

Infectious Disease Epidemiology

Symbiosis refers to the interactive relation between different species. It encompasses a broad range of patterns ranging from *mutualism* at one end of the spectrum, in which both species benefit, to *parasitism* at the other end, in which one species, the parasite, obtains nutriment from the other, the host, while offering little or nothing in return. Parasitism is a ubiquitous feature of life. Virtually every animal and plant is either a parasite or host to a parasite during part or all of its life cycle. Parasites tend to reproduce more quickly than their hosts and to evolve rapidly in response to host defenses, perpetuating a continual struggle that determines the boundary between disease and health and life or death. An infectious parasite is typically much smaller than its host, living within or on the host, on which it depends for its sustenance. Agents that infect humans include a range of microorganisms, including viruses, bacteria, fungi, and protozoa, as well as some larger animals such as helminths. In this chapter, we refer to the microscopic agents as *pathogens* and reserve the term *parasite* for larger animals.

Evolution has fostered the development of defenses against infection. The skin is an effective, if passive, barrier against most bacteria and viral infections. Surface responses that help resist infection include sweating and desquamation, cilia movement in the respiratory tract, and production of mucus along interior epithelial surfaces. Mucous membranes have antibacterial properties; stomach acid, saliva, and tears help to resist infection. In the gut, entrenched but friendly bacteria compete with pathogens, limiting opportunities for the pathogens to establish themselves. For pathogens that manage to penetrate skin or mucous membranes, the immune system provides two more levels of defense. The first comes from the *innate immune system*. Injury to cells triggers a nonspecific inflammatory reaction, which is a cascade of events involving chemical and cellular responses to the local injury. The inflammatory reaction recruits a variety of blood cells, including mast cells, phagocytes, neutrophils, and others that play various roles in the host response. The innate immune system also activates the *adaptive immune system*, which allows a specific response to infectious agents. This system produces antibodies that are designed to attach to specific sites on the pathogen or its toxins, neutralizing the threat. Specialized B-cell lymphocytes work in conjunction with

helper T cells to produce antibodies. These cells also record the antigenic pattern that stimulated their response, enabling a faster and more effective response if the antigen is encountered again. This antigenic memory is what is commonly referred to as *immunity* to an infectious agent. Immunity occurs naturally after an infection, but it can also be stimulated by vaccination, which is intended to provoke an immunogenic reaction without causing an initial pathogenic infection. Immunity can vary in duration from a relatively short period to lifetime protection.

The sophistication of host defenses implies that humans have always had to reckon with infectious disease. The balance between host and pathogen, however, is readily tipped by changing social conditions. For example, human invasions or migrations sometimes brought immunologically naïve populations into contact with diseases to which they had not previously been exposed. Urbanization during the Middle Ages brought on the conditions that fostered spread of the plague. Europeans brought with them to the New World a host of infections, such as smallpox, measles, typhus, and cholera, which had catastrophic consequences for natives of the Western Hemisphere. Europeans had adapted to these agents, but the newly exposed natives of the Americas had no natural defenses. Conversely, some speculate that syphilis was prevalent in the Americas but unknown in Europe until after Columbus' first voyage to the New World.

The public-health burden from infectious disease began to diminish after the acceptance of the germ theory and the arrival of greatly improved sanitation and hygiene. Wealthy nations saw much faster progress than poorer ones, because implementing the needed public-health programs was expensive. The advent of antibacterials was another crucial development in fighting infection. This tool was also more available to wealthy nations. Nevertheless, sanitation and hygiene had the more powerful effect, as can be seen in Figure 6-1. This graph depicts the steady decline in mortality from infectious disease in the United States over the course of the 20th century. The figure also indicates the spike in deaths during 1919, the year with the majority of cases of pandemic H1N1 influenza that

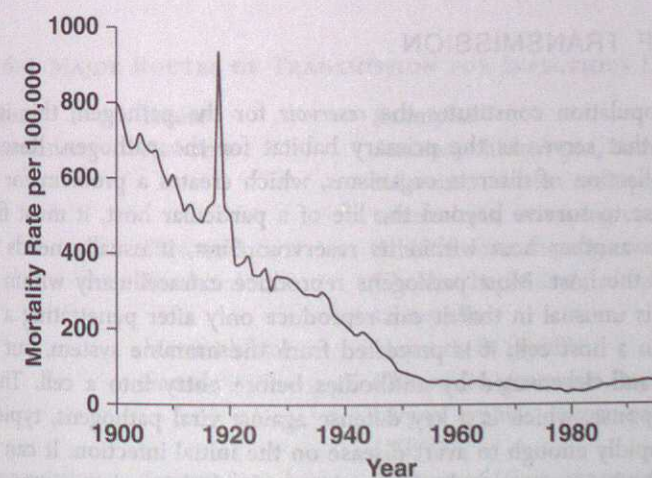


Figure 6-1 Crude death rate from infectious disease in the United States between 1900 and 1996.

