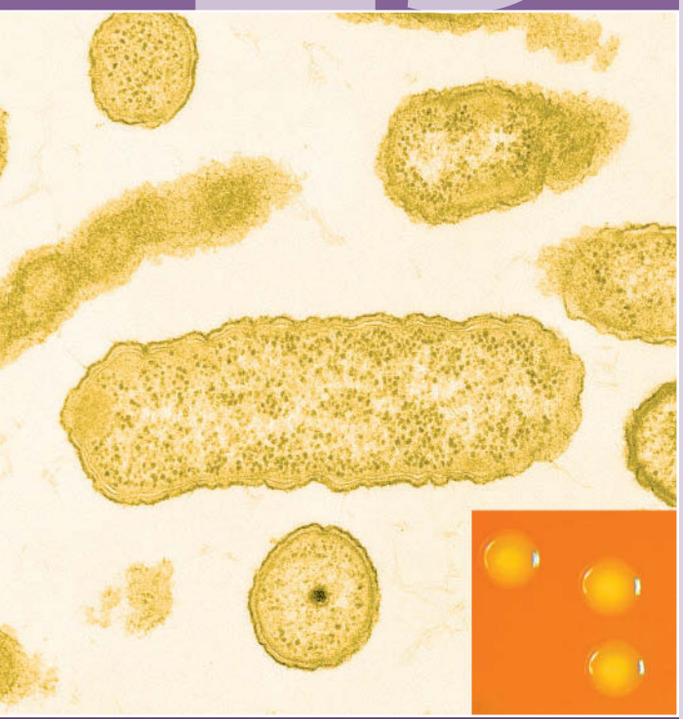
29

Epidemiology



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A Mysterious New Disease Outbreak

Although epidemiologists pay particular attention to large-scale disease outbreaks—cholera and the like—a disease tracker's job often entails investigating a very restricted outbreak. Such was the case with the recent *Elizabethkingia* outbreak in southern Wisconsin (USA).

Elizabethkingia anophelis is a gram-negative bacterium (main photo) of the phylum *Bacteroidetes* that forms translucent colonies on blood agar media (inset photo). The genus name *Elizabethkingia* honors American medical bacteriologist Elizabeth King, and the species epithet *anophelis* reflects the fact that this organism is the dominant bacterium in the gut of *Anopheles gambiae*, the mosquito that carries the malarial parasite. *Elizabethkingia* inhabits soil and water and is rarely linked to disease. However, in the spring of 2016, the Wisconsin Department of Public Health received reports of at least 63 confirmed cases of *E. anophelis* infection, and two additional cases, one each in Illinois and Michigan, were also reported. Of these 65 cases, 20 deaths (~30% mortality) occurred, showing that *E. anophelis* infections were indeed a serious threat.

E. anophelis is an opportunistic pathogen that can cause meningitis or bloodstream infections and can also colonize the respiratory tract. In the 2016 outbreak, the majority of infections and deaths were in patients over the age of 65 who had serious underlying health issues such as cancer, diabetes, recent surgery, or the like. This epidemiological observation suggested the possibility of a common source of infection. However, because *E. anophelis* is so widespread in the environment, many potential sources had to be checked. Common disease vehicles such as contaminated food or water were almost completely ruled out, as was person-to-person transmission. Contaminated medical equipment and a few other sources were suggested as possible explanations for the infections. However, pinpointing the primary source of the Wisconsin *E. anophelis* outbreak has thus far proven elusive.

Nevertheless, epidemiologists remain busy using their well-honed analytical skills to systematically eliminate some explanations for the Wisconsin *E. anophelis* outbreak while grouping together the most likely possibilities for further analysis. Using epidemiological methods, the source and the mode(s) of transmission of this pathogen will eventually be revealed and this should reduce *Elizabethkingia* infections to the usual number (5–10) typically reported from the entire United States each year.

Source: Multistate outbreak of infections caused by *Elizabethkingia anophelis*. 2016. Centers for Disease Control and Prevention, Atlanta, Georgia (USA). June 16, 2016.

We begin a new unit here with a focus on infectious diseases. Everything we have learned up to this point—cell structure, metabolism, growth, genetics, and genomics; microbial evolution, diversity, and ecology; and host–microbe relationships and the immune response—will help us better understand the disease strategies and exploitable weaknesses of infectious microbial agents.

As a prelude to our coverage of the clinical aspects of infectious diseases in the following four chapters, we explore the "big picture" of how infectious diseases flow through populations. **Epidemiology** is the study of the occurrence, distribution, and determinants of health and disease in populations and also deals with **public health**, the health of the population as a whole. Although in developed countries infectious diseases are not leading causes of death, in developing countries infectious diseases can account for nearly half of all deaths. Hence, identifying and solving problems associated with infectious disease transmission is a major goal of the epidemiologist.

I • Principles of Epidemiology

Here we consider the principles of epidemiology and define key terms in the lexicon of the epidemiologist.

29.1 The Language of Epidemiology

The epidemiologist traces the spread of a disease to identify its origin and mode of transmission in a population. The population might be all people in a certain city, country, or region, or it could be the entire human population. Alternatively, the population under study could be a particular cohort of a larger population, such as only males or only those of a specific race or age group. Raw data are gathered from disease-reporting networks such as city, county, state, and national public health departments, clinical records, and patient interviews.

A major job of the epidemiologist is to carry out **disease surveillance**—the observation, recognition, and reporting of diseases as they occur—and then analyze the data provided by local and national health authorities to reveal trends and signals of disease outbreaks. The epidemiologist thus stands in contrast to the clinical health provider—the one who actually treats the infected patient. However, in order to both track a disease and predict its spread in a population, the epidemiologist must integrate clinical and surveillance results to formulate effective public health measures for disease control.

Disease Incidence and Prevalence

The epidemiologist often uses the words *incidence* and *prevalence* when discussing infectious diseases. The **incidence** of a particular disease is the *number of new cases* in a population in a given time period (Figure 29.1). For example, in 2013 there were 47,352 new cases of HIV infection in the United States, for an incidence of 15 new cases per 100,000 people per year. The **prevalence** of a given disease is the *total number of new and existing disease cases* in a population in a given time period (Figure 29.1). For example, within the United States there were 1,194,039 persons living with HIV/AIDS at the end of 2013. Expressed another way, the prevalence of HIV/AIDS in the United States was about 375 cases per 100,000 persons in 2013.

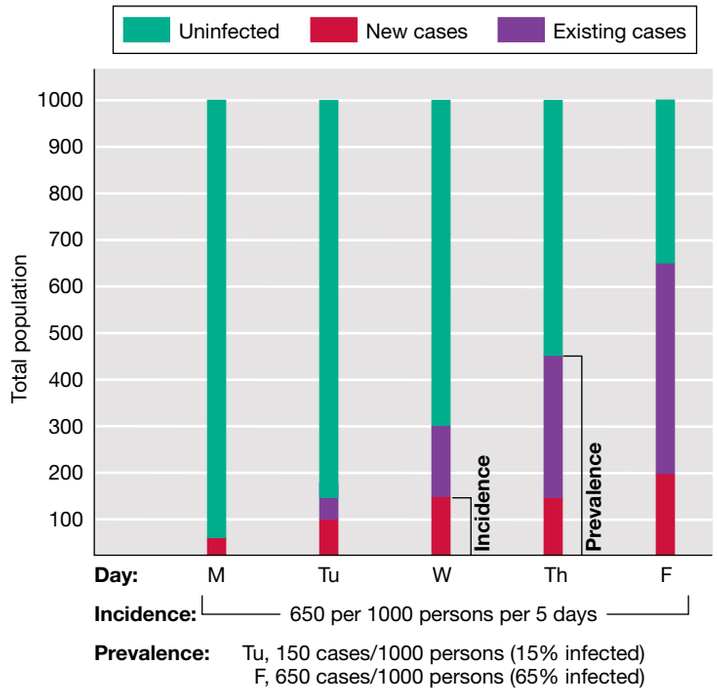


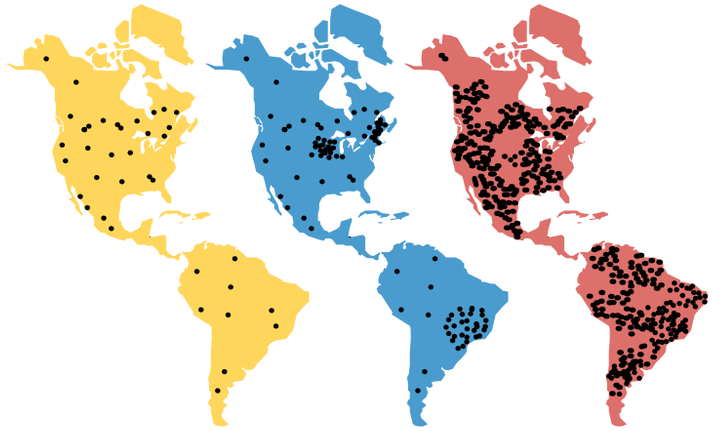
Figure 29.1 The concepts of disease incidence and disease prevalence. Disease incidence is a rate function and is defined as the number of new cases over a given time period (day[s], week, month, etc.); incidence is an indicator of infection risk. Disease prevalence is the total number of diseased individuals at some time point and is a snapshot of the extent of a disease in a population at any given time.

Essentially a *rate* measurement, disease incidence can be used to predict the *risk* of disease for an individual in a defined population within a specific time period. By contrast, prevalence measures the total disease burden in a population and can be thought of as a "snapshot" of the disease at a specific instant (Figure 29.1). The incidence and prevalence of disease are also major indicators of the public health of a population.

The Scope of Disease

Other common epidemiological terms speak to the scope of a disease. A disease is an **epidemic** when it simultaneously infects an unusually high number of individuals in a population; a **pandemic** is a widespread, usually global epidemic. By contrast, an **endemic disease** is one that is constantly present—typically in low numbers—in a population (Figure 29.2). An endemic disease implies that the pathogen may not be highly virulent or that the majority of individuals in the population may be immune, resulting in low but persistent numbers of cases. Individuals infected with a pathogen that causes an endemic disease are **reservoirs** of infection, a source of infectious agents from which susceptible individuals may be infected.

Sporadic cases of a disease occur one at a time in geographically separated areas, suggesting that the cases are not related. A disease **outbreak**, on the other hand, is the appearance of a large number of cases in a short time in an area previously experiencing only



(a) **Endemic disease** *(b)* **Epidemic disease** *(c)* **Pandemic disease**

Figure 29.2 Endemic, epidemic, and pandemic disease. Each dot represents a disease case or outbreak. *(a)* Endemic diseases are present in the population in specific geographical areas. *(b)* Epidemic diseases show high incidence in a wider area, usually developing from an endemic focus. *(c)* Pandemic diseases are distributed worldwide.

sporadic or endemic disease. Diseased individuals that show no symptoms or only mild symptoms are said to have *subclinical infections*. Subclinically infected individuals are frequently **carriers** of the particular pathogen, with the pathogen reproducing within them and being shed into the environment where it can infect others. Finally, the term **virulence**, often used in epidemiological parlance, is a measure of the *relative ability* of a pathogen to cause disease. Some pathogens are highly virulent while others are only weakly so (Section 25.3).

Stages of Disease

A well-adapted pathogen lives in balance with its host, taking what it needs for existence and causing only minimal harm. Such pathogens may cause **chronic infections** (long-term infections) in the host. When there is a balance between host and pathogen, both host and pathogen survive. Tuberculosis (Section 30.4) is a good example of a chronic infection. On the other hand, a host whose resistance is compromised because of factors such as poor diet, age, and other stressors can be harmed or even killed; for example, a chronic tuberculosis infection can eventually kill the host.

New pathogens occasionally emerge to which specific populations or even an entire species has not developed resistance. Such emerging pathogens often cause **acute infections**, characterized by rapid and dramatic disease onset and a relatively quick return to health. Influenza caused by a new strain of influenza virus (Section 30.8) would be an example of an acute infection, as would many other infectious diseases that show a rapid onset and recovery, such as various food infections and food poisonings (Chapter 32), or even the common cold (Chapter 30). The progression of clinical symptoms for an acute infectious disease can be divided into stages, and the terms used to describe these stages are also part of the epidemiologist's lexicon:

1. *Infection:* The organism invades, colonizes, and grows in the host.
2. *Incubation period:* Some time always passes between infection and the appearance of disease signs and symptoms. Some diseases, like influenza, have very short incubation periods, measured in days; others, like AIDS, have longer ones, sometimes extending for years. The incubation period for a given disease is determined by the inoculum size, the virulence and life cycle of the pathogen, and the resistance of the host. At the end of the incubation period, the first signs and symptoms, for example, a mild cough and a feeling of general fatigue in the case of an ensuing cold, usually appear.
3. *Acute period:* The disease is at its height, with overt symptoms and signs such as fever and chills.
4. *Decline period:* Disease signs and symptoms subside. As fever subsides, usually following a period of intense sweating, a feeling of well-being develops. The decline period may be rapid (within one day), in which case decline occurs by *crisis*, or it may be slower, extending over several days, in which case decline occurs by *lysis*.
5. *Convalescent period:* The patient regains strength and returns to the normal healthy state.

After the acute period, the immune mechanisms of the host (Chapters 26 and 27) become increasingly important for complete recovery from the disease.

Mortality, Morbidity, and DALY

The terms *morbidity* and *mortality* are commonly used in epidemiology. **Mortality** is the incidence of *death* in a population. Infectious diseases were the major causes of death worldwide in 1900, but they are now less prevalent in developed countries. Noninfectious "lifestyle" diseases such as heart disease and cancer are now much more prevalent in developed regions and cause higher mortality than do infectious diseases (Figure 1.8). However, this could change rapidly if public health measures were to break down. Worldwide, and especially in developing countries, infectious diseases are still major causes of mortality (Table 29.1 and see Figure 29.9).

Morbidity is the incidence of *disease* in a population and includes both fatal and nonfatal diseases. Morbidity statistics indicate the public health of a population more precisely than mortality statistics because many diseases have relatively low mortality. Put another way, the major causes of *illness* are quite different from the major causes of *death*. For example, high-morbidity infectious diseases include acute respiratory diseases such as the common cold and acute digestive disorders. However, seldom do these diseases cause death in populations living in developed countries. Thus, both of these diseases have high morbidity, but low mortality. On the other hand, Ebola virus infects relatively few people worldwide every year, but the mortality in some outbreaks approaches 70% and averaged 40% in the West African Ebola outbreak of 2013–2015. Thus, Ebola has low morbidity, but high mortality.

Epidemiologists tend to focus on morbidity and mortality statistics as a means of ranking the severity of pathogens and tracking disease trends. However, illness and death are not the only outcomes of an infectious disease. Lost among these statistics is the reduction in life quality and productivity due to a disease. The **disability-adjusted life year (DALY)** is a quantitative measure of disease burden and is defined as the cumulative number of

TABLE 29.1 Worldwide deaths due to infectious diseases[a]

Disease	Deaths (% of deaths from all infectious diseases)	Causative agent(s)
Respiratory infections[b]	31	Bacteria, viruses, fungi
Diarrheal diseases	15	Bacteria, viruses
Acquired immunodeficiency syndrome (AIDS)	13	Virus
Tuberculosis[c]	15	Bacterium
Malaria	6	Protist
Measles[c]	3	Virus
Meningitis, bacterial[c]	2	Bacterium
Pertussis (whooping cough)[c]	2	Bacterium
Tetanus[c]	1	Bacterium
Hepatitis (all types)[d]	1	Viruses
Other communicable diseases	11	Various agents

[a]Data show the ten leading causes of death due to infectious diseases and are representative of recent years. Worldwide in 2012 there were 56 million total deaths and 32% of these were from infectious diseases, nearly all in developing countries. In the United States in 2012, deaths from infectious diseases were about 4% of total deaths (influenza, pneumonia and septicemia were leading causes). Data adapted from data published by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia (USA).
[b]For some acute respiratory agents such as influenza and *Streptococcus pneumoniae* there are effective vaccines; for others, such as colds, there are no vaccines.
[c]Diseases for which effective vaccines are available.
[d]Vaccines are available for hepatitis A virus and hepatitis B virus. There are no vaccines for other hepatitis agents.

years lost due to an illness itself, a disability due to an illness (whether an infectious disease or not), or premature death.

The leading causes of death are not the leading causes of disability; about one-third of all disability years lost are due to psychiatric and neurological conditions. But many infectious diseases cause chronic disability and thus such data are important measures of the overall burden of disease. This is especially true of a series of *neglected tropical diseases*, a group of infectious diseases found mainly in tropical countries that are major disablers rather than killers. These include in particular parasitic worm infections such as hookworm, filariases, and schistosomiasis (Section 33.7). Hundreds of millions of people suffer from these infections worldwide, and although some die, most do not. However, life quality and longevity of survivors is oftentimes greatly diminished, and DALY numbers attempt to quantify this often overlooked but nevertheless important aspect of epidemiological statistics.

With some of the epidemiologist's common lingo in mind, we are now able to move on to consider how infectious diseases spread (or do not spread) in susceptible populations.

MINIQUIZ

- Why do epidemiologists acquire population-based data about infectious diseases?
- Distinguish between an endemic disease, an epidemic disease, and a pandemic disease.
- Which is more severe, a disease with a high mortality or one with a high morbidity? What is a DALY?

29.2 The Host Community

The colonization of a susceptible host population by a pathogen may lead to explosive infections, transmission to uninfected hosts, and an epidemic. As the host population develops resistance, however, the spread of the pathogen is checked, and eventually a balance is reached in which host and pathogen populations reach a state of equilibrium. In an extreme case, failure to reach equilibrium could result in death and eventual extinction of the host species. If the pathogen has no other host, then the extinction of the host also results in extinction of the pathogen. The evolutionary success of a pathogen thus depends on its ability to establish an equilibrium with its host rather than destroy the host population altogether. In most cases, the evolution of the host and the pathogen affect one another; that is, the host and pathogen *coevolve*.

Coevolution of a Host and a Pathogen

A classic example of host and pathogen coevolution is a case where myxoma virus was intentionally introduced to control an exploding wild rabbit population in Australia. The virus, spread by the bite of mosquitoes and also from animal to animal by direct contact, is extremely virulent for rabbits and causes fatal infections in susceptible animals. Within several months, the infection had spread over a large area, rising to peak incidence in the summer when the mosquito vectors were present, and then declining in the winter as mosquitoes disappeared. In this experiment, over 95% of the infected rabbits died during the first year, but within six years, wild rabbit mortality dropped to about 30%, indicating that the resistance of the wild rabbit population had increased dramatically (**Figure 29.3**). When virus isolated from these wild rabbits was used to infect laboratory rabbits that had not previously been

Figure 29.3 Myxoma virus and host coevolution. Myxoma virus was introduced into Australia to control the wild rabbit population. Virus virulence was measured as the average mortality in laboratory rabbits for infection with myxoma virus recovered from the field each year. Rabbit mortality was determined by removing young wild rabbits from dens and infecting them with a viral strain that killed 90–95% of control laboratory rabbits.

exposed to the virus, the virus could be seen to have lost virulence over the six-year period. This was further confirmed by the resistance observed in newborn wild rabbits exposed to the virus. Within three years, mortality of wild rabbits decreased by over 80% and maintained this resistance at a constant level (Figure 29.3). Thus, within just a few years, the rabbit population had evolved to reach an equilibrium with the pathogen.

For pathogens that do not exhibit host-to-host transmission, there is no selection for decreased virulence to support mutual coexistence, as was seen in the rabbit myxoma virus experiment. An example of this is *Clostridium tetani*, a common soil bacterium that causes tetanus when accidently introduced into flesh through a penetrating wound (Sections 25.6 and 31.9). Vector-borne pathogens transmitted solely by the bite of ticks or other arthropods, such as in spotted fever rickettsiosis (Rocky Mountain spotted fever, Section 31.3), are also under no evolutionary pressure to spare the human host. As long as the vector is only a *carrier* of the pathogen and does not contract the disease itself, there is no selection for weakened strains of the pathogen and thus the pathogen can maintain a high level of virulence.

Herd Immunity

Spread of an infectious disease through a highly susceptible population is typically much different than through a population where many, or even just some, potential hosts are immune, either from a previous natural infection with the same pathogen or by artificial means through vaccination. If a high enough proportion of the individuals in a population are immune to a pathogen, then the whole population can be protected, resulting in a collective level of resistance to infection called **herd immunity** (Figure 29.4).

The concept of herd immunity is easy to understand. In essence, what herd immunity amounts to is a breakage in the chain of pathogen transmission from one susceptible host to another because most hosts in the population are immune (Figure 29.4). Herd immunity is not a fixed number, and the assessment of herd immunity is important for understanding the development of epidemics. The more highly infectious a pathogen, or the longer its period of infectivity, the greater the proportion of immune individuals necessary to prevent epidemic disease spread. For a highly infectious disease such as measles, 90–95% of the population must be immune to confer herd immunity (see Table 29.3). By contrast, a lower proportion of immune individuals can prevent an epidemic of a less infectious agent or one with only a brief period of infectivity. Mumps virus, which is less infectious than measles virus, exhibits this pattern. In the absence of immunity, even poorly infectious agents can be transmitted from person to person if susceptible hosts have repeated or constant contact with an infected individual. This is the case for the transmission of H5N1 avian influenza among humans (Section 29.8).

MINIQUIZ

- Explain coevolution of host and pathogen. Cite a specific example.
- How does herd immunity prevent a nonimmune individual from acquiring a disease? Give an example.

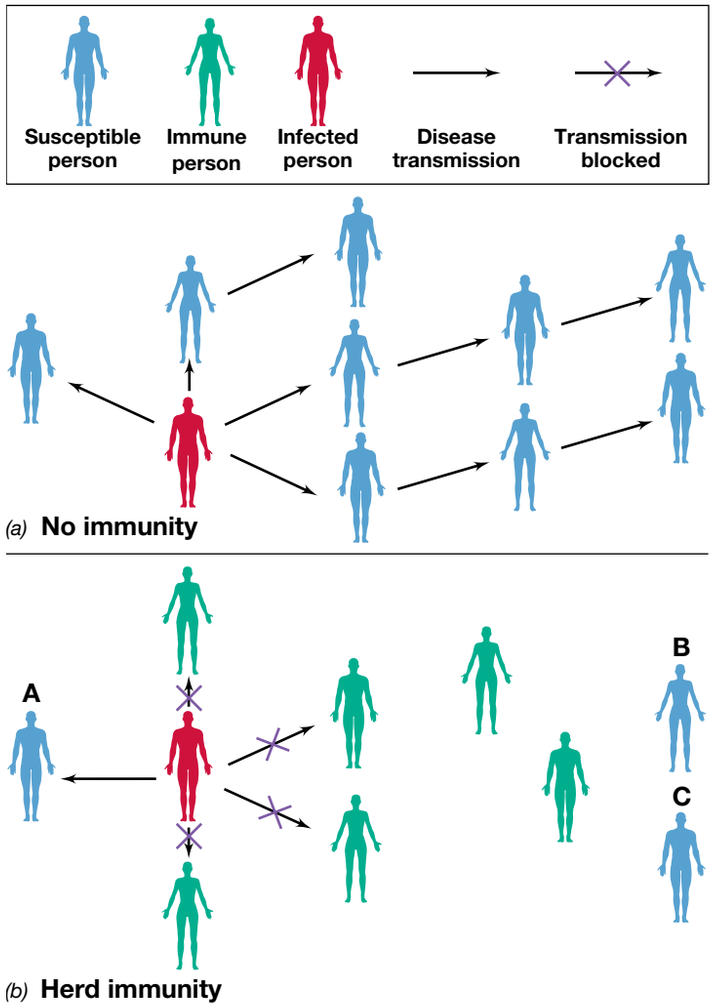


Figure 29.4 Herd immunity and transmission of infection. Immunity in some individuals protects individuals without immunity from infection. *(a)* In a population with no immunity, transfer of a pathogen from one infected individual can ultimately infect (arrows) all the individuals as newly infected individuals in turn transfer the pathogen to other individuals. *(b)* In a population that is only moderately dense and that has some immunity against a moderately transmissible pathogen such as influenza, an infected individual cannot transfer the pathogen to all susceptible individuals because resistant individuals, immune from previous exposure or immunization, break the cycle of pathogen transmission: Susceptible individual A becomes infected, but susceptible individuals B and C are protected. The proportion of a population that must be immune for herd immunity to be effective also varies with the disease; highly infectious diseases require a higher proportion of immune individuals for herd immunity to prevent transmission (see Table 29.3).

29.3 Infectious Disease Transmission and Reservoirs

Epidemiologists follow the transmission of a disease by correlating geographic, climatic, social, and demographic data with disease incidence. These correlations are then used to identify possible modes of transmission and disease patterns. Epidemiologists group infectious diseases by their *mode of transmission*. This approach reflects the ecology of the organism and is the pattern we will use in Chapters 30–33.

TABLE 29.2 Major means of human infectious disease transmission

Mode of transmission	*Examples*
Person to person	
Direct contact: Sexual intercourse; handshakes	Gonorrhea; *Staphylococcus aureus* infection
Indirect contact: Water glasses and other fomites	Influenza; common cold
Airborne droplets: Sneezes, coughing	Influenza; measles; tuberculosis
Vehicle	
Waterborne: Sewage-contaminated water	Cholera; giardiasis
Foodborne: Contaminated foods	Staphylococcal food poisoning; salmonellosis
Airborne: Fungal spores	Histoplasmosis; coccidioidomycosis
Soilborne: Puncture wound contaminated with soil	Tetanus
Soil aerosol or infected animal	Anthrax
Vector	
Arthropods/insects: Mites, ticks, mosquitoes	Typhus; Lyme disease; malaria

Modes of Disease Transmission

Three major modes of infectious disease transmission are known and are summarized in Table 29.2. These include diseases transmitted from *person to person*; diseases transmitted by some inanimate object or substance, called a *vehicle*; and diseases transmitted by *vectors*, that is, other organisms, especially those that access the bloodstream, such as ticks and biting insects. Each mechanism has three stages in common: (1) escape from the host or reservoir, (2) travel, and (3) entry into a new host.

Person-to-person disease transmission occurs when an infected host transmits a disease directly to a susceptible host without the assistance of an intermediate host or inanimate object. Upper respiratory infections such as the common cold and influenza are most often transmitted person to person by droplets resulting from sneezing or coughing. Many of these droplets, however, do not remain airborne for long, and so transmission requires close, although not necessarily intimate, person-to-person contact. Some pathogens are extremely sensitive to environmental factors such as drying and heat and are unable to survive for significant periods of time away from the host. These pathogens, transmitted only by intimate person-to-person contact such as exchange of body fluids in sexual intercourse, include those responsible for sexually transmitted diseases including syphilis (*Treponema pallidum*), gonorrhea (*Neisseria gonorrhoeae*), and HIV/AIDS (HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome). Direct person-to-person contact is also how pathogens such as staphylococci (boils and pimples) and fungi (ringworm) are transmitted. Some of these pathogens (*Staphylococcus aureus* is a good example) can spread by vehicle transmission as well because when inoculated into a vehicle such as food, they grow rapidly and produce poisonous toxins.

A marked seasonality or periodicity of a disease often signals a particular mode of transmission. For example, human influenza occurs in an annual cyclic pattern, causing epidemics propagated among schoolchildren and other populations of susceptible individuals. Cases of influenza are often high in schools or crowded offices because the virus is transmitted person to person by the respiratory route; peak incidence occurs in midwinter and early spring when schools are in session and people are indoors much of the day. However, seasonality can also result from environmental factors such as weather patterns that influence the survival of the pathogen or its vector. For example, California encephalitis—a viral disease transmitted by mosquitoes—shows a pattern opposite that of influenza; the disease peaks during the summer and fall months but disappears in the winter, coinciding with the activity of its mosquito vector (Figure 29.5).

Diseases are often transmitted to humans by other organisms and by inanimate objects. Living disease carriers are called **vectors**, and arthropods (mites, ticks, or fleas) and vertebrates (dogs, cats, or rodents) are common disease vectors. Vectors are often not definitive hosts for the pathogen but simply carry the pathogen from one host to another. For instance, many arthropods obtain their nourishment by biting and sucking blood, and if the pathogen is present in the blood, the arthropod will ingest the pathogen and transmit it when biting another individual. In some cases viral pathogens multiply in the arthropod vector, which is then considered an *alternate host*. Such is the case for West Nile virus (in the *Culex* mosquito) and the bacterium *Yersinia pestis* (in the rat flea), the causative agent of plague (Sections 31.6 and 31.7). Such

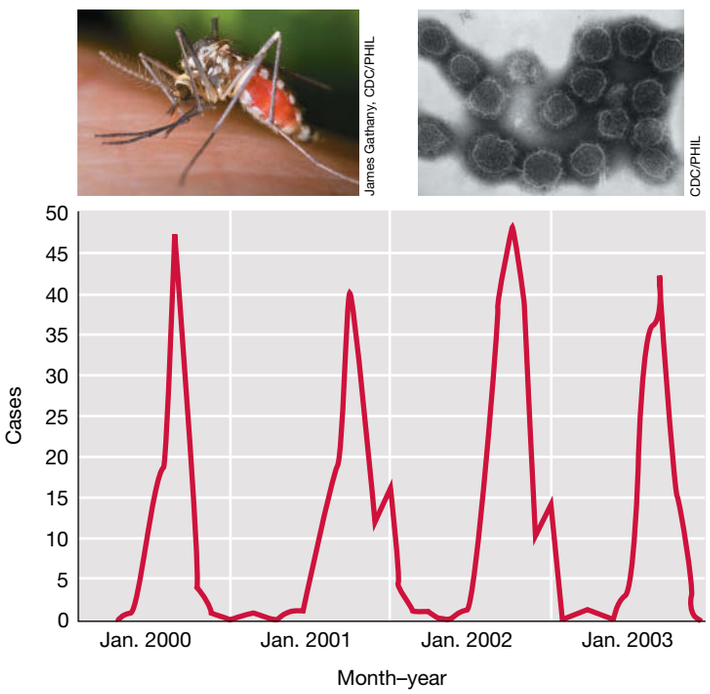


Figure 29.5 Cyclical nature of California encephalitis in the United States. California encephalitis is transmitted by the mosquito *Ochlerotatus triseriatus* (left photo) and is caused by the La Crosse encephalitis virus, a negative-strand and enveloped RNA virus (right photo). Because it depends on a seasonally available vector, disease incidence shows a sharp rise in late summer, followed by a complete decline in winter. Data are from the CDC, Atlanta, Georgia, USA.

replication leads to greater pathogen abundance in the vector, and this increases the probability that a subsequent bite will lead to infection.

Inanimate agents such as bedding, toys, books, and surgical instruments can also transmit disease. Inanimate objects that, when contaminated with a viable pathogen, can transfer the pathogen to a host are called **fomites**. The term **vehicle** is used to describe nonliving sources of pathogens that, upon entering the body, may transmit disease to large numbers of individuals; common disease vehicles are contaminated food or water (Table 29.2). A key distinction here is that fomites are nonliving objects that are touched or handled by a limited number of individuals, whereas vehicle-source epidemics are typically traced to contaminated food or water—shared commodities consumed in large amounts by local or regional populations.

Disease Carriers and Disease Reservoirs and Control

As described earlier, a disease *carrier* is a pathogen-infected individual who has a subclinical infection and shows either no symptoms or only mild symptoms of the disease; carriers are thus potential sources of infection for others. Carriers may be in the incubation period of the disease, in which case the carrier state precedes the development of actual symptoms (Section 29.1). Respiratory infections such as colds and influenza, for example, are often spread via carriers who are unaware of their infection and so are not taking any precautions against infecting others. The carrier state lasts only a short time for carriers who develop acute disease. However, *chronic carriers* usually appear healthy and may spread disease for extended periods of time. Some examples here include carriers of hepatitis B, typhoid fever, HIV/AIDS, tuberculosis, and upper respiratory *Staphylococcus aureus* infections.

Disease reservoirs are sites at which infectious agents remain viable and from which individuals may become infected. Reservoirs may be either animate or inanimate. Some pathogens whose reservoirs are not in animals only incidentally infect humans and cause disease. For example, some species of *Clostridium*, common soil bacteria, occasionally infect humans, causing life-threatening diseases such as tetanus, botulism, and gangrene. In these cases, the pathogen is not dependent on the host for survival, so host–pathogen balance is not required. For many pathogens (including many human pathogens) however, living organisms are the only reservoirs. In these cases, the host is essential for the life cycle of the infectious agent; maintenance of human pathogens of this kind requires host-to-host transmission. Many viral and bacterial respiratory pathogens and sexually transmitted pathogens fall into this category. When humans are the main or only disease reservoir, infection control may be easy or not so easy. With diphtheria, for example, confirmed cases must be isolated and quarantined (Section 29.5). However, for a disease like gonorrhea, where inapparent symptoms are common in females, tracking down and treating disease carriers can be difficult if not impossible.

Some infectious diseases are caused by pathogens that reproduce in both humans and animals. A disease that primarily infects animals and is only occasionally transmitted to humans is called a **zoonosis**; rabies is a good example. The reservoir for rabies is wild mammals, primarily skunks, raccoons, foxes, and certain bats. Although person-to-person transmission of zoonoses is rare, control of zoonoses in humans is nearly impossible because of the frequent contact some humans have with wild animals and the fact that the animal reservoir can probably never be effectively controlled. Certain other infectious diseases are caused by organisms such as protists and helminths (parasitic worms) that undergo complex life cycles including an obligate transfer from a nonhuman host to a human host back to the nonhuman host; the diseases malaria and schistosomiasis (Chapter 33) are good examples here. In the case of malaria, the major reservoir other than humans is the mosquito *Anopheles gambiae*, and some control of the disease can be achieved by chemical or physical controls on the insect reservoir. In schistosomiasis, by contrast, the reservoir is an aquatic snail and therefore although treatments for the disease are possible, eliminating the reservoir is not an option.

MINIQUIZ

- What is a zoonotic disease? A disease reservoir?
- What is the difference between a disease vehicle and a disease vector?
- Why will a disease such as human rabies likely never be eliminated?

29.4 Characteristics of Disease Epidemics

Endemic infectious diseases are constantly present over long periods of time but typically occur at only low incidence in the

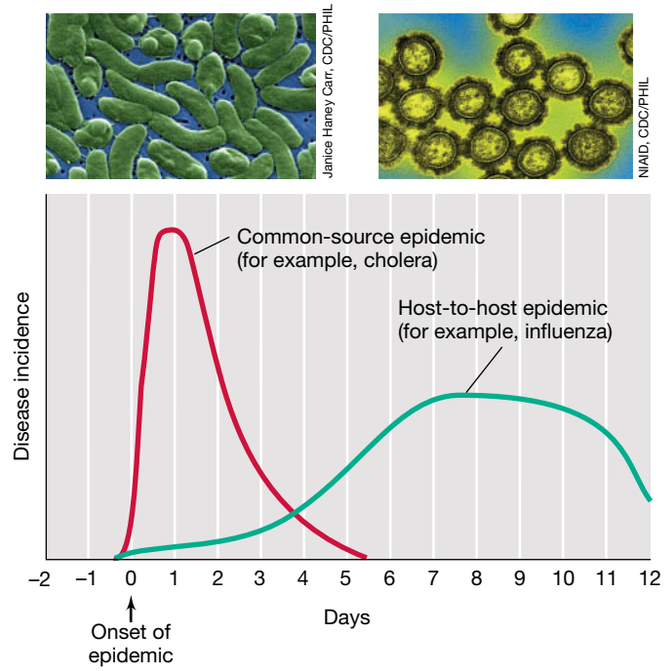


Figure 29.6 Types of epidemics. The shape of the curve that plots incidence of an epidemic disease against time identifies the likely type of the epidemic. For a common-source epidemic, such as cholera resulting from contaminated water shared by many people, the curve rises sharply to a peak and then declines rapidly. Host-to-host infectious disease incidence rises relatively slowly as new cases accumulate. Inset photos: left, scanning electron micrograph of a *Vibrio* sp. closely related to *Vibrio cholerae*, the cholera agent; right, transmission electron micrograph of virions of H1N1 influenza virus.

TEXTBOOK EPIDEMIOLOGY: THE SARS EPIDEMIC

Handling of the *s*evere *a*cute *r*espiratory *s*yndrome (SARS) epidemic early in this century is an excellent example of the successful application of the principles of epidemiology. Like many other rapidly emerging diseases, SARS is viral and originated in animals. Such characteristics have the potential to trigger explosive disease in humans when the infectious agents cross host species barriers.

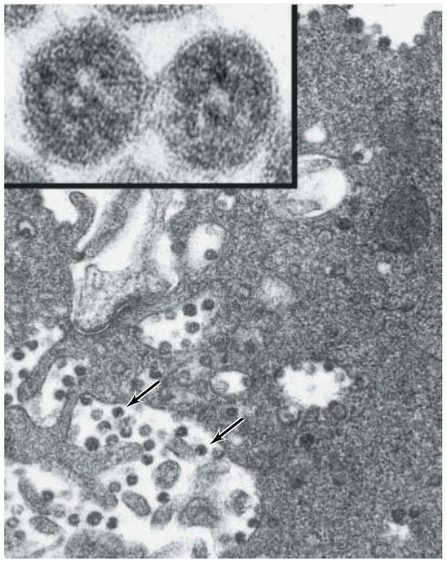
The SARS epidemic began in late 2002 in China, and by early 2003, the virus had spread to 28 countries, primarily via international travelers. The cause of SARS was quickly traced to a coronavirus coined SARS-CoV (**Figure 1**) that most probably originated in bats. From bats, the virus infected civets (a small, nocturnal, catlike animal used as a food source in China) and from there jumped to humans.

Much like common cold viruses, SARS-CoV is a relatively hardy, very infectious RNA virus that is difficult to contain (R_0 of 3.6). Once in humans, SARS-CoV quickly spreads from person to person by sneezing and coughing or by contact with contaminated fomites or feces. Ordinarily, a new coldlike virus would be of little concern, but SARS-CoV caused infections with significant mortality. From the 8500 known SARS-CoV infections, there were over 800 deaths, for an overall mortality rate approaching 10%. In persons over 65 years of age, the mortality rate approached 50%, attesting to the virulence of SARS-CoV as a human pathogen.

About 20% of all SARS cases were in healthcare workers, demonstrating the high infectivity of the virus. Standard containment and infection-control methods practiced by healthcare personnel were not effective in controlling spread of the disease. As a result, SARS patients were placed in strict isolation in negative-pressure rooms, and healthcare staff caring for SARS patients wore respirators when working with patients or when handling fomites (bed linens, eating utensils, and so on) to prevent infection.

The recognition and containment of the SARS outbreak was the start of an international response that included clinicians, scientists, and public officials. Almost immediately, travel to and from the endemic area was restricted, limiting further outbreaks. SARS-CoV was quickly isolated and cultured, and its genome was rapidly sequenced; this allowed simple PCR tests to be developed to detect the virus in samples. As laboratory work progressed, epidemiologists traced the virus back to the civet food source in China and stopped further transmission to humans by restricting the sale of civets and other foods from wild sources. These actions collectively stopped the outbreak.

As international travel and trade expand, the chances for propagation and rapid dissemination of new exotic diseases will increase. SARS is an example of a serious infection that emerged very rapidly from a unique source. However, rapid identification and characterization of the SARS pathogen, nearly instant development of worldwide notification procedures and diagnostic tests, and a concerted effort to understand the biology and genetics of this novel pathogen controlled the disease; there have been no cases of SARS since early 2004. The rapid emergence of SARS, and the equally rapid and successful international effort to identify and control the outbreak, provide a textbook example of the explosive nature of some emerging pathogens and how control of emerging epidemics is possible if strict disease surveillance and infection control are practiced.



CDC/C.S. Goldsmith, T.G. Ksiazek, S.R. Zaki/Public Health Image Library

Figure 1 Severe acute respiratory syndrome coronavirus (SARS-CoV). The upper left panel shows isolated SARS-CoV virions. An individual virion is 128 nm in diameter. The large panel shows coronaviruses (arrows) within cytoplasmic membrane–bound vacuoles and in the rough endoplasmic reticulum of host cells. The virus replicates in the cytoplasm and exits the cell by way of the cytoplasmic vacuoles.

population. In tropical Africa, for example, malaria is endemic; both morbidity and mortality from malaria have remained relatively constant on a long-term basis. The 2014 outbreak of Ebola hemorrhagic fever in West Africa, by contrast, ran to epidemic proportions in major districts of Sierra Leone, Liberia, and Guinea.

Disease epidemics show characteristic features (**Figure 29.6**) and require that rapid epidemiological conclusions be reached and clinical treatment instituted if the epidemic is to be contained. The characteristic features of epidemics include distinct patterns in the disease cycle and inherent properties of the pathogen that affect its virulence and herd immunity. A good example is the 2003 SARS epidemic that began in Asia (see Explore the Microbial World, "Textbook Epidemiology: The SARS Epidemic"). The SARS *epidemic* could potentially have grown to a SARS *pandemic* but was rapidly suppressed by a combination of quick and effective epidemiological and clinical action.

Epidemics

Major epidemics are usually classified as either *common-source epidemics* or *host-to-host epidemics*. The patterns of disease incidence observed in these two types of epidemics are contrasted in Figure 29.6.

A **common-source epidemic** results from an infection (or intoxication) of a large number of people from a contaminated source such as food or water that all infected individuals have ingested. Such epidemics are often caused by a breakdown in the sanitation of a central food or water distribution system, but they can also be more local, such as contaminated food in a particular

restaurant. Foodborne and waterborne common-source epidemics are primarily intestinal diseases; the pathogen leaves the body in fecal material, contaminates food or water supplies as a result of improper sanitation, and then enters the intestinal tract of the recipient during ingestion of the food or water (Chapter 32).

Common-source disease outbreaks are characterized by a rapid rise to a peak incidence because a large number of individuals become ill within a relatively brief period of time (Figure 29.6). Moreover, assuming that epidemiological surveillance quickly identifies the disease vehicle, cases of a common-source disease declines fairly rapidly, as well. Cholera is the classic example of a common-source epidemic as the disease is almost exclusively waterborne; if a sanitation breakdown occurs (or if sanitation is totally lacking, as is often the case in developing countries), the cholera bacterium can be shed from a carrier or an active infection into a water source used by many other people and quickly trigger an epidemic (Figure 29.6).

In contrast to the common-source disease pattern, in a **host-to-host epidemic** the disease incidence shows a relatively slow, progressive rise (Figure 29.6) and a gradual decline. Cases continue to be reported over a period of time equivalent to several incubation periods of the disease. A host-to-host epidemic can be initiated by the introduction of a single infected individual into a susceptible population, with this individual infecting one or more people depending on the extent of herd immunity (Figure 29.4) in that population. In a host-to-host epidemic, the pathogen replicates in susceptible individuals, reaches a communicable stage, is transferred to other susceptible individuals, and again replicates and becomes communicable; such epidemics are often controlled by effective herd immunity due to previous infection or vaccination. Influenza and chicken pox (Chapter 30) are examples of diseases that can spread in host-to-host epidemics.

Basic Reproduction Number (R_0)

The infectivity of a pathogen can be predicted using mathematical models that estimate the **basic reproduction number (R_0)** that the pathogen may trigger. The R_0 is defined as the number of expected secondary transmissions from each single case of a disease in an entirely susceptible population, and Table 29.3 lists the R_0 of selected infectious diseases. R_0 directly correlates with the herd immunity necessary to prevent spread of infection; the higher the R_0 value, the greater the herd immunity required to stop infection (Table 29.3). Unfortunately, conditions are not always ideal and the mathematical models that predict R_0 may not take into account such factors as numbers of recovered individuals, population density (close contact), length of contact time, populations of high-risk individuals, and other variables that may affect disease spread. As a result, R_0 is a theoretical construct and can only estimate infectivity. Nevertheless, R_0 is still useful as a gauge of the relative infectivity of a pathogen and helps to establish targets for immunization coverage to prevent spread of a particular infectious disease.

The *observed reproduction number, R*, calculated from studies of actual disease spread, is a more empirical term because it takes into account observed transmissions from infected to susceptible individuals. Gathering the epidemiological data necessary to calculate an accurate *R* is often problematic, but for some diseases an empirical reproduction number has been obtained. For example, for the SARS epidemic of 2003 (see Explore the Microbial World, "Textbook Epidemiology: The SARS Epidemic"), the observed *R* was 3.6, matching its R_0 value (Table 29.3). Public health officials, recognizing the potential for a serious epidemic, instituted major infection controls including isolation of infected individuals and strict barrier protection for healthcare personnel. These measures reduced the SARS *R* value to 0.7 and ended the threat of further disease spread.

TABLE 29.3 Basic reproduction number (R_0) and herd immunity necessary for community protection from selected infectious diseases

Disease	[a]R_0	*Herd immunity*[a]
Diphtheria	7	85%
Ebola	1.8	—
Influenza[b]	1.6	29%
Measles	18	94%
Mumps	7	86%
Pertussis	17	94%
Polio	7	86%
Rubella	7	85%
SARS-CoV	3.6	—
Smallpox	7	85%

[a] R_0 and herd immunity values are the highest estimates for each disease. Herd immunity values are shown only for those diseases for which vaccines are available.
[b] Values shown are for the pandemic (H1N1) 2009 influenza. Each influenza epidemic has a different R_0 and herd immunity value. Herd immunity values assume a 100% effective vaccine. Vaccine efficacy for influenza is about 60% and observed herd immunity values are 40% or greater depending on the susceptible host populations.

MINIQUIZ

- Distinguish between direct and indirect transmission of disease. Cite at least one example of each.
- By using epidemiological surveillance data, how can a common-source epidemic be recognized?
- Define the basic reproduction number for a pathogen.

II • Epidemiology and Public Health

In Part II, we focus on public health issues including some of the methods and tools used to identify, track, contain, and eradicate infectious diseases within populations. We also draw a stark contrast between the causes of mortality in developed versus developing countries. Although noninfectious diseases are the major killer in developed countries, infectious disease remains the leading cause of mortality in other countries.

29.5 Public Health and Infectious Disease

Public health refers to the health of the general population and to the activities of public health authorities in the control of disease. The incidence and prevalence of many infectious diseases

dropped dramatically during the twentieth century, especially in developed countries, because of universal improvements in public health from advances in basic living conditions. Access to safe water and food, improved public sewage treatment, less crowded living conditions, and lighter workloads have all contributed immeasurably to disease control. Several historically important diseases, including smallpox, typhoid fever, diphtheria, brucellosis, and poliomyelitis, have been controlled (and in the case of smallpox, even eliminated) by active, disease-specific public health measures, and we review these here.

Controls Directed against Common Vehicles and Major Reservoirs

Common vehicles for pathogen dispersal include food, water, and air. The control of foodborne and waterborne pathogens (Chapter 32) has seen the greatest successes through improved methods of preventing microbial contamination of food and water. For example, water purification methods have dramatically reduced the incidence of typhoid fever (**Figure 29.7**), and laws controlling food purity, preparation, and storage coupled with strict monitoring of the food and water distribution network have greatly decreased the incidence of common-source disease. However, in contrast to food and water, controlling transmission of respiratory (airborne) pathogens is much more difficult. Other than wearing personal protection such as face masks and avoiding individuals you know are infected, few effective measures of airborne infection control are possible except in specialized environments such as hospital operating rooms where chemical and physical agents can treat the rather small amount of circulating air.

When the disease reservoir is primarily *domestic* animals, infection of humans can be prevented if the disease is eliminated from the infected animal population by vaccinating herds and removing diseased individuals. However, as we have seen (Section 29.3), when the disease reservoir is a *wild* animal, eradication is much more difficult. Eradication of rabies, for example, would require the immunization or destruction of all wild animal reservoirs, a virtually impossible task. When insect vectors are involved, effective control can often be accomplished with insecticides. However, the use of chemicals must be balanced with health and environmental concerns because in some cases, the elimination of one public health problem (the disease vector) simply creates another (toxic chemical exposure).

When humans are the disease reservoir—as, for example, in HIV/AIDS—control and eradication can be difficult, especially, as mentioned previously in reference to gonorrhea, if there are asymptomatic carriers. By contrast, certain diseases that are limited to humans and have no asymptomatic phase can be prevented through immunization or treatment with antimicrobial or other drugs. However, the disease can be eradicated only if those who have contracted the disease and all possible contacts are immunized, treated, or if necessary, quarantined. Such a strategy was successfully employed by the World Health Organization to eradicate smallpox worldwide (see later) and is currently being used to eradicate polio.

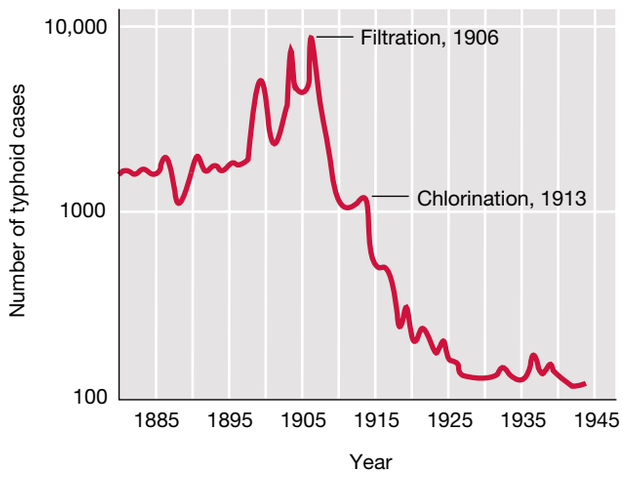


Figure 29.7 Historical progression of typhoid fever in Philadelphia. The introduction of filtration and chlorination eliminated typhoid fever in Philadelphia and other cities with well-regulated water supplies. The risk of typhoid in the United States today is very low but occasional cases are reported.

Immunization

Smallpox, diphtheria, tetanus, pertussis (whooping cough), measles, mumps, rubella, and poliomyelitis have been controlled primarily by immunization. Diphtheria, for example, is no longer considered even endemic in the United States. Vaccines are routinely administered in childhood for a number of other infectious diseases (Figure 28.25). As we discussed in Section 29.4, 100% immunization is not necessary for effective disease control in a population because of herd immunity, although the percentage needed to ensure disease control varies with the infectivity and virulence of the pathogen (Table 29.3).

