Chapter 2 – The Dynamics of Disease Transmission

I keep six honest serving-men

(They taught me all I knew);

Their names are What and Why and When

And How and Where and Who.

—Rudyard Kipling[1] (1865–1936)

Human disease does not arise in a vacuum. It results from an interaction of the host (a person), the agent (e.g., a bacterium), and the environment (e.g., a contaminated water supply). Although some diseases are largely genetic in origin, virtually all disease results from an interaction of genetic and environmental factors, with the exact balance differing for different diseases. Many of the underlying principles governing the transmission of disease are most clearly demonstrated using communicable diseases as a model. Hence, this chapter primarily uses such diseases as examples in reviewing these principles. However, the concepts discussed are also applicable to diseases that do not appear to be of infectious origin.

Disease has been classically described as the result of an epidemiologic triad shown in Figure 2-1 . According to this diagram, it is the product of an interaction of the human host, an infectious or other type of agent, and the environment that promotes the exposure. A vector, such as the mosquito or the deer tick, is often involved. For such an interaction to take place, the host must be susceptible. Human susceptibility is determined by a variety of factors including genetic background and nutritional and immunologic characteristics. The immune status of an individual is determined by many factors including prior experience both with natural infection and with immunization.

The factors that can cause human disease include biologic, physical, and chemical factors as well as other types, such as stress, that may be harder to classify (Table 2-1).

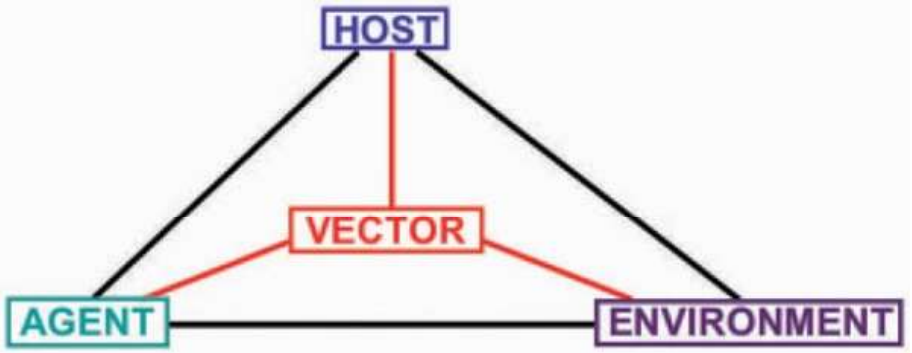

Figure 2-1 The epidemiologic triad of a disease.

TABLE 2-1 -- Factors That May Be Associated with Increased Risk of Human Disease

Host Characteristics	Types of Agents and Examples	Environmental Factors
Age	Biologic	Temperature
Sex	Bacteria, viruses	Humidity
Race	Chemical	Altitude
Religion	Poison, alcohol, smoke	Crowding
Customs	Physical	Housing
Occupation	Trauma, radiation, fire	Neighborhood
Genetic profile	Nutritional	Water
Marital status	Lack, excess	Milk
Family background		Food
Previous diseases		Radiation
Immune status		Air pollution
		Noise

MODES OF TRANSMISSION

Diseases can be transmitted *directly* or *indirectly*. For example, a disease can be transmitted person to person (direct transmission) by means of direct contact. Indirect transmission can occur through a common vehicle such as a contaminated air or water supply, or by a vector such as the mosquito. Some of the modes of transmission are shown in Table 2-2 .

TABLE 2-2 -- Modes of Disease Transmission

1. Direct
   - a. Person-to-person contact
2. Indirect
   - a. Common vehicle
     - (1) Single exposure
     - (2) Multiple exposures
     - (3) Continuous exposure
   - b. Vector

Figure 2-2 is a classic photograph showing droplet dispersal after a sneeze. It vividly demonstrates the potential for an individual to infect a large number of people in a brief period of time. As Mims has pointed out:

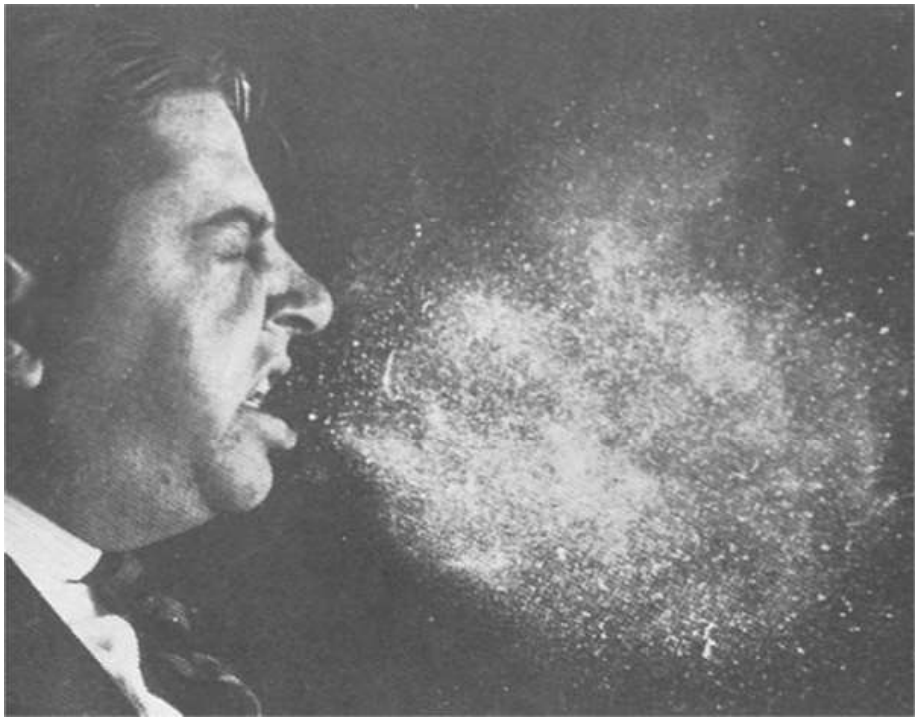

Figure 2-2 Droplet dispersal following a violent sneeze. *(Reprinted with permission from Jennison MW: Aerobiology 17:102, 1947. Copyright 1947 American Association for the Advancement of Science.)*

An infected individual can transmit influenza or the common cold to a score of others in the course of an innocent hour in a crowded room. A venereal infection also must spread progressively from person to person if it is to maintain itself in nature, but it would be a formidable task to transmit venereal infection on such a scale. [2]

Thus, different organisms spread in different ways, and the potential of a given organism for spreading and producing outbreaks depends on the characteristics of the organism, such as its rate of growth and the route by which it is transmitted from one person to another.

Figure 2-3 is a schematic diagram of the human body surfaces as sites of microbial infection and shedding. The alimentary tract can be considered as an open tube that crosses the body, and the respiratory and urogenital systems can be seen as blind inpouchings. Each offers an opportunity for infection. The skin is another important portal of entry for infectious agents, primarily through scratch or injury. Agents that often enter through the skin include streptococci or staphylococci and fungi

such as tinea (ringworm). Two points should be made in this regard: First, the skin is not the exclusive portal of entry for many of these agents, and infections can be acquired through more than one route. The same routes also serve as points of entry for noninfectious disease-causing agents. Environmental toxins can be ingested, inspired during respiration, or absorbed directly through the skin. With both infectious and noninfectious conditions, the clinical and epidemiologic characteristics of the condition often relate to the site of the exposure and the portal of entry.

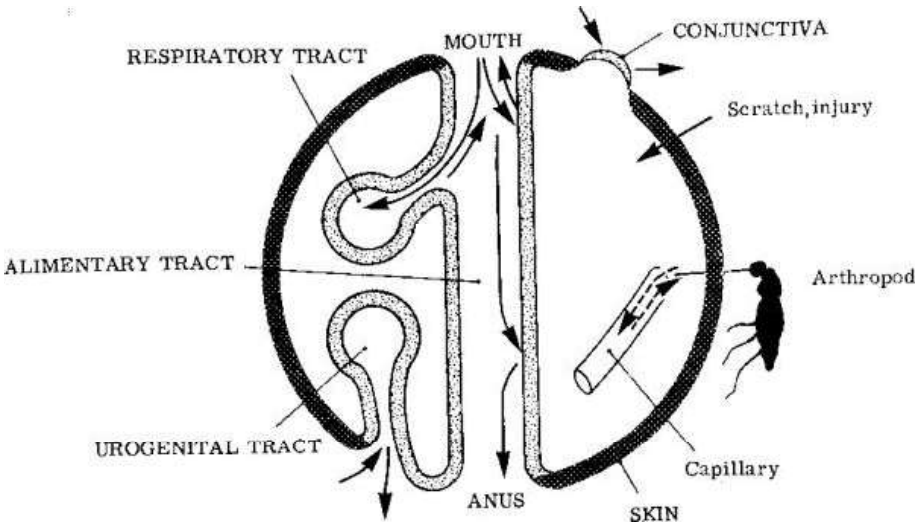

Figure 2-3 Body surfaces as sites of microbial infection and shedding. *(From Mims CA, Nash A, Stephen J: Mims—Pathogenesis of Infectious Disease, 5th ed. London, Academic Press, 2001.)*

CLINICAL AND SUBCLINICAL DISEASE

It is important to recognize the broad spectrum of disease severity. Figure 2-4 shows the iceberg concept of disease. Just as most of an iceberg is underwater and hidden from view with only its tip visible, so it is with disease: only clinical illness is readily apparent (see Fig. 2-4 , *right*). But infections without clinical illness are important, particularly in the web of disease transmission, although they are not visible clinically. In Figure 2-4 , the corresponding biologic stages of pathogenesis and disease at the cellular level are seen on the *left*. The iceberg concept is important because it is not sufficient to count only the clinically apparent cases we see; for example, most cases of polio in prevaccine days were subclinical, but they were still capable of spreading the virus. The epidemiology of polio cannot be explained without a recognition and assessment of the pool of inapparent cases.