Adapted from Armstrong et al.²

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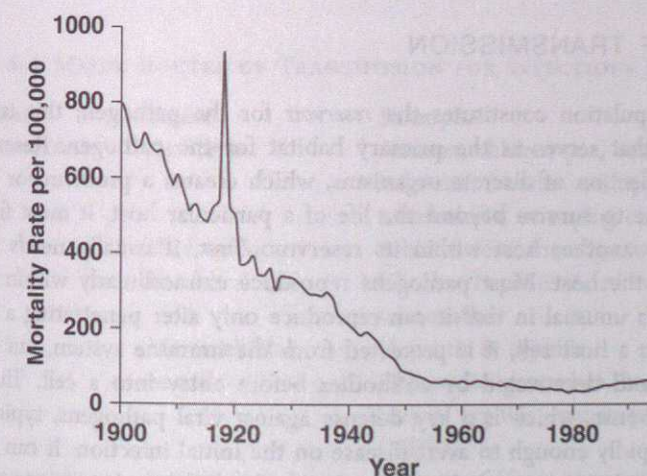


Figure 6-1 Crude death rate from infectious disease in the United States between 1900 and 1996.

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swept the world beginning in 1918 and continuing into 1919. This epidemic may have accounted for more human deaths than any catastrophe humanity has faced, apart from bubonic plague, the notorious Black Death that swept Europe in the 14th century. (In light of this graph, it is understandable that the 2009 outbreak of H1N1 was initially a cause for great concern¹ and fortunate that it turned out to be much less deadly than the 1918 version.) Antibiotics did not come into widespread use in medicine until the mid-20th century, when most of the decline in mortality rates from infectious disease had already occurred.

WHAT MAKES A PANDEMIC?

In Chapter 4, an epidemic was defined as an unusually high occurrence of disease. A *pandemic* is defined in the *Dictionary of Epidemiology*² as "an epidemic occurring worldwide or over a very wide area, crossing boundaries of several countries and usually affecting a large number of people." The World Health Organization (WHO) had a more specific description that it had used for *pandemic influenza*: "An influenza pandemic occurs when a new influenza virus appears against which the human population has no immunity, resulting in several, simultaneous epidemics worldwide with enormous numbers of deaths and illness." Just before WHO announced that the H1N1 influenza of 2009 (swine flu) had become pandemic, it changed its description of pandemic by dropping the phrase "with enormous numbers of deaths and illness." This new description of pandemic was more consistent with the definition quoted from the *Dictionary of Epidemiology*.² It also allowed the WHO to declare a pandemic for a disease that did not have extraordinary mortality and morbidity. The announcement of the pandemic in 2009 led to criticism that the declaration was motivated by ties between the WHO and the pharmaceutical industry, a claim that the WHO denied.³⁻⁵

TYPES OF TRANSMISSION

The host population constitutes the *reservoir* for the pathogen; this is the biologic space that serves as the primary habitat for the pathogen. Reservoirs are usually a collection of discrete organisms, which creates a problem for the pathogen, because to survive beyond the life of a particular host, it must find a way to spread to another host within its reservoir. First, it usually needs to reproduce within the host. Most pathogens reproduce extracellularly within the host, but a virus is unusual in that it can reproduce only after penetrating a host cell. While within a host cell, it is protected from the immune system, but it can be intercepted and deactivated by antibodies before entry into a cell. The specific immune response, which is a key defense against viral pathogens, typically does not occur rapidly enough to avert disease on the initial infection. It can take days for the antibody response to build, so those who lack previous contact are generally susceptible to infection from a virus. After an initial infection, the antibody response is typically rapid enough to prevent subsequent disease or at least to mitigate it, leading to immunity.

To move from one host to another, pathogens have evolved a variety of mechanisms. Pathogens whose infection leads to early death of the host have a more pressing problem, because they may not long survive the death of the host. This problem exerts an evolutionary pressure for the pathogen to spread more efficiently or to become more benign, at least to the extent that it allows the host to survive long enough for the pathogen to be transmitted to a new host.