Measles epidemics offer an example of the power of herd immunity. The occasional resurgence of the highly contagious measles virus ($R_0 = 18$, Table 29.3) emphasizes the importance of maintaining appropriate immunization levels for a given pathogen. Until 1963, the year an effective measles vaccine was licensed, nearly every child in the United States acquired measles through natural infections, resulting in over 300,000 annual cases. However, after introduction of the vaccine, the number of annual measles infections decreased rapidly (**Figure 29.8**). Case numbers reached a low of 1497 by 1983. However, by 1990, the percentage of children immunized against measles fell to 70%, and the number of new cases rose to 27,786. A concerted effort to increase measles immunization levels to above 90% (about that needed for effective herd immunity, Table 29.3) virtually eliminated measles in the United States.

Isolation, Quarantine, and Surveillance

Isolation and quarantine are effective public health measures. **Isolation** is the separation of persons who have an infectious disease from those who are healthy. **Quarantine** is the separation and restriction of well persons who may have been exposed to an infectious disease to see if they develop the disease. The length of isolation or quarantine for a given disease varies and is typically the longest period of communicability for that disease. To be effective, these measures must prevent infected or potentially infected individuals from contacting uninfected susceptible individuals. By international agreement, six infectious diseases

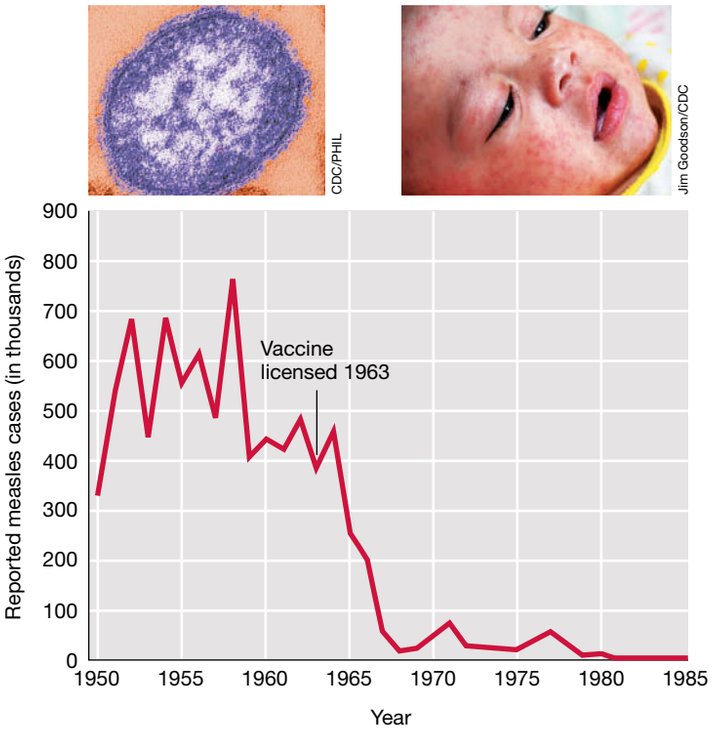


Figure 29.8 Measles immunization in the United States. The introduction of a measles vaccine eliminated measles as a common childhood infection within 20 years. Inset photos: left, transmission electron micrograph of a measles virion (a negative-strand enveloped RNA virus); right, photo of an infant showing the spotted rash characteristic of measles. With an extremely high R_0 (Table 29.3), measles outbreaks can spike quickly in unvaccinated populations.

require isolation and quarantine: *smallpox, cholera, plague, yellow fever, typhoid fever*, and *relapsing fever*. Each is a very serious, particularly communicable disease. Spread of certain other highly contagious diseases such as Ebola hemorrhagic fever, SARS, H5N1 influenza, and meningitis may also be subject to quarantine or isolation as outbreaks emerge in particular regions.

As mentioned earlier (Section 29.1), disease surveillance is a major job of the epidemiologist. Table 29.4 lists the infectious diseases currently under surveillance (referred to as *reportable diseases*) in the United States. The **Centers for Disease Control and Prevention (CDC)** is the agency of the United States Public Health Service that tracks disease trends reported by physicians and other health professionals, provides the latest disease information, and forms public policy regarding disease prevention. The CDC operates a number of infectious disease surveillance programs and also carries out surveillance of major noninfectious diseases, such as cancers, heart disease, and stroke. The overall practical goal of disease surveillance is to formulate and implement plans for diagnosis and treatment of infections.

Pathogen Eradication

Concerted disease eradication programs can sometimes completely eradicate an infectious disease and such was the case with naturally occurring smallpox, eradicated worldwide in 1980. Smallpox was a viral disease with a virus reservoir consisting solely of the individuals with acute smallpox infections, and transmission was exclusively person-to-person through direct contact. Although smallpox cannot be treated once acquired, immunization practices have been very effective. The World Health Organization (WHO) implemented a smallpox eradication plan in 1967. Because of the success of previous vaccination programs, smallpox had already been confined to endemic status in parts of Africa, the Middle East, and the Indian subcontinent. WHO field health workers proceeded to vaccinate everyone in these areas they could locate with the goal of providing either direct or herd immunity (Section 29.2) to the entire population. Each subsequent outbreak or suspected outbreak was targeted by WHO teams that quickly traveled to the outbreak site, quarantined individuals with active disease, and vaccinated all contacts. To break the chain of possible infection, they then immunized everyone who had contact with the contacts, and this aggressive vaccination policy eventually eliminated smallpox.

Several other communicable diseases are candidates for global eradication. Poliomyelitis, like smallpox a viral disease with a human-only reservoir, is on its way to elimination using the same

TABLE 29.4 Reportable infectious agents and diseases in the United States, 2016

Diseases caused by bacteria
- Anthrax
- Botulism
- Brucellosis
- Chancroid
- *Chlamydia trachomatis* infection
- Cholera
- Diphtheria
- Ehrlichiosis/Anaplasmosis
- Gonorrhea
- *Haemophilus influenzae*, invasive disease
- Hansen's disease (leprosy)
- Hemolytic uremic syndrome
- Legionellosis
- Listeriosis
- Lyme disease
- Meningococcal disease (*Neisseria meningitidis*)
- Pertussis
- Plague
- Psittacosis
- Q fever
- Salmonellosis
- Shiga toxin–producing *Escherichia coli* (STEC)
- Shigellosis
- Spotted fever rickettsiosis
- Streptococcal toxic shock syndrome
- *Streptococcus pneumoniae*, invasive disease
- Syphilis, all stages
- Tetanus
- Toxic shock syndrome (staphylococcal)
- Tuberculosis
- Tularemia
- Typhoid fever
- Vancomycin-intermediate *Staphylococcus aureus* (VISA)
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Vibriosis (non-cholera *Vibrio* infections)

Diseases caused by viruses
- Arboviruses (encephalitis, non-neuroinvasive disease, and Zika)
- Dengue
- Hantavirus pulmonary syndrome
- Hepatitis A, B, C
- HIV infection/AIDS
- Novel influenza A
- Measles
- Mumps
- Polio
- Rabies
- Rubella
- Severe acute respiratory syndrome (SARS-CoV)
- Smallpox
- Varicella (chicken pox)
- Viral hemorrhagic fevers
- West Nile virus
- Yellow fever

Diseases caused by protists
- Babesiosis
- Cryptosporidiosis
- Cyclosporiasis
- Malaria
- Giardiasis

Disease caused by a helminth
- Trichinellosis (trichinosis)

Disease caused by a fungus
- Coccidioidomycosis/Valley fever

vaccination strategy used against smallpox; in 2014, a total of only 359 cases of polio were reported worldwide. Diseases caused by parasites have also been targeted, including Chagas disease (by treating active cases and destroying the insect vector) and dracunculiasis (by treating drinking water to prevent transmission of *Dracunculus medinensis*, the Guinea helminth parasite). Eradication of certain bacterial diseases is also on the horizon. For example, syphilis is a candidate because the disease is found only in humans and is readily treatable with antibiotics. Diphtheria, caused by the bacterium *Corynebacterium diphtheriae*, could also be eradicated worldwide by application of the strict immunization protocols that have virtually eliminated diphtheria from North America.

MINIQUIZ

- Compare public measures for controlling infectious disease caused by insect vectors and human carriers.
- Outline the steps taken to eradicate smallpox.
- Describe some of the public health activities of the U.S. Centers for Disease Control and Prevention.

29.6 Global Health Comparisons

The World Health Organization (WHO) has divided the world into six geographic regions for the purpose of collecting and reporting health information such as causes of morbidity and mortality. These geographic regions are Africa, the Americas (North America, the Caribbean, Central America, and South America), the eastern Mediterranean, Europe, Southeast Asia, and the western Pacific. Here we compare mortality data from a relatively developed region, the Americas, to those from a developing region, Africa, to emphasize the fact that infectious diseases are still major causes of morbidity and mortality in many regions of the world.

Infectious Disease in the Americas and Africa

Mortality statistics in developed and developing countries are significantly different, as illustrated by a comparison of data from the Americas and from Africa in 2008 when the worldwide population was nearly 6.8 billion. Worldwide, 60.8 million individuals died, giving a mortality rate of 8.8 deaths per 1000 inhabitants per year, and 15.8 million (26%) of these deaths were attributable to infectious diseases. There were 924 million people in the Americas in 2008 and there were 5.6 million deaths, or 6.1 deaths per 1000 persons per year. In Africa, there were 837 million people in 2008 and 14.1 million deaths, or 16.8 deaths per 1000 persons per year. These statistics clearly show differences in overall mortality between developed and developing countries, but a comparative examination of the *causes* of mortality is even more instructive.

Figure 29.9 indicates that infectious diseases caused the most deaths in Africa, whereas in the Americas, noninfectious diseases such as cancer and cardiovascular disease were the leading causes of mortality. In Africa, there were about 6.6 million deaths due to infectious diseases and the life expectancy was 54 years of age. The African death toll due to infectious diseases was 10% of the total deaths in the world. In stark contrast, only 672,000 died of infectious disease in the Americas and the life expectancy was 76 years

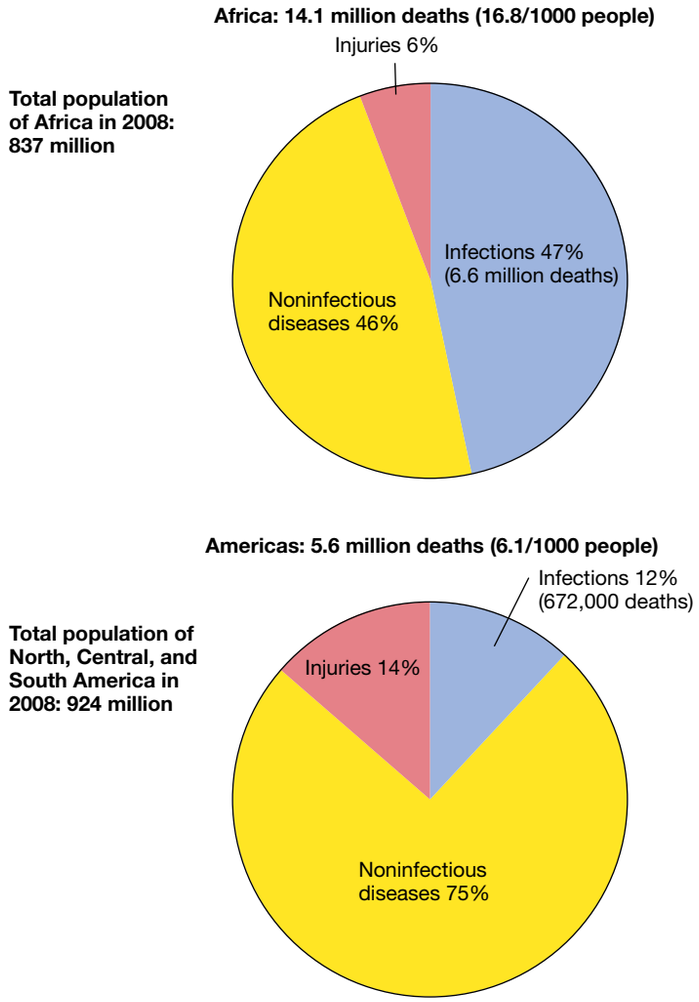


Figure 29.9 Causes of death in Africa and the Americas, 2008. Noninfectious diseases include cancer, cardiovascular diseases, and diabetes. Injuries include accidents, murder, suicide, and war. Data are from the World Health Organization, Geneva.

of age. In developed countries, the increased life expectancy is a direct consequence of the reduction in death rates from infection over the last century, and most of these gains are due to the advances in public health. By contrast, lack of resources in developing countries limits access to adequate sanitation, safe food and water, immunizations, healthcare, and medicines, leading to increases in infectious diseases and, as a consequence, to dramatically shorter life expectancy.

Data for 2012 (the most recent year for which complete morbidity and mortality statistics have been compiled by the WHO) show little change in these trends. That is, the majority of deaths in sub-Saharan Africa continue to be due to infectious diseases or to perinatal, maternal, and nutritional causes, whereas in developed countries, lifestyle diseases continue to lead the way, with obesity-related health issues such as type 2 diabetes and lack of mobility rapidly emerging.

Travel to Endemic Areas

The high incidence of disease in many parts of the world is a concern for people traveling to such areas. However, travelers can be

immunized against many of the diseases that are endemic in foreign countries. Specific recommendations for immunization for those traveling abroad are updated biannually and published by the U.S. Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/).

For many countries, immunization certificates for yellow fever are required for entry from areas with endemic yellow fever. These areas include much of equatorial South America and Africa. Most other nonstandard immunizations such as those for rabies and plague are recommended only for people who are expected to be at high risk, such as veterinary healthcare providers. The CDC summarizes current information for the potential for infectious disease transmission throughout the world, including diseases for which currently there are no effective immunizations (for example, HIV/AIDS, malaria, Ebola hemorrhagic fever, dengue fever, amebiasis, encephalitis, and typhus). Travelers should take precautions such as avoiding insect and animal bites, drinking only water that has been properly treated to kill all microorganisms, eating properly stored and prepared food (and avoiding fresh uncooked foods), and undergoing antibiotic and chemotherapeutic programs for prophylaxis or for suspected exposures. Although these precautions do not guarantee that one will remain disease-free, adhering to them greatly reduces the risk of infection.

MINIQUIZ

- Contrast mortality due to infectious diseases in Africa and the Americas.
- List infectious diseases for which you have not been immunized and with which you could come into contact next year.

III • Emerging Infectious Diseases, Pandemics, and Other Threats

In recent years, new infectious diseases have emerged and established diseases have reemerged with alarming frequency. In Part III of this chapter, we discuss some of these diseases and the reasons for their sudden emergence or reemergence. We also investigate the potential for the purposeful use of infectious microbes as agents of war or civilian terror.

29.7 Emerging and Reemerging Infectious Diseases

Infectious diseases are global, dynamic health problems. In this section we examine some recent patterns of infectious disease, some reasons for the changing patterns, and the methods used by epidemiologists to identify and deal with new threats to public health.

Emerging and Reemerging Diseases

The worldwide distribution of diseases can change dramatically and rapidly. Alterations in the pathogen, the environment, or the host population contribute to the spread of new diseases, with potential for high morbidity and mortality. Diseases that suddenly become prevalent are called **emerging diseases** and are not limited to "new" diseases; they also include **reemerging diseases**, diseases that were previously under control but suddenly appear as a new epidemic. Examples of global emerging and reemerging disease are shown in Figure 29.10, and select diseases with high potential for emergence or reemergence are described in

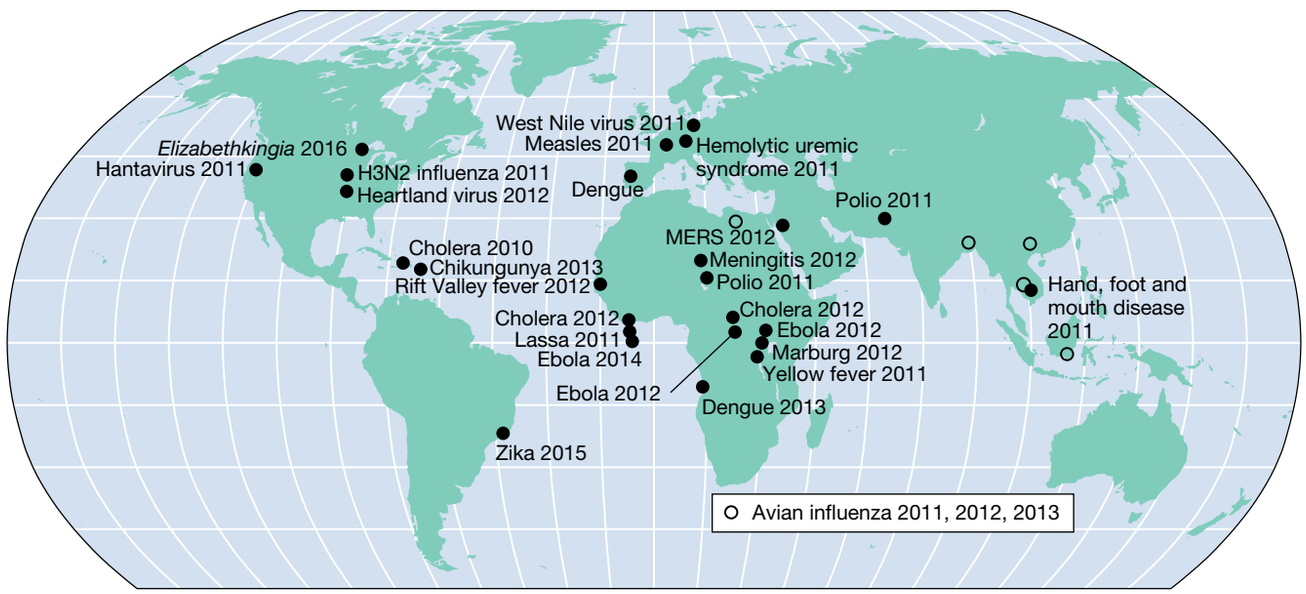


Figure 29.10 Recent outbreaks of emerging and reemerging infectious diseases. The diseases shown are local outbreaks capable of producing widespread epidemics and pandemics. Not shown are established pandemic diseases such as HIV/AIDS and cholera, and predictable annual epidemic diseases such as seasonal epidemic human influenza. MERS, Middle East respiratory syndrome. Avian influenza is caused by influenza A H5N1 (Section 29.8). For more on the *Elizabethkingia* oubreak, see page 902.

TABLE 29.5 Emerging and reemerging epidemic infectious diseases

Agent	*Disease and symptoms*	*Mode of transmission*	*Cause of emergence*
Borrelia burgdorferi	Lyme disease: rash, fever, neurological and cardiac abnormalities, arthritis	Bite of infective *Ixodes* tick	Increase in deer and human populations in wooded areas
Mycobacterium tuberculosis	Tuberculosis: cough, weight loss, lung lesions	Sputum droplets (exhaled through a cough or sneeze) from a person with active disease	Antimicrobial drug resistance as multidrug-resistant and extensively drug-resistant tuberculosis
Vibrio cholerae	Cholera: severe diarrhea, rapid dehydration	Water contaminated with the feces of infected persons; food exposed to contaminated water	Poor sanitation and hygiene; carried to non-endemic areas via infected travelers and commerce
Viruses			
Dengue	Hemorrhagic fever	Bite of an infected mosquito (primarily *Aedes aegypti*)	Poor mosquito control; increased urbanization in tropics; increased travel and shipping
Filoviruses (Marburg, Ebola)	Fulminant, high mortality, hemorrhagic fevers	Direct contact with infected blood, organs, secretions, and semen	Contact with vertebrate reservoirs
Influenza H5N1 (avian influenza)	Fever, headache, cough, pneumonia, high mortality	Direct contact with infected animals or humans, not easily spread via respiratory aerosols	Danger of animal–human virus reassortment; antigenic shift
Zika	Asymptomatic, or fever, rash, muscle and joint pain, headache	Bite of an infected mosquito (primarily *Aedes aegypti*), mother to fetus, sexual contact, blood transfusion	Poor mosquito control; increased urbanization in tropics
Fungi			
Candida	Candidiasis: fungal infections of the gastrointestinal tract, vagina, and oral cavity	Member of endogenous microbiota becomes an opportunistic pathogen; contact with secretions or excretions from infected persons	Immunosuppression; medical devices (catheters); antibiotic use

Table 29.5. Occasionally, new diseases emerge very unexpectedly and for totally unknown reasons; for example, an emerging infection due to the unusual bacterium *Elizabethkingia* in Wisconsin (USA) in 2016 posed a real medical mystery (see page 902).

Emerging epidemic diseases are not a new phenomenon. Among the diseases that rapidly and sometimes catastrophically emerged in the past are plague (caused by the bacterium *Yersinia pestis*) and influenza. For example, in the Middle Ages, up to one-third of all humans were killed by the periodic plague epidemics that swept Europe, Asia, and Africa. Influenza caused a devastating worldwide pandemic in 1918–1919, claiming up to 100 million lives, and the pandemic H1N1 influenza virus that emerged in 2009 killed up to a half million people in its first year. In the 1980s, HIV/AIDS and Lyme disease emerged as new diseases, and health officials worldwide are paying particular attention to the potential for rapid emergence of pandemic influenza developing from H5N1 avian influenza. More recently, isolation of patients and extra protections for their caregivers was practiced during the West African Ebola hemorrhagic fever epidemic (Section 30.12 and Figure 30.34*b*) to prevent spread of this extremely dangerous viral disease.

Emergence Factors

Many factors play into the emergence of new pathogens including human demographics and behavior, economic development, transportation, public health breakdowns, and other factors. The trend for human populations to reside in urban rather than rural areas facilitates disease transmission. For example, the high density of human hosts in cities has facilitated transmission of dengue fever, a serious viral disease spread by mosquitoes. Dengue infects nearly 400,000 people yearly, primarily in urban regions of tropical and subtropical countries including far southern reaches of the United States (**Figure 29.11**). Human behavior in large population centers also contributes to disease spread. For example, sexually promiscuous practices in population centers contribute to the spread of hepatitis and HIV/AIDS. Economic development and changes in land use also promote disease spread. For example, Lyme disease, the most common vectorborne disease in the

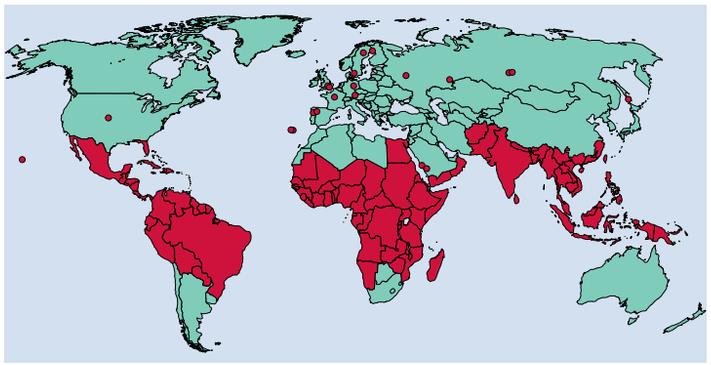


Figure 29.11 Dengue virus 2013. Dengue virus is now found in all tropical and subtropical countries as a result of the spread of its *Aedes aegypti* mosquito vector. The red areas are now endemic for the virus and mosquito vector. The red dots indicate outbreaks outside the known endemic areas. Prior to 1981, dengue virus was unknown in the Americas. Data are from the CDC, Atlanta, Georgia, USA.

United States, is on the rise largely due to residential reforestation and related changes in land use patterns. These activities increase deer habitat and thus contact between Lyme-infected deer ticks and humans, consequently increasing disease incidence.

Transportation, bulk processing, and central distribution methods have become increasingly important for quality assurance and economy in the food industry. However, these same factors have increased the potential for common-source foodborne disease epidemics when sanitation measures fail. For example, a single U.S. meat-processing plant spread *Escherichia coli* O157:H7 to people in eight states in 2009. The contaminated food source, ground beef, was recalled and the epidemic was eventually stopped, but not before several people died. International travel and commerce also affect the spread of pathogens. For example, a single person showing symptoms from an Ebola infection on an international flight could infect many other passengers because of the ease with which the Ebola virus spreads (Section 30.12). If such a situation were not immediately recognized, the disease could rapidly spread to major population centers when healthy passengers who had contact with the diseased passenger and were now carrying the virus disembarked and continued their travels.

Pathogen adaptation and change can contribute to disease emergence. For example, most RNA viruses, including influenza, HIV, and the hemorrhagic fever viruses, mutate rapidly. These mutant RNA viruses present major epidemiological problems because their altered genomes often affect their antigens, making immunity to old viral antigens ineffective for neutralizing the mutant viruses. Bacterial genetic mechanisms are also capable of enhancing virulence and promoting emergence of new epidemics. Virulence-enhancing factors are often carried by mobile genetic elements (Chapter 11) that can be transferred between and among members of the same species, and sometimes to other species and genera. Such transfers can quickly generate emerging pathogens, and multidrug-resistant strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa* are good examples of this.

A breakdown of public health measures is sometimes responsible for the emergence or reemergence of diseases. For instance, cholera (caused by *Vibrio cholerae*) can be adequately controlled, even in endemic areas, by providing proper sewage disposal and water treatment. In 2010 contaminated water supplies following a major earthquake triggered a cholera outbreak in Haiti for the first time in over 100 years (Section 29.8). Inadequate public vaccination programs can also lead to the resurgence of previously controlled diseases. For example, pertussis, a vaccine-preventable childhood respiratory disease, has increased recently in Eastern Europe and in the United States partly because of inadequate immunization among adults and children.

Finally, weather patterns can also upset the usual host–pathogen balance. Disease vectors such as mosquitoes have been moving northward in response to climate change. Even a single seasonal weather abnormality can have an effect, as evidenced by the 1993 hantavirus hemorrhagic fever outbreak in the American Southwest (Section 31.2). A very mild winter coupled with record rainfall led to an explosive increase in rodents that can host hantavirus. This increased exposures for susceptible human hosts and led to the spread of this zoonotic infection.

Addressing Emerging Diseases

The keys for addressing emerging diseases are recognition of the disease and intervention to prevent pathogen transmission. Emerging diseases have, at least at first, low incidence and are usually absent from the official notifiable disease list for the United States prepared by the Centers for Disease Control and Prevention (Table 29.4). Emerging diseases are first recognized from their unique epidemic incidence, clusterings and other epidemiological patterns, and clinical symptoms unrelated to known pathogens (see page 902). Such disease patterns trigger intensive public health surveillance followed by specific interventions designed to control further outbreaks. Methods such as isolation, quarantine, immunization, and drug treatment can be applied to contain outbreaks. For vectorborne and zoonotic diseases, the nonhuman host or vector must be identified to intervene in the life cycle of the pathogen and stop human infection.

International public health surveillance and intervention programs were instrumental in controlling the emergence of severe acute respiratory syndrome (SARS), a disease that emerged rapidly, explosively, and unpredictably from a zoonotic source (Section 29.4). On the other hand, even a rapid and focused response was unsuccessful in containing the spread of pandemic (H1N1) 2009 influenza, as we will see in the next section.

MINIQUIZ

- What is the difference between an emerging and a reemerging infectious disease?
- What factors are important in the emergence or reemergence of potential pathogens?
- Indicate general and specific methods that would be useful for identifying emerging infectious diseases.

29.8 Examples of Pandemics: HIV/AIDS, Cholera, and Influenza

Through the centuries, several diseases have reached pandemic proportions. Here we consider three—HIV/AIDS, cholera, and influenza—for which epidemiological studies have been extensive.

HIV/AIDS

HIV/AIDS is a continuum of disease, starting with the infection of an individual with the human immunodeficiency virus (HIV). Eventually, infection results in acquired immunodeficiency syndrome (AIDS), a disease which if not treated cripples the immune system, leading to opportunistic infections that can be fatal (Section 30.15). The first reported cases of AIDS were diagnosed in the United States in 1981. Since then, more than 1.2 million cases have been reported in the United States with over 635,000 deaths (**Figure 29.12**); worldwide, over 25 million AIDS deaths have occurred.

Epidemiological studies in the United States in the 1980s suggested a high AIDS prevalence among men who have sex with men and among intravenous drug abusers. Individuals receiving blood or blood products were also at high risk. Collectively, these epidemiological data indicated a transmissible agent, presumably transferred

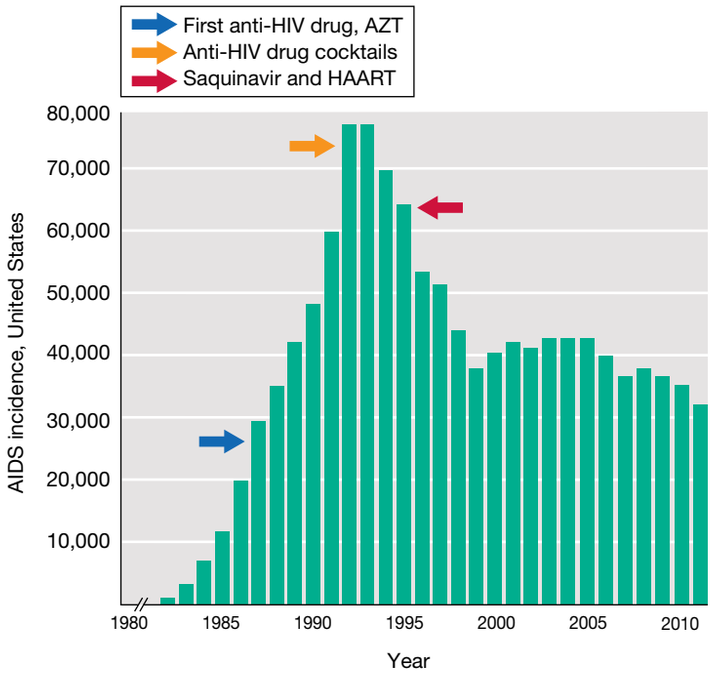


Figure 29.12 Annual new cases of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in the United States. Cumulatively, there were about 1.1 million cases of HIV/AIDS through 2011. In 2009, the HIV/AIDS case definition changed to include all new HIV infections and AIDS diagnoses (Section 30.15). Colored arrows indicate the introduction of different anti-HIV drugs. See Sections 28.11 and 30.15 for a discussion of anti-HIV therapies. Data are from the HIV/AIDS Surveillance Report and Division of HIV/AIDS Prevention—Surveillance and Epidemiology, CDC, Atlanta, Georgia, USA.

during sexual activity or by contaminated blood. Soon after the discovery of HIV in 1983, laboratory tests were developed to detect antibodies to the virus in blood. With this tool in hand, surveys of HIV incidence and prevalence defined the spread of HIV and showed conclusively that body fluids, primarily blood and semen, were the vehicles for transmission of the virus (Figure 29.13).

The HIV/AIDS data showed that in the United States, the number of AIDS cases was disproportionately high in men who have sex with men, but among women, heterosexuals were the largest risk group (Figure 29.13). Further analyses of the epidemiological data showed that the new infection rate for African American men was seven times that of Caucasian males, indicating that social and economic factors may also influence infection risk. However, regardless of gender or racial specifics, AIDS epidemiology provided a clear picture of HIV transmission: Virtually all who acquired HIV engaged in sex or intravenous drug use in which body fluids—semen or blood—were transferred and commonly had sex or exchanged syringe needles with multiple partners. We discuss the pathology and therapy of HIV/AIDS in Section 30.15.

Cholera

Cholera is primarily a waterborne infection (Section 32.3) that is normally kept in check by appropriate public health measures for water treatment (Chapter 22). Cholera is caused by ingestion of contaminated water containing *Vibrio cholerae*, a gram-negative, curved rod–shaped species of *Proteobacteria* that produces a powerful enterotoxin that triggers severe diarrhea (Section 25.6). Cholera is endemic in Africa, Southeast Asia, the Indian subcontinent, and Central and South America. Epidemic cholera occurs frequently in areas where sewage treatment is either inadequate, altogether absent, or suffers a major breakdown, for example, from a flood or an earthquake. In 2014, the World Health Organization (WHO) reported over 190,000 cases of cholera that led to 2231 deaths. However, the WHO estimates that only 5–10% of cholera cases are actually reported because diarrheal diseases from various pathogens are so common (Table 29.1); thus total worldwide incidence of cholera likely exceeds 1 million cases per year.

Epidemic cholera may develop into pandemics when travelers from endemic areas carry the pathogen to new locations with susceptible populations and poor sanitation. Since 1817, cholera has swept the world in seven major, and nearly consecutive, pandemics (Figure 29.14). All but one of these originated on the Indian subcontinent, where cholera is endemic. Two distinct pandemic strains of *V. cholerae* are recognized, known as the *classic* and the *El Tor* biotypes. The *V. cholerae* O1 El Tor biotype started the seventh pandemic in Indonesia in 1961, and its spread continues to the present day. This pandemic has caused over 5 million cases of cholera and at least 250,000 deaths and continues to be a major cause of morbidity and mortality, especially in developing countries (Figure 29.14).

In October 2010 Haiti experienced its first cholera in over 100 years, and in just two years experienced nearly 600,000 cases and 8000 deaths. The outbreak began in the aftermath of the catastrophic 2010 earthquake. There were likely two triggers of this cholera outbreak, the first being a classic scenario of poor sanitation following a disaster and the second an accidental importation from an outside source. *Vibrio cholerae* is present in marine waters and as a result of the earthquake, it may have been washed into coastal freshwaters where it contaminated drinking water sources. But in addition, United Nations aid workers that arrived

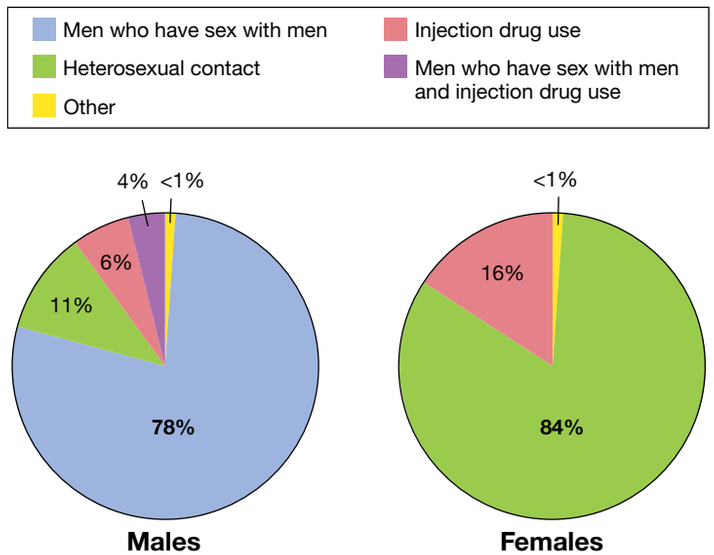


Figure 29.13 Distribution of AIDS cases by risk group and gender in the United States, 2010. Data from the CDC, Atlanta, Georgia, USA, were gathered from 38,000 males and 9,500 females diagnosed with HIV/AIDS in 2010.

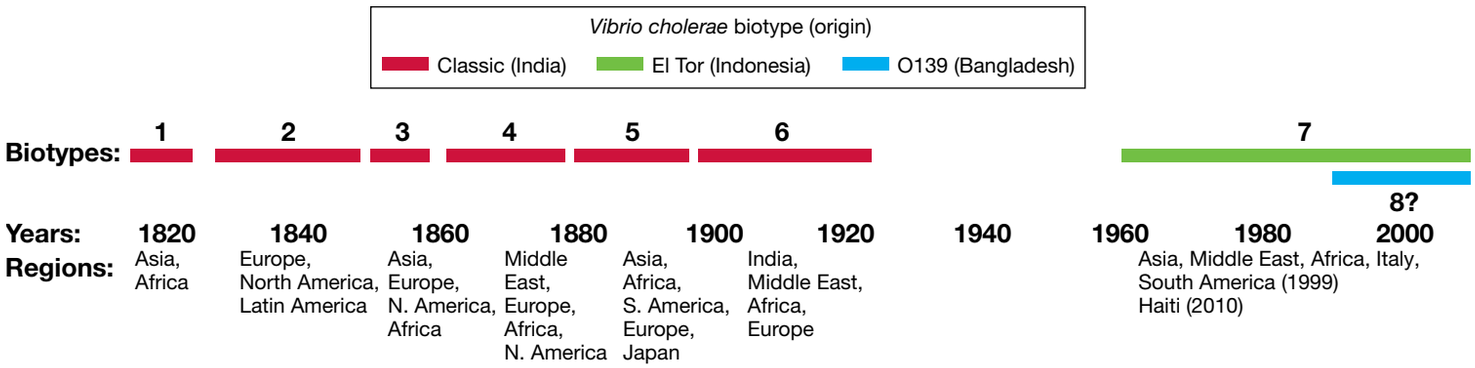


Figure 29.14 Cholera pandemic timeline. Seven cholera pandemics have been nearly consecutive for over 200 years. The seventh pandemic started in 1961 and is ongoing. The O139 strain that appeared in 1991 is endemic to Bangladesh and the Bay of Bengal and is causing epidemics that may be the prelude to an eighth pandemic.

from Nepal, where a recent cholera outbreak had occurred, are thought to have shed *V. cholerae* into sanitation streams that found their way into Haitian drinking water sources; if true, this would have contributed to the Haitian epidemic. Cholera has since spread from Haiti to the Dominican Republic and other areas of the Caribbean, and to Mexico.

Pandemic (H1N1) 2009 and Future Influenza Pandemics

Human influenza pandemics occur every 10 to 40 years as a result of major genetic changes in the influenza A virus genome that affect the virus's immune status (*antigenic drift* and *antigenic shift*, Section 30.8 and Figure 30.26). The most devastating influenza pandemic of all time occurred in 1918; this flu infected over half a *billion* people worldwide and killed approximately 50 *million* people before it ran its course. The 1918 pandemic was caused by a strain of influenza termed H1N1.

A more recent influenza pandemic began in March 2009 with the outbreak of epidemics in Mexico. The culprit virus, a strain designated (H1N1) 2009, was a hybrid of the 1918 strain and a later strain that caused a pandemic in 1957; (H1N1) 2009 contained genes from bird, swine, and human influenza viruses. Such *reassortant viruses*, as they are called (Section 30.8), can be highly virulent, as they tend to produce antigens to which humans have no prior exposure and thus no immunity; the only way to obtain immunity to such a virus is to become infected or artificially immunized.

Without an effective vaccine at the ready and with the rapidity with which influenza is spread, the stage was set for the reassortant (H1N1) 2009 flu to reach pandemic proportions. Within six months of its emergence, (H1N1) 2009 had spread to almost every country in the world, qualifying it as a true pandemic (**Figure 29.15**). Although official numbers range widely, it is estimated that more than a quarter of the world's population was infected in the pandemic. In the United States, about 60 million persons were infected, with mortality confirmed as due to (H1N1) 2009 numbering about 3400 persons. By late 2010 the (H1N1) 2009 pandemic was fading, and today few cases are observed because antigens from this strain of virus are typically included in seasonal influenza vaccines (Table 28.4).

Could new influenza pandemics sweep the world? Perhaps the greatest threat to global stability would be another influenza pandemic that has the virulence and infectivity of the 1918 pandemic. Because epidemiological surveillance is currently so extensive, this possibility is unlikely, but the risk can never be zero. In recent years public health officials worldwide have been following the emergence and reemergence of a potentially devastating strain of influenza virus designated influenza A H5N1, originally found in birds. This virus first appeared in Hong Kong in 1997, jumping directly from chickens and ducks to humans. Since then H5N1 has reemerged several times in small outbreaks, with the most recent occurring in Egypt, Indonesia, Cambodia, Bangladesh, and China (Figure 29.10). Through 2014, 638 cases of human H5N1 infection have been confirmed, resulting in 379 deaths, for a mortality rate of almost 60%. This high mortality rate underscores the dangerous aspects of this virus.

Besides poultry and humans, H5N1 has also infected swine. If a reassortant strain were to emerge from pigs that had the capacity

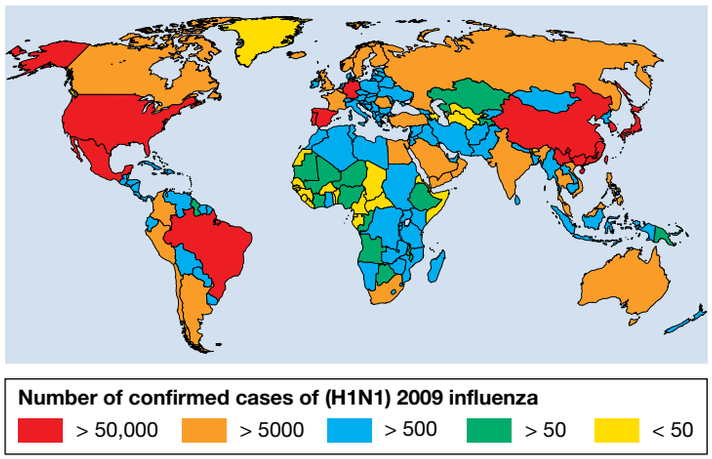


Figure 29.15 Pandemic (H1N1) 2009 influenza incidence. Data show minimal estimates of cases worldwide by country. It is estimated that approximately 1.7 billion people were infected by the (H1N1) 2009 pandemic flu (24% of the total population) and that deaths were between 150,000 and 575,000 (the large range for mortality estimates is because many deaths that were likely due to (H1N1) 2009 were not confirmed as such).

to spread from person to person, such a virus could trigger an influenza pandemic of unprecedented mortality. Because of this, plans are in place nationally and internationally to provide appropriate vaccines and support for potential pandemics initiated by this and other emergent influenza strains. We discuss the disease influenza in detail in Section 30.8.

MINIQUIZ

- Describe the major risk factors for acquiring HIV infection in the United States. How do these differ in males and females?
- Identify the most likely means of acquiring cholera. Why do cholera epidemics keep occurring?
- What is a reassortant influenza virus and why can such viruses be so dangerous?

29.9 Public Health Threats from Microbial Weapons

As if avoiding the wrath of pathogenic microbes that can infect us naturally is not enough, humans have researched the use of certain pathogens as weapons to be intentionally deployed on others. **Biological (microbial) warfare** is the use of microbial agents to incapacitate or kill a military or civilian population in an act of war or terrorism. Although the use and development of microbial weapons are forbidden by international law, microbial weapons have already seen use, and facilities for their production likely exist in rogue countries and perhaps also in avowed terrorist groups. Because of this, microbial weapons research continues in many peaceful nations so as to best understand the most serious threats and learn how to counter them.

Characteristics of Microbial Weapons

Effective microbial weapons are pathogens, or in a few cases toxins, that are (1) relatively easy to produce and deliver, (2) safe for use by the offensive forces, and (3) able to incapacitate or kill people in a systematic and consistent manner. Although microbial weapons are potentially useful in the hands of conventional military forces, the greatest likelihood of microbial weapons use is by terrorists because of the ready availability and low cost of producing and propagating many of the organisms.

Virtually all pathogenic bacteria or viruses are potentially useful for biological warfare, and *select agents* that have significant potential for use as microbial weapons are listed in Table 29.6. The most frequently mentioned candidates are smallpox virus and *Bacillus anthracis*, the bacterium that causes anthrax. Both of these microbes can be easily disseminated, are transmissible from person to person, and typically cause high mortality. Other agents have their advantages and disadvantages as microbial weapons and are categorized as to their potential risk from Category A to Category C in Table 29.6.

The United States government, through the Centers for Disease Control and Prevention, has developed the Select Agent Program surveillance system to monitor possession and use of potential bioterrorism agents. In addition, the CDC Laboratory Response Network and the Health Alert Network have been upgraded to enhance their diagnostic capabilities and increase the reporting abilities of local and regional healthcare centers to rapidly identify bioterrorism events as well as emerging diseases.

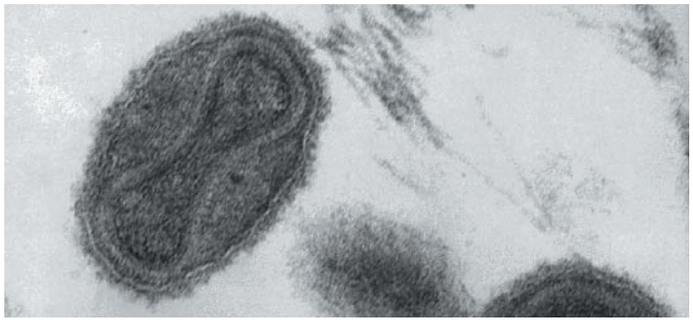
TABLE 29.6 Select agents and diseases by bioweapons threat category[a]

Category A
Highest-priority agents that pose a risk to national security. These agents are easily disseminated or transmitted and result in high mortality rates. They require special action for public health preparedness.
Disease/Pathogen
Anthrax (*Bacillus anthracis*)
Botulism (*Clostridium botulinum* toxin)
Plague (*Yersinia pestis*)
Smallpox (*Variola major*)
Tularemia (*Francisella tularensis*)
Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])
Category B
Second-highest-priority agents. These agents are moderately easy to disseminate, result in moderate morbidity and low mortality, and require specific enhancements of public health diagnostic capacity and disease surveillance.
Disease/Pathogen
Brucellosis (*Brucella* species)
Epsilon toxin of *Clostridium perfringens*
Food safety threats (e.g., *Salmonella* spp., *Escherichia coli* O157:H7, *Shigella*)
Glanders (*Burkholderia mallei*)
Melioidosis (*Burkholderia pseudomallei*)
Psittacosis (*Chlamydophila psittaci*)
Q fever (*Coxiella burnetii*)
Ricin toxin from *Ricinus communis* (castor beans)
Staphylococcal enterotoxin B (*Staphylococcus aureus*)
Typhus fever (*Rickettsia prowazekii*)
Viral encephalitis (alphaviruses such as Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis)
Water safety threats (*Vibrio cholerae*, *Cryptosporidium parvum*, and others)
Category C
Third-highest-priority agents are emerging pathogens that are available, easily produced and disseminated, with high potential for high morbidity and mortality.
Pathogens
Emerging infectious diseases such as hantavirus

[a]*Source:* Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

Smallpox and Anthrax

Smallpox virus (Figure 29.16*a*) has intimidating potential as a microbial weapon because it can be spread easily by direct contact or by aerosol spray, is highly debilitating, causes a high fever, severe fatigue, and the eventual formation of pus-filled skin blisters (Figure 29.16*b*), and has a mortality rate of 30% or higher. Although an extremely effective smallpox vaccine is available, it has not been in use in the general population since smallpox was eradicated worldwide in 1980. Moreover, the potential of smallpox virus being deployed as a military weapon is considered low because military personnel are routinely vaccinated. Nevertheless, preparations for



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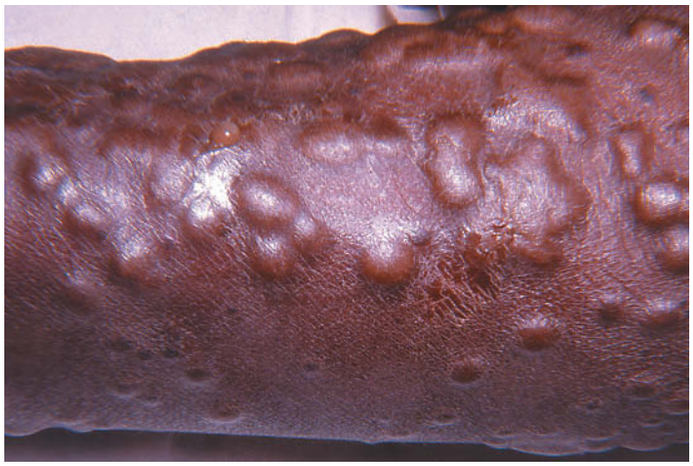


(b)

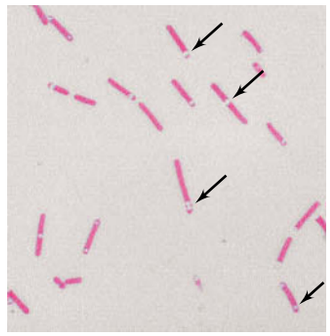
Figure 29.16 Smallpox and its use as a microbial weapon. *(a)* Smallpox virus, a double-stranded DNA virus (Section 10.6). *(b)* Characteristic papular smallpox rash and blisters on the arm. Smallpox was officially declared eradicated worldwide in 1980.

a potential smallpox attack on civilians in the United States have been made and would include immunization of key individuals such as those evaluating, caring for, or transporting smallpox patients; laboratory personnel handling clinical specimens from smallpox patients; and other persons as necessary who might come into contact with infectious materials from smallpox patients.

Bacillus anthracis is the causative agent of anthrax, and its unique properties make it particularly attractive as a bioweapon. Chief among these is that it is easily grown aerobically, producing distinctive colonies on enriched culture media, and it differentiates into highly resistant endospores (**Figure 29.17*a, b***; Section 2.10). Once prepared, endospores can be dried and stored indefinitely and then disseminated as a weapon by aerosol or in powdered suspension. There are three clinical forms of anthrax (Section 31.8). *Cutaneous anthrax* is contracted when abraded skin is contaminated by *B. anthracis* endospores; the organism grows and kills the skin, forming a necrotic tissue lesion called an *eschar* (Figure 29.17*c*). The most rare form—*gastrointestinal anthrax*—is contracted from consumption of endospore-contaminated plants or meat from animals infected with anthrax. *Inhalation anthrax* (also called *pulmonary anthrax*) is the deadliest form and is contracted when *B. anthracis* endospores are inhaled. The symptoms of inhalation anthrax include pulmonary and cerebral hemorrhage (Figure 29.17*d*), which makes this form of anthrax so dangerous. All forms of anthrax have the potential to become systemic infections; however, cutaneous anthrax is easily treatable with antibiotics and is fatal in only about 20% of untreated cases. Without treatment, gastrointestinal anthrax is fatal in about half those infected, whereas inhalation anthrax mortality approaches 100%.