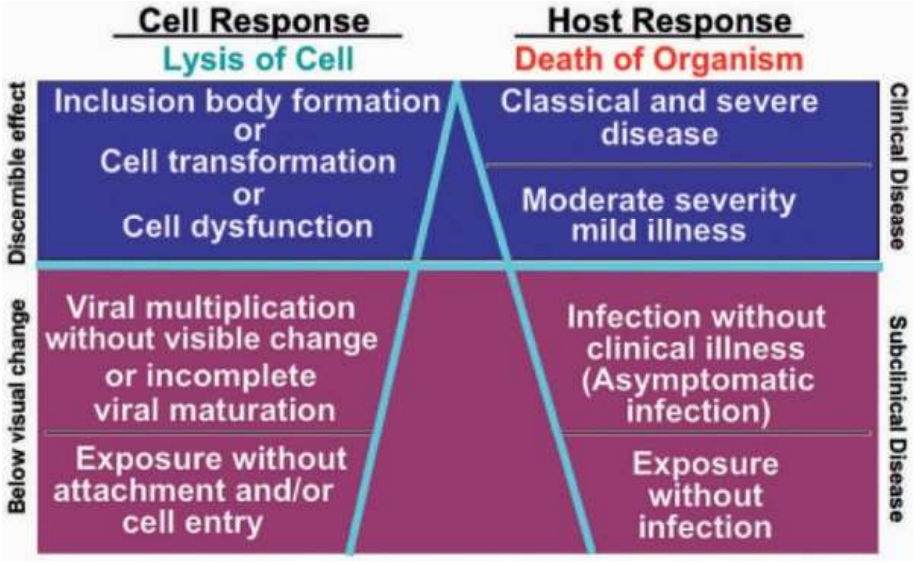

Figure 2-4 The "iceberg" concept of infectious diseases at the level of the cell and of the host. *(Adapted from Evans AS, Kaslow RA (eds): Viral Infections of Humans: Epidemiology and Control, 4th ed. New York, Plenum, 1997.)*

Figure 2-5 shows the spectrum of severity for several diseases. Most cases of tuberculosis, for example, are inapparent. However, because inapparent cases can transmit the disease, such cases must be identified to control spread of the disease. In measles, many cases are of moderate severity and only a few are inapparent. At the other extreme, without intervention, rabies has no inapparent cases, and most untreated cases are fatal. Thus, we have a spectrum of severity patterns that varies with the disease. Severity appears to be related to the virulence of the organism (how good the organism is at producing disease) and to the site in the body at which the organism multiplies. All of these factors, as well as such host characteristics as the immune response, need to be appreciated to understand how disease spreads from one individual to another.

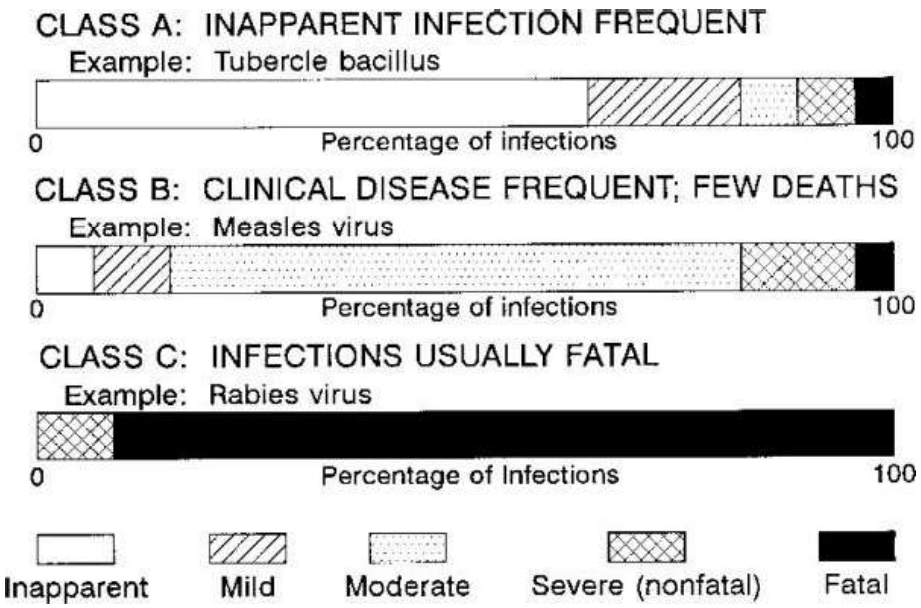

Figure 2-5 Distribution of clinical severity for three classes of infections (not drawn to scale). *(Adapted from Mausner JS, Kramer S: Epidemiology: An Introductory Text. Philadelphia, WB Saunders, 1985, p 265.)*

As clinical and biologic knowledge has increased over the years, so has our ability to distinguish different stages of disease. These include clinical and nonclinical disease:

Clinical Disease

Clinical disease is characterized by signs and symptoms.

Nonclinical (Inapparent) Disease

Nonclinical disease may include the following:

1. *Preclinical Disease*. Disease that is not yet clinically apparent, but is destined to progress to clinical disease.
2. *Subclinical Disease.* Disease that is not clinically apparent and is not destined to become clinically apparent. This type of disease is often diagnosed by serologic (antibody) response or culture of the organism.
3. *Persistent (Chronic) Disease*. A person fails to "shake off" the infection, and it persists for years, at times for life. In recent years, an interesting phenomenon has been the manifestation of symptoms many years after an infection was thought to have been resolved. Some adults who recovered from poliomyelitis in childhood are now reporting severe fatigue and weakness; this has been called post-polio syndrome in adult life. These have thus become cases of clinical disease, albeit somewhat different from the initial illness.
4. *Latent Disease*. An infection with no active multiplication of the agent, as when viral nucleic acid is incorporated into the nucleus of a cell as a provirus. In contrast to persistent infection, only the genetic message is present in the host, not the viable organism.

CARRIER STATUS

In this situation, the individual harbors the organism, but is not infected as measured by serologic studies (no evidence of an antibody response) or by evidence of clinical illness. This person can still infect others, although the infectivity is often lower than with other infections. Carrier status may be of limited duration or may be chronic, lasting for months or years. One of the best-known examples of a long-term carrier was Typhoid Mary, who carried *Salmonella typhi* and died in 1938. Over a period of many years, she worked as a cook in the New York City area, moving from household to household under different names. She was considered to have caused at least 10 typhoid fever outbreaks that included 51 cases and 3 deaths.

ENDEMIC, EPIDEMIC, AND PANDEMIC

Three other terms need to be defined: *endemic, epidemic*, and *pandemic*. *Endemic* is defined as the habitual presence of a disease within a given geographic area. It may also refer to the usual occurrence of a given disease within such an area. *Epidemic* is defined as the occurrence in a community or region of a group of illnesses of similar nature, clearly in excess of normal expectancy, and derived from a common or from a propagated source (Fig. 2-6). *Pandemic* refers to a worldwide epidemic.

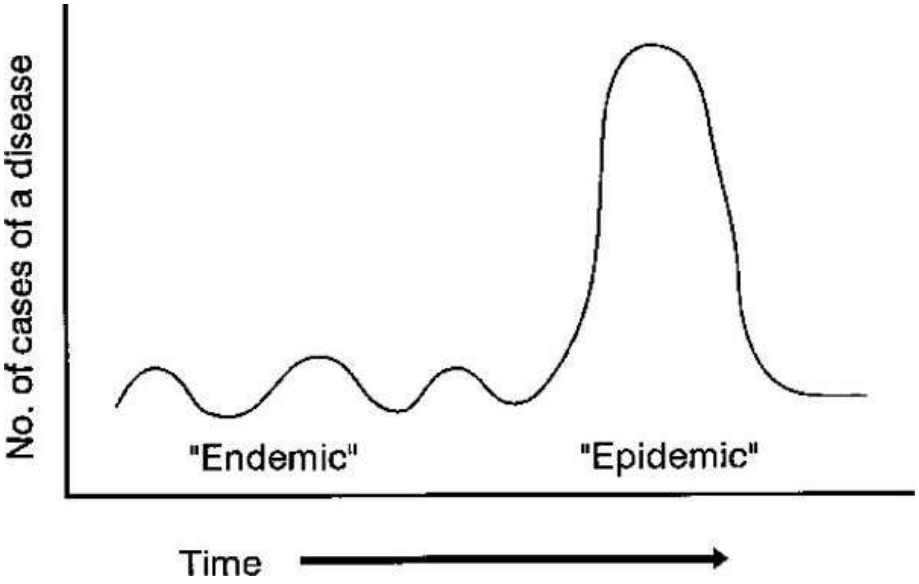

Figure 2-6 Endemic versus epidemic disease.

