are more common than cohort studies in the investigation of an outbreak.

As we discussed in Lesson 1, in a case-control study you ask both case-patients and a comparison group of persons without disease ("controls") about their exposures. You then compute a measure of association–an **odds ratio**–to quantify the relationship between exposure and disease. Finally, as in a cohort study, you can compute a chi-square or other test of statistical significance to determine your likelihood of finding this relationship by chance alone.

This method, while not *proving* that a particular exposure caused disease, certainly has served epidemiologists well over time in implicating sources and vehicles associated with disease, and leading them to appropriate control and prevention measures.

Choosing controls. When you design a case-control study, your first, and perhaps most important, decision is who the controls should be. Conceptually, the controls must not have the disease in question, but should represent the population that the cases come from. In other words, they should be similar to the cases except that they don't have the disease. If the null hypothesis were true, the controls would provide us with the level of exposure that you should expect to find among the cases. If exposure is much higher among the cases than the controls, you might choose to reject the null hypothesis in favor of a hypothesis that says exposure is associated with disease.

In practice, it is sometimes difficult to know who the controls should be. Precisely what is the population that the cases came from? In addition, we must consider practical matters, such as how to contact potential controls, gain their cooperation, ensure that they are free of disease, and get appropriate exposure data from them. In a community outbreak, a random sample of the healthy population may, in theory, be the best control group. In practice, however, persons in a random sample may be difficult to contact and enroll. Nonetheless, many investigators attempt to enroll such "population-based" controls through dialing of random telephone numbers in the community or through a household survey.

Other common control groups consist of:

- neighbors of cases
- patients from the same physician practice or hospital who do not have the disease in question
- friends of cases

While controls from these groups may be more likely to participate in the study than randomly identified population-based controls, they may not be as representative of the population. These **biases** in the control group can distort the data in either direction, masking an association between the exposure and disease, or producing a spurious association between an innocent exposure and disease.

In designing a case-control study, you must consider a variety of other issues about controls, including how many to use. Sample size formulas are widely available to help you make this decision. In general, the more subjects (cases and controls) you use in a study, the easier it will be to find an association.

Often, the number of cases you can use will be limited by the size of the outbreak. For example, in a hospital, 4 or 5 cases may constitute an outbreak. Fortunately, the number of potential controls will usually be more than you need. In an outbreak of 50 or more cases, 1 control per case will usually suffice. In smaller outbreaks, you might use 2, 3, or 4 controls per case. More than 4 controls per case will rarely be worth your effort.

As an example, consider again the outbreak of Legionnaires' disease which occurred in Louisiana. Twenty-seven cases were enrolled in a case-control study. The investigators enrolled 2 controls per case, or a total of 54 controls. Using descriptive epidemiology, the investigators did not see any connection with the town's various cooling towers. Using analytic epidemiology, the investigators determined quantitatively that cases and controls were about equally exposed to cooling towers. However, cases were far more likely to shop at Grocery Store A, as shown in the following two-by-two table (6).

Table 6.7
Exposure to Grocery Store A among cases and controls, Legionellosis outbreak, Louisiana, 1990

		Cases	Controls	Total
Shopped at Grocery Store A?	Yes	25	28	53
	No	2	26	28
	Total	27	54	81

In a case-control study, we are unable to calculate attack rates, since we do not know the total number of people in the community who did and did not shop at Grocery Store A. Since we cannot calculate attack rates, we cannot calculate a relative risk. The measure of association of choice in a case-control study is the **odds ratio**. Fortunately, for a rare disease such as legionellosis or most other diseases which cause occasional outbreaks, the odds ratio approximately equals the relative risk we would have found if we had been able to conduct a cohort study.

The odds ratio is calculated as ad / bc. The odds ratio for Grocery Store A is thus 25 x 26 / 28 x 2, or 11.6. These data indicate that persons exposed to Grocery Store A were 11.6 times more likely to develop Legionnaires' disease than persons not exposed to that store!

To test the statistical significance of this finding, we can compute a chi-square test using the following formula:

$$\text{Chi-square} = \frac{T\left[|ad - bc| - (T/2)\right]^2}{V1 \times V2 \times H1 \times H2}$$

For Grocery Store A, the chi-square becomes:

$$= \frac{81 \times \left[|25 \times 26 - 28 \times 2| - 81/2\right]^2}{27 \times 54 \times 53 \times 28}$$

$$= 24{,}815{,}342.25 / 2{,}163{,}672$$

$$= 11.47$$

Referring to Table 6.6, a chi-square of 11.47 corresponds to a p-value less than 0.001. A p-value this small indicates that the null hypothesis is highly improbable, and the investigators rejected the null hypothesis.

Exercise 6.5

You are called to help investigate a cluster of 17 men who developed leukemia in a community. Some of them worked as electrical repair men, and others were ham radio operators. Which study design would you choose to investigate a possible association between exposure to electromagnetic fields and leukemia?

Answers on page 401.

Exercise 6.6

To study rash illness among grocery store workers, investigators conducted a cohort study. The following table shows the data for exposure to celery. What is the appropriate measure of association? Calculate this measure and a chi-square test of statistical significance.

		Rash	No rash	Total	Attack Rate
Exposed to celery?	Yes	25	31	56	44.64%
	No	5	65	70	7.14%
	Total	30	96	126	23.81%

How would you interpret your results?

Answer on page 401.

Step 8: Refining Hypotheses and Executing Additional Studies

Epidemiologic studies

Unfortunately, analytic studies sometimes are unrevealing. This is particularly true if the hypotheses were not well founded at the outset. It is an axiom of field epidemiology that if you cannot generate good hypotheses (by talking to some cases or local staff and examining the descriptive epidemiology and outliers), then proceeding to analytic epidemiology, such as a case-control study, is likely to be a waste of time.

When analytic epidemiology is unrevealing, you need to reconsider your hypotheses. This is the time to convene a meeting of the case-patients to look for common links and to visit their homes to look at the products on their shelves. Consider new vehicles or modes of transmission.

An investigation of an outbreak of *Salmonella muenchen* in Ohio illustrates how a reexamination of hypotheses can be productive. In that investigation, a case-control study failed to implicate any plausible food source as a common vehicle. Interestingly, *all* case-households, but only 41% of control households, included persons 15 to 35 years. The investigators thus began to consider vehicles of transmission to which young adults were commonly exposed. By asking about drug use in a second case-control study, the investigators implicated marijuana as the likely vehicle. Laboratory analysts subsequently isolated the outbreak strain of *S. muenchen* from several samples of marijuana provided by case-patients (24).

Even when your analytic study identifies an association between an exposure and disease, you often will need to refine your hypotheses. Sometimes you will need to obtain more specific exposure histories. For example, in the investigation of Legionnaires' disease (page 380), what about Grocery Store A linked it to disease? The investigators asked cases and controls how much time they spent in the store, and where they went in the store. Using the epidemiologic data, the investigators were able to implicate the ultrasonic mist machine that sprayed the fruits and vegetables. This association was confirmed in the laboratory, where the outbreak subtype of the Legionnaires' disease bacillus was isolated from the water in the mist machine's reservoir (6).

Sometimes you will need a more specific control group to test a more specific hypothesis. For example, in many hospital outbreaks, investigators use an initial study to narrow their focus. They then conduct a second study, with more closely matched controls, to identify a more specific exposure or vehicle. In a large community outbreak of botulism in Illinois, investigators used three sequential case-control studies to identify the vehicle. In the first study, investigators compared exposures of cases and controls from the general public to implicate a restaurant. In a second study they compared restaurant exposures of cases and healthy restaurant patrons to identify a specific menu item, a meat and cheese sandwich. In a third study, investigators used radio broadcast appeals to identify healthy restaurant patrons who had eaten the implicated sandwich. Compared to cases who had also eaten the sandwich, controls were more likely to have avoided the onions that came with the sandwich. Type A Clostridium botulinum was then identified from a pan of leftover sauteed onions used only to make that particular sandwich (17).

Finally, recall that one reason to investigate outbreaks is research, that is, to expand our knowledge. An outbreak may provide an "experiment of nature," which would be unethical for us to set up deliberately, but which we can learn from when it occurs naturally. For example, in the previously described outbreak of hypervitaminosis D in Massachusetts, investigators quickly traced the source to a dairy that was adding too much vitamin D to its milk. After they had instituted the appropriate control measures, the investigators used the "experiment of nature" to characterize the spectrum of health effects caused by overexposure to vitamin D (CDC, unpublished data, 1991). Thus the investigation led to increased knowledge about an unusual problem as well as to prompt action to remove the source.