Inhalation anthrax is the form of the disease that makers of microbial weapons would aim for, as has already transpired in the United States. At least 22 cases of anthrax leading to 5 deaths occurred in a 2001 bioterrorism attack where dense *B. anthracis* endospore preparations were mailed in envelopes to certain news outlets and government officials. Of the 22 anthrax cases, 11 were inhalational and 11 cutaneous. These *weaponized* anthrax strains were endospore preparations mixed within a fine particulate material that allowed the endospores to be spread by air currents. Thus, opening an envelope containing endospores or releasing the powder–endospore mixture into a ventilation system or other air exchange could contaminate surrounding areas and personnel.

Vaccination for anthrax is possible and is restricted to individuals who are considered at risk. This includes agricultural animal



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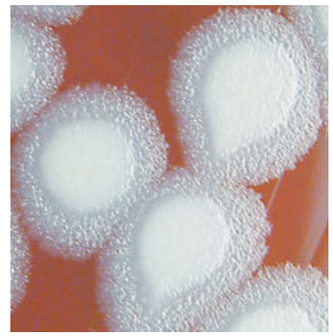

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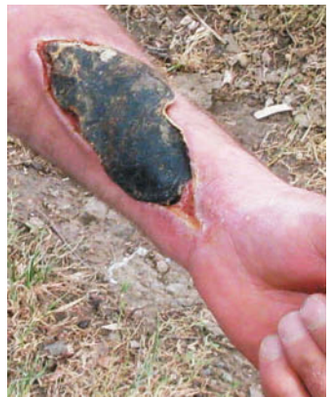

(c)

(d)

Figure 29.17 *Bacillus anthracis* and anthrax. *(a) Bacillus anthracis* is a gram-positive, endospore-forming rod approximately 1 μm in diameter and 3–4 μm in length. Note the developing endospores (arrows). *(b)* Characteristic "ground glass" appearance of colonies of *B. anthracis* on blood agar plates. *(c)* Cutaneous anthrax. The blackened lesion seen on this forearm is called an eschar, and results from tissue necrosis. *(d)* Inhalation anthrax can cause cerebral hemorrhage, as shown by the dark coloration in this fixed and sectioned human brain removed at autopsy.

workers (livestock tenders and those working with animal products), laboratory personnel working with anthrax, veterinarians, and military personnel. As was discussed with smallpox, anthrax is an unlikely military weapon but could be a very effective means of terrorizing a civilian population because the vast majority of the population is unvaccinated.

MINIQUIZ

- What characteristics make a pathogen or its products particularly useful as a biological weapon?
- Indicate the steps you would take to identify and treat infections from smallpox virus or anthrax in a bioterror attack.

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Chapter Review

I • Principles of Epidemiology

29.1 Epidemiology is the study of the occurrence, distribution, and determinants of health and disease in populations. Epidemiologists employ surveillance measures to record the incidence and prevalence of infectious diseases and track disease outbreaks that may lead to epidemics or pandemics. The morbidity and mortality of any given disease is a function of the transmissibility of the pathogen and the severity of the disease symptoms. Disease carriers may be symptom-free or they may have chronic infections that are never resolved.

Q How does the job of an epidemiologist differ from that of a clinical healthcare provider?

29.2 Effects on populations as well as individuals must be studied to understand infectious disease. The interactions of pathogens with hosts can be dynamic, affecting the long-term evolution and survival of all species involved. Herd immunity provides disease protection for uninfected or unimmunized hosts.

Q Explain how the infectivity of a pathogen is correlated with the epidemic spread of a disease in various populations.

29.3 Infectious diseases can be transmitted directly from person to person, indirectly from living vectors or inanimate objects (fomites), or from common-source vehicles such as food and water. Disease reservoirs can include soil, insects, seemingly healthy people, chronic carriers, and many other sources. An understanding of disease reservoirs, carriers, and pathogen life cycles is critical for controlling disease epidemics.

Q Compared with a fomite—such as a contaminated cup—why is a disease vehicle such as food a much more powerful disease transmitter?

29.4 Epidemics may be of host-to-host origin or originate from a common source. The basic reproduction number (R_0) of a pathogen gives a relative picture of its seriousness and an indication of how effective herd immunity must be to prevent its spread.

Q If an emerging pathogen was found to have an R_0 of 30, would herd immunity need to be higher or lower than for an emerging pathogen with an R_0 of 3?

II • Epidemiology and Public Health

29.5 Food and water purity regulations, vector control, immunization, quarantine, isolation, and disease surveillance are all public health measures that reduce the incidence of communicable diseases. In the case of some diseases, such as smallpox, total eradication worldwide has been possible.

Q If an outbreak of yellow fever occurred, who would be isolated and who would be quarantined?

29.6 Infectious diseases account for about 30% of all mortality worldwide. Most cases of infectious diseases occur in developing countries. Control of many infectious diseases can be accomplished by public health measures that include adequate sanitation, food and water protections, and widespread vaccination programs. A high infectious disease load can significantly reduce the average life expectancy of the population in a country.

Q Contrast the leading causes of death in Africa and in the United States.

III • Emerging Infectious Diseases, Pandemics, and Other Threats

29.7 Changes in host, vector, or pathogen conditions, whether natural or artificial, can encourage the explosive emergence or reemergence of infectious diseases. Global surveillance and intervention programs by organizations such as the World Health Organization and the U.S. Centers for Disease Control and Prevention are especially attuned to emerging and reemerging pathogens to prevent local epidemics from spreading.

Q How can bacterial genetic exchange fuel the emergence of new pathogens?

29.8 Several infectious diseases with significant mortality show pandemic characteristics. HIV/AIDS affects those who exchange bodily fluids, most often by either promiscuous unprotected sex or intravenous drug use. Cholera is primarily a waterborne infection and control can be achieved by maintaining adequate clean water and waste

sanitation measures. New pandemic influenza strains resulting from bird–swine–human influenza reassortments present the biggest infectious disease threat worldwide.

Q Why is H5N1 avian influenza considered a major threat to public health?

29.9 Bioterrorism from smallpox or anthrax is a threat in a world of rapid international travel and easily accessible technical information. Aerosols or disease vehicles are the most likely modes of delivery of microbial weapons. Prevention and containment measures rely on a well-prepared public health infrastructure.

Q Why are smallpox and anthrax more likely to be bioterrorism threats to civilians than to military personnel?

Application Questions

1. Smallpox, a disease that was limited to humans, was eradicated, whereas plague, a zoonotic disease with a reservoir in rats and related rodents, will likely never be eradicated worldwide. Explain this statement. Devise a plan to eradicate plague in a limited area such as a town or city. Be sure to consider methods that involve the reservoir, the pathogen, and the host.
2. Like smallpox, HIV/AIDS is considered to be a disease that could be eliminated worldwide because it is propagated by known means and there are no animal reservoirs. Although eliminating HIV infection is possible, why would it be much more difficult than eliminating smallpox? What would be involved in an HIV infection eradication program?
3. H5N1 avian influenza has high potential for causing a pandemic under certain circumstances. If such a highly transmittable human–avian strain were to evolve in Asia, from the perspective of a national public health official, what measures would you employ to stop the spread of the new influenza to the United States? If you failed to contain the new virus, where would you expect to see the first cases of such pandemic influenza, in metropolitan areas or in the rural Midwest?

Chapter Glossary

Acute infection a short-term infection, usually characterized by dramatic onset

Basic reproduction number (R_0) the number of expected secondary transmissions from each single case of a disease in an entirely susceptible population

Biological (microbial) warfare the use of biological agents to incapacitate or kill a military or civilian population in an act of war or terrorism

Carrier a subclinically infected individual who may spread a disease

Centers for Disease Control and Prevention (CDC) the agency of the United States Public Health Service that tracks disease trends, provides disease information to the public and to healthcare professionals, and forms public policy regarding disease prevention and intervention

Chronic infection a long-term infection

Common-source epidemic an infection (or intoxication) of a large number of people from a contaminated common source such as food or water

Disability-adjusted life year (DALY) a quantitative measure of disease burden defined as the cumulative number of years lost due to an illness itself, a disability due to an illness, or premature death

Disease surveillance the observation, recognition, and reporting of diseases as they occur

Emerging disease an infectious disease whose incidence recently increased or whose incidence threatens to increase in the near future

Endemic disease a disease that is constantly present, usually in low numbers, in a population

Epidemic the occurrence of a disease in unusually high numbers in a localized population

Epidemiology the study of the occurrence, distribution, and determinants of health and disease in a population

Fomite an inanimate object that when contaminated with a viable pathogen can transfer the pathogen to a host

Herd immunity the resistance of a population to a pathogen as a result of the immunity of a large portion of the population

Host-to-host epidemic an epidemic resulting from person-to-person contact, characterized by a gradual rise and fall in number of new cases

Incidence the number of new disease cases reported in a population in a given time period

Isolation in the context of infectious disease, the separation of persons who have an infectious disease from those who are healthy

Morbidity the incidence of disease in a population

Mortality the incidence of death in a population

Outbreak the occurrence of a large number of cases of a disease in a short period of time

Pandemic a worldwide epidemic

Prevalence the total number of new and existing disease cases reported in a population in a given time period

Public health the health of the population as a whole

Quarantine the separation and restriction of well persons who may have been exposed to an infectious disease to see if they develop the disease

Reemerging disease an infectious disease previously under control but that produces a new epidemic

Reservoir a source of infectious agents from which susceptible individuals may be infected

Vector a living agent that transfers a pathogen (differs from genetic vector, discussed in Chapter 12)

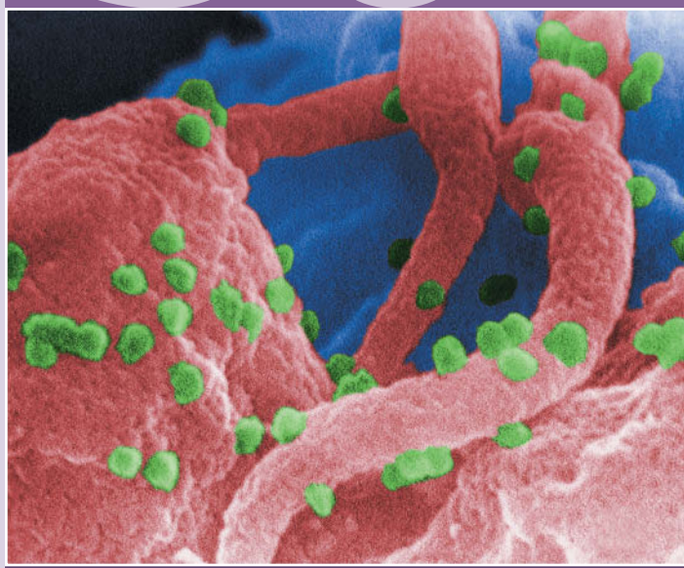
Vehicle a nonliving source of pathogens that transmits the pathogens to large numbers of individuals; common vehicles are food and water

Virulence the relative ability of a pathogen to cause disease

Zoonosis any disease that occurs primarily in animals but can be transmitted to humans

30

Person-to-Person Bacterial and Viral Diseases



microbiologynow

A New Weapon against AIDS?

Decades after it was first recognized as a communicable disease in 1981, acquired immunodeficiency syndrome (AIDS) is still a major human disease. Worldwide, nearly 80 million people are infected with the causative agent of AIDS—human immunodeficiency virus (HIV)—and AIDS-related illnesses claim over 1.1 million lives each year.

The list of viral diseases to which effective vaccines have been developed is lengthy and includes influenza, smallpox, measles, yellow fever, and rabies. However, thus far, no effective human HIV vaccine has emerged. One reason is that HIV attacks important immune cells called CD4 T lymphocytes, turning them into viral production factories (in this colorized scanning electron micrograph, green HIV virions are budding out of a pink CD4 lymphocyte) while simultaneously shutting down CD4 T cell division. This gradual dilution of CD4 T cells renders HIV-infected persons helpless to attack by opportunistic pathogens that ultimately cause death.

Some HIV-infected persons survive in good health for long periods—even decades. These individuals remain HIV-positive yet maintain adequate levels of CD4 T cells. A recent study of these patients has shown that they have an unusual immunological profile; they produce a special class of anti-HIV antibodies called broadly neutralizing antibodies (bnAbs). These antibodies keep HIV levels low and in this way prevent the progression to AIDS. However, a high proportion of bnAb-producers also make autoantibodies (antibodies that attack the body's own antigens) and show reduced levels of regulatory T (Treg) cells (T cells that function to modulate the immune response and help maintain tolerance to self antigens). These findings have suggested a new strategy to fight AIDS.

B lymphocytes are the immune cells that produce antibodies, and the activities of B cells are under the control of Treg cells. Because of their lower Treg cell levels, bnAb-producing HIV-infected individuals are thought to contain a "less regulated" pool of B cells, and this condition allows for a broad range of antibodies to be produced. These include the beneficial anti-HIV bnAbs but also undesirable antibodies, such as autoantibodies. However, if a vaccine could be developed that would temper Treg cell activities in HIV-infected persons that lack anti-HIV bnAbs, it might stimulate them to produce these helpful antibodies and be a new weapon in the fight against AIDS.

Source: Moody, M.A., et al. 2016. Immune perturbations in HIV-1-infected individuals who make broadly neutralizing antibodies. *Science Immunology 1*, aag0851.

Several million species of microorganisms likely exist in nature, but only a few hundred cause disease. In this and the next three chapters we focus on this vitally important subset of the microbial world. We investigate the biology of the pathogens as well as the diseases they cause, including disease diagnosis, treatment, and prevention.

Our infectious disease coverage is ecological, being organized around each pathogen's *mode of transmission*. Although the biology of the different causative agents will certainly be highlighted, an ecological approach to infectious disease coverage emphasizes the single most important feature that links diseases caused by different microbes. Hence, tuberculosis and influenza are caused by a bacterium and a virus, respectively, but both diseases are transmitted from person to person by airborne emissions.

In this chapter we explore diseases transmitted from person to person, whether through the air, by direct contact, or through sexual contact. In Chapters 31 and 32 we focus on diseases transmitted by animal and arthropod vectors or from soil, and diseases transmitted from common sources such as water or food, respectively. We end our tour of the microbial world in Chapter 33 where we examine fungal and parasitic infections.

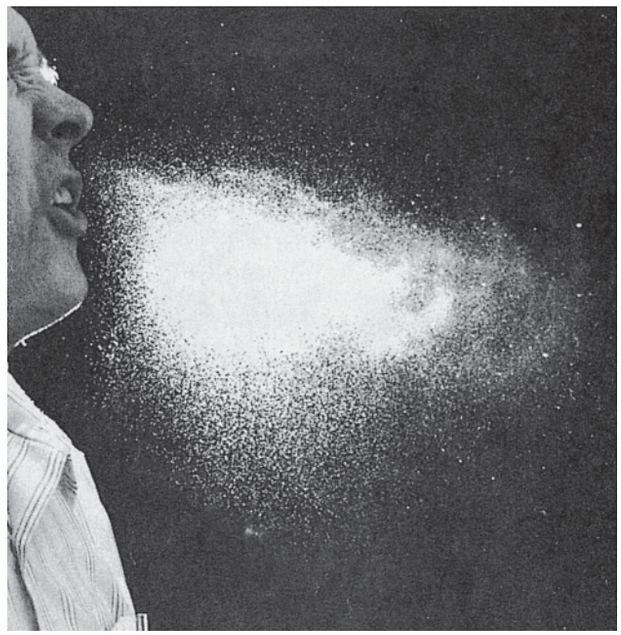

T. D. Brock

Figure 30.1 High-speed photograph of an unstifled sneeze. Effluent is emerging at over 100 m/s (200 miles/h).

I • Airborne Bacterial Diseases

Worldwide, acute respiratory infections kill more than 4 million people a year, mainly in developing countries. Children and the elderly make up most of the fatalities, but in general, respiratory infections are the most common of all human diseases. Aerosols, such as those generated by a sneeze (**Figure 30.1**), as well as by coughing, talking, or breathing, are major vehicles for person-to-person transmission of respiratory diseases. Besides directly infecting a new host, infectious mucus from an aerosol can also contaminate objects, such as a door handle, and transmit infection well after the aerosol event. In these ways, respiratory diseases spread quickly, especially in congested areas, as airborne pathogens exploit a simple yet highly effective means of infecting new hosts.

30.1 Airborne Pathogens

Microorganisms found in air are derived from soil, water, plants, animals, people, surfaces, and other sources. Most microorganisms survive poorly in air. As a result, airborne pathogens are effectively transmitted between people only over short distances. Certain pathogens, however, survive drying well and can remain alive in dust or on fomites for long periods of time. For example, because of their thick, rigid cell walls, gram-positive bacteria (*Staphylococcus, Streptococcus*) are generally more resistant to drying than are gram-negative bacteria. Likewise, the waxy layer of *Mycobacterium* cell walls resists drying and promotes survival of pathogens such as *Mycobacterium tuberculosis*.

Large numbers of droplets can be expelled during a sneeze (Figure 30.1). Infectious droplets are about 10 µm in diameter and each droplet can contain one or more microbial cells or virus virions. The initial speed of the droplet movement is about 100 m/s (200 miles/h) in a violent sneeze and ranges from 15 to 50 m/s during coughing or shouting. The number of bacteria in a single sneeze varies from 10^4 to 10^6, and viral numbers can be much higher than this. Because of their small size, the droplets evaporate quickly in the air, leaving behind dried mucus in which the airborne pathogens remain embedded.

The human respiratory tract is divided into upper and lower regions, and specific airborne pathogens tend to exploit one region or the other, or sometimes both (**Figure 30.2**). The speed at which air moves through the human respiratory tract varies, and in the lower respiratory tract the rate is quite slow. As air slows down, particles in it stop moving and settle. Large particles settle first and the smaller ones later; only particles smaller than about 3 µm travel as far as the bronchioles in the lower respiratory tract (Figure 30.2).

Upper respiratory infections such as the common cold are typically acute and non-life-threatening. By contrast, *lower* respiratory infections, such as bacterial or viral pneumonia, are often chronic and can be quite serious, especially in the elderly or an immune-compromised person. Also, although most common respiratory infections are not serious in an otherwise healthy host, they can set the stage for *secondary infections* that can be life-threatening. For example, death of an elderly person from pneumonia following a severe case of influenza is not an uncommon event.

Most human respiratory pathogens are transmitted from person to person because humans are the only reservoir for the pathogens. However, many airborne pathogens, such as *Streptococcus* spp., cold viruses, and influenza, can also be transmitted by direct contact (for example, by a handshake) or on fomites. Accurate and rapid diagnosis and treatment of respiratory infections are well

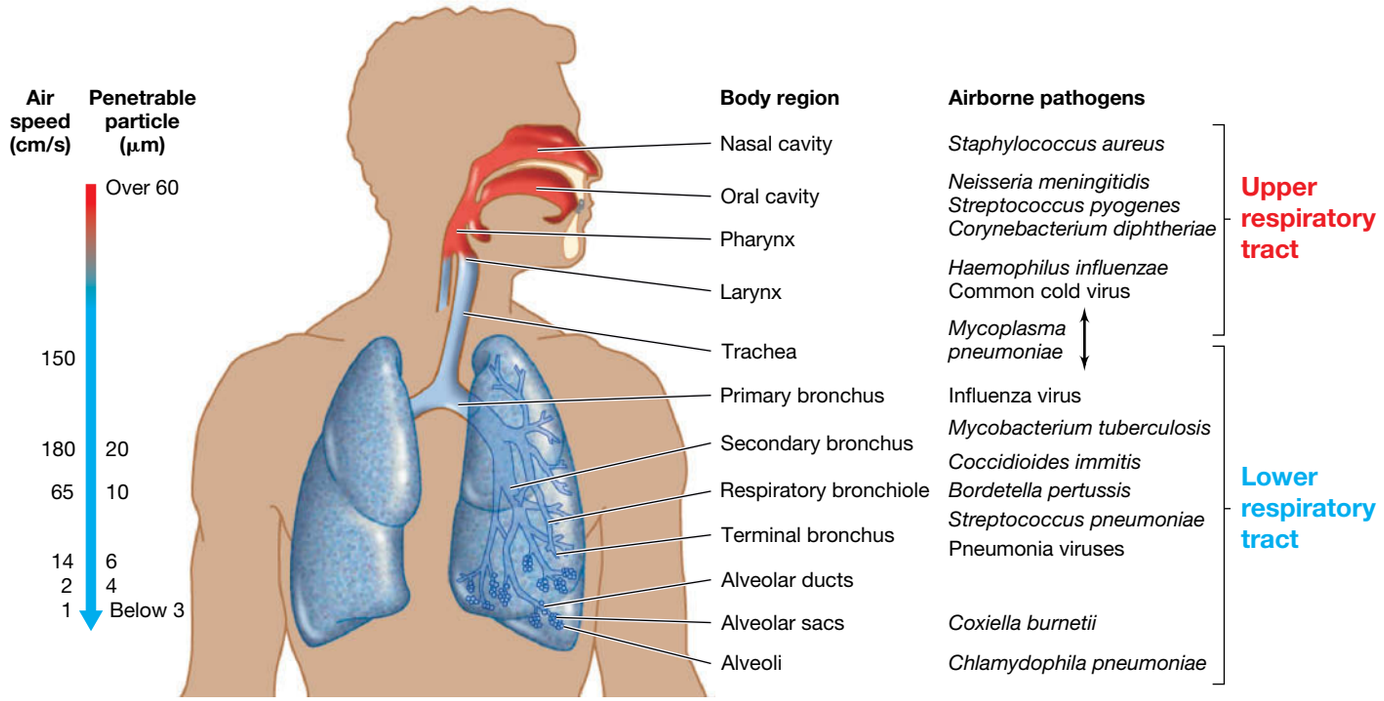


Figure 30.2 The human respiratory system. The microorganisms listed typically initiate infections at the locations indicated. The scale on the left combined with the respiratory tract diagram shows approximately where particles come to rest, determined by their size and air speed.

developed in the clinical setting and, if practiced effectively, can limit host damage. Many bacterial and viral pathogens transmitted by an airborne route can be controlled by immunization, and most respiratory bacterial pathogens respond readily to antibiotic therapy. Antiviral therapies, on the other hand, are rather limited, and recovery from viral infections is often due solely to the immune response.

MINIQUIZ

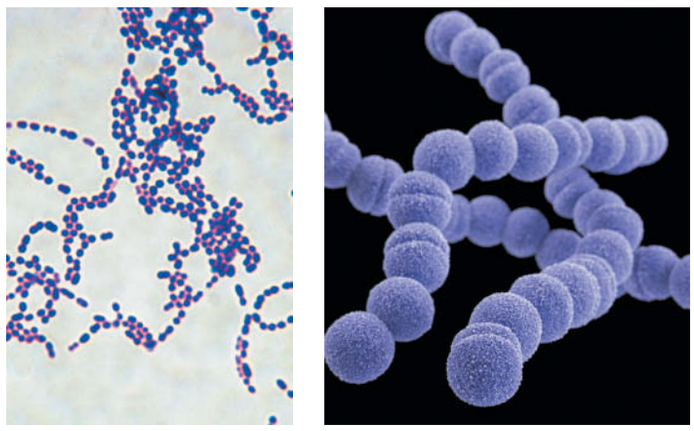
- Why can it be said that respiratory pathogens have exploited an effective means of transmission?
- Identify pathogens more commonly found in the upper respiratory tract. Identify pathogens more commonly found in the lower respiratory tract.

30.2 Streptococcal Syndromes

Streptococcal diseases are transmitted by airborne droplets or by direct contact, and the species *Streptococcus pyogenes* (Figure 30.3) and *Streptococcus pneumoniae* are the most important human respiratory pathogens. Streptococci are nonsporulating, homofermentative but aerotolerant gram-positive cocci (Section 16.6). Cells of *S. pyogenes* typically grow in elongated chains (Figure 30.3), as do many other species of the genus. Pathogenic strains of *S. pneumoniae* grow in pairs or short chains, and virulent strains produce an extensive polysaccharide capsule (see Figure 30.11). Virulent strains of *Streptococcus* can form vicious pus-forming wounds in humans and other warm-blooded (endothermic) animals (Figure 30.4 and see Figure 30.10). Many other serious conditions whose symptoms are less dramatic than these are also associated with streptococcal infections.

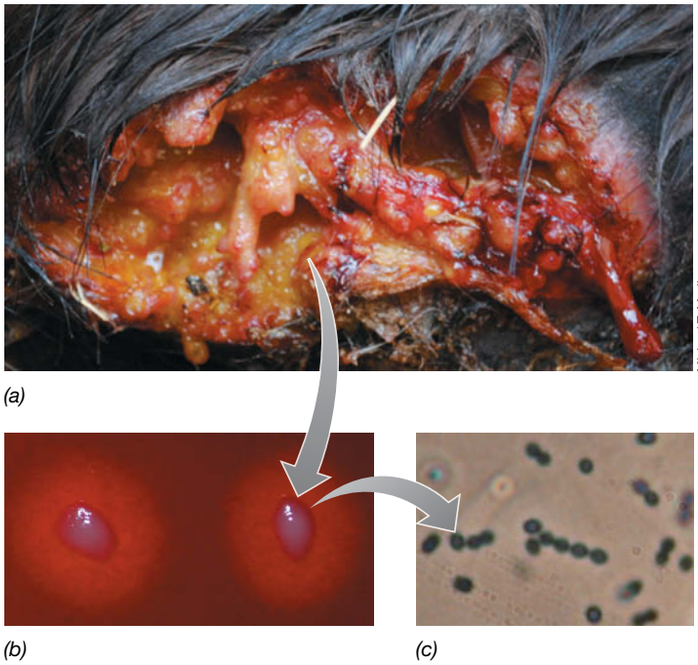
Streptococcus pyogenes

Streptococcus pyogenes (Figure 30.3), the major species in the *group A streptococci*, is frequently isolated from the upper respiratory tract of healthy adults. Although numbers are typically low, if host defenses are weakened or a new, highly virulent strain is encountered, serious infections are possible.



(a) (b)

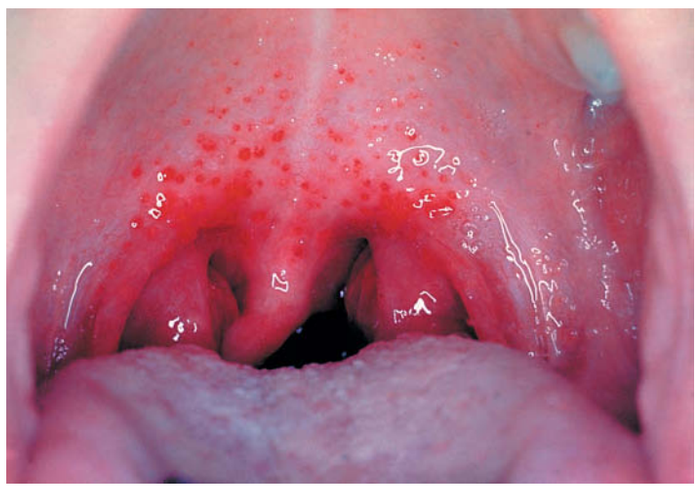
Figure 30.3 *Streptococcus pyogenes.* *(a)* Gram stain of cells of *Streptococcus pyogenes*. Cells grow in chains and range in size from 0.6 to 1 μm in diameter. *(b)* Computer-generated image of a scanning electron micrograph of cells of *S. pyogenes*.



Michael T. Madigan

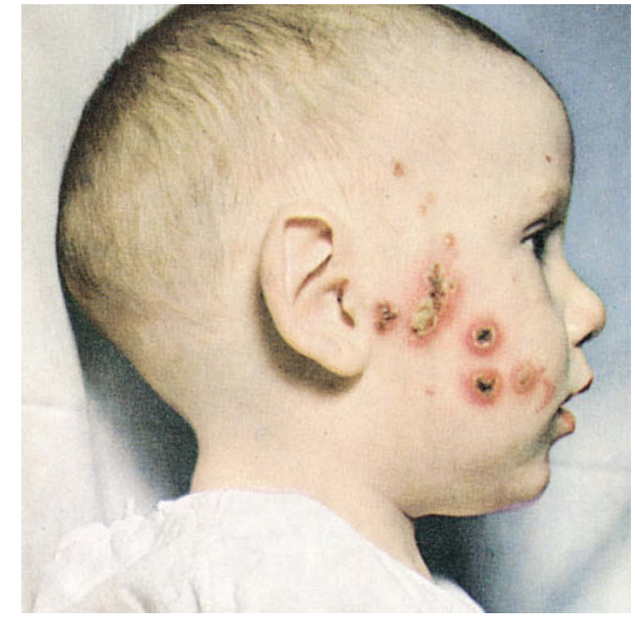
Figure 30.4 Pus-forming wound from β-hemolytic streptococci. *(a)* Pus and coagulated blood from a *Streptococcus equi* infection of a horse's salivary glands (the salivary glands have burst open from the infection). *(b)* Colonies of *S. equi* showing β-hemolysis on blood agar (compare with Figure 30.8). *(c)* Phase-contrast photomicrograph of cells of *S. equi*. Cells are 1 μm in diameter.

S. pyogenes is the cause of *streptococcal pharyngitis*, better known as *strep throat* (**Figure 30.5**). Most clinical isolates of *S. pyogenes* produce an exotoxin (Sections 25.6 and 25.7) that lyses red blood cells in culture media, a condition called *β-hemolysis* (Figure 30.4*b* and see Figure 30.8). Streptococcal pharyngitis is characterized by a severe sore throat with enlarged tonsils and red spots on the soft palate (Figure 30.5); tender cervical lymph nodes; and a mild fever and feeling of general malaise. *S. pyogenes* can also cause



CDC/PHIL

Figure 30.5 A case of strep throat caused by *Streptococcus pyogenes*. The back of the throat is inflamed and shows small red spots, typical of streptococcal pharyngitis.

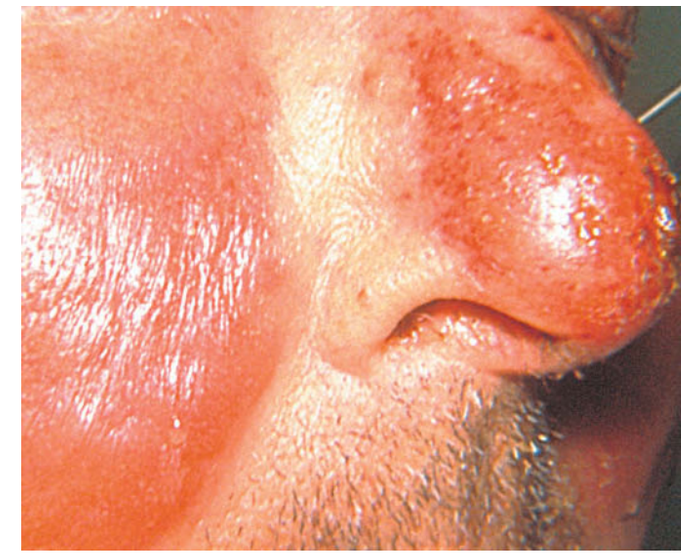


Franklin H. Top

Figure 30.6 Typical lesions of impetigo. Impetigo is commonly caused by *Streptococcus pyogenes* or *Staphylococcus aureus*.

infections of the middle ear (*otitis media*) and of the mammary glands (*mastitis*); infections of the superficial layers of the skin called *impetigo* (**Figure 30.6**); *erysipelas*, an acute streptococcal skin infection (**Figure 30.7**); and other conditions linked to the after effects of streptococcal infections.

About half of the clinical cases of severe sore throat are due to *S. pyogenes*; most others are due to viral infections. Because of this, an accurate and rapid diagnosis of a severe sore throat is important. If the sore throat is due to *S. pyogenes*, immediate treatment is important because untreated group A streptococcal infections can



CDC/Dr. Thomas F. Sellers

Figure 30.7 Erysipelas. Erysipelas is a *Streptococcus pyogenes* infection of the skin, shown here on the nose and cheeks, characterized by redness and distinct margins of infection. Other commonly infected body sites include the ears and the legs.

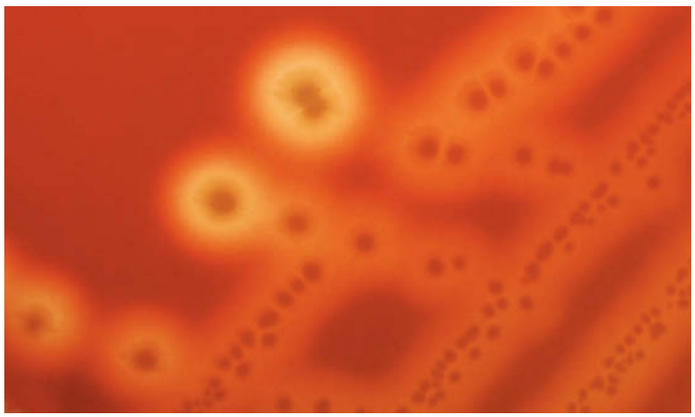


Figure 30.8 β-Hemolysis. The ability of a bacterium to lyse red blood cells and form a clear zone around a colony on a blood agar plate indicates secretion of the protein β-hemolysin. See also Figures 25.16*a* and 30.4*b*.

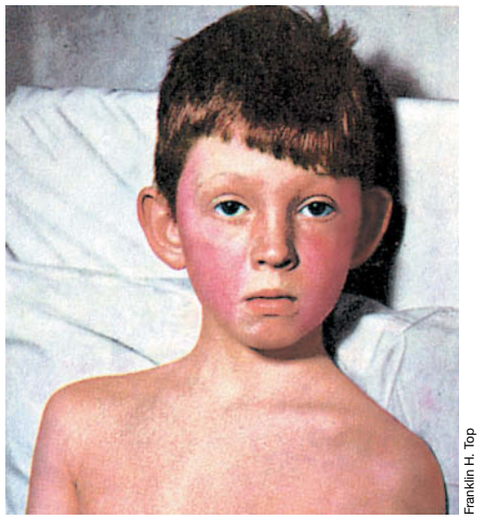


Figure 30.9 Scarlet fever. The typical rash of scarlet fever results from the activity of the pyrogenic exotoxins produced by *Streptococcus pyogenes*.

lead to serious secondary diseases such as scarlet fever, rheumatic fever, acute glomerulonephritis, and streptococcal toxic shock syndrome. On the other hand, if the sore throat is due to a virus, treatment with antibiotics will be useless and will only promote drug resistance on the part of the normal microbiota.

Clinical tools for quickly diagnosing strep throat are widely available and in routine use in primary care clinics. These tools include, in particular, rapid antigen detection systems that contain antibodies specific for cell surface proteins of *S. pyogenes* (Section 28.7). A more sensitive and accurate confirmation is possible by obtaining an actual culture of *S. pyogenes* from the throat or other suspected lesion on a blood agar plate (Figure 30.8). In contrast to rapid tests, however, results of a throat culture may take up to 48 h to process and such a delay in treatment can have adverse effects, as we consider now.

Scarlet and Rheumatic Fevers and Other Group A Strep Syndromes

Certain strains of group A streptococci carry a lysogenic bacteriophage that encodes streptococcal pyrogenic exotoxin A (SpeA), SpeB, SpeC, and SpeF. These exotoxins are responsible for most of the symptoms of *streptococcal toxic shock syndrome* and **scarlet fever** (Figure 30.9). Streptococcal pyrogenic exotoxins are superantigens that recruit large numbers of T cells to the infected tissues (Sections 25.6 and 27.10). Toxic shock results when the activated T cells secrete cytokines, which in turn activate large numbers of macrophages and neutrophils, causing severe inflammation and tissue destruction.

Scarlet fever, signaled by a severe sore throat, fever, and characteristic rash (Figure 30.9), is readily treatable with antibiotics or may be self-limiting. But treatment is always advisable because several undesirable conditions can emerge from a case of scarlet fever. Occasionally group A streptococcal infections cause fulminant (sudden and severe) invasive systemic infections, such as cellulitis, a skin infection in subcutaneous layers; or *necrotizing fasciitis*, a rapid and progressive disease resulting in extensive destruction of subcutaneous tissue, muscle, and fat (Figure 30.10). Necrotizing fasciitis is a clinical term for the condition caused by "flesh-eating bacteria." In these cases, SpeA, SpeB, SpeC, and SpeF exotoxins and the bacterial cell surface M protein function as superantigens; the associated host inflammation results in extensive tissue destruction and can be fatal (Figure 30.10).

Untreated or insufficiently treated *S. pyogenes* infections may lead to other severe conditions 1 to 4 weeks after the onset of infection. For example, the immune response to the invading pathogen can produce antibodies that cross-react with host tissue antigens of the heart, joints, and kidneys, resulting in damage to these tissues. The most serious of these syndromes is **rheumatic fever** caused by rheumatogenic strains of *S. pyogenes*. These strains contain cell surface antigens that are similar in structure to heart valve and joint proteins. Thus rheumatic fever is, in effect, an *autoimmune disease* (Section 27.9) because antibodies directed against streptococcal antigens cross-react with heart valve and joint antigens, causing inflammation and tissue

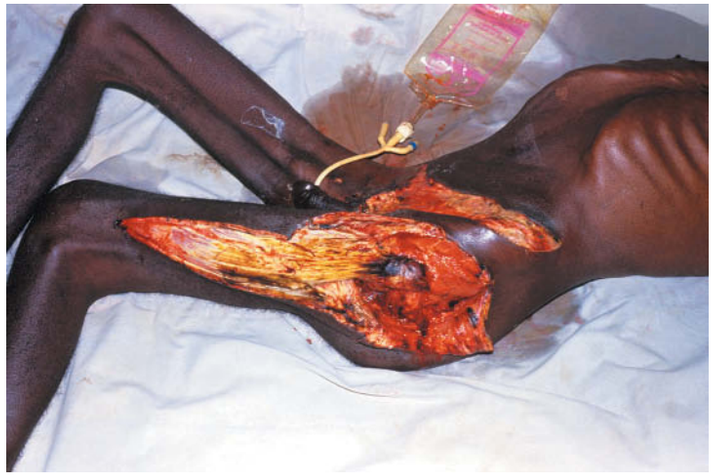


Figure 30.10 Necrotizing fasciitis (flesh-eating bacteria). Soft tissue infection of human hip and thigh by group A *Streptococcus pyogenes*. The flesh has split open to reveal muscle tissues.

destruction. Damage to host tissues may be permanent, and is often exacerbated by subsequent streptococcal infections that lead to recurring bouts of rheumatic fever. Another streptococcal syndrome is *acute poststreptococcal glomerulonephritis*, a painful kidney disease. This "immune complex" disease develops transiently when streptococcal antigen–antibody complexes in the blood lodge in the glomeruli (filtration membranes of the kidney) and cause inflammation, a condition called *nephritis*.

Streptococcus pneumoniae

A second major human streptococcal pathogen is *Streptococcus pneumoniae* (Figure 30.11), a species that can cause invasive lung infections, typically as secondary infections to other respiratory disorders. Encapsulated strains of *S. pneumoniae* (Figure 30.11; Figure 25.4) are particularly pathogenic because they are very invasive. Cells invade the lower respiratory tract where the capsule enables the cells to resist phagocytosis yet generate a strong host inflammatory response. Reduced lung function, called *pneumonia*, results from the accumulation of recruited phagocytic cells and fluid. Cells of *S. pneumoniae* can then spread from the focus of infection as a bacteremia, sometimes infecting the bones, middle ear, and heart valves (endocarditis). *S. pneumoniae* infection is often the cause of death in elderly persons whose death is reported to be from "respiratory failure."

Unlike the case with *S. pyogenes*, effective vaccines are available for preventing infection by the most common strains of *S. pneumoniae*. An older vaccine widely used in adults consisted of a mixture of 23 capsular polysaccharides (Figure 30.11) from the most prevalent pathogenic strains. The vaccine is recommended for those over age 60, healthcare providers, individuals with compromised immunity, and any other high-risk population. A newer vaccine, PREVNAR 13®, is an update of the traditional vaccine and is effective against the 13 *S. pneumoniae* strains most commonly seen today and is recommended for adults age 50 or older.

S. pneumoniae infections typically respond quickly to penicillin therapy, but up to 30% of pathogenic isolates now exhibit resistance to this drug. Resistance to the antibiotics erythromycin and cefotaxime is also found in some strains but thus far, all strains have been found sensitive to vancomycin, an antibiotic held in reserve for treating pneumonia and several other bacterial diseases where antibiotic resistance is widespread (Section 28.12).

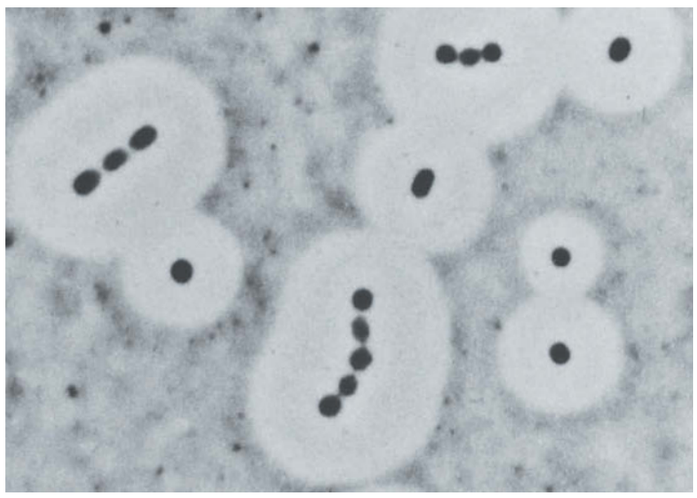

Isaac Shechmeister

Figure 30.11 *Streptococcus pneumoniae*. India ink negative stain of cells of *Streptococcus pneumoniae*. An extensive capsule surrounds the cells, which are 1.0–1.2 µm in diameter.

MINIQUIZ

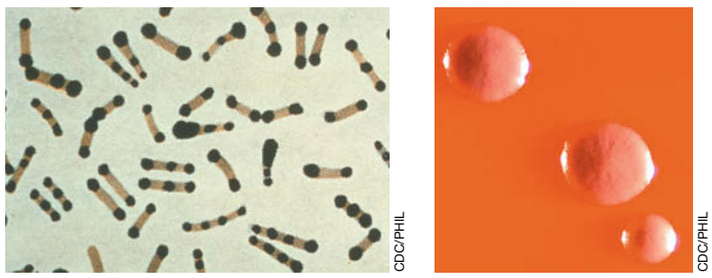
- How does *Streptococcus pyogenes* infection cause rheumatic fever?
- What is the primary virulence factor for *Streptococcus pneumoniae*?

30.3 Diphtheria and Pertussis

Diphtheria is a severe respiratory disease that typically infects young children. Diphtheria is caused by *Corynebacterium diphtheriae*, a gram-positive, nonmotile, and aerobic club-shaped bacterium that forms small, smooth colonies on blood agar plates (Figure 30.12). **Pertussis**, also known as **whooping cough**, is a serious respiratory disease caused by infection with *Bordetella pertussis*, a small, gram-negative, aerobic coccobacillus (see Figure 30.14). Pertussis mostly affects children but can cause serious respiratory disease in adults as well. Both diphtheria and pertussis can be prevented by vaccination and cured with antibiotics.

Diphtheria

Cells of *C. diphtheriae* (Figure 30.12*a*) enter the host from airborne droplets, infecting the tissues of the throat and tonsils. A child with diphtheria often displays a swollen neck (Figure 30.13*a*), and throat tissues respond to *C. diphtheriae* infection by forming a characteristic lesion called a *pseudomembrane* consisting of damaged host cells and cells of *C. diphtheriae* (Figure 30.13*b*). Not all strains of *C. diphtheriae* cause diphtheria. *Pathogenic* strains of *C. diphtheriae* carry a lysogenic bacteriophage whose genome encodes a powerful exotoxin called *diphtheria toxin*. This toxin inhibits protein synthesis in the host, leading to cell death (Figure 25.12). Death from diphtheria is due to a combination of partial suffocation by the pseudomembrane and tissue destruction by diphtheria exotoxin. *C. diphtheriae* isolated from


CDC/PHIL

(a) (b)

Figure 30.12 *Corynebacterium* and diphtheria. *(a)* Cells of *Corynebacterium diphtheriae* showing typical club-shaped appearance. The gram-positive cells are 0.5–1 µm in diameter and may be several micrometers in length. *(b)* Colonies of *C. diphtheriae* grown on a selective medium of blood agar plus tellurite.

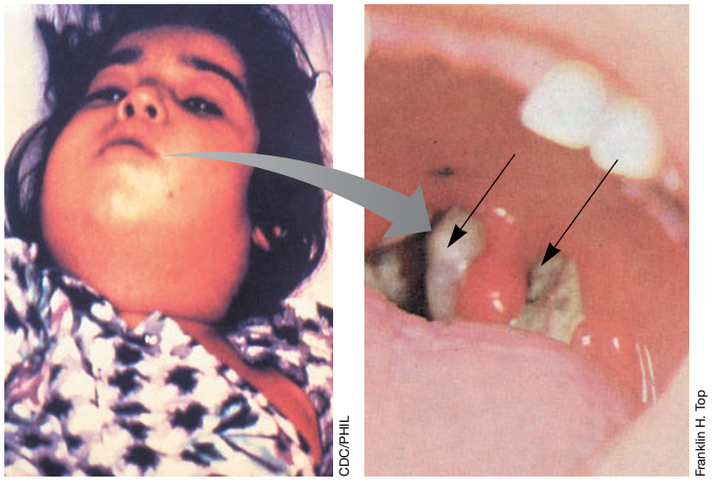


Figure 30.13 Diphtheria. *(a)* A swollen neck is a common symptom of diphtheria. *(b)* The pseudomembrane (arrows) in an active case of diphtheria restricts airflow and swallowing and is associated with a severe sore throat.

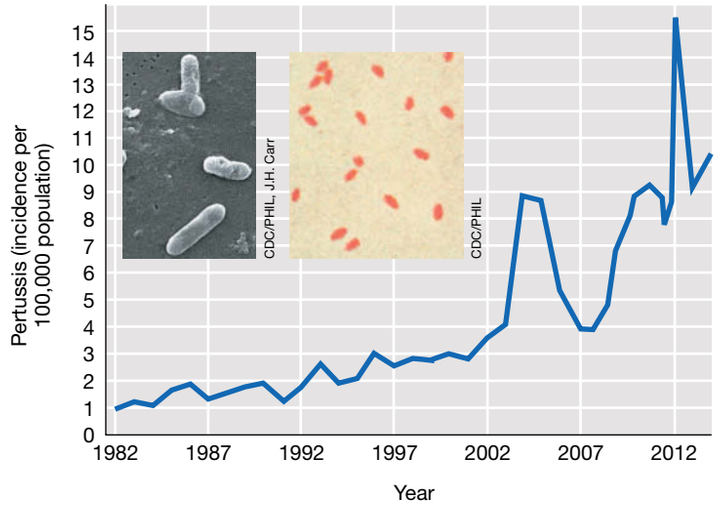


Figure 30.14 *Bordetella* and pertussis. Cells of *B. pertussis* are typically coccobacilli 0.2–0.5 µm in diameter and about 1 µm long. Pertussis incidence has been on the rise since 2007. Data are from the CDC. Inset photos: left, scanning electron micrograph of cells of *Bordetella*; right, Gram-stained cells of *B. pertussis*.

the throat is diagnostic for diphtheria. Nasal or throat swabs are used to inoculate blood agar containing tellurite (Figure 30.12*b*) or Loeffler's medium, a selective medium that inhibits the growth of most other respiratory pathogens.

Prevention of diphtheria is accomplished with a highly effective toxoid vaccine, part of the *DTaP* (*d*iphtheria toxoid, *t*etanus toxoid, and *a*cellular *p*ertussis) *vaccine* (Section 28.9). Diphtheria is all but absent from developed countries where this vaccine is widely used. Penicillin, erythromycin, and gentamicin are generally effective treatments for diphtheria, but in life-threatening cases, diphtheria antitoxin (an antiserum to diphtheria toxoid produced in horses) may be administered in addition to antibiotic therapy.

Pertussis

Pertussis (whooping cough) is an acute, highly infectious respiratory disease. Infants less than 6 months old, who are too young to be effectively vaccinated, have the highest incidence of disease and also have the most severe symptoms. Cells of *B. pertussis* (**Figure 30.14**) attach to host cells of the upper respiratory tract and excrete *pertussis exotoxin*. This potent toxin induces synthesis of cyclic adenosine monophosphate (cyclic AMP, Figure 6.13), which is at least partially responsible for the events that lead to host tissue damage. *B. pertussis* also produces an endotoxin (Section 25.8), which may induce some of the symptoms of whooping cough. Clinically, whooping cough is characterized by a recurrent, violent cough that can last up to 6 weeks. The spasmodic coughing gives the disease its name; a whooping sound results from the patient inhaling deep breaths to obtain sufficient air.

Worldwide, up to 50 million cases and over 250,000 deaths occur each year from pertussis, most in developing countries. *B. pertussis* is endemic worldwide and pertussis remains a problem, even in developed countries, usually as a result of inadequate immunization. In the United States there has been a gradual upward trend of pertussis since the 1980s, with spikes in reported cases in 2005, 2010, and 2012 (Figure 30.14); many of these have been in young adults under age 20. In 2014 there were nearly 33,000 cases of pertussis in the United States and 13 deaths, all but two in children under age 4. Pertussis is a classic endemic disease; incidence rises cyclically as populations become susceptible and are exposed to the pathogen. A combination of lax vaccination protocols and the fact that pertussis is a much more common disease than diphtheria have probably fueled the overall higher incidence of pertussis in recent years.

Whooping cough can be treated with ampicillin, tetracycline, or erythromycin, although antibiotics alone do not seem to effect a complete cure, as patients continue to show symptoms and remain infectious for up to 2 weeks after beginning antibiotic therapy. This indicates that the immune response may be as important as antibiotics in ridding the pathogen from the body.

MINIQUIZ

- Contrast the disease symptoms of diphtheria and pertussis.
- What measures can be taken to decrease the current incidence of pertussis in a population?