How do we know when we have an excess over what is expected? Indeed, how do we know how much to expect? There is no precise answer to either question. Through ongoing surveillance, we may determine what the usual or expected level may be. With regard to excess, sometimes an “interocular test” may be convincing: the difference is so clear that it hits you between the eyes.

For example, in December 1952, a dense smoke-laden fog (smog) descended on London. From December 6 to 9, the fog was so thick that visibility was reduced to 30 feet in parts of London. Pedestrians had difficulty finding their way, even in familiar neighborhoods. At times, people could not see their own hands and feet. Figure 2-7 shows trends over this time in the mortality rates and in sulfur dioxide (SO_2) level. The SO_2 level serves as a useful indicator of general levels of air pollution. As seen in Figure 2-7 , the fog was accompanied by a rapid rise in the mortality rate, clearly exceeding the usual mortality rate. This rate remained elevated for some time after the fog dissipated. More than 4,000 deaths were attributed to the fog. Recently, further analyses have suggested that about 12,000 excess deaths occurred from December 1952 through February 1953. [3] Many of these deaths occurred in people who were already suffering from chronic lung or cardiovascular disease. The disaster of the London Fog, or the Great Smog, as it became known, led to legislation, including the Clean Air Acts of 1956 and 1968, which banned emissions of black smoke and required residents of urban areas and operators of factories to convert to smokeless fuel.

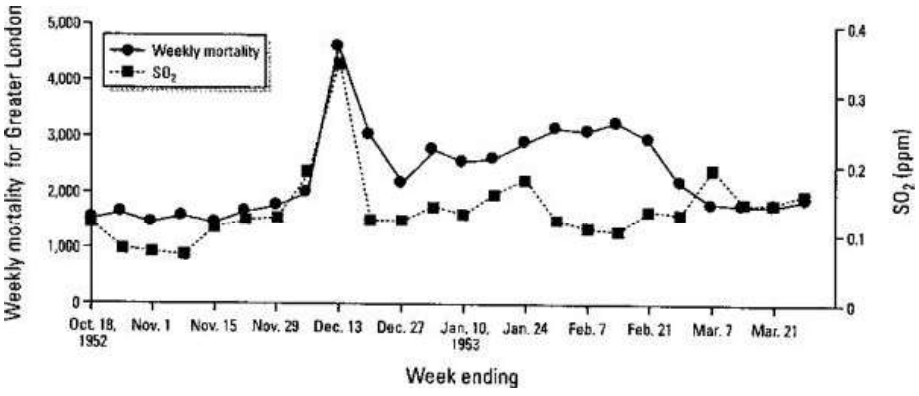

Figure 2-7 Approximate weekly mortality and SO_2 concentrations for Greater London, 1952–1953. *(From Bell ML, Davis DL: Reassessment of the lethal London*

Fog of 1952: Novel indicators of acute and chronic consequences of acute exposure to air pollution. Environ Health Perspect 109[Suppl 3]:389–394, 2001.)

DISEASE OUTBREAKS

Let us assume that a food becomes contaminated with a microorganism. If an outbreak occurs in the group of people who have eaten the food, it is called a *common-vehicle exposure*, because all the cases that developed were in persons exposed to the food in question. The food may be served only once, for example, at a catered luncheon, resulting in a *single exposure* to the people who eat it, or the food may be served more than once, resulting in *multiple exposures* to people who eat it more than once. When a water supply is contaminated with sewage because of leaky pipes, the contamination can be either *periodic*, causing multiple exposures as a result of changing pressures in the water supply system that may cause intermittent contamination, or *continuous*, in which a constant leak leads to persistent contamination. The epidemiologic picture that is manifested depends on whether the exposure is single, multiple, or continuous.

For purposes of this discussion, we will focus on the *single-exposure, common-vehicle outbreak* because the issues discussed are most clearly seen in this type of outbreak. What are the characteristics of such an outbreak? First, such outbreaks are explosive; there is a sudden and rapid increase in the number of cases of a disease in a population. Second, the cases are limited to people who share the common exposure. This is self-evident, because in the first wave of cases we would not expect the disease to develop in people who were not exposed unless there were another source of the disease in the community. Third, in a food-borne outbreak, cases rarely occur in persons who acquire the disease from a primary case. The reason for the relative rarity of such secondary cases in this type of outbreak is not well understood.

Over recent decades, a growing number of outbreaks of acute gastroenteritis (AGE) have occurred aboard cruise ships. During the first 11 months of 2002, the Centers for Disease Control and Prevention (CDC) received reports of 21 outbreaks of AGE, of which 9 were confirmed by laboratory tests of stool specimens to be associated with noroviruses (from the Norwalk virus family). One of these outbreaks is shown in Figure 2-8 .[4] On October 25, a cruise ship with 2,882 passengers and 944 crew members left Spain for a 14-day cruise to Florida. On October 28, a total of 70 (2.5%) of the passengers reported to the infirmary with AGE. By November 2, a total of 106 passengers (5%) and 25 (3%) of the crew had reported illnesses. Figure 2-8 shows the rapid rise in the number of cases and the tapering off of the epidemic curve, typical of single-exposure common-vehicle outbreaks. Results of tests on stool specimens from four of six passengers were positive for a strain of norovirus that was different from that observed in previous outbreaks on cruise ships. Ill crew members were quarantined until they were symptom-free for 72 hours, the ship was disinfected, and sanitary practices were reinforced. No additional outbreaks were reported in subsequent cruises on this ship.[4]

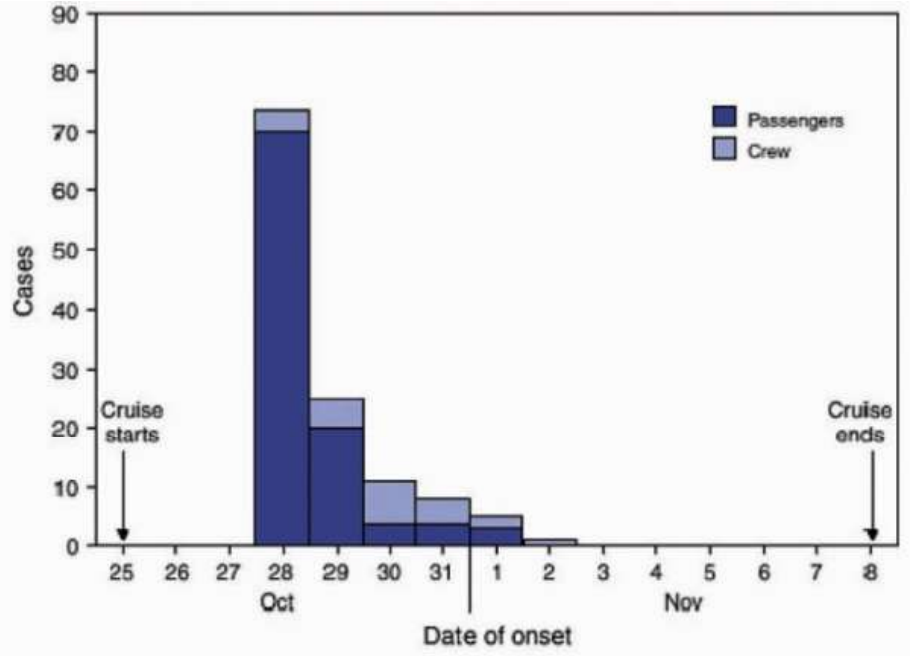

Figure 2-8 Number of passengers and crew members reporting to the ship's infirmary with symptoms of acute gastroenteritis during a 14-day cruise by date of illness onset, Spain to Florida, October 25–November 8, 2002. *(From Centers for Disease Control and Prevention: Outbreaks of gastroenteritis associated with noroviruses on cruise ships—United States, 2002. MMWR 51[49]:112–115, 2002.)*

DETERMINANTS OF DISEASE OUTBREAKS

The amount of disease in a population depends on a balance between the number of people in that population who are susceptible, and therefore at risk for the disease, and the number of people who are not susceptible, or immune, and therefore not at risk. They may be immune because they have had the disease previously or because they have been immunized. They also may be not susceptible on a genetic basis. Clearly, if the entire population is immune, no epidemic will develop. But the balance is usually struck somewhere in between immunity and susceptibility, and when it moves toward susceptibility, the likelihood of an outbreak increases. This has been observed particularly in formerly isolated populations who were exposed to disease. For example, in the 19th century, Panum observed that measles occurred in the Faroe Islands in epidemic form when infected individuals entered the isolated and susceptible population. [5] In another example, severe outbreaks of streptococcal sore throats developed when new susceptible recruits arrived at the Great Lakes Naval Station. [6]

HERD IMMUNITY

Herd immunity may be defined as the resistance of a group of people to an attack by a disease to which a large proportion of the members of the group are immune. If a large percentage of the population is immune, the entire population is likely to be protected, not just those who are immune. Why does herd immunity occur? It happens because disease spreads from one person to another in any community. Once a certain proportion of people in the community are immune, the likelihood is small that an infected person will encounter a susceptible person to whom he can transmit the infection; more of his encounters will be with people who are immune. The presence of a large proportion of immune persons in the population lessens the likelihood that a person with the disease will come into contact with a susceptible individual.