When an outbreak occurs, whether it is routine or unusual, consider what questions remain unanswered about that particular disease and what kind of study you might do in this setting to answer some of those questions. The circumstances may allow you to learn more about the disease, its modes of transmission, the characteristics of the agent, host factors, and the like. For example, an outbreak of mumps in a highly immunized population may be an opportunity to study vaccine efficacy and duration of protection.

Laboratory and environmental studies

While epidemiology can implicate vehicles and guide appropriate public health action, laboratory evidence can clinch the findings. The laboratory was essential in both the outbreak of salmonellosis linked to marijuana and in the Legionellosis outbreak traced to the grocery store mist machine. You may recall that the investigation of Legionnaires' disease in Philadelphia in 1976 was not considered complete until the new organism was isolated in the laboratory some 6 months later (10).

Environmental studies are equally important in some settings. They are often helpful in explaining **why** an outbreak occurred. For example, in the investigation of the outbreak of shigellosis among swimmers in the Mississippi (Figure 6.7), the local sewage plant was identified as the cause of the outbreak (20). In the study of thyrotoxicosis described earlier, a review of the procedures used in a slaughterhouse near Luverne, Minnesota, identified a practice that caused pieces of the animals' thyroid gland to be included with beef (13). Use a camera to photograph working conditions or environmental conditions. Bring back physical evidence to be analyzed in the laboratory, such as the slabs of beef from the slaughterhouse in the thyrotoxicosis study or the mist machine from the grocery store in the Legionellosis outbreak investigation.

Step 9: Implementing Control and Prevention Measures

In most outbreak investigations, your primary goal will be control and prevention. Indeed, although we are discussing them as Step 9, you should implement control measures as soon as possible. You can usually implement control measures early if you know the source of an outbreak. In general, you aim control measures at the weak link or links in the chain of infection. You might aim control measures at the specific agent, source, or reservoir. For example, an outbreak might be controlled by destroying contaminated foods, sterilizing contaminated water,

or destroying mosquito breeding sites. Or an infectious food handler could be removed from the job and treated.

In other situations, you might direct control measures at interrupting transmission or exposure. You could have nursing home residents with a particular infection "cohorted," put together in a separate area to prevent transmission to others. You could instruct persons wishing to reduce their risk of acquiring Lyme disease to avoid wooded areas or to wear insect repellent and protective clothing.

Finally, in some outbreaks, you would direct control measures at reducing the susceptibility of the host. Two such examples are immunization against rubella and malaria chemoprophylaxis for travelers.

Step 10: Communicating the Findings

Your final task in an investigation is to communicate your findings. This communication usually takes two forms: (1) an oral briefing for local authorities and (2) a written report.

Your oral briefing should be attended by the local health authorities and persons responsible for implementing control and prevention measures. Usually these persons are not epidemiologists, so you must present your findings in clear and convincing fashion with appropriate and justifiable recommendations for action. This presentation is an opportunity for you to describe what you did, what you found, and what you think should be done about it. You should present your findings in scientifically objective fashion, and you should be able to defend your conclusions and recommendations.

You should also provide a written report that follows the usual scientific format of introduction, background, methods, results, discussion, and recommendations. By formally presenting recommendations, the report provides a blueprint for action. It also serves as a record of performance and a document for potential legal issues. It serves as a reference if the health department encounters a similar situation in the future. Finally, a report that finds its way into the public health literature serves the broader purpose of contributing to the knowledge base of epidemiology and public health.

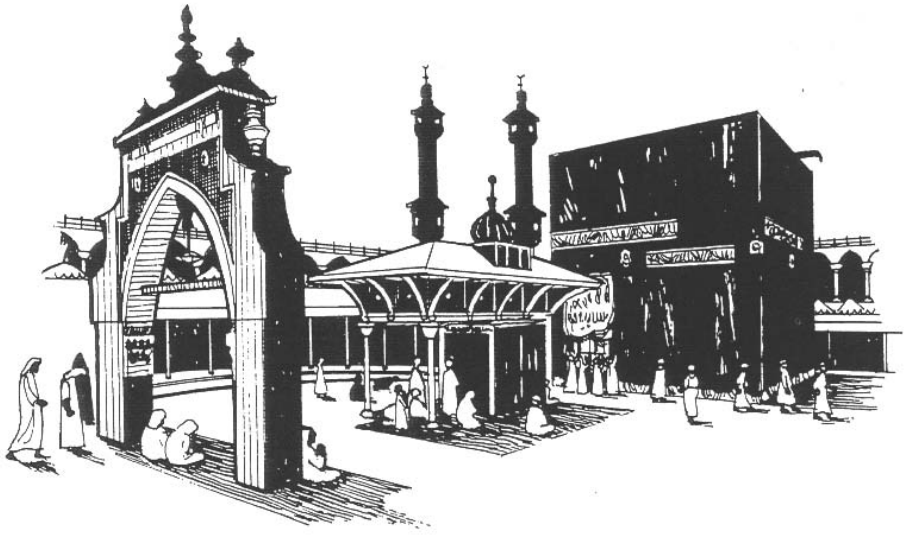
Review Exercise

Exercise 6.7

This review exercise is a case study of an outbreak of enteritis during a pilgrimage to Mecca. After reading this case study and answering all 16 imbedded questions, a student will be able to do the following:

- Define an epidemic, an outbreak, and a cluster
- Create and understand the uses of a case definition
- Draw an epidemic curve
- Calculate food-specific attack rates
- List the steps in investigating an acute outbreak

Figure 6.9
Illustration of the Kaaba in Mecca



An Outbreak of Enteritis During a Pilgrimage to Mecca

Part I

On the morning of November 1, 1979, during a pilgrimage to Mecca, the epidemiologist assigned to the Kuwaiti medical mission experienced acute onset of abdominal cramps and diarrhea at the holy mosque before the walk around the Kaaba. He subsequently learned that other members of the mission had developed similar symptoms. When he returned that evening to Muna, he initiated an investigation.

Question 1. What information do you need to decide if this is an epidemic?

The epidemiologist interviewed several ill members of the mission to better characterize the illness. On the basis of these interviews, the epidemiologist quickly prepared a questionnaire and conducted interviews with the 112 members of the Kuwaiti medical mission.

A total of 66 cases of illness were identified; 2 had onset in Kuwait prior to the beginning of the pilgrimage and 64 had onset of symptoms beginning late in the afternoon on October 31.

Question 2. Is this an epidemic? Explain your answer.

Description of the Pilgrimage

The Kuwaiti medical mission, consisting of 112 members, traveled by automobile from Kuwait to Mecca. On October 30 all members of the mission slept in Muna. At sunrise on October 31 they traveled to Arafat, where at 8:00 a.m. they had tea with or without milk for breakfast. The milk was prepared immediately before consumption by mixing powdered milk with boiled water. The remainder of the day was devoted to religious services. At 2:00 p.m., a lunch was served for all members of the mission who wished to partake. It was a typical Kuwaiti meal consisting of three dishes: rice, meat, and tomato sauce. Most individuals consumed all three dishes. The lunch had been prepared in Muna on October 30 and transported to Arafat by truck early on October 31. At sunset on October 31 the mission members returned to Muna.

Clinical Description

The investigator identified a total of 66 cases of gastroenteritis. The onset of all cases was acute, characterized chiefly by diarrhea and abdominal pain. Nausea, vomiting, and blood in the stool occurred infrequently. No case-patient reported fever. All recovered within 12-24 hours. Approximately 20 percent of the ill individuals sought medical advice. The investigator did not obtain any fecal specimens for examination.

Question 3. Develop a preliminary case definition.

Question 4. List the broad categories of diseases that must be considered in the differential diagnosis of an outbreak of gastrointestinal illness.

Note: These concepts have not been covered in this course. If you are not familiar with disease agents, review the answer to this question.

Question 5. What clinical and epidemiologic information might be helpful in determining the etiologic agent(s)?

Question 6. The Kuwaiti investigators distributed a questionnaire to all members of the mission. What information would you solicit on this questionnaire?