30.4 Tuberculosis and Leprosy

The famous pioneering microbiologist Robert Koch, the founder of the field of medical microbiology, isolated and described the causative agent of tuberculosis, *Mycobacterium tuberculosis*, in 1882 (Section 1.10). A related species, *Mycobacterium leprae*, causes leprosy (Hansen's disease). Mycobacteria are gram-positive bacteria and share the property of being *acid-fast* because of the waxy mycolic acid constituent of their cell walls (Section 16.11). Mycolic acid allows these organisms to retain the red dye carbolfuchsin after a mycobacterial smear on a slide is washed in 3% hydrochloric acid in alcohol. Colonies of *M. tuberculosis* grow

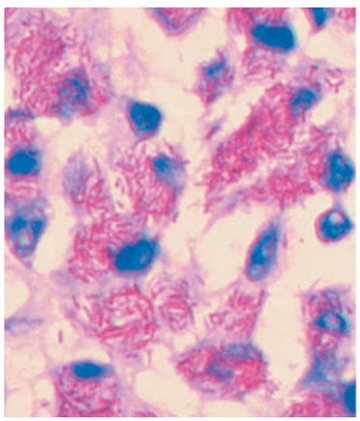
slowly on plates and have a characteristically wrinkled morphology (Figure 30.15).

Tuberculosis

Tuberculosis (TB) is easily transmitted by the respiratory route, and at one time it was the most important infectious disease of humans. TB kills nearly 1.5 million people per year, making it the top infectious disease killer worldwide. About one-third of the world's population has been infected with *M. tuberculosis*, though most do not show active disease because cell-mediated immunity (Section 27.9) plays a critical role in the prevention of active disease after infection.

Tuberculosis can take several forms. TB can be a *primary* infection (initial infection) or *postprimary* infection (reinfection). Primary infection typically results from inhalation of droplets containing *M. tuberculosis*, after which the bacteria settle in the lungs and grow. The host mounts an immune response to *M. tuberculosis*, resulting in the formation of aggregates of activated macrophages, called *tubercles*. Bacteria are found in the sputum of individuals with active disease, and areas of destroyed tissue can be seen in chest X-rays (Figure 30.16). Mycobacteria survive and grow within macrophages in the tubercles, forming granulomas, and if the disease is not controlled, extensive destruction of lung tissue can occur. If the disease reaches this stage, the pulmonary infection is often fatal.

In most individuals infected with *M. tuberculosis*, however, acute disease does not occur; instead, the infection is inapparent. Nevertheless, the infection hypersensitizes the individual to *M. tuberculosis* or its products and typically protects the individual against postprimary infections. A diagnostic skin test, called the **tuberculin test**, can detect this hypersensitivity (Figure 27.27), and many healthy adults are *tuberculin-positive* as a result of previous or current inapparent infections. In most cases, the cell-mediated immune response to *M. tuberculosis* is protective and lifelong. However, some tuberculin-positive patients develop postprimary tuberculosis through reinfection from bacteria that have remained dormant in lung macrophages for years. Because of this, individuals who have a positive tuberculin test are typically treated with anti-tuberculosis drugs for extended periods to ensure that all mycobacteria have been killed.



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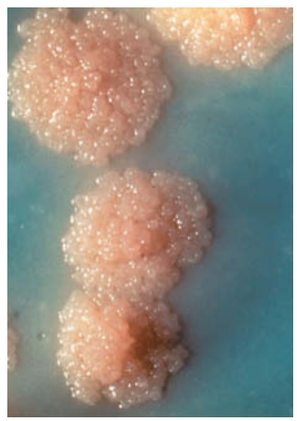
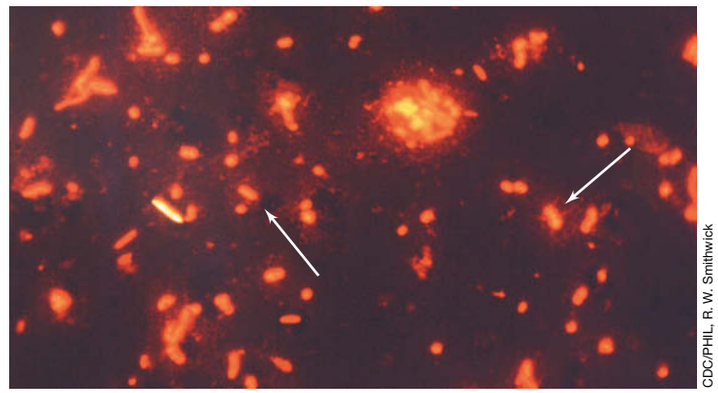


(b)

Figure 30.15 Mycobacteria. *(a)* Acid-fast stained lymph node biopsy from a patient with HIV/AIDS shows cells of *Mycobacterium avium*, a relative of *M. tuberculosis*. Multiple bacilli, stained red with carbol-fuchsin and treated with 3% hydrochloric acid, are evident inside each human cell. The individual rods are about 0.4 μm in diameter and up to 4 μm in length. *(b)* Colonies of *M. tuberculosis*. The rough, wrinkled surface is typical of mycobacterial colonies.



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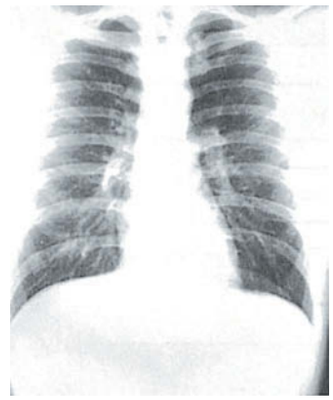

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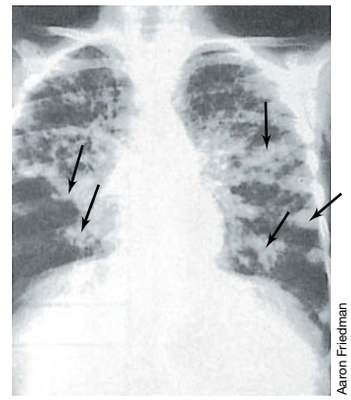


(c)

Figure 30.16 Tuberculosis symptoms. *(a)* Sputum sample from a patient with tuberculosis stained by the Smithwick acridine orange method. Cells of *Mycobacterium tuberculosis* are the yellow-orange rod-shaped structures (arrows). *(b)* Normal chest X-ray. The faint white lines are arteries and other blood vessels. *(c)* Chest X-ray showing an advanced case of pulmonary tuberculosis; white patches (arrows) indicate areas of tubercles that contain viable cells of *M. tuberculosis*.

Antimicrobial therapy of TB has been a major means of controlling the disease. Streptomycin was the first effective anti-tuberculosis antibiotic, but the real revolution in tuberculosis treatment came with the discovery of isonicotinic acid hydrazide, called *isoniazid* (INH). This drug is highly effective and readily absorbed when given orally. Isoniazid is a growth factor analog (Section 28.10 and Table 28.5) of the structurally related molecule nicotinamide; in mycobacteria the drug inhibits mycolic acid synthesis and this compromises cell wall integrity. Following treatment with isoniazid, mycobacteria lose their acid-fast properties, in keeping with the role of mycolic acid in this staining property.

Treatment of tuberculin-positive individuals is typically achieved with daily doses of isoniazid and the antibiotic rifampin for 2 months, followed by biweekly doses for a total of 9 months. This treatment eradicates pockets of *M. tuberculosis* cells and prevents emergence of antibiotic-resistant derivatives. Multiple drug therapy reduces the possibility that strains having resistance to more than one drug will emerge. Resistance of *M. tuberculosis* to isoniazid and other drugs, however, is increasing, especially in

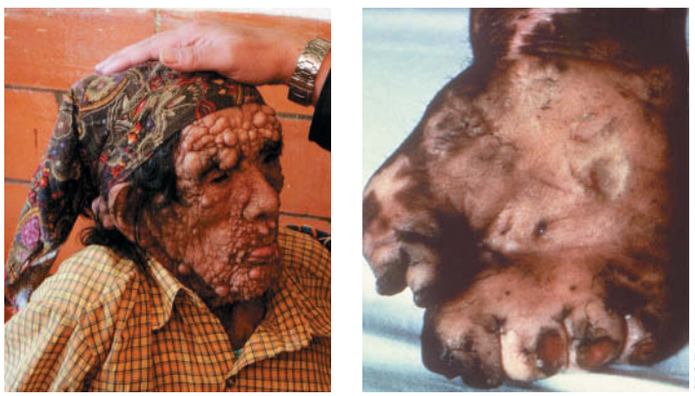
HIV/AIDS patients, in whom TB is a common infection (see Figure 30.45*g*). Treatment of these strains, called *multidrug-resistant tuberculosis strains*, requires the use of second-line tuberculosis drugs that are generally more toxic, less effective, and more costly than rifampin and isoniazid.

Leprosy

Mycobacterium leprae, a relative of *M. tuberculosis*, causes the disease *leprosy*, more formally known as *Hansen's disease*. The most serious form of Hansen's disease is *lepromatous* leprosy, characterized by folded, bulblike lesions on the body, especially on cooler parts of the body such as the face and extremities (**Figure 30.17*a***). The lesions are due to the growth of *M. leprae* cells in skin Schwann cells that insulate the nerves, and the lesions contain large numbers of bacterial cells. Like cells of other mycobacteria (Figure 30.15*a*), cells of *M. leprae* from the lesions stain deep red with carbol-fuchsin in the acid-fast staining procedure, providing a definitive demonstration of active infection.

In severe untreated cases of leprosy, the disfiguring lesions lead to destruction of peripheral nerves; muscles then atrophy and motor function is impaired. The loss of sensation in the extremities leads to inapparent injuries, such as burns and cuts. Loss of bone calcium leads to a slow shrinking of the digits and their transition to clawlike forms in late-stage leprosy (Figure 30.17*b*). Pathogenicity in the disease is due to a combination of delayed-type hypersensitivity (Section 27.9) and the highly invasive activities of *M. leprae*, which can grow within macrophages and lead to the characteristic lesions (Figure 30.17*a*). Leprosy is transmitted by direct contact as well as by an airborne route, but is not as highly contagious as TB. Historically, leprosy has been associated with poverty, malnutrition, and poor sanitation and hygiene. Among other things, these factors undoubtedly affect an individual's ability to resist infection.

Many Hansen's disease patients exhibit less-pronounced lesions from which *M. leprae* cells cannot be obtained; these individuals have the *tuberculoid* form of the disease. Tuberculoid leprosy is characterized by a vigorous immune response and a good prognosis for spontaneous recovery. Hansen's disease of either form, and the continuum of intermediate forms, is treated using a multiple drug therapy protocol, which includes some combination of extended therapy of up to 1 year with *dapsone* (4,4′-sulfonylbisbenzeneamine, an inhibitor of folic acid synthesis), *rifampin*, a bacterial RNA polymerase inhibitor, and *clofazimine*, a drug that targets bacterial respiration and ion transport.



(a) (b)

Figure 30.17 Lepromatous leprosy lesions on the skin. *(a)* Lepromatous leprosy is caused by infection with *Mycobacterium leprae*. The lesions can contain up to 10^9 bacterial cells per gram of tissue, indicating an active uncontrolled infection with a poor prognosis. *(b)* The palm of the right hand of a leprosy patient showing the clawlike form and digit deformation characteristic of late-stage leprosy.

Nearly 214,000 new cases of leprosy were reported in 2014, with most cases occurring in Africa, the Indian subcontinent, and Brazil. In the United States only about 200 cases of leprosy are diagnosed per year, mainly in immigrants from countries with endemic disease. Until recently, a leprosy diagnosis relied on the identification of *M. leprae* cells from lesions. However, a quick, inexpensive, and specific blood test is now available that should greatly assist in identifying early-stage leprosy, the most treatable form.

In addition to *M. tuberculosis* and *M. leprae*, several other mycobacteria are human pathogens. These include in particular *M. bovis*, a close relative of *M. tuberculosis* and a common pathogen of dairy cattle. *M. bovis* can initiate classic symptoms of TB in humans; however, a combination of the pasteurization of milk and the culling of infected cattle has greatly reduced the incidence of bovine-to-human transmission of this form of TB.

MINIQUIZ

- Why is *Mycobacterium tuberculosis* a widespread respiratory pathogen?
- Describe three common characteristics of pathogenic mycobacteria.

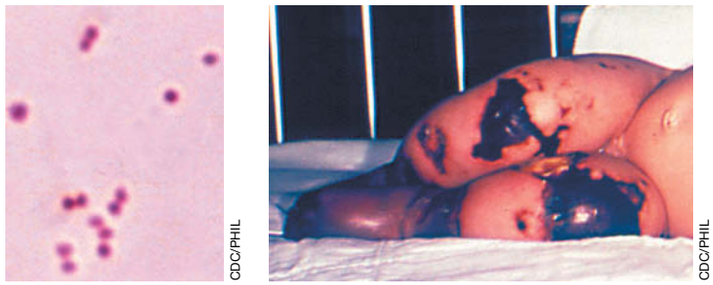
30.5 Meningitis and Meningococcemia

Meningitis is an inflammation of the meninges, the membranes that are the protective covering of the central nervous system, that is, the spinal cord and brain. Several different microorganisms, including certain viruses, bacteria, fungi, and protists, can cause meningitis. Here we focus on the severe bacterial form of the disease called *infectious meningitis*, caused by the bacterium *Neisseria meningitidis*.

Pathogen and Disease Syndromes

Neisseria meningitidis, often called the *meningococcus*, is a gram-negative and obligately aerobic coccus about 0.6–1 μm in diameter (**Figure 30.18*a***); it is a relative of the bacterium that causes gonorrhea, *Neisseria gonorrhoeae*. The bacterium is transmitted to a new host, usually via the airborne route from an infected individual, and attaches to the cells of the nasopharynx. Once there, the organism quickly gains access to the bloodstream, causing widespread dissemination (bacteremia) and upper respiratory tract symptoms. Meningitis is characterized by the sudden onset of a headache accompanied by vomiting and a stiff neck, and can progress to coma and death in less than a day. Instead of or in addition to full-blown meningitis, *N. meningitidis* bacteremia sometimes leads to fulminant **meningococcemia**, a condition characterized by intravascular coagulation and tissue destruction (gangrene, Figure 30.18*b*), shock, and death in over 10% of cases.

Meningococcal meningitis often occurs in epidemics, usually in populations living in close proximity such as in military barracks or college dormitories. Anyone can get meningococcal disease, but the incidence is much higher in infants, school-age children, and young adults. Up to 30% of people carry *N. meningitidis* in their nasopharynx



(a) (b)

Figure 30.18 *Neisseria meningitidis*. The organism causes meningitis and meningococcemia. *(a)* Gram stain of cells of *N. meningitidis*; cocci are about 0.6–1 µm in diameter. *(b)* Four-month-old infant with gangrene on legs from meningococcemia.

with no apparent harmful effects, and the trigger for conversion from the asymptomatic carrier state to the disease state is unknown.

Diagnosis, Treatment, and Vaccines

Meningococcal meningitis is definitively diagnosed from cultures of *N. meningitidis* isolated from nasopharyngeal swabs, blood, or cerebrospinal fluid. Thayer–Martin medium, a selective medium for the growth of pathogenic *Neisseria*, including both *N. meningitidis* and *N. gonorrhoeae*, is used to isolate *N. meningitidis*, and colonies containing gram-negative diplococci (Figure 30.18*a*) are further tested. However, due to the rapid onset of life-threatening symptoms in infectious meningitis, preliminary diagnosis is often based on clinical symptoms and treatment is started before culture tests confirm infection with *N. meningitidis*. Treatment is typically with penicillin, and intravenous application is often needed to speed antibiotic infusion.

Naturally occurring antibodies acquired by subclinical infections with *N. meningitidis* are effective for preventing infectious meningitis in most adults. Vaccines consisting of purified polysaccharides or polysaccharides from the most prevalent pathogenic strains are available to immunize certain susceptible populations such as military recruits and students living in dormitories, especially if an outbreak has already occurred. In addition, the antibiotic rifampin is often used to eradicate the carrier state and prevent meningococcal disease in close contacts of infected individuals.

MINIQUIZ

- Identify the symptoms and causes of meningitis.
- Describe the infection by *Neisseria meningitidis* and the resulting development of meningococcemia.

II • Airborne Viral Diseases

30.6 MMR and Varicella-Zoster Infections

The most prevalent and difficult to treat of all human infectious diseases are those caused by viruses. This is because viruses can often remain infectious for long periods in dried mucus (Figure 30.1) or on fomites, and because viruses require host cells for replication. Hence, killing the virus often means killing the cell as well.

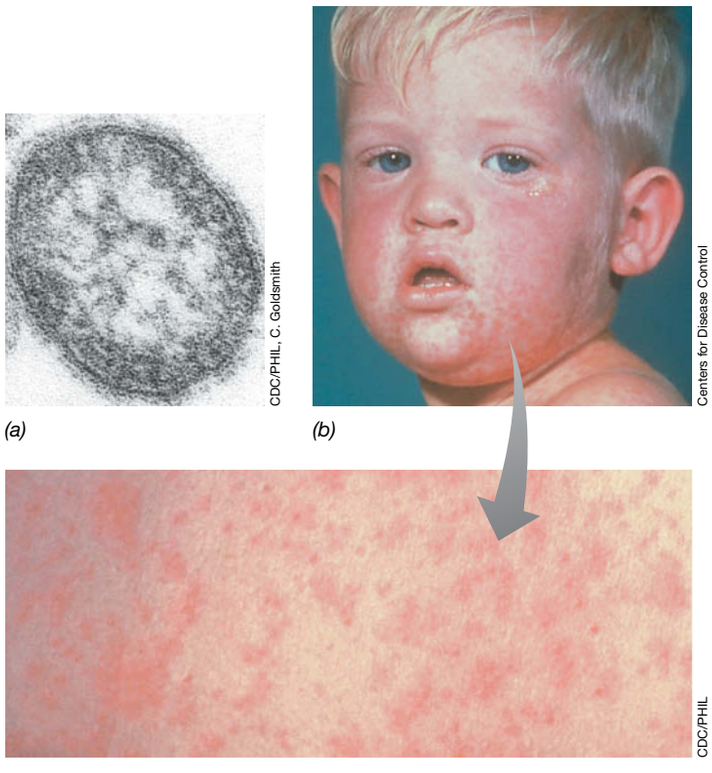
Most viral diseases are acute, self-limiting infections, but some can be problematic in healthy adults. We begin with measles, rubella, mumps, and chicken pox, all common, endemic viral diseases transmitted in infectious droplets by an airborne route.

Measles and Rubella

Measles (*rubeola* or *7-day measles*) affects susceptible children as an acute, highly infectious, often epidemic disease. The measles virus (**Figure 30.19*a***) is a *paramyxovirus*, a single-stranded, minus-sense RNA virus (Section 10.9) that enters the nose and throat by airborne transmission, quickly leading to a systemic viremia. Symptoms start with nasal discharge and redness of the eyes. As the disease progresses, fever and cough appear and rapidly intensify, followed by a characteristic rash (Figure 30.19*b, c*).

Symptoms of measles generally persist for 7–10 days, and no drugs are available that will eliminate symptoms. However, the measles virus generates a strong immune response. Circulating antibodies to measles virus are measurable within 5 days of infection; these serum antibodies along with T-cytotoxic lymphocytes combine to eliminate the virus from the host. Possible postinfection complications include middle ear infection, pneumonia, and, in rare cases, measles encephalomyelitis.

Although once a common childhood illness, measles is limited to rare, isolated outbreaks in the United States because of widespread immunization programs begun in the 1960s. Those outbreaks that have occurred have been in populations that were either not immunized or inadequately immunized. In 2015, fewer than 200 cases were reported in the United States. Worldwide, measles remains



(a) (b) (c)

Figure 30.19 Measles in children. *(a)* Transmission electron micrograph of a measles virus virion; a virion is about 150 nm in diameter. *(b, c)* Measles rash. The light pink rash starts on the head and neck, and can spread to the chest, trunk, and limbs. Discrete papules coalesce into blotches as the rash progresses for several days.

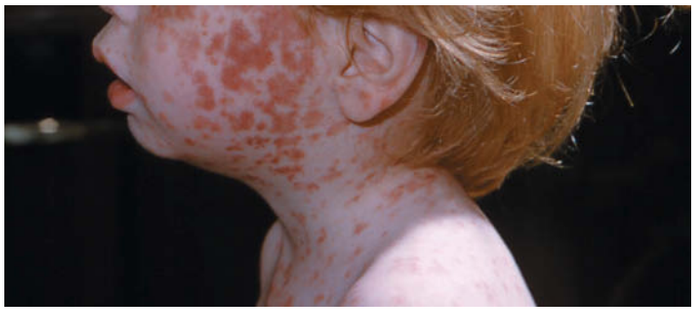


Figure 30.20 Rubella. The rash of rubella (German measles) on the face of a young child.

endemic, however, and still causes over 100,000 annual deaths, mostly in children. Active immunity to measles is conferred with an attenuated virus preparation as part of the *MMR* (*m*easles, *m*umps, *r*ubella) vaccine (Section 28.9). Because the disease is highly infectious, all public school systems in the United States require proof of measles immunization before a child can enroll. A childhood case of measles generally confers lifelong immunity.

Rubella (sometimes called *German measles* or *3-day measles*) is caused by a single-stranded, positive-sense RNA virus (Section 10.8). Symptoms of rubella resemble those of measles (**Figure 30.20**) but are often restricted to just the upper torso. Rubella is less contagious than measles, and thus a significant proportion of the population has never been infected. However, during the first three months of pregnancy, rubella virus can infect the fetus by placental transmission and cause serious fetal abnormalities including stillbirth, deafness, heart and eye defects, and brain damage, events called *congenital rubella syndrome*. Thus, women should not be immunized with the rubella vaccine or contract a rubella infection during pregnancy. Also for this reason, routine childhood immunization against rubella should be practiced. An attenuated rubella virus is administered as part of the MMR vaccine. The low incidence of rubella since 2001, coupled with the high degree of protection by the vaccine and the relatively low infectivity of the virus, combine to make rubella very rare in the United States. An active rubella vaccination program worldwide is also decreasing case numbers significantly, as total reported active cases in 2009 were fewer than 125,000 and cases of congenital rubella syndrome were 165.

Mumps

Mumps, like measles, is caused by a paramyxovirus and is also highly infectious by the airborne route. Mumps is spread by airborne droplets, and the disease is characterized by inflammation of the salivary glands, typically the parotid gland, the largest of the salivary glands, leading to swelling of the jaws and neck (**Figure 30.21**). The virus spreads through the bloodstream and may infect other organs, including the testes and pancreas, and may cause encephalitis in rare severe cases. As for measles, the immune response rather than drug treatment is what cures a case of mumps. The host immune response produces antibodies to mumps virus surface proteins, and this generally leads to a quick recovery and lifelong immunity to reinfection.

An attenuated mumps vaccine (part of the MMR) is highly effective in preventing disease. Hence, the prevalence of mumps in developed countries is low, with disease generally restricted to individuals

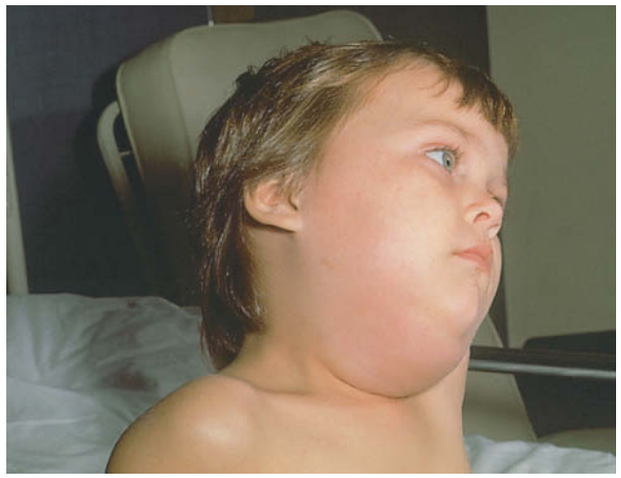


Figure 30.21 Mumps. Glandular swelling characterizes infection with the mumps virus. Mumps symptoms typically last about one week and a person is infectious both before and during the symptomatic stages.

who did not receive the vaccine. However, an outbreak of mumps in the midwestern United States in 2006 involved more than 5000 cases. The outbreak affected mainly young adults (18–34). As a result, recommendations for immunizations were revised to target school-age children, healthcare workers, and adults who had not previously had mumps. Since 2013, mumps cases in the United States have fluctuated between about 500 and 1200 annually.

Chicken Pox and Shingles

Chicken pox (*varicella*) is a common childhood disease caused by the varicella-zoster virus (VZV), a double-stranded DNA herpesvirus (Section 10.7). VZV is a mild but highly contagious disease and is transmitted by infectious droplets, especially when susceptible individuals are in close contact. In schoolchildren, for example, close confinement during the winter months leads to the spread of VZV through airborne droplets from infected classmates and through direct contact with chicken pox blisters of other children or contaminated fomites. The virus enters the respiratory tract, multiplies, and is quickly disseminated via the bloodstream, resulting in a systemic papular rash (**Figure 30.22**)

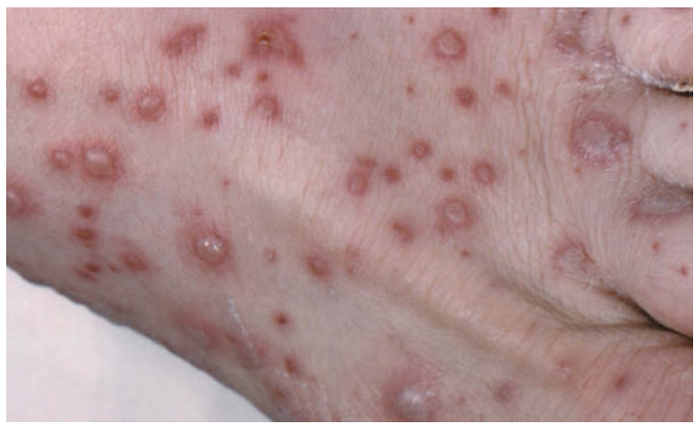


Figure 30.22 Chicken pox. Papular rash on the foot of an adult. The papules are due to infection by varicella-zoster virus, the herpesvirus that causes chicken pox.

that heals quickly without scarring. An attenuated chicken pox virus vaccine (Varivax) is used in the United States but not as widely as the MMR vaccine for measles, rubella, and mumps. Consequently, the reported incidence of chicken pox in 2011 was about 15,000 cases per year, which is about 10% of the number of cases reported in 1995, the year the vaccine was first licensed. Deaths from chicken pox are extremely rare, with six deaths reported in 2011.

VZV establishes a lifelong latent (permanent) infection in nerve cells. The virus can remain dormant there indefinitely, but in some individuals the virus migrates from this reservoir to the skin surface, often years or decades later, causing a painful skin eruption called *shingles* (*zoster*). Shingles most commonly strikes immunosuppressed individuals or the elderly, causing severe blisters and a rash on the head, neck, or upper torso. A fairly effective shingles vaccine containing concentrated attenuated virus (Zostavax) is available for individuals over 50 years of age. The vaccine stimulates antibody- and cell-mediated immunity to VZV, which keeps VZV from migrating out of nerve ganglia to skin cells and triggering shingles symptoms.

MINIQUIZ

- How do the genomes of the measles virus and the German measles virus differ?
- Describe the potential serious outcomes of infection by measles, mumps, rubella, and VZV viruses.
- Identify the effects of immunization on the incidence of measles, mumps, rubella, and chicken pox.

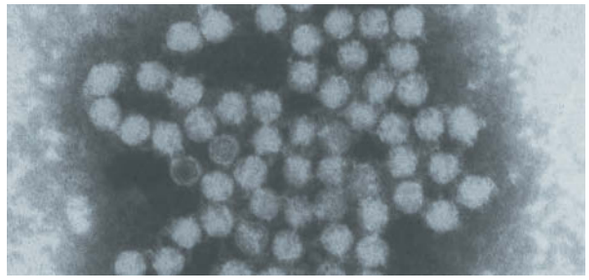
30.7 The Common Cold

Colds are the most common of infectious diseases. Colds are typically upper respiratory tract viral infections that are transmitted via droplets spread from coughs, sneezes, and respiratory secretions. Colds are usually of short duration, lasting a week or so, and the symptoms are milder than other respiratory diseases such as influenza. Table 30.1 contrasts the usually distinct symptoms and incidence of colds and influenza.

TABLE 30.1 Colds and influenza

Symptoms	*Cold*	*Influenza*
Fever	Rare	Common (39–40°C); sudden onset
Headache	Rare	Common
General malaise	Slight	Common; often quite severe; can last several weeks
Nasal discharge	Common and abundant	Less common; usually not abundant
Sore throat	Common	Less common
Vomiting and/or diarrhea	Rare	Common in children
Incidence[a]	340	50

[a]Cases/100 people per year in the United States for recent years. Incidence of all other infectious diseases totals about 30 cases/100 people per year.



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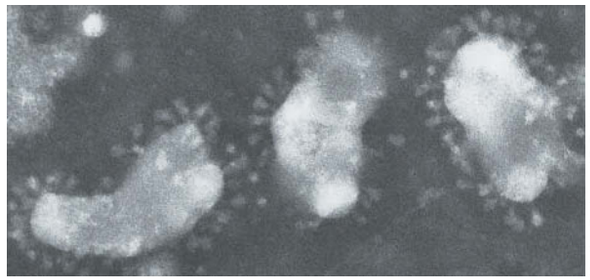


(b)

Figure 30.23 Transmission electron micrographs of common cold viruses. *(a)* Human rhinovirus; a virion is about 30 nm in diameter. *(b)* Human coronavirus; a virion is about 60 nm in diameter.

Symptoms and Transmission of the Common Cold

Cold symptoms include *rhinitis* (inflammation of the nasal region, especially the mucous membranes), nasal obstruction, watery nasal discharges, muscle aches, and a general feeling of malaise, usually without fever. *Rhinoviruses* are single-stranded plus-sense RNA viruses of the picornavirus group (Figure 30.23*a*) (Section 10.8) and are the most common causes of colds. Over 100 different rhinoviruses have been identified. About one-quarter of all colds are due to infections with other viruses. These include in particular the *coronaviruses* (Figure 30.23*b*). Adenoviruses, coxsackie viruses, respiratory syncytial viruses (RSV), and orthomyxoviruses are collectively responsible for only a small percentage of common colds.

Aerosol transmission is a major means of spreading colds, although experiments with volunteers suggest that direct contact and indirect contact involving fomites are also important means of transmission, perhaps even more important than aerosols. Incidence of the common cold rises when people are indoors in the winter months, although it is possible to "catch a cold" at any time of year. Most antiviral drugs are ineffective against common cold viruses, although some have shown promise for preventing the onset of symptoms following rhinovirus exposure. Moreover, new antiviral drugs are being designed based on knowledge of the three-dimensional structure of cold viruses. For example, antirhinovirus drugs that bind to the virus and change its surface properties in such a way as to prevent it from attaching to host cells have been developed. But thus far, most "cold drugs" on the market simply help to reduce the severity of symptoms—the cough, nasal discharges, headache, and the like.

Treatment

Because colds are generally self-limiting and not serious diseases, treatment is aimed at controlling symptoms, especially nasal

discharges, with antihistamine and decongestant drugs. A plethora of such drugs are available without prescription, each touting its superior features. Many of these work well, but some have unwanted side effects such as drowsiness, headache, and the like. The severity of symptoms of any cold event is a function of both the virulence of the cold virus, the overall health and well-being of the person at the time of infection, and the nature of supportive factors during infection. In the long run, immunity is more important in ridding the body of a cold virus than anything drugs can achieve. Cold viruses induce an antibody-mediated immune response that targets the current cold virus. However, the number of immunologically unique strains of each type of cold virus makes any long-term immunity to the common cold impossible.

On average, a person in the United States gets about three colds per year compared with less than one case of influenza per person per year (Table 30.1). This is an indication of the ease of transmission of the common cold and the large number of different viruses that cause the same general symptoms. Thus the common cold is a recurrent event that humans must simply live with. Preventive measures such as avoiding contact with common fomites (door handles and other surfaces touched by others) and frequent hand washing are best practices for avoiding the common cold.

MINIQUIZ

- Define the cause and symptoms of common colds.
- Discuss the possibilities for effective treatment and prevention of colds.

30.8 Influenza

Influenza is a highly infectious airborne disease of viral origin. Influenza viruses contain a single-stranded, negative-sense, segmented RNA genome surrounded by an envelope composed of protein, a lipid bilayer, and external glycoproteins (**Figure 30.24**) (↔ Section 10.9). There are three classes of influenza viruses: influenza A, B, and C. Here we consider only influenza A because it is the most important human pathogen.

Antigenic Drift and Antigenic Shift

Each strain of influenza A virus can be identified by a unique set of surface glycoproteins. These glycoproteins are *hemagglutinin* (HA or the "H antigen") and *neuraminidase* (NA or the "N antigen"). Each virus has one type of HA and one type of NA on its viral capsid and is named for the antigens it contains; for example, "H1N1." The HA antigen is important in *attaching* the influenza virus to host cells, while the NA antigen is instrumental in *releasing* the virus from host cells; each antigen is composed of several individual proteins (**Figure 30.25**).

Infection or immunization with influenza virus results in the production of antibodies that react with the HA and NA glycoproteins. When these antibodies bind to HA or NA, the virus is blocked from either attaching or releasing and is effectively neutralized, stopping the infection process. However, over time, the viral genes encoding the HA and NA glycoprotein antigens mutate, rendering minor changes to their amino acid sequence

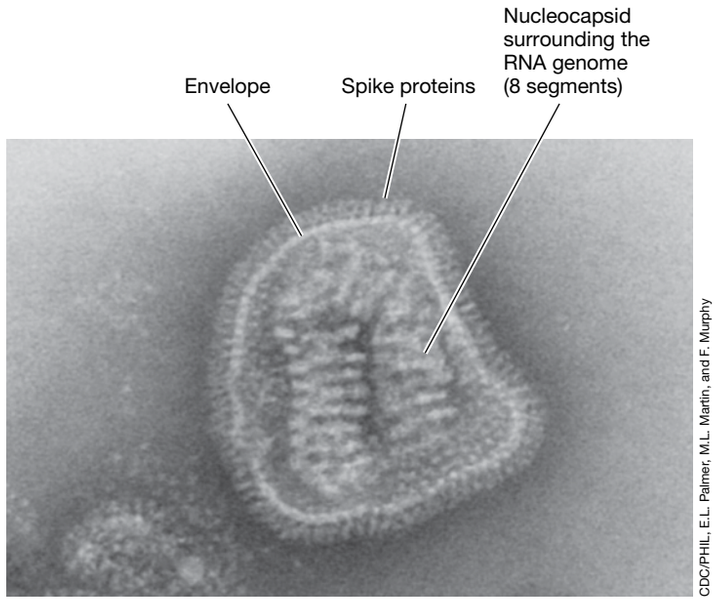


Figure 30.24 Influenza A virus. The virus contains a single-stranded, negative-sense RNA genome in eight segments; a virion is about 100 nm in diameter. Major factors in the success of influenza virus as a pathogen are antigenic drift and antigenic shift (see Figure 30.26).

and hence antigenic structure. Mutations that alter as few as one amino acid in the glycoprotein can affect how an antibody binds to these antigens. This slight variation in the structure of influenza viral surface antigens is at the heart of a phenomenon in influenza biology called **antigenic drift**. As a result of these subtle yet important changes, host immunity to a given virus strain diminishes as the strain mutates, and reinfection with the mutated strain can occur. This phenomenon is why last year's influenza vaccine may work only poorly against this year's crop of influenza viruses (**Figure 30.26*a***).

In addition to antigenic drift, there is a second feature of influenza virus biology that aids virulence. The single-stranded RNA genome of influenza viruses is *segmented*, with genes found on each of eight distinct segments (↔ Figure 10.21*b*). During virus maturation in the host cell, the viral RNA segments are packaged

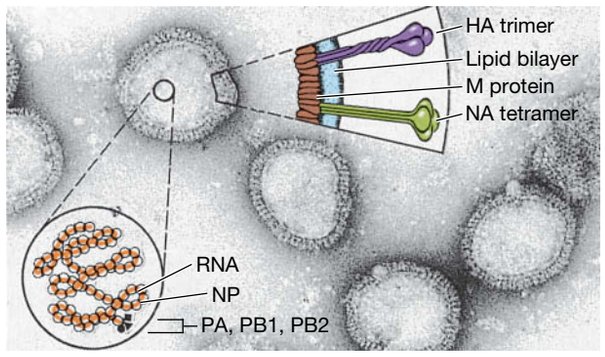
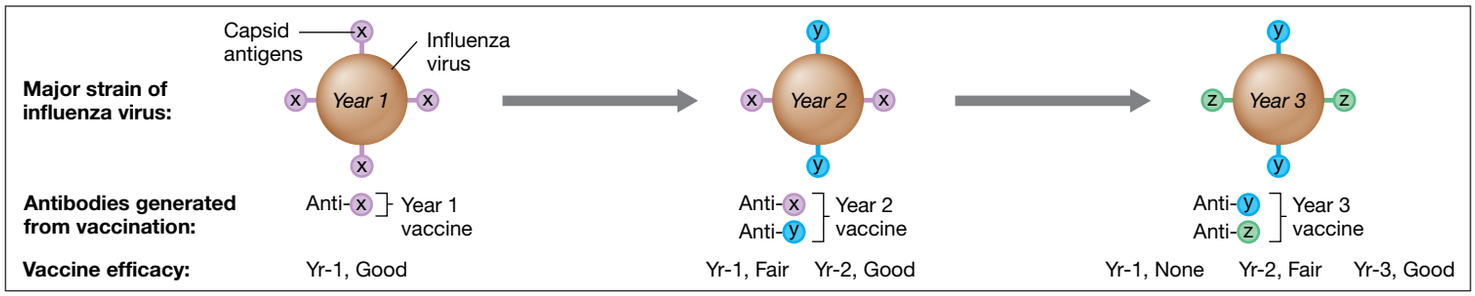
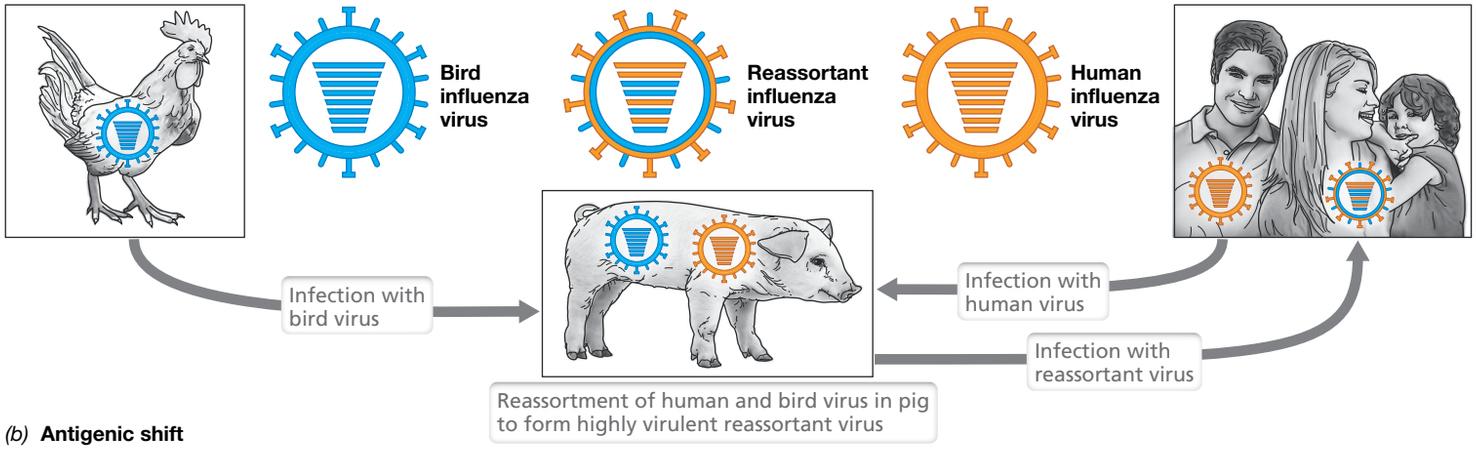


Figure 30.25 Influenza virus structure. Major viral coat proteins are: HA, hemagglutinin (three copies make up the HA coat spike); NA, neuraminidase (four copies make up the NA coat spike); M, coat protein; NP, nucleoprotein; PA, PB1, PB2, and other internal proteins, some of which have enzymatic functions.



(a) **Antigenic drift**



(b) **Antigenic shift**

Figure 30.26 Antigenic drift and antigenic shift in influenza virus biology. *(a)* Antigenic drift. A new vaccine is prepared each year against the major strain of influenza circulating among the population. However, vaccine efficacy wanes with time as immunologically new surface antigens appear from mutations in genes encoding viral surface proteins. *(b)* Antigenic shift. Influenza strains that originate in birds and humans can also infect swine. If a pig becomes infected with both bird and human viruses simultaneously, the viral genomes can be mixed, forming reassortant viruses. If such viruses, which now contain several unique antigens, infect humans, influenza pandemics can be triggered because of an ineffective immune response (Section 29.8).

randomly. To be infective, a virus must be packaged so it contains one copy of each of the eight gene segments. Occasionally, however, more than one strain of influenza virus infects a single animal at one time. In such cases, if the two strains infect the same cell, both viral genomes are replicated; when genome packaging occurs, the segments from the two strains may intermix. The result is a genetically unique virus that is now a *new virus strain*. This mixing of gene fragments between different strains of influenza virus is called *reassortment*.

Unique *reassortant viruses* trigger the phenomenon known as **antigenic shift** (Figure 30.26*b*), a major change in a surface antigen resulting from the total replacement of the RNA that encoded it. Antigenic shift can immediately and completely change one or both of the major HA and NA viral glycoproteins in a major way. As a result, reassortant viruses are essentially unrecognized by immune responses to previous influenza infections. Reassortant viruses also frequently display one or more unique virulence properties that help to trigger unusually strong clinical symptoms and are the usual catalysts of influenza *pandemics*, which we consider shortly.

Symptoms and Treatment of Influenza

Human influenza virus is transmitted from person to person through the air, primarily in droplets expelled during coughing and sneezing (Figure 30.1). The virus infects the mucous membranes of the upper respiratory tract and occasionally invades the lungs. Symptoms include a low-grade fever lasting up to a week, chills, fatigue, head and muscle aches, a cough and/or a sore throat, and general malaise (Table 30.1). Most of the serious consequences of seasonal influenza occur not from the disease itself but from bacterial secondary infections, especially in persons whose resistance has been lowered by the influenza infection. For example, in infants and the elderly, influenza can be followed by bacterial pneumonia (Section 30.2), sometimes in fatal form.

Most individuals develop protective immunity to the infecting strain of influenza virus, making it impossible for that strain or a very closely related strain to cause widespread infection (an epidemic) until the virus encounters another susceptible population. Immunity occurs from both antibody- and cell-mediated immune responses directed at HA and NA glycoproteins. Influenza epidemics can be controlled by immunization. Developing an effective vaccine, however, is complicated by the large number of existing influenza viral strains resulting from antigenic drift and antigenic shift (Figure 30.26). Through careful worldwide surveillance, samples of the major emerging strains of influenza virus are obtained each year before the onset of seasonal epidemics and used to prepare that year's vaccine. In most

years, this approach confers adequate protective immunity.

Most human influenza viruses respond to antiviral drugs. The adamantanes—*amantadine* and *rimantadine*—are synthetic amines that inhibit viral replication, and the neuraminidase inhibitors *oseltamivir* (Tamiflu) and *zanamivir* (Relenza) (Table 28.6) block release of newly replicated human influenza virions. These drugs are often used early on to shorten the course and severity of infection, especially in immune-compromised people or the elderly.

Influenza Pandemics

Influenza pandemics—worldwide epidemics—are much less frequent than outbreaks and epidemics, occurring from 10 to 40 years apart (Section 29.8). Flu pandemics result from antigenic shift, and virtually all have been due to avian and human influenza viruses reassorting in swine (Figure 30.26*b*) because swine can propagate both avian and human influenza viruses. This results in a highly virulent influenza strain for which there is no preexisting immunity in humans.

The "Spanish flu" pandemic of 1918 was the most catastrophic in recorded history, and the extreme virulence of the 1918 H1N1 virus is thought to have triggered host production and release of unusually large amounts of inflammatory substances, resulting in systemic inflammation and more severe symptoms than those typical of yearly flu epidemics. The 1957 Asian flu was also a memorable pandemic (**Figure 30.27**), beginning in China and spreading to the United States and shortly thereafter to Europe and South America. In this case, the pandemic influenza strain was a highly virulent H2N2 virus, differing antigenically from all previous strains. Pandemic influenza A (H1N1) 2009 virus, nicknamed the "swine flu," spread much more rapidly in 2009 than even the 1957 Asian flu, starting in Mexico and spreading quickly to the United States, Europe, and Central and South America. H1N1 was a classic case of influenza virus genome reassortment in swine (Figure 30.26*b*), and from the swine reservoir, a highly virulent virus emerged to infect humans. Influenza A H5N1, nicknamed the "bird flu," emerged in Hong Kong in 1997, and is the major virus health officials are monitoring closely today. H5N1 has been detected in birds in many countries, and if this virus were to infect swine and form an easily transmissible reassortant virus that subsequently jumps to humans (Figure 30.26*b*), such a virus could initiate a very deadly influenza pandemic.

MINIQUIZ

- Distinguish between antigenic drift and antigenic shift in influenza.
- Discuss the possibilities for effective immunization programs for influenza and compare them to the possibilities for immunization for colds.

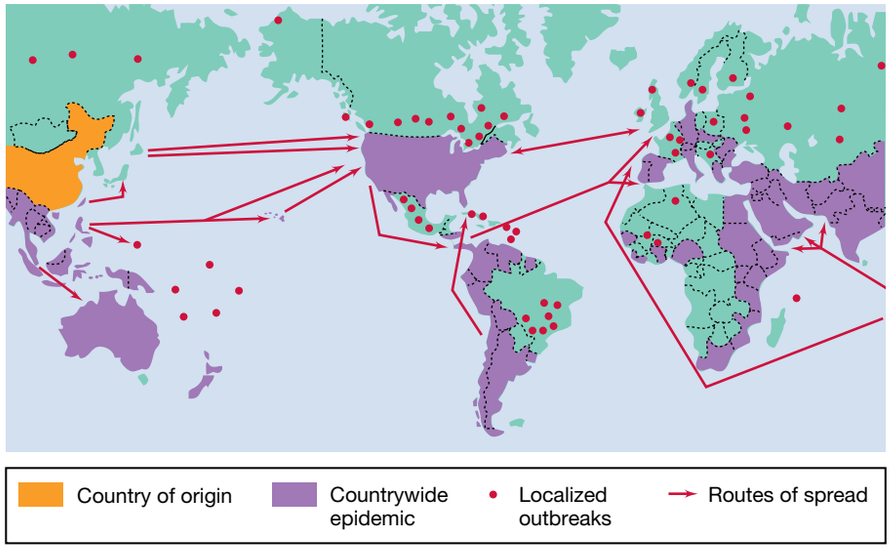


Figure 30.27 An influenza pandemic. Map of the Asian influenza pandemic of 1957. Lax agricultural practices with poultry and swine coupled with human interactions with these animals allowed the reassortment of influenza viral genomes from the three host species, producing a new strain for which there was no immune memory in humans. See Section 29.8 for more coverage of influenza pandemics.

III • Direct-Contact Bacterial and Viral Diseases

Some pathogens are spread primarily by direct contact with an infected person or by direct contact with blood or excretions from an infected person. Many of the respiratory diseases we have just discussed can also be spread by direct contact, but here we consider diseases spread primarily through direct contact with infected individuals rather than by an airborne route. These include staphylococcal infections, ulcers, certain types of hepatitis, and the very dangerous Ebola hemorrhagic fever.

30.9 *Staphylococcus aureus* Infections

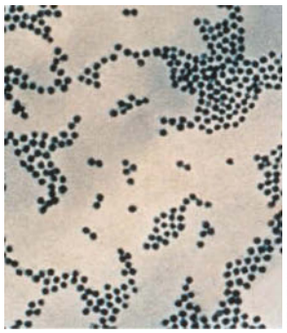
The genus *Staphylococcus* contains pathogens of humans and other animals. Staphylococci commonly infect skin and wounds and may also cause pneumonia. Most staphylococcal infections result from the transfer of staphylococci in the normal microbiota of an infected, asymptomatic individual to a susceptible individual. Others result from toxemia following the ingestion of contaminated food ("staph food poisoning," Section 32.8).

Staphylococci are nonsporulating, gram-positive cocci about 0.5–1.5 μm in diameter that divide in multiple planes to form irregular clumps of cells (**Figure 30.28*a, b***). They are resistant to drying and tolerate high concentrations of salt (up to 10% NaCl) when grown on artificial media. Staphylococci are readily dispersed in dust particles through the air and on surfaces. In humans, two species are important: *Staphylococcus epidermidis*, a nonpigmented species usually found on the skin or mucous membranes, and *Staphylococcus aureus*, a yellow-pigmented species. Both species are potential pathogens, but *S. aureus* is more commonly associated with human disease. Both species are frequently present in the normal microbiota of the upper respiratory tract

and the skin (Figure 30.2 and see Figure 30.30*b*), making many people potential carriers (Sections 29.1 and 29.3).

Epidemiology and Pathogenesis

Staphylococcal diseases include acne, boils, pimples, impetigo, pneumonia, osteomyelitis, carditis, meningitis, and arthritis. Many of these diseases are *pyogenic* (pus-forming) (Figure 30.28*c* and Figure 30.29). Those strains of *S. aureus* that cause human disease produce a variety of virulence factors (Section 25.3). At least four different *hemolysins* (proteins that lyse red blood cells, see Figure 30.8) have been recognized, and a single strain often produces several. A key virulence factor produced by *S. aureus* is *coagulase*, an enzyme that converts fibrin to fibrinogen, forming a localized clot (Figure 25.11*b*). Clotting induced by coagulase results in the accumulation of fibrin around the bacterial cells, making it difficult for host immune cells to contact the bacteria and initiate phagocytosis. Most *S. aureus* strains also produce *leukocidin*, a protein that destroys white blood cells. Production of leukocidin in skin lesions such as boils and pimples results in host cell destruction and is one of the factors responsible for pus (Figures 30.28 and 30.29). Some strains of *S. aureus* also produce other virulence proteins including *hyaluronidase, fibrinolysin, lipase, ribonuclease*, and *deoxyribonuclease*.



