CHAPTER TWO

EPIDEMIOLOGY OF INFECTIOUS DISEASE: GENERAL PRINCIPLES

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Studies of the epidemiology of infectious diseases include evaluation of the factors leading to infection by an organism, factors affecting the transmission of an organism, and those associated with clinically recognizable disease among those who are infected. Many epidemiologic concepts were originally developed in studies of infectious diseases. Some of these fundamental concepts were applied later to the study of noninfectious disease. Among these concepts are the following:

- The incubation period—Diseases caused by either an infectious agent or a noninfectious agent, such as a toxin or carcinogen, have an intrinsic incubation period after contact with the agent before disease occurs.
- Resistance—Some individuals may have immunity or resistance to infection on a biologic basis, such as from previous infection, immunization, or because of host genetics, and remain uninfected after exposure.

When new epidemics of infectious diseases are described, they are usually first studied and described according to their epidemiologic characteristics. New infectious diseases can be classified according to their epidemiologic, clinical, or microbiologic features. Certainly, knowledge of all of these characteristics is important. However, the epidemiologic features of a disease are of paramount importance for a public health professional or an epidemiologist who is concerned primarily with controlling or preventing the epidemic spread of an infection. On the other hand, a clinician whose primary role is to treat an individual patient may be more concerned with the clinical symptoms or pathophysiology of the disease. For example, an infectious agent that causes secretory diarrhea will be treated empirically with fluid replacement and symptomatic management of the pathophysiology, irrespective of how the infection was acquired or what the organism is. A microbiologist may

be primarily interested in the characteristics of the organism and may try to determine the following:

- How the organism can be isolated?
- How infection can be diagnosed or confirmed in the laboratory?
- Is it possible to prepare a vaccine or treat the infection with an antibiotic?
- What are the essential growth requirements of the organism?

The control, treatment, and prevention of an epidemic usually involves the cooperative efforts of all three groups of specialists: clinicians, microbiologists, and epidemiologists. However, each has a unique orientation and contribution. The perspectives from each of these three areas of study can best be appreciated by considering how infectious diseases are classified by each specialist.

The Classification of Infectious Diseases

Clinicians tend to classify infectious diseases according to their most common or most important clinical manifestation or by the organ systems that are primarily affected. An example of a clinical classification is given in Table 2-1.

The second group of specialists, microbiologists, tend to classify infectious diseases according to the characteristics of the causative organism. An example of a typical microbiologic classification of infectious diseases is shown in Table 2-2.

Epidemiologists usually classify infectious diseases according to two important epidemiologic characteristics—their means of transmission and the reservoir of the organism.

When a new disease appears on the scene, the detailed microbiologic characteristics of the organism usually are not known. The full range of symptoms that may occur after infection often is appreciated only later, after detailed clinical studies of many patients have been carried out. For example, the fact that infection with *Borrelia burgdorferii*, the cause of Lyme disease,

TABLE 2-1 Clinical Classification of Infections

Classification	Infection
Diarrheal diseases	Secretory Invasive
Respiratory diseases	Upper respiratory Lower respiratory
Central nervous system infection	Meningitis (bacterial vs. aseptic) Encephalitis Abscess
Cardiovascular infection	Endocarditis Myocarditis Vasculitis
Sepsis	Disseminated

was responsible not only for the classical skin lesion, erythema chronica migrans (ECM), but also for acute and chronic arthritis, vascular and cardiac disease, and neurologic symptoms, including Bell's palsy and encephalitis, was not appreciated initially. In fact, the full range of clinical manifestations of infection with *B. burgdorferii* is still being defined. Infectious diseases can be classified according to their means of transmission into five distinct categories, as shown in Table 2-3.

The second means for the epidemiologic classification of infectious diseases is according to their major reservoirs in nature. If one is aware of the reservoir of the agent in addition to the means of transmission, it is generally possible to develop a strategy to prevent transmission, even when the microbiologic characteristics of the organism are not known. The demonstration of the water reservoir of cholera by John Snow in London in 1853 preceded the identification of the *Vibrio* cholera by Robert Koch in 1884.[1] The epidemiologic information alone was sufficient to develop public health strategies to

TABLE 2-2 Microbiologic Classification of Infectious Diseases

Classification	Organism
Bacterial	Gram-negative Gram-positive
Viral	DNA virus RNA virus Enveloped vs. nonenveloped viruses
Fungal	Disseminated (biphasic) Localized
Parasitic	Protozoa Helminths Trematodes Cestodes
Prion	Protein

TABLE 2-3 Means of Transmission of Infectious Diseases and Their Characteristic Features

Transmission	Characteristics
Contact	Requires direct or indirect contact (indirect = infected fomite, blood, or body fluid; direct = skin or sexual contact)
Food- or water-borne	Ingestion of contaminated food (outbreaks may be large and dispersed, depending on distribution of food)
Airborne	Inhalation of contaminated air
Vector-borne	Dependent on biology of the vector (mosquito, tick, snail, etc), as well as the infectivity of the organism
Perinatal	Similar to contact infection; however, the contact may occur in utero during pregnancy or at the time of delivery

limit exposure to contaminated water and prevent human infections. Similarly, the demonstration of the importance of human carriers of *Salmonella typhi* as the important reservoir in outbreaks of typhoid fever by Budd in 1858 antedated by 22 years the isolation of the organism in the laboratory by Eberth in 1880. Walter Reed succeeded in transmitting yellow fever by the bite of infected *Aedes aegypti* mosquitoes in 1901. It wasn't until 1928 that Stokes and colleagues isolated the causative virus in the laboratory. In more recent times, investigation of the epidemic at the American Legion convention in Philadelphia in 1976 demonstrated that the outbreak of Legionnaires' disease was due to airborne spread of microorganisms from a contaminated reservoir, the air conditioning system in the Bellevue-Stratford Hotel, and suggested that further infections could be prevented by avoiding exposures to the air in the hotel.[2] The implicated organism, *Legionella pneumophila*, wasn't isolated and characterized in the laboratory until 1978 by McDade and Sheppard at the Centers for Disease Control and Prevention (CDC).

When organisms are classified according to their reservoirs in nature, four general categories are often considered:

1. Human
2. Animal (often called *zoonoses*)
3. Soil
4. Water

Some common examples of infectious diseases classified according to their reservoir are shown in Table 2-4.

Knowledge of the reservoir often is essential prior to devising rational and effective means of preventing transmission of infectious diseases. Prior to John Snow's demonstration that contaminated water was the reservoir of *Vibrio cholerae* in the outbreak in London in the 1850s, the predominant theories were that miasma, or exposure to foul or malodorous air, was the critical exposure leading to infection. However, there were no successful efforts to control the outbreak that were based on the miasma theory.

When Snow demonstrated that attack rates of cholera were highest in those receiving their water from one particular water company and subsequently terminated an epidemic by closing down the pump at one water source, the evidence was persuasive.[1]

TABLE 2-4 Classification of Infectious Organisms by Their Reservoir in Nature

Reservoir	Some Typical Organisms
Human	*Treponema pallidum, Neisseria gonorrhoeae*, HIV, hepatitis B and C virus, *Shigella, S. typhi*
Animals (zoonoses)	Rabies, *Yersinia pestis*, *Leptospira*, nontyphoid *Salmonella, Brucella*
Soil	*Histoplasma capsulatum* (and other systemic fungi), *Clostridium tetani, Clostridium botulinum*
Water	*Legionella, Pseudomonas aeruginosa, Mycobacterium marinum*

In the Philadelphia outbreak of Legionnaires' disease, the critical exposure was to the contaminated air in the hotel. It was especially noteworthy in this epidemic that no secondary cases occurred among the household contacts of ill patients with pneumonia who did not visit or stay in the hotel.[2] Subsequent study of this outbreak and subsequent Legionellosis outbreaks have found that aerosolization of water contaminated with *L. pneumophila*, often from a cooling tower, was the critical exposure leading to infection and disease.[3–5] Studies of water from a variety of sources have found that contamination with various pathogenic species of *Legionella* is quite common, even in the absence of human illness.[6] Human infection usually requires inhalation of a contaminated droplet of a small particle-sized aerosol (less than 5 μ in diameter) so that the organism can reach the lower respiratory system. However, in the case of *Legionella*, procedures to disinfect the reservoir usually are only undertaken when aerosolization is posing a risk of infection and disease to humans. The water can be decontaminated by heating to temperatures above 120°F, and growth of the organism is inhibited below 70°F.[7]

Infectious Diseases Transmitted by More Than One Means

Some organisms may be spread by several different means, depending on the epidemiologic circumstances. Therefore, it is important for an epidemiologist to keep an open mind to detect unusual epidemiologic features of an infection. A few examples of infectious diseases that have been spread by multiple means are described below.

Tularemia

Perhaps a typical example of a disease that can be spread by more than one means is tularemia, which can be acquired by the bite of infected ticks or deer flies,[8] by contact with infected rabbits or other animals during the hunting season,[9,10] or by inhalation of an aerosol[11,12] Also, nosocomial infection among microbiology laboratory workers has been reported from inhalation of infected aerosols of the causative organism, *Francisella tularensis*.[13] Curiously, none of the investigators who have studied epidemics of tularemia have found evidence that human-to-human transmission has occurred.[14]

Plague

Plague, the disease that has been associated with perhaps the most serious and extensive epidemic in human history is caused by the plague bacillus, *Yersinia pestis*. The disease is a zoonotic disease of rodents that is transmitted to humans and other mammalian hosts from infected rodents by rat fleas. Percutaneous inoculation of the plague bacillus in humans initiates inflammation of lymph nodes draining the inoculation site, resulting in bubonic plague. Bloodstream invasion may lead to septicemic plague or to infection of other organ systems, such as the lung or meninges. Involvement of the lungs may result in pneumonic plague, which can then be transmitted from person to person via the respiratory route.

Historically, many epidemics of plague have spread rapidly through populations, causing very high mortality. The earliest description of plague dates from the sixth century AD in Egypt, when the epidemic spread throughout North Africa and into Europe. Epidemic plague reappeared in the Far East in the 1300s and subsequently spread to Europe. During the "Great Plague" epidemic in London, which peaked in August and September 1665, 7000 deaths per week were reported in a population of an estimated 500,000 persons. For unknown reasons, plague gradually disappeared from Europe in the 1700s, and the entire continent was free of plague by 1840.[15] Zinsser considers the disappearance of epidemics of plague from Europe to be one of the great mysteries of the epidemiology of infectious diseases.[16]

However, epidemics of plague have occurred in Asia in the late 1800s and more recently in Vietnam, during the war between 1962 and 1975.[17] An epidemic of plague was reported in India in 1994.[18] Sporadic cases of plague have occurred throughout the American Southwest for the past several decades, related to epizootics in infected prairie dogs.[19,20] The organism was first isolated by Yersin in Hong Kong in 1894.[21] A vaccine is available, but its efficacy in preventing pneumonic plague is unknown.

Anthrax

Anthrax is an infection with *Bacillus anthracis*, a gram-positive spore-forming organism that is a zoonotic disease in herbivorous animals. It can be transmitted to humans from contact with infected animals and has three clinical forms in humans: cutaneous, gastrointestinal, and inhalation anthrax.

The organisms from infected animals most often infect humans by contact with contaminated animal hides or pelts; this disease has been called *woolsorter's disease*.[22] Infection can occur also by inoculation of organisms into the skin during butchering of an infected animal; this type of exposure usually leads to cutaneous anthrax, consisting of a black eschar on the skin with swelling and inflammation of the draining lymphatics. Consumption of meat from an infected animal leads to gastrointestinal anthrax, which has a much higher mortality than does cutaneous anthrax. Inhalation anthrax occurs when an infectious aerosol of *B. anthracis* spores is inhaled and germinates in the pulmonary lymphatic tissues. This form of anthrax is rare, which is fortunate because it usually is rapidly fatal.