Table 6-1 lists a variety of mechanisms that pathogens have evolved to move from one human host to another. The most direct of these involve *person-to-person transmission*. Diseases that spread from one person to another, such as measles, are described as *communicable* or *contagious*. The only reservoir for measles virus is humans. It spreads from one infected person to another largely through coughing or sneezing, which produces a cloud of infected droplets. These droplets can be inhaled directly by a susceptible person or spread indirectly after landing on a contaminated surface, where the virus will remain viable for a couple of hours.

Some agents have both human and animal reservoirs, and they spread from person to person by means of a transmitting animal, which is called *vector-borne transmission*. Technically, when pathogens are spread through vectors, the vector represents an intermediate host for the pathogen that is necessary to its life cycle and its transmission. Human malaria is an infection with the *Plasmodium* protozoa, which is transmitted from human to human by certain species of the *Anopheles* mosquito, the vector of malaria transmission. A mosquito that bites an infected person acquires a blood meal that contains infected *Plasmodium* gametocytes, and it can transmit the infection to other people during subsequent blood meals. In rare cases, malaria can spread from person to person without the *Anopheles* vector (eg, through contaminated blood, from a pregnant mother to a fetus), but most transmission occurs through the mosquito vector. Many other infectious diseases, such as yellow fever, Chagas disease, Lyme disease, plague, West Nile encephalitis, and dengue fever are spread by animal vectors. In all these examples, the vectors are arthropods. (Viruses that are transmitted through arthropod vectors are called *arboviruses*, which is short for arthropod-borne viruses.)

Table 6-1 MAJOR ROUTES OF TRANSMISSION FOR INFECTIOUS DISEASE

| Transmission | Route | Examples |
|-----------------------|-------------------|---|
| Direct transmission | Airborne | Anthrax, chicken pox, common cold, influenza, measles, mumps, rubella, tuberculosis, whooping cough |
| | Direct contact | Athlete's foot, impetigo, warts |
| | Fecal-oral | Cholera, hepatitis A, rotavirus, salmonella |
| | Maternal-fetal | Hepatitis B, syphilis |
| | Sexual | Chlamydia, gonorrhea, hepatitis B, herpes, syphilis, human papillomavirus (HPV) |
| Indirect transmission | Intermediate host | Tapeworm (from consuming inadequately cooked pork) |
| | Vector-borne | Bubonic plague, malaria, typhus, West Nile encephalitis, yellow fever |

Diseases that spread from animal reservoirs to humans are called *zoonoses*. Zoonoses may be vector-borne, as with equine encephalitis or plague, or may spread from the animal reservoir directly to humans, as with toxoplasmosis (for which the primary reservoir is cats) and Ebola virus (for which the primary reservoir is thought to be bats). Influenza virus infects humans, birds, and pigs and frequently jumps from one species to another. Rabies is a zoonotic virus that infects all warm-blooded animals. The case-fatality rate from untreated rabies is close to 100%, but despite killing its hosts, the virus is an old one that has spread throughout the world. Like some other pathogens, it causes changes in behavior in infected hosts that are conducive to its transmission. In the case of rabies, it affects the brain directly and leads to hyperexcitability, spasms, and aggressive behavior that can help the parasite spread through bite wounds from infected hosts. Because the disease is transmitted to humans from animal bites but rarely is transmitted from a human host, humans are considered an incidental or "dead-end" host for rabies.

Giardia is a protozoan parasite, a zoonosis that infects many species. It spreads through contaminated water or by oral-fecal transmission. It takes the form of dormant cysts that get excreted in feces and can survive for weeks or months in warm water, from which it may be ingested by a susceptible host. Cholera is another infection that spreads by oral-fecal transmission; its spread through contaminated water was the focus of Snow's landmark investigations in London (see Chapters 4 and 5).

In Chapter 4, two types of epidemic outbreaks were described, *point source* and *propagated*. Person-to-person transmission of a pathogen can manifest as either type of outbreak. The famous outbreak of cholera in Golden Square that Snow investigated was a point-source epidemic, transmitted from one infected person to the population that partook of water from the Broad Street pump. In a propagated epidemic, infection may begin from a single source, but it spreads through propagation in the population, transmitted from many infected people to uninfected people who come in contact with them.