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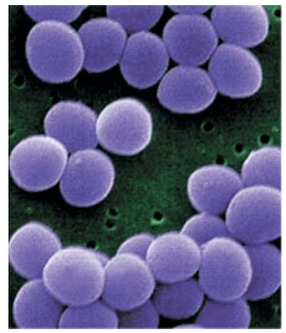
(a)



CDC/PHIL, M.J. Arduino and J.H. Carr

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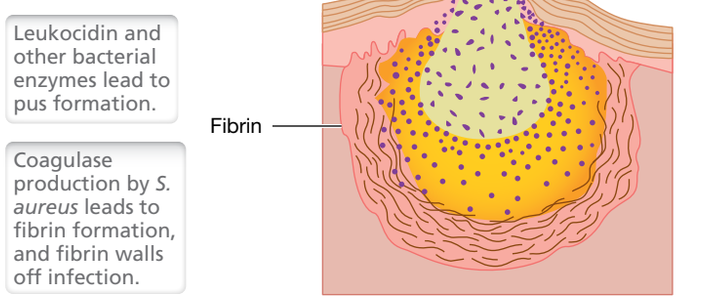
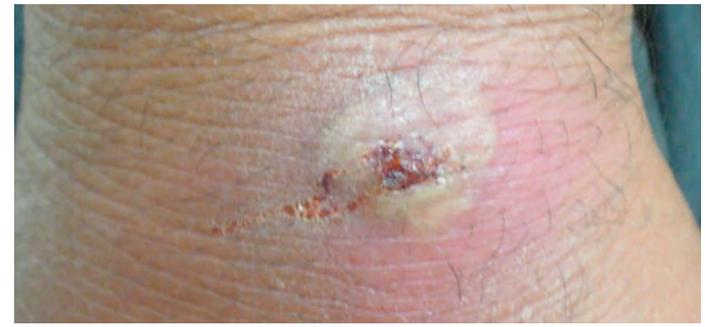


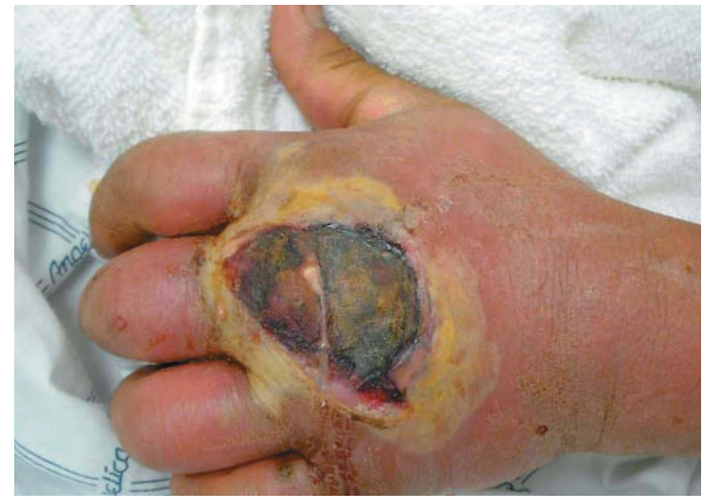
(c)

Figure 30.28 *Staphylococcus aureus* and *S. aureus* infections. Cells divide in several planes, giving the appearance of a cluster of grapes. *(a)* Gram stain; an individual coccus is about 1 μm in diameter. *(b)* Scanning electron micrograph of cells. *(c)* Structure of a boil. Staphylococci initiate a localized skin infection and become walled off by coagulated blood and fibrin through the activity of the enzyme coagulase, a major virulence factor. The ruptured boil releases pus, consisting of dead host cells and bacteria. See also Figure 30.29.



Gregory Moran, M.D.

(a)



Gregory Moran, M.D.

(b)

Figure 30.29 Pus-forming staphylococcal wounds. *(a)* A typical pus-forming wound on the hand. Pus lies just under the epidermal layer. *(b)* Abscess on the hand caused by a methicillin-resistant strain of *Staphylococcus aureus* (MRSA strain). If no treatment for a pus-forming wound is sought or if penicillin is administered first, MRSA infections can cause extensive tissue destruction, as shown here.

Certain strains of *S. aureus* cause **toxic shock syndrome (TSS)**, a serious outcome of staphylococcal infection, characterized by high fever, rash, vomiting, diarrhea, and death. TSS was first recognized in women and was associated with the use of highly absorbent tampons. However, TSS is now seen in both men and women and is typically initiated by staphylococcal infections following surgery. The symptoms of TSS result from an exotoxin called *toxic shock syndrome toxin-1*. This very potent toxin is a superantigen (Sections 25.7 and 27.10) that is released during cell growth and recruits large numbers of T cells to the site of infection. These then cause a major inflammatory response that is fatal in about 70% of cases. TSS can also result from superantigens from other pathogens, including *Streptococcus pyogenes* (Section 30.2).

Diagnosis and Treatment and the MRSA Epidemic

To diagnosis an *S. aureus* infection through laboratory culture, a specimen, typically from a pus-forming wound (Figure 30.29*a*), is cultured on a selective and differential medium containing 7.5% NaCl, mannitol, and phenol red, a pH indicator (mannitol–salt agar, Figure 30.30). The salt inhibits the growth of nonhalotolerant bacteria while allowing staphylococci to grow. In addition,

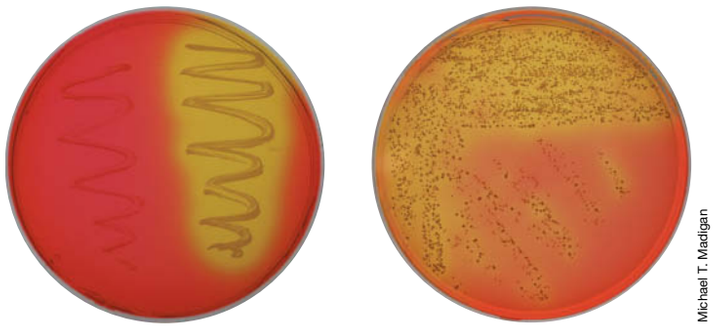


Figure 30.30 Mannitol–salt agar in the isolation of staphylococci. *(a)* Mannitol–salt agar (MSA) is both selective and differential for staphylococci. The presence of 7.5% NaCl makes MSA selective and phenol red makes it differential. Left, *Staphylococcus epidermidis*; right, *Staphylococcus aureus*. *(b)* A nasal swab of the senior author of this textbook supports the observation that most humans are carriers of *S. aureus*.

because *S. aureus* ferments mannitol, it generates acidity and changes the medium from red to yellow; other staphylococci, such as *S. epidermidis*, do not (Figure 30.30).

In major clinical laboratories, the polymerase chain reaction (PCR) is used to amplify genes unique to *S. aureus* from DNA isolated from a clinical sample, and this speeds up the diagnosis (results from laboratory culture take 24 h). For specific identification of methicillin-resistant strains of *S. aureus* (MRSA), a special selective and differential medium is available as well as a PCR protocol to identify *mecA* (the gene that encodes methicillin resistance in MRSA strains) and a rapid immunological test where cells of *S. aureus* in suspension are agglutinated by antibodies to specific surface proteins (Figure 28.15).

Historically, *S. aureus* infections have been treated with various penicillin and cephalosporin antibiotics. However, extensive use of these antibiotics for many years has selected for resistant strains that now predominate, especially in the clinical environment. Surgical patients, for example, may acquire staphylococci from healthcare personnel who are asymptomatic carriers of drug-resistant strains. As a result, appropriate antimicrobial drug therapy for *S. aureus* infections is a major problem in healthcare environments. The antibiotics clindamycin and various tetracycline drugs are currently used to treat MRSA infections.

MRSA infections (Figure 30.29*b*) are becoming more common (see Explore the Microbial World "MRSA—A Formidable Clinical Challenge" in Chapter 28). Over 80,000 cases of MRSA are reported each year in the United States, but infections are actually probably closer to ten times this number. Many of these cases are hospital-acquired (nosocomial) MRSA (Section 28.2), but many others are not. Because of the potential severity of MRSA infections, it is important to rapidly identify these strains in clinical specimens so that an effective treatment is begun as soon as possible. Delayed treatment of a MRSA infection, whether due to hesitation to seek treatment or treatment with an ineffective antibiotic, can lead to extensive tissue damage (Figure 30.29*b*).

Prevention of staphylococcal infections is virtually impossible because many people are asymptomatic carriers of *S. aureus*, either on their skin or upper respiratory tract. However, identification and treatment or isolation of MRSA-carrying healthcare providers who serve in surgical or nursery units has helped limit transmission of these very aggressive strains. As is true of many direct-contact diseases, MRSA transmission can also be greatly diminished by practicing good basic hygiene, avoiding contact with the personal items (including clothing and towels) of others, and keeping wounds covered.

MINIQUIZ

- What is the normal habitat of *Staphylococcus aureus*? How does *S. aureus* spread from person to person?
- What is MRSA, and why is it a health problem?

30.10 *Helicobacter pylori* and Gastric Diseases

Helicobacter pylori is a gram-negative, highly motile, spiral-shaped bacterium (Figure 30.31) associated with gastritis, ulcers, and gastric cancers. This bacterium colonizes the non-acid-secreting mucosa of the stomach and the upper intestinal tract. It is estimated that half the world's population is chronically infected with *H. pylori*. Up to 80% of gastric ulcer patients have concomitant *H. pylori* infections, and up to 50% of asymptomatic adults in developing countries are chronically infected. Although there is no known nonhuman reservoir of *H. pylori*, infection occurs in high incidence within families, suggesting person-to-person transmission. *H. pylori* infections also occasionally occur in clusters, suggesting that transmission from common sources such as food or water is also possible.

The *Helicobacter* Infection Process

H. pylori is only slightly invasive and colonizes the surfaces of the gastric mucosa, where it is protected from the effects of stomach acids by the gastric mucus layer. Cells of *H. pylori* reach these relatively

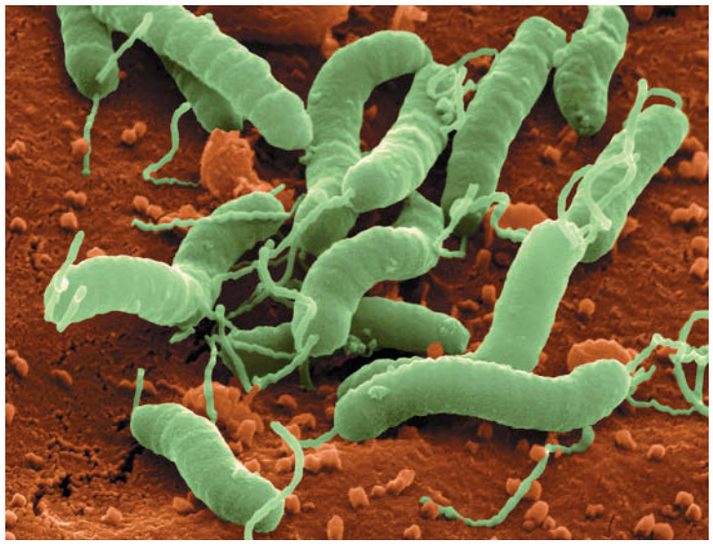


Figure 30.31 *Helicobacter pylori*. Colorized scanning electron micrograph of cells attached to the mucous lining of the stomach. Cells range in length from 3 to 5 μm and are about 0.5 μm in diameter. Note the flagella.

protected regions by employing a chemoreceptor (↩ Sections 2.13 and 6.7) that tracks the gradient of urea produced by gut epithelia to direct flagellar rotation up the gradient. The organism is strongly ureolytic and cleaves the urea into ammonia and bicarbonate, which help buffer the region of cell colonization.

After *H. pylori* cells colonize the mucosa, a combination of virulence factors and host responses cause inflammation, tissue destruction, and ulceration. Pathogen products such as the cytotoxin VacA (an exotoxin), urease, and an autoimmune response triggered by *H. pylori* lipopolysaccharide all contribute to localized tissue destruction and ulceration. Individuals who acquire *H. pylori* tend to have chronic infections unless they are treated with antibiotics. Treatment is both simple and important, as chronic inflammation of the gastroduodenum (gastritis) due to untreated *H. pylori* infection may lead to the development of gastric cancers.

H. pylori and Clinical Disease

Clinical signs of *H. pylori* infection include belching and stomach (epigastric) pain. Definitive diagnosis requires the isolation or observation of *H. pylori* from a gastric ulcer biopsy. However, a simple diagnostic test for the *H. pylori* enzyme urease is used for a noninvasive diagnosis. In this test, a small amount of ^{13}C- or ^{14}C-labeled urea ($H_2N–CO–NH_2$) is ingested; if *H. pylori* is present, the bacterium will hydrolyze the urea, forming labeled CO_2 and ammonia. Hence, the presence of labeled CO_2 in the patient's breath is highly suggestive of *H. pylori* infection.

The best evidence for a causal association between *H. pylori* and gastric ulcers comes from antibiotic treatments for the disease. Long-term treatment with antacids helps alleviate gastric ulcer symptoms temporarily, but most patients relapse within 1 year. However, by treating the *cause* rather than the *effect* of the disease, actual cures can be obtained. *H. pylori* infection is typically treated with a combination of drugs, including the antibacterial compound metronidazole, an antibiotic such as tetracycline or amoxicillin, and a bismuth-containing antacid preparation. The combination treatment, administered for 14 days, abolishes the *H. pylori* infection and provides a true cure.

Like the link with gastric ulcers, the link between *H. pylori* infection and certain forms of gastric cancers, in particular, gastric adenocarcinoma (the most prevalent form of gastric cancer), is also strong. Gastric cancers are the second leading cause of cancer deaths worldwide. Although how *H. pylori* infection actually triggers adenocarcinomas is unclear, it is believed that long-term infection with this bacterium coupled with host and possibly environmental factors combine to predispose an individual to stomach malignancies.

For their contributions to unraveling the connection between *H. pylori* and peptic and duodenal ulcers, the Australian scientists Robin Warren and Barry Marshall were awarded the 2005 Nobel Prize in Physiology or Medicine. For an interesting story on the antiquity of *H. pylori*, see page 765.

MINIQUIZ

- Describe infection by *Helicobacter pylori* and the resulting development of an ulcer.
- How can gastric ulcers be diagnosed? How can they be cured?

30.11 Hepatitis

Hepatitis is a liver inflammation, commonly caused by an infectious agent. Hepatitis sometimes results in acute illness followed by destruction of functional liver anatomy and cells, a condition known as **cirrhosis**. Hepatitis due to infection can cause chronic or acute disease, and some forms lead to liver cancer.

Although many viruses and a few bacteria can cause hepatitis, a restricted group of viruses is often associated with liver disease. Hepatitis viruses A, B, C, D, and E are phylogenetically diverse viruses but share in common their ability to infect the liver (Table 30.2). Hepatitis A and E viruses, although occasionally transmitted person to person, are more commonly transmitted by food (hepatitis A virus) or water (hepatitis E virus). We cover hepatitis A viral disease in Chapter 32. Here our focus is on hepatitis viruses transmitted by direct contact, with the major focus on hepatitis B, the causative agent of "bloodborne hepatitis."

The incidence of hepatitis A and B, the most common forms, has decreased significantly in the past 20 years because of effective vaccines and increases in surveillance. And, by comparison to hepatitis A and B, hepatitis C infections have risen significantly in recent years (Figure 30.32).

Epidemiology

Infection with *hepatitis B virus* (HBV) is called bloodborne hepatitis (or serum hepatitis) because it is transmitted in blood or in body fluids in contact with blood. HBV is a hepadnavirus, a partially double-stranded DNA virus (↩ Section 10.11). The mature virus particle containing the viral genome is called a *Dane particle* (Figure 30.33). HBV causes acute, often severe disease that can lead to liver failure and death. Chronic HBV infection can lead to cirrhosis and liver cancer.

TABLE 30.2 Hepatitis viruses

Disease	*Virus and genome*[a]	*Vaccine*	*Clinical illness*	*Transmission route*
Hepatitis A	*Hepatovirus* (HAV) ssRNA	Yes	Acute	Enteric (food)
Hepatitis B	*Orthohepadnavirus* (HBV) dsDNA	Yes	Acute, chronic, oncogenic	Parenteral, sexual
Hepatitis C	*Hepacivirus* (HCV) ssRNA	No	Chronic, oncogenic	Parenteral
Hepatitis D	*Deltavirus* (HDV) ssRNA	No	Fulminant, only with HBV	Parenteral
Hepatitis E	*Caliciviridae* family (HEV) ssRNA	No	Fulminant disease in pregnant women	Enteric (water)

[a]Examples and discussion of each of these genomes can be found in Chapter 10 (↩ Figures 10.2 and 10.3).

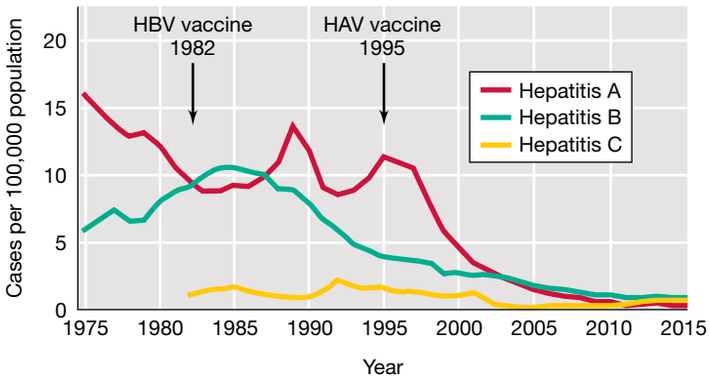
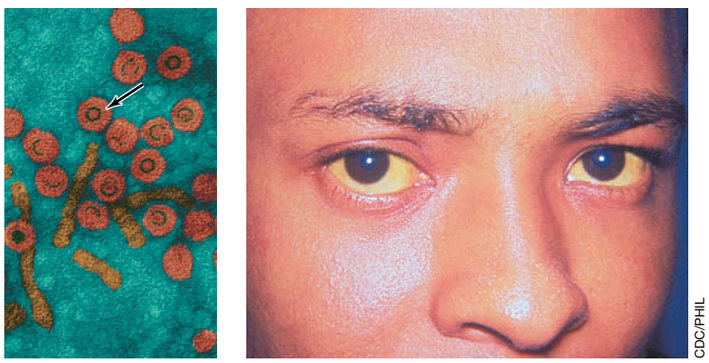


Figure 30.32 Hepatitis A, B, and C in the United States. In 2014 there were 1239 reported cases of hepatitis A, 2953 reported cases of hepatitis B, and 2194 reported cases of hepatitis C. The number of actual new cases of hepatitis A, B, or C infection is likely to be much higher than the reported new cases. Data obtained from the CDC, Atlanta, Georgia, USA.

HBV is transmitted by a *parenteral route*, which means "outside the gut." The main means of HBV transmission is from blood transfusions, contact with infected blood in a hypodermic needle, and from mother to child during childbirth. HBV may also be transmitted through exchanges of body fluids during sex. The number of new HBV infections has remained low and more or less constant since the year 2000 (Figure 30.32). Nevertheless, over 100,000 people worldwide and nearly 5000 people in the United States die yearly from liver failure or liver cancer caused by chronic HBV infection.

Hepatitis D virus (HDV) is a *defective virus* (Section 11.7) that lacks genes encoding its own capsid. HDV is also transmitted by parenteral routes, but because it is a defective virus, it cannot replicate and form an intact virion unless the cell is also infected with HBV. The HDV genome replicates independently but relies on HBV to produce capsid proteins (which are the same as those used by HBV) to form infectious virions. Thus, HDV infections are always coinfections with HBV.

Hepatitis C virus (HCV) is also transmitted parenterally. HCV generally produces a mild or even asymptomatic disease at first, but later on up to 85% of those infected develop chronic hepatitis, with up to 20% proceeding to chronic liver disease and cirrhosis. Chronic infection with HCV leads to hepatocarcinoma (liver cancer) in 3–5% of infected individuals. The latency period for development of cancer can be several decades after the primary infection. Only a fraction of the estimated 25,000 annual new infections with HCV in the United States are recognized and formally reported (Figure 30.32). Large numbers of HCV-related deaths occur annually as a result of chronic HCV infections that develop into liver cancer. HCV-induced liver disease accounts for up to 10,000 of the 25,000 annual deaths due to liver cancer, other chronic liver diseases, and cirrhosis.



(a) (b)

Figure 30.33 Hepatitis. *(a)* Hepatitis B virus. The arrow indicates a complete HBV virion, which is called a Dane particle. A Dane particle is about 40 nm in diameter. *(b)* Jaundice, a yellowing of the facial skin and eye conjunctiva, is a common symptom of hepatitis infections and results from the accumulation of bilirubin (a by-product of degraded red blood cells) that results from reduced liver function.

Other Aspects of Hepatitis Syndromes

Hepatitis is an acute disease of the liver, a vital organ that plays a role in several key metabolic processes, including carbohydrate, lipid, and protein syntheses, as well as detoxification and many other functions. Symptoms of hepatitis include fever, jaundice (yellowing of the skin and the whites of the eyes, Figure 30.33*b*), and liver enlargement and cirrhosis. All hepatitis viruses cause similar acute symptoms and cannot be readily distinguished based on clinical findings alone. Chronic hepatitis infections, usually caused by HBV or HCV, are often asymptomatic or produce very mild symptoms, but nonetheless cause serious liver disease, even in the absence of liver cancer.

Diagnosis of hepatitis is based on a combination of clinical symptoms and laboratory tests that assess liver function, especially key liver enzymes. Cirrhosis is diagnosed by visual examination of biopsied liver tissue. Virus-specific molecular assays are typically used to confirm a diagnosis, positively identify the infectious agent, and determine a course of treatment; isolation and culture of hepatitis viruses is usually not attempted.

Many of the immunological and molecular diagnostic tools discussed in Chapter 28 are used in hepatitis diagnoses. These include enzyme immunoassays that target viral-specific proteins or antiviral antibodies in a blood sample, immunoblots (Western blots), and immunofluorescence (microscopic) methods. Polymerase chain reaction (PCR) tests are also used to detect hepatitis viral genomes in blood or in liver tissue obtained by biopsy.

Infection with HAV or HBV can be prevented with effective vaccines. HBV vaccination is recommended and in most cases is required for school-age children in the United States. No effective vaccines are available for the other hepatitis viruses. For those unvaccinated, the practice of *universal precautions* will prevent infection. The precautions prescribe a high level of vigilance and aseptic handling and containment procedures to deal with patients, body fluids, and infected waste materials (Section 28.1). Most treatment of hepatitis is supportive, providing rest and time for the immune system to attack the infection and allow liver damage to be repaired. In some cases, in particular for HBV infections, some antiviral drugs are available that offer effective treatment.

MINIQUIZ

- What host organ do hepatitis viruses attack? How are hepatitis A, B, and C viruses transmitted?
- Describe potential prevention and treatment methods for hepatitis A, B, and C viruses.

30.12 Ebola: A Deadly Threat

A recent example of a highly infectious and deadly serious emerging pathogen that spreads by direct contact is Ebola virus, which ravaged parts of West Africa in 2014 and early 2015. Ebola infected about 29,000 people and killed over 11,000 of them.

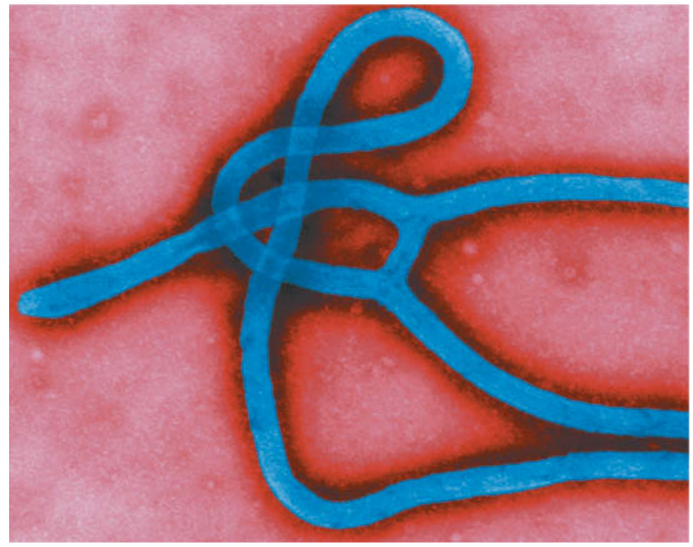
Ebola emerged in 1976 in Zaire, and since then several small outbreaks have occurred in West African countries. But not until the 2014 outbreak in Guinea, Liberia, Nigeria, Senegal, and Sierra Leone did the disease kill such large numbers of people. However, nearly as fast as the disease reemerged, strong efforts to contain the spread of infection were put in place and these, along with unknown natural events that control cycles of this disease, combined to significantly reduce Ebola incidence. By the end of 2015, only a handful of cases were reported. Today, significant epidemiological surveillance for Ebola remains in place because of the ease of transmission of the virus and thus the rapidity by which a single infection can trigger an outbreak.

Ebola: The Virus and Its Transmission

Ebola hemorrhagic fever is caused by a *filovirus*, a filamentous virus that can take on many shapes (**Figure 30.34*a***). The Ebola virus genome contains single-stranded and linear RNA of the negative sense, similar in this respect to influenza and rabies virus genomes. The genome contains only 19 kilobases of RNA, enough to encode just seven proteins; about a third of the genome encodes the RNA-dependent RNA polymerase (RNA replicase) needed to replicate the genome of negative-sense RNA viruses (Section 10.9).

Ebola virus is transmitted from person to person by direct contact through breaks in the skin or mucous membranes as well as by body fluids (including semen) and fomites (bedding, clothing, utensils) contaminated with the virus. The ease with which Ebola can be transmitted seems remarkable compared with other pathogens that rely on direct-contact transmission. For example, in a few documented instances of Ebola transmission to healthcare workers, significant precautions had been taken to ensure that full-body personal protection equipment (PPE, Section 28.1) was in place to specifically prevent such transmission. Thus, the disease is not only deadly for those infected but can be an extremely dangerous risk for healthy medical providers as well. If PPE is not worn, healthcare workers who either treat patients or dispose of dead Ebola victims run a high risk of becoming infected. Thus PPE is made widely available by international health organizations to all health workers who might come in contact with an Ebola patient (Figure 30.34*b*).

The natural reservoir of Ebola virus that triggered the West African outbreak is unknown, although related filoviruses—such as hantavirus (Section 31.2)—are known to be spread from arthropods and rodents. Among the suspected reservoirs of Ebola are a variety of animals and possibly insects that inhabit tropical forests. In addition to person-to-person transmission, likely responsible for virtually all of the cases in the recent West Africa epidemic, natural Ebola infection in humans probably originates from an animal bite. In this regard, bats, and in particular fruit bats in which the virus has been documented, may be a major disease reservoir.



(a)

(b)

Figure 30.34 Ebola. *(a)* Colorized transmission electron micrograph of a negatively stained preparation of Ebola virus virions. A virion is about 80 nm in diameter. *(b)* Ugandan Red Cross workers donning their personal protective equipment before collecting the body of an Ebola victim.

Ebola: The Disease and Its Treatment

Ebola virus migrates from the initial site of infection to lymph nodes, from which it travels systemically to infect the liver and spleen. Once the virus has entered the body, several different types of cells can become infected. One to two weeks postinfection, an Ebola patient experiences an abrupt fever and general malaise, conditions that make Ebola difficult to distinguish from many other tropical diseases including malaria. But then more severe symptoms appear. These typically include severe fever and fatigue, diarrhea, nausea, vomiting and abdominal pain, and major loss of appetite. Bleeding through the skin and blood in vomit and feces can occur, but such bleeding is not a common symptom.

Ebola virus causes major problems in the liver, killing liver cells and disrupting normal blood clotting events. It is thought that the

virus triggers host cells to release various cytokines that cause widespread inflammation (Section 26.8) and internal bleeding; these lead to multiple organ failure, shock, and renal failure. The mortality rate in the West African Ebola outbreak averaged 35–70% depending on access to treatment, the initial state of health of those infected, viral load (abundance of the virus in the blood), and age; mortality was as high as 85% among infected people over the age of 45.

There is currently no drug treatment for Ebola, but survival rates among those that receive supportive care to help alleviate symptoms are significantly higher than in those that do not. Therapy includes the maintenance of fluids and electrolytes, oxygen supplements, and transfusions of blood to replace that lost from internal bleeding. Ebola survivors develop an antibody-mediated immune response to the virus, and some treatment success has been achieved by transfusing blood or serum from Ebola survivors into those infected. An Ebola vaccine is in development and several promising candidates have appeared. It is thus likely that putting a person's immune system to work against Ebola might be the best preventive measure against the disease. However, it is unlikely that an Ebola vaccine would help an already infected person, considering the rapidity with which the disease progresses and the major organ damage that viral infection triggers.

The 2014 Ebola outbreak is now well under control and much has been learned from it about the logistics of handling large-scale outbreaks of such a deadly disease. The ease by which Ebola is transmitted made a public education campaign about the dangers of Ebola just as important as dealing with the morbidity and mortality of the outbreak. When epidemiologists develop a better understanding of the natural reservoirs of Ebola virus, outbreaks like that in West Africa—which likely began by animal-to-person transmission—may well be preventable by reducing or eliminating the major reservoirs and educating the populace about the dangers of encounters with known reservoirs. Also, rigorous campaigns to educate people who put themselves at risk by handling an Ebola patient or the corpse of an Ebola victim without PPE in place are also helping to reduce spread of Ebola when a case or case cluster does appear.

MINIQUIZ

- What do influenza virus and Ebola virus have in common? In what ways do their modes of transmission differ?
- Contrast mortality rates for influenza and Ebola hemorrhagic fever. Which is the more serious disease?

IV • Sexually Transmitted Infections

Sexually transmitted infections (STIs), also called *sexually transmitted diseases* (*STDs*), are caused by a wide variety of bacteria, viruses, protists, and even fungi (Table 30.3). Unlike respiratory pathogens that can be shed constantly in large numbers by an infected individual, sexually transmitted pathogens are typically found only in body fluids from the genitourinary tract (and blood, in the case of HIV). Because they require a protected and moist environment, sexually transmitted pathogens preferentially and sometimes exclusively colonize the genitourinary tract.

Because the transmission of STIs is limited to sexual activity, their spread can be controlled by sexual abstinence and minimized by the use of condoms that stop the exchange of body fluids during sex. With the exception of HIV/AIDS, most STIs are curable and

TABLE 30.3 Sexually transmitted infections and treatment guidelines

Disease	*Causative organism(s)*[a]	*Recommended treatment*[b]
Gonorrhea	*Neisseria gonorrhoeae* (B)	Cefixime or ceftriaxone, *and* azithromycin or doxycycline
Syphilis	*Treponema pallidum* (B)	Benzathine penicillin G
Chlamydia trachomatis infections	*Chlamydia trachomatis* (B)	Doxycycline or azithromycin
Nongonococcal urethritis	*C. trachomatis* (B) or *Ureaplasma urealyticum* (B) or *Mycoplasma genitalium* (B) or *Trichomonas vaginalis* (P)	Azithromycin or doxycycline Metronidazole
Lymphogranuloma venereum	*C. trachomatis* (B)	Doxycycline
Chancroid	*Haemophilus ducreyi* (B)	Azithromycin
Genital herpes	Herpes simplex 2 (V)	No known cure; symptoms can be controlled by several antiviral drugs
Genital warts	Human papillomavirus (HPV) (certain strains)	No known cure; symptomatic warts can be removed surgically, chemically, or by cryotherapy
Trichomoniasis	*Trichomonas vaginalis* (P)	Metronidazole
Acquired immunodeficiency syndrome (AIDS)	Human immunodeficiency virus (HIV)	No known cure; several drugs can stop viral replication and slow disease progression
Pelvic inflammatory disease	*N. gonorrhoeae* (B) or *C. trachomatis* (B)	Cefotetan and doxycycline
Vulvovaginal candidiasis	*Candida albicans* (F)	Butoconazole

[a]B, bacterium; V, virus; P, protist; F, fungus.
[b]Recommend.Tab Tr Td .Note Pations as of 2016 of the U.S. Department of Health and Human Services, Public Health Service.

many can have only minor symptoms. These realities, combined with the fact that those infected are sometimes reluctant to seek treatment, make treatment of STIs an ongoing public health challenge. However, delaying or forgoing treatment of STIs only serves to maintain lines of transmission and can lead to long-term health problems such as infertility, cancer, heart disease, degenerative nerve disease, birth defects, stillbirth, or destruction of the immune system, any of which can result in death.

30.13 Gonorrhea and Syphilis

Gonorrhea and *syphilis* are ancient STIs, but because of major differences in their symptoms, the overall pattern of disease differs significantly between the two. In the United States, cases of gonorrhea peaked following the introduction of birth control pills in the mid-1960s, and gonorrhea is still quite prevalent today; cases of syphilis, on the other hand, have a much lower incidence (**Figure 30.35**). This is partly because syphilis exhibits very obvious symptoms in its primary stage and infected individuals usually seek immediate treatment.

Gonorrhea

Neisseria gonorrhoeae, often called the *gonococcus*, causes gonorrhea. *N. gonorrhoeae* is a gram-negative and obligately aerobic diplococcus related biochemically and phylogenetically to *Neisseria meningitidis* (Section 30.5). Cells of *N. gonorrhoeae* are killed rapidly by drying, sunlight, and ultraviolet radiation and thus normally do not survive away from the mucous membranes of the pharynx, conjunctiva, rectum, or genitourinary tract (**Figure 30.36**). Because of this, gonorrhea can only be transmitted by intimate person-to-person contact. We discussed the clinical microbiology and diagnosis of gonorrhea in Section 28.3.

The symptoms of gonorrhea are quite different in the male and female. In females, gonorrhea may be asymptomatic or cause a mild vaginitis that is difficult to distinguish from vaginal infections caused by other organisms; hence, the infection may easily go unnoticed. Complications from untreated gonorrhea in females, however, can lead to a chronic condition called *pelvic inflammatory disease* (*PID*), which can cause sterility. In men, *N. gonorrhoeae* causes a painful infection of the urethral canal and typical puslike urethral discharge. Complications from untreated gonorrhea affecting both males and females include damage to heart valves and joint tissues due to inflammatory reactions from immune complexes that deposit in these areas. In addition to disease in adults, *N. gonorrhoeae* can also cause eye infections in newborns. Infants born of infected mothers may acquire eye infections during birth. Therefore, prophylactic treatment of the eyes of all newborns with an ointment containing erythromycin is mandatory in many states in the United States to prevent gonococcal and other bacterial eye infections in infants.

Treatment of gonorrhea with penicillin was the method of choice until the 1980s when strains of *N. gonorrhoeae* resistant to penicillin emerged. The quinolones ciprofloxacin, ofloxacin, or

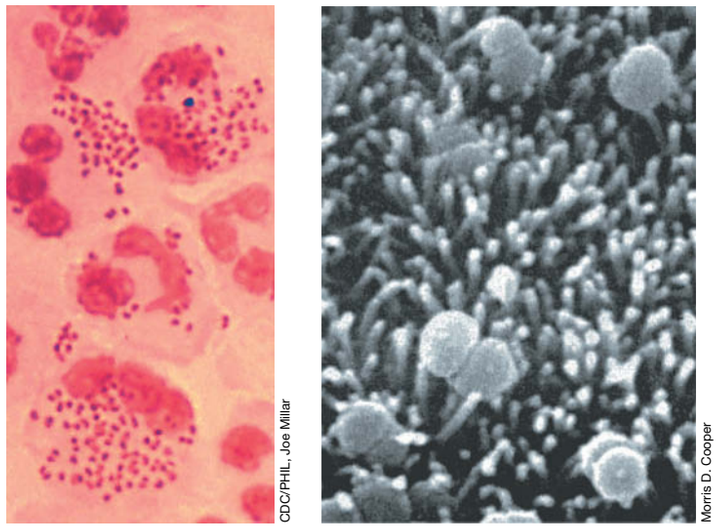


Figure 30.36 The causative agent of gonorrhea, *Neisseria gonorrhoeae*. *(a)* Gram stain of a urethral discharge. *(b)* Scanning electron micrograph of the microvilli of human fallopian tube mucosa with cells of *N. gonorrhoeae* attached to the surface of epithelial cells. Cells of *N. gonorrhoeae* are about 0.8 μm in diameter. *Neisseria* species are *Betaproteobacteria* (Section 16.2).

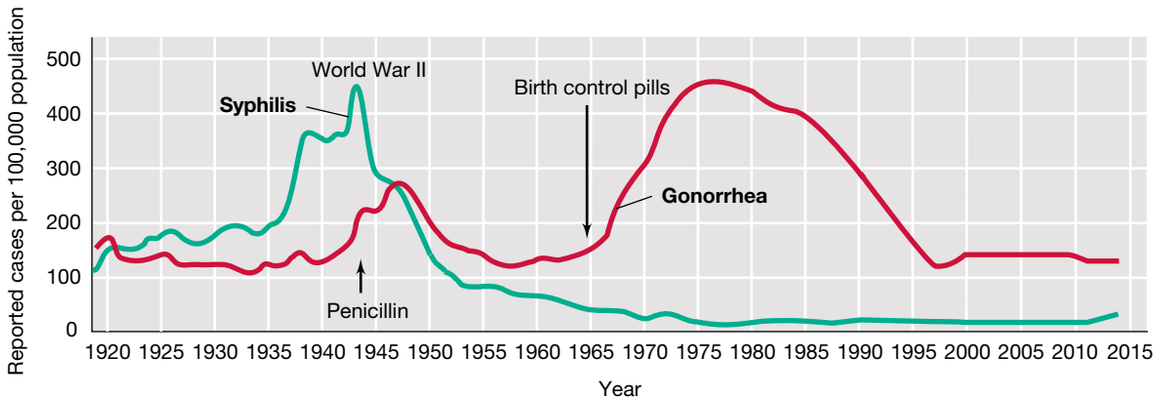


Figure 30.35 Reported cases of gonorrhea and syphilis in the United States. Note the downward trend in disease incidence after the introduction of antibiotics and the upward trend in the incidence of gonorrhea after the introduction of birth control pills. In 2014 there were 350,062 new cases of gonorrhea and 19,999 new cases of primary and secondary syphilis in the United States.

levofloxacin were also used, but by 2006, a significant fraction of *N. gonorrhoeae* strains isolated in the United States had developed resistance to these drugs as well. Strains resistant to penicillin and quinolones respond to alternative antibiotic therapy with a single dose of the β-lactam antibiotics cefixime or ceftriaxone.

Despite the fact that drugs are still effective in treating gonorrhea, incidence of gonorrhea remains relatively high (Figure 30.35) for at least three reasons. First, although anti-gonococcal antibodies are generated by an infection, they are strain-specific and provide no protection from infection by other strains of *N. gonorrhoeae*. As a consequence, gonorrhea reinfection is possible and quite common in high-risk populations (primarily sex workers and those with multiple sex partners). In addition, within a single *N. gonorrhoeae* strain, antigenic switches can thwart the immune response. For example, by mutation *N. gonorrhoeae* can alter the structure of its pilus proteins, thus creating new serotypes to challenge the immune response. Second, oral contraceptives cause a rise in vaginal pH; when this occurs, lactic acid bacteria normally found in the adult vagina fail to develop, and this reduces competition for colonization by *N. gonorrhoeae*. And finally, and most importantly, symptoms of gonorrhea in the female are often so mild that the disease may go unrecognized; a promiscuous infected female can then infect many males.

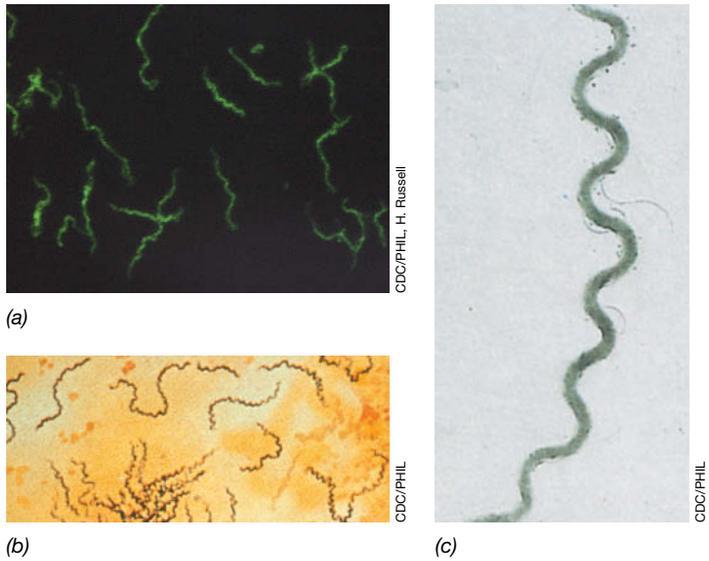


Figure 30.37 The syphilis spirochete, *Treponema pallidum*. *(a)* Cells from a chancre stained with a fluorescent antibody measure 0.15 μm wide and 10–15 μm long. *(b)* Silver-stained (Fontana method) preparation of a specimen from a syphilitic chancre. *(c)* Shadow-cast electron micrograph of a cell of *T. pallidum*. The endoflagella are typical of spirochetes (↪ Section 15.19).

Syphilis

Syphilis is caused by a spirochete, *Treponema pallidum*, a long and extremely thin coiled cell (**Figure 30.37**). Like *N. gonorrhoeae*, *T. pallidum* is very sensitive to environmental stress and drying, and thus syphilis is only transmitted through intimate sexual contact or from mother to fetus during pregnancy. The biology of the spirochetes and the genus *Treponema* is discussed in Section 15.19.

Syphilis is often transmitted along with gonorrhea as coinfections. However, syphilis is potentially the more serious disease. For example, syphilis kills about 100,000 people per year worldwide, whereas gonorrhea kills fewer than 1000 people per year. Nevertheless, largely because of differences in the symptoms and pathobiology of the two diseases, the incidence of syphilis in the United States is much lower than the incidence of gonorrhea. The incidence of syphilis in the United States, however, has increased in recent years, with over 16,000 new infections reported in 2013 from a low of around 6000 in 1997.

The syphilis spirochete (Figure 30.37) does not pass through unbroken skin, and initial infection takes place through tiny breaks in the epidermal layer. In the male, initial infection is usually on the penis; in the female it is most often in the vagina, cervix, or perineal region. In about 10% of cases, infection is extragenital, usually in the oral region (**Figure 30.38*a***). During pregnancy,

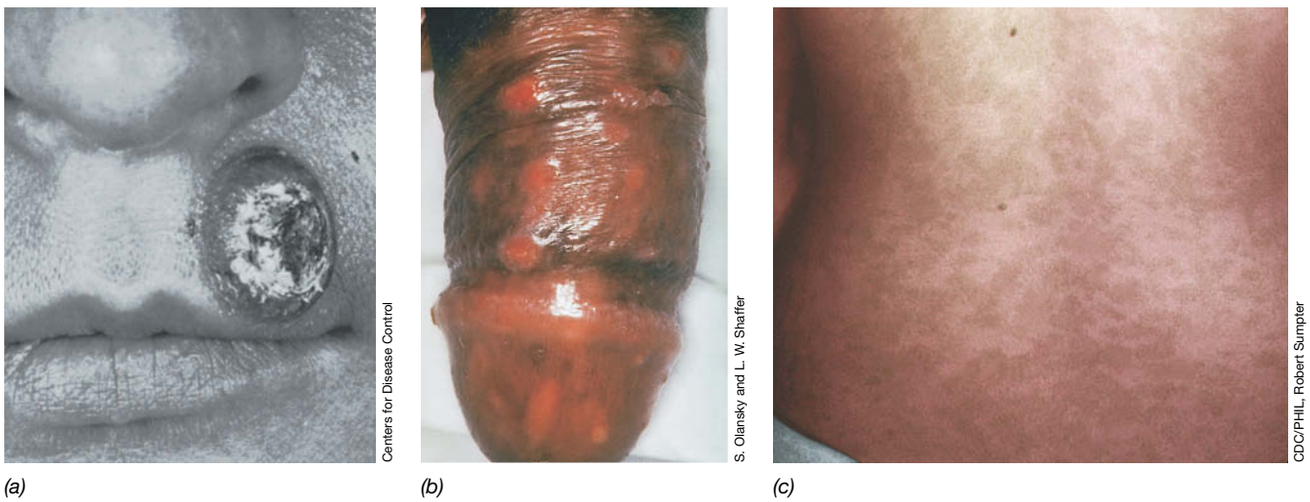


Figure 30.38 Primary and secondary syphilis. *(a)* Chancres on the lip and *(b)* the penis in cases of primary syphilis. The chancre is the characteristic lesion of primary syphilis at the site of infection by *Treponema pallidum*. *(c)* Syphilitic rash on the lower back of a patient showing secondary syphilis.

the organism can be transmitted from an infected woman to the fetus; the disease acquired by the infant is called **congenital syphilis**.

Syphilis is an extremely complex disease and can progress into increasingly serious stages. Syphilis always begins with a localized infection called *primary syphilis*. In primary syphilis, *T. pallidum* multiplies at the initial site of entry, and a characteristic lesion called a *chancre* forms within 2 weeks to 2 months (Figure 30.38*a, b*). Microscopy of a syphilitic chancre exudate reveals the actively motile spirochetes (Figure 30.37*a, b*). In most cases the chancre heals spontaneously and *T. pallidum* disappears from the site. In untreated cases, however, some cells spread from the initial site to various parts of the body, such as the mucous membranes, eyes, joints, bones, or central nervous system, where extensive multiplication occurs. A hypersensitivity reaction to the treponemes often takes place, revealed by the development of a generalized skin rash; this rash is the key symptom of *secondary syphilis* (Figure 30.38*c*).

In the absence of treatment, the subsequent course of the disease varies from case to case. About one-fourth of infected individuals undergo a spontaneous cure and are free of any further disease symptoms. Another one-fourth exhibit no further symptoms but maintain a persistent, chronic syphilitic infection. Roughly half of untreated patients develop *tertiary syphilis*, with symptoms ranging from relatively mild infections of the skin and bone to serious and even fatal infections of the cardiovascular system or central nervous system. This may occur many years after the primary infection. Involvement of the nervous system can cause paralysis or other severe neurological damage. Relatively low numbers of *T. pallidum* are present in individuals with tertiary syphilis; most of the symptoms probably result from inflammation due to delayed-type hypersensitivity reactions (Section 27.9) to the syphilis spirochetes. Tertiary syphilis can still be treated, usually with long-term intravenous antibiotic administration, but prior neurological damage from the syphilitic infection is typically irreversible.

Several laboratory tests that can be used to diagnose syphilis were discussed in Chapter 28. However, the single most important physical sign of a primary syphilis infection, the chancre (Figure 30.38*a, b*), is highly diagnostic for the disease. Infected individuals generally seek treatment for syphilis because of the chancre. Penicillin remains highly effective in syphilis therapy, and the primary and secondary stages of the disease can typically be cured by a single injection of benzathine penicillin G. Unlike the case with gonorrhea, antibiotic resistance has not seriously affected the treatment of syphilis. Resistance by *T. pallidum* to the macrolide antibiotic azithromycin has emerged, but a number of mainline antibiotics still are highly effective in treating syphilis.

MINIQUIZ

- How are gonorrhea and syphilis diagnosed?
- Explain at least one potential reason for the high incidence of gonorrhea as compared with syphilis.
- Describe the progression of untreated gonorrhea and untreated syphilis. Do treatments produce a cure for each disease?

30.14 Chlamydia, Herpes, and Human Papillomavirus

STIs caused by *Chlamydia* (a bacterium) and herpesvirus and human papillomavirus are very prevalent among sexually active adults and are often more difficult to diagnose and treat than are syphilis and gonorrhea.

Chlamydia

A number of sexually transmitted diseases can be ascribed to infection by the obligately intracellular bacterium *Chlamydia trachomatis* (**Figure 30.39**). This organism is one of a small group of parasitic bacteria that form their own phylum (the *Chlamydiae*) of *Bacteria* (Section 16.15). Because *C. trachomatis* must be grown in host cells (tissue culture), its rapid isolation and identification is not as straightforward as for *Neisseria gonorrhoeae*.

The total incidence of sexually transmitted *C. trachomatis* infections probably greatly outnumbers the incidence of gonorrhea. Over 1 million chlamydial cases are now reported annually in the United States, but because of their often inapparent nature, there may be more than 4 million new sexually transmitted chlamydial infections every year. Because of this, chlamydia is the most prevalent STI and reportable communicable disease in the United States. *C. trachomatis* also causes a serious eye infection called *trachoma*, but the strains of *C. trachomatis* responsible for STIs are distinct from those causing trachoma. Chlamydial infections may also be transmitted congenitally to the newborn in the birth canal, causing newborn conjunctivitis and pneumonia.

Nongonococcal urethritis (*NGU*) due to *C. trachomatis* is one of the most frequently observed sexually transmitted diseases in males and females, but the infections are often inapparent. In a small percentage of cases, chlamydial NGU leads to serious acute complications, including testicular swelling and prostate inflammation in men and cervicitis, pelvic inflammatory disease, and fallopian tube damage in women. These are due to the ability of *C. trachomatis* to

(a) (b)

Figure 30.39 Cells of *Chlamydia trachomatis* (arrows) attached to human fallopian tube tissues. *(a)* Cells attached to the microvilli of a fallopian tube. *(b)* A damaged fallopian tube containing a cell of *C. trachomatis* (arrow) in the lesion.

trigger an overblown immune response and inflammation in the host. During NGU, cells of *C. trachomatis* can attach to microvilli of fallopian tube cells, enter, multiply, and eventually lyse the cells (Figure 30.39*b*). Untreated NGU in a female can thus lead to infertility, ectopic pregnancy, and chronic pelvic pain. Infections with the protist *Trichomonas vaginalis* can cause symptoms similar to those of chlamydial NGU, and we consider trichomoniasis along with other parasitic infections in Chapter 33.