An epidemic of inhalation anthrax occurred in persons living in Sverdlovsk, Union of Soviet Socialist Republics, in April and May 1979. There were at least 96 cases and 66 deaths. The outbreak also affected cattle within 50 km of the city. Interestingly, Sverdlovsk was known to have a military facility that was suspected of manufacturing biologic weapons, including anthrax spores, for potential use in warfare. Initially, the Soviet authorities maintained that this outbreak was from gastrointestinal exposure due to the consumption of contaminated meat from cattle that had died of anthrax. However, in 1992, Meselson and colleagues visited the site of the epidemic and were able to conduct an epidemiologic investigation, together with Russian scientists. Their study found that all of the human cases were living or working in a narrow belt south of the city on the day the outbreak occurred.[23] Furthermore, the animal deaths also occurred in this belt, up to 50 km distant (Figure 2-1). The wind pattern on the day of the outbreak could explain the geographic

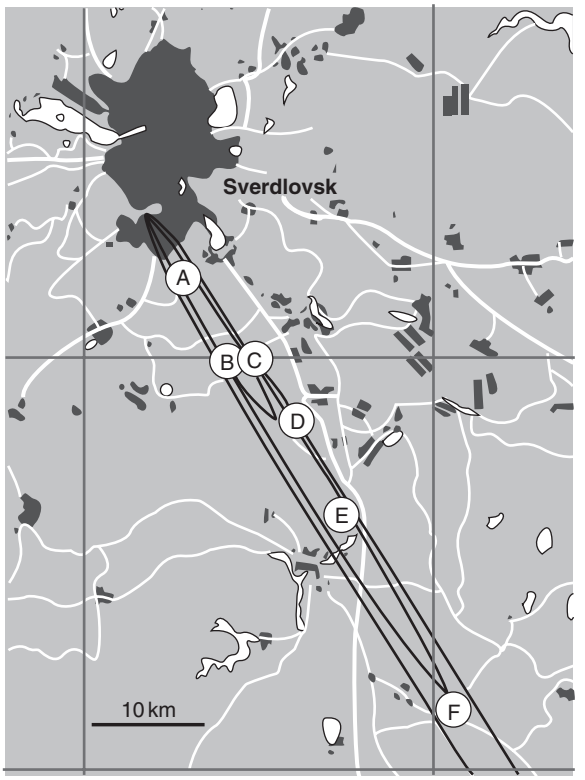

FIGURE 2-1 Russian villages with animal anthrax. Six villages where livestock died of anthrax in April 1979 are shown. Settled areas are shown in gray, roads in white, and calculated contours of constant dosage in black.

distribution of cases. Subsequently, evidence was discovered that many of the human cases had pneumonic anthrax. They concluded that this outbreak, the largest outbreak of human inhalation anthrax ever recorded, was due to an infectious aerosol emanating from the military facility. One very interesting finding in their study was that human cases continued to occur for up to 6 weeks after this point source exposure. Apparently, spores were inhaled and continued to germinate and cause disease for several weeks after they were inhaled. This outbreak has raised considerable concern among scientists and policy makers about the potential for the use of aerosolized *B. anthracis* spores as an agent of biologic terrorism. Indeed, these fears were confirmed in 2001 when an outbreak of 22 cases of anthrax occurred in the United States from intentional contamination of the US mail delivered to a number of persons by the US Postal Service. This outbreak is described in detail in the chapter on emerging infections.

Rabies

Rabies is a nearly uniformly fatal infection of the central nervous system that is almost always transmitted by a bite from an animal infected with the rabies virus. Historically, rabies has nearly always been acquired by a bite from an infected dog, skunk, fox, bat, or other animal. It has been regarded

as a typical contact-transmitted infection, in that percutaneous inoculation of rabies virus by a bite is usually required. Nevertheless, a few persons have developed rabies from exposure to infected aerosols in caves harbored by many infected bats.[24] Also, rabies has occurred in a laboratory worker who was exposed to an infectious aerosol[25] and in persons who have received corneal transplants from a donor who died of undiagnosed rabies.[26] In recent years, in the United States, only 2–3 cases have occurred annually; however, reported bite exposures in these cases has been unusual. Of the 32 cases of rabies that were diagnosed in the United States between 1980 and 1996, 25 (78%) had no history of a bite exposure.[27] Some of these non-bite-transmitted cases in the United States have been in persons exposed in the same room (or closed space) to an infected bat; presumably, the transmission in these cases was by aerosol. Genetic analysis of the viruses has shown that 17 (53%) of these cases in the United States were related to rabies viruses found in insectivorous bats.

Brucellosis

Brucellosis is an infectious disease of humans acquired through contact with an infected animal (i.e., a zoonosis). Four species of *Brucellae* have infected humans: *B. abortus* (from cattle), *B. melitensis* (from goats or sheep), *B. suis* (from pigs), and *B. canis* (from dogs). Human infections with the two other known species, *B. ovis* (from sheep) and *B. neotomae* (from desert wood rats), have not been reported. Clinically, the most serious human infections are seen with *B. melitensis*. However, in the early decades of the 1900s infections with *B. abortus* were common, and these infections often were acquired by the consumption of contaminated milk from infected cows. However, after World War II, the US Department of Agriculture (USDA) undertook a campaign to eliminate milk-borne brucellosis as a human health problem in the United States. The program included testing of cattle for *B. abortus* and slaughtering of infected animals or animals from infected herds, and pasteurization of all milk and dairy products.[28] This program was quite successful. More than 6000 cases of human brucellosis were reported each year at the start of this program; the rate was 4.5 cases per 100,000 population in 1948. In the 1990s, only about 100 cases per year were reported; 0.05 cases per 100,000 population were reported in 1993. Furthermore, in recent years, the cases usually had an occupation that directly exposed them to infected animals, such as slaughterhouse workers, farmers, or veterinarians. Brucellosis in these workers was acquired by direct contact with infected animals, not through consumption of infected milk. Also, *B. suis* infections from infected pigs have become proportionally more common, because the brucellosis control program was directed at eliminating the disease in cattle.

1 *Transmission of Microbial Agents by Transfusions*

There is evidence that several microbial agents can be transmitted by blood transfusion or contaminated injection if exposure occurs during a time when the organisms are present in the blood stream. Hepatitis B virus, hepatitis C virus, and HIV are commonly transmitted by the transfusion of blood or blood products. *Trypanosoma cruzii*, a protozoan parasite that causes Chagas'

disease, is usually transmitted to humans by the bite of a reduviid bug but can be transmitted by blood transfusion from a carrier.[29] Malaria usually is caused by the transmission of one of four species of *Plasmodium* parasites by the bite of an infected female *Anopheline* mosquito, but it can also be transmitted by blood transfusion or to an infant by perinatal transmission. Hepatitis A virus is generally transmitted by ingestion of contaminated food or water but can be transmitted by blood transfusion during the brief viremic stage early in the infection.

Perinatal Infections

Infections of an infant may be acquired from the mother in utero via placental transfer, during passage through the birth canal, or in the postpartum period.

Rubella

The dramatic effect of rubella infections during the first trimester of pregnancy in producing congenital anomalies in the infant was first reported by Sir Norman Gregg following an outbreak of rubella in Australia in 1940.[30] Gregg noted ocular defects and cardiac lesions in the affected infants. Subsequently, these findings were confirmed by studies during rubella outbreaks in Australia, the United States, and the United Kingdom. These studies further defined the congenital rubella syndrome (CRS) from intrauterine exposure to rubella during the first trimester of pregnancy to include cataracts and other ocular abnormalities, cardiac defects, deafness, microcephaly, and mental retardation. Infants exposed during the first trimester of pregnancy have a 90% risk of developing congenital rubella syndrome; during the early second trimester, the risk of congenital abnormalities declines to 20–40% and often involves only deafness.

In 1962, the rubella virus was isolated by investigators at Harvard University[31] and independently by scientists at the Walter Reed Army Institute of Research.[32] Shortly thereafter, in 1964, a major epidemic of rubella and CRS occurred in the United States.[33] An attenuated live rubella virus vaccine was developed and licensed in the United States in 1969.[34] Subsequently, congenital rubella infections have become rare in the United States, due to routine immunization of infants and screening and selective immunization of susceptible women of childbearing age.

Cytomegalovirus

Cytomegalovirus (CMV) infections during the first trimester of pregnancy are known to lead to congenital malformation, especially of the central nervous system. Cytomegalovirus was first isolated in human fibroblast cultures in 1956.[35–37] It is possible to screen pregnant women for susceptibility to infection during pregnancy. Epidemiologic studies suggest that CMV infection may occur in about 1% of all US births, or about 40,000 infants annually.[38] However, in most instances, these infections are asymptomatic. A national surveillance registry was established in the United States in 1990 by the CDC to monitor congenital CMV infections.[39] The most common clinical

manifestation reported was petechiae, observed in 50% of cases, which was often accompanied by hepatosplenomegaly, intracranial calcification, and thrombocytopenia.

Herpes Simplex Virus

In contrast to CMV and rubella, in utero infection with herpes simplex virus (HSV) is rare, and when it does occur, it is most likely to lead to a miscarriage, rather than a congenital malformation. However, infants can be infected when passing through the birth canal if the mother has an active infection, especially with HSV type 2 (HSV-2), which causes recurrent genital tract infection. When the mother has an active HSV infection at the time of delivery, the infant can develop a generalized infection, which is quite serious. The risk to the newborn is higher when the mother has a primary HSV infection than when the HSV is a recurrence; the risk to the newborn is about 40% when exposed to a mother with primary infection, compared with 2–5% when the mother has a recurrent infection. In the latter situation, the infant's risk is modified by maternal passive transfer of antibodies to HSV-2 and by lower maternal viral load. Cesarean section is recommended to prevent neonatal herpes in children born to women with active HSV at the time of delivery. However, most cases of neonatal HSV occur where the mother was not identified as having active HSV infection. For example, during an 18-month hospital-based surveillance study, CDC identified 184 cases of neonatal herpes but only 22% of the mothers had a history of genital HSV infection, and only 9% had lesions at the time of delivery.[40]

Toxoplasmosis

Congenital infection with *Toxoplasma gondii* occurs when a pregnant woman develops infection, especially early in pregnancy. Clinical manifestations in the infant at birth include a maculopapular rash, generalized lymphadenopathy, hepatomegaly, splenomegaly, jaundice, or thrombocytopenia. Also, the infant can develop meningoencephalitis with cerebrospinal fluid abnormalities, hydrocephalus, microcephaly, chorioretinitis, and/or convulsions. However, congenital infection is usually asymptomatic at birth, although sequelae can become apparent several years later. Sequelae of congenital toxoplasma infection include mental retardation and learning disability. Also, ocular toxoplasmosis most often results from reactivation of a congenital infection, but it can occur from an acquired infection, as well. Ocular toxoplasmosis usually occurs among adults.

Syphilis

Syphilis is caused by infection with the spirochete, *Treponema pallidum*. Syphilis is usually transmitted sexually but can be transmitted by the perinatal (congenital) route by infection through the placenta, especially in the second and third trimester, or, more rarely, transmission can occur during delivery by contact of an infant with the mucosa of a woman with primary or secondary syphilis during the birth process. Congenital syphilis can be asymptomatic or it may manifest as multisystem involvement, including osteitis, hepatitis, lymphadenopathy, pneumonitis, mucocutaneous lesions,

anemia, and hemorrhage. Late manifestation may involve the central nervous system, bones, teeth, and/or eyes. Rates of congenital syphilis parallel the rates of primary and secondary syphilis in women and can be prevented by treatment of infected pregnant women with penicillin, to which the organism is uniformly sensitive. Rates of congenital syphilis have increased in the late 1980s and early 1990s, in part related to the epidemic of crack cocaine use in the United States.[41]

Because newborns infected with each of these agents have similar clinical symptoms, pediatricians often consider all of them in the differential diagnosis of perinatal infections. The syndrome of congenital infection is often referred to by the abbreviation *TORCHS* to signify the most common etiologies: toxoplasmosis, rubella, CMV, HSV, and syphilis.