HERD IMMUNITY AND BASIC REPRODUCTIVE NUMBER

For an infection that depends on person-to-person transmission, the relative proportions of immune and susceptible persons in a population can determine whether the infection will take hold in the community or die out quickly. If a substantial proportion of the population is immune from previous experience with the pathogen or from vaccination, an infected person will be less likely to spread the infection to another susceptible person because many of the contacts who might have provided an opportunity for person-to-person transmission will be immune and therefore not susceptible to infection. If enough are immune, the prevalence of the infection will decrease with time and the outbreak will wane until it is extinguished. This situation is described as *herd immunity*. When it exists, susceptible people in the population are protected indirectly by the immunity of the people with whom they interact. The immunity of potential contacts limits the interactions that can expose a susceptible person to infection. Thus, vaccination campaigns protect those who get vaccinated and also confer protection on the unvaccinated.

A key concept in assessing whether an outbreak that is spread by person-to-person transmission will ignite or die out is the *basic reproductive number*, usually written as R_0 . It is the average number of secondary cases that occur from a single index case in a susceptible population in which no interventions are being taken. If the basic reproductive number is less than 1, each case will on average lead to less than one additional case, and the outbreak will die out, unless fueled by external re-infections. The rate at which disease disappears from the population depends on how much below 1 the basic reproductive number is and on the interval between successive generations of infection. If the basic reproductive number is above 1, each case in the early stage of an outbreak produces more than one new secondary case, and the epidemic grows. The speed at which it grows depends on the magnitude of the basic reproductive number for that disease and the time between successive infections.

The reproductive number reflects the biologic potential of the infectious agent and the social intercourse that leads to situations in which transmission might occur. For example, if infected persons are too sick to move about while they are infectious, there may be few contacts and a low reproductive number. The basic reproductive number varies from population to population, because the number of potential contacts differs by population. For the same reason, it also varies by subgroups within a population. The overall basic reproductive number is an average over these subgroups. Even if the basic reproductive number is low, transmission probabilities may vary considerably from person to person, and some social networks within a population may form a subset in which an epidemic spreads rapidly even if the overall basic reproductive number for the total population is low, perhaps even below 1.⁶ A few "superspreaders" such as needle-sharers transmitting a blood-borne infection can suffice to spark an outbreak. Table 6-2 gives some examples of the basic reproductive number for various human diseases that are spread by person-to-person transmission.

Table 6-2 BASIC REPRODUCTIVE NUMBER FOR VARIOUS DISEASES
SPREAD BY PERSON-TO-PERSON TRANSMISSION

| Disease | Primary Mode of Transmission | Basic Reproductive Number |
|---------------------------|------------------------------|---------------------------|
| Measles | Airborne | 15 |
| Pertussis | Airborne droplet | 15 |
| Diphtheria | Saliva | 6 |
| Smallpox | Social contact | 6 |
| Polio | Fecal-oral route | 6 |
| Rubella | Airborne droplet | 6 |
| Mumps | Airborne droplet | 5 |
| HIV/AIDS | Sexual contact | 3 |
| SARS | Airborne droplet | 3 |
| Ebola | Bodily fluids | 2 |
| 1918 influenza (H1N1) | Airborne droplet | 2 |
| 2009 influenza (H1N1) flu | Airborne droplet | 1.5 |

Abbreviations: AIDS, acute immunodeficiency syndrome; HIV, human immunodeficiency virus; SARS, severe acute respiratory syndrome.

The basic reproductive number indicates the potential for spread of an outbreak in a population of susceptibles. In practice, given some immunity (which may come from vaccinations, recovery from the infection during the outbreak, or previous exposure to the same or a similar agent) and given attempts to reduce person-to-person contact after an outbreak begins, the reproductive number that characterizes an outbreak as it develops will be lower than the basic reproductive number. The *effective reproductive number*, R_t , is the value of the reproductive number that takes into account the mix of immunity and social interaction at any point in time as an outbreak progresses. The effective reproductive number changes with time, usually decreasing as immunity spreads among those who have recovered from their infection. While the effective reproductive number remains above 1, an epidemic spreads, but the effective reproductive number eventually decreases to 1 or below as the proportion of susceptible people remaining in the population diminishes or as control measures are implemented. In the long run, R_t will fall below 1, and the epidemic will sputter out, or it will maintain an *endemic equilibrium* at an R_t of 1. In the equilibrium state, the prevalence of infection remains level over time as new susceptibles are added to the population to balance those who acquire immunity. In such an endemic equilibrium, $R_t = 1 = R_0 \times p_s$, where p_s is the proportion of the population susceptible to infection at equilibrium. Therefore, in an equilibrium state one can estimate the basic reproductive number, R_0 , as $1/p_s$.