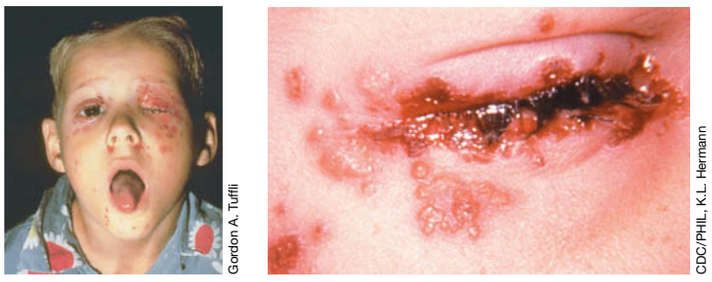
Chlamydial NGU is frequently observed as a secondary infection following gonorrhea. Both *N. gonorrhoeae* and *C. trachomatis* are often transmitted to a new host simultaneously. However, treatment of gonorrhea does not eliminate the chlamydia. Although cured of gonorrhea, these patients are still infected with chlamydia and eventually experience an apparent recurrence of gonorrhea that is instead a case of chlamydial NGU. Thus, patients treated for gonorrhea with drugs such as cefixime or ceftriaxone are also given azithromycin or doxycycline to treat a potential coinfection with *C. trachomatis*. A variety of clinical techniques including nucleic acid and immunological analyses are available for making a positive diagnosis of *C. trachomatis* infection, but drug therapy in the absence of a positive diagnosis is often prescribed.

Lymphogranuloma venereum (*LGV*) is a sexually transmitted disease caused by distinct strains of *C. trachomatis* (LGV 1, 2, and 3). The disease occurs most frequently in males and is characterized by infection and swelling of the lymph nodes in and about the groin. From the infected lymph nodes, chlamydial cells may travel to the rectum and cause a painful inflammation of rectal tissues called *proctitis*. LGV has the potential to cause regional lymph node damage and the complications of proctitis. It is the only chlamydial infection that invades beyond the epithelial cell layer.

Herpes

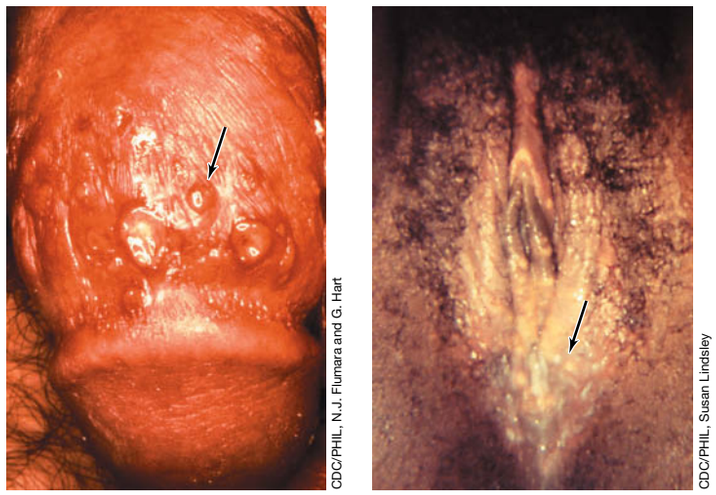
Herpesviruses are a large group of double-stranded DNA viruses (Section 10.7), many of which are human pathogens. The herpes simplex viruses are responsible for both cold sores and genital infections.

Herpes simplex 1 virus (*HSV-1*) infects the epithelial cells around the mouth and lips, causing cold sores, also known as fever blisters (**Figure 30.40**). HSV-1 is spread via direct contact with infectious lesions or through saliva. The incubation period of HSV-1 infections is short (3–5 days), and the lesions heal without treatment in 2–3 weeks. However, latent herpes infections are common, because the virus typically persists in low numbers in nerve tissue.



(a) (b)

Figure 30.40 Herpes simplex 1 virus infections. *(a)* A severe case of herpes blisters on the face due to infection with herpes simplex 1 virus. *(b)* Close-up view of herpes blisters by the eye.



(a) (b)

Figure 30.41 Herpes simplex 2 virus infections. Herpes simplex 2 virus blisters on the *(a)* penis and *(b)* vulva. As for herpes type 1, acute type 2 herpes infections can seemingly be cured only to reappear later from a persistent virus infection (Figure 8.20).

Recurrent acute herpes infections can then occur when the virus is triggered by coinfections with other pathogens or by bodily stress. Oral herpes caused by HSV-1 is quite common and apparently has no long-term harmful effects on the host, beyond the discomfort of the oral blisters.

Herpes simplex 2 virus (*HSV-2*) infections are associated primarily with the anogenital region, where the virus causes painful blisters on the penis of males or on the cervix, vulva, or vagina of females (**Figure 30.41**). HSV-2 infections are generally transmitted by direct sexual contact, and the disease is most easily transmitted when active blisters are present, but may also be transmitted during asymptomatic periods, even when the infection is presumably latent. HSV-2 occasionally infects other sites such as the mucous membranes of the mouth and can also be transmitted to a newborn by contact with herpetic lesions in the birth canal at birth. The disease in the newborn varies from latent infections with no apparent damage to systemic disease resulting in brain damage or even death. To avoid herpes infections in newborns, delivery by cesarean section is advised for pregnant women with genital herpes infections.

The long-term effects of genital herpes infections are not fully understood. However, studies have indicated a significant correlation between genital herpes infections and cervical cancer in females. Genital herpes infections are presently incurable, although a limited number of drugs have been successful in controlling the infectious blister stages. The guanine analog acyclovir (**Figure 30.42**), given orally and also applied topically, is particularly effective in limiting the shed of active virus from blisters and promoting the healing of blistering lesions (Figure 30.41). Acyclovir, and the related drugs valacyclovir and vidarabine, are nucleoside analogs that interfere with herpesvirus DNA polymerase, inhibiting viral DNA replication (Section 28.11).

Human Papillomavirus

As for herpesviruses, **human papillomaviruses (HPV)** comprise a family of double-stranded DNA viruses. Of more than 100

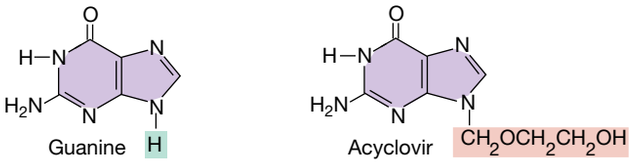


Figure 30.42 Guanine and the guanine analog acyclovir. Acyclovir has been used therapeutically to control genital herpes (HSV-2) blisters (Figure 30.41).

different strains, about 30 are transmitted sexually, and several of these cause genital warts and cervical cancer. About 20 million people in the United States are infected, and up to 80% of women over age 50 have had at least one HPV infection. Over 6 million people acquire new HPV infections annually, leading to almost 10,000 cases of cervical cancer and about 3700 deaths.

Most HPV infections are asymptomatic, with some progressing to cause genital warts. Others cause cervical neoplasia (abnormalities in cells of the cervix), and a few progress to cervical cancers. Most HPV infections resolve spontaneously but, as with many viral infections, there is no adequate treatment or cure for active infections. Because human papillomaviruses are potentially oncogenic (cancer-causing), HPV vaccines are available (a widely used one is marketed as Gardasil) and are currently recommended for use in females 11–26 years of age. The HPV vaccine is also recommended for males because immunized males no longer carry HPV and thus cannot infect females, and because HPV infection in males can lead to anal and penile cancers. In addition, the HPV vaccine should reduce incidence of certain neck and throat cancers in both males and females caused by the same strains of HPV linked to the sexually transmitted infections.

MINIQUIZ

- Describe pertinent clinical features and treatment protocols for chlamydia, herpes, and human papillomavirus.
- Why are these diseases more difficult to diagnose than gonorrhea or syphilis?

30.15 HIV/AIDS

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). Worldwide, nearly 80 million people have been infected with HIV and about 34 million have died. In the United States, from a total of 5 cases diagnosed in 1981, over 1.1 million people are infected with HIV today. We covered some aspects of the epidemiology of HIV/AIDS in Section 29.8 and will pick up on that theme here.

HIV and a Definition of AIDS

HIV is of two types, *HIV-1* and *HIV-2*, but because more than 99% of global AIDS cases are due to HIV-1, we focus on HIV-1 here. HIV-1 is a retrovirus (Sections 8.8 and 10.11) that replicates in macrophages and T cells of the human immune system (Chapters 26 and 27). HIV infection eventually leads to the destruction of key immune system cells, virtually eliminating the host immune response. Death from AIDS is usually the result of a secondary infection, typically one caused by an **opportunistic pathogen**, pathogens that in a healthy individual would be controlled by the immune system.

The current definition of a case of HIV/AIDS is a patient who tests positive for HIV in immunological and/or nucleic acid-based tests and meets at least one of the following two criteria:

1. A CD4 T cell number of less than 200/μl of whole blood (the normal count is 600–1000/μl) or a CD4 T cell/total lymphocytes percentage of less than 14%.
2. A CD4 T cell number of more than 200/μl *and* any of the following diseases: candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, cystoisosporiasis, *Pneumocystis jirovecii* pneumonia, cryptosporidiosis, or toxoplasmosis of the brain (all fungal or protozoal diseases) (Chapter 33); pulmonary tuberculosis or other mycobacterial infections, or recurrent *Salmonella* septicemia (bacterial diseases); cytomegalovirus infection, HIV-related encephalopathy, HIV wasting syndrome, chronic ulcers, or bronchitis due to herpes simplex (viral infections); or certain malignant diseases such as invasive cervical cancer, Kaposi's sarcoma, Burkitt's lymphoma, primary lymphoma of the brain, or immunoblastic lymphoma, or recurrent pneumonia due to any agent.

Pathogenesis of HIV/AIDS

HIV infects cells that have the CD4 cell surface protein. The two cell types most commonly infected are macrophages and a class of lymphocytes called T-helper (Th) cells, both of which are important components of the immune system. Infection normally occurs first in macrophages. At the macrophage cell surface, the CD4 molecule binds to the gp120/gp41 capsid protein of HIV as the virus interacts with the macrophage receptor CCR5 (**Figure 30.43**). CCR5 is a coreceptor for HIV and, together with CD4, forms the docking site where the HIV envelope fuses with the host cytoplasmic membrane; this is required for the viral nucleocapsid to be inserted into the cell (Figure 30.43*b*). Within the macrophage, HIV replicates and makes an altered form of gp120 that recognizes a different coreceptor, CXCR4, on Th cells. HIV virions are released from macrophages and proceed to infect and replicate in Th lymphocytes; Th cells that produce HIV no longer divide and are eventually diminished by attrition.

In some HIV/AIDS patients, HIV infection does not progress immediately to killing host immune cells. HIV can exist in a dormant state as a provirus; under these conditions, the reverse-transcribed HIV genome, now in the form of DNA, is integrated into host chromosomal DNA (Figure 10.23). At this point the cell may show no outward sign of infection. Indeed, HIV DNA can remain latent for long periods, replicating only as the host cell DNA replicates. However, sooner or later, HIV begins to replicate, and progeny virus are produced and released from the cell.

Symptoms of HIV/AIDS

Ongoing HIV infection results in a progressive decline in CD4 cell numbers. In a healthy human, CD4 cells constitute about 70% of the total T cell pool. In those with HIV/AIDS, CD4 numbers steadily decrease, and by the time opportunistic infections begin

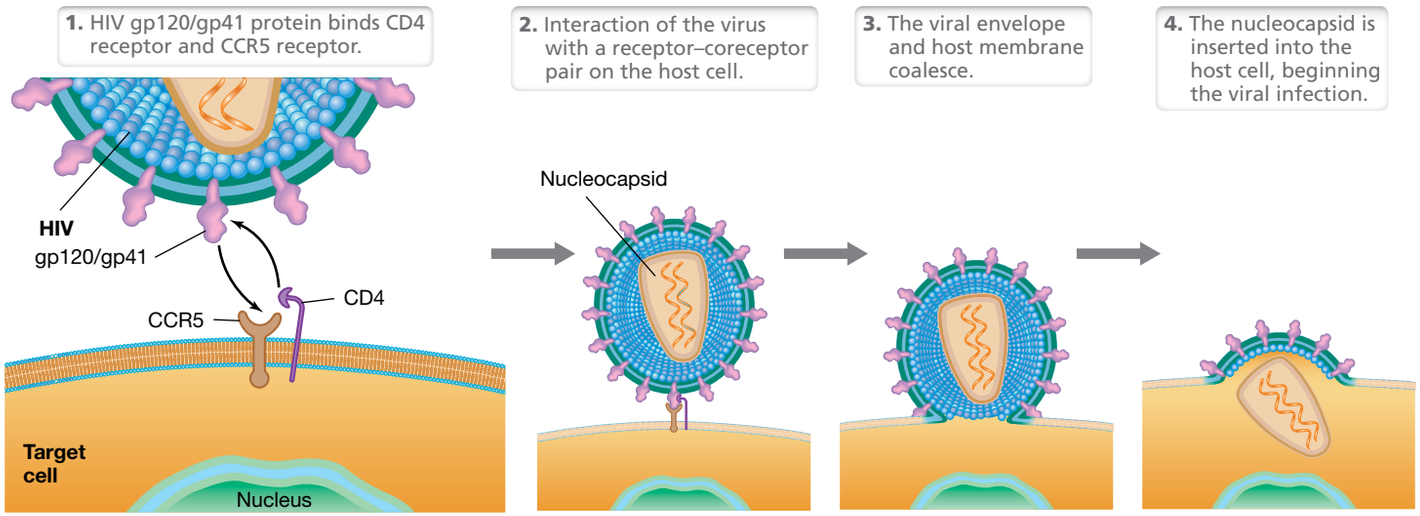


Figure 30.43 Infection of a CD4 target cell with HIV. *(a)* Recognition and binding of HIV by CCR5 and CD4 receptors. *(b)* The viral nucleocapsid eventually enters the cell. Details of the replication of the HIV genome were shown in Figure 10.23.

to appear, CD4 cells are all but absent (**Figure 30.44**). The progression of untreated HIV infection to AIDS follows a typical pattern. First, there is an intense immune response to HIV and HIV numbers drop. But eventually, the immune response is overwhelmed and HIV levels slowly increase while CD4 T cells slowly decrease. When T cell numbers have dropped below about 200/mm^3 of blood, the door is open for infections by opportunistic pathogens (Figure 30.44).

Opportunistic infections caused by normally controllable protists, fungi, bacteria, and viruses occur with high prevalence in those with HIV/AIDS and are typically the actual cause of death (**Figure 30.45**). The most common opportunistic disease in HIV/AIDS patients is pneumonia caused by the fungus *Pneumocystis jirovecii* (Figure 30.45*d*), but infections by various molds, yeasts, protists, and bacteria are also seen (Figure 30.45). Bacterial infections are less common than those of eukaryotic pathogens, but when they occur, they are frequently of strongly antibiotic-resistant bacteria, such as multiple-drug-resistant *Mycobacterium tuberculosis*.

Eukaryotic opportunistic pathogens are difficult to treat in general because many of the drugs used to treat infections from fungi and protists have significant negative side effects on the host, which of course is also a eukaryote. A cancer frequently seen in HIV/AIDS patients is *Kaposi's sarcoma*, a cancer of the cells lining the blood vessels and characterized by purple splotches on the

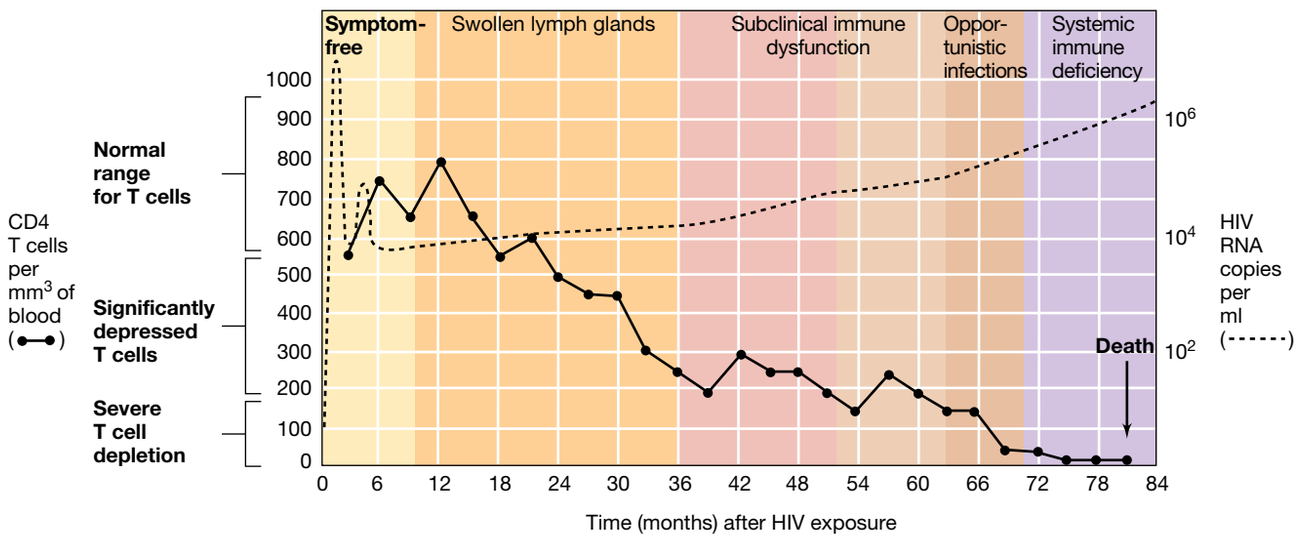


Figure 30.44 Decline of CD4 T lymphocytes and progress of HIV infection. During the typical progression of untreated AIDS, there is a gradual loss in the number and functional ability of the CD4 T cells, while the viral load, measured as HIV-specific RNA copies per milliliter of blood, gradually increases after an initial decline.

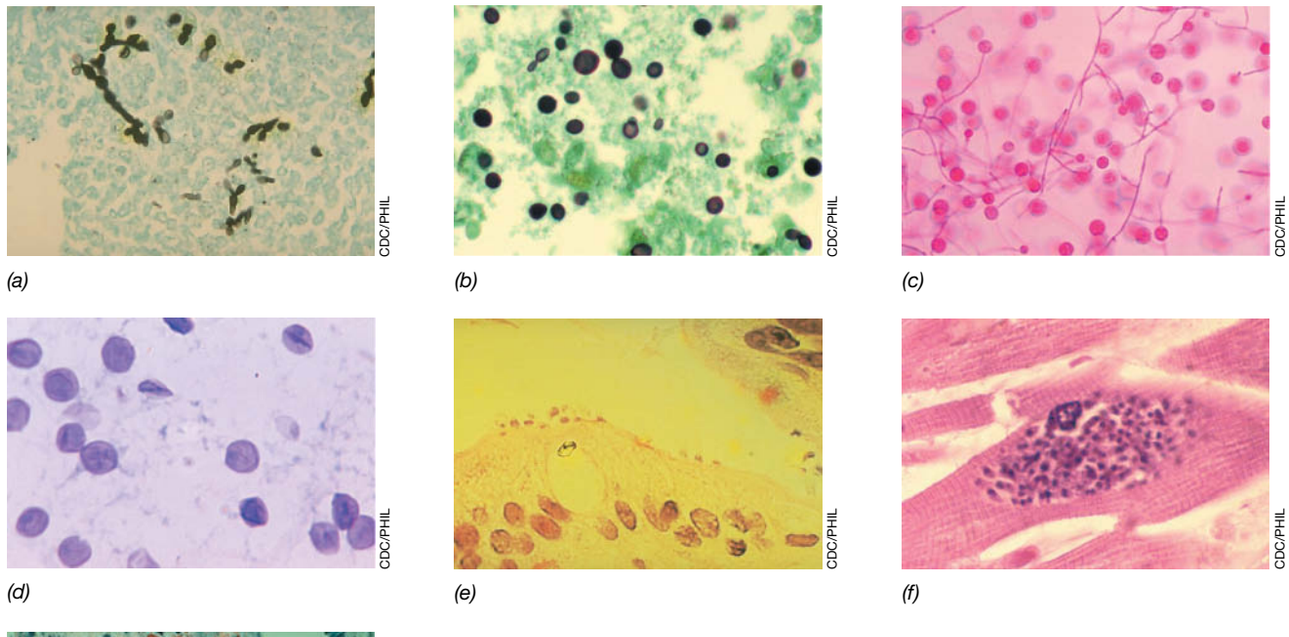


Figure 30.45 Opportunistic pathogens associated with HIV/AIDS. *(a) Candida albicans*, from heart tissue of patient with systemic *Candida* infection. *(b) Cryptococcus neoformans*, from lung tissue of an AIDS patient. *(c) Histoplasma capsulatum*, showing reproductive structures called macroconidia. *(d) Pneumocystis jirovecii*, from lungs of an immune-compromised patient. *(e) Cryptosporidium* sp. from small intestine of a patient with cryptosporidiosis. *(f) Toxoplasma gondii*, from heart tissue of patient with toxoplasmosis. *(g) Mycobacterium* spp. infection of the small bowel (acid-fast stain). *Candida, Cryptococcus, Histoplasma* and *Pneumocystis* are fungi; *Cryptosporidium* and *Toxoplasma* are protists; *Mycobacterium* is a species of *Bacteria*. Coverage of many of these fungal and parasitic diseases can be found in Chapter 33.

skin, especially in the extremities (**Figure 30.46**). Kaposi's sarcoma is caused by coinfection of HIV and human herpesvirus 8 (HHV-8) and is rarely seen outside of HIV/AIDS patients.

Diagnosing HIV/AIDS

HIV infection is typically diagnosed by identifying antibodies to the pathogen in a patient blood sample. An enzyme immunoassay (EIA, Figure 28.19) is used for HIV screening purposes, typically for screening done on a large scale such as with donated blood. A positive HIV EIA must be confirmed by an HIV immunoblot (Western blot, Figure 28.21) or by immunofluorescence (Section 28.6) to rule out the possibility of a false-positive screening test. Rapid and inexpensive HIV tests are also available for preliminary screening of blood in clinics. One test requires only a single drop of patient blood and detects the gp41 HIV surface antigen (Figure 30.43) by producing a visible agglutination reaction. A second uses saliva as a source of anti-HIV antibodies and yields a colored product. In general, however, these rapid tests are not as sensitive or specific as the standard HIV EIA and thus positive tests should be confirmed by more sensitive and specific tests. Unfortunately, no matter how sensitive or specific, none of the antibody tests will detect those who have recently acquired the virus and are infectious but have not yet made a detectable antibody response to HIV; this antibody response can require a period of 6 weeks or more following infection.

Diagnostic procedures also are available that directly measure the number of HIV virions in a blood sample. These tests use a virus-specific reverse transcription–polymerase chain reaction assay (RT-PCR, Section 12.1). RT-PCR estimates the number

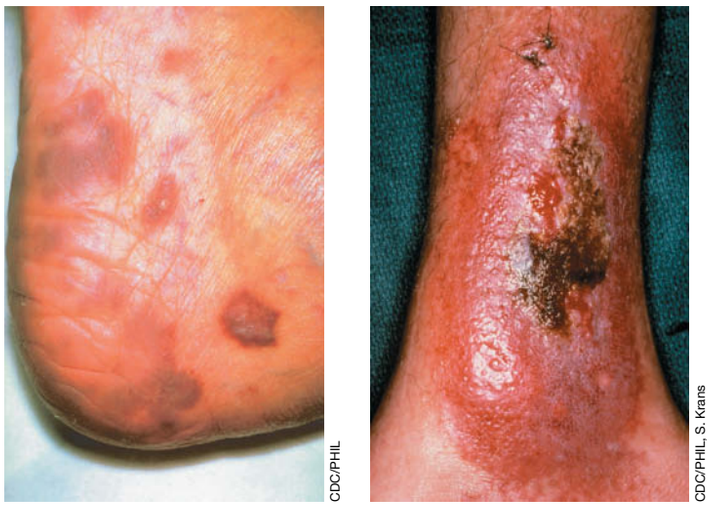
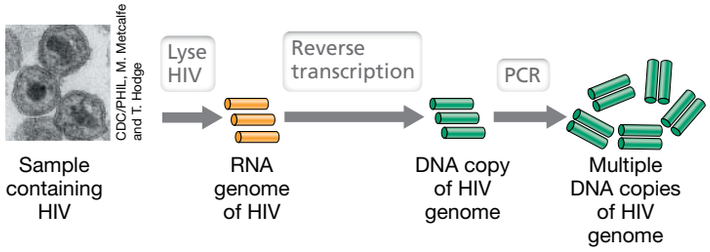
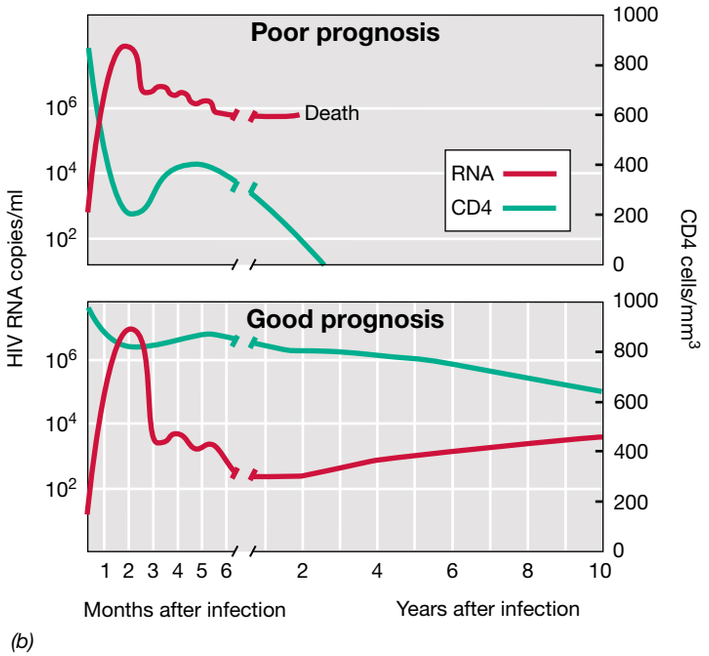


Figure 30.46 Kaposi's sarcoma. Lesions are shown as they appear on *(a)* the heel and lateral foot, and *(b)* the distal leg and ankle.



(a)



(b)

Figure 30.47 Monitoring of HIV load. *(a)* Procedure for detecting HIV by reverse transcription–polymerase chain reaction (RT-PCR) techniques. *(b)* Time course for HIV infection as monitored by HIV load and CD4 T cell counts. In the upper panel, a viral load greater than 10^4 copies/ml correlates with below normal CD4 cell numbers (normal = 600–1500/mm^3), indicating a poor prognosis and early death of the patient. In the lower panel, a viral load less than 10^4 copies/ml correlates with normal CD4 cell numbers, indicating a good prognosis and extended survival of the patient. Data are adapted from the CDC, Atlanta, Georgia, USA.

of HIV virions present in the blood, the so-called **viral load** (Figure 30.47). The RT-PCR test for HIV load is not routinely used to screen for HIV because it is costly and technically demanding. However, after an initial diagnosis, the test is often used to monitor progression of an HIV infection (Figure 30.47) and the effectiveness of chemotherapy.

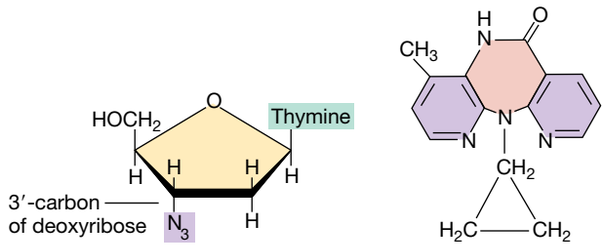
Treatment of HIV/AIDS

The prognosis for an *untreated* HIV-infected individual is poor, as opportunistic pathogens or malignancies (Figures 30.45 and 30.46) eventually kill virtually all infected persons. Long-term studies indicate that the average person infected with HIV progresses through several stages of decreasing immune function, with CD4 cells dropping from a normal range of 600–1000/mm^3 of blood to near zero over a period of 5–7 years (Figure 30.44). Although the rate of decline varies from one HIV-infected individual to another, it is rare for an HIV-positive individual to live for more than 10 years without anti-HIV drug therapy (see page 923 for exceptions).

Several drugs have been developed that delay the progression of HIV/AIDS and significantly prolong the life of those infected with HIV. Therapy is aimed at reducing the viral load of HIV-infected individuals to below detectable levels. The strategy to accomplish this is called *highly active anti-retroviral therapy* (HAART) and is carried out by administering at least three anti-retroviral drugs at once to inhibit the replication of HIV and prevent the development of drug-resistant strains. Multiple drug therapy, however, is not a cure for HIV infection. In individuals who have no detectable viral load after drug treatment, a significant viral load returns if therapy is interrupted or discontinued, or if multiple drug resistance develops.

Effective anti-HIV drugs fall into four categories, including two classes of *reverse transcriptase inhibitors*, various *protease inhibitors, fusion inhibitors*, and *integrase inhibitors*. Reverse transcriptase is the enzyme that converts the single-stranded RNA genome of HIV into cDNA and then double-stranded DNA and is essential for viral replication (Sections 8.8 and 10.11). Cells lack reverse transcriptase and thus reverse transcriptase inhibitors are viral-specific. *Azidothymidine* (AZT), also called zidovudine, closely resembles the nucleoside thymidine but lacks the correct attachment site for the next base in a replicating nucleotide chain, resulting in termination of the growing DNA chain. AZT is thus a **nucleoside reverse transcriptase inhibitor** (Figure 30.48*a*). **Nonnucleoside reverse transcriptase inhibitors**, such as *nevirapine* (Figure 30.48*b*), inhibit the activity of reverse transcriptase in a different way by interacting with the protein and altering the conformation of the catalytic site.

Another category of anti-HIV drugs is the **protease inhibitors**, such as *saquinavir* (Figure 28.35*b*). These are peptide analogs that inhibit processing of retroviral polypeptides (Figure 10.24) by binding to the active site of the processing enzyme, *HIV protease*; this effectively inhibits viral maturation. **Fusion inhibitors** include *enfuvirtide*, a synthetic peptide that functions by binding to the gp41 protein on HIV capsids (Figure 30.43); this stops fusion of the viral envelope and the CD4 cell cytoplasmic membrane. Finally, there are the **integrase inhibitors**, such as *elvitegravir* and *raltegravir*. These drugs target HIV integrase, the protein that integrates the HIV genome into host cell DNA. The interference



(a) **Azidothymidine (zidovudine)** (b) **Nevirapine**

Figure 30.48 HIV/AIDS chemotherapeutic drugs. *(a)* Azidothymidine (AZT), also called zidovudine, a nucleoside reverse transcriptase inhibitor. This nucleoside analog is missing the –OH group on the 3′-carbon, causing nucleotide chain elongation to terminate when the analog is incorporated, inhibiting virus replication. *(b)* Nevirapine, a nonnucleoside reverse transcriptase inhibitor, binds directly to the catalytic site of HIV reverse transcriptase, also inhibiting elongation of the nucleotide chain.

with integration of viral DNA into the host cell genome interrupts the HIV replication cycle.

All anti-HIV drugs rapidly decrease the viral load when given to HIV-infected individuals, but drug-resistant strains of HIV arise quickly if only a single drug is administered. A typical HAART protocol for treatment of an established HIV infection includes at least one protease or nonnucleoside reverse transcriptase inhibitor plus a combination of two nucleoside reverse transcriptase inhibitors. A resistant virus would, therefore, have to develop resistance to three drugs simultaneously, and the probability of this occurring is very small. A patient receiving this combination therapy is then monitored to track changes in viral load (Figures 30.44 and 30.47). An effective HAART protocol reduces viral load to nondetectable levels within several days. Drug therapy is then continued and the patient monitored for viral load indefinitely. If the viral load again reaches detectable limits, the drug cocktail is changed because an increase in viral load indicates the emergence of drug-resistant HIV.

In addition to drug resistance, some anti-retroviral drugs are toxic to the host. In many cases, nucleoside analogs are not well tolerated by patients, presumably because they interfere with host functions such as cell division. In general, the nonnucleoside reverse transcriptase inhibitors and the protease inhibitors are better tolerated because they target virus-specific functions. However, drug resistance and host toxicity are major problems in all forms of HIV therapy. Thus, new chemotherapeutic agents and drug protocols are constantly being developed and tailored to the needs of individual patients.

HIV/AIDS Prevention

Public education about how HIV/AIDS is transmitted, sexual abstinence, and avoidance of high-risk behavior remain the major tools used to prevent HIV/AIDS. HIV spread is linked to promiscuous sexual activities and other activities that involve exchange of body fluids, which include not only men who have sex with men, but also prostitution and intravenous drug use where needles are shared. In some countries, the fastest growing mode of HIV transmission is actually between heterosexual partners. Effective prevention of HIV transmission therefore requires avoiding high-risk behaviors, regardless of sexual partners.

The United States Surgeon General has issued specific recommendations for avoiding HIV infection. These include, in addition to the avoidance of intravenous drug use where needles are shared:

1. Avoiding mouth contact with penis, vagina, or rectum.
2. Avoiding all sexual activities that could cause cuts or tears in the linings of the rectum, vagina, or penis.
3. Avoiding sexual activities with individuals from high-risk groups. These include prostitutes (both male and female); those who have multiple sex partners, particularly homosexual men and bisexuals; and intravenous drug users.
4. If a person has had sex with someone in a high-risk group, a blood test should be done to determine if infection with HIV has occurred. The blood test should be repeated at intervals for a year or longer because of the lag time in the immune response. If the test is positive, the sexual partners of the HIV-positive individual must be protected by use of a condom during sexual activities.

MINIQUIZ

- Review the definition of HIV/AIDS. Which symptoms of HIV/AIDS are shared by all HIV/AIDS patients?
- What does the enzyme reverse transcriptase do and why is it a good target for anti-HIV drugs?
- What are the current prevention guidelines for HIV/AIDS infection? Are they effective?

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Chapter Review

I • Airborne Bacterial Diseases

30.1 Bacterial and viral respiratory pathogens are transmitted in air. Most respiratory pathogens are transferred from person to person via respiratory aerosols generated by coughing, sneezing, talking, or breathing, or by direct or fomite contact. Respiratory pathogens infect either the upper or lower respiratory tracts and sometimes both.

Q What enables *Staphylococcus* and *Mycobacterium* to survive drying and persist in dust for long periods?

30.2 Major streptococcal diseases include strep throat and pneumococcal pneumonia. *Streptococcus pyogenes* infections may progress into serious conditions such as scarlet and rheumatic fevers, and pneumococcal pneumonia can have high mortality. Both pathogens can be cultured and both are treatable with antimicrobial drugs including penicillin.

Q Describe one method to diagnose strep throat quickly. Why may this method be better than a throat culture?

30.3 Diphtheria is an acute respiratory disease caused by the bacterium *Corynebacterium diphtheriae*. Early childhood immunization is effective for preventing this very serious respiratory disease. Whooping cough is an endemic disease caused by the bacterium *Bordetella pertussis*. Immunization of children, adolescents, and adults can control its propagation and spread.

Q What causes a strain of *C. diphtheriae* to be pathogenic? Describe how such a strain may cause death in an infected patient?

30.4 Tuberculosis is one of the most prevalent and dangerous infectious diseases in the world. Its incidence is increasing in developed countries in part because of the emergence of drug-resistant strains of *Mycobacterium tuberculosis*. The pathology of tuberculosis and other mycobacterial syndromes such as Hansen's disease (leprosy) is influenced by the cell-mediated immune response.

Q Describe the process of infection by *Mycobacterium tuberculosis*. Does infection always lead to active tuberculosis? Why or why not? How is exposure to *M. tuberculosis* detected in humans?

30.5 *Neisseria meningitidis* is a common cause of meningococcemia and meningitis in young adults and occasionally occurs in epidemics in enclosed populations. Bacterial meningitis and meningococcemia can have high mortality rates, and treatment and prevention strategies including vaccines are available.

Q How is *Neisseria meningitides* typically transmitted and what are the symptoms of full-blown meningitis caused by this bacterium?

II • Airborne Viral Diseases

30.6 Viral respiratory diseases are highly infectious and may cause serious health problems, although most are controllable and not life-threatening. The measles/mumps/rubella (MMR) vaccine is highly effective in controlling these diseases.

Q Compare and contrast measles, mumps, and rubella. Include a description of the pathogen, major symptoms encountered, and any potential consequences of these infections. Why is it important that women be vaccinated against rubella before puberty?

30.7 Colds are the most common infectious viral diseases. Usually caused by a rhinovirus, colds are generally mild and self-limiting diseases; "cold drugs" may help to moderate symptoms but are not a cure. Each infection induces specific, protective immunity, but the large number of cold viruses precludes complete protective immunity or vaccines.

Q Why are colds such common respiratory diseases, and why are vaccines not used to prevent colds?

30.8 Influenza is caused by an RNA virus that contains a segmented genome and is easily transmitted by the airborne route. Influenza outbreaks occur annually as a result of the plasticity of the influenza genome. Antigenic drift varies the nature of the viral envelope of influenza viruses in minor ways, causing influenza seasonal epidemics, while antigenic shift varies the virus in major ways and can trigger periodic influenza pandemics. Surveillance and immunization are used to control influenza.

Q Why is influenza such a common respiratory disease? How are influenza vaccines chosen?

III • Direct-Contact Bacterial and Viral Diseases

30.9 Staphylococci are usually benign inhabitants of the upper respiratory tract and skin, but several serious diseases can result from pyogenic infection or from the activity of staphylococcal superantigen exotoxins. Antibiotic resistance is common, even in community-acquired infections. MRSA strains of *Staphylococcus aureus* can be very difficult to treat and cause significant tissue damage.

Q Distinguish between pathogenic staphylococci and those that are part of the normal microbiota.

30.10 *Helicobacter pylori* infection is the common cause of gastric ulcers. Gastric ulcers are now treated with antibiotics as an infectious disease, promoting a permanent cure.

Q Describe the evidence linking *Helicobacter pylori* to gastric ulcers. How can these ulcers be cured?

30.11 Viral hepatitis can result in acute liver disease, which may be followed by chronic liver disease (cirrhosis). Hepatitis B and C viruses in particular are transmitted by direct contact and can cause chronic infections leading to liver cancer. Vaccines are available for hepatitis viruses A and B. Viral hepatitis is still a major public health problem because of the high infectivity of the viruses and the lack of effective treatments.

Q Describe the major hepatitis viruses. How are they related to one another? How is each spread?

30.12 Ebola hemorrhagic fever is a deadly viral disease spread by direct contact through the skin or from contaminated bodily fluids. Mortality rates from Ebola are near the highest of all diseases. Treatment is primarily supportive of symptoms, but vaccine trials have shown that effective vaccination protocols should be possible.

Q The Ebola virus cannot depend on the host to synthesize its genome; why not?

IV • Sexually Transmitted Infections

30.13 Gonorrhea and syphilis, caused by *Neisseria gonorrhoeae* and *Treponema pallidum*, respectively, are STIs with potential serious consequences if infections are not treated. In the United States, the incidence of gonorrhea has decreased in the last several years, but the incidence of syphilis has increased.

Q Why did the incidence of gonorrhea rise dramatically in the mid-1960s, while the incidence of syphilis actually decreased at the same time?

30.14 Chlamydia is the most prevalent of STIs, and if left untreated, it can cause serious complications in both males and females. Herpes simplex viruses cause incurable infections transmitted by oral or genital contact with herpes 1 or herpes 2, respectively. Human papillomaviruses

cause widespread STIs that may lead to cervical and other cancers, but effective HPV vaccines are available.

Q For the sexually transmitted infections of chlamydia, herpes, and human papillomavirus, describe the organism that causes each. In each case, is treatment possible, and if so, is it an effective cure? Why or why not?

30.15 HIV is a retrovirus that destroys the immune system, leading to AIDS, and opportunistic pathogens eventually kill the host. There is no effective cure or vaccine for HIV infection, although antiviral drugs may slow or stop the progress of AIDS. Preventing HIV infection requires education and avoidance of high-risk behaviors involving exchange of body fluids.

Q Describe how human immunodeficiency virus (HIV) effectively shuts down both antibody-mediated and cell-mediated immunity. What is HAART therapy?

Application Questions

1. Why is it that you get a cold or two each year but if you have had a case of measles, it was a one-time occurrence?
2. Your college roommate goes home for the weekend, becomes extremely ill, and is diagnosed with bacterial meningitis at a local hospital. Because he was away, university officials are not aware of his illness. What should you do to protect yourself against meningitis? Should you notify university health officials?
3. Contrast an HIV infection with an infection by any other viral pathogen considered in this chapter, regardless of mode of transmission. Why do untreated cases of HIV infection almost always lead to death whereas untreated cases of chicken pox, influenza, or even hepatitis typically do not?
4. Discuss the molecular biology of antigenic shift in influenza viruses and comment on the immunological consequences for the host. Why has antigenic shift prevented the production of a single universally effective vaccine for influenza control? Next, compare antigenic shift to antigenic drift. Which causes the greatest antigenic change? Which creates the biggest problems for vaccine developers? Which can lead to pandemic influenza, and why?

Chapter Glossary

Antigenic drift a minor change in influenza virus antigens due to gene mutation

Antigenic shift a major change in influenza virus antigen due to gene reassortment

Cirrhosis breakdown of normal liver architecture, resulting in fibrosis

Congenital syphilis syphilis contracted by an infant from its mother during pregnancy

Fusion inhibitor a synthetic polypeptide that binds to viral glycoproteins, inhibiting fusion of viral and host cell membranes

Hepatitis liver inflammation, commonly caused by an infectious agent

Human papillomavirus (HPV) a sexually transmitted virus that causes genital warts, cervical neoplasia, and cancer

Integrase inhibitor a drug that interrupts the HIV replication cycle by interfering with integrase, the HIV protein that catalyzes the integration of viral dsDNA into host cell DNA

Meningitis inflammation of the meninges (brain tissue), sometimes caused by *Neisseria meningitidis* and characterized by sudden onset of headache, vomiting, and stiff neck, often progressing to coma within hours

Meningococcemia a rapidly progressing severe disease caused by *Neisseria meningitidis* and characterized by septicemia, intravascular coagulation, and shock

Nonnucleoside reverse transcriptase inhibitor a nonnucleoside compound that inhibits the action of retroviral reverse transcriptase by binding directly to the catalytic site

Nucleoside reverse transcriptase inhibitor a nucleoside analog compound that inhibits the action of retroviral reverse transcriptase by competing with nucleosides

Opportunistic pathogen an organism that causes disease in the absence of normal host resistance

Pertussis (whooping cough) a disease caused by an upper respiratory tract infection with *Bordetella pertussis*, characterized by a deep, persistent cough

Protease inhibitor a compound that inhibits the action of viral protease by binding directly to the catalytic site, preventing viral protein processing

Rheumatic fever an inflammatory autoimmune disease triggered by an immune response to infection by *Streptococcus pyogenes*

Scarlet fever characteristic reddish rash resulting from an exotoxin produced by *Streptococcus pyogenes*

Sexually transmitted infection (STI) an infection that is usually transmitted by sexual contact

Toxic shock syndrome (TSS) the acute systemic shock resulting from a host response to an exotoxin produced by *Staphylococcus aureus*

Tuberculin test a skin test for previous infection with *Mycobacterium tuberculosis*

Viral load a quantitative assessment of the amount of virus in a host organism, usually in the blood

31

Vectorborne and Soilborne Bacterial and Viral Diseases

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A New Look at Rabies Vaccines

Dog owners just *love* their dogs (see photo of author Michael Madigan's spouse, Nancy, with Kato), and for good reasons: Besides the loyal companionship one gets from "man's best friend," surveys have shown that dog owners lead healthier and happier lives than those who do not own dogs. Keeping your dog up to date on vaccinations is essential for the dog's health and happiness, too, and the most important vaccination is the periodic rabies booster.

Rabies can affect any mammal and is still a major human health problem. Nearly 60,000 humans die from rabies each year, mostly in developing countries in Asia and Africa where rabies vaccines are not widely administered to domestic animals. Highly effective preexposure and postexposure rabies vaccines are available for use in humans, where the incubation period is typically one to two months. In domestic animals, however, rabies symptoms appear much more quickly (in under 10 days in dogs), and once symptoms begin, death is inevitable. Hence, an effective rabies vaccine for use in animals and humans where disease symptoms have already begun would give medicine a new tool for controlling this disease.

Ongoing research is working to fill this void in the arsenal of rabies vaccines. Scientists have developed a recombinant rabies vaccine that uses parainfluenza virus (a virus that causes only mild infections in dogs or humans) as a carrier of a key rabies virus protein. The recombinant virus was genetically engineered to contain and express the gene encoding rabies virus glycoprotein, a protein that elicits a strong adaptive immune response. In experimental trials, the vaccine was found to protect half of rabies-infected mice when administered as late as 6 days postinfection, which in mice is a time when classical rabies symptoms have already begun.

Recombinant vaccines are attractive because they carry no risk of accidental infection and can be given in high doses. Although this experimental rabies vaccine has only been used in mice, it is possible that a similar vaccine strategy could work in other animals and in humans. If so, such a vaccine could help reduce the heavy toll of human rabies deaths worldwide, most of which result from seemingly minor bites or scratches from unvaccinated dogs or other domestic animals.

Source: Huang, Y., et al. 2015. Parainfluenza virus 5 expressing the G protein of rabies virus protects mice after rabies virus infection. *J. Virol. 89:* 3427–3429. Photo courtesy of Christina Davis, Logan, Ohio.

In this chapter we focus on pathogenic bacteria and viruses transmitted to humans by animals, arthropods, or soil. Animal-transmitted pathogens have their origins in nonhuman vertebrates, and these infected animal populations can transmit infections to humans. Some arthropods are disease vectors, spreading pathogens to new hosts from a bite. Soilborne pathogens are transmitted to humans through either direct contact with soil or contact with infected animal fur or hides. A few of the diseases we will explore in this chapter produce only mild symptoms and are typically self-limiting. But most are highly dangerous with life-threatening symptoms and high mortality rates. These include such dreaded diseases as rabies, hantavirus syndromes, yellow fever, and plague.

I • Animal-Transmitted Viral Diseases

A **zoonosis** is an animal disease transmissible to humans, generally by direct contact, aerosols, or bites. Immunization and veterinary care control many infectious diseases in domesticated animals, reducing the transfer of zoonotic pathogens to humans. However, wild animals neither receive veterinary care nor are they immunized, making them a source of potential zoonoses. Diseases in animals may be **enzootic**, present endemically in certain populations, or **epizootic**, with incidence reaching epidemic proportions. In this part of the chapter we focus on two typically enzootic viral diseases, rabies and hantavirus syndromes, both of which can be transmitted to humans.

31.1 Rabies Virus and Rabies

Rabies occurs in wild animals, and the major enzootic reservoirs of rabies virus in the United States are raccoons, skunks, coyotes, foxes, and bats. A small number of rabies cases also occur annually in domestic animals (Figure 31.1).

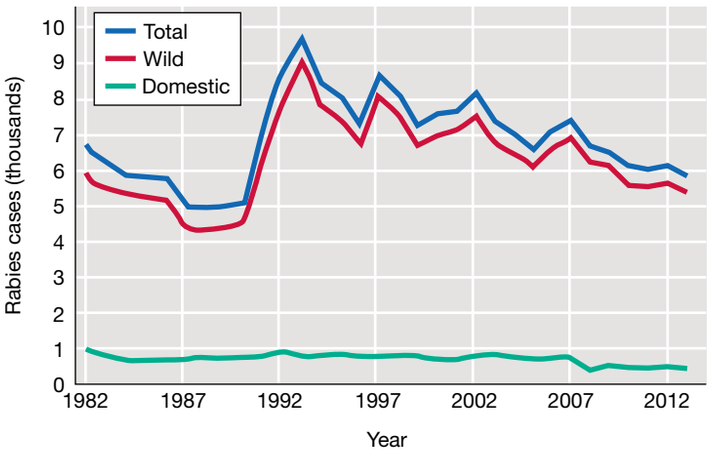
Symptoms and Pathology of Rabies

Rabies is caused by a rhabdovirus, a single-stranded minus-sense RNA virus (Section 10.9) that infects cells of the central nervous system in most warm-blooded animals, almost invariably leading to death once symptoms have developed. The virus (Figure 31.2*a*) enters the body from virus-contaminated saliva through a wound from a bite or through contamination of mucous membranes. Rabies virus multiplies at the site of inoculation and travels to the central nervous system. The incubation period before the onset of symptoms is highly variable and depends on the host; the size, location, and depth of the inoculating wound; and the titer of rabies virions transmitted in the bite. In dogs, the incubation period for rabies is less than 2 weeks. By contrast, in humans, 9 months or more may pass before rabies symptoms become apparent.

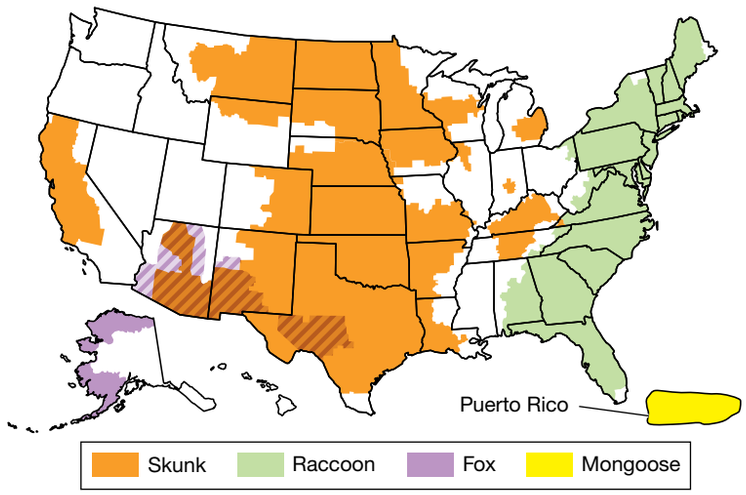
Rabies virus proliferates in the brain, especially in the thalamus and hypothalamus. Infection leads to fever, excitation, dilation of the pupils, excessive salivation, and anxiety. A fear of swallowing (*hydrophobia*, an early name for rabies) develops from uncontrollable spasms of the throat muscles, and death eventually results from respiratory paralysis. In humans, an *untreated* rabies infection in which symptoms have begun is almost always fatal (but see page 955). Fortunately for both domestic animals and humans, a very effective rabies vaccine exists and this keeps the incidence of rabies low in domestic animals (Figure 31.1*a*) and a rarity in humans.