Hepatitis B Virus

Women who are carriers of hepatitis B virus (HBV) may transmit the virus to their infants in utero or at the time of birth (peripartum). Infection of a newborn with HBV carries a very high risk of chronic infection, with the possibility of subsequent chronic active hepatitis, cirrhosis, or liver cancer when carriage persists for decades. Most perinatal transmission of HBV can be prevented by screening pregnant women for HBsAg and administering hepatitis B immunoglobulin and a course of HBV vaccine to the infants of HBsAg carriers, beginning immediately after birth.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is an important viral infection that can be transmitted perinatally from an infected woman to her newborn infant. Worldwide, the number of infected infants born each year in the 1990s was estimated to be about 500,000.

Although the risk of the prenatal transmission of HIV can be reduced to 5–10% or less by screening pregnant women and treating them with antiviral drugs, perinatal transmission still commonly occurs in sub-Saharan Africa. The various reported studies and research strategies to reduce perinatal HIV transmission are discussed in detail in the chapter on HIV.

Other Infectious Agents

The most important infectious diseases that are transmitted by the perinatal route are discussed above; however, there is some evidence of transmission of several other agents, such as parvovirus B-19, varicella-zoster virus, and others. The most common agents incriminated in perinatal infection and the effects of perinatal infection with these agents on the fetus and newborn infant are listed in Table 2-5.

Epidemiologic Characteristics of Infectious Diseases

Incubation Period

The incubation period of an infectious disease is the time between exposure to an infectious agent and the onset of symptoms or signs of infection. Each

TABLE 2-5 Effects of Transplacental Fetal Infection

	Effect of Infection on the Fetus and Newborn Infant			
	Intrauterine Growth Retardation and Low Birth Weight	Developmental Congenital Anomalies	Developmental Congenital Disease	Persistent Postnatal Infection
Organism or Disease	Prematurity			
Viruses Rubella	–	+	–	++
Cytomegalovirus	+	+	+	+ –
Herpes simplex	+	–	–	+ +
Varicella-zoster	–	(+)	–	+ –
Mumps	–	–	–	(+)–
Rubeola	+	–	–	+–
Vaccinia	–	–	–	+–
Smallpox	+	–	–	+–
Coxsackieviruses B	–	–	(–)	+ –
Echoviruses	–	–	–	– –
Polioviruses	–	–	–	– –
Influenza	–	–	–	—
Hepatitis B	+	–	–	+ +
Human immuno deficiency virus	(+)	(+)	(–)	+ +
Lymphocytic chorio meningitis virus	–	–	–	+ –
Parvovirus	–	–	(+)	–

Notes: +, evidence for effect; –, no evidence for effect; (–), association of effect with infection has been suggested and is under consideration.

infectious disease has a typical incubation period that requires multiplication of the infectious agent to a threshold necessary to produce symptoms or laboratory evidence of infection, such as antibodies, viral isolation, and nucleic acids in the host. The incubation period for infectious diseases shows some variation, which occurs for a variety of reasons, including the dose or inoculum of the infectious agent, the route of inoculation, and the rate of replication of the organism. Even when numerous persons are exposed at the same time to a similar inoculum of the same strain of an infectious agent, such as consumption of food contaminated with *Salmonella* at a picnic, the length of the incubation period varies between individuals. A plot of the incubation period for persons exposed at the same time usually follows a log normal distribution. The antilogarithm of 1 standard deviation from the mean log incubation period has been referred to by Sartwell as the *dispersion factor.*[45] The dispersion factor multiplied by the mean log of the incubation period will define an interval above which 16% of the periods will fall, and the mean divided by the dispersion factor will define the period below which 16% will occur. Even diseases with very long incubation periods have been shown to follow similar patterns of distribution of their incubation periods. A recent study of the incubation periods of AIDS found that a log normal distribution reasonably described the incubation period of this disease as well.[46]

The usual ranges of the incubation periods for a number of infectious diseases are shown in Figure 2-2. These incubation periods range from 6 to 12 hours for *B. cereus* and staphylococcal food poisoning to 5–10 years for AIDS and leprosy. The extrinsic incubation period applies to vector-borne infections; it is the time that a vector-borne agent requires for maturation to infectivity in the vector before it becomes infectious to humans. The extrin-

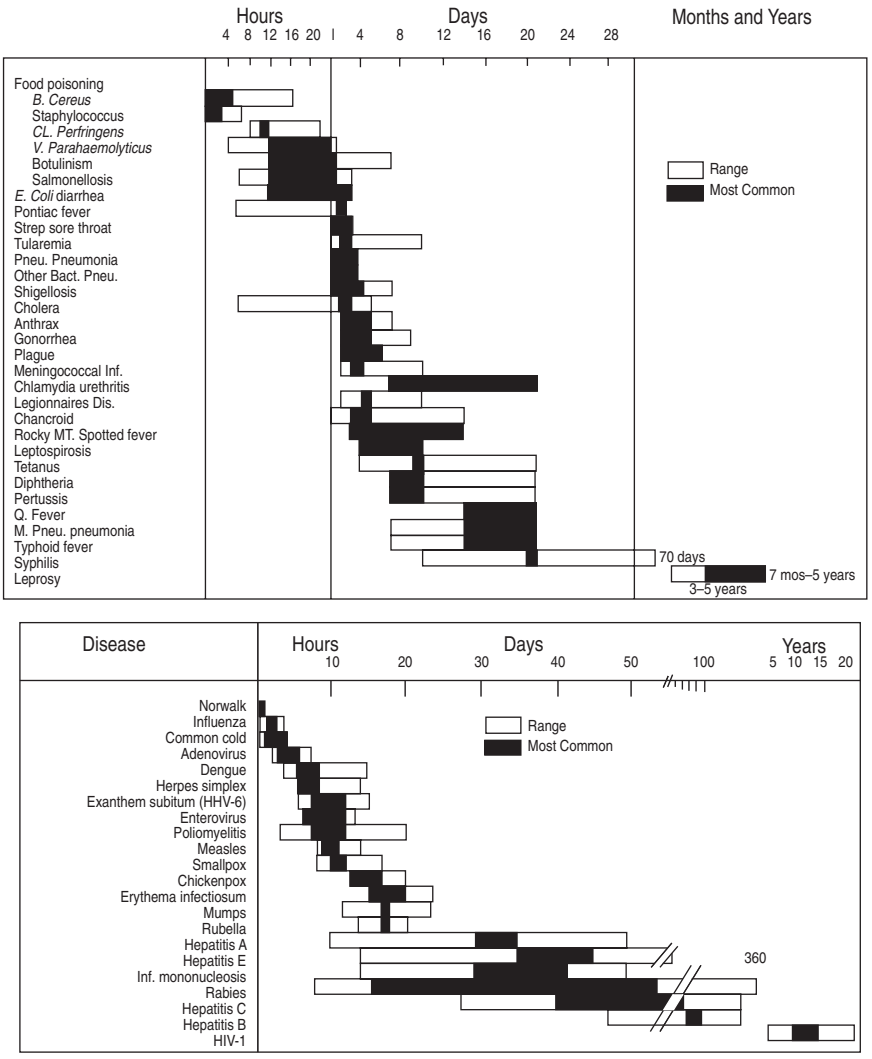

FIGURE 2-2 Incubation periods of common bacterial diseases (*top panel*) and viral diseases (*bottom panel*).

sic incubation period also has a medium and range that are unique to each organism. Also, the extrinsic incubation period can be affected by environmental conditions. For example, when *A. aegypti* mosquitoes were infected with dengue type 2 virus and held at 30°C, the mean extrinsic incubation period before they become infectious was 12 days, whereas between 32° and 35°C, they became infectious after only 7 days.[47] The extrinsic incubation periods for various species of *Plasmodium* are discussed in more detail in the chapter on malaria.

Biologic Characteristics of the Organism

Infectivity

Infectivity is defined as the ability of an agent to cause infection in a susceptible host. The basic measure of infectivity is the minimum number of infectious particles required to establish infection. In diseases spread from person to person, the proportion of susceptible individuals who develop infection after exposure—the secondary attack rate—is a measure of the infectivity of an organism (see Table 2-6 below).

Pathogenicity

Pathogenicity refers to the ability of a microbial agent to induce disease. Diseases such as rabies, smallpox, measles, chicken pox, and rhinovirus colds have high pathogenicity. Others, such as polio and arbovirus (mosquito-borne) infections, have low pathogenicity.

Virulence

Some dictionaries use the terms *virulence* and *pathogenicity* interchangeably. However, it is useful to consider them to be separate properties of an infectious agent. *Virulence* can be defined as the severity of the disease after infection occurs. Although smallpox and rhinoviruses both usually cause symptoms (both are pathogenic), smallpox infections are much more virulent. Virulence can best be measured by the case fatality rate or as the proportion of clinical cases that develop severe disease. It is possible to classify organisms based on their infectivity, pathogenicity, and virulence. Only a few diseases, such as smallpox, airborne anthrax, and Ebola virus, will be classified as ranking high in all three characteristics. Several diseases are ranked by these characteristics in Table 2-6.

TABLE 2-6 Ranking of Infection by Infectivity, Pathogenicity, and Virulence

Severity*	Infectivity (Secondary Attack Rate = Ill/Number Exposed)	Pathogenicity (Illness Rate = Ill/Number Infected)	Virulence (Severe/Fatal Cases) Total Cases
High	Smallpox Measles Chicken pox	Smallpox Rabies Measles Chicken pox Common cold	Rabies Smallpox Tuberculosis Leprosy
Intermediate	Rubella Mumps Common cold	Rubella Mumps	Poliomyelitis Measles
Low	Tuberculosis	Poliomyelitis Tuberculosis	Measles Chicken pox
Very low	Leprosy	Leprosy	Rubella Common cold

*The "severity" of an infection varies by how it is being measured.

It is important to recognize that these properties of an infection may change over time under different circumstances. At one time, syphilis and streptococcal infections were highly virulent infections with high mortality rates, but these diseases are now much less virulent. Changes in the epidemiologic characteristics of infectious diseases will be discussed in greater detail later in this chapter and elsewhere in this book.

Immunogenicity

Immunogenicity is the ability of an organism to produce an immune response after an infection that is capable of providing protection against reinfection with the same or a similar organism. Some organisms, such as measles, polio, HBV, or rubella, lead to solid, lifelong immunity after an infection. Others, such as *Neisseria gonorrhoeae* or *Plasmodium falciparum*, are weakly immunogenic, and reinfection commonly occurs. Studies of the antigens that produce protective immunity after natural infections often have led to the development of effective vaccines. It should be noted that some microorganisms may provoke an immune response that is not protective from future infections. In a sense, they are immunogenic. However, sometimes these immune responses even may be deleterious to the host. Several types of group A streptococci can provoke an immune response that leads to glomerulonephritis or acute rheumatic fever because of cross-reactive antibodies elicited in response to the streptococcal infection that react with endocardial or glomerular basement membrane antigens. In other instances, antibodies may occur that are markers of a previous or current infection but do not provide immunity to the organism or terminate an ongoing infection. These antibodies are often called *binding antibodies*, and they react to nonneutralizing antigens (or epitopes) of the organism. Examples of antibodies of this type are found in patients with hepatitis C virus infection, HIV infection, and HSV-2 infection. Persons with these antibodies have been or are infected with the virus and have antibodies but are not immune.

Inapparent Infections

An inapparent infection is an infection that can be documented by isolation of an organism by culture, demonstration of nucleic acid by polymerase chain reaction (PCR) amplification, or by demonstrating a specific immune response in a person who remains asymptomatic. The proportion of individuals with asymptomatic or clinically inapparent infections is a measure of the pathogenicity of the organism, as defined above. Inapparent infections are quite common in many infections and may play an important role in the propagation of an epidemic in some circumstances. The proportion of infected individuals who do not develop symptoms varies with different organisms. For example, most polio infections are inapparent. Also, inapparent nasopharyngeal carriage of meningococci is quite common during an epidemic especially. Identification and treatment of carriers of meningococci or *Staphylococcus aureus* have been shown to help control epidemic transmission, because healthy carriers may play an important role in transmission. In the United States, persons who convert their tuberculin skin test and are

infected but asymptomatic carriers of *Mycobacterium tuberculosis* are often treated to prevent clinically active tuberculosis from developing later in their life and subsequent spread of infection to their contacts. On the other hand, inapparent infections with some organisms are quite rare. Most persons with measles, varicella, smallpox, or hanta virus infection are symptomatic. The proportion of infections that are symptomatic is of considerable importance in understanding the transmission during an epidemic and in designing methods to control epidemic or endemic transmission. The proportion of infections that are clinically inapparent among individuals infected with some important organisms is shown in Table 2-7.