Why is the concept of herd immunity so important? When we carry out immunization programs, it may not be necessary to achieve 100% immunization rates to immunize the population successfully. We can achieve highly effective protection by immunizing a large part of the population; the remaining part will be protected because of herd immunity.

For herd immunity to exist, certain conditions must be met. The disease agent must be restricted to a single host species within which transmission occurs, and that transmission must be relatively direct from one member of the host species to another. If we have a reservoir in which the organism can exist outside the human host, herd immunity will not operate because other means of transmission are available. In addition, infections must induce solid immunity. If immunity is only partial, we will not build up a large subpopulation of immune people in the community.

What does this mean? Herd immunity operates if the probability of an infected person encountering every *other individual* in the population (random mixing) is the same. But if a person is infected and all his interactions are with people who are susceptible (i.e., there is no random mixing of the population), he is likely to transmit the disease to other susceptible people. Herd immunity operates optimally when populations are constantly mixing together. This is a theoretical concept because, obviously, populations are never completely randomly mixed. All of us associate with family and friends, for example, more than we do with strangers. However, the degree to which herd immunity is achieved depends on the extent to which the population approaches a random mixing. Thus, we can interrupt the transmission of disease even if not everyone in the population is immune, so long as a critical percentage of the population is immune.

What percentage of a population must be immune for herd immunity to operate? This percentage varies from disease to disease. For example, in the case of measles, which is highly communicable, it has been estimated that 94% of the population must be immune before the chain of transmission is interrupted.

Let us consider poliomyelitis immunization and herd immunity. From 1951 to 1954, an average of 24,220 cases of paralytic poliomyelitis occurred in the United States each year. Two types of vaccine are available. The oral polio vaccine (OPV) not only protects those who are vaccinated, but also protects others in the community through secondary immunity, produced when the vaccinated individual spreads the active vaccine virus to contacts. In effect, the contacts are immunized by the spread of virus from the vaccinated person. If enough people in the community are protected in this way, the chain of transmission is interrupted. However, even inactivated poliovirus vaccine (IPV), which does not produce secondary immunity (does not spread the virus), can produce herd immunity if enough of the population is immunized; even those who are not immunized will be protected because the chain of transmission in the community has been interrupted.

From 1958 to 1961, only IPV was available in the United States. Figure 2-9 shows both the expected number of cases each year if the vaccine had protected only those who received the vaccine and the number of polio cases actually observed. Clearly, the number of cases that occurred was far less than what would have been expected from the direct effects of the vaccine alone. The difference between the two curves represents the effect of herd immunity from the vaccine. Thus, nonimmunized individuals can gain some protection from either the OPV or IPV.

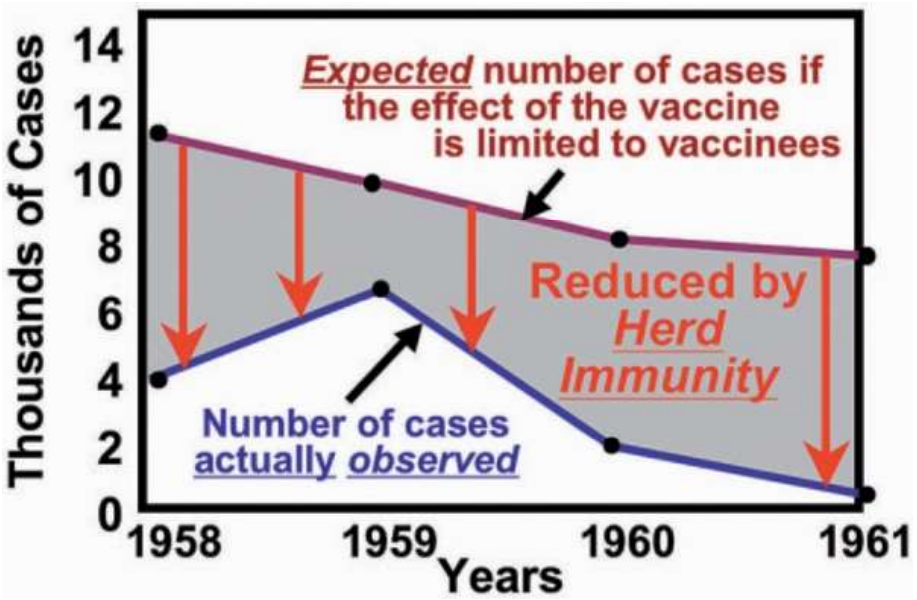

Figure 2-9 Effect of Herd Immunity: expected and observed numbers of paralytic poliomyelitis cases, United States, 1958–1961. *(Adapted by permission of American Academy of Pediatrics News. Copyright 1998. From Stickle G: Observed and expected poliomyelitis in the United States, 1958–1961. Am J Public Health 54:1222–1229, 1964.)*

INCUBATION PERIOD

The incubation period is defined as the *interval from receipt of infection to the time of onset of clinical illness*. If you become infected today, the disease with which you are infected may not develop for a number of days or weeks. During this time, the *incubation period*, you feel completely well and show no signs of the disease.

Why doesn—t disease develop immediately at the time of infection? What accounts for the incubation period? It may reflect the time needed for the organism to replicate sufficiently until it reaches the critical mass needed for clinical disease to result. It probably also relates to the site in the body at which the organism replicates—whether it replicates superficially, near the skin surface, or deeper in the body. The dose of the infectious agent received at the time of infection may also influence the length of the incubation period. With a large dose, the incubation period may be shorter.

The incubation period is also of historical interest because it is related to what may have been the only medical advance associated with the Black Death in Europe. In 1374, when people were terribly frightened of the Black Death, the Venetian Republic appointed three officials who were to be responsible for inspecting all ships entering the port and for excluding ships that had sick people on board. It was hoped that this intervention would protect the community. In 1377, in the Italian seaport of Ragusa, travelers were detained in an isolated area for 30 days (*trentini giorni*) after arrival to see whether infection developed. This period was found to be insufficient, and the period of detention was lengthened to 40 days (*quarante giorni*). This is the origin of the word *quarantine*.

How long would we want to isolate a person? We would want to isolate a person until he or she is no longer infectious to others. When a person is clinically ill, we generally have a clear sign of potential infectiousness. An important problem arises *before* the person becomes clinically ill—that is, during the incubation period. If we knew when he or she became infected and also knew the general length of the incubation period for the disease, we would want to isolate the infected person during this period to prevent the communication of the disease to others. In most situations, however, we do not know that a person has been infected, and we may not know until signs of clinical disease become manifest.

This leads to an important question: Is it worthwhile to quarantine—isolate—a patient, such as a child with chickenpox? The problem is that, during at least part of the incubation period, when a person is still free of clinical illness, he or she can transmit the disease to others. Thus, we have people who are not (yet) clinically ill, but who have been infected and are able to transmit the disease. For many common childhood diseases, by the time clinical disease develops in the child, he or she has already transmitted the disease to others. Therefore, isolating such a person at the point at which he or she becomes clinically ill will not necessarily be effective. On the other hand, isolation can be very valuable. In February 2003 a serious respiratory illness was first reported in Asia (having occurred in 2002) and was termed *severe acute respiratory syndrome* (SARS). The disease is characterized by fever over 38°C, headache, overall discomfort, and, after 2 to 7 days, development of cough and difficulty in breathing in some patients. The cause of SARS has been shown to be infection with a previously unrecognized human coronavirus, called SARS-associated coronavirus.

SARS appears to spread by close, person-to-person contact. Because modern travel, particularly air travel, facilitates rapid and extensive spread of disease, within a few months the illness had spread to more than two dozen countries in North America, South America, Europe, and Asia. However, by late July 2003, no new cases were being reported and the outbreak was considered contained. However, the possibility remains that SARS outbreaks will occur again in the future.

The World Health Organization reported that worldwide, 8,437 people became ill with SARS during the November 2002 to July 2003 outbreak and of those, 813 died (Table 2-3). The differences in case-fatality among different countries are at least partially attributable to differences in completeness of reporting and to international variations in defining and diagnosing SARS. A major contributor to control of the epidemic was probably the strong measures implemented early for isolating probable SARS cases and for reducing interpersonal contacts of travelers with a history of travel to highly affected areas.

TABLE 2-3 -- Probable Cases of Severe Acute Respiratory Syndrome (SARS), SARS-Related Deaths, and SARS Case-Fatality, by Country, November 1, 2002–July 11, 2003

Country	Cumulative Number of Cases	Number of Deaths	Case-Fatality (%)
Canada	250	38	15.2
China	5,327	348	6.5
China, Hong Kong	1,755	298	17.0
Singapore	206	32	15.5
Taiwan	671	84	12.5
United States	75	0	0.0
Vietnam	63	5	7.9
All other countries	90	8	8.9
All countries	8,437	813	9.6

Data from SarsNet-Isolates, Activity, http://rhone.b3e.jussieu.fr/sarsnet/www/activity.html, July 19, 2003.

Different diseases have different incubation periods. A precise incubation period does not exist for a given disease; rather, a range of incubation periods is characteristic for that disease. Figure 2-10 shows the range of incubation periods for several diseases. In general, the length of the incubation period is characteristic of the infective organism.