Diagnosis, Treatment, and Prevention of Rabies

Rabies is diagnosed in the laboratory by examining tissue samples for the virus. Fluorescent antibodies that bind to rabies virus in brain tissues are used to confirm a case of rabies in a postmortem examination. Infected nerve cells stained for light microscopy also

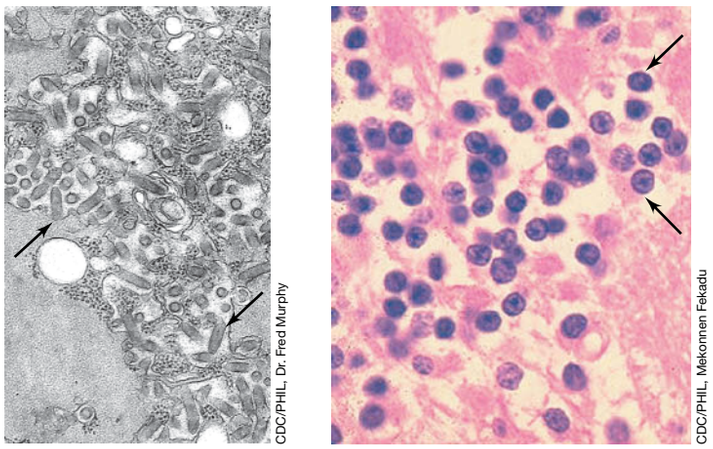


(a) **Incidence of rabies in the United States**



(b) **Major vectors of rabies in the United States and Puerto Rico**

Figure 31.1 Rabies cases in wild and domestic animals in the United States. *(a)* Incidence of rabies by year. Human cases are fewer than five per year. *(b)* Major vectors of rabies virus. In some areas, for example, southwest Texas, both skunks and foxes are the major vectors (shown by hatched lines). Over 90% of all reported rabies cases occur in wild animals. However, actual numbers are probably significantly higher than shown in part *a* because of undiagnosed cases and undiscovered rabid animal carcasses. Data are from the Centers for Disease Control and Prevention, Atlanta, Georgia, USA.



(a) (b)

Figure 31.2 Rabies virus. *(a)* The bullet-shaped rabies virions (arrows) shown in this transmission electron micrograph of a tissue section from a rabid animal are about 75 × 180 nm. *(b)* Pathology of rabies in humans. In brain tissue, rabies virus causes characteristic cytoplasmic inclusions called Negri bodies (arrows), which contain rabies virus antigens. Negri bodies are about 2–10 μm in diameter.

show viral inclusions called *Negri bodies* in their cytoplasm, and these characteristic structures confirm rabies virus infection as well (Figure 31.2*b*).

Because rabies is such a serious disease, firm guidelines for treating possible human exposure to rabies have been established, and the details can be found in the rabies section of the World Health Organization website (http://www.WHO.int). In summary, the guidelines state that if a wild or stray animal is suspected of being rabid, it should be immediately examined for evidence of the rabies virus. If a domestic animal, generally a dog, cat, or ferret, bites a human, especially if the bite is unprovoked, the animal should be held in quarantine for 10 days to check for signs of rabies. If the animal exhibits rabies symptoms, or a definitive diagnosis of its illness cannot be made after 10 days, the human should be passively immunized with rabies immune globulin (purified human antibodies to rabies virus) injected at both the site of the bite and intramuscularly. The patient should also be actively immunized with a rabies virus vaccine. Because of the very slow progression of rabies in humans, this combination of passive and active immune therapy (Section 27.2) is nearly 100% effective, stopping the onset of the disease.

Rabies is prevented largely through immunization. An inactivated rabies vaccine is used in the United States for both humans and domestic animals. Prophylactic rabies immunization is practiced for individuals at high risk, such as veterinarians, animal control personnel, animal researchers, and individuals who work in rabies research or rabies vaccine production laboratories. The rabies problem is primarily with wild animals (Figure 31.1), where traditional means of vaccination are impossible. However, experimental trials with an oral rabies vaccine administered in food "baits" have reduced the incidence and spread of rabies in limited geographic areas. If herd immunity (Section 29.2) could be established in some of the key carriers of rabies (Figure 31.1*b*), it might be possible to reduce incidence of the disease dramatically. Some states and countries, such as Hawaii and Great Britain, are rabies-free, and any animal imported into these areas is subject to quarantine.

Although rabies is vaccine-preventable, nearly 60,000 people per year die from rabies worldwide, primarily in developing countries in Asia and Africa where rabies is enzootic in domestic animals because of inadequate vaccination practices. Worldwide, nearly 14 million people receive prophylactic treatment for rabies after exposure annually, and in the United States, over 20,000 individuals receive such treatment. Fewer than three cases of human rabies are reported in the United States each year, nearly always the result of bites from wild animals, most frequently from bats. Because domestic animals often have exposure to wild animals, dogs and cats are routinely vaccinated against rabies beginning at 3 months of age. Large farm animals, especially horses, are often immunized against rabies as well. One other rare but possible mode of rabies transmission is from organ transplants. In 2013, a rabies death in the U.S. was linked to a transplanted kidney received from a donor who died from rabies that was misdiagnosed as severe gastroenteritis. Past cases of rabies transmission in a cornea and other transplants have also been documented where the donor had yet to show signs of clinical rabies.

MINIQUIZ

- What is the procedure for treating a human bitten by an animal if the animal cannot be found?
- What major advantage does an oral vaccine have over a parenteral (injected) vaccine for rabies control in wild animals?

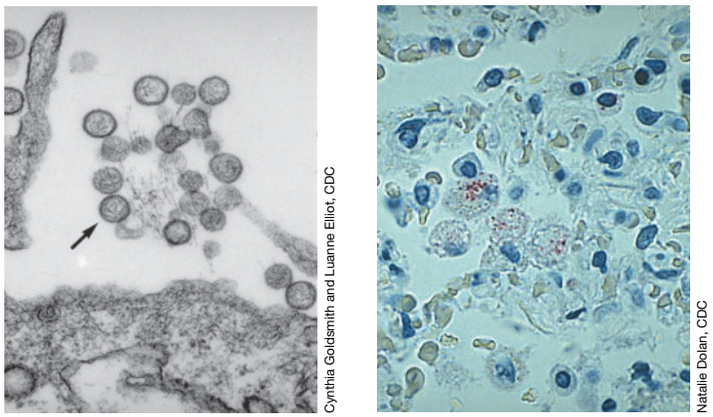
31.2 Hantavirus and Hantavirus Syndromes

Hantaviruses cause two severe, emerging diseases, **hantavirus pulmonary syndrome (HPS)**, an acute respiratory and cardiac disease, and **hemorrhagic fever with renal syndrome (HFRS)**, an acute disease characterized by shock and kidney failure. Both diseases are caused by hantaviruses transmitted from infected rodents. Hantavirus is named for Hantaan, Korea, the site of a hemorrhagic fever outbreak where the virus was first recognized as a human pathogen.

Symptoms and Pathology of Hantavirus Syndromes

Hantaviruses are enveloped viruses with single-stranded minus-sense RNA genomes arranged in segments (Figure 31.3*a*; Section 10.9); hantaviruses are related to other hemorrhagic fever viruses such as Lassa fever virus and Ebola virus (Section 30.12). Hantaviruses infect rodents including mice, rats, lemmings, and voles, without causing disease. The virus is transmitted from these reservoirs to humans by inhalation of virus-contaminated rodent excreta. Humans are accidental hosts and are infected only when they come into contact with rodents, their waste, or their saliva.

HPS is characterized by a sudden onset of fever, muscle pain, a reduction in the number of blood platelets along with an increase in the number of circulating leukocytes, and hemorrhaging. Death (if it occurs) takes several days, and is usually a result of systemic shock and cardiac complications precipitated by leakage of fluid into the lungs, causing suffocation and heart failure. These symptoms are typical of hantaviruses, but other symptoms such



(a) (b)

Figure 31.3 Hantavirus. *(a)* A transmission electron micrograph of the Sin Nombre hantavirus. The arrow indicates one of several virions that are about 100 nm in diameter. *(b)* Immunofluorescent staining of Andes hantavirus antigens in alveolar macrophages. Each granular dark blue–stained area indicates cellular infection of an individual macrophage that contains many hantavirus virions (each cell is about 15 μm in diameter).

as kidney failure are common, depending on the strain of virus causing the disease. HFRS is characterized by intense headache, back and abdominal pain, renal dysfunction, and various hemorrhagic complications. HFRS strains are more prevalent in hantavirus outbreaks in Eurasia, whereas HPS strains are more prevalent in the Americas and elsewhere in the world. HPS strains typically show a significantly higher mortality rate than HFRS strains and are found in rodents elsewhere in the world outside the Americas.

Hantaviruses can be cultured in the laboratory, but because of the danger involved, they must be handled with biosafety level 4 (BSL-4; Section 28.1) precautions. In the world of infectious diseases, hantavirus, Ebola, and other BSL-4 viral pathogens are considered "the worst of the worst" and are thus handled in the United States by the Special Pathogens Branch of the Centers for Disease Control and Prevention in Atlanta (Georgia, USA).

Epidemiology, Diagnosis, and Prevention of Hantavirus Syndromes

A significant HPS outbreak in the United States occurred near the Four Corners region of Arizona, Colorado, New Mexico, and Utah in 1993. The outbreak resulted from an enlarged population of deer mice in the spring of 1993. The previous winter was mild and was followed by abundant spring rains, triggering unusually high food levels for the mice. The HPS outbreak caused 27 deaths among 48 infected people (56% mortality), illustrating the potential danger of outbreaks due to pathogens that can be directly transmitted from animal reservoirs. In total from 1993 through 2015, there have been 659 cases of HPS in the United States, with 235 deaths (36%), mostly in western states. On a global basis, it is estimated that 200,000 infections occur annually, chiefly in China, Korea, and Russia, but mortality rates are typically very low.

Hantavirus syndromes can be diagnosed using immunological techniques that identify anti-hantavirus antibodies in a blood sample. These include immunoassays (Figure 31.3*b* and Section 28.6) that detect both exposure to the virus and the strength of the immune response. The presence of the viral RNA genome from circulating virions can also be detected using RT-PCR (Sections 12.1 and 28.8) on patient tissue or blood samples.

There is no virus-specific treatment or vaccine for hantavirus diseases. Treatment amounts to isolation, rest, rehydration, and alleviation of other symptoms. Hantavirus infection can be prevented by avoiding rodent contact and rodent habitat. Destruction of mouse habitat, restricting food supplies (for example, keeping human food in sealed containers), and aggressive rodent extermination measures are the only effective controls because areas that have experienced a hantavirus outbreak have a high proportion of mice that carry the virus, animal surveys have shown.

MINIQUIZ

- Why are hantaviruses considered a major public health problem in the United States?
- Describe the spread of hantaviruses to humans. What are some effective measures for preventing infection by hantaviruses?

II • Arthropod-Transmitted Bacterial and Viral Diseases

Pathogens can be spread to new hosts from the bite of an infected arthropod. In the bacterial and viral diseases we consider here—the rickettsial illnesses; yellow and dengue fevers; Lyme, Chikungunya, and Zika virus diseases; and plague—humans are only *accidental hosts* for the pathogen. The *reservoir* of the pathogen is the arthropod vector. Nevertheless, the diseases can be devastating and often fatal.

31.3 Rickettsial Diseases

The **rickettsias** are small *Bacteria* that live an obligate intracellular existence and are associated with bloodsucking arthropods such as fleas, lice, or ticks. We discussed the biology of rickettsias in Section 16.1. Of the diseases that rickettsias can cause in humans and other vertebrates, the most important are *typhus fever, spotted fever rickettsiosis* (*Rocky Mountain spotted fever*), and *ehrlichiosis*. Rickettsias have not been cultured in artificial culture media but can be grown in laboratory animals, ticks and lice, mammalian tissue culture cells, and the yolk sac of chick embryos (see Figure 31.6*b*). In animals, growth takes place primarily in phagocytes, such as macrophages.

Rickettsias are divided into three groups based on the clinical diseases they cause. The groups are (1) the *typhus group*, such as *Rickettsia prowazekii*; (2) the *spotted fever group*, such as *Rickettsia rickettsii*; and (3) the *ehrlichiosis group*, characterized by *Ehrlichia chaffeensis*.

The Typhus Group: *Rickettsia prowazekii*

Typhus is transmitted from person to person by the common body or head louse (Figure 31.4*a*), and humans are the only known mammalian host. During World War I, a typhus epidemic spread throughout Eastern Europe and caused almost 3 million deaths. Typhus has historically been a problem among troops in wartime.

(a)

(b)

Figure 31.4 Arthropod vectors of rickettsial diseases. *(a)* The female body louse, about 3 mm long, can carry *Rickettsia prowazekii*, the agent that causes typhus. In addition, the body louse can carry *Borrelia recurrentis*, the agent of relapsing fever, and *Bartonella quintana*, the agent of trench fever. *(b)* The American dog tick that carries *Rickettsia rickettsii*, the causative agent of Rocky Mountain spotted fever, is about 5 μm long, but can expand to three times this size when engorged with blood.

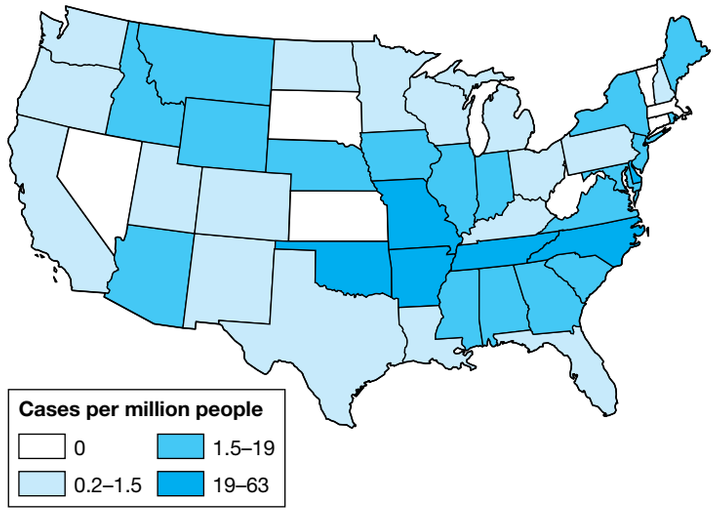


Figure 31.5 Spotted fever rickettsiosis (Rocky Mountain spotted fever) in the United States, 2010. Despite the name, cases of Rocky Mountain spotted fever are currently concentrated in the eastern and mid-South states west to Oklahoma.

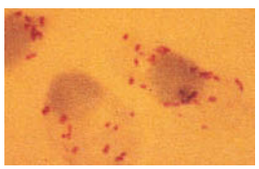
Because of the unsanitary, cramped conditions characteristic of wartime military operations, infected lice can spread easily among soldiers with devastating results. Up until World War II, typhus caused more military deaths than did combat.

Cells of *R. prowazekii* are introduced through the skin when a puncture caused by a louse bite becomes contaminated with louse feces that contain the rickettsial cells. During an incubation period of 1–3 weeks, the organism multiplies inside cells lining the small blood vessels. Symptoms of typhus (fever, headache, and general body weakness) then begin to appear. Several days later, a characteristic rash is observed in the armpits and generally spreads over the body, except for the face, palms of the hands, and soles of the feet. Complications from untreated typhus include damage to the central nervous system, lungs, kidneys, and heart. Epidemic typhus has a mortality rate of as much as 30%. Tetracycline and chloramphenicol are most commonly used to control infections caused by *R. prowazekii*. *Rickettsia typhi*, the organism that causes murine typhus, is another important pathogen in the typhus group and can also infect humans. A typhus vaccine is available but is typically only administered to those traveling to typhus endemic areas.

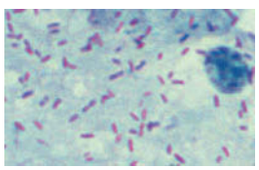
The Spotted Fever Group: *Rickettsia rickettsii*

Spotted fever rickettsiosis, commonly called *Rocky Mountain spotted fever* (*RMSF*), was first recognized in the western United States about 1900 but is more prevalent today in the central and mid-South region (**Figure 31.5**). RMSF is caused by *R. rickettsii* and is transmitted to humans by various ticks, most commonly the dog tick (Figure 31.4*b*) and wood ticks. Over 2000 people acquire RMSF yearly in the United States, nearly double the number reported in 2002, which is likely due to increased human activities in tick-infested areas. Fatalities in treated patients occur in less than 1% of those infected. Humans acquire the pathogen from the bite of an infected tick; rickettsial cells are present in the salivary glands of the tick and in the ovaries of female ticks.

Cells of *R. rickettsii*, unlike other rickettsias, grow within the nucleus of the host cell as well as in host cell cytoplasm (**Figure 31.6*a, c***). Following an incubation period of 3–12 days, characteristic symptoms,



(a)



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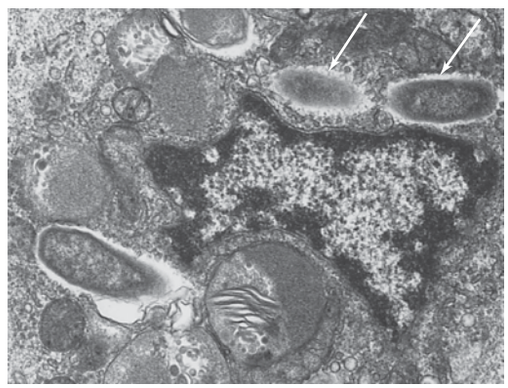

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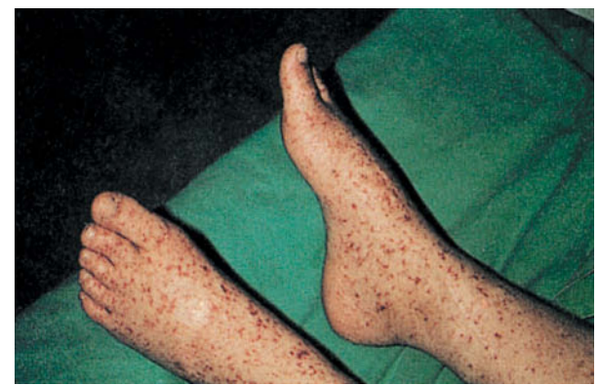


(d)

Figure 31.6 *Rickettsia rickettsii* and spotted fever rickettsiosis. *(a)* Cells of *R. rickettsii*, growing in the cytoplasm and nucleus of tick hemocytes and *(b)* in chicken egg yolk sacs; cells are about 0.4 μm in diameter. *(c)* Transmission electron micrograph of *R. rickettsii* (arrows) in a granular hemocyte of an infected wood tick. *(d)* Rash of spotted fever rickettsiosis on the feet. The whole-body rash is indicative of spotted fever rickettsiosis and helps distinguish it from typhus, in which the rash does not cover the whole body.

including fever and a severe headache, occur. A few days later, a systemic rash breaks out (Figure 31.6*d*), generally accompanied by gastrointestinal problems such as diarrhea and vomiting. The clinical symptoms of RMSF persist for over 2 weeks if the disease is untreated. Tetracycline or chloramphenicol generally promotes a prompt recovery from RMSF if administered early in the course of the infection. Mortality in untreated cases of RMSF resembles that of typhus, up to 30%. No effective vaccine against RMSF is currently available.

Ehrlichiosis and Tickborne Anaplasmosis

Ehrlichia and related genera (Section 16.1) are responsible for two emerging tickborne diseases in the United States, *human monocytic ehrlichiosis* (*HME*) and *human granulocytic anaplasmosis* (*HGA*). The pathogens that cause HME are *Ehrlichia chaffeensis* and *Rickettsia sennetsu*, and those that cause HGA are *Ehrlichia ewingii* and *Anaplasma phagocytophilum*.

The onset of these clinically indistinguishable rickettsial diseases is characterized by flulike symptoms that can include fever, headache, malaise, changes in liver function, and a reduction in white blood cell numbers. Peripheral blood leukocytes such as monocytes have visible inclusions of rickettsial cells, a diagnostic indicator for the diseases (**Figure 31.7*a***). The symptoms, except for the inclusions, are similar to other rickettsial infections, and can range from subclinical to fatal. Long-term complications for progressive untreated cases may include respiratory and renal insufficiency and serious neurological involvement.

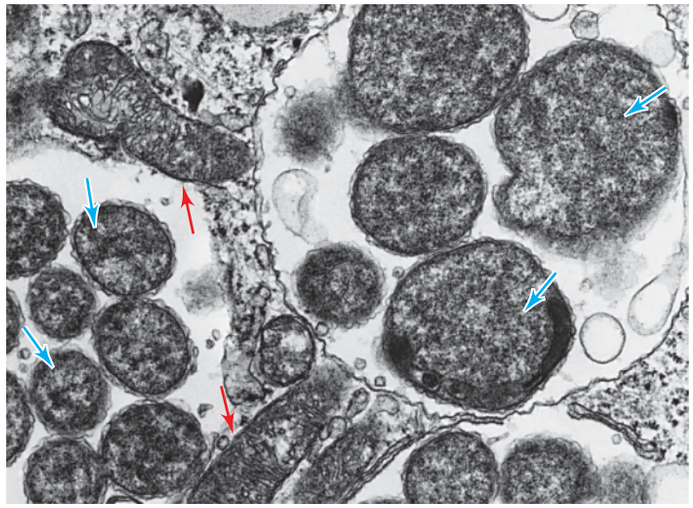
HGA and HME are spread by ticks of various species, and mammalian reservoirs of the pathogens include deer, some rodents, and humans. In the United States, HGA occurs primarily in the upper Midwest and coastal New England, while HME is concentrated in the lower Midwest and the East Coast; together, almost 2000 cases are reported each year, with cases of HGA predominating. Diagnosis of rickettsial syndromes is not straightforward because the rash observed can be mistaken for other diseases, such as scarlet fever, or even measles or syphilis. Confirmation of a rickettsial disease requires immunological tests, including fluorescent antibodies or immunoassays, or PCR-based analyses that detect pathogen DNA.

Prevention of HGA and HME is best achieved either by avoiding tick habitat or by wearing tick-proof clothing and applying insect repellents containing diethyl-*m*-toluamide (DEET). It is also good practice to examine yourself carefully for ticks after hiking in tick habitat and to remove any ticks immediately, taking care to remove all tick mouthparts if the tick has already attached. Doxycycline, a tetracycline antibiotic, is the drug of choice for the treatment of HGA and HME. Vaccines are currently unavailable for the prevention of HGA and HME.

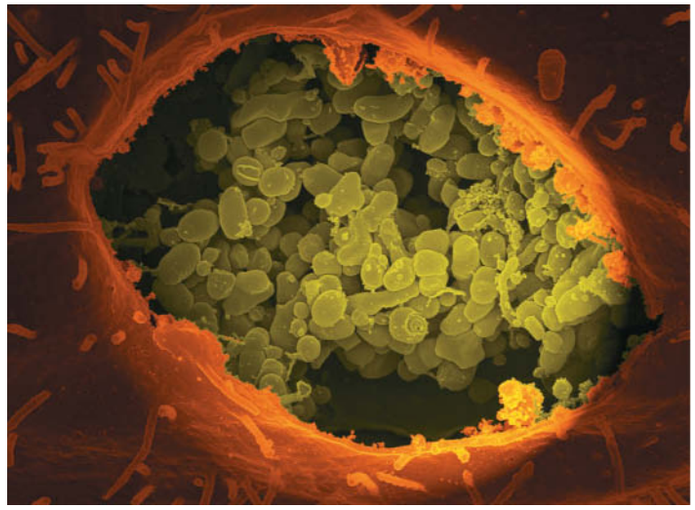
Q Fever

Q fever (the Q stands for "query") is a pneumonia-like infection caused by the intracellular parasite *Coxiella burnetii* (Figure 31.7*b*), a bacterium related to the rickettsias (Section 16.1). Although not transmitted to humans by an insect bite, *C. burnetii* cells are transmitted to animals such as sheep, cattle, and goats by insect bites, and from these reservoirs are transmitted to humans. Domestic animals generally have inapparent infections but may shed large quantities of *C. burnetii* cells in their urine, feces, milk, and other body fluids. Infected animals or contaminated animal products such as wool, meat, and milk are potential sources for human infection. The resulting influenza-like illness can progress to include prolonged fever, headache, chills, chest pains, pneumonia, and endocarditis (inflammation of the inner lining of the heart). In the United States, Q fever is most prevalent in rural states with large farm or ranch animal populations, and about 100–150 cases have been reported annually in recent years.

As for rickettsial infections, laboratory diagnosis of *C. burnetii* infection is typically made by immunological tests designed to measure host antibodies to the pathogen. Q fever responds well to tetracycline, and therapy should be started quickly in any suspected case to prevent endocarditis and heart valve damage. Q fever is also a potential biological warfare agent (Section 29.9).



(a)



(b)

Figure 31.7 *Ehrlichia* and *Coxiella*. *(a) Ehrlichia chaffeensis*, the causative agent of human monocytic ehrlichiosis (HME). The electron micrograph shows inclusions in a human monocyte that contains large numbers of *E. chaffeensis* cells. The blue arrows indicate bacteria in each inclusion. The *E. chaffeensis* cells are about 0.3–0.9 μm in diameter. Mitochondria are indicated by red arrows. *(b)* Colorized scanning electron micrograph of cells of *Coxiella burnetii*, the causative agent of Q fever. The *Coxiella* cells were grown in animal cell culture and are shown inside a fractured host cell. A single *C. burnetii* cell is about 0.4 μm in diameter.

Unlike its relatives in the *Rickettsia* group, the Q fever pathogen *C. burnetii* can now be grown in pure culture outside a host. This was accomplished by taking into account both the resources and conditions likely to exist in the intracellular host environment along with a careful analysis of the *C. burnetii* genome sequence to reveal the metabolic capacities and limitations of this pathogen. One major discovery gleaned from genomic analysis of the *C. burnetii* complement of cytochromes was the fact that the organism was likely to be microaerophilic (Section 5.14). And indeed, one of the major secrets to its axenic culture turned out to be to incubate cultures under low oxygen tensions, which is somewhat surprising considering that host cells should be fully oxic.

MINIQUIZ

- What are the arthropod vectors and animal hosts for typhus, spotted fever rickettsiosis, ehrlichiosis, and anaplasmosis?
- What precautions can be taken to prevent rickettsial infections?

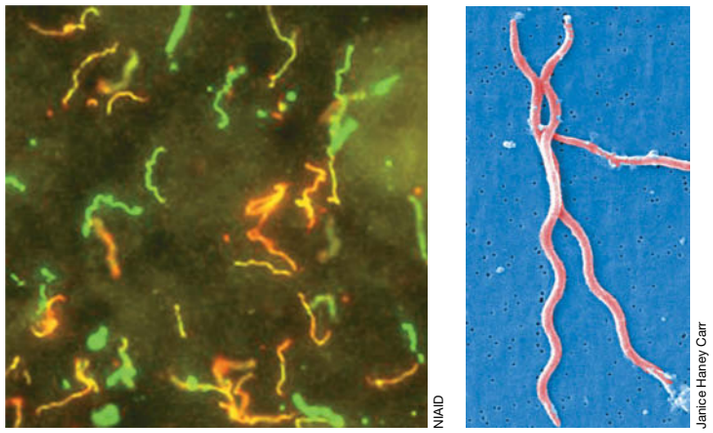
31.4 Lyme Disease and *Borrelia*

Lyme disease is a tickborne disease that affects humans and other animals. Lyme disease was named for Old Lyme, Connecticut, where cases were first recognized, and is currently the most prevalent arthropod-borne disease in the United States. Lyme disease is caused by infection with a spirochete, *Borrelia burgdorferi* (**Figure 31.8**; Section 15.19), transmitted by a tick bite. The ticks that carry *B. burgdorferi* feed on the blood of birds, domesticated animals, various wild animals, and humans. *B. burgdorferi* is of interest in a nonmedical way as well, because it is one of only a handful of *Bacteria* that contain a linear (as opposed to a circular) chromosome (Section 4.2).

Pathology, Diagnosis, and Treatment of Lyme Disease

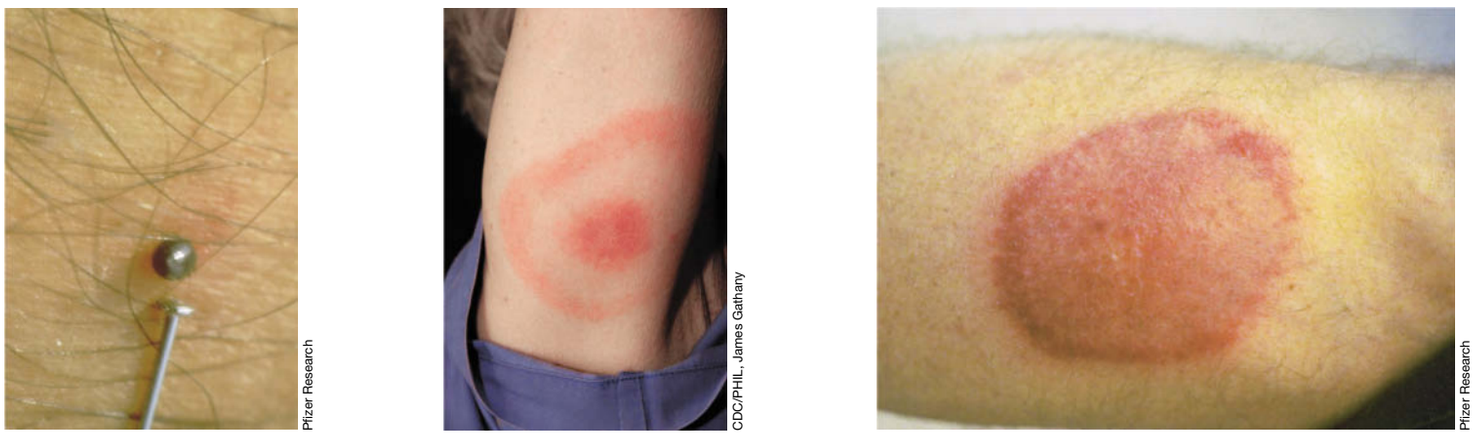
Cells of *B. burgdorferi* are transmitted to humans while the tick is obtaining a blood meal (**Figure 31.9*a***). A systemic infection develops, leading to the acute symptoms of Lyme disease: headache, backache, chills, and fatigue. In about 75% of Lyme cases, a concentric circular or "bull's-eye" rash forms within a week at the site of the tick bite (Figure 31.9*b, c*). During this acute stage, Lyme disease is readily treatable with tetracycline or penicillin.

Untreated cases of Lyme disease may progress to a chronic stage weeks to months after the initial tick bite, causing arthritis in about half of those infected. Neurological problems such as palsy, weakness in the limbs, and heart damage can also occur. In untreated cases, cells of *B. burgdorferi* infecting the central nervous system may lie dormant for long periods before causing additional chronic symptoms, including problems with vision and facial muscle movements, or seizures. Interestingly, the symptoms of chronic Lyme disease, especially neurological symptoms,



(a) (b)

Figure 31.8 The Lyme spirochete, *Borrelia burgdorferi*. *(a)* Fluorescent antibody staining (Section 28.6) of cells of *B. burgdorferi* from a Lyme rash. Two different fluorescent antibodies were used, each specific for a different *B. burgdorferi* antigen and linked to either an orange or a green fluorescent tag. If both antibodies bind, cells appear yellow. *(b)* Colorized scanning electron micrograph of cells of *B. burgdorferi.* A single cell is approximately 0.4 µm in diameter and 5–20 µm long.



(a) (b) (c)

Figure 31.9 Lyme disease infection. *(a)* A blood-engorged deer tick obtaining a blood meal from a human is the route of transmission (see Figure 31.10 for photos of deer ticks). *(b, c)* Characteristic Lyme disease rashes. The rash starts at the site of a tick bite and grows in a concentric circular fashion over a period of several days. A typical rash is about 5 cm in diameter.

mimic those of chronic syphilis, caused by a different spirochete, *Treponema pallidum* (Sections 15.19 and 30.13). Unlike syphilis, however, Lyme disease is not spread person to person.

No toxins or other major virulence factors have been identified in Lyme disease pathogenesis, but the pathogen triggers a strong immune response. Antibodies to *B. burgdorferi* appear 4–6 weeks after infection and can be detected by various immunological assays. However, because antibodies to *B. burgdorferi* antigens persist for years after infection, the presence of these antibodies does not necessarily indicate a recent infection. A PCR assay (Sections 12.1 and 28.8) is also in use to detect *B. burgdorferi* DNA in body fluids and tissues. In practice, however, Lyme disease is typically diagnosed from clinical symptoms and only confirmed later by laboratory assays. If a patient has Lyme disease symptoms and other findings such as facial tics or arthritis, or has had recent tick exposure or exhibits the characteristic Lyme rash (Figure 31.9), a presumptive diagnosis of Lyme disease is made and antibiotic treatment is initiated.

Treatment of early-stage Lyme disease is usually with doxycycline or amoxicillin for 20 to 30 days. For patients having neurological or cardiac symptoms, the antibiotic ceftriaxone is administered intravenously because this drug crosses the blood–brain barrier and can thus kill spirochetes in the central nervous system.

Epidemiology and Prevention of Lyme Disease

White-footed field mice and other small rodents are the major mammalian reservoir of *B. burgdorferi* in the northeastern United States, a hotbed of Lyme infection (see Figure 31.11). These animals become infected from bites by the deer tick, *Ixodes scapularis* (**Figure 31.10**), although some other ticks can transmit the Lyme spirochete as well. Deer themselves are not *B. burgdorferi* reservoirs but are major reproductive hosts for the tick. Lyme disease has also been identified in Europe and Asia. In these countries, both the tick vector and the species of *Borrelia* differ from those in the United States, which shows that Lyme disease has a broad geographic distribution. But in all cases, Lyme disease is caused by related species of pathogenic *Borrelia* transmitted to humans by tick vectors.

Deer ticks are typically smaller than many other ticks, making them easy to overlook. Moreover, unlike the case with ticks that carry other tickborne diseases (Figure 31.4*b*), a very high percentage of deer ticks carry *B. burgdorferi*. Both of these factors—small vector size and high occurrence of the pathogen—undoubtedly contribute to the fact that Lyme is the most commonly reported vector-borne disease in the United States. Most cases of Lyme disease in the United States have been reported from the Northeast and upper Midwest—areas of the country where deer are abundant—but cases have been observed in nearly every state (**Figure 31.11**). The incidence of Lyme disease in the United States is significant, with over 33,000 confirmed and probable cases reported in 2014.

Figure 31.10 Deer ticks, the major vector of Lyme disease. Left to right, male and female adult ticks, nymph, and larva forms. The length of an adult female is about 3 mm. Although all forms feed on humans, the female nymphal and adult ticks are principally responsible for transmitting *Borrelia burgdorferi*.

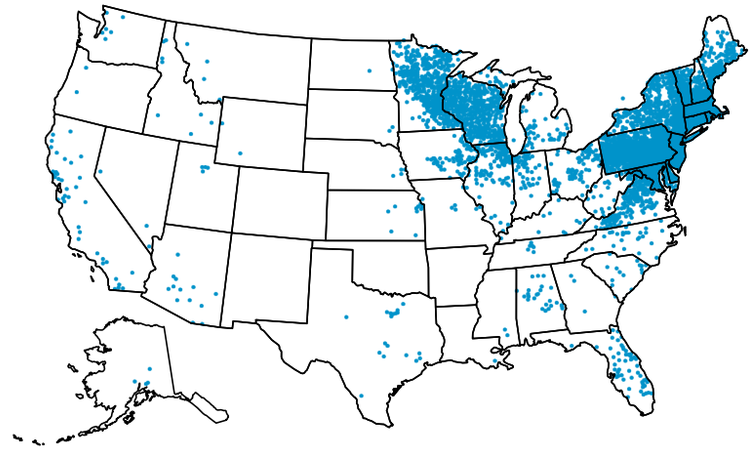


Figure 31.11 Lyme disease in the United States, 2014. Each dot represents a confirmed case. Confirmed and probable cases in 2014 totaled over 33,000, with 96% of these localized to 13 states in the upper regions of the Midwest and East Coast. Lyme disease is reported through the National Notifiable Diseases Surveillance System of the Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

As for any tickborne infection, prevention of Lyme disease begins by avoiding contact with the vector. Insect repellents containing DEET or the wearing of snug-fitting clothing is helpful, as is a thorough body exam following walks in tick-infested environments. Lyme disease vaccines are available for domestic animals, but no human Lyme disease vaccine is currently in use.

MINIQUIZ

- What are the primary symptoms of Lyme disease?
- In the United States, where is Lyme disease most prevalent?
- Outline methods for prevention of *Borrelia burgdorferi* infection.

31.5 Yellow Fever, Dengue Fever, Chikungunya, and Zika

Several arthropod-transmitted diseases are caused by flaviviruses. These are single-stranded plus-sense RNA viruses (Section 10.8) transmitted by the bite of an infected arthropod. Because of this characteristic mode of transmission, these viruses are also called *arboviruses* (*ar*thropod-*bo*rne viruses).

Many serious human diseases are caused by arboviruses including various types of encephalitis and hemorrhagic fevers. Here we consider two potentially fatal flavivirus diseases common in some

developing countries, yellow fever and dengue. Both viruses are transmitted by the same vector, mosquitoes of the genus *Aedes* (**Figure 31.12**), and some of the disease symptoms are similar. We also consider Zika and Chikungunya, both emerging viral diseases transmitted by mosquitoes.

Yellow Fever

Yellow fever is an endemic disease of tropical and subtropical climates, especially in Latin America and Africa. Brazil, Colombia, Venezuela, and parts of Bolivia and Peru, along with most countries in sub-Saharan central Africa, experience the greatest incidence. Yellow fever is absent from the United States except in unvaccinated individuals who contract the disease through travel to an endemic area. Yellow fever virus is related to dengue virus (see later), West Nile virus (Section 31.6), and certain encephalitis viruses. Yellow fever is one of only a handful of infectious diseases for which isolation and quarantine are practiced (Section 29.5). In the case of yellow fever, although the disease is not transmitted person to person, isolation of active cases prevents local mosquitoes from taking a blood meal from the infected individual and transmitting the disease to others.

Following a bite from an infected mosquito, the yellow fever virus replicates in lymph nodes and certain immune system cells and eventually travels to the liver. Once a person is infected, symptoms range anywhere from none to major organ failure and death. Most infected individuals display a mild fever with accompanying chills, a headache and back pains, nausea, and other symptoms that are not diagnostically useful. Presumably these are cases in which the immune system has the infection under control. However, in about one in five yellow fever cases, the disease enters its toxic phase, characterized by jaundice (thus the name, *yellow fever*) and by hemorrhaging from the mouth, eyes, and gastrointestinal tract. This triggers the onset of bouts of bloody vomit, and if bleeding continues, it leads to toxic shock and multiple organ failure. About 20% of cases that reach this stage are fatal. Humans and nonhuman primates are the main reservoirs for the yellow fever virus.

Yellow fever is fully preventable by an effective vaccine. A yellow fever vaccine was developed in the 1930s and widely used by military and support personnel in tropical battlefields. Historically, the disease has been controlled by a combination of vaccination and elimination of both the vector (mosquito) population by chemical agents and vector breeding grounds by draining swamps and low-lying wetlands in endemic areas.

The yellow fever vaccine is highly recommended for those traveling to endemic areas, and many countries require proof of vaccination for anyone entering their country from a foreign country where yellow fever is endemic. In addition, the World Health Organization (WHO) has initiated a mass vaccination program in Africa. Despite the availability of a vaccine, the WHO estimates that each year nearly 200,000 cases of yellow fever occur, mostly unreported, and that about 15% of all cases are fatal. No treatment for yellow fever is known. However, once the disease is diagnosed, typically by detecting anti–yellow fever virus antibodies in a blood sample, the patient is isolated and prescribed rest and drugs to control symptoms. Recovery without entering the toxemia stage is due to the immune response.

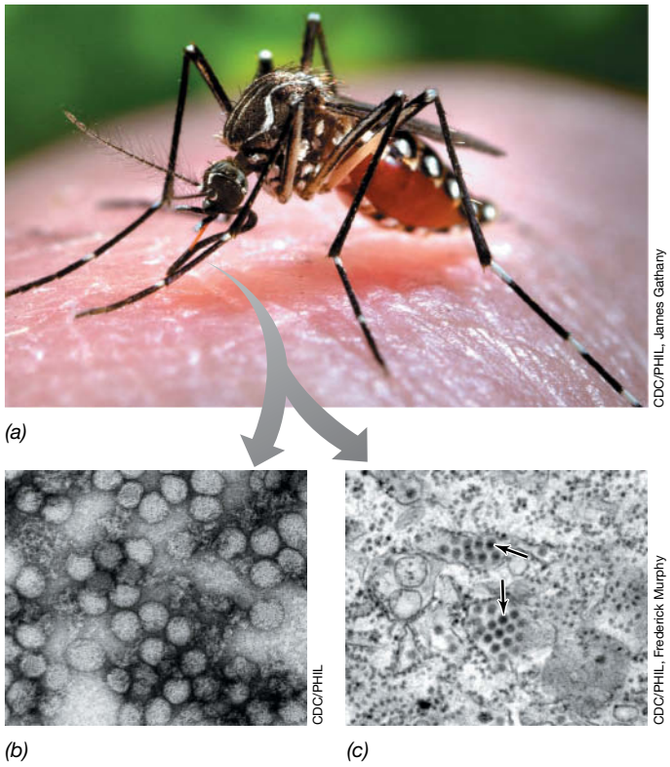


Figure 31.12 Yellow fever and dengue fever. *(a)* Yellow and dengue fever viruses are both transmitted by the bite of an infected *Aedes aegypti* mosquito. Transmission electron micrographs of *(b)* yellow fever virus and *(c)* dengue fever virus (arrows, in a tissue specimen). Both yellow and dengue fever viruses are about 50 nm in diameter and are plus-sense RNA viruses that replicate by way of polyprotein formation, as in poliovirus (Figure 10.18).

Dengue Fever

Like yellow fever, dengue (pronounced deng-gay) fever is transmitted by mosquitoes of the genus *Aedes* (Figure 31.12) and is a disease of tropical and subtropical regions. Up to 100 million cases of dengue are estimated worldwide per year with concentrations in Mexico, Latin America, India, Indonesia, and Africa (Figure 29.11).

Dengue begins with a high fever and headache or joint pains and in some patients, severe eye pain and a systemic rash. Most infected individuals show self-improvement within a week and no further symptoms, presumably because of an immune response to the dengue virus. But, as for yellow fever, a dengue infection can take a more severe course of events and proceed to *dengue hemorrhagic fever*. This condition is characterized by severe symptoms that can include bleeding from the nose and gums, bloody vomit and/or feces, intense abdominal pain, respiratory distress, and a general feeling of malaise. The blood pressure of a dengue patient can drop dramatically during the hemorrhagic fever stage, and a small percentage of these cases are fatal. Treatment for dengue is primarily to relieve symptoms, particularly dehydration from loss of blood and other fluids. Unlike yellow fever, no effective vaccine exists for dengue, and thus rest and symptom relief, even in cases of dengue hemorrhagic fever, is the only effective treatment.

Dengue can be controlled by eliminating either the vector or contact with the vector. Extensive chemical spraying for mosquito eradication was widely practiced in urban centers of the southern United States and kept dengue in check in the twentieth century. Now, however, spraying programs are less common and global climate change is moving tropical temperature patterns northward. In response, the *Aedes* mosquito has become entrenched in southern and central regions of the United States. Besides *Aedes aegypti* (Figure 31.12), the Asian tiger mosquito (*Aedes albopictus*), which is spreading quickly in the United States, also carries the dengue virus. Drainage of small puddles of water, such as those in discarded tires or other water traps, removes mosquito breeding grounds and greatly reduces the opportunities for a dengue outbreak. Personal protection from mosquito bites by using effective insect repellents and clothing is also a proven means of preventing infection.

The WHO estimates that nearly a half million cases of dengue hemorrhagic fever occur yearly with about 22,000 being fatal. Cases of dengue in the United States are rare, and virtually all of them are imported from endemic areas. Dengue is a prime example of an *emerging disease* (Section 29.7), as cases were geographically restricted until the mid-twentieth century when global commerce is thought to have transmitted species of the *Aedes* mosquito beyond their original range.

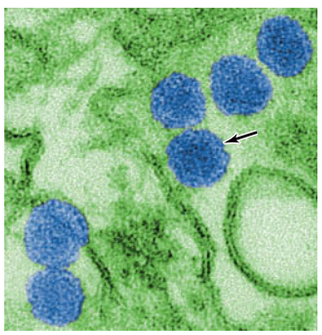
Zika and Chikungunya Disease

Zika and Chikungunya are both typically mild viral diseases transmitted by the same mosquito vector. Zika virus disease is a typically mild infection characterized by headache, fever, joint pain, and general malaise; a rash is occasionally seen. The disease is caused by the Zika virus (**Figure 31.13*a***), a relative of the dengue virus and also transmitted by mosquitoes. Zika first emerged over 65 years ago in the Zika forest (Uganda), and occasional small outbreaks occurred periodically in west central Africa and Indonesia. However, in 2015, Zika appeared in Brazil, and by 2016, outbreaks of Zika virus disease were reported in the United States, primarily in individuals who had traveled to areas with endemic disease. However, a major outbreak in the U.S. territory of Puerto Rico has been linked to local mosquito-borne transmission, and the fear is that the disease will spread northward within the range of the *Aedes* mosquito. Zika infections were reported in Florida in late 2016 and will likely appear in other regions of the southern United States.

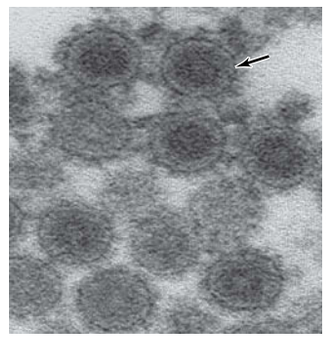
Besides vectorborne transmission, Zika can be transmitted through sexual contact and by contaminated blood and, of most concern, from mother to fetus. The incidence of brain abnormalities and other birth defects in infants born to Zika-infected mothers is significantly higher than in those born to uninfected mothers and so it is thought that Zika in some way affects development of the fetus. It is known that the Zika virus readily infects a type of neural cell that eventually forms the cerebral cortex, a major part of the brain that governs intellectual capacity, and this likely leads to the brain defects observed in Zika-infected newborns. This danger has led to advisories for pregnant women to take great precautions to avoid contact with mosquitoes during the entire pregnancy period. Other than in pregnant women, Zika virus disease seems to be a rather mild, self-limiting infection. However, in rare instances, Zika infection may trigger Guillain–Barré syndrome, an autoimmune disease (Section 27.9) caused by an infection with any of several different viruses and bacteria in which the immune system attacks the peripheral nervous system. For more on the Zika virus, see page 310.

Too little is known about the Zika virus and the various conditions it can or may cause to draw firm conclusions about the seriousness of this threat to public health. Deaths directly attributable to a Zika infection have been extremely rare, and thus the pathogen seems to be of only passing concern to the general public, even in the typical high-risk groups for infectious diseases such as the very young or very old. However, the birth defect connection is extremely serious. At this writing, it seems that pregnant women (or those trying to get pregnant, as Zika can also be transmitted by sexual intercourse) are the only major group known to be at risk from Zika infection.

Like Zika, Chikungunya disease is caused by single-stranded plus-sense RNA virus (Figure 31.13*b*), but the virus is not otherwise closely related to the Zika, dengue, and yellow fever viruses. Chikungunya virus is transmitted by species of *Aedes* mosquitoes and is currently endemic in South and Central America, Southeast Asia, central Africa, and Indonesia. Thus far, cases of Chikungunya in the United States have been limited to travelers returning from endemic areas and in 2015, a total of 679 confirmed cases were reported. As for Zika, mortality in Chikungunya disease is rare, about 0.1% of all cases. The symptoms of Chikungunya are mild and self-limiting and the immune response to the virus is strong, conferring active immunity against reinfection. Unlike with Zika, no direct connection between Chikungunya viral infection and birth defects has been observed because Chikungunya virus is not transmitted from mother to fetus.



(a)



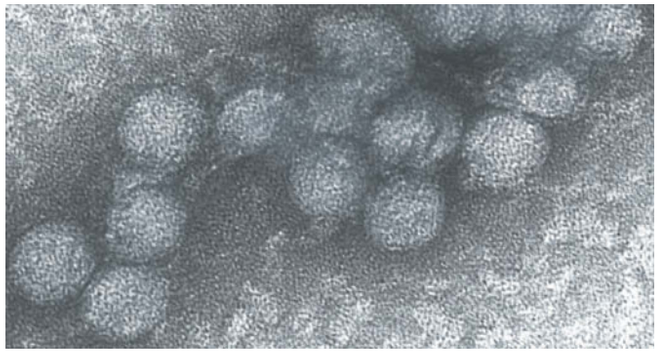
(b)

Figure 31.13 Zika and Chikungunya viruses. Both viruses contain single-stranded plus-sense RNA genomes and are surrounded by an envelope (Sections 8.1, 8.2, and 10.8). *(a)* Colorized transmission electron micrograph of virions of the Zika virus embedded in a tissue sample. A single virion (shown in blue, arrow) is about 40 nm in diameter. *(b)* Transmission electron micrograph of virions of Chikungunya virus (arrow). A virion is about 50 nm in diameter.

MINIQUIZ

- Identify the vector and reservoir for yellow fever and dengue viruses.
- Contrast the procedures for preventing infection in yellow and dengue fevers.
- Why is Zika virus disease considered dangerous even though it rarely kills?