The Carrier State

The epidemiologic importance of the asymptomatic carrier in the transmission of infectious diseases has been recognized for some time. An early classic example was an Irish cook in New York City in the early 1900s, Mary Mallon, who became known as "Typhoid Mary." She was quite healthy but had worked as a cook in many homes where the residents developed typhoid fever after she was hired. Eventually, 53 cases of typhoid fever were traced to her. After she was located and cultures of her stool consistently grew *S. typhi*, she was confined and not allowed to work in food service between 1907 and 1910. After her release, she disappeared and changed her name. Two years later, outbreaks of typhoid fever involving over 200 persons were detected in hospitals in New York and New Jersey that were

TABLE 2-7 Subclinical/Clinical Ratio in Selected Viral Infections (Inapparent/Apparent Ratio) 4

Virus	Clinical Feature	Age at Infection (Years)	Estimated Subclinical/Clinical Ratio	Percentage of Infection with Clinical Features
Poliomyelitis	Paralysis	Child	±1000:1	0.1–1
Epstein-Barr	Heterophil-positive infectious mononucleosis	1–5	>100:1	1
		6–15	10–100:1	1–10
		16–25	2–3:1	35–50
Hepatitis A	Jaundice	<5	20:1	5
		5–9	11:1	10
		10–15	7:1	14
		Adult	2–3:1	35–50
Rubella	Rash	5–20	2:1	50
Influenza	Fever, cough	Young adult	1.5:1	60
Measles	Rash, fever	5–20	1:99	95
Rabies	CNS symptoms	Any age	0:100	100

traced to her.[48] This remarkable story illustrates the potential importance of the carrier state in the transmission of typhoid fever. Patients infected with *S. typhi* may carry the organism in their gall bladders and excrete the organism in their stool for many years. Generally, antibiotic therapy is ineffective in curing their infections, but many chronic carriers can be cured by cholecystectomy.[49]

Another, more modern example is that of "patient zero," who was at the center of a large cluster of men who developed Kaposi's sarcoma (KS), with or without *Pneumocystis carinii* pneumonia (PCP), in 1980–1981. This patient was a male homosexual flight attendant who had visited several large US cities. He had sexual contact with all of the men who later became ill. This cluster of cases of KS and PCP was one of the early outbreaks of AIDS in the United States.[50] The carrier state may be of epidemiologic importance in any infectious disease that is transmitted from person to person. However, the average length of the carrier state, the site of replication and infectivity of the organism, and the usual means of spread determine the epidemiologic importance of asymptomatic carriers.

Outbreaks have been documented from chronic carriers in the respiratory tract, stool, genital tract, or blood. Nosocomial transmission from hospital workers to patients, from one patient to another, or from patients to health care workers is common. Currently, transmission of antibiotic-resistant staphylococci by healthy carriers of these organisms is of major concern in hospitals in the United States. Patients who are chronic carriers of hepatitis B virus pose a significant risk to health care workers. As a result, use of HBV vaccine is routinely recommended for health care professionals who are likely to be exposed. These issues are covered in more detail in the chapter on nosocomial infection.

Transfusion-Transmitted Infection

The transmission of infections by transfusion has received increasing attention in the last 20 years. Although transfusion-transmitted HBV was recognized for several decades, the introduction of screening of donors for HBsAg in 1973 reduced this risk. Subsequently, it became apparent that after screening of blood donors for hepatitis virus was introduced, posttransfusion hepatitis declined to about half of the previous rate but was not eliminated. The hepatitis C virus was identified and screening implemented in 1990. Also, the occurrence of HIV infection and AIDS among transfusion recipients and hemophiliacs has highlighted the risks of the transmission of infection by transfusion of blood or blood products from healthy carriers.

Currently, blood donors undergo extensive questioning about their risks to a variety of infectious agents, and they are screened for the presence of several pathogens. Pooled plasma products also undergo several viral inactivation steps and are heat-treated prior to their use. Nevertheless, the list of agents that may possibly be transmitted by the transfusion of blood or blood products continues to expand (Exhibit 2-1).

Exhibit 2-1 Infections Transmitted by Transfusion

- Viruses
  - HIV, HTLVI/II
  - HBV, HCV, HAV (rare)
  - Parvovirus B-19
  - CMV
  - KSHV (HHV-8) (unproven)
  - Others
- Bacteria
  - *T. pallidum* (rare)
  - *Y. enterocolitica*
  - Various gram-positive organisms by platelet transfusion (especially)
  - *Ehrlichea* (rare)
- Parasites
  - *Trypanosoma cruzii*
  - *Plasmodium* species
  - *Babesia necrotica*
- Other agents
  - New variant Creutzfeldt-Jakob disease prion

The Host–Parasite Relationship

Patterns of Natural History

After infection occurs, the subsequent course or natural history of an infection can be quite variable. Many infections are characterized by acute symptoms, some of which may be severe and even terminate fatally. In some infections, the proportion of patients with asymptomatic or clinically inapparent infections varies, but once the acute phase is over, the patient is immune to reinfection with the same agent. The common childhood contagious diseases, such as measles, mumps, and rubella, are characterized by this type of natural history.

In other infections, some patients may develop chronic or recurring infection, and others may recover and develop lasting immunity. Hepatitis B virus and herpes virus types 1 and 2 typify this type of natural history. Infection with some agents may lead to chronic sequelae, due to an autoimmune reaction or chronic tissue damage that occurs after the acute infection has subsided and without persistence of the organism or chronic infection. Poststreptococcal glomerulonephritis or rheumatic fever are typical of this type of natural history.

Some infectious agents may recur or relapse, even after the acute infection has resolved without sequelae. Typical of this pattern is HSV-1 and HSV-2, varicella-zoster virus, and cytomegalovirus infections. Some infections may become chronic, with a variable proportion leading to progressive tissue damage at the primary site of the infection. Typical of this pattern is hepatitis C virus, HBV, and HIV.

Finally, some infections may become chronic and eventually lead to cancer in the target organ of the infection. Typical of this type of infection are human papillomavirus, HBV, and *Helicobacter pylori* infections. Infections that often exhibit each of these various natural history patterns are listed in Table 2-8.

It has been estimated by the World Health Organization (WHO) that greater than 15% of human cancers worldwide are caused by chronic infections. The proportion and types of human cancers associated with infectious agents are shown in Table 2-9.

TABLE 2-8 Natural History Patterns of Some Important Infectious Diseases

Natural History	Disease
Acute with recovery and long-term immunity	Measles, mumps, rubella, polio, diphtheria
Acute with some chronic carriers	HBV, HSV-1 and HSV-2, V2V, *Chlamydia trachomatis* infections
Acute disease, chronic sequelae without carrier state	Group A streptococcal (ARF, AGN), syphilis, Lyme disease
Chronic carriers common (or usual)	HIV, HBV, HSV-2, HPV, HCV, *H. pylori* infections, *Opisthorchis viverrini*, *Schistosoma* infections
Chronic carriers may develop cancer	HBV—Hepatocellular CA HCV—Hepatocellular CA HPV—Cervical or laryngeal CA *H. pylori*—Gastric CA HTLV-1—T-cell leukemia EBV—Nasopharyngeal carcinoma HHV-8—Kaposi's sarcoma Opisthorchis—Cholangiocarcinoma

TABLE 2-9 Infection and the Burden of Cancer Worldwide (1990)

Cancer	No. of Cases	Agent	% of Total Cancers
Stomach	504,928	*H. pylori*	5.3
Cervix, vulva	447,400	HPV	4.8
Liver	398,600	HBV, HCV	4.3
Lymphoma	46,779	EBV	0.5
Kaposi's sarcoma	43,525	HIV, HHV-8	0.5
Bladder	10,249	*Schistosoma hematobium*	.1
Leukemia	2,662	HTLV-1	.1
Cholangiocarcinoma	808	Liver flukes (microns)	.1
Total infection-related cancers	1,454,951		15.6
Total no. of cancers	9,327,165		

The Immune Response to Infection

A detailed discussion of the immune responses to infection is well beyond the scope of this chapter. The topic is covered in the chapter on immunology. However, it might be useful to provide a very brief overview to introduce some concepts and nomenclature relative to the immune responses to infection.

Protection against infection consists of both specific immune responses against particular pathogens and nonspecific defenses directed against organisms or foreign antigens. Several compounds present in the normal intact skin, including lipids, lipoproteins, and peptides, are toxic to many organisms. Lysozyme in the tears and several proteins in the oral cavity have bactericidal activity. The acidic pH of the stomach is lethal to moderate doses of many enteric pathogens. The normal ciliary activity of the respiratory tract and the mucous layer coating the bronchus and bronchioles are an important first line of defense against respiratory organisms. The low pH of the vagina serves as a first line of defense against many sexually transmitted pathogens. Furthermore, natural killer (NK) cells and cells of the monocyte-macrophage lineage can provide some nonspecific defense against a pathogen. However, the immune responses generated by cells and antibodies that have been stimulated to respond to a specific pathogen usually are more effective.

The immune system consists of a few main classes of cells and a large variety of cell subsets. Lymphocytes provide direction for the main activities of the immune system and govern the nature of the immune response. Those that originate in the bone marrow are called *B lymphocytes*; those that originate in or traffic through the thymus are called *T lymphocytes*. Other cells of the immune system include circulating monocytes or macrophages, tissue macrophages, dendritic cells, Langerhans cells, NK cells, mast cells, eosinophils, and basophils. Granulocytes are involved in phagocytosis of bacterial pathogens, and eosinophils are involved in the reaction to parasitic pathogens and in allergic and autoimmune reactions.

B Lymphocytes and Humoral Immunity

The B lymphocytes are responsible for humoral immunity. These cells produce antibodies in the form of immunoglobulins that are reactive with foreign antigens. Five different isotypes of antibody are produced by B cells, namely, IgM, IgD, IgG, IgE, and IgA. Generally, the acute response to infection is characterized by a predominance of IgM antibodies that switch later to an IgG predominance. This pattern is useful in differentiating a recent, as in within the past 3–6 months, from a more remote infection. For example, persons with IgM antibodies to hepatitis A virus (HAV) or the core antigen of HBV have had their primary HAV or HBV infections in the past 6 months. Persons with only IgG antibodies to HAV or HBV but no IgM antibodies were infected longer than 6 months ago. Antibodies of the IgA class may provide neutralization of pathogens on mucosal surfaces. IgE antibodies are often involved in the immune responses to parasites and in allergic reactions to foreign protein antigens.

Local Immunity—The Mucosal Secretory IgA System

B lymphocytes secrete IgA antibodies, both in the blood and at the mucosal surfaces. These antibodies may be critical for resistance to infection in the respiratory, intestinal, and urogenital tracts. They are secreted after natural infection or following the administration of some whole virus vaccines. Vaccines given parenterally are less effective in inducing mucosal IgA. Therefore, some live virus vaccines, such as oral polio virus vaccines, may be more effective in preventing infection than killed vaccines because they provide resistance to mucosal infection, as well as resistance to invasive infection.