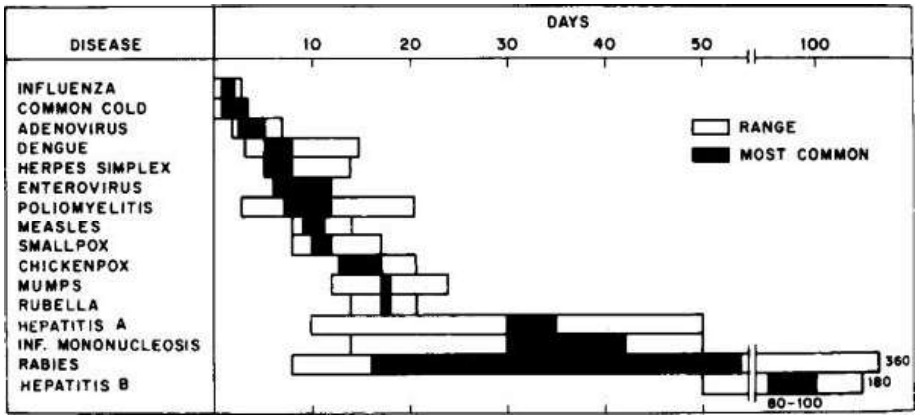

Figure 2-10 Incubation periods of viral diseases. *(From Evans AS, Kaslow RA [eds]: Viral Infections of Humans: Epidemiology and Control, 4th ed. New York, Plenum, 1997.)*

The incubation period for infectious diseases has its analogue in noninfectious diseases. Thus, even when an individual is exposed to a carcinogen or other toxin, the disease is often manifest only after months or years. For example, mesotheliomas resulting from asbestos exposure may occur 20 to 30 years after the exposure.

Figure 2-11 is a graphic representation of an outbreak of *Salmonella typhimurium* at a medical conference in Wales in 1986. Each bar represents the number of cases of disease developing at a certain point in time after the exposure; the number of hours since exposure is shown along the horizontal axis. If we draw a line connecting the tops of the bars it is called the *epidemic curve*, which is defined as the distribution of the times of onset of the disease. In a *single-exposure, common-vehicle epidemic,* the epidemic curve represents the distribution of the incubation periods. This should be intuitively apparent: if the infection took place at one point in time, the interval from that point to the onset of each case is the incubation period in that person.

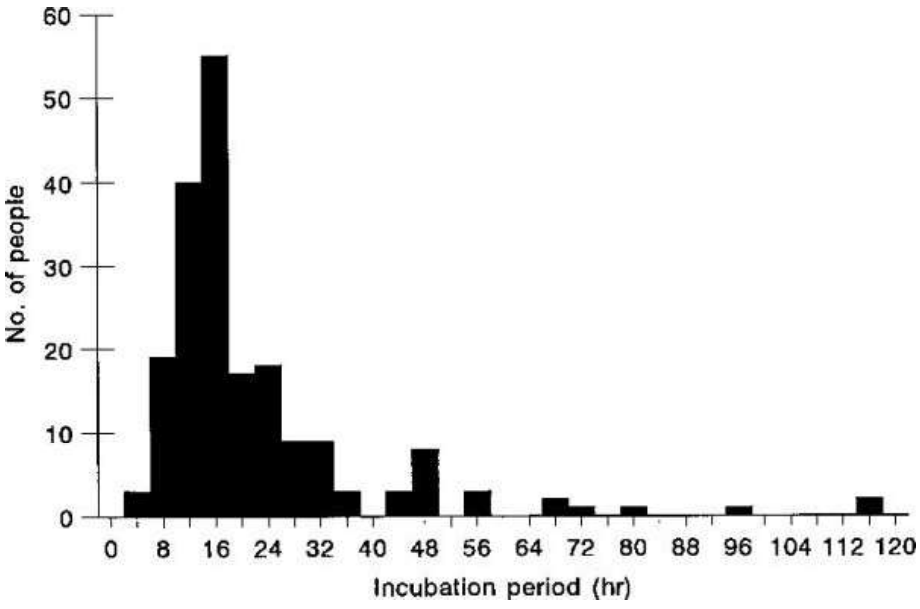

Figure 2-11 Incubation periods for 191 delegates affected by a *Salmonella typhimurium* outbreak at a medical conference in Wales, 1986. *(Adapted from Glynn JR, Palmer SR: Incubation period, severity of disease, and infecting dose: Evidence from a Salmonella outbreak. Am J Epidemiol 136:1369–1377, 1992.)*

As seen in Figure 2-11 , there was a rapid, explosive rise in the number of cases within the first 16 hours, which suggests a single-exposure, common-vehicle epidemic. In fact, this pattern is the classic epidemic curve for a single-exposure common-vehicle outbreak (Fig. 2-12 , *left*). The reason for this configuration is not known. But it has an interesting property: if the curve is plotted against the logarithm of time rather than against time, the curve becomes a normal curve (see Fig. 2-12 , *right*). If plotted on log-normal graph paper, we obtain a straight line, and estimation of the median incubation period is facilitated.

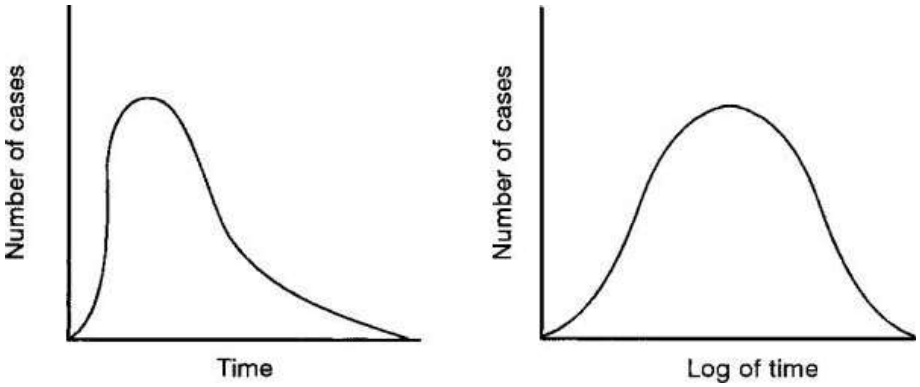

Figure 2-12 Number of cases plotted against time and against the logarithm of time.

The three critical variables in investigating an outbreak or epidemic are: (1) When did the exposure take place? (2) When did the disease begin? and (3) What was the incubation period for the disease? If we know any two of these, we can calculate the third.

ATTACK RATE

An attack rate is defined as:

$$\frac{\text{Number of people at risk in whom a certain illness develops}}{\text{Total number of people at risk}}$$

The attack rate is similar to the incidence rate, which is also used for less acute diseases. The attack rate (or the incidence rate) is useful for comparing the risk of disease in groups with different exposures. The attack rate can be specific for a given exposure. For example, the attack rate in people who ate a certain food is called a *food-specific attack rate*. It is calculated by:

$$\frac{\text{Number of people at risk in whom a certain illness develops}}{\text{Total number of people at risk}}$$

In general, *time* is not explicitly specified in an attack rate; given what is usually known about how long after an exposure most cases develop, the time period is implicit in the attack rate. Examples of calculating attack rates are seen in Table 2-5 (p. 34).

TABLE 2-5 -- Food-Specific Attack Rates for Items Consumed August 16, 1974, Dade County Jail, Miami

	ATE			DID NOT EAT			
Item Consumed	**Sick**	**Total**	**% Sick (Attack Rate)**	**Sick**	**Total**	**% Sick (Attack Rate)**	**P**
Beverage	179	264	67.8	22	50	44.0	<.010
Egg salad sandwiches	176	226	77.9	27	73	37.0	<.001

From Centers for Disease Control and Prevention: Outbreak of foodborne streptococcal disease. MMWR 23:365, 1974.

A person who acquires the disease from that exposure (e.g., from a contaminated food) is called a *primary case*. A person who acquires the disease from exposure to a primary case is called a *secondary case*. The *secondary attack rate* is therefore defined as the attack rate in susceptible people who have been exposed to a primary case. It is a good measure of person-to-person spread of disease after the disease has been introduced into a population, and it can be thought of as a ripple moving out from the primary case. We often calculate the secondary attack rate in family members of the index case.

The secondary attack rate also has application in noninfectious diseases when family members are examined to determine the extent to which a disease clusters among first-degree relatives of an index case, which may yield a clue regarding the relative contributions of genetic and environmental factors to the cause of a disease.

EXPLORING THE OCCURRENCE OF DISEASE

The concepts outlined in this chapter form the basis for exploring the occurrence of disease. When a disease appears to have occurred at more than an endemic level, and we wish to investigate its occurrence, we ask:

Who was attacked by the disease?

When did the disease occur?

Where did the cases arise?

It is well known that disease risk is affected by all of these factors.

Who

The characteristics of the human host are clearly related to disease risk. Factors such as sex, age, and race have a major effect.

Gonorrhea

As shown in Figure 2-13 , rates of gonorrhea have been higher in men than in women, and this sex differenceis observed at least as far back as 1960 (not shown in this graph). Because women are more likely to be asymptomatic, the disease in women has probably been underreported. Rates have been decreasing in both men and women over the past few decades, and in recent years, the sex difference has largely disappeared, possibly as a result of increased screening in women. However, despite the declines in rates, neither male nor female rates reached the level of the national objective in the United States, that of the Healthy People Year 2010 target, shown by the dotted line. Indeed, since 1997, rates in both men and women have increased slightly.

