INTRODUCTION

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 factors associated with clinically recognizable disease among those who are infected. Epidemiologic concepts such as the incubation period and resistance were originally developed in studies of infectious diseases and later applied to noninfectious diseases.

Epidemiologic characterization is the first step in defining a new disease, although diseases can also be classified according to their clinical or microbiologic features. 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 infectious organism is. A microbiologist will be concerned primarily with the characteristics of the organism and will focus on the tasks of isolation, identification, and development of targeted treatments.

The control, treatment, and prevention of an epidemic usually requires the cooperative efforts of all three groups of specialists—clinicians, microbiologists, and epidemiologists. However, each has a unique orientation and contribution to make to this field. 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.

Microbiologists use classification schemes focused on the characteristics of the causative organism. An example of a typical microbiologic classification of infectious diseases is shown in Table 2-2.

Epidemiologists focus on the epidemiologic characteristics of a disease and classify diseases according to either the means of transmission or the reservoir of the organism. Infectious diseases can be classified according to their means of transmission into five distinct categories, as shown in Table 2-3. With the epidemiologic classification of infectious diseases according to where the pathogen is found, the most generalized form of categorization is based on whether a pathogen is either native to humans, animals, soil, or water. Some common examples of infectious diseases classified according to their reservoir are shown in Table 2-4.

When a new disease appears on the scene, the detailed microbiologic characteristics of the organism are typically unknown. Likewise, the full clinical manifestation may be undefined. For example, the fact that infection with *Borrelia burgdorferi*, the cause of Lyme disease, 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. burgdorferi* is still being defined.

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. In this case, the epidemiologic information alone was sufficient to develop public health strategies to 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 infectious 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, but it was not until 1928 that Stokes and colleagues isolated the causative virus in the laboratory. In more recent times, investigation of pneumonia at the American Legion convention in Philadelphia in 1976 demonstrated that disease was due to airborne spread of microorganisms from the air-conditioning system and suggested that infection could be prevented by avoiding the air in the hotel.\(^2\) The implicated organism, *Legionella pneumophila*, was not isolated and characterized in the laboratory until 1978, when it was identified by McDade and Sheppard at the Centers for Disease Control and Prevention (CDC).

Knowledge of the reservoir often is essential before one can devise 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—that is, 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 persons who received 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.\(^1\)

**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 here.

**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,\(^6\) by contact with infected rabbits or other animals during the hunting season,\(^9,12\) or by inhalation of aerosols.\(^11,12\) In addition, 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 of human-to-human transmission.\(^14\)

**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*. This zoonotic disease of rodents 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 pneumatic 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, 7,000 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 did occur 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 infectious organism was first isolated by Yersin in Hong Kong in 1894.\(^21\) Although a vaccine is available, its efficacy in preventing pneumatic plague is unknown.

**Anthrax**

Anthrax is an infection with *Bacillus anthracis*, a gram-positive spore-forming organism that causes a zoonotic disease in herbivorous animals. The pathogen can be transmitted to humans from contact with infected animals, and the resulting disease 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.\textsuperscript{22} Infection can also occur 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 \textit{B. anthracis} spores is inhaled and germinates in the pulmonary lymphatic tissues. This form of anthrax is rare, which is fortunate because it usually proves rapidly fatal.

An epidemic of inhalation anthrax occurred among persons living in Sverdlovsk, Union of Soviet Socialist Republics, in April and May 1979. At least 96 cases and 66 deaths occurred. The outbreak also affected cattle within 50 kilometers 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.\textsuperscript{23} Furthermore, the animal deaths also occurred in this belt, up to 50 kilometers distant (Figure 2-1). The wind pattern on the day of the outbreak could explain the geographic distribution of cases. Subsequently, evidence was discovered that many of the human cases had pneumonic anthrax. The researchers 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 this study was that human cases continued to occur for as long as 6 weeks after the initial 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 policymakers about the potential for the use of aerosolized \textit{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 U.S. mail delivered to a number of persons by the U.S. 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 that harbored many infected bats.\textsuperscript{24} In addition, rabies has occurred in a laboratory worker who was exposed to an infectious aerosol\textsuperscript{25} and in persons who have received corneal transplants from a donor who died of undiagnosed rabies.\textsuperscript{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
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 and 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. After World War II, the U.S. 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. This program was quite successful. More than 6000 cases of human brucellosis were reported each year at the start of this program; the rate had declined to 4.5 cases per 100,000 population in 1948. In the 1990s, only about 100 cases per year were reported; 0.05 case per 100,000 population was reported in 1993.