A basic strategy to reduce transmission and contain an outbreak of a disease spread by person-to-person transmission is isolation of infected persons. By reducing contacts of infectious persons, isolation can limit the spread of an infection, and if applied on a broad enough scale, it can lower the effective reproductive number. A related strategy that has been used since antiquity is *quarantine* (see Chapter 2). The intent of quarantine is to restrict contacts among people who are not yet ill but who have come into contact with infected persons. Like isolation, quarantine can lower the effective reproductive number. The combination of isolating infected patients and quarantining contacts together can be effective in cutting short an outbreak.

This strategy of isolation and quarantine worked well against severe acute respiratory syndrome (SARS), a viral disease that nearly became a pandemic in 2003. The disease rapidly spread from its index location in China to 37 countries, infecting more than 8000 people, with a case-fatality rate of almost 10%. Within months of the first appearance of SARS, the possibility of a calamitous pandemic with a high case-fatality rate seemed like a strong possibility. In Toronto, where it seemed that the spread of SARS was nearly out of control, Canadian officials quarantined more than 23,000 people who had been in contact with SARS cases, about 100 persons for every identified case of SARS. The movement of those under quarantine was restricted until 10 days after their last patient contact. Such stringent methods ultimately contained the epidemic.

SARS was a new disease in 2003, and no vaccine was available. If vaccine is available, a vaccination campaign can contain an outbreak. The basic strategy is to lower the reproductive number from the basic value to an effective reproductive number < 1 , providing sufficient herd immunity to stop the outbreak. In a population in which some people are vaccinated, the effective reproductive number depends on vaccine efficacy and the vaccination coverage of the population. If V_e

GLOSSARY OF KEY TERMS IN INFECTIOUS DISEASE EPIDEMIOLOGY

Communicable: capable of person-to-person transmission.

Generation time: the time interval between one person getting infected and another person getting infected from the first.

Herd immunity: a prevalence of susceptibles in a population low enough so that transmission cannot be sustained.

Immunity: resistance to infection.

Incubation period: the time interval between getting infected and developing symptoms.

Reproductive number: the average number of infected persons resulting from contact with a single infected person. The basic reproductive number is the average number of infections that would be caused by one infected person when everyone else is susceptible. The effective reproductive number is the average number of infections resulting from one infected person given that not everyone is susceptible.

Reservoir: the host population for an infectious agent.

Secondary cases: cases of infection that occur from contact with a primary case.

Secondary attack rate: risk of infection among susceptibles exposed to an infected source.

Susceptibility: at risk of contracting disease (lack of immunity).

Transmission probability: probability of transmission from an infected person to a susceptible person during a contact.

Vector: an animal that transmits disease from an infected person to an uninfected person.

Virulence: the degree to which a pathogen can cause disease and death.

is vaccine efficacy and V_c is vaccine coverage, the proportional reduction in the basic reproductive number will be $(1 - V_e \times V_c)$. The effective reproductive number, R_t , will be $R_0 (1 - V_e \times V_c)$. From this relation, it can be shown that to lower R_t so that it is less than 1, V_c must exceed the following quantity:

$$V_c > \frac{1 - 1/R_0}{V_e} \quad [6-1]$$

When R_0 is large, high coverage and high efficacy are required for vaccination to succeed in curtailing the epidemic. If R_0 is 10 and the vaccine efficacy is 95%, the vaccine coverage must be greater than $(1 - 1/10)/0.95 = 95\%$ to reduce the effective reproductive number below 1. Measles, with a basic reproductive number of 15, requires more than 93% coverage with a vaccine of 100% efficacy to stop an epidemic. For a vaccine with the same high efficacy aimed at preventing infection of a disease for which R_0 is 2, the vaccine coverage need only exceed $(1 - 1/2)/0.95 = 53\%$ to reduce the effective reproductive number below 1. From the inequality in Equation 6-1, we observe that if the vaccine efficacy is less than

$1 - 1/R_0$, even 100% coverage of the population will not be sufficient to lower the effective reproductive number below 1. In this situation, herd immunity cannot be achieved from the vaccine. Although the vaccine would still be valuable in lowering the risk of infection among those who were vaccinated, there would be enough secondary infections to keep the epidemic growing, perhaps until natural immunity lowered the effective reproductive number further.