Part II

Investigators determined that of the 64 cases with onset during the pilgrimage, all had eaten lunch in Arafat at 2:00 p.m. on October 31. Fifteen members of the mission did not eat lunch; none became ill.

Question 7. Calculate the attack rate for those who ate lunch and those who did not. What do you conclude?

Table 6.8 (page 394-395) presents some of the information collected by the investigators. The two members who developed illness prior to October 31 have been excluded. The 15 members of the mission who did not eat lunch are not included in Table 6.8.

Question 8. Using appropriate time periods, draw an epidemic curve.

Question 9. Are there any cases for which the time of onset seems inconsistent? How might they be explained?

Question 10. Modify the graph you have drawn (Question 8) to illustrate the distribution of incubation periods.

Question 11. Determine or calculate the minimum, maximum, mean, median, mode, range, and standard deviation of the incubation periods.

Question 12a. Calculate the frequency of each clinical symptom among the cases.

Question 12b. How does the information on the symptoms and incubation periods help you to narrow the differential diagnosis? (You may refer to the attached "Abbreviated Compendium of Acute Foodborne Gastrointestinal Diseases" in Appendix E).

Question 13a. Using the food consumption histories in Table 6.8, complete item 7 of the "Investigation of a Foodborne Outbreak" report form in Appendix F.

Question 13b. Do these calculations help you to determine which food(s) served at the lunch may have been responsible for the outbreak?

Question 14. Outline further investigations which should be pursued. List one or more factors that could have led to the contamination of the implicated food.

Table 6.8
Selected characteristics of Kuwaiti medical mission members who ate lunch at Arafat, Saudi Arabia, October 31, 1979

			Onset of Illness		Foods			Signs and Symptoms*					
Id #	Age	Sex	Date	Hour	Rice	Meat	TS*	D	C	BS	N	V	F
31	36	M	Oct. 31	5 p.m.	X	X	X	D	C	BS			
77	28	M	Oct. 31	5 p.m.	X	X		D	C				
81	33	M	Oct. 31	10 p.m.	X	X	X	D	C				
86	29	M	Oct. 31	10 p.m.	X	X	X	D	C				
15	38	M	Oct. 31	10 p.m.		X		D		BS	N		
17	48	M	Oct. 31	10 p.m.	X	X		D	C				
18	35	M	Oct. 31	10 p.m.	X	X	X	D	C				
35	30	M	Oct. 31	11 p.m.	X	X	X	D	C				
88	27	M	Oct. 31	11 p.m.	X	X	X	D	C				
76	29	M	Oct. 31	11 p.m.	X	X	X	D	C	BS			
71	50	M	Oct. 31	12 MN	X	X	X	D					
1	39	F	Nov. 1	1 a.m.	X	X	X	D	C			V	
27	36	M	Nov. 1	1 a.m.	X	X	X	D	C		N		
28	44	M	Nov. 1	1 a.m.	X	X	X	D	C				
29	48	M	Nov. 1	1 a.m.	X	X	X	D	C	BS			
30	35	M	Nov. 1	2 a.m.	X	X	X	D	C				
50	29	M	Nov. 1	2 a.m.	X	X	X	D	C				
59	51	M	Nov. 1	2 a.m.	X	X	X	D	C				
67	40	M	Nov. 1	2 a.m.	X	X		D					
72	58	M	Nov. 1	2 a.m.	X	X	X	D	C				
73	28	M	Nov. 1	3 a.m.	X	X	X	D	C				
60	31	M	Nov. 1	3 a.m.	X	X	X	D	C				
61	38	M	Nov. 1	3 a.m.	X	X	X	D		BS			
51	32	M	Nov. 1	3 a.m.	X	X	X	D	C			V	
52	37	M	Nov. 1	3 a.m.	X	X		D					
58	30	M	Nov. 1	3 a.m.	X	X	X	D	C				
22	35	M	Nov. 1	3 a.m.	X	X	X	D	C				
25	30	M	Nov. 1	3 a.m.	X	X		D	C				
32	50	M	Nov. 1	3 a.m.	X	X	X	D	C				
38	26	M	Nov. 1	3 a.m.	X	X	X	D	C				
79	29	M	Nov. 1	3 a.m.	X	X	X	D	C				
80	28	M	Nov. 1	3 a.m.	X	X	X	D	C				
37	30	M	Nov. 1	4 a.m.	X	X	X	D					
65	34	M	Nov. 1	4 a.m.	X	X		D		BS			
66	45	M	Nov. 1	4 a.m.	X	X		D	C				
87	41	M	Nov. 1	4 a.m.	X	X	X	D	C				
89	43	M	Nov. 1	4 a.m.	X	X	X	D	C				
90	43	M	Nov. 1	4 a.m.	X	X	X	D	C				
91	38	M	Nov. 1	4 a.m.	X	X	X	D	C				
92	37	M	Nov. 1	4 a.m.	X	X	X	D	C				
70	31	M	Nov. 1	5 a.m.	X	X	X	D	C				
2	34	F	Nov. 1	5 a.m.	X	X	X	D	C				
21	38	M	Nov. 1	5 a.m.	X	X	X	D	C				
40	38	M	Nov. 1	5 a.m.	X	X	X	D					
78	27	M	Nov. 1	5 a.m.	X	X	X	D	C				
82	39	M	Nov. 1	5 a.m.	X	X	X	D	C				
83	40	M	Nov. 1	5 a.m.	X	X	X	D	C				

*TS = Tomato sauce, D = diarrhea, C = cramps, BS= blood in stool, N= nausea, V= vomiting, F = fever

Table 6.8 (continued)
Selected characteristics of Kuwaiti medical mission members who ate lunch at Arafat, Saudi Arabia, October 31, 1979

			Onset of Illness		Foods			Signs/Symptoms					
Id #	Age	Sex	Date	Hour	Rice	Meat	TS*	D	C	BS	N	V	F
84	34	M	Nov. 1	5 a.m.	X	X		D	C				
14	52	M	Nov. 1	6 a.m.	X	X	X	D					
16	40	M	Nov. 1	6 a.m.	X	X	X	D		BS			
93	30	M	Nov. 1	6 a.m.	X	X	X	D	C				
94	39	M	Nov. 1	6 a.m.	X	X	X	D	C				
33	55	M	Nov. 1	7 a.m.	X	X	X	D	C				
34	28	M	Nov. 1	7 a.m.	X	X	X	D	C				
85	38	M	Nov. 1	7 a.m.	X	X		D	C				
43	38	M	Nov. 1	9 a.m.	X	X		D	C				
69	30	M	Nov. 1	9 a.m.	X	X	X	D	C				
4	30	F	Nov. 1	10 a.m.	X			D	C				
5	45	F	Nov. 1	10 a.m.		X			C				
3	29	F	Nov. 1	1 p.m.	X	X		D	C				
12	22	F	Nov. 1	2 p.m.	X	X	X		C				
74	44	M	Nov. 1	2 p.m.	X	X	X	D					
75	45	M	Nov. 1	5 p.m.	X	X	X	D		BS			
95	40	M	Nov. 1	11 p.m.	X	X	X	D	C				
6	38	F	WELL		X	X							
7	52	F	WELL		X	X	X						
8	35	F	WELL		X		X						
9	27	F	WELL		X	X	X						
10	40	F	WELL		X	X	X						
11	40	F	WELL		X	X	X						
13	50	M	WELL		X	X	X						
19	38	M	WELL		X	X	X						
20	38	M	WELL		X	X	X						
23	29	M	WELL		X	X	X						
24	27	M	WELL		X	X	X						
26	47	M	WELL		X	X	X						
36	60	M	WELL		X								
39	27	M	WELL		X	X	X						
41	30	M	WELL		X	X	X						
42	38	M	WELL		X	X	X						
44	50	M	WELL		X	X	X						
45	27	M	WELL		X	X	X						
46	31	M	WELL		X	X	X						
47	46	M	WELL		X	X	X						
48	38	M	WELL		X	X	X						
49	36	M	WELL		X								
53	36	M	WELL		X	X	X						
54	27	M	WELL		X	X	X						
55	40	M	WELL		X	X	X						
56	30	M	WELL		X	X	X						
57	25	M	WELL		X	X	X						
62	50	M	WELL		X								
63	44	M	WELL		X								
64	47	M	WELL		X		X						
68	31	M	WELL		X	X	X						

*TS = Tomato sauce, D = diarrhea, C = cramps, BS = blood in stool, N = nausea, V = vomiting, F = fever

Part III

The lunch which was served in Arafat at 2:00 p.m. on October 31 was prepared at 10:00 p.m. the night before in Muna. It consisted of boiled rice, chunks of lamb fried in oil, and tomato sauce prepared from fresh tomatoes which were sectioned and stewed. The cooked rice was placed in two large pots and the lamb was divided evenly on top. The tomato sauce was kept in a third pot.