T Lymphocytes and Cell-Mediated Immunity

T lymphocytes are important regulatory cells of the immune system. They interact with antigen-presenting cells and secrete numerous cytokines that activate effector cells and interact with cells through the major histocompatibility complex (MHC) proteins at the cell surface. T lymphocytes can be classified as helper cells if they have $CD4^+$ markers on their surface. The $CD4^+$ helper cells activate B cells, monocytes-macrophages, and other helper T cells by binding directly to these cells or by secreting specific cytokines that stimulate cell proliferation. The cells that have $CD8^+$ markers on their surface are cytotoxic T cells that lyse other cells that contain foreign proteins or viruses. Also, $CD8^+$ T cells can help modulate the immune response by suppressing the activation of effector cells, such as macrophages. [6]

Granuloma reactions to an infection with a mycobacteria consists of an organized cellular immune response with phagocytic effector cells, surrounded by $CD4^+$ cells and $CD8^+$ T suppressor cells on the periphery to provide a localized and controlled immune response to the organism. Natural killer cells resemble lymphocytes but have some distinctive properties, such as expression of a specific receptor for the Fc portion of IgG. In some circumstances, these NK cells can kill virus-infected or neoplastic cells by secretion of interferon gamma (IFN-G), especially when induced to do so by tumor necrosis factor (TNF) and other cytokines produced by macrophages. Macrophages and monocytes function to process and deliver antigens for recognition by lymphocytes. Macrophages also can destroy intracellular virus-infected cells. These cells can respond to IFN-G secreted by the T cell, which activates the toxic oxygen and enzymatic pathways of the macrophage. [7] [8]

Granulocytes and Complement

Granulocytes are phagocytic cells that are involved in the protection against bacterial infections by ingesting and killing extracellular bacteria. The complement system is a set of enzymes and other proteins that attach to bacteria or foreign proteins and promote their destruction by phagocytosis. Persons who are deficient in some components of the complement system (especially C6, C7, or C8) have markedly increased susceptibility to recurrent infection with meningococci.[51]

Innate Immunity

In addition to acquired immunity it has long been recognized that animals are protected from invasion by pathogenic organisms by a system of innate or native immunity. A few years ago transmembrane receptor named Toll was identified In Drosophila insects that was responsible for establishing dorsoventral polarity during embryogenesis. Subsequently it was found that Toll was also responsible for protecting insects against fungal Infections. More recently it was discovered that humans and all animals have Toll-like receptors (humans have 10TLRS) that recognize patterns of non-self molecules, such as bacterial lipopolysaccharides or viral DNA or RNA, which then sets off an intracellular defense reaction involving cytokines and enzymes, to destroy the foreign material. Innate immunity has been recognized recently as a critical component of the defense against infection.

Quantitation of Infectious Diseases

Epidemiologists use a variety of measurements to quantify the occurrence of disease. Fundamentally, these measurements are intended to estimate the burden of disease in a population or the incidence of disease—the rate at which the disease is spread among persons in the population. The prevalence of disease in a population is the number of people who are infected divided by the number of people in the population. The numerator is those who are ill, those who have specific symptoms of the illness, or those who have microbiologic evidence of infection but do not exhibit symptoms. Each of these definitions yields different information, and each is a valid measure of the prevalence. However, it is critical that the definition of what constitutes infection be defined. The denominator in the prevalence equation is also defined by the epidemiologist. It may be the number of persons in the population, regardless of known exposure status, or it may be persons who were exposed. In the former case, the measurement of prevalence defines the burden of disease in the population overall; in the latter case, the definition gives the prevalence of disease among those exposed. Where exposure is common, age-specific population prevalence is commonly measured. Where exposure is rare, prevalence rates by exposure group are more frequently used.

The other commonly used measure is the incidence of disease. The incidence is the rate at which persons acquire the disease or the rate at which the infectious agent is being transmitted throughout the population. The incidence of disease always includes a unit of time—the number of cases of influenza in a given year, month, or week, for example.

The incidence and prevalence of disease are related to each other by the duration of disease. In cases where the duration of disease is short, the prevalence of disease will be approximately equal to the incidence of disease because most infections will be relatively recent. If, in contrast, the duration of the disease is long, the prevalence of disease will include both new and former cases of disease and will be larger than the incidence of disease. This relationship can be described by the equation:

$$\text{Prevalence} = \text{Incidence} \times \text{Duration}$$

At times, the incidence may be decreasing at the same time that prevalence is rising. Such may be the case with HIV infections in the United States and Western Europe at present, because combined antiretroviral therapy has prolonged survival and thereby increased the prevalence, but because of the effect of the drugs in reducing viral load, the transmission, or incidence of new cases, may be decreasing.

In other infectious diseases that have short duration but infected persons remain susceptible to reinfection, the incidence may exceed the point prevalence. Persons may have several episodes of diarrheal disease or rhinovirus respiratory infections per year that last only a few days. In these diseases, the point prevalence may be low but the annual incidence may be quite high. It may be preferable to measure the impact of these diseases with annual incidence rates. In contrast, in malaria hyperendemic areas, young children may receive hundreds of bites from infected mosquitoes every year. In this situation, the annual incidence of malaria is so high that it is difficult to measure. However, a blood film will allow determination of the point prevalence of infection, because the parasites persist in the blood for some time. Malaria prevalence data are more useful to differentiate populations at very high risk or of hyperendemic foci in an endemic area. These issues are discussed further in the chapters on malaria, diarrheal infections, and respiratory infections.

Surveillance of Infectious Diseases

9

Surveillance of infectious diseases is essential to understand their epidemiology. *Surveillance* can be defined as the ongoing and systematic collection, collation, and analysis of data, and the dissemination of the results to those who need to know to avoid or prevent infections or epidemics.

In the United States, surveillance of infectious diseases is done by physicians and other health care workers, laboratories, clinics, and public health departments. Cases or outbreaks of selected infectious diseases are reported to the local health department by health care providers, laboratories, or hospitals. These reports are analyzed and forwarded to each state's health department, which reports the data to the CDC in Atlanta. Additional details of infectious disease surveillance are covered in Chapter 4.

Temporal Trends of Infectious Diseases

Many infectious diseases undergo temporal variation in incidence. This temporal variability is sometimes easy to explain by changes in the exposure to the agent over time, such as in different seasons of the year or in different years.

Seasonal Variation

Vector-transmitted diseases, such as malaria, dengue, or St. Louis encephalitis (SLE), depend on exposure to infected mosquito vectors for their transmission. Therefore, these diseases are present only during the warm months of the year in temperate climates when the appropriate mosquito vectors are present. The

seasonal distribution of SLE virus infections of the central nervous system in the United States that were reported to the CDC between 1988 and 1997 is shown in Figure 2-3. The marked and consistent seasonality of SLE is readily apparent and easily understood, because the transmission depends on bites of susceptible humans by infected *Culex pipiens* or other related mosquitoes. These mosquitoes breed only in the summer in temperate climates and must reach a certain density and level of infection with SLE virus before human infections occur.

A description of the epidemiologic cycle of SLE in nature is shown in Figure 2-4.

The important reservoir hosts for SLE are infected birds, both wild and domestic, that carry the virus without illness and develop high-level, persistent viremia with SLE virus after infection. These birds serve as the reservoir to infect mosquitoes. Because humans and other animals that may be bitten by SLE-infected mosquitoes have low levels of virus in the blood that is very transient, they are not effective as reservoir hosts to infect additional mosquitoes and maintain the epidemic. For this reason, they are termed *dead-end hosts*. In other mosquito-borne arboviral infections, such as Eastern equine encephalitis, Western equine encephalitis, or Venezuelan encephalitis, horses may commonly be infected when bitten by infected mosquitoes and develop symptomatic, even fatal, illness after infection. The rate of inapparent infections in humans may be 1000 to 1 or higher; whereas, a much higher proportion of infected horses is symptomatic. Therefore, severe or fatal encephalitis in horses may serve as a harbinger that a subsequent human epidemic may follow. Substantial variations in the number of reported SLE infections by year are seen in the CDC data. Beyond the seasonal pattern, the year-to-year variation in the number of cases is not readily predictable. These mosquito-borne viral infections vary in relation to the number of mosquitoes, which may vary in density due to rainfall and temperature patterns; the number of reservoir hosts (especially wild birds) that are infected; and contact patterns between mosquitoes and birds and between infected mosquitoes and sus-

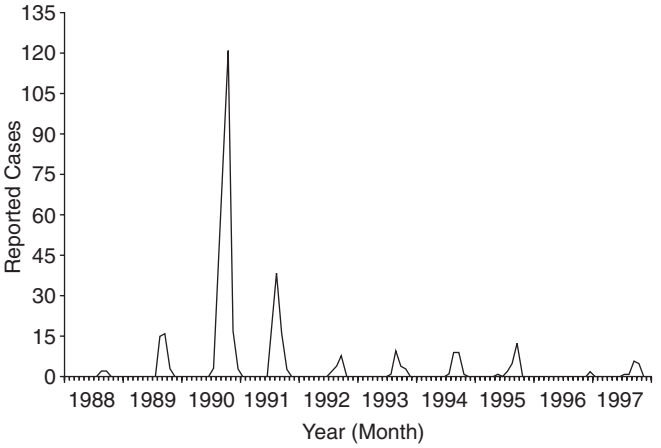

FIGURE 2-3 Arboviral infections (of the central nervous system)—reported laboratory-confirmed cases caused by St. Louis encephalitis virus, by month of onset, United States, 1988–1997.

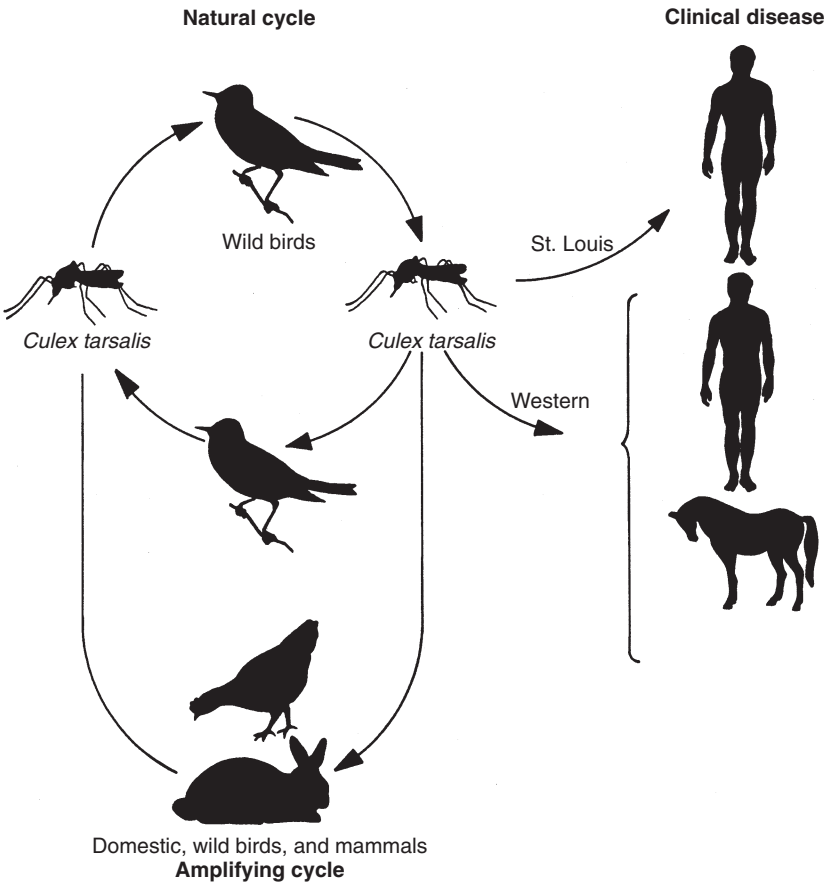

FIGURE 2-4 The sylvatic cycles of Western and St. Louis encephalitis viruses. The natural inapparent cycle is between *Culex tarsalis* and nestling and juvenile birds, but this cycle may be amplified by infection of domestic birds and wild and domestic mammals. Western encephalitis virus can replicate in mosquitoes at cooler temperatures, so epidemic disease in horses and humans may occur earlier in the summer and farther north into Canada. St. Louis encephalitis virus in the eastern United States involves *Culex pipiens* and other urban mosquitoes and causes urban epidemics.

ceptible humans. Because of the interaction of these variables, it is difficult to predict from one year to the next whether an epidemic will occur. The important arthropod borne virus infections of humans are discussed further in the Chapter on emerging vector-borne infections.