THE REED-FROST EPIDEMIC MODEL

In 1928, Lowell Reed and Wade Hampton Frost developed a simple deterministic mathematical model to simulate the spread of an outbreak through a susceptible population. The model assumes that the epidemic began with one or few infected people and progressed through a succession of time periods, which correspond to the *generation time*, defined as the time between acquiring an infection and transmitting it. Within each of these time periods, the basic Reed-Frost model assumes that (1) there is random mixing, with contact between infected people and susceptible people within the population during each time period; (2) there is a uniform, fixed probability that a contact between an infected person and a susceptible person would result in transmission; (3) an infection is always followed by immunity; (4) the population is isolated from other populations; and (5) these conditions remain constant with time. Despite these mostly unrealistic assumptions, the model serves as a reasonable teaching tool about the course of an outbreak.

The Reed-Frost model uses the following formula:

$$C_{t+1} = S_t(1 - (1 - p)^{C_t})$$

In this equation, C_t is the number of infected people at time t , C_{t+1} is the number of infected people at time $t + 1$, S_t is the number of susceptible people at time t , and p is the probability that within one time period an infected person will transmit the infection to a susceptible person with whom there is contact. If $S_t \times p$ is above 1, the epidemic grows, and when $S_t \times p$ declines below 1, the epidemic abates.

Figure 6-2 shows the application of a Reed-Frost model to a population of 100 people, all of whom are susceptible except for a single initially infected person. In the upper diagram, the probability of effective contact is set at 4%. Because one person is infected initially, with a 4% probability of transmission on contact, four will be infected after one generation time. This corresponds to an R_0 of 4, a high value that produces an explosive outbreak and infects most of the population within a few generation times. In the lower diagram, the probability of effective contact is set at 1.5%, corresponding to a lower R_0 of 1.5, which leads to a more gradual epidemic that ultimately infects only about 60% of the population.

The Reed-Frost and many other mathematical models of the spread of infection make unrealistic assumptions. For example, the assumption that there is random mixing with contact between infected and susceptible people may be extremely unrealistic, because subgroups of any community form affinities that may well be

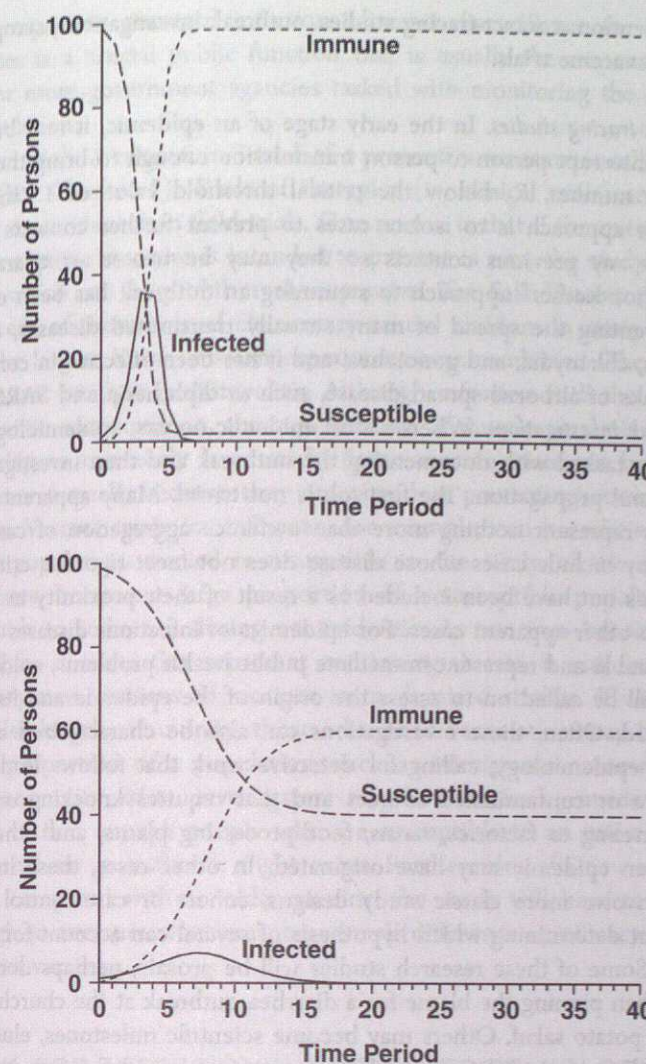


Figure 6-2 Reed-Frost projection of epidemic curve for infected, susceptible, and immune subpopulations among 100 people with one initial infected person and an effective contact probability of 4% (high R_0 in upper panel) and 1.5% (low R_0 in bottom panel). The time scale is measured in generation times.