In recent years, persons affected brucellosis have 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.

**Transmission of Microbial Agents by Transfusions**

Evidence shows 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 bloodstream.

For example, hepatitis B virus, hepatitis C virus, and HIV are commonly transmitted by the transfusion of blood or blood products. *Trypanosoma cruzi*, a protozoan parasite that causes Chagas’s disease, is usually transmitted to humans by the bite of a reduviid bug but can be transmitted by blood transfusion from a carrier. Malaria usually is caused by the transmission of one of four species of *Plasmodium* parasites by the bite of an infected female *Anopheles* 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.

**Rabies**

Rabies that were diagnosed in the United States between 1980 and 1996, 25 (78%) had no history of a bite exposure. Some of these non-bite-transmitted cases in the United States have occurred 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.

Rabies that were diagnosed in the United States between 1980 and 1996, 25 (78%) had no history of a bite exposure. Some of these non-bite-transmitted cases in the United States have occurred 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.
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.\(^\text{15-17}\) 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 U.S. births, or approximately 40,000 infants annually.\(^\text{18}\) In most instances, these infections are asymptomatic.

In 1990, the CDC established a national surveillance registry in the United States to monitor congenital CMV infections.\(^\text{19}\) 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 approximately 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. Nevertheless, 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.\(^\text{20}\)

Risks of congenital HSV infection are higher for infants delivered by cesarean section compared with infants delivered vaginally. In a 1996–1998 national surveillance system, 40% of infants delivered vaginally acquired active HSV infection at birth compared with 2–5% when the mother has an active genital HSV infection. In contrast to CMV and rubella, in utero infection with 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 approximately 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. Nevertheless, 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.\(^\text{20}\)

Toxoplasmosis

Congenital infection with Toxoplasma gondii occurs when a pregnant woman develops a infection with this pathogen, especially early in pregnancy. Clinical manifestations in the infant at birth may include a maculopapular rash, generalized lymphadenopathy, hepatomegaly, splenomegaly, jaundice, or thrombocytopenia. In addition, the infant can develop meningoencephalitis with cerebrospinal fluid abnormalities, hydrocephalus, microcephaly, chorioretinitis, and convulsions. More typically, congenital infection is asymptomatic at birth, although sequelae can become apparent several years later. Sequelae of congenital Toxoplasma infection include mental retardation and learning disability.

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 a spirochete, Treponema pallidum. It 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 of pregnancy. More rarely, transmission may 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 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 increased in the late 1980s and early 1990s, in part related to the epidemic of crack cocaine use in the United States.\(^\text{31}\)

Because newborns infected with each of the agents so far 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 born 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 hepatitis B surface antigen (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 approximately 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 were discussed in the preceding subsections; however, some evidence indicates that transmission of several other agents—such as parvovirus B-19, varicella-zoster virus, and others—via this route is possible. 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.

### Table 2-5  Effects of Transplacental Fetal Infection

<table>
<thead>
<tr>
<th>Organism or Disease</th>
<th>Prematurity</th>
<th>Intrauterine Growth Retardation and Low Birth Weight</th>
<th>Developmental Anomalies</th>
<th>Congenital Disease</th>
<th>Persistent Postnatal Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Varicella-zoster</td>
<td>–</td>
<td>(+)</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Mumps</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(+)</td>
<td>–</td>
</tr>
<tr>
<td>Rubeola</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Vaccinia</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Smallpox</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Coxackieviruses B</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Echoviruses</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Polioviruses</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Influenza</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymphocytic chorio-meningitis virus</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>(+)</td>
<td>–</td>
</tr>
</tbody>
</table>

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


**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 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. 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.

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

![Figure 2-2](image_url)
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 the organism becomes infectious to humans. The extrinsic incubation period also has a median and range that are unique to each organism. The extrinsic incubation period can be affected by environmental conditions as well. 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°C and 35°C, they became infectious after only 7 days. 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.

**Pathogenicity**

Pathogenicity refers to the ability of a microbial agent to induce disease. Diseases such as rabies, smallpox, measles, chickenpox, 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. For example, 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, rank high in all three characteristics.