Annual Variation

Prior to the development of effective vaccines for the prevention of many of the common childhood infections (measles, mumps, rubella, and varicella), these infections exhibited marked and repetitive cyclical trends, which depended largely on an epidemic exhausting the susceptible population and another birth cohort replenishing it. For measles, the cycle for a major epidemic in an urban population in the United States repeated every other

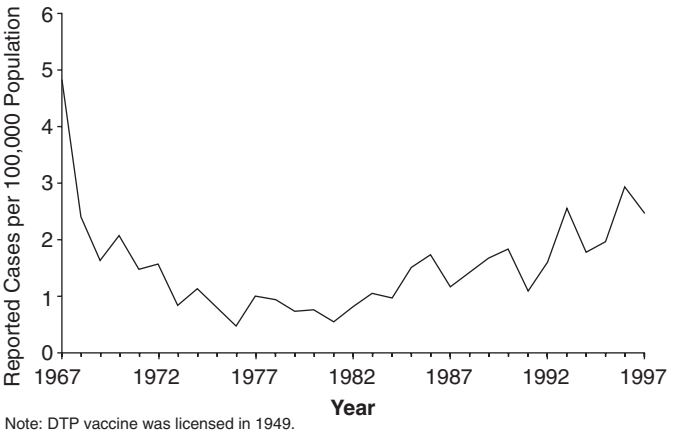

FIGURE 2-5 Pertussis (whooping cough) by year, United States, 1967–1997.

year, at which time, the number of cases roughly doubled, compared with the preceding and following years. With the widespread routine use of effective measles vaccine, the rates of measles have decreased dramatically, and the cyclical occurrence of cases has changed. However, cycles at 3- to 4-year intervals have persisted for reported cases of pertussis between 1967 and 1997 (Figure 2-5). This cyclical pattern indicates that persistent transmission of pertussis related to contact between an infected case and a susceptible host still occurs, despite the availability of a vaccine that has been used quite widely. In part, this persistence may relate to waning of the immunity induced by the whole-cell pertussis vaccine over time, the role of older children and adults in maintaining the transmission cycle of pertussis, and the periodic replenishment of the susceptible population. Most of the childhood infections are more common in the winter and early spring seasons. This seasonality has been postulated to be related to greater transmissability when populations spend more time indoors during the winter. Also, the low humidity of indoor air and the presence of other respiratory infections, which cause coughing and sneezing, may be critical factors in promoting the transmission during the winter.

Herd Immunity

Prior to the epidemiologic theories proposed by Kermack and McKendrick and by Reed and Frost from Johns Hopkins, the predominant theory was that epidemics occurred due to variation in the infectivity of the organism. Instead, these investigations showed that patterns of epidemics could be explained by the proportion and distribution of susceptible persons. In certain diseases that are spread from person to person, the level of immunity of the population may be critical in determining whether an epidemic will occur and, therefore, the risk of infection for a susceptible individual in the population. Because transmission is based on contact between an infected person and a susceptible person, if the number of immune persons is high enough that it is unlikely that a susceptible will have contact with an infected person, the population is

said to have *herd immunity*. Even though some susceptible persons remain in the population, epidemics are not sustained because the day-to-day contacts between persons do not result in contact between infected persons during the period that they are contagious and others who are still susceptible. The level of immunity required to attain herd immunity is dependent on the characteristics of the infectious disease. Those that are spread more readily will require a higher level of immunity in the population than will those that are less infectious. The levels of herd immunity and individual susceptibility to infections are major epidemiologic factors that have influenced the periodicity and secular trends observed in many diseases, such as measles, rubella, varicella, and polio. A new epidemic of measles, prior to the era of widespread immunization, was dependent on the existence of a large cohort of susceptible individuals. A large enough pool of susceptibles to sustain an epidemic occurred every other year as new children were born. After an effective measles vaccine became available, epidemics were less common, less predictable, and often involved older individuals. Epidemics occurred even in immunized populations when clusters of susceptibles were exposed to an infectious case, such as on college campuses. The theoretical modeling of epidemics is covered more thoroughly in the chapter on modeling.

Variations of Infectious Diseases Over Decades

Tuberculosis

Many classic infectious diseases, such as tuberculosis, have decreased in incidence and mortality in the United States and Europe during the past century. Tuberculosis is still one of the most important infectious diseases globally. However, in the United States, the mortality rates from tuberculosis began to decline in the late 1800s. Between 1950 and 1985, tuberculosis morbidity declined at a rate of about 5% per year. Tuberculosis mortality by age in the United States is highest in older age groups.[52] However, the age-specific tuberculosis mortality data were studied in another way by Wade Hampton Frost. He examined the risk of tuberculosis death by birth cohort, rather than as cross-sectional age-specific mortality.[53] When the data are studied in this way (as the risk of mortality from tuberculosis in a cohort of persons born in the same year), different conclusions are reached about the age-specific risk of mortality. In Figure 2-6, the mortality rates are depicted as age-specific mortality by birth cohort. The cohort analysis shows tuberculosis mortality. The reason for the higher mortality among older persons is that they were born at a time when the risk of tuberculosis was higher than it is at present. Their higher mortality reflects their elevated risk of infection due to subsequent activation of an infection that originally occurred when the incidence of tuberculosis was higher than more recent cohorts.[53,54]

Changes in Infectious Disease Morbidity and Mortality During the 1800s and 1900s

During the 1700s, 1800s, and early 1900s, infectious diseases were the major cause of morbidity and mortality. Reliable mortality data are available from

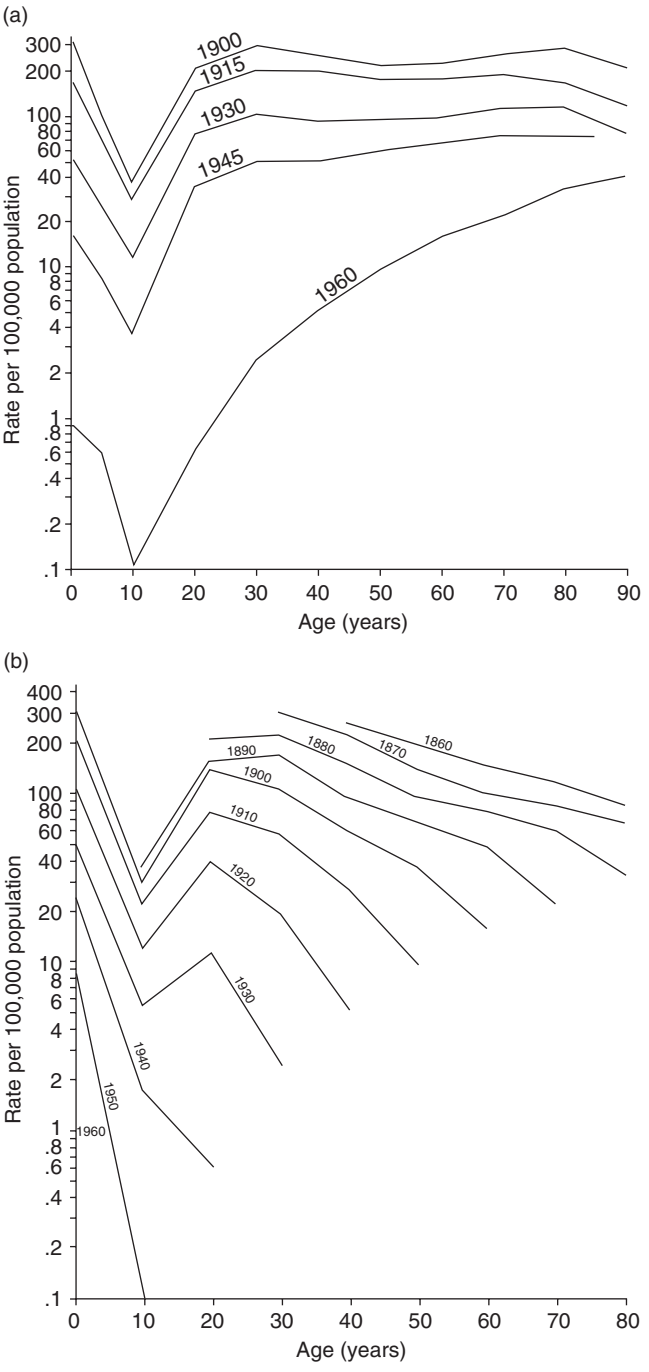

FIGURE 2-6a & b (a) Death rates from tuberculosis by age group for selected years; (b) Cohort analysis of death rates from tuberculosis by age group, 1860–1960. The line associated with each year indicates death rates by age group for persons born in that year.

the United Kingdom from the 1800s because early leaders, such as John Graunt and William Farr, recognized the importance of surveillance data to evaluate improvements in public health and promoted routine reporting of infectious disease mortality. The mortality rates from whooping cough, enteric fevers, and tuberculosis decreased over 100-fold between 1900 and 1960 in persons living in the United Kingdom. The mortality rates from these diseases decreased in the United States and other developed countries in Europe in a parallel fashion to those reported from the United Kingdom. In 1900, the death ratio from 10 of the most common infectious diseases varied from 202.2 per 100,000 population for influenza and pneumonia to 6.8 per 100,000 population for meningococcal infections. By 1970, only influenza and pneumonia infections were associated with mortality rates above 3 per 100,000 (Table 2-10).

A recent analysis of the trends in infectious disease mortality in the United States during the 1900s documented the effect of the control of infectious diseases. The overall mortality from infectious diseases, which was 797 deaths per 100,000 in 1900, declined to 36 deaths per 100,000 in 1980.[55] However, the decline in mortality was reversed between 1980 and 1995, when the death rate increased to 63 deaths per 100,000 persons.[56] The trend of a steady decline was interrupted by a sharp spike of increased mortality during the 1918 influenza epidemic. Between 1938 and 1952, the decline was particularly rapid, with mortality decreasing by 8.2% per year. Pneumonia and influenza were responsible for the largest number of infectious disease deaths throughout the century. Tuberculosis caused a large number of deaths early in the century, but tuberculosis mortality declined sharply after 1945. Although the crude mortality rate for infectious diseases was dramatically reduced during the first eight decades of the 1900s, the mortality from all noninfectious diseases has not shown a similar change (Figure 2-7). In fact, most of the decline in mortality during the 1900s can be attributed to the dramatic reduction in infectious disease mortality. In the last two decades of

TABLE 2-10 Death Rates for Common Infectious Diseases in the United States in 1900, 1935, and 1970

	Mortality Rate per 100,000 Population		
Infectious Disease	1900	1935	1970
Influenza and pneumonia	202.2	103.9	30.9
Tuberculosis	194.4	55.1	2.6
Gastroenteritis	142.7	14.1	1.3
Diphtheria	40.3	3.1	0.0
Typhoid fever	31.3	2.7	0.0
Measles	13.3	3.1	0.0
Dysentery	12.0	1.9	0.0
Whooping cough	12.0	3.7	0.0
Scarlet fever (including streptococcal sore throat)	9.6	2.1	0.0
Meningococcal infections	6.8	2.1	0.3

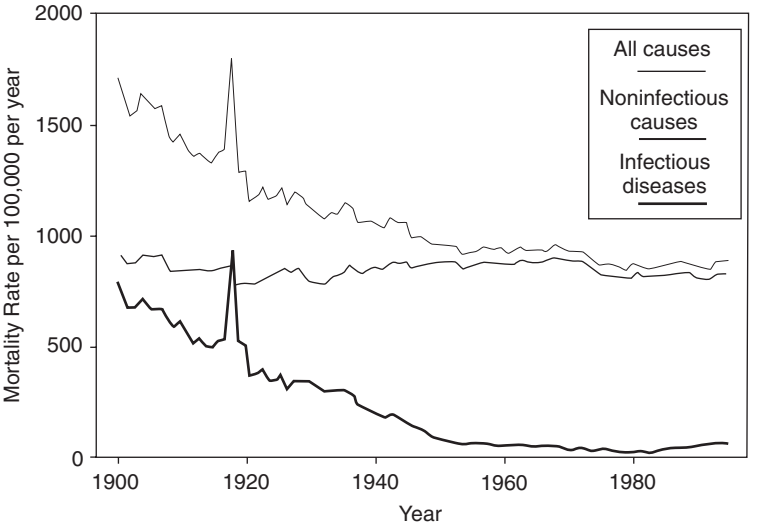

FIGURE 2-7 Crude mortality rates for all causes, noninfectious causes, and infectious diseases.

the 1900s, the mortality from coronary heart disease has declined substantially; however, this has been offset by increasing mortality for lung cancer and other diseases. Clearly, the decline in mortality from infectious diseases during the 1900s stands as a tribute to the advances in public health and safer lifestyles, compared with that in previous centuries.