related to susceptibility. Such was the case in an extended outbreak of measles in Quebec, where more than 95% of the population was vaccinated, but pockets of those who objected to vaccination on religious grounds had numerous contacts with one another and created conditions in which the epidemic could spread over an extended period.⁷

INFECTIOUS DISEASE EPIDEMIOLOGY INVESTIGATIONS

Several types of epidemiologic studies are unique to the investigation of infectious disease or figure more prominently than in other areas. Four types of studies are

worthy of mention: contact-tracing studies, outbreak investigations, seroprevalence surveys, and vaccine trials.

1. *Contact-tracing studies.* In the early stage of an epidemic, it may be possible to interrupt person-to-person transmission enough to bring the reproductive number, R_0 , below the critical threshold value of 1. The most effective approach is to isolate cases to prevent further contacts and to identify any previous contacts so they may be treated or quarantined. This "shoe-leather" approach to stemming an outbreak has been effective in preventing the spread of many sexually transmitted diseases, such as syphilis, chlamydia, and gonorrhea, and it has been effective in containing outbreaks of airborne-spread disease, such as diphtheria and SARS.
2. *Outbreak investigations.* When a local epidemic occurs, epidemiologists are typically tasked with documenting the outbreak and then investigating its origin and propagation. The first job is not trivial. Many apparent disease clusters represent nothing more than a chance aggregation of cases, and they may include cases whose disease does not meet rigorous criteria for diagnosis but have been included as a result of their proximity in time or place to other apparent cases. For epidemics of infectious diseases that are indisputable and represent immediate public-health problems, epidemiologists will be called on to assess the origin of the epidemic and its means of spread. Often, these investigations can also be characterized as shoe-leather epidemiology, calling for detective work that follows leads about infective or contaminated sources and that requires knocking on doors and traveling to factories, farms, food-processing plants, and other spots where an epidemic may have originated. In other cases, these investigations involve more classic study designs, cohort or case-control studies aimed at determining which hypothesis of several can account for an outbreak. Some of these research studies will be prosaic, perhaps doing little more than pinning the blame for a diarrhea outbreak at the church supper on the potato salad. Others may become scientific milestones, elucidating a new disease, as did early studies of acute immunodeficiency syndrome (AIDS), toxic shock syndrome, and SARS.
3. *Seroprevalence surveys.* Seroprevalence surveys are like any other prevalence study, aiming to estimate the prevalence of a characteristic in a population. Like other prevalence surveys, they usually rely on sampling methods to estimate the population prevalence and require a representative sample for the prevalence estimates to be valid. The characteristic of interest is immunity to a specific antigen, which requires obtaining a blood sample to measure antibody response. Getting blood samples from representative cross sections of a population can be challenging. It often is easier to collect samples in the context of delivering health care, although patient populations may differ in the immune status from the general population. Seroprevalence data are invaluable for assessing the vulnerability of a population to existing infectious agents, for finding subgroups that are susceptible to outbreaks, and for setting priorities for vaccination campaigns. Seroprevalence studies may be an important component of surveillance activities that are conducted to monitor the health of a population

with respect to potential infectious diseases. Surveillance for epidemic diseases is a crucial public function that is usually the responsibility of one or more government agencies tasked with monitoring the health of a population.

4. *Vaccine trials.* A randomized trial of a preventive measure is called a *field trial* (see Chapter 5). Trials of therapies (ie, clinical trials) are usually easier to conduct than field trials. One reason is that if the outcome that the preventive measure is intended to prevent is rare, the study must be large, which can be prohibitively expensive. The Salk Vaccine trial, with hundreds of thousands of elementary school children as study subjects, was the largest formal human experiment ever conducted. The aim was to prevent paralytic poliomyelitis. Although infection with the poliomyelitis virus was common, the complication of muscle paralysis was rare, requiring an extremely large study. Some vaccine trials can be successful even if small, because they are aimed at preventing common outcomes. Vaccine trials for influenza, for example, can be relatively small if the population studied is susceptible to the strain of the virus that circulates, because a large proportion of a susceptible population will succumb to influenza during an epidemic. As vaccines become established for diseases that represent continuing threats, it may be difficult to study new versions of vaccines in randomized studies. If vaccination provides lengthy immunity, those who need vaccination may be only a small proportion of a population, such as immigrants or newborns. If herd immunity exists, investigators may have to look outside a population to find enough people who are susceptible to an infective agent and in whom an outbreak might occur. Furthermore, if a new vaccine is being compared with an older vaccine, the study will have to be large enough to measure what may be a small difference in efficacy between the two vaccines.