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. Contact with some organisms, such as measles, polio, HBV, and rubella, leads to solid, lifelong immunity after an infection. Other organisms, such as *Neisseria gonorrhoeae* and *Plasmodium falciparum*, are weakly immunogenic, so that reinfection commonly occurs. Studies of the antigens that produce protective immunity after natural infections often have led to the development of effective vaccines.

Some microorganisms may provoke an immune response that is not protective from future infections. In a sense, they are immunogenic. Even so, these immune responses may sometimes 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. Pathogenesis research in HIV infection is examining the role of immune activation in disease outcome. Inflammation of the immune system is a contributor to cardiovascular, renal, hepatic, and neural disease, and is also being studied as a component of aging and the development of frailty.

In other instances, antibodies may be generated that are markers of a previous or current infection but do not provide immunity to the organism or terminate an ongoing infection. These so-called *binding antibodies* react to non-neutralizing antigens (or epitopes) of the organism. Examples of such antibodies 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 the presence of a nucleic acid by polymerase chain reaction (PCR) amplification, or demonstration of a specific immune response in a
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 previously. 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. Likewise, inapparent nasopharyngeal carriage of meningococci is quite common, especially during an epidemic. 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 to curtail the subsequent spread of infection to their contacts. Inapparent infections with other organisms are quite rare—for example, most persons with measles, varicella, smallpox, or hanta virus infection are asymptomatic.

The proportion of infections that are symptomatic is of considerable importance in understanding the transmission of a disease 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 2-6.

### 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 Mallon 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 more than 200 persons were detected in hospitals in New York and New Jersey that were traced to her. After Mallon 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 more than 200 persons were detected in hospitals in New York and New Jersey that were traced to her. 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 gallbladders 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.

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 U.S. 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.\(^{59}\) 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 persons who chronically carried organisms in their 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 healthcare workers. As a result, use of HBV vaccine is routinely recommended for healthcare professionals who are likely to be exposed to this virus. 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, post-transfusion hepatitis declined to roughly half of the previous rate but was not eliminated. The hepatitis C virus was identified and screening for it was introduced 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 infected donors.

Currently, blood donors undergo extensive questioning about their risks related 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

<table>
<thead>
<tr>
<th>Category</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td>HIV, HTLV/II, HBV, HCV, HAV (rare), Parvovirus B-19, CMV, KSHV (HHV-8), West Nile Virus, Chikungunya Virus, Dengue, Others</td>
</tr>
<tr>
<td>Bacteria</td>
<td>T. pallidum (rare), Y. enterocolitica, Various gram-positive organisms by platelet transfusion (especially), Ehrlichia (rare)</td>
</tr>
<tr>
<td>Parasites</td>
<td>Trypanosoma cruzi, Plasmodium species, Babesia necrotica, Other agents, New variant Creutzfeldt-Jakob disease prion</td>
</tr>
</tbody>
</table>

### 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 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 and 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 are HSV-1 and HSV-2, varicella-zoster virus, and cytomegalovirus infections. Some infections may become chronic, with a variable proportion leading to progressive
Chapter 2  Epidemiology of Infectious Disease: General Principles

Tissue damage at the primary site of the infection. Typical of this pattern are 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 2-7.

The World Health Organization (WHO) estimates that more 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 2-8.

### Table 2-7  Natural History Patterns of Some Important Infectious Diseases

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

### Table 2-8  Infection and the Burden of Cancer Worldwide, 2008

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Incidence, N (age standardized rate per 100,000)</th>
<th>Mortality, N (age standardized rate per 100,000)</th>
<th>Infectious Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>988,602 (14.0)</td>
<td>737,419 (10.3)</td>
<td>H. pylori</td>
</tr>
<tr>
<td>Liver</td>
<td>749,744 (10.8)</td>
<td>695,726 (9.9)</td>
<td>HBV, HEV</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>530,232 (15.2)</td>
<td>275,008 (7.8)</td>
<td>HPV</td>
</tr>
<tr>
<td>Bladder</td>
<td>382,600 (5.3)</td>
<td>150,282 (2.0)</td>
<td>S. hematobium</td>
</tr>
<tr>
<td>Larynx</td>
<td>150,677 (2.2)</td>
<td>81,892 (1.2)</td>
<td>HPV</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>67,919 (1.0)</td>
<td>29,902 (0.4)</td>
<td>EBV</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>356,431 (5.1)</td>
<td>191,599 (2.7)</td>
<td>HBV, HCV, EBV</td>
</tr>
<tr>
<td>Leukemia</td>
<td>350,434 (5.0)</td>
<td>257,161 (3.6)</td>
<td>HTLV-1</td>
</tr>
</tbody>
</table>