These pots were covered with metal tops and placed in an open spot among some rocks near the kitchen and allowed to stand overnight. They were presumably not touched by anyone during this period. Early in the morning on October 31, the pots were transported by truck from Muna to Arafat where they stood in the truck until 2:00 p.m. The temperature in Arafat at noon that day was 35 degrees Centigrade. The food was not refrigerated from the time of preparation to the time of consumption.

Cooks and all other individuals who helped in preparing the meal were intensively interviewed regarding any illness present before or at the time of preparation. All individuals interviewed denied having any illness and knew of no illness among any other members of the group responsible for meal preparation. No specimens were obtained from any of the cooks for laboratory examination.

The following is quoted verbatim from the report prepared by the epidemiologist who investigated the outbreak:

> "This clinical picture probably suggests an infection by *Clostridium perfringens*. This organism could be detected in the food elements consumed as well as in the patient's stool. However, no laboratory diagnostic procedures were possible in the outbreak site. All the investigations conducted were based entirely on epidemiologic grounds.
>
> The incubation period as well as other data extrapolated from epidemiological analysis suggests that *Clostridium perfringens* is the causative agent. This organism is widely distributed in nature especially in soil and dust. So there is ample opportunity for contamination of the food. If cooked meat is allowed to cool slowly under suitable anaerobic conditions, spores which might have survived cooking or have subsequently come from dust may germinate and within a few hours produce large numbers of vegetative bacilli. In fact, the pilgrimage camp in Muna lacks sanitary cooking facilities. The food is usually prepared in a dusty place open to the blowing winds creating an ideal situation for *Clostridium perfringens* contamination.
>
> The type of the organism, the type of food dish it usually contaminates, its mode of spread and the differences in the attack rates for those who consumed meat and those who did not points to the meat as the probable source of infection in this outbreak.
>
> Conclusion: The acute illness of enteritis in Arafat affected many persons in an epidemic form. It was a common-source outbreak, the source being the meat consumed at the Arafat lunch. The incubation period was about 13 hours. The illness was characterized by colicky abdominal pain and diarrhea with no elevation of temperature. The responsible

agent for this outbreak is most probably *Clostridium perfringens*.

The lunch at Arafat should have been prepared in the same day of consumption, or kept refrigerated if it had to be prepared the day before. Although kitchens could not be fully equipped to fulfill the essential safety measures in a place like Muna, they should be supplied by essential measures to protect food from contamination. The remaining food in Arafat should have been condemned after the investigation, but none remained at that time.

The epidemiological investigations carried out in this epidemic could explore the nature of this epidemic and answer most of the questions raised. The laboratory investigation, although helpful to detect the causative organisms, should not replace the more efficient epidemiological methods in the exploration of such epidemics. The lack of the necessary laboratory facilities to detect the causative organisms in foodborne outbreaks should not discourage the investigative epidemiologist and make him doubtful and lose confidence in his epidemiological tools."

Question 15. In the context of this outbreak, what control measures would you recommend?

Question 16. Was it important to work up this outbreak?

Answers to Exercises

Answer–Exercise 6.1 (page 352)

One reason to investigate is simply **to determine how many cases we would expect in the community**. In a large community, nine cases of a common cancer (for example, lung, breast, or colon cancer) would not be unusual. In a very small community, nine cases of even a common cancer may seem unusual. If the particular cancer is a rare type, then nine cases even in a large community may be unusual.

If the number of cancer cases turns out to be high for that community, we might pursue the investigation further. We may have a **research** motive–perhaps we will identify a new risk factor (workers exposed to a particular chemical) or predisposition (persons with a particular genetic marker) for the cancer.

Control and prevention may be a justification. If we find a risk factor, control / prevention measures could be developed. Alternatively, if the cancer is one which is generally treatable if found early, and a screening test is available, then we might investigate to determine not why these persons developed the disease, but why they died of it. If the cancer were cancer of the cervix, detectable by Pap smear and generally treatable if caught early, we might find (1) problems with access to health care, or (2) physicians not following the recommendations to screen women at the appropriate intervals, or (3) laboratory error in reading or reporting the test results. We could then develop measures to correct the problems we found (public screening clinics, education of physicians, or laboratory quality assurance.)

If new staff need to gain experience on a cluster investigation, **training** may be a reason to investigate. More commonly, cancer clusters frequently generate **public concern**, which, in turn, may generate **political pressure**. Perhaps one of the affected persons is a member of the mayor's family. A health department must be responsive to such concerns, but does not usually need to conduct a full-blown investigation. Finally, **legal concerns** may prompt an investigation, especially if a particular site (manufacturer, houses built on an old dump site, etc.) is accused of causing the cancers.

Answer–Exercise 6.2 (page 356)

Tuberculosis does not have a striking seasonal distribution. The number of cases during August could be compared with (a) the numbers reported during the preceding several months, and (b) the numbers reported during August of the preceding few years.

Aseptic meningitis is a highly seasonal disease which peaks during August-September-October. As a result, the number of cases during August is expected to be higher than the numbers reported during the preceding several months.

To determine whether the number of cases reported in August is greater than expected, we must look at the numbers reported during August of the preceding few years.

Answer–Exercise 6.3 (page 362)

Which items to include in a line listing is somewhat arbitrary.
The following categories of information are often included:

Identifying information

- Identification number or case number, usually in the leftmost column
- Names or initials as a cross-check

Information on diagnosis and clinical illness

- Physician diagnosis
- Was diagnosis confirmed? If so, how?
- Symptoms
- Laboratory results
- Was the patient hospitalized? Did the patient die?

Descriptive epidemiology–time

- Date of onset
- Time of onset

Descriptive epidemiology–person

- Age
- Sex
- Occupation, if relevant, or other seemingly relevant characteristics

Descriptive epidemiology–place

- Street, city, or county
- Worksite, school, day care center, etc., if relevant

Risk factors and possible causes

- Specific to disease and outbreak setting

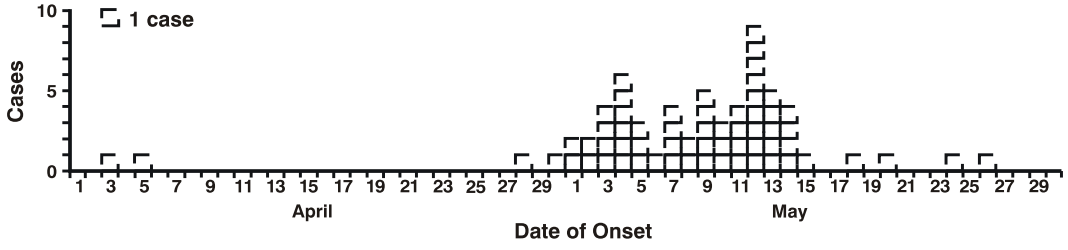
An example of a line listing from the six case report forms is shown below.

ID #	Initials	Dateof Onset	Diagnosis	How Confirmed	Age	Sex	County	Physician	Cleveland-McKay Wedding
1	KR	7/23	Probable Trichinosis	Not done	29	M	Columbia	Goodman	Yes
2	DM	7/27	Trichinosis	Biopsy	33	M	Columbia	Baker	Yes
3	JG	8/14	Probable Trichinosis	Not done	26	M	Columbia	Gibbs	Yes
4	RD	7/25	Trichinosis	Serologic	45	M	King	Webster	Yes
5	NT	8/4	Trichinosis	Not done	27	F	Columbia	Stanley	Yes
6	AM	8/11	R/O trichinosis	pending	54	F	Clayton	Mason	Yes

Answer–Exercise 6.4 (page 369)

The epidemic curve shown in Figure 6.10 suggests a common source outbreak. We can estimate time of exposure by starting at the peak of the epidemic and going back the mean incubation period, or by starting at the rise of the epidemic and going back the minimum incubation period. Going back 30 days (mean incubation period for hepatitis A) from the epidemic peak on May 9 puts the estimated exposure on April 9. Assuming the minimum incubation period (15 days) for the April 28 case, exposure would have occurred on April 13. So, we can estimate that exposure occurred between April 9 and April 13, give or take a few days on either side.