OUTLOOK FOR INFECTIOUS DISEASE EPIDEMIOLOGY

For a brief time at the dawn of the antibiotic era, it seemed that humans might have found the ultimate defense against infection from bacteria. During the same era, continued progress in the development of vaccines gave rise to hope that viral illness also might be tamed and in some cases eradicated, as was the case for smallpox. With these successes, it looked like infectious disease might become a historical problem. Unfortunately, the high reproductive rate of microorganisms and their ability to mutate have enabled them to evade many of our technologically driven defenses. Widespread and possibly some unnecessary use of antibiotics has produced antibiotic-resistant bacteria. Increasing urbanization and intercontinental travel have added to the risks of communicating infectious illnesses. Social and medical practices that change rapidly have opened new routes of transmission for infectious agents to spread, as illustrated by the spread of human immunodeficiency virus (HIV) through needle sharing, blood banks, and increased sexual contacts. Even good sanitation and hygiene, the most important weapon in the struggle against infectious disease, is unavailable to an appallingly large proportion

of the world's population, and where present, it is easily disrupted by natural disaster or economic instability.

Infectious disease epidemiology is a frontier that has observed two remarkable triumphs that go beyond the good news conveyed by Figure 6-1. One is the eradication from the planet of an age-old human scourge, smallpox. By a combination of vaccination, contact tracing, and other containment methods employing a rapid response to contain any new outbreak, the spread of smallpox was gradually constricted until, in 1977, the last case was reported. With no animal reservoir, smallpox cannot recur in humans, apart from the risk of deliberate spread from biologic samples stored for research purposes. The second triumph is the near-elimination of a second disease, poliomyelitis, currently the focus of a global eradication campaign. In 2009, there were fewer than 1600 cases of poliomyelitis recorded. Control of smallpox and poliomyelitis are major achievements of epidemiology and public health. There is hope that other diseases can also be eradicated. Malaria is one candidate, but eradication has proved challenging. An effective malaria vaccine has been elusive because the life cycle of the multistage *Plasmodium* parasites that cause malaria is complex, the parasite is spread by mosquito, and some forms of *Plasmodium* have a primate reservoir other than humans.⁸

Our vulnerability to infectious agents remains high. Nevertheless, these successes indicate that the prospect of eradication of some infectious diseases and better control of others is a realistic, if ambitious, goal. This combination of vulnerability on some fronts and the hope of success on others ensures that infectious disease epidemiology will remain an important subdiscipline for epidemiologists in the 21st century and beyond.

QUESTIONS

1. Give reasons why crowding can foster the spread of infection.
2. Figure 6-1 displays crude death rates over time. The age distribution of the population was changing over the time scale shown, gradually shifting toward an older age distribution. If age had been controlled so that the curve reflected the change in death rates among people with the same age distribution, would the curve drop more steeply or less steeply than what is shown in Figure 6-1? Comment on the apparent rise in the crude death rate in the past 15 years covered by the graph.
3. Explain the relation between quarantine and the effective reproductive number.
4. The Reed-Frost model is a simplified model of transmission that assumes the population is closed. Suppose that with each generation time there is some migration into and out of the population. Under what conditions would that mixing hasten the transmission of disease, and under what conditions would it slow the transmission?

5. Varicella infection (chicken pox) results in long-term immunity to the virus that causes it, but infected people can experience a recrudescence of their infection, known as *shingles*, years or decades after their initial infection. How does the virus persist in the body over such a long period despite an immune system that is primed to deactivate the virus with specific antibodies?

6. Despite evidence of person-to-person spread, contact tracing was not widely used to control the spread of HIV in the early stages of the epidemic. Give pro and con arguments regarding the desirability of contact tracing to contain the transmission of HIV.

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SUGGESTED READING

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