The Immune Response to Infection

A detailed discussion of the immune responses to infection is well beyond the scope of this chapter. Instead, this topic is covered fully in the chapter on immunology. For now, however, it is 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 represent 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, although 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 and 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 (Ig) that are reactive with foreign antigens. Five different isoforms 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, but later an IgG predominance emerges. This pattern is useful in differentiating a recent infection (i.e., 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 play critical roles in 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 the former 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; they 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.

Granuloma reactions to an infection with mycobacteria consist 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-γ), 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-γ secreted by the T cell, which activates the toxic oxygen and enzymatic pathways of the macrophage.

**Granulocytes and Complement** Granulocytes are phagocytic cells that become involved in protection of the body against bacterial infections by ingesting and killing extracellular bacteria. The complement system comprises 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.11

**Innate Immunity** In addition to benefiting from acquired immunity, animals are protected from invasion by pathogenic organisms by a system of innate or native immunity. The innate immune system is prepared to control a range of pathogens immediately after they enter a host and does not have to develop and activate as the adaptive immune system does. A transmembrane receptor, named Toll, was first identified in Drosophila embryogenesis and subsequently found to be responsible for protecting insects against fungal infections. Toll-like receptors (TLRs) have since been identified in invertebrates, vertebrates, bacteria, and even plants. Given this diversity, they are probably among the most ancient of immune responses. These proteins recognize patterns of non-self molecules, such as bacterial lipopolysaccharides or RNA; such recognition triggers the intracellular defenses, including cytokines and enzymes, to destroy the foreign material.

**Quantification 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—that is, 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 dividing by the number of people in the population. The numerator is the number of persons who are ill, who have specific symptoms of the illness, or 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 prevalence. No matter which definition is used, it is critical that 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 only those persons who were exposed to the disease. 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 typically measured. Where exposure is rare, prevalence rates by exposure group are more frequently used.

The other commonly used measure in epidemiology is the incidence of disease. The incidence is either 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. In contrast, if 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 following equation:

\[
\text{Prevalence} = \frac{\text{Incidence} \times \text{Duration}}{100}
\]

At times, the incidence of a disease may be decreasing at the same time that the 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; concurrently, because of the effect of the drugs in reducing viral load, the transmission—that is, the incidence of new cases—may be decreasing.

In other infectious diseases that have short duration but for which infected persons remain susceptible to reinfection, the incidence may exceed the point prevalence. Affected 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. In this scenario, it may be preferable to measure the impact of a disease by determining its annual incidence rate. 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.

**SURVEILLANCE OF INFECTIOUS DISEASES**

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 healthcare workers, laboratories, clinics, and public health departments. Cases or outbreaks of selected infectious diseases are reported to the local health department by healthcare 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.

**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, and 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 2-4. 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. Figure 2-5 depicts the epidemiologic cycle of SLE in nature.

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 and the virus 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
Figure 2-4  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. Reproduced from MMWR. November 20, 1998/46(54):1–87. Figure 6.

Figure 2-5  The sylvatic cycles of Western and St. Louis encephalitis viruses. The natural inapparent cycles is between Culex tarsalis and nesting 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. Reprinted from Richard T. Johnson, Viral Infections of the Nervous System, © 1982. Raven Press, Lippincott Williams & Williams; p. 113.
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 are 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, however, 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 susceptible 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 was repeated every other 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, however, the rates of measles have decreased dramatically, and the cyclical occurrence of cases has changed. In contrast, cycles at 3- to 4-year intervals persisted quite stubbornly for reported cases of pertussis between 1967 and 1997 (Figure 2-6). 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 transmissibility 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. The investigations carried out by these researchers showed that, in fact, 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 large enough that it is unlikely that a susceptible individual 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 depends on the characteristics of the infectious disease. Those diseases 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 susceptible individuals to sustain an epidemic occurred every other year as new children were born. After an effective measles vaccine became available, however, epidemics were less common, were less predictable, and often involved older individuals. Epidemics occurred even in immunized populations when clusters of susceptible persons 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 remains 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 approximately 5% per year.