Figure 6.10
Epidemic curve for Exercise 6.4: Hepatitis A by date of onset, April-May



Answer–Exercise 6.5 (page 382)

A case-control study is the design of choice, since 17 persons with the disease of interest have already been identified. We would need to enroll these 17 persons as the case group. We would also need to determine what group might serve as an appropriate comparison or control group. Neighbors might be used for the control group, for example. In our case-control study we would determine whether each case and each control was exposed to electromagnetic fields (however we defined that exposure). Finally, we would compare the exposure experience of cases and controls.

The alternative to a case-control study is a cohort study. For a cohort study we would have to enroll a group of persons exposed to electromagnetic fields (however we defined that exposure), and a comparison group of persons not exposed. We would then have to determine how many in each group developed leukemia. Since leukemia is a relatively rare event, we would need rather large groups in order to have enough leukemia cases to make our study valid. Therefore, a cohort study is less practical than a case-control study in this setting.

Answer–Exercise 6.6 (page 383)

The appropriate measure of association for a cohort study is the relative risk, calculated as the ratio of attack rates.

Relative risk = 44.64/7.14 = 6.2

Chi-square = $\frac{T[|ad-bc|-(T/2)]^2}{V1\times V2\times H1\times H2}$

For the table shown above, the chi-square becomes:

$$= \frac{126\times[|25\times 65-31\times 5|-126/2]^2}{30\times 96\times 56\times 70}$$

= 249,435,774/11,289,600

= 22.09

A chi-square of 22.09 corresponds to a p-value of < 0.00001. A p-value this small indicates that the null hypothesis is highly improbable, and the investigators rejected the null hypothesis.

Answer--Exercise 6.7 (page 387)

An Outbreak of Enteritis During a Pilgrimage to Mecca

Question 1. What information do you need to decide if this is an epidemic?

Answer 1.

- Is the number of cases more than the number expected?
- Therefore, we need to know background rate.

Question 2. Is this an epidemic?

Answer 2. Yes. An epidemic can be defined as the occurrence of more cases in a place and time than expected in the population being studied. Of the 110 members without signs and symptoms of gastroenteritis prior to the pilgrimage, 64 (58%) developed such signs and symptoms during this trip. This is clearly above the expected or background rate of gastroenteritis in most populations. Gastroenteritis prevalence rates from recent surveys are approximately 5% and are consistent with this population (2/112 had such signs and symptoms at the time of the pilgrimage).

One could survey other groups of pilgrims originating from the same country to determine their rates of diarrheal illness if the existence of an outbreak was uncertain. Practically speaking, however, an attack rate of 58% is an epidemic until proven otherwise.

The term “outbreak” and “epidemic” are used interchangeably by most epidemiologists. The term “outbreak” is sometimes preferred, particularly when talking to the press or public, because it is not as frightening as “epidemic.” The term “cluster” may be defined as the occurrence of a group of cases in a circumscribed place and time. In a cluster, the number of cases may or may not be greater than expected.

Question 3. Develop a preliminary case definition.

Answer 3.

Points to consider:

- As a general rule, during the initial phase of an investigation, the case definition should be broad.
- The case definition should include four components: **time, place, person,** and **diagnosis** (or signs, symptoms). Depending on the frequency of the symptoms observed and the probable etiologic agent, a more precise case definition can be developed later.

Case definition:

Clinical:	acute onset of abdominal cramps and/or diarrhea
Time:	onset after noon on October 31 and before November 2
Place/Person:	member of the Kuwaiti medical mission in route to Mecca

Note. The Kuwaiti investigators had already decided that lunch on October 31 was the responsible meal and defined an outbreak-associated case of enteritis as a person in the Kuwaiti mission who ate lunch at Arafat at 2:00 p.m. on October 31 and subsequently developed abdominal pain and/or diarrhea prior to November 2, 1979.

However, at this point in your consideration of the outbreak you have not implicated the lunch, and it would probably be premature to limit your case definition to those who ate lunch.

Question 4. List the broad categories of diseases that must be considered in the differential diagnosis of an outbreak of gastrointestinal illness.

Answer 4.

Broad categories: Bacterial
Viral
Parasitic
Toxins

More specifically:

Differential Diagnosis of Acute Foodborne Enteric Illness

Bacteria and bacterial toxins
*Bacillus cereus**
Campylobacter *jejuni*
Clostridium botulinum (initial symptoms)
*Clostridium perfringens**
*Escherichia coli**
Salmonella, non-typhoid
Salmonella typhi
Shigella
Staphylococcus aureus
Vibrio cholerae O1
Vibrio cholerae non-O1
Vibrio parahemolyticus
Yersinia enterocolitica

Viruses
Norwalk-like agents (i.e., 27 nm viruses)
Rotavirus*

Toxins
Heavy metals (especially cadmium, copper, tin, zinc)
Mushrooms
Fish & shellfish (e.g., scombroid, ciguatera)
Insecticides

Parasites
Cryptosporidium
Entamoeba histolytica
Giardia lamblia

*These agents are most compatible with the following characteristics of this outbreak:

- acute onset
- lower GI signs and symptoms
- no fever
- appreciable proportion seeking medical advice
- no mention of non-enteric (dermatologic, neurologic) manifestations

However, you have not yet reached the point in your investigation to consider the most likely etiologic possibilities for the illness.

Question 5. What clinical and epidemiologic information might be helpful in determining the etiologic agent(s)?

Answer 5.
Incubation period
Symptom complex
Duration of symptoms
Severity of symptoms
Seasonality
Geographic location
Biologic plausibility of pathogens

Question 6. The Kuwaiti investigators distributed a questionnaire to the persons who ate the implicated lunch. What information would you solicit on this questionnaire?

Answer 6.

- **Identifying information**
- **Demographics (age, sex, race)**
- **Clinical information**
  - Symptoms
  - Date & time of onset of symptoms
  - Duration of symptoms
  - Medical intervention, if required
- **Information on possible causes**
  - Exposure information regarding foods consumed, including amounts
  - Other potential exposures
  - Other factors that may modify risk of diarrhea (e.g., antacids, antibiotics)

Question 7. Calculate the attack rate for those who ate lunch and those who did not. What do you conclude?

Answer 7.

112 members of the mission
-15 members who didn't eat lunch
- 2 members sick before pilgrimage
95 *at risk of developing illness*
64 became ill among those who ate lunch
0 *became ill among those who didn't eat lunch*

Attack rate for those who ate lunch:
64 ill/95 at risk = 67%

Attack rate for those not eating lunch:
0 ill/15 at risk = 0%

Conclusion: Lunch is strongly associated with disease.

Question 8. Using appropriate time periods, draw an epidemic curve.

Answer 8.
Points for consideration about epi curves:

1. The epi curve is a basic tool of epidemiologists to
   a. establish existence of epidemic vs. endemic illness
   b. delineate time course and magnitude of an epidemic
   c. develop inferences about transmission, e.g., common source, person to person, intermittent exposure. Note that changing the interval on the *x*-axis can significantly alter the shape of an epi curve.
   d. predict future course of an epidemic: when it will end, that a second wave is underway, that secondary cases are occurring, etc.
2. With common source outbreaks, the width of the curve is determined by the incubation period, varying doses, and host susceptibility.
3. Often a few cases don't fit into the body of an epi curve. Such exceptions may be quite important--as index cases or other special situations.
4. A rule of thumb: When the incubation period is known, the maximum time period on the *x*-axis should not usually exceed 1/4 - 1/3 of the incubation period.

Summary of the temporal distribution (see Figure 6.11a).

a. Onsets of cases occurred over a period of 31 hours extending from 5 p.m. on October 31 to 11 p.m. on November 1.