What caused these remarkable reductions in the mortality from common infectious diseases? One might surmise that the development of modern microbiology with the understanding the discipline provided about the pathogenesis of specific infections led to the development of vaccines and effective antibiotics to prevent or treat infections. However, for most of these infections, the evidence suggests a more complex scenario. The decline in the annual death rates for tuberculosis in England and Wales antedated the identification of the tuberculosis bacillus; however, the slope of the declining mortality increased after 1948, with the availability of streptomycin, isoniazide, and other chemotherapeutic agents (Figure 2-8).

Similarly, death rates from scarlet fever, diphtheria, and whooping cough (pertussis) in children under age 15 in England and Wales began to decline well before these organisms were identified in the laboratory, and the availability of effective antibiotics had a small effect on the overall mortality decline (Figure 2-9).[57]

Also, dramatic declines in the death rates from measles and pertussis were seen among children in England and Wales decades prior to the identification of these organisms and the availability of vaccines or antibiotics to treat infected persons. What, then, can account for these declines in mortality? Recent experience with some of these diseases in poor and often malnourished children from developing countries in Africa has shown that some of these diseases still have high mortality in certain populations. For example, measles, which is rarely fatal when it occurs in children in the United States,

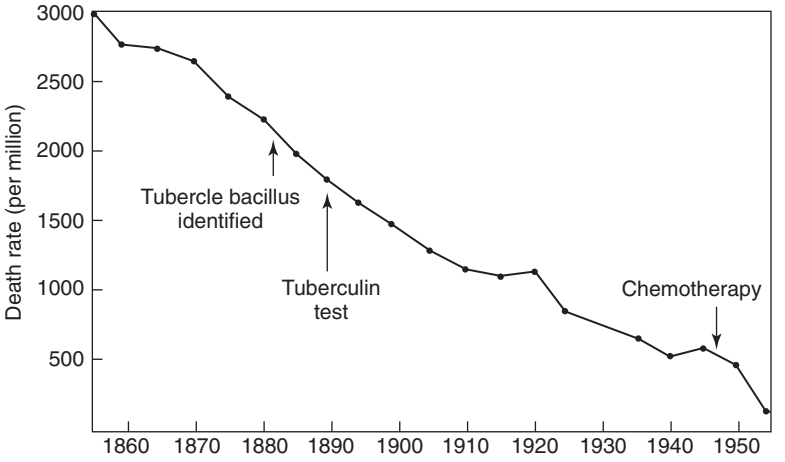

FIGURE 2-8 Mean annual death rate from respiratory tuberculosis, England and Wales.

is still associated with a 15–20% mortality in infants and children in sub-Saharan Africa. Hypotheses to explain this difference have included poorer nutritional status, earlier ages at exposure, other concomitant infections, higher infectious dose, and greater crowding during epidemic spread among infants in Africa.[58,59] All of these factors may play a role, but it is difficult to evaluate their independent contribution. Clearly, the complex changes that have occurred in society, hygiene, and lifestyle in the United States and in Europe during the late 1800s and early 1900s have had a profound effect on these diseases.

Recent Trends in Infectious Disease Morbidity and Mortality in the United States

Although the mortality from the classical infectious diseases declined dramatically in the late 1800s and the first 80 years of the 1900s, several cultural and environmental changes occurred that fostered the emergence of a number of new infections and the reemergence of older, well-recognized infections. Indeed, it has been estimated that a larger number of new infections have emerged in the last decade or so than in the hundred years previously.

The most heralded, of course, is the HIV/AIDS epidemic, which probably originated as a mutant or recombinant primate retrovirus that was spread to humans from chimpanzees in Africa in the 1950s or 1960s. The ensuing pandemic of AIDS has led to the emergence of many new and previously recognized but rare human pathogens, such as *P. carinii*, *Mycobacteria avium*, *Cryptosporidia parvum*, *Microsporidia*, *Bartonella rochelimea*, and *Penicillium marneffei*. The epidemic of AIDS is covered in more detail in the chapter on AIDS. In addition to HIV and AIDS, modern chemotherapy of neoplasms, aging of the population, increased invasive therapeutic procedures in hospitalized patients, crowding of elderly patients in nursing homes and

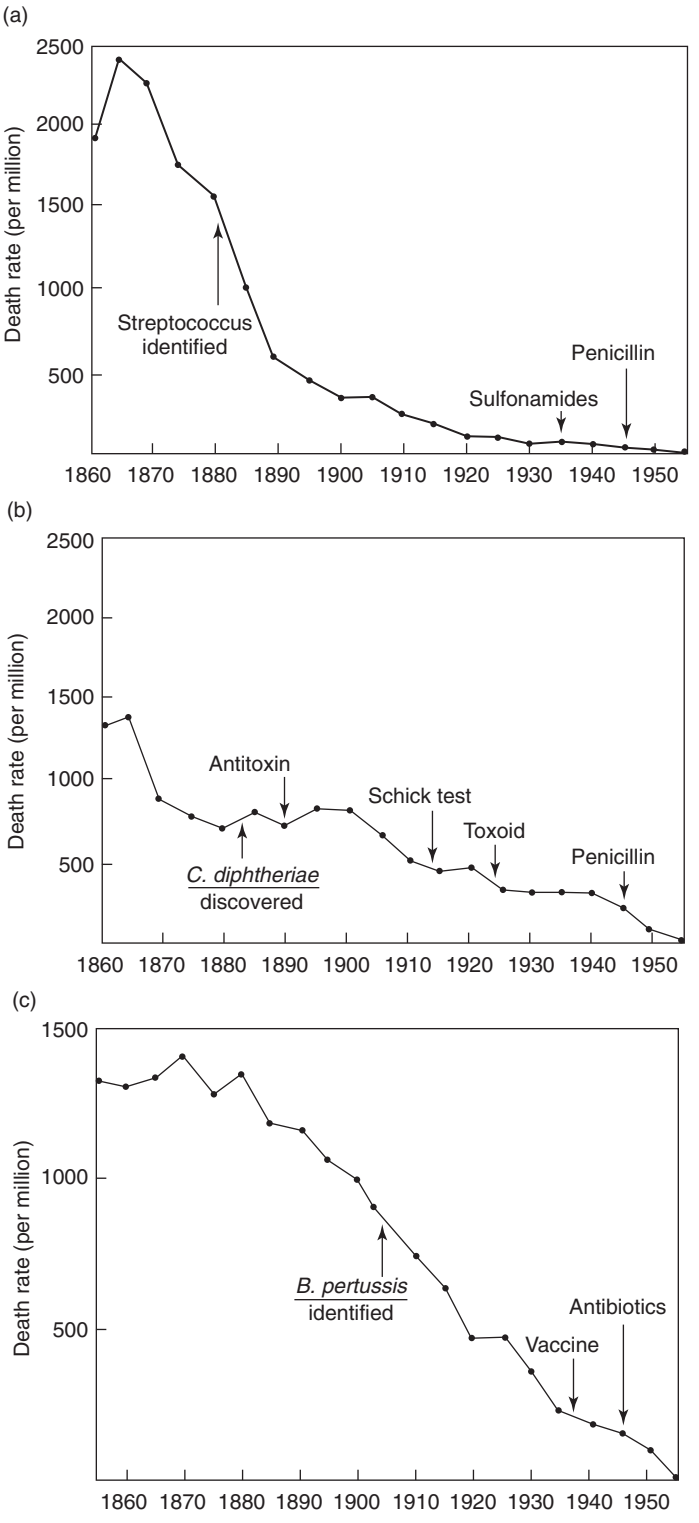

FIGURE 2-9 a, b &c. (a) Mean annual death rate from scarlet fever in children under 15 years of age, England and Wales;

TABLE 2-11 Leading Underlying Causes of Mortality Caused by Infectious Diseases in the United States, 1980 and 1992

1992 Rank	Infectious Disease Group	No. of Deaths	Mortality per 100,000	1980 Rank	Infectious Disease Group	No. of Deaths	Mortality per 100,000
1	Respiratory tract infections	56,966	25.1	1	Respiratory tract infections	77,336	30.3
2	Septicemia	9,438	4.2	HIV/AIDS	33,581	13.2	
3	Infections of kidney/urinary tract	8,006	3.5	Septicemia	19,667	7.7	
4	Infections of the heart	2,486	1.1	Infections of kidney/urinary tract	12,399	4.9	
5	Tuberculosis	2,333	1.0	Infections of the heart	3,950	1.5	
6	Bacterial meningitis	1,402	0.6	Hepatobiliary disease	2,494	1.0	
7	Gastrointestinal tract infections	1,377	0.6	Mycoses	2,298	0.9	
8	Hepatobiliary disease	1,227	0.5	Tuberculosis	1,851	0.7	
9	Perinatal infections	1,035	0.5	Gastrointestinal tract infections	985	0.4	
10	Mycoses	680	0.3	Perinatal infections	965	0.4	
Total	infectious diseases	93,407	41.1			166,047	65.1
All deaths		1,989,841	878.0			2,175,613	852.7

infants and children in day care centers, widespread use of broad spectrum antibiotics, environmental pollution, and other factors have led to the emergence of infectious diseases. These issues are covered in detail in Chapter 12.

An analysis was done by investigators for the CDC of all deaths in the United States between 1980 and 1992.[56] In this interval, the death rate due to infectious diseases as the underlying cause of death increased 58%, from 41 to 65 deaths per 100,000 population in the United States. Age-adjusted mortality from infectious diseases increased 39% during the same period. Infectious disease mortality increased 25% among those aged 65 years or older, from 271 to 338 per 100,000 population, and 5.5 times among 25- to 44-year-olds, from 6.9 to 38 deaths per 100,000 population. Mortality due to respiratory tract infections increased 20%, the death rate from septicemia increased 83%, and AIDS emerged as a major cause of death. These national data are quite sobering because they clearly demonstrate that an increased infectious disease mortality has occurred recently in the US population, which is not limited to newly emerging diseases, such as AIDS. The 10 leading underlying causes of mortality caused by infectious diseases in the United States in 1980 and 1992 are listed in Table 2-11.

Recent Worldwide Trends in Infectious Disease Morbidity and Mortality

Infectious diseases play a leading role in mortality and morbidity globally, due in large part to the continued importance of infectious diseases in sub-Saharan Africa, Asia, and Latin America. Data were published recently from the Global Burden of Disease Study, which was initiated in 1992 in collaboration with the World Bank and the WHO. The goals of this study were to make reasonable estimates from the available data of the impact of various diseases as causes of disability, to develop unbiased assessments for major disorders, and to quantify the burden of disease with a measure that could be used for cost-effectiveness analysis. This study found that 98% of all deaths in children younger than 15 years of age are in the developing

world, and 50% of deaths between ages 15 and 59 years of age were in the developing world.[60] The probability of death between birth and 15 years of age ranges from 22% in sub-Saharan Africa to 1.1% in the established market economics. Probabilities of death between 15 and 50 years of age range from 7.2% for women in established market economics to 39.1% in sub-Saharan Africa. Worldwide in 1990, communicable, maternal, perinatal, and nutritional disorders accounted for 17.2 million deaths, noncommunicable diseases for 28.1 million deaths, and injuries for 5.1 million deaths. The leading causes of death in 1990 were ischemic heart disease (6.3 million deaths), cerebrovascular accidents (4.4 million deaths), lower respiratory infections (4.3 million deaths), diarrheal diseases (2.9 million), perinatal disorders (2.4 million), chronic obstructive pulmonary disease (2.2 million), tuberculosis (2.0 million), measles (1.1 million), road traffic accidents (1.0 million), and lung cancer (0.9 million).