Tuberculosis mortality by age in the United States is highest in older age groups. 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. 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 2-7, the mortality rates are depicted as age-specific mortality by birth cohort. This 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 in more recent cohorts.

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 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 more than 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 deaths per 100,000 population for influenza and pneumonia to 6.8 deaths per 100,000 population for meningococcal infections. By 1970, only influenza and pneumonia infections were associated with mortality rates greater than 3 per 100,000 (Table 2-9).

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. However, this decline in mortality was reversed between 1980 and 1995, when the death rate increased to 63 deaths per 100,000 persons. In the early 20th century, the trend of a steady decline in infectious disease mortality 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 mortality from this cause declined sharply after 1945. Although the crude mortality rate for infectious diseases was dramatically reduced during the first eight

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

Data from the National Office of Vital Statistics, U.S. Public Health Service, and from the Centers for Disease Control and Prevention.
decades of the 1900s, the mortality from all noninfectious diseases has not shown a similar trend (Figure 2-8). 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 the 1900s, the mortality from coronary heart disease declined substantially, but this trend was 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 creation of vaccines and effective antibiotics to prevent or treat infections. In reality, 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 2-9). Similarly, death rates from scarlet fever, diphtheria, and whooping cough (pertussis) in children younger than 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 2-10). In addition, dramatic
Figure 2-10  (a) Mean annual death rate from scarlet fever in children under 15 years of age, England and Wales; (b) Mean annual death rate from diphtheria in children under 15 years of age, England and Wales; and (c) Mean annual death rate from whooping cough in children under 15 years of age, England and Wales. Reproduced from E. Kass. Infectious Diseases and Social Change. *Journal of Infectious Diseases*, Vol. 23(1):110–114. © 1971. By permission of Oxford University Press.
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 might 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, is still associated with a 15–20% mortality rate 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. 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 re-emergence 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 in West Africa possibly as early as the turn of the 20th century. 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 rochetlnea, and Penicillium marneffei. 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 infants and children in daycare centers, widespread use of broad-spectrum antibiotics, environmental pollution, and other factors have fostered the emergence of infectious diseases.

An analysis was done by investigators for the CDC of all deaths in the United States between 1980 and 1992. In this interval, the death rate due to infectious diseases as the underlying cause increased 38%, from 41 to 65 deaths per 100,000 population in the United States. Age-adjusted mortality from infectious diseases increased 83% 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 U.S. population, and that this trend 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 2-10.

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 through a collaboration of 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 95% of all deaths in children younger than 15 years of age occur in the developing world, and 50% of deaths in persons between ages 15 and 59 years of age happen in the developing world. The probability of death between birth and 15 years of age ranges from 22% in sub-Saharan Africa to 1.1% in the established
RECENT WORLDWIDE TRENDS IN INFECTIOUS DISEASE MORBIDITY AND MORTALITY

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 preventing mortality and increasing disability-adjusted life years (DALY). 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. Few other interventions are as cost-effective as tuberculosis case treatment. The WHO analysis estimated that $150 million would be needed to treat 65% of smear-positive cases in low-income countries and 85% of smear-positive individuals in 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. The roll-out of antiretroviral therapy for HIV infection coupled with a new resolve to tackle the TB epidemic holds promise that this combined effect may be successful. To be sure, the emergence of multidrug-resistant TB (MDR-TB)

<table>
<thead>
<tr>
<th>Table 2-10 Leading Underlying Causes of Mortality Caused by Infectious Diseases in the United States, 1980, 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rank</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>Total infectious diseases</td>
</tr>
<tr>
<td>All deaths</td>
</tr>
</tbody>
</table>

and extremely resistant TB (XDR-TB) has added new challenges to the control of TB. Nevertheless, it should be emphasized that active tuberculosis is usually sensitive to current chemotherapeutic regimes and can be controlled in both HIV-negative and -positive patients.

Other health interventions that are cost-effective for the prevention of infectious disease morbidity and mortality include 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 measures in this sense.

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, underlie the need for accurate surveillance and the development of newer strategies for their control and prevention. At the same time, the successes of the last century provide reason for hope that infectious diseases can be controlled with the proper understanding and effort.

*References*