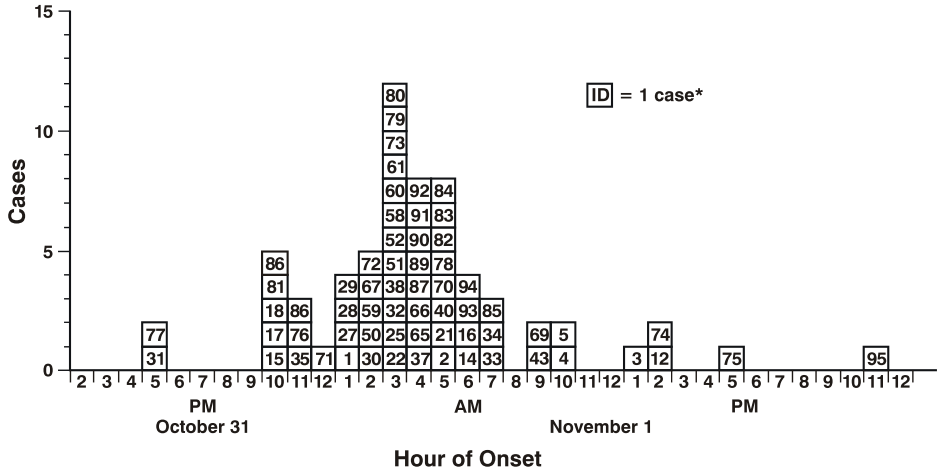
b. Onsets of 53 (82.8%) of the cases occurred throughout the 10 hour interval from 10 p.m. on October 31 through 7 a.m. on November 1.

c. The peak (12 cases) occurred at 3 a.m. on November 1.

d. The median hour of onset = 3:30 a.m. November 1 (actual middle rank = 32.5 which falls between the 3 and 4 a.m. measurement intervals).

e. It is likely that the way the questionnaire was designed forced the interviewees to give a rounded time for onset of symptoms.

Figure 6.11a
Outbreak associated cases of enteritis
by hour of onset of illness, Kuwaiti Mission,
Arafat, Saudi Arabia, October 31 – November 1, 1979



*ID# included for reference only.

Question 9. Are there any cases for which the times of onset seem inconsistent? How might they be explained?

Answer 9.

1. The two cases (#31 and 77) with onsets at 5 p.m. on October 31
   a. Illnesses unrelated to the outbreak?
   b. Earlier exposures to food items? Cooks?
   c. Short incubation periods? Large doses? Enhanced susceptibility?
   d. Times of onset incorrect?

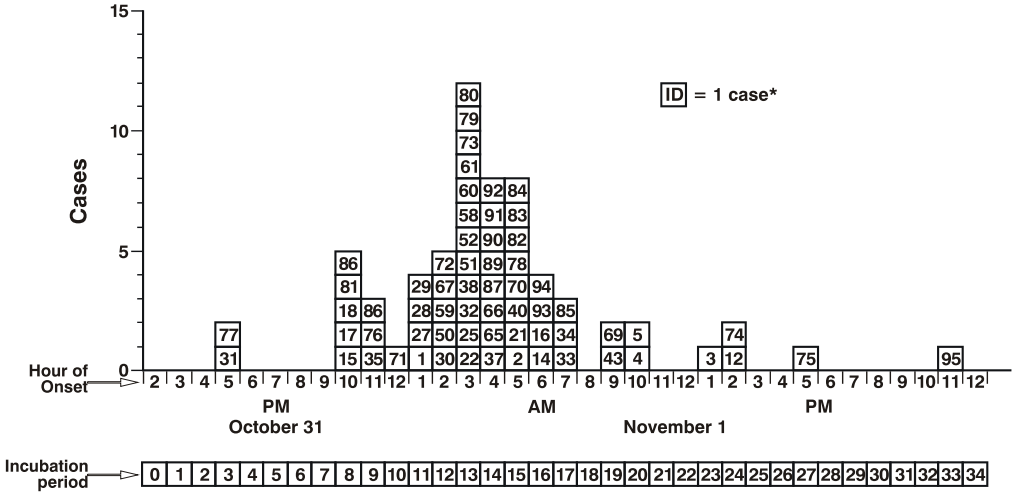
2. The two cases (#75 and 95) occurring late on November 1
   a. Illnesses unrelated to the outbreak?
   b. Foods eaten at later time?
   c. Secondary cases?
   d. Times of onset incorrect?
   e. Long incubation periods? Small doses? Enhanced resistance?

Question 10. Modify the graph you have drawn (Question 8) to illustrate the distribution of incubation periods.

Answer 10.

Since all meal participants were served at 2:00 p.m. the distribution of onsets and incubation periods is the same. Therefore, to illustrate the distribution of incubation periods, you need only to show a second label for the *x*-axis, as in Figure 6.11b.

Figure 6.11b
Outbreak associated cases of enteritis by hour of onset of illness and incubation period, Kuwaiti Mission, Arafat, Saudi Arabia, October 31 – November 1, 1979



Question 11. Determine or calculate the minimum, maximum, mean, median, mode, range, and standard deviation of the incubation periods.

Answer 11.

Minimum = 3 hours

Maximum = 33 hours

Mean = 14 hours

Median = 13.5 hours (middle rank = 64 + 1)/2 = 32.5, which falls between the intervals for 13 and 14 hours.)

Mode = 13 hours

Range = maximum - minimum = 30 hours

Standard deviation = 5 hours

Note: The range in which roughly 95% of the observations fall = $\bar{x}$ ± 1.96 (rounded to 2) standard deviations = 4 to 24 hours (see Lesson 3 for calculation steps).

Comment

The incubation period (though not necessarily the clinical features) are about right for *Clostridium perfringens*, *Salmonella*, *Vibrio parahemolyticus*, and *Bacillus cereus*. The incubation period is a bit short for enterotoxigenic E. Coli and *Vibrio cholerae* non-O1. Too long for staph enterotoxin, heavy metals, chemicals, and most toxins produced by fish, shellfish, and mushrooms. Illnesses that have upper GI signs and symptoms, such as nausea and vomiting, and intoxications due to chemicals, metals, etc., usually have short incubation periods, while illnesses with predominately lower GI signs and symptoms, such as diarrhea, have longer incubation periods.

Question 12a. Calculate the frequency of each clinical symptom among the cases.

Answer 12a.

Frequency distribution of signs and symptoms among outbreak-associated cases of enteritis, Kuwaiti Mission, Arafat, Saudi Arabia, October 31 – November 1, 1979 (N = 64)

Sign or Symptom	Number of Cases	Percent
Diarrhea	62	96.9
Abdominal Pain	52	81.3
(Diarrhea + abdominal pain)	(50)	(78.1)
Blood in stool	8	12.5
(Diarrhea + blood in stool)	(5)	(7.8)
(Diarrhea + abdominal pain + blood in stool	(3)	(4.7)
Nausea	2	3.1
Vomiting	2	3.1
Fever	0	0

The distribution of signs and symptoms are given in the table above. Diarrhea occurred among all but two of the cases, with 78.1% experiencing both diarrhea and abdominal pain.

Blood in the stool was reported by 8 (12.5%) of the cases. Symptoms of upper GI distress occurred among 4 (6.3%) of the cases (2 persons experienced nausea while two others reported vomiting). No temperature elevations were recorded.

Question 12b. How does the information on the symptoms and incubation period help you to narrow the differential diagnosis? (You may refer to the attached compendium in Appendix F, which describes a number of acute foodborne gastrointestinal diseases.)

Answer 12b.

The clinical findings, including an apparent absence of malaise, myalgias, chills, and fever, are more consistent with an intoxication resulting from the presence of toxin in the lower GI tract than with an invasive infectious agent. The recovery of all cases within 24 hours is also consistent with such an intoxication. The absence of dermatologic and neurologic signs and symptoms in conjunction with the incubation period (the median was 13.5 hours and the mean was 14 hours) would lessen the likelihood of heavy metals, organic and inorganic chemicals, and toxins produced by fish, shellfish and mushrooms. The incubation period and clinical features help narrow the list to the following: *Clostridium perfringens*, *Bacillus cereus*, *Vibrio parahemolyticus*, and, less likely, *Vibrio cholerae* non-O1, and enterotoxin producing *E. coli.*

Question 13a. Using the food consumption histories in Table 6.8, complete item 7 of the "Investigation of a Foodborne Outbreak" report form in Appendix F.