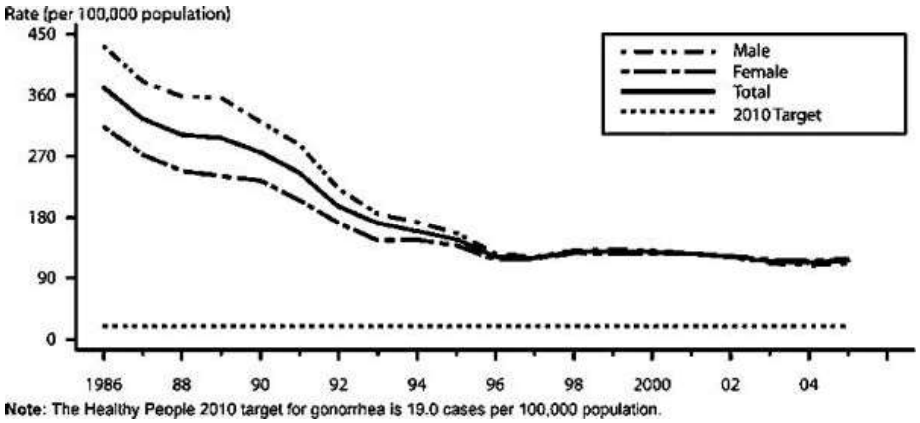

Figure 2-13 Gonorrhea, repor-ted cases per 100,000 by sex, United States, 1986–2005, and the Healthy People Year 2010 target. *(From Centers for Disease Control and Prevention: STD Surveillance, National Profile—Gonorrhea, 2005. www.cdc.gov/std/stats05/figures/fig12.htm.)*

Pertussis

In 2004, the incidence rate of reported pertussis in the United States increased for the third year in a row. The rate reached 8.9 cases per 100,000 population, more than twice that reported in 2003. In 1994, the rate was 1.8. The number of cases in 2004 was the highest reported since 1959. Although childhood pertussis vaccine coverage levels are high in the United States, pertussis continues to cause morbidity. Some of this increase may result from improved diagnostics, as well as recognition and reporting of cases. As seen in Figure 2-14 , the lowest rates for pertussis in the United States were observed from 1974 to 1981. Interestingly, since 1993, the number of cases reported after each epidemic year has not returned to the baseline of the pre-epidemic year.

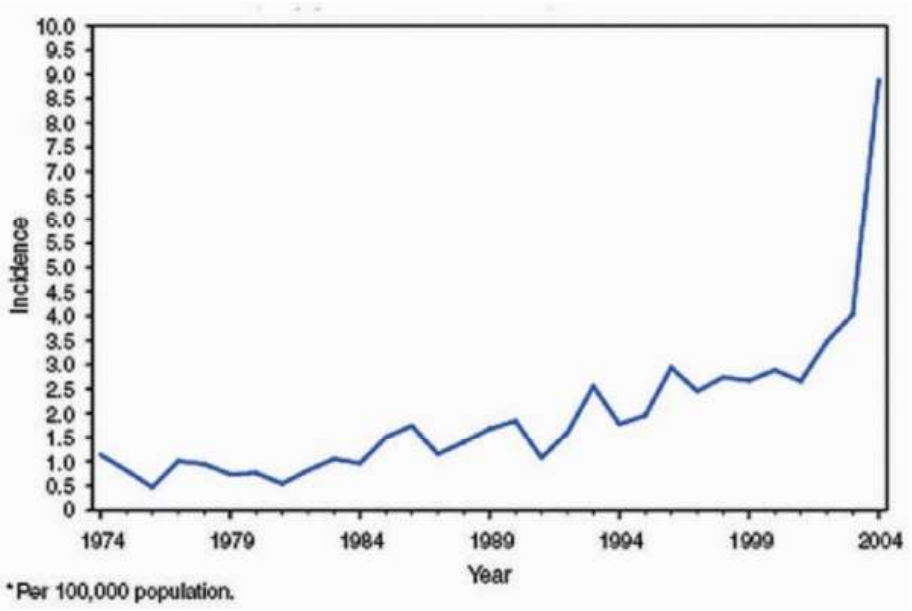

Figure 2-14 Pertussis (whooping cough), reported cases per 100,000 population by year, United States, 1974–2004. *(From Centers for Disease Control and Prevention: Summary of notifiable diseases, United States: 2004. MMWR 53[53]:1–79, 2006.)*

Pertussis occurrence is clearly related to age (Fig. 2-15). Although, the *number* of reported cases was highest in children ages 10 to 14 (as seen in Fig. 2-15), the highest *rate* of pertussis was in infants less than 6 months of age (136.5 per 100,000 population) (not shown in Fig. 2-15). Among older infants aged 6 to 11 months, the rate was 31.8 per 100,000. Two thirds of pertussis cases in the United States are now seen in adolescents and adults. Although the specific cause of this phenomenon is unknown, it could result from a waning of protection 5 to 10 years after pertussis immunization.

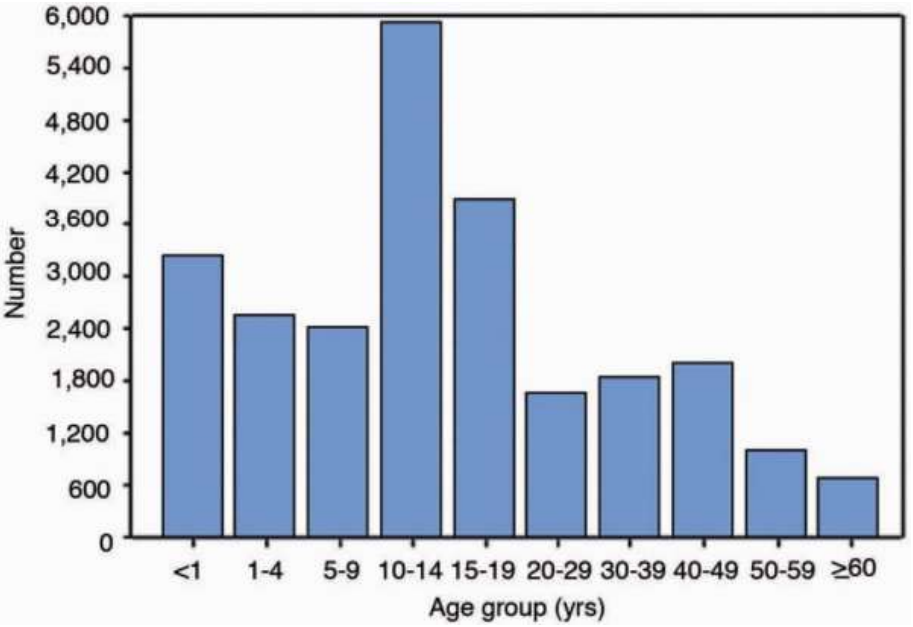

Figure 2-15 Pertussis (whooping cough), reported numbers of cases by age group, United States, 2004. *(From Centers for Disease Control and Prevention: Summary of notifiable diseases, United States: 2004. MMWR 53[53]:1–79, 2006.)*

When

Certain diseases occur with a certain periodicity. For example, aseptic meningitis peaks yearly (Fig. 2-16). Often, there is a seasonal pattern to the temporal variation. For example, diarrheal disease is most common during the summer months, and respiratory disease is most common during the winter months. The question of *when* is also addressed by examining trends in disease incidence over time. For example, in the United States, both incidence of, and deaths from, acquired immunodeficiency syndrome (AIDS) increased for many years, but began to decline in 1996, largely as a result of new

therapy and health education efforts.

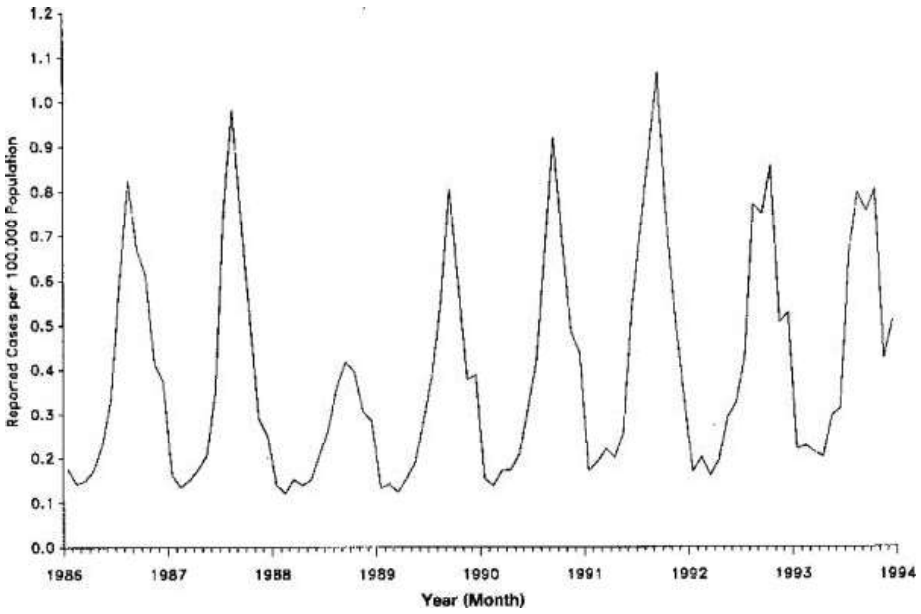

Figure 2-16 Aseptic meningitis, reported cases per 100,000 population by month, United States, 1986–1993. *(From Centers for Disease Control and Prevention: Summary of notifiable diseases, United States: 1993. MMWR 42:22, 1994.)*

Where

Disease is not randomly distributed in time or place. For example, Figure 2-17 shows the geographic distribution of Lyme disease in the United States, by county, in 2005. There is a clear clustering of cases along the Northeast coast, in the north-central part of the country, and in the Pacific coast region. The states in which established enzootic cycles of *Borrelia burgdorferi*, the causative agent, have been reported accounted for 94% of the cases. The distribution of the disease closely parallels that of the deer tick vector.