This WHO–World Bank study also concluded that effective treatment of tuberculosis is the most cost-effective health measure that could be implemented in developing countries in terms of prevention of mortality and increasing disability-adjusted life years (DALY).[61] The analysis of tuberculosis programs in Malawi, Mozambique, and Tanzania has shown that treating smear-positive tuberculosis costs $20–52 per death averted. The cost per discounted year of life saved, therefore, is $1–3. There are few other interventions that are as cost-effective as is tuberculosis case treatment. This WHO analysis estimated that $150 million would be needed to treat 65% of smear-positive cases in low-income countries and 85% of middle-income countries with short-course chemotherapy. Clearly, the interaction between HIV and tuberculosis has made the tuberculosis problem more acute and intractable. The rapid and extensive spread of AIDS in countries in the developing world, where a high proportion of the population has latent tuberculosis, indicates that a public health strategy that is limited to treating active cases is unlikely to control the emerging tuberculosis epidemic effectively. However, recent research has shown that active tuberculosis generally is treatable with current chemotherapeutic regimes, even in the face of HIV infection. This issue is reviewed in greater detail in the chapter on tuberculosis.

Other health interventions are cost-effective for the prevention of infectious disease morbidity and mortality, including effective sexually transmitted disease (STD) treatment; oral rehydration therapy for diarrhea; immunization for childhood diseases, including HBV; ivermectin for the treatment and prevention of onchocerchiasis and schistosomiasis; and zidovudine for the prevention of the perinatal transmission of HIV. The chemotherapy and chemoprophylaxis of malaria and antibiotic prophylaxis for the prevention of postsurgical infections are also cost-effective; these issues are reviewed in the chapters on malaria and nosocomial infections.

Currently, the world's population is in a very delicate balance with respect to infectious diseases. The continual emergence of new infectious diseases and the reemergence of old infections, together with the potential for their global spread, underline the need for accurate surveillance and the development of newer strategies for their control and prevention. However, the successes of the last century should provide hope that infectious diseases can be controlled with the proper understanding and effort.

References

1. Snow J. *On Cholera*. New York, NY: Commonwealth Fund; 1996.
2. Fraser DW, Tsai TR, Orenstein W, et al. Legionnaire's disease. Description of an epidemic of pneumonia. *N Engl J Med*. 1977;297:1189–1197.
3. Dondero TJ, Rentdorff RL, Mallison GF, et al. An outbreak of Legionnaire's disease associated with a contaminated air-conditioning cooling tower. *N Engl J Med*. 1980;302:365–370.
4. Cords LG, Fraser DW, Skailly P, et al. Legionnaire's disease outbreak at an Atlanta, Georgia, country club: evidence for spread from an evaporative condenser. *Am J Epidemiol*. 1980;111:425–431.
5. Garbe PL, Davis BJ, Weisfeld JS, et al. Nosocomial Legionnaire's disease: epidemiologic demonstration of cooling towers as a source. *JAMA*. 1985;254:521–524.
6. Morris GK, Patton CM, Feeley JC, et al. Isolation of the Legionnaire's disease bacterium from environmental samples. *Ann Intern Med*. 1979;90:664–666.
7. Moraca E, Yu VC, Goetz A. Disinfection of water distribution system for Legionnella: a review of applicator procedures and methodologies. *Infect Control Hosp Epidemiol*. 1990;11:79–88.
8. Francis E. Deer-fly fever: a disease of man of hitherto unknown etiology. *Public Health Rep*. 1991;34:2061–2062.
9. Waring WB, Ruffin JJ. A tick-borne epidemic of tularemia. *N Engl J Med*. 1946;234:137.
10. Young LS, Bickewell DS, Archer BG, et al. Tularemia epidemic: Vermont 1968: forty-seven cases linked to contact with muskrats. *N Engl J Med*. 1969;280:1253–1260.
11. Teutsch SM, Martone WJ, Brink EW, et al. Pneumonic tularemia on Martha's Vineyard. *N Engl J Med*. 1979;301:826–828.
12. Dahlstrand S, Ringertz O, Zetterberg B. Airborne tularemia in Sweden. *J Infect Dis*. 1971;3:7–16.
13. Barbeito MS, Alg RL, Wedum AG. Infectious bacterial aerosol from dropped Petri disk cultures. *Am J Med Technol*. 1961;27:318–322.
14. Hornick RB. Tularemia. In: Evans A, Brachman PS, eds. *Bacterial Infections of Humans: Epidemiology and Control*. 3rd ed. New York, NY: Plenum Publishing; 1998:823–837.
15. Hirst CF. *The Conquest of Plague*. London, England: Oxford University Press; 1953.
16. Zinsser H. *Rats, Lice and History*. Boston, Mass: Little, Brown; 1934.
17. Marshall JD Jr, Joy RJT, Ai NY, et al. Plague in Vietnam 1965–1966. *Am J Epidemiol*. 1967;86:603–616.
18. Campbell GL, Hughes JM. Plague in India: a new warning from an old nemesis. *Am Int Med*. 1995;122:151–153.
19. Eskey CR, Haas V. Plague in the western part of the United States. *Public Health Bull*. 1940;254:1–82.
20. Mann JM, Martone WJ, Myoce JM, et al. Endemic human plague in New Mexico: risk factors associated with infections. *J Infect Dis*. 1979;140:397–401.
21. Butler T. *Plague and Other Yersinia Infections*. New York, NY: Plenum Publishing; 1983.
22. Laforce FM. Woolsorter's disease. *Acad Med*. 1978;54:956–963.
23. Meselson M, Guillemin J, Hugh-Jones M, et al. The Sverdlousk anthrax outbreak of 1979. *Science*. 1994;266:1202–1208.

24. Constantine DG. Rabies transmission by non-bite route. *Public Health Rep*. 1963;77:287–289.
25. Winkler WG, Fashinell TR, Leffingwell C, Howard P, Conomy JP. Airborne rabies transmission in a laboratory worker. *JAMA*. 1973;226:1219–1221.
26. Hooff SA, Burton RC, Wilson RW, et al. Human-to-human transmission of rabies by a corneal transplant. *N Engl J Med*. 1979;300:603–604.
27. Noah DC, Drenzik CL, Smith JS, et al. Epidemiology of human rabies in the United States, 1980 to 1996. *Ann Intern Med*. 1998;128:922–930.
28. Brown GM. The history of the brucellosis eradication program in the United States. *Ann Selavo*. 1977;19:20–34.
29. Grant IH, Gold JW, Witner M, et al. Transfusion-associated Chagas' disease acquired in the United States. *Ann Intern Med*. 1989;111:849–851.
30. Gregg NM. Congenital cataract following German measles in the mother. *Trans Ophthalmol Soc*. 1941;3:35–46.
31. Weller TH, Neva FA. Propagation in tissue culture of cytopathic agents from patients with rubella-like illness. *Proc Soc Exp Biol Med*. 1962;11:215–225.
32. Parkman PD, Bueschler EL, Artenstein MS. Recovery of rubella virus from army recruits. *Proc Soc Exp Biol Med*. 1962;111:225–230.
33. Krugman S, ed. Rubella symposium. *Am J Dis Child*. 1965;110:345–476.
34. Krugman S, ed. International conference on rubella immunization. *Am J Dis Child*. 1969;118:2–410.
35. Smith MG. Propagation in tissue culture of a cytopathic virus from human salivary gland virus (SGV) disease. *Proc Soc Exp Biol Med*. 1956;92:424–430.
36. Rowe WP, Hartley JW, Waterman S, Turnan HC, Huebner RJ. Cytopathic agent resembling human salivary gland virus recovered from tissue culture of human adenoids. *Proc Soc Exp Biol Med*. 1956;92:418–424.
37. Weller TH, MaCaulay JC, Craig JM, Wirth P. Isolation of intranuclear inclusion producing agents from infants with illness resembling cytomegalic inclusion disease. *Pro Soc Exp Biol Med*. 1957;94:4–12.
38. Gershon AH, Gold E, Nankervis GA. Cytomegalovirus. In: Evans AS, Kaslow RA, eds. *Viral Infections of Humans, Epidemiology and Control*. New York, NY: Plenum Publishing; 1997:229–251.
39. Dobbins JG, Stewart JAS. Surveillance of congenital cytomegalovirus disease 1990–1991. *MMWR*. 1992;41:SS-2.
40. Stone KM, Brooks CA, Guinan ME, Alexander ER. National surveillance for neonatal herpes virus infections. *Sex Transm Dis*. 1989;16:152–156.
41. Mcllinger AK, Goldberg M, Wade A, et al. Alternative case-finding in a crack-related syphilis epidemic—Philadelphia. *MMWR*. 1991;40:77–80.
42. Conner EM, Sperling RS, Gelber R, et al. Reduction of maternal–infant transmission of human immunodeficiency virus type 1 without zidovudine treatment. *N Engl J Med*. 1997;31:1173–1180.
43. Shaffer N, Chunchoonong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand. *Lancet*. 1999;353:773–780.
44. Guay CA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomized trial. *Lancet*. 1999;254:795–802.
45. Sartwell PE. The distribution of incubation of disease. *Am J Epidemiol*. 1950;51:310–318.

46. Muñoz A, Kirby AJ, He DY, et al. Long-term survivors with HIV-1 longitudinal patterns of $CD4^+$ lymphocytes. *J Acquir Immunodeficiency Syndr.* 1995;8:496–505.
47. Watts DM, Burke DS, Harrison BA, et al. Effect of temperature on the vector efficiency of *Aedes aegypti* for dengue 2 virus. *Am J Trop Med Hyg.* 1987;36:143–152.
48. Soper GA. The curious case of typhoid Mary. *Acad Med.* 1939;15:698–712.
49. Anders W, Conde F, Stephen W. Surgical treatment of the chronic typhoid carrier: report of 102 operated cases. *Dtsch Med Wochenschr.* 1955;89:1637–1648.
50. Shilts R. *And the Band Played On.* New York, NY: St. Mortons Press; 1987.
51. Peterson BH, Lee TJ, Snyderman, Brooks GF. *Neisseria meningitidis* and *Neisseria gonorrhoeae* bacteremia associated with C6, C7, C8 deficiency. *Ann Intern Med.* 1979;90:917–920.
52. Rieder HL, Cauthen GM, Kelly GD, et al. Tuberculosis in the United States. *JAMA.* 1989;262:385–389.
53. Frost WH. The age selection of mortality from tuberculosis in successive decades. *Am J Hyg.* 1939 (Section A);30:91–96.
54. Doege TG. Tuberculosis mortality in the United States, 1900 to 1960. *JAMA.* 1965;192:1045–1048.
55. Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. *JAMA.* 1999;281:61–66.
56. Pinner RW, Teutsch SM, Simonsen L, et al. Trends in infectious diseases mortality in the United States. *JAMA.* 1996;225:189–193.
57. Kass EM. Infectious disease and social change. *J Infect Dis.* 1971;123:110–114.
58. Aaby P, Bakh J, Lisse IM, Snits AJ. Measles mortality, state of nutrition, and family structure: a community study on Guinea-Bissau. *J Infect Dis.* 1983;147:693–701.
59. Aaby P. Malnutrition and overcrowding-exposure in severe measles infection: a review of community studies. *Rev Infect Dis.* 1988;10:478–491.
60. Murray CJ, Lopez AD. Alternative projections of mortality and disability by course, 1990–2020: global burden of disease study. *Lancet.* 1997;349:1498–1504.
61. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. *Lancet.* 1997;349:1269–1276.

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