Answer 13a.

	# persons who ATE specified food				# who DID NOT EAT specified food			
	Ill	Well	Total	Attack Rate	Ill	Well	Total	Attack Rate
Rice	62	31	93	66.7%	2	0	2	100.0%
Meat	63	25	88	71.6 %	1	6	7	14.3%
T.S.	50	26	76	65.8%	14	5	19	73.7%

You may analyze these data with 2 x 2 tables:

		ILL	WELL	TOTAL	Attack Rate	
Exposed?	Yes	a	b	a + b	AR1 = a/a + b	RR = AR1/AR2
	No	c	d	c + d	AR2 = c/c + d	
		a + c	b + d	T = a + b + c + d		

		ILL	WELL	TOTAL	Attack Rate	
Ate	Yes	62	31	93	62/93 = 66.7%	RR = 66.7/100
Rice	No	2	0	2	2/2 = 100.0%	= 0.67
		64	31			

		ILL	WELL	TOTAL	Attack Rate	
Ate	Yes	63	25	88	63/88 = 71.6%	RR = 72.6/14.3
Meat	No	1	6	7	1/7 = 14.3%	= 5.0
		64	31			

		ILL	WELL	TOTAL	Attack Rate	
Ate	Yes	50	26	76	50/76 = 65.8%	RR = 65.8/73.7
Tomato	No	14	5	19	14/19 = 73.7%	0.89
Sauce		64	31			

Question 13b. Do these calculations help you to determine which food(s) served at the lunch may have been responsible for the outbreak?

Answer 13b. Attack rates were high for those who ate rice, meat, and tomato sauce. However, meat is the likely culprit because it was the only food associated with a high attack rate among those who ate it, but a low attack rate among those who did not. Almost all (63/64) who ate meat also ate the other items, which probably accounts for the high attack rates for those items, too.

One of the cases did not admit to eating meat and could be explained in any number of ways:

- Unrelated illness
- Cross-contamination, e.g., common server, spoon, dish, counter, etc., or from meat to rice
- Reporting error (e.g., forgot or purposely denied eating meat)
- Transcription error (e.g., misrecorded response)

NOTE: Epidemiologic evidence shows an association between exposure and subsequent disease but **does not prove causal relationship.**

Question 14. Outline further investigations which should be pursued. List one or more factors that could have led to the contamination of the implicated food.

Answer 14.

A. Detailed review of ingredients, preparation, and storage of incriminated food. For bacterial food poisoning need:

1) initial contamination (point of origin vs point of consumption)

2) improper time-temperature relationships with respect to preparation, cooking, serving, and storage

B. Specific things about which one might inquire:

1) Origin of the meat – some sources may be at higher risk than others. Animal meats are often contaminated at time of slaughter. This aspect is usually quite difficult to control.

2) Storage of meat to time of cooking (should be kept frozen or refrigerated). This usually doesn't pose problems and since most meat is **not** eaten raw, subsequent cooking would considerably lessen the risk of disease.

3) Cooking procedures – often difficult to control both in public/private sectors. Temperatures attained and duration of optimum cooking temperatures poorly monitored. Failure to reach adequate cooking temperatures associated with diseases other than *C. perfringens* for the most part.

4) Cross-contamination – a factor difficult to control since knives, counter space, cutting boards, and pots or pans, are often used for both raw foods and cooked foods without interim cleansing.

5) Inadequate refrigeration of cooked foods – common in *C. perfringens* outbreaks. Cooked foods essentially allowed to incubate for several hours during cooling process. Not easy to correct as may involve expenditures for additional refrigeration appliances and use of shallow pans.

6) Inadequate reheating of cooked foods – as with 3).

7) Improper holding temperatures while serving – Here again, difficult to control, but commonly associated with disease outbreaks including *C. perfringens*. The food was essentially held at temperatures that permitted the growth of contaminating organisms rather than at 140 degrees Fahrenheit or above which would have prevented their multiplication.

Question 15. In the context of this outbreak, what control measures would you recommend?

Answer 15.

1. After collecting appropriate specimens for laboratory analysis, destroy remaining foods to prevent their consumption.

2. Prevent recurrence of similar event in the future.

a. Educate food handlers in proper techniques, stressing importance of time-temperature relationships.

b. Acquire necessary equipment for properly cooking, cooling, serving, and storing foods.

c. When applicable, eliminate sources of contaminated food.

3. Basic principles in prevention of *C. perfringens*.

a. Cook all foods to minimum internal temperature of 165 degrees Fahrenheit.

b. Serve immediately or hold at > 140 degrees Fahrenheit.

c. Any leftovers should be discarded or immediately chilled and held at < 40 degrees Fahrenheit using shallow pans.

d. All leftovers should be reheated and held at temperatures given above for cooked foods.

Question 16. Was it important to work up this outbreak?

Answer 16.

Reasons why it was important:

1. To identify factors associated with its occurrence in order to institute the necessary measures to prevent future recurrences.

2. To provide reassurance that a deliberate act of poisoning was not involved.

3. To demonstrate that public health officials can react promptly to a problem and identify causative factors utilizing epidemiologic methods.

Self-Assessment Quiz 6

Now that you have read Lesson 6 and have completed the exercises, you should be ready to take the self-assessment quiz. This quiz is designed to help you assess how well you have learned the content of this lesson. You may refer to the lesson text whenever you are unsure of the answer, but keep in mind that the final is a closed book examination. Circle ALL correct choices in each question.

1. The most common way(s) that a local health department uncovers outbreaks is/are by: (Circle ALL that apply.)

A. receiving calls from affected residents

B. receiving calls from health care providers

C. reviewing all case reports received each week to detect common features

D. performing descriptive analysis of surveillance data each week

E. performing time series analysis to detect deviations from expected values based on the previous few weeks and comparable time periods during the previous few years

2. In an ongoing outbreak of a disease with *no* known source and mode of transmission, the primary reason for an investigation relates to:

A. prevention and control

B. training of staff

C. learning more about the disease

D. being responsive to the concerns of the community

E. legal responsibility

1. Analyze data by time, place, and person
2. Conduct a case-control study
3. Generate hypotheses
4. Conduct active surveillance for additional cases
5. Verify the diagnosis
6. Confirm that the number of cases exceeds the expected number
7. Coordinate who will talk to the press about the investigation

3. For an investigation of an outbreak, what is the logical order of the activities listed above?

A. 1-2-3-4-5-6-7

B. 5-6-4-1-2-3-7

C. 6-5-1-3-2-4-7

D. 7-6-5-4-1-3-2

E. 5-6-1-3-2-4-7

4. If you were a state employee, the first step in the investigation of an outbreak of meningococcal meningitis 200 miles away might include: (Circle ALL that apply)

A. talking with someone knowledgeable about meningococcal meningitis

B. talking with someone knowledgeable about field investigations

C. talking with a couple of the initial case-patients

D. discussing the feasibility of mass vaccination

E. stopping your mail

5. The appropriate role for an epidemiologist from the CDC in the investigation of a local outbreak of botulism (possibly foodborne):

A. is to lead the investigation in consultation with CDC experts

B. is to provide consultation to the local staff who will conduct the investigation

C. is to lend a hand to the local staff

D. is whatever is negotiated in advance with the local health department

6. As described in this lesson, the primary distinction between the terms "outbreak" and "epidemic" is:

A. "outbreak" does not imply that the cases are all related

B. "outbreak" implies a grouping of cases but not necessarily more than expected

C. "outbreak" is limited to fewer than 20 cases, epidemic to more than 20

D. "outbreak" does not generate as much anxiety among the public

Number of cases of Disease X reported to the state health department by Counties A-D

	Week Ending					
County	12/13	12/20	12/27	1/3	1/10	1/17
A	4	3	2	2	3	1
B	12	9	0	0	24	15
C	1	0	1	2	7	9
D	1	1	0	1	0	0

7. Explanations most consistent with the pattern of case reports received from County B include: (Circle ALL that apply.)

A. changes in the case definition

B. change in the denominator

C. new physician in the county

D. change in diagnostic procedures

E. batch processing

8. Why should an investigator who has no clinical background nonetheless talk to a patient or two as an early step in the outbreak investigation? (Circle ALL that apply.)