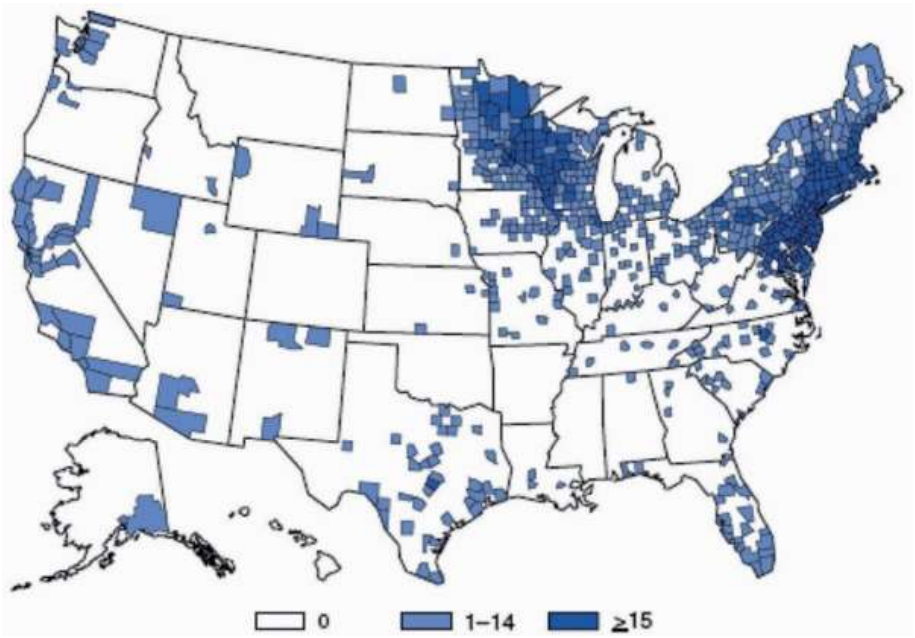

Figure 2-17 Lyme disease, reported cases by county, United States, 2005. *(From Centers for Disease Control and Prevention: Summary of notifiable diseases, United States, 2005. MMWR 54[53]:2–92, 2007.)*

A dramatic example of spread of disease is seen with West Nile virus (WNV) in the United States. [7] WNV was first isolated and identified in 1937 in the West Nile region of Uganda, and for many years, it was found only in the Eastern hemisphere. The basic cycle of the disease is bird-mosquito-bird. Mosquitoes become infected when they bite infected birds. When

mosquitoes that bite both birds and humans become infected, they pose a threat to people. Most human infections are subclinical, but approximately 1 of 150 infections in recent years has resulted in meningitis or encephalitis. The risk of neurologic disease is significantly increased in people older than 50 years of age. Other symptoms include fever, nausea and vomiting, rash, headache, and muscle weakness. The case-fatality can be as high as 14%. Advancing age is a major risk factor for death from WNV, with one study reporting death nine times as frequently in older compared with younger patients. Treatment is supportive, and prevention is largely addressed through mosquito control and the use of insect repellents. Tracking the distribution of the disease depends on surveillance for human cases, and on monitoring birds and animals for the disease and deaths from the disease.

WNV was first identified in New York City in 1999. Figure 2-18 shows the rapid spread of WNV across the United States from 1999 to 2002. In 2002, human cases were reported from 619 counties in 37 states and the District of Columbia. Of the 3,389 cases of WNV-associated disease reported, 2,354 patients (69%) had West Nile meningoencephalitis. Looking at data from the 2002 outbreak of WNV meningoencephalitis in Figure 2-19 , we see that the epidemic peaked in August, with the peak occurring 1 week earlier in the south (gray bars) than in the north (blue bars). Nine percent of people who developed West Nile meningoencephalitis died. Figure 2-20 shows the picture for 2006 and the number of cases reported by state. Much remains to be learned about this disease to facilitate treatment, prevention, and control.

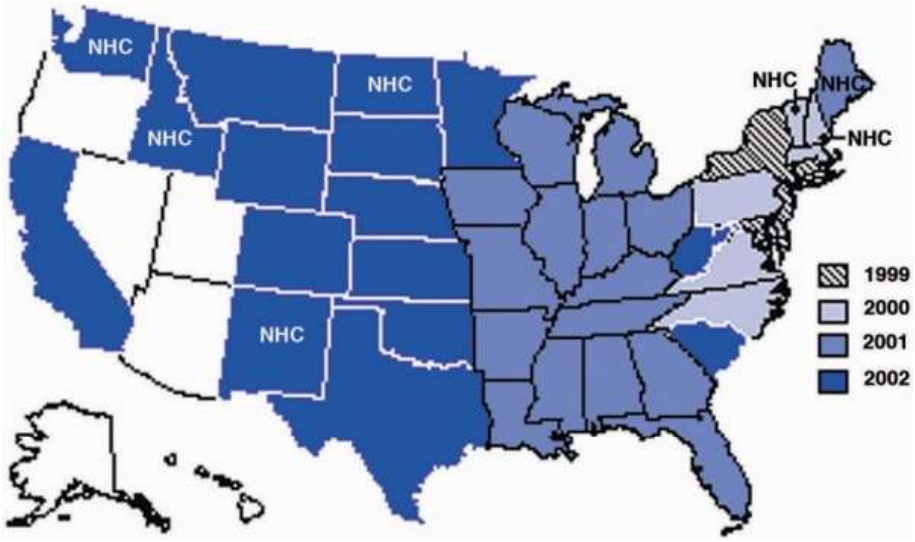

Figure 2-18 West Nile virus activity by state, United States, 1999–2002. NHC, no human cases. *(From Centers for Disease Control and Prevention: Provisional surveillance summary of the West Nile Virus epidemic, United States, January–November, 2002. MMWR 51[50]:1129–1133, 2002.)*

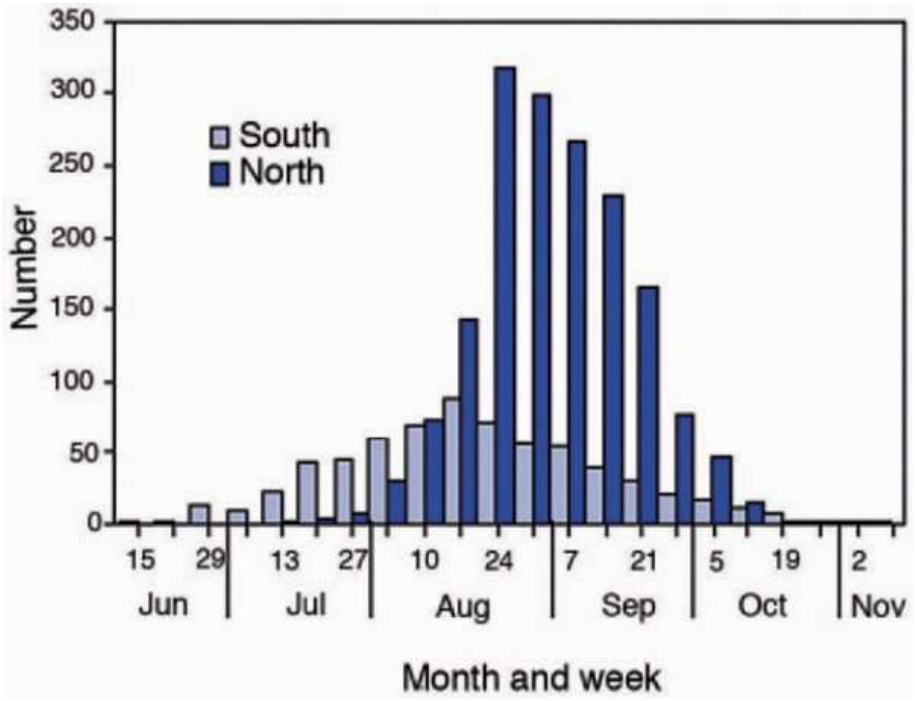

Figure 2-19 Number of human West Nile meningoencephalitis cases, by location and week and month of illness onset, United States, June–November 2002. *(From*

Centers for Disease Control and Prevention: Provisional surveillance summary of the West Nile Virus epidemic, United States, January–November, 2002. MMWR 51[50]:1129–1133, 2002.)

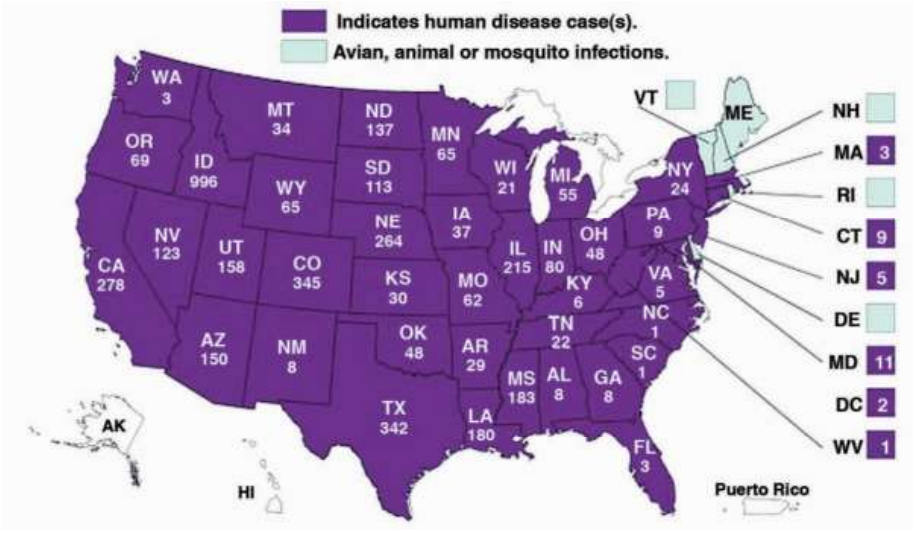

Figure 2-20 West Nile Virus activity in the United States, 2006 (Reported to CDC as of February 6, 2007). *(From Centers for Disease Control and Prevention: West Nile Virus: Statistics, Surveillance and Control. www.cdc.gov/ncidod/dvbid/westnile/Mapsactivity/surv&control06Maps.htm.)*

OUTBREAK INVESTIGATION

The characteristics just discussed are the central issues in virtually all outbreak investigations. The steps for investigating an outbreak follow this general pattern (Table 2-4).

TABLE 2-4 -- Steps in Investigating an Acute Outbreak

Investigating an acute outbreak may be primarily deductive (i.e., reasoning from premises or propositions proved previously) or inductive (i.e., reasoning from particular facts to a general conclusion), or it may be a combination of both.
Important considerations in investigating an acute outbreak of infectious diseases include determining that an outbreak has in fact occurred and defining the extent of the population at risk, determining the measure of spread and reservoir, and characterizing the agent.
Steps commonly used are listed below, but depending on the outbreak, the exact order may differ.

1. *Define the outbreak and validate the existence of an outbreak*
   - a. Define the “numerator” (cases)
     - (1) Clinical features: is the disease known?
     - (2) What are its serologic or cultural aspects?
     - (3) Are the causes partially understood?
   - b. Define the “denominator”: What is the population at risk of developing disease?
   - c. Determine whether the observed number of cases clearly exceeds the expected number
   - d. Calculate the attack rates
2. *Examine the distribution of cases by the following:*
   - a. time
   - b. Place}Look for time–place interactions
3. *Look for combinations (interactions) of relevant variables*
4. *Develop hypotheses based on the following:*
   - a. Existing knowledge (if any) of the disease
   - b. Analogy to diseases of known etiology
   - c. Findings from investigation of the outbreak
5. *Test hypotheses*
   - a. Further analyze existing data (case-control studies)
   - b. Refine hypotheses and collect additional data that may be needed
6. *Recommend control measures*
   - a. Control of current outbreak
   - b. Prevention of future similar outbreaks
7. *Prepare a written report of the investigation and the findings*
8. *Communicate findings to those involved in policy development and implementation and to the public*

Cross-Tabulation

When confronted with several possible causal agents as is often the case in a food-borne disease outbreak, a very helpful method for determining which of the possible agents is likely to be the cause is called *cross-tabulation*.This is illustrated by an outbreak of food-borne streptococcal disease in a Florida jail reported some years ago by the CDC. [8]

In August 1974, an outbreak of group A β-hemolytic streptococcal pharyngitis affected 325 of 690 inmates. On a questionnaire administered to 185 randomly selected inmates, 47% reported a sore throat between August 16 and August 22. Based on a second questionnaire, food-specific attack rates for items that were served to randomly selected inmates showed a significant association between two food items and the risk of developing a sore throat: beverage and egg salad served at lunch on August 16 (Table 2-5).

In Table 2-5 , for each of the suspected exposures (beverage and egg salad), the attack rate was calculated for those who ate or drank the item (were exposed) and those who did not eat or drink the item (were not exposed). For both the beverage and the egg salad, attack rates are clearly higher among those who ate or drank the item than among those who did not. However, this table does not permit us to determine whether the beverage or the egg salad accounted for the outbreak.

In order to answer this question, we use the technique of cross-tabulation. In Table 2-6 , we again examine the attack rates in those who ate egg salad compared with those who did not, but this time we do so separately for those who drank the beverage and for those who did not.

TABLE 2-6 -- Cross-Table Analysis for Egg Salad and Beverage Consumed August 16, 1974, Dade County Jail, Miami

	ATE EGG SALAD				DID NOT EAT EGG SALAD			
	Sick	Well	Total	% Sick (Attack Rate)	Sick	Well	Total	% Sick (Attack Rate)
Drank beverage	152	49	201	75.6	19	53	72	26.4
Did not drink beverage	12	3	15	80.0	7	21	28	25.0

From Centers for Disease Control and Prevention: Outbreak of foodborne streptococcal disease. MMWR 23:365, 1974.

Looking at the data by columns, we see that both among those who ate egg salad and among those who did not, drinking the beverage did not increase the incidence of streptococcal illness (75.6% vs. 80% and 26.4% vs. 25%, respectively). However, looking at the data in the table horizontally, we see that eating the egg salad significantly increased the attack rate of the illness, both in those who drank the beverage (75.6% vs. 26.4%) and in those who did not (80% vs. 25%). Thus, the egg salad is clearly implicated.

This example demonstrates the use of crosstabulation in a food-borne outbreak of an infectious disease, but the method has broad applicability to any condition in which multiple etiologic factors are suspected. It is discussed further in Chapter 15 .

CONCLUSION

This chapter reviewed some basic concepts that underlie the epidemiologic approach to acute communicable diseases. Many of these concepts apply equally well to nonacute diseases that at this time do not appear to be infectious in origin. Moreover, for an increasing number of chronic diseases originally thought to be noninfectious, infection seems to play some role. Thus, hepatitis B infection is a major cause of primary liver cancer. Papillomaviruses have been implicated in cervical cancer, and Epstein-Barr virus has been implicated in Hodgkin disease. The boundary between the epidemiology of infectious and noninfectious diseases has blurred in many areas. In addition, even for diseases that are not infectious in origin, the patterns of spread share many of the same dynamics, and the methodologic issues in studying them are similar. Many of these issues are discussed in detail in Section II .

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8. *Outbreak of foodborne streptococcal disease. MMWR* 1974; 23:365.

REVIEW QUESTIONS FOR CHAPTER 2

1. *Endemic* means that a disease
- **a.** Occurs clearly in excess of normal expectancy
- **b.** Is habitually present in human populations
- **c.** Affects a large number of countries simultaneously
- **d.** Exhibits a seasonal pattern
- **e.** Is prevalent among animals

Questions 2 and 3 are based on the information given below:
The first table shows the total number of persons who ate each of two specified food items that were possibly infective with group A streptococci. The second table (p. 36) shows the number of sick persons (with acute sore throat) who ate each of the various specified combinations of the food items.

Total Number of Persons Who Ate Each Specified Combination of Food Items

Ate Tuna	Did Not	Eat Tuna
Ate egg salad	75	100
Did not eat egg salad	200	50

Total Number of Persons Who Ate Each Specified Combination of Food Items and Who Later Became Sick (with Acute Sore Throats)

Ate Tuna	Did Not	Eat Tuna
Ate egg salad	60	75
Did not eat egg salad	70	15

2. What is the sore throat attack rate in persons who ate both egg salad and tuna?
- **a.** 60/75
- **b.** 70/200
- **c.** 60/135
- **d.** 60/275
- **e.** None of the above

3. According to the results shown in the preceding tables, which of the following food items (or combination of food items) is most likely to be infective?
- **a.** Tuna only
- **b.** Egg salad only
- **c.** Neither tuna nor egg salad
- **d.** Both tuna and egg salad
- **e.** Cannot be calculated from the data given

4. In the study of an outbreak of an infectious disease, plotting an epidemic curve is useful because:
- **a.** It helps to determine what type of outbreak (e.g., single-source, person-to-person) has occurred
- **b.** It shows whether herd immunity has occurred
- **c.** It helps to determine the median incubation period
- **d.** *a* and *c*
- **e.** *a, b,* and *c*

5. Which of the following is characteristic of a single-exposure, common-vehicle outbreak?
- **a.** Frequent secondary cases
- **b.** Increasing severity with increasing age
- **c.** Explosive
- **d.** Cases include both people who have been exposed and those who were not exposed
- **e.** All of the above