A. To verify the clinical findings as part of verifying the diagnosis

B. To verify the laboratory findings as part of verifying the diagnosis

C. To learn more about the clinical manifestations of the disease

D. To develop hypotheses about the cause of the outbreak

E. To advise the patient about the common risk factors and usual course of the illness, after reviewing *Control of Communicable Diseases in Man*

9. A case definition during an outbreak investigation should specify: (Circle ALL that apply.)

A. clinical criteria

B. time

C. place

D. person

E. hypothesized exposure

10. A characteristic of a well conducted outbreak investigation is that:

A. every case is laboratory confirmed

B. a few cases are laboratory confirmed and the rest meet the case definition

C. a "loose" case definition is used during the analytic epidemiology phase

D. the case definition includes three categories: definite, probable, and possible

11. Common methods of identifying additional cases (expanding surveillance) as part of an outbreak investigation include: (Circle ALL that apply.)

A. sending a letter to physicians

B. telephoning the infection control nurse at the local hospital

C. advising the public through newspapers, TV, and radio to contact the local health department

D. asking case-patients who they were with at the time of exposure (if known)

E. reviewing morbidity and mortality data for the local area from the National Center for Health Statistics

12. The ultimate purpose for characterizing an outbreak by time, place, and person is to:

A. identify errors and miscodes in the data

B. provide a comprehensive description of an outbreak by portraying its time course, geographic extent, and populations most affected by the disease

C. ensure that all true cases are captured by the surveillance system

D. generate hypotheses

E. test hypotheses

13. For a disease of unknown etiology and incubation period, an epidemic curve can be used to derive which of the following? (Circle ALL that apply.)

A. Peak dates of onset of the illness

B. Peak dates of reporting of the cases to the health department

C. Probable period of exposure

D. Future direction of the epidemic

14. Which of the following apply to drawing an epidemic curve? (Circle ALL that apply.)

A. The *y*-axis is dates of onset of the illness

B. The time interval should be less than one-eighth the minimum incubation period of the disease

C. The type of graph should be a histogram

D. The graph should begin with the first case of the epidemic

15. For *Clostridium perfringens* food poisoning, the minimum incubation period is 8 hours, and the average incubation period is 10 to 12 hours. Based on the graph shown below, when is the probable period of exposure?

A. October 6, periods 1-2 (12:01 A.M. to 8:00 A.M.)

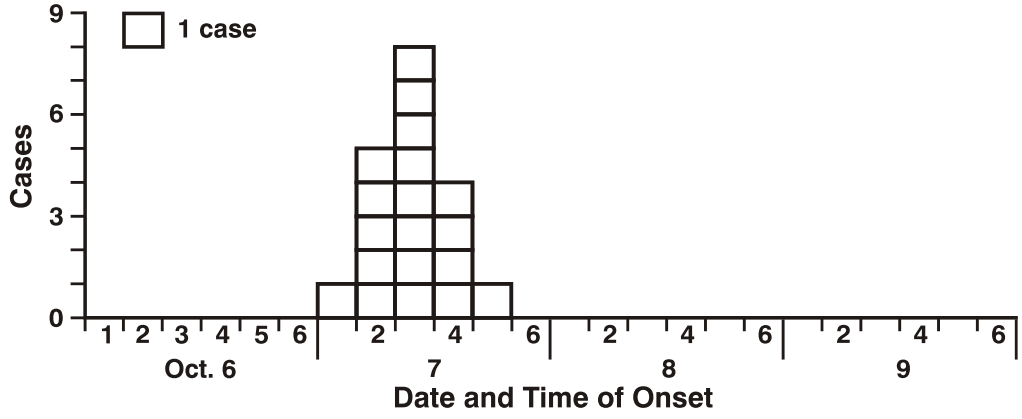
B. October 6, periods 2-3 (4:01 A.M. to noon)

C. October 6, periods 3-4 (8:01 A.M. to 4 P.M.)

D. October 6, periods 4-5 (12:01 P.M. to 8:00 P.M.)

E. October 6, periods 5-6 (4:01 P.M. to midnight)

Figure 6.12
Data and time of onset (by 4 hour periods starting at 12:01 A.M. each day)



16. The geographic distribution of cases should be tabulated or mapped according to:

A. residence of each case

B. place of usual occupation, school, or other primary daytime exposure

C. health care facility where diagnosis was made

D. location where disease onset occurred

E. variable of "place" that produces a meaningful pattern

17. Reasonable ways of generating hypotheses in an outbreak investigation include: (Circle ALL that apply.)

A. asking the local health officer what he/she thinks is the cause

B. asking the case-patients what they think is the cause

C. reviewing a textbook about the disease under investigation

D. postulating explanations for the patterns seen in the descriptive epidemiology

E. focusing on the patients who do not fit the general patterns seen in the descriptive epidemiology

18. During an investigation of an outbreak of gastroenteritis on a small college campus, the investigators confirmed the diagnosis, searched for additional cases, and characterized the cases by time, place, and person. No obvious hypotheses regarding source or mode of transmission came to mind. The investigators should next:

A. interview a few cases in depth

B. conduct a case-control study

C. conduct a cohort study

D. sample and test foods from the school dining hall for the incriminated agent

E. interview and test the dining hall foodhandlers for the incriminated agent

19. In an epidemiologic study, investigators enrolled 100 children with Kawasaki syndrome and 100 children *without* Kawasaki syndrome. Among children with Kawasaki syndrome, 50 had been exposed to compound C in the previous 3 weeks. Among those without Kawasaki syndrome, 25 had been exposed to compound C. In this study, the best estimate of the relative risk of Kawasaki syndrome associated with exposure to compound C is:

A. 1.0

B. 1.5

C. 2.0

D. 3.0

E. not calculable from the information provided

20. In the epidemiologic study of Kawasaki syndrome described in the previous question, the mean serum porcelain levels of children with Kawasaki syndrome was lower than the mean serum porcelain levels of children without Kawasaki syndrome. The difference was statistically significant at the 5% level ($p < 0.05$). This means that:

A. elevated serum porcelain causes Kawasaki syndrome

B. deficiency of serum porcelain causes Kawasaki syndrome

C. the difference between mean serum porcelain levels is unlikely to have occurred by chance alone

D. the difference between mean serum porcelain levels is likely to have occurred by chance alone

21. The report of an epidemiologic study described the association between a particular exposure and a particular disease as “a weakly positive association, but not statistically significant at the 0.05 level.” The data most consistent with this statement is:

A. odds ratio = 10.0, p-value = 0.20

B. odds ratio = 1.5, p-value = 0.03

C. relative risk = 1.8, p-value = 0.01

D. relative risk = 10.0, p-value = 0.10

E. risk ratio = 1.8, p-value = 0.20

Use the data in this table for questions 22 and 23.

	Ate specified food			Did not eat specified food		
Food item	**Ill**	**Well**	**Total**	**Ill**	**Well**	**Total**
Macaroni salad	25	15	40	20	39	59
Potato salad	17	38	55	28	16	44
Three-bean salad	43	47	90	2	7	9
Punch	40	52	92	5	4	7
Ice cream	20	1	21	25	53	78

22. After attending a retirement party for the agency director, many of the health department staff developed gastroenteritis. All attendees were interviewed by the public health nurse who had recently completed the CDC *Principles of Epidemiology* self study course. Calculate the appropriate measure of association for each of the home-made food items shown in the table above. For which food is the measure of association largest?

A. Macaroni salad

B. Potato salad

C. Three-bean salad

D. Punch

E. Ice cream

23. Which of the food items do you think is most likely to have caused this outbreak?

A. Macaroni salad

B. Potato salad

C. Three-bean salad

D. Punch

E. Ice cream

24. Control and prevention measures should be implemented:

A. as early as possible after verifying the diagnosis

B. as early as possible after performing the descriptive epidemiology

C. as early as possible after performing the analytic epidemiology (testing hypotheses)

D. as early as possible after refining the hypotheses and executing additional studies

25. For a federal investigator, which of the following communication modes should be used first to announce the findings of an outbreak investigation?

A. Written report for local authorities

B. Written report for state newsletter

C. Written report for the *Morbidity and Mortality Weekly Report*

D. Oral report for the local authorities

E. Press conference to explain findings the public

Answers in Appendix J

If you answered at least 20 questions correctly, you understand
Lesson 6 well enough to begin to prepare for the final examination.

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