(a)



(b)

Figure 31.14 West Nile virus. *(a)* The mosquito *Culex quinquefasciatus*, shown here engorged with human blood, is a West Nile virus vector. *(b)* An electron micrograph of the West Nile virus. The icosahedral virion is about 40–60 nm in diameter and contains a plus-sense single-stranded RNA genome.

31.6 West Nile Fever

West Nile virus (WNV) causes **West Nile fever**, a human viral disease that is transmitted through the bite of a mosquito and thus is a seasonal disease. WNV is a flavivirus, as are the yellow fever, dengue, and Zika viruses (Section 31.5), and has an enveloped capsid (**Figure 31.14*b***) containing a plus-sense single-stranded RNA genome (↻ Section 10.8). The virus can invade the nervous system of its warm-blooded hosts, which include some species of both birds and mammals.

WNV Transmission and Pathology

WNV causes active disease in over 100 species of birds and is transferred to hosts by the bite of an infected mosquito. Over 40 species of mosquito can carry the virus including *Culex* species (Figure 31.14*a*), common in central and eastern states of the United States and in urban centers throughout the country. Infected birds develop a systemic viral infection (viremia) that is often fatal. Mosquitoes feeding on viremic birds are infected and can then infect other susceptible birds, renewing the cycle. In contrast to birds, humans and other animals are dead-end hosts for the virus because they do not develop the viremia necessary to infect mosquitoes.

Mortality rates for WNV infection are species-specific. For example, the human mortality rate from WNV is about 4% while that for horses is significantly higher, near 40%. Most human infections are asymptomatic or mild and are not reported. After an incubation period of 3–14 days, about 20% of infected individuals develop West Nile fever, a mild illness lasting 3–6 days. The fever may be accompanied by headache, nausea, muscle pain, rash, lymphadenopathy (swelling of lymph nodes), and malaise. Less than 1% of infected individuals develop serious neurological diseases such as *West Nile encephalitis* or *West Nile meningitis* from viral replication in neural tissues (**Figure 31.15**). These are more common in adults over age 50, and the neural effects may be permanent. About 5% of West Nile cases that progress to these forms are fatal. Diagnosis of WNV disease includes assessment of clinical symptoms followed by confirmation by immunological tests that detect WNV antibodies in blood.

Control and Epidemiology of WNV

Human WNV disease was first identified in the West Nile region of Africa in 1937 and spread from there to Egypt and Israel. In the 1990s there were WNV outbreaks in horses, birds, and humans in African and European countries. The first cases of WNV were reported in the United States in the Northeast in 1999, but in the years since, the disease has spread to every state (**Figure 31.16**). In the 1999–2014 period, the number of reported WNV cases per year has fluctuated wildly, from as few as about 20 to as many as 9800. The major U.S. foci of infection appear to be in the south central states and the Great Plains from the Texas coast to the Canadian border (Figure 31.16). West Nile disease is now enzootic in the bird population in the United States and in only low incidence in the human population, its accidental host.

Control of WNV illness is much the same as for other vectorborne diseases: Limit exposure to mosquitoes using insect repellents or wear tight-fitting clothing. Spraying for mosquitoes has limited effectiveness, but removal of mosquito breeding grounds, particularly sources of standing water, is very helpful in controlling mosquito populations. A veterinary WNV vaccine is widely used in

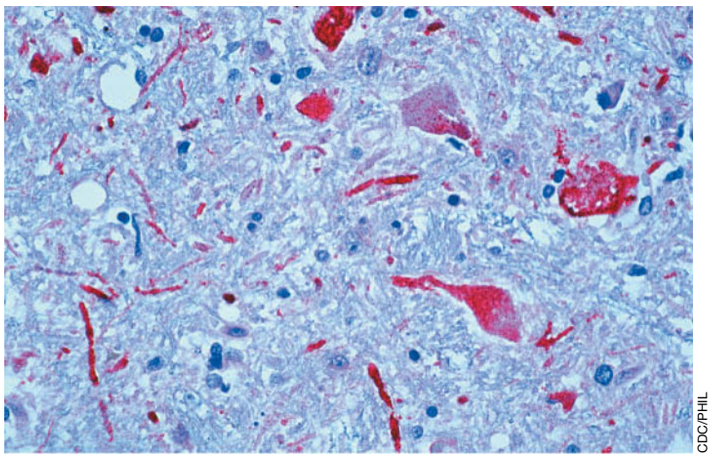


Figure 31.15 West Nile encephalitis. Brain section from a West Nile encephalitis victim. Red areas in the tissue are neurons containing West Nile virus as detected using an immunofluorescent staining technique (↻ Section 28.6).

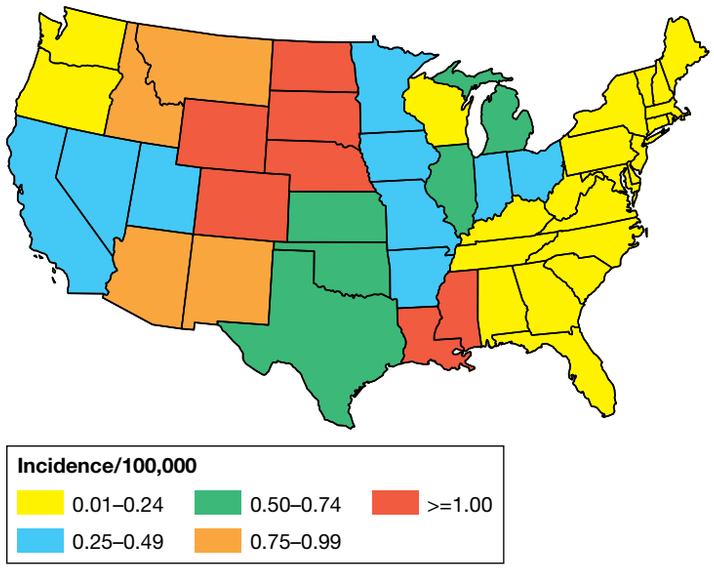


Figure 31.16 Average annual incidence of West Nile disease in the United States, 1999–2014. In 2015, 2060 cases of human West Nile disease were reported, resulting in 119 deaths (5–6% mortality). West Nile virus is now endemic in mosquitoes and birds throughout the United States. Data are from the Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

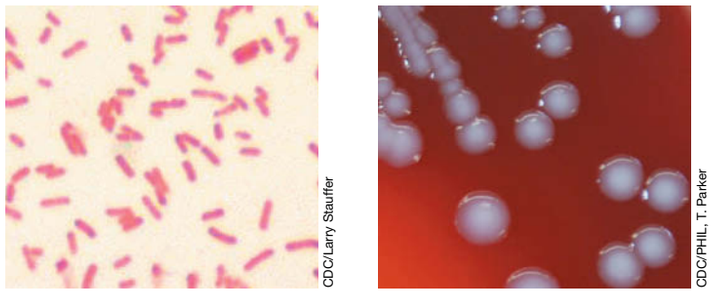
horses where the mortality risk demands it, but no human WNV vaccine is currently available.

MINIQUIZ

- Identify the vector and reservoir for West Nile virus.
- Trace the progress of West Nile virus in the United States since 1999.

31.7 Plague

Plague has caused more human deaths than any other infectious disease except for malaria and tuberculosis. Plague is primarily a zoonosis of wild rodents, but humans can become accidental hosts when rodent populations experience a die-off. Plague is caused by *Yersinia pestis*, a gram-negative, facultatively aerobic, rod-shaped, and encapsulated enteric bacterium (*Gammaproteobacteria*, Section 16.3) that is easily grown in laboratory culture (Figure 31.17).



(a) (b)

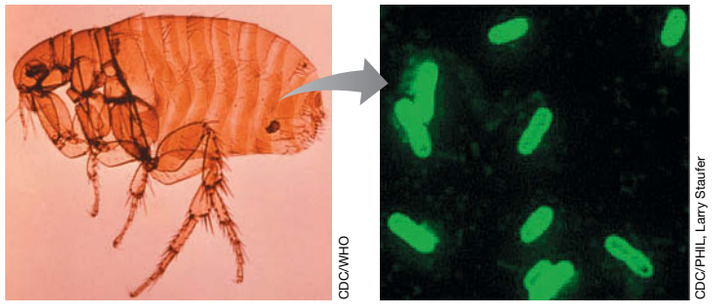
Figure 31.17 *Yersinia pestis*. *(a)* Gram stain of cells of *Yersinia pestis*. The cells are about 0.8 μm in diameter. *(b)* Colonies of *Y. pestis* grown on blood agar.

Pathology and Treatment of Plague

The pathogenesis of plague is not clearly understood, but cells of *Y. pestis* produce several virulence factors that contribute to the disease process. The V and W antigens in *Y. pestis* cell walls are protein–lipoprotein complexes that inhibit immune cell phagocytosis. *Murine toxin*, an exotoxin (Section 25.6) that is lethal for mice, is produced by virulent strains of *Y. pestis*. Murine toxin is a respiratory inhibitor that causes systemic shock, liver damage, and respiratory distress in mice. The toxin likely plays a role in human plague as well, because these symptoms are common in plague patients. *Y. pestis* also produces a highly immunogenic endotoxin (Section 25.8) that may play a role in the disease process.

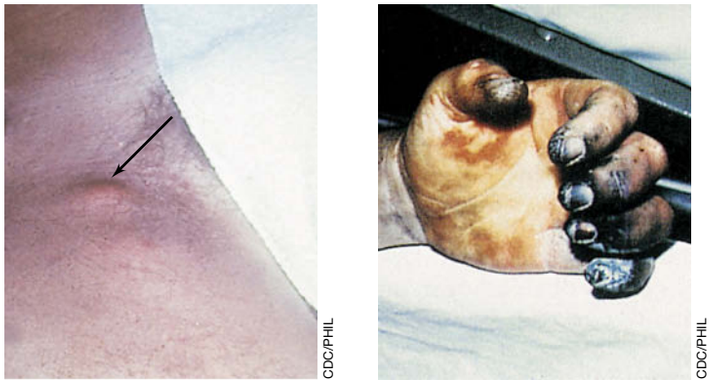
Plague can occur in several forms (see Figures 31.19 and 31.20). *Sylvatic plague* is enzootic among wild rodents. Plague is transmitted by several species of fleas, a main one being the rat flea *Xenopsylla cheopis* (Figure 31.18*a*). Fleas ingest *Y. pestis* cells in a blood meal and the bacterium multiplies in the flea's intestine. From there, the infected flea transmits the disease to rodents or humans in the next bite. The most common form of plague in humans is *bubonic plague*. In this case, cells of *Y. pestis* travel to the lymph nodes, where they replicate and cause swelling. The regional and pronounced swollen lymph nodes are called *buboes*, and the disease gets its name from these structures (Figure 31.19*a*). The buboes become filled with *Y. pestis* cells, and the bacterium's capsule prevents phagocytosis and destruction by cells of the immune system. Secondary buboes form in peripheral lymph nodes, and cells eventually enter the bloodstream, causing septicemia. Multiple local hemorrhages produce dark splotches on the skin and eventual tissue necrosis, giving plague its historical name, the "Black Death" (Figure 31.19*b*). If the infection is not treated quickly, the symptoms of plague (lymph node swelling and pain, prostration, shock, gangrene, and delirium) usually progress and cause death within 3–5 days.

Pneumonic plague occurs when cells of *Y. pestis* are either inhaled directly or reach the lungs via the blood or lymphatic circulation. Significant symptoms are usually absent until the last day or two of the disease when large amounts of bloody sputum are produced. Greater than 90% of untreated cases of pneumonic plague



(a) (b)

Figure 31.18 The rat flea, a major vector of plague. *(a)* The rat flea *Xenopsylla cheopis* carries cells of *Yersinia pestis*. The bacterium replicates in the flea gut and *(b)* cells of *Y. pestis* are transmitted to a host in a flea bite. The rat flea was the major vector for the pandemics of plague that ravaged medieval Europe in the fourteenth century. Cells in part *b* were stained with a fluorescent antibody prepared against *Y. pestis* cell surface antigens.



(a) (b)

Figure 31.19 Plague in humans. *(a)* A bubo formed in the groin. *(b)* Gangrene and sloughing of skin in the hand of a plague victim. Human plague can manifest itself in three different forms: bubonic, pneumonic, and septicemic (see Figure 31.20).

result in death within 48 h. Moreover, pneumonic plague is highly contagious and can spread rapidly from person to person if those infected are not immediately isolated. *Septicemic plague* is the rapid spread of *Y. pestis* throughout the body via the bloodstream without the formation of buboes and is so severe that it usually causes death before a diagnosis can be made.

Bubonic plague can be successfully treated with streptomycin or gentamicin, administered by injection. Alternatively, doxycycline, ciprofloxacin, or chloramphenicol may be given intravenously. If treatment is started promptly, mortality from bubonic plague can be reduced to less than 5%. Pneumonic and septicemic plague can also be treated, but these forms progress so rapidly that antibiotic therapy, even if begun when symptoms first appear, is usually too late.

Plague Epidemiology and Control

Sylvatic plague is enzootic in a variety of rodents including ground squirrels, prairie dogs, chipmunks, and mice; rats are the primary hosts in urban communities and were typically the hosts in episodes of sylvatic plague that triggered human pandemics during the Middle Ages. Fleas are intermediate hosts and vectors for plague (Figure 31.18), spreading the disease between rodent hosts and humans (**Figure 31.20**). Most infected rats or other rodents die soon after symptoms appear, but a small proportion of survivors develop a chronic infection, providing a persistent reservoir of *Y. pestis* cells to fuel new outbreaks.

Plague is endemic in developing countries in Africa, Asia, the Americas, and in south-central Eurasia; most cases occur in sub-Saharan Africa. Pandemic plague was historically associated with unsanitary surroundings, a major factor supporting large rat populations. In sparsely populated rural areas, this is not so great a problem as the disease runs its course when the rodent population dies off, leaving a shortage of hosts. But in urban centers where alternative hosts (humans) are plentiful, an outbreak of sylvatic plague can set the stage for a human plague epidemic. In the United States only a handful of cases of plague are diagnosed annually, mostly in southwestern states (New Mexico, Colorado, and Arizona in particular) where sylvatic plague is enzootic among wild rodents (Figure 31.20). In 2014, 14 cases of human plague were reported, with no deaths. From 2006 through mid-2015, a total of 68 cases were reported and resulted in 11 deaths.

Plague control is accomplished through good sanitation practices, surveillance and control of rodent reservoirs and vectors (fleas), isolation of active cases, and imposing quarantine on those who have had contact with diseased individuals. Improved public health practices and the control of rodent populations are the major reasons that outbreaks of plague are extremely rare in developed countries.

MINIQUIZ

- Distinguish among sylvatic, bubonic, septicemic, and pneumonic plague.
- What are the insect vector, the natural host reservoir, and the treatment for plague?

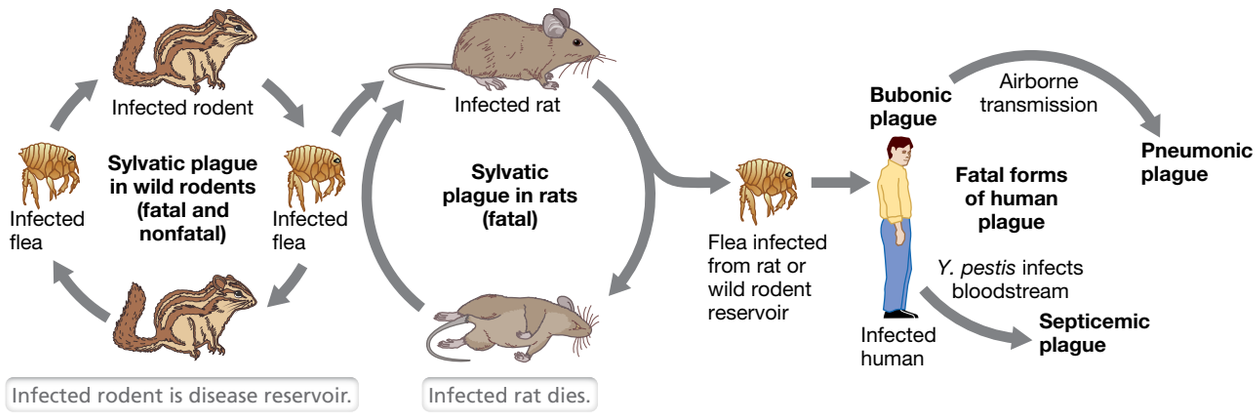


Figure 31.20 Plague epidemiology. In some wild rodents, sylvatic plague causes only a mild infection but diseased animals remain a reservoir of *Yersinia pestis*. In rodents that act as disseminating hosts, for example, rats, and in humans, plague is often fatal. When the domestic rodent reservoir dies off in an epidemic, infected fleas seek alternate hosts in humans.

III • Soilborne Bacterial Diseases

31.8 Anthrax

Some human diseases are caused by microorganisms whose major habitat is soil, and anthrax is an excellent example. We covered some aspects of the disease anthrax in Section 29.9 in the context of its use as a potential bioterrorism or biological warfare agent. Here we focus more on the biology of the organism and the disease process.

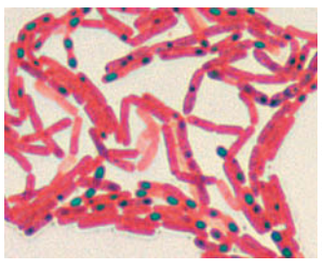
Discovery and Properties of Anthrax

The famous pioneering medical microbiologist Robert Koch (Section 1.10) first isolated the causative agent of the disease anthrax, the endospore-forming bacterium *Bacillus anthracis* (**Figure 31.21**). Using mice caught in the wild as experimental animals, Koch used the disease anthrax to develop his principles for linking cause and effect in infectious disease—Koch's postulates (Figure 1.29). Anthrax is quickly fatal in mice, but in humans, anthrax can take on several different forms, from mild to severe skin infections to respiratory failure and death.

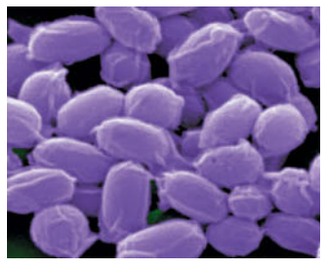
Anthrax is an enzootic disease of worldwide occurrence. *B. anthracis* lives a saprophytic existence in soils, growing as an aerobic chemoorganotroph and forming endospores (Figure 31.21) when conditions warrant. From soil, cells or spores of *B. anthracis* can become embedded in animal hair, hides, or other animal materials, or can be ingested, and from here the disease can develop, allowing *B. anthracis* spores to be transmitted to humans. Anthrax is primarily seen in domesticated farm animals, particularly in cattle, sheep, and goats, and is transmitted from them to humans.

Forms of Human Anthrax

The disease anthrax can manifest itself in one of three forms: cutaneous (on the skin), intestinal, and respiratory (inhalation anthrax). In all forms, disease symptoms are due to two major toxins called *lethal toxin* and *edema toxin*. The different forms of anthrax show increasing severity, which is primarily a function of where in the body these toxins are excreted. Growth and toxin production by *B. anthracis* in the lymph nodes and lymphatic tissues leads to progressively worsening symptoms, beginning with a sore throat, muscle aches, and fever, and escalating to respiratory distress and systemic shock. In addition to anthrax toxins, the unusual protein capsule that surrounds cells of *B. anthracis* (**Figure 31.22*a***) is also an important virulence factor of this pathogen as it prevents destruction of the bacterium following phagocytosis by immune cells such as macrophages. Instead, cells of *B. anthracis* grow within the macrophage, eventually killing it and giving the bacterium access to the bloodstream.



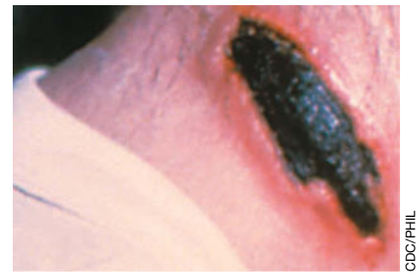
(a)



(b)

Figure 31.21 *Bacillus anthracis*. The anthrax pathogen produces endospores. *(a)* Light micrograph of a malachite green–stained smear of *B. anthracis* cells showing greenish-blue endospores. *(b)* Colorized scanning electron micrograph of *B. anthracis* endospores. Cells of *B. anthracis* are about 1.2 μm in diameter.

(a)



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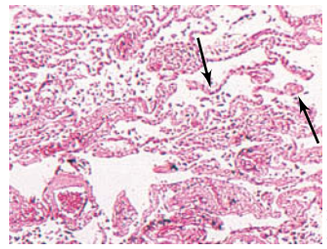

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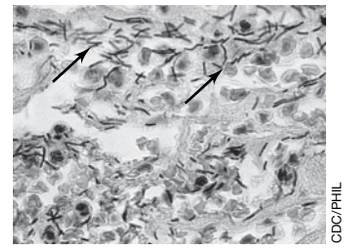

(d)

Figure 31.22 Anthrax pathology. *(a)* The protein capsule of *Bacillus anthracis* cells is a major virulence factor because it prevents killing by macrophages. *(b)* Cutaneous anthrax, with its characteristic black scabby appearance on the neck of a patient. *(c, d)* Inhalation anthrax. *(c)* The lung fills with bacterial cells (arrows) and fluids (cleared zones). *(d)* From the systemic infection, *B. anthracis* cells can be found almost anywhere, including the lining of the central nervous system (arrows).

Virtually all cases of human anthrax are *cutaneous anthrax*, where spores of *B. anthracis* have entered through a skin lesion, germinate, and form a painless, black and swollen pustule of dead tissue called an *eschar* (Figure 31.22*b*); the eschar is highly characteristic of the disease and allows for a firm diagnosis even though human anthrax is rarely seen in clinical medicine. In cutaneous anthrax the bacterium usually remains localized and the disease is readily treatable. Although cutaneous anthrax is fatal for about 20% of those untreated, most cases are treated because of the obvious symptoms, and thus fatalities are rare. *Intestinal anthrax* is very uncommon and is triggered by the ingestion of spores of *B. anthracis* (Figure 31.21*b*) in undercooked meat from diseased animals. Symptoms of intestinal anthrax include abdominal pain, bloody diarrhea, and ulcer-like lesions throughout the intestinal tract. The disease is still treatable at this stage but because of its rarity, diagnoses are easily missed. As a result, about half of all cases of intestinal anthrax are fatal.

Inhalation anthrax is the most severe form of the disease and is fatal in almost every case (Figure 31.22*c, d*). Inhalation anthrax occurs from the inhalation of endospores of *B. anthracis* and, along with cutaneous anthrax, is an occupational hazard for farm workers that process wool and hides (inhalation anthrax is also known as "woolsorter's disease"). In inhalation anthrax, the

organism enters the bloodstream from inhaled dust or animal dander and multiplies to become systemic. The mounting toxemia from this runaway growth of *B. anthracis* triggers septic shock and fluid accumulation in the lungs (Figure 31.22*c*) that can kill a patient in less than a day.

Prevention and Vaccines

Complete prevention of anthrax is impossible because the reservoir of the organism is the soil. However, anthrax is avoidable by limiting close exposure to farm animals and is easily treatable with antibiotics. For the cutaneous form this is a routine treatment, but antibiotic therapy is less effective in intestinal anthrax and especially in inhalation anthrax. By the time the latter is diagnosed, the disease has progressed to the point where it is usually too late to save the patient. An anthrax vaccine is available but because the disease is so rare, it is only recommended for high-risk individuals such as scientists working with the organism, slaughterhouse or livestock workers, and military personnel (for biowarfare reasons). An effective and inexpensive anthrax vaccine is available for vaccinating livestock and is commonly used in cattle, sheep, goats, and horses.

MINIQUIZ

- What are the major virulence factors of *Bacillus anthracis*?
- What are the three forms of anthrax, and which is most dangerous?

31.9 Tetanus and Gas Gangrene

Tetanus is a serious, life-threatening disease. Although tetanus is completely preventable through immunization, it still causes over 150,000 deaths per year, mostly in countries in Africa and Southeast Asia. *Gas gangrene* is caused by the growth in dead tissues of bacteria related to the tetanus pathogen, leading to a gassy putrefaction and loss of an infected limb or death from systemic shock. Both diseases are caused by clostridia.

Biology and Epidemiology of Tetanus

Tetanus is caused by an exotoxin produced by *Clostridium tetani*, an obligately anaerobic, endospore-forming rod (**Figure 31.23*a***; ↻ Section 16.8). The natural reservoir of *C. tetani* is soil, where it is a ubiquitous resident, although it is occasionally found in the gut of healthy humans, as are other *Clostridium* species.

Cells of *C. tetani* normally gain access to the body through a soil-contaminated wound, typically a deep puncture. In the wound, anoxic conditions develop around the dead tissue and allow germination of endospores, growth of the organism, and production of a potent exotoxin, the *tetanus toxin* (also called *tetanospasmin*). *C. tetani* is essentially noninvasive; its sole ability to cause disease is through toxemia, and thus tetanus is observed only as the result of untreated deep tissue injuries. The onset of tetanus symptoms may take from four days to several weeks, depending on the number of endospores inoculated at the time of the injury.

Pathogenesis of Tetanus

We have already examined the activity of tetanus toxin at the cellular and molecular level (↻ Section 25.6). The toxin directly affects the release of inhibitory signaling molecules in the nervous system. These inhibitory signals control the "relaxation" phase of muscle contraction. The absence of inhibitory signaling molecules results in rigid paralysis of the voluntary muscles, often called *lockjaw* because it is observed first in the muscles of the jaw and face. Preceding actual lockjaw, tetanus symptoms typically include mild spasms of facial muscles and muscles of the neck and upper back. Later on, the paralysis extends to the torso and lower body (Figure 31.23*b*). When tetanus is fatal, death is usually due to respiratory failure. Mortality is relatively high, occurring in about 10% of all reported cases, and up to 50% of cases in which treatment is delayed until generalized full body tetanus has set in.

(a) (b)

Figure 31.23 Tetanus. *(a) Clostridium tetani* showing the "drumstick" appearance of sporulating cells with their terminal endospores. Cells of *C. tetani* are about 0.8 µm in diameter. *(b)* A tetanus patient showing the rigid paralysis characteristic of tetanus. Tetanus paralysis typically begins with the facial muscles ("lockjaw") and descends to lower body regions.

Diagnosis, Control, Prevention, and Treatment of Tetanus

Diagnosis of tetanus is based on exposure, clinical symptoms (Figure 31.23*b*), and, rarely, identification of the toxin in the blood or tissues of the patient. The natural reservoir of *C. tetani* is the soil and thus control measures must focus on disease prevention rather than pathogen removal. The tetanus toxoid vaccine is highly effective, and thus virtually all tetanus cases occur in individuals who were inadequately immunized.

A second line of tetanus protection is to administer appropriate medical care to serious cuts, lacerations, and punctures. Even though vaccination against tetanus is widely practiced, any serious wound should be thoroughly cleaned and the damaged tissue removed. If the vaccination status of the individual is unclear or the last tetanus booster was more than 10 years ago, revaccination is recommended. If a deep wound is severe or heavily contaminated by soil, treatment might also include administration of a tetanus antitoxin preparation, especially if the patient's immunization status is unknown or is out of date.

Acute symptomatic tetanus (Figure 31.23*b*) is treated with antibiotics, usually penicillin, to stop growth and toxin production by *C. tetani*, and antitoxin is injected intramuscularly (or into the sheath surrounding the spinal cord if necessary) to prevent binding of newly released toxin to cells. Supportive therapy such as sedation, administration of muscle relaxants, and mechanical respiration may be necessary to control the effects of paralysis. Treatment cannot provide a quick reversal of symptoms because toxin that is already bound to tissues cannot be neutralized. Even with

antitoxin and antibiotic administration and supportive therapy, tetanus patients show significant morbidity and mortality. A complete recovery from tetanus often takes many months.

Gas Gangrene

Tissue destruction due to the growth of proteolytic and gas-producing clostridia is called **gas gangrene**. In this life-threatening condition, amino acids obtained from the breakdown of muscle proteins are fermented to the gases H_2 and CO_2 plus a variety of foul-smelling organic compounds, including short-chain fatty acids and other putrid molecules; ammonia released during amino acid fermentation (Section 14.21) adds to the stench. In addition, a variety of bacterial toxins are produced that accelerate tissue destruction.

Although *C. tetani* is a proteolytic *Clostridium* species, it does not cause gangrene but can be associated with cases of gangrene triggered by a deep tissue wound. The most common causes of gangrene are *Clostridium perfringens* (**Figure 31.24a**), which is also a common cause of foodborne illness unrelated to gangrene, *C. novyi*, and *C. septicum*. These organisms reside in soil and are also part of the normal human intestinal microbiota. When these species reach deep into tissues, typically from traumatic tissue invasion such as a war wound or other puncture wound, or occasionally from gastrointestinal tract surgery, spores and vegetative cells of proteolytic clostridia are inserted into what are now dead tissues. As the bacteria grow, they release enzymes that destroy collagen and tissue proteins and also excrete a series of toxins. *C. perfringens* (Figure 31.24*a*) *alpha toxin*, which is distinct from the toxins the bacterium produces in perfringens food poisoning (Section 32.9), is a major virulence factor in gangrene, as is the general ability of the pathogens to grow rapidly in the warm, moist, and protein-rich environment created by an invasive injury. Alpha toxin is a phospholipase that hydrolyzes the membrane phospholipids of host cells, leading to cell lysis and the typical accumulation of gas and fluids that accompanies gas gangrene (Figure 31.24*c*).

In severe cases of gas gangrene, the toxemia can become systemic and cause death. Antibiotic treatment is taken as a preventive measure in cases of gangrene in addition to the typical though dramatic treatment: amputation of the infected limb. Gangrenous tissues are dead and will not regenerate, and amputation prevents the infection from reaching healthy tissues.

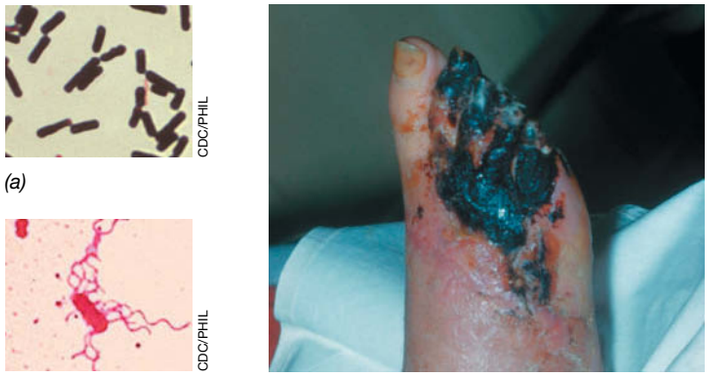

Figure 31.24 Gas gangrene. *(a)* Gram stain of cells of *Clostridium perfringens*, the most common cause of gangrene. *(b)* Flagellum stain showing a cell of *Clostridium novyi*, also an agent of gangrene. *(c)* A case of gas gangrene on the foot. Cells of both *C. perfringens* and *C. novyi* are about 1.2 µm in diameter.

Hyperbaric oxygen treatment of the infected limb is attempted in some cases to try to save it, with the high levels of O_2 inhibiting growth of the obligately anaerobic clostridia. In hyperbaric treatment, the patient sits in an enclosed chamber containing 100% O_2 at about twice atmospheric pressure. This enriches the blood in O_2 and helps still-living blood vessels seed the formation of new tissue. Several hyperbaric treatments are administered and may be accompanied by surgical removal of some of the dead tissue. If an adequate blood supply can be established in damaged tissues, a skin graft may also be done to help connect regenerating with damaged tissues.

MINIQUIZ

- Describe infection by *Clostridium tetani* and the effects of tetanus toxin. How does the mode of action of tetanus toxin differ from that of alpha toxin produced by *C. perfringens*?
- Describe the steps necessary to prevent tetanus in an individual who has sustained a puncture wound.
- How does the physiology of *C. perfringens* make it suitable for growing in puncture wounds?

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Chapter Review

I • Animal-Transmitted Viral Diseases

31.1 Rabies occurs primarily in wild animals but can be transmitted to humans and domestic animals. In the United States, rabies is transmitted primarily from the wild animal reservoir to domestic animals or, very rarely, to humans. Vaccination of domestic animals is key to the control of rabies. Most human deaths from rabies occur in developing countries.

Q What pathogen causes rabies? How does it enter the body? What are the factors that determine the incubation period before the onset of symptoms of rabies?

31.2 Hantaviruses are present worldwide in rodent populations and cause zoonotic diseases such as hantavirus pulmonary syndrome and hemorrhagic fever with renal syndrome in humans. Hantavirus is a highly dangerous hemorrhagic fever virus related to Ebola. In the Americas, hantavirus infections have case fatality rates of over 30%.

Q Describe the conditions that may cause emergence of hantavirus pulmonary syndrome (HPS). How can HPS be prevented?

II • Arthropod-Transmitted Bacterial and Viral Diseases

31.3 Rickettsias are obligate intracellular parasitic bacteria transmitted to hosts by arthropod vectors. The incidence of spotted fever rickettsiosis and other rickettsial syndromes is increasing as a result of several factors. Most rickettsial infections can be controlled by antibiotic therapy, but prompt recognition and diagnosis of these diseases remains difficult.

Q Identify the three major categories of organisms that cause rickettsial diseases. For typhus, spotted fever rickettsiosis, and ehrlichiosis, identify the most common reservoir and vector.

31.4 Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is the most prevalent arthropod-borne disease in the United States today. Lyme is transmitted from several mammalian host vectors to humans by ticks. Prevention and treatment of Lyme disease are straightforward, but accurate and timely diagnosis of infection is essential.

Q Identify the most common reservoir and vector for Lyme disease in the United States. How can the spread of Lyme disease be controlled? How can Lyme disease be treated?

31.5 Yellow, dengue, and Zika fevers are caused by related flaviviruses transmitted to humans by mosquito bites; Chikungunya fever shows similar disease symptoms and mode of transmission but is caused by a different class of virus. These mainly tropical and subtropical diseases can show mild to very severe symptoms, including hemorrhagic fevers. An effective vaccine for yellow fever is in use, but no vaccine is currently available to prevent dengue, Zika, and Chikungunya infections.

Q Why are people with active cases of yellow fever put in isolation?

31.6 West Nile fever is a mosquito-borne viral disease. In the natural cycle of the pathogen, birds are infected with West Nile virus by the bite of infected mosquitoes. Humans and other vertebrates are occasional terminal hosts. Most human infections are asymptomatic and undiagnosed, but complications of some infections cause about 5% mortality.

Q Describe the spread of West Nile virus infections in the United States. Which animals are the primary hosts? Are humans productive alternate hosts?

31.7 Plague can be transmitted to individuals who have had contact with rodent populations and their parasitic fleas, the enzootic reservoirs for the plague bacterium, *Yersinia pestis*. A systemic infection or a pneumonic infection leads to rapid death, but the bubonic form is treatable with antibiotics.

Q For a potentially serious disease like bubonic plague, vaccines are not routinely recommended for the general population; why not? Identify the public health measures used to control plague.

III • Soilborne Bacterial Diseases

31.8 Anthrax is caused by the endospore-forming bacterium *Bacillus anthracis* and can take on three different forms: cutaneous, intestinal, or inhalation. Cutaneous anthrax is most common and along with inhalation anthrax is an occupational hazard for livestock workers, where *B. anthracis* endospores can be transmitted from animal hides to humans.

Q Which key feature of the bacterium *Bacillus anthracis* allows this organism to persist for extended periods on animal hides or other environments where growth may not occur? Which form of anthrax is the most serious?

31.9 *Clostridium tetani* is a soil bacterium that causes tetanus, a potentially fatal disease characterized by a toxemia and rigid paralysis. Treatment for acute tetanus includes antibiotics and active and passive immunization, and the disease is preventable by toxoid immunization. Gas gangrene occurs from the growth of various proteolytic clostridia in traumatic wounds, leading to gas and toxin formation.

Q Discuss the major mechanism of pathogenesis for tetanus and define measures for prevention and treatment. Why is it possible that a traumatic puncture wound could end up causing both tetanus and gas gangrene?

Application Questions

1. Describe the sequence of steps you would take if your child received a bite (provoked or unprovoked) from a stray dog with no collar and record of rabies immunization. Present one scenario in which you were able to capture and detain the dog and another for a dog that escaped. How would these procedures differ from a situation in which the child was bitten by a dog that had a collar and rabies tag with documented, up-to-date rabies immunizations?

2. Contrast the modes of transmission of the following diseases: rabies, Lyme disease, yellow fever, West Nile disease, anthrax, and plague. Which of these diseases could be virtually eliminated in humans by control of the disease vector and which could not, and why?
3. Devise a plan to prevent the spread of West Nile virus to humans in your community. Identify the relative costs involved in such a plan, both at the individual level and at the community level. Find out if a mosquito abatement program is active in your community. What methods, if any, are used in your area for the reduction of mosquito populations? What is a simple way to limit mosquito numbers around your residence?

Chapter Glossary

Enzootic an endemic disease present in an animal population

Epizootic an epidemic disease present in an animal population

Gas gangrene tissue destruction due to the growth of proteolytic and gas-producing clostridia

Hantavirus pulmonary syndrome (HPS) an emerging, acute disease characterized by pneumonia and caused by rodent hantavirus

Hemorrhagic fever with renal syndrome (HFRS) an emerging acute disease characterized by shock and kidney failure, caused by rodent hantavirus

Lyme disease a tick-transmitted disease caused by the spirochete *Borrelia burgdorferi*

Plague an enzootic disease in rodents caused by *Yersinia pestis* that can be transferred to humans through the bite of a flea

Rabies a usually fatal neurological disease caused by the rabies virus, which is usually transmitted by the bite or saliva of an infected animal

Rickettsias obligate intracellular bacteria of the genus *Rickettsia* and related genera responsible for diseases including typhus, spotted fever rickettsiosis, and ehrlichiosis

Spotted fever rickettsiosis a tick-transmitted disease caused by *Rickettsia rickettsii*, characterized by fever, headache, rash, and gastrointestinal symptoms; also called Rocky Mountain spotted fever

Tetanus a disease characterized by rigid paralysis of the voluntary muscles, caused by an exotoxin produced by *Clostridium tetani*

Typhus a louse-transmitted disease caused by *Rickettsia prowazekii*, characterized by fever, headache, weakness, rash, and damage to the central nervous system and internal organs

West Nile fever a neurological disease caused by West Nile virus, a virus transmitted by mosquitoes from birds to humans

Zoonosis an animal disease transmissible to humans

32

Waterborne and Foodborne Bacterial and Viral Diseases

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The Classic Botulism Scenario

Botulism is a food poisoning that causes severe symptoms and occasional deaths. Botulism results from highly poisonous exotoxins produced by the endospore-forming anaerobic bacterium *Clostridium botulinum*. This soil microbe can easily travel on the surface of fresh vegetables pulled from the home garden. If the vegetables are not thoroughly washed and properly canned (if intended for later use), botulism is a possibility. Unfortunately, such circumstances unfolded at a church potluck supper in Fairfield, Ohio (USA) in April 2015 when contaminated potatoes sent 29 people to the hospital with symptoms of botulism and caused one death—the largest botulism outbreak in the United States in nearly 40 years.

Most cases of botulism not linked to restaurant foods are traced to home-canned foods. In the Ohio outbreak, potato salad similar to that shown here was the disease vehicle. The potato salad was prepared from home-canned potatoes that were heat processed in boiling water rather than a pressure cooker. Temperatures in a boiling water canner cannot exceed 100°C and this is insufficient to kill bacterial endospores, the most heat-tolerant of all biological structures. When the potatoes were later used to prepare potato salad, the stage was set for the botulism outbreak.

Quick epidemiological work and early recognition of botulism symptoms by a local clinician helped keep the Ohio botulism outbreak from claiming more than the one life it did. Once it was clear what they were facing, health officials in Fairfield were immediately sent 50 doses of botulinum antitoxin from the strategic stockpile of this life-saving drug maintain by the Centers for Disease Control and Prevention; antitoxin treatment quickly ended the Ohio botulism crisis.

The circumstances surrounding the Ohio outbreak formed the "perfect storm" for a botulism outbreak. Potato salad made from fresh potatoes and refrigerated until consumption is not a botulism threat. By contrast, home-canned potatoes not treated in a pressure cooker are a botulism threat because the sealed (and thus anoxic) container provides ideal conditions for the growth of any viable *C. botulinum* endospores that remain after heat treatment. Human botulism is a rare occurrence, but its common link to home-canned foods reminds us of the critical importance of strict adherence to proper heat-processing procedures when preparing home-canned vegetables.

Source: McCarty, C.L., et al. 2015. Large outbreak of botulism associated with a church potluck meal—Ohio, 2015. *Morbidity and Mortality Weekly Report 64:* 802–803.

In this chapter we consider microbial pathogens whose mode of transmission is either water or food. The diseases these pathogens cause are called "common-source" diseases because they occur only in those who have consumed the same contaminated water or eaten the same contaminated food. Waterborne and foodborne illnesses are common infectious diseases worldwide. While foodborne illnesses are most commonly of bacterial or viral origin, waterborne illnesses can have bacterial, viral, or parasitic causes.

I • Water as a Disease Vehicle

Water is used in enormous quantities, and its microbiological safety rests in the hands of wastewater and drinking water engineers and microbiologists. Indeed, water quality is the single most important factor for ensuring public health. In Chapter 22 we examined the microbiology of wastewater and examined how highly polluted water can be cleaned by microbial activities and reused for many purposes, including for drinking. Here we see what can happen when water intended for human use becomes a vehicle for disease.

Waterborne diseases begin as infections (or occasionally as toxemias), and contaminated water may cause an infection even if only small numbers of the particular pathogen are present. Whether or not exposure causes disease is a function of the virulence of the pathogen and the ability of the host to resist infection.

32.1 Agents and Sources of Waterborne Diseases

Many different microorganisms can cause waterborne infectious diseases, and some of the major ones are summarized in Table 32.1.

TABLE 32.1 Major waterborne pathogens

Pathogen	*Disease*
Bacteria[a]	
Vibrio cholerae	Cholera
Legionella pneumophila	Legionellosis
Salmonella enterica (typhi)	Typhoid fever
Escherichia coli	Gastrointestinal illness
Pseudomonas aeruginosa	Nosocomial pneumonia, septicemia, and skin infections
Campylobacter jejuni	Gastrointestinal illness
Viruses	
Norovirus	Gastrointestinal illness
Hepatitis A virus	Viral hepatitis
Parasites[b]	
Cryptosporidium parvum	Cryptosporidiosis
Giardia intestinalis	Giardiasis
Schistosoma	Schistosomiasis

[a]Except for *S. enterica* (*typhi*), these bacteria have been associated with major outbreaks of waterborne illness in the United States in recent years, as have the bacteria *Shigella sonnei* and *Leptospira* sp.
[b]See Chapter 33. *C. parvum* and *G. intestinalis* are unicellular microbial parasites; *Schistosoma* is a microscopic worm 10–20 mm long.

Many different microbes can be waterborne pathogens, but here we will consider bacterial pathogens with a major focus on cholera, a waterborne disease of pandemic proportions (Section 29.8). We consider parasitic diseases in Chapter 33 and a few viral pathogens that can be either foodborne or waterborne later in this chapter.

We begin by considering the disease vehicle itself—water. Waterborne illnesses can be transmitted through untreated or improperly treated water used for drinking or food preparation or from water used for swimming and bathing (recreational water sources). The major waterborne illnesses traced to drinking water and recreational waters are typically quite different, and these different disease patterns are shown in Table 32.2.

Potable Water

Water supplies in developed countries typically meet rigid quality standards, greatly reducing the spread of waterborne diseases. Drinking water in particular undergoes extensive treatment that includes both filtration and chlorination. Although filtration removes turbidity and many microorganisms, it is *chlorination* that makes drinking water safe. Chlorine gas (Cl_2) is a strong oxidant and oxidizes both organic matter dissolved in the water and microbial cells themselves. Drinking water chlorination facilities add sufficient chlorine to allow a residual level to remain in the water all the way to the consumer. Water suitable for human consumption is called **potable** water (Sections 22.6–22.9).

Despite filtration and chlorination, waterborne disease outbreaks from potable water occasionally occur. In the United States an average of 25 outbreaks of disease associated with drinking water are recorded in a year (a waterborne outbreak is defined as two or more human illnesses specifically linked to the consumption of the same water at the same time). Nearly 80% of drinking water disease outbreaks are due to *bacterial* pathogens, most notably *Legionella*, the causative agent of legionellosis (Table 32.2 and Section 32.4).

Recreational Waters

Recreational waters include freshwater aquatic systems such as ponds, streams, and lakes, as well as public swimming and wading

TABLE 32.2 Sources of outbreaks of acute gastrointestinal illness in drinking and recreational waters, 2009–2010[a]

	Drinking water (n = 33) (%)	*Recreational water (n = 81) (%)*
Bacteria	76	19
Legionella pneumophila	58	5
Other	18	14
Parasites	9	35
Viruses	6	1
Chemical/toxin	3	4
Multiple causes[b]	6	1
Unknown[c]	0	40

[a]Numbers are rounded to the nearest percent and were obtained from the Centers for Disease Control Waterborne Disease and Outbreak Surveillance System.
[b]Outbreak linked to more than one cause.
[c]Suspected to be caused by one or more microbes or chemicals but not confirmed.

pools. Recreational waters can be sources of waterborne disease, and on average they cause more disease outbreaks than those due to drinking water. Moreover, in contrast to drinking water, where *bacterial* pathogens are most common, disease outbreaks from recreational waters are more frequently linked to *parasitic* pathogens. In addition, recreational waters often transmit gastrointestinal illnesses that are either of unknown microbial origin or due to chemicals or other toxic materials (Table 32.2).

In the United States, the operation of public swimming pools is regulated by state and local health departments. The United States Environmental Protection Agency (EPA) establishes limits for bacterial numbers in both potable and public recreational water sources, but local and state governments can set standards above or below these guidelines for nonpotable sources. By contrast, the water quality of *private* recreational waters, such as swimming pools, spas, and hot tubs, is totally unregulated, and these are therefore prime vehicles for waterborne disease outbreaks.

MINIQUIZ

- What is potable water?
- Contrast the major pathogens responsible for disease outbreaks in drinking water versus recreational waters.

32.2 Public Health and Water Quality

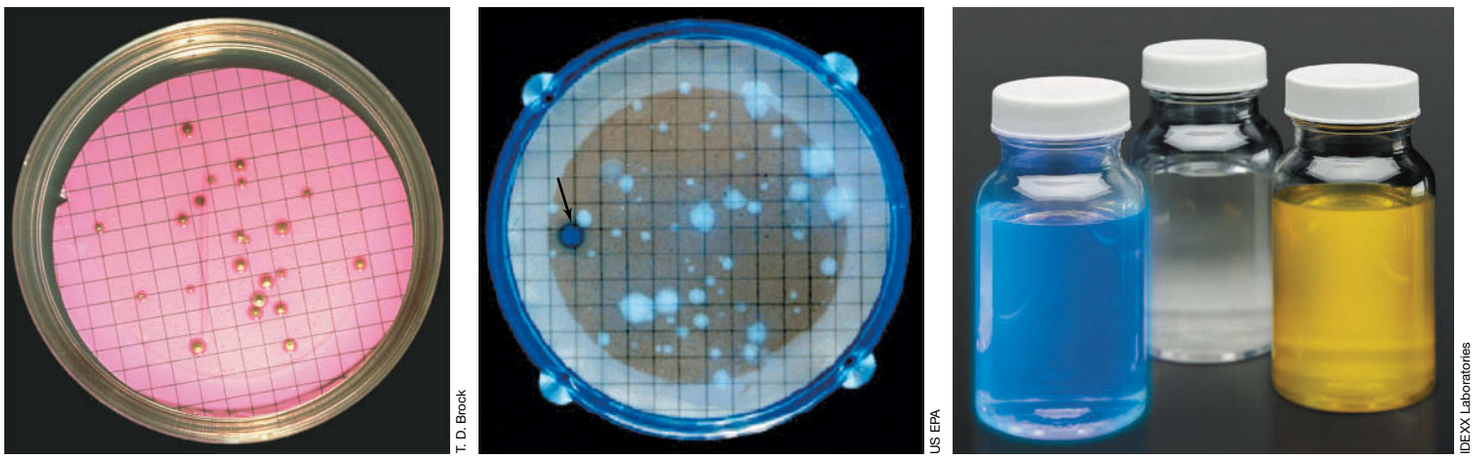
Water that looks perfectly transparent may still be contaminated with high numbers of microorganisms and thus pose a risk of disease. It is impractical to screen water for every pathogenic organism that may be present (Table 32.1), and so both potable and recreational waters are routinely tested for specific *indicator organisms*, the presence of which signals the potential for waterborne disease.

Coliforms and Water Quality

A widely used indicator for microbial water contamination is the **coliform** group of bacteria. Coliforms are useful because many of them inhabit the intestinal tract of humans and other animals. Thus, the presence of coliforms in water indicates likely fecal contamination. Coliforms are defined as facultatively aerobic, gram-negative, rod-shaped, nonsporulating bacteria that ferment lactose with the production of gas within 48 h at 35°C. However, this definition includes several bacteria that are not necessarily restricted to the intestine; for this reason, it is *fecal coliforms* that are important in water safety assessments. *Escherichia coli*, a coliform whose only habitat is the intestine and that survives only a relatively short time outside the intestine, is the key fecal coliform of interest. The presence of cells of *E. coli* in a water sample is taken as evidence of fecal contamination and means that the water is unsafe for human consumption. Conversely, however, the absence of *E. coli* does not ensure that a water source is potable, because other pathogenic bacteria or pathogenic viruses or protists may still be present.

Testing for Fecal Coliforms and the Importance of *Escherichia coli*

Well-developed and standardized methods are in routine use for detecting coliforms and fecal coliforms in water samples. A common method is the *membrane filter* (*MF*) procedure where at least 100 ml of freshly collected water is passed through a sterile membrane filter, trapping any bacteria on the filter surface. The filter is placed on a plate of eosin–methylene blue (EMB) medium, which is selective for gram-negative, lactose-utilizing bacteria. EMB medium is also differential, allowing strongly fermentative species such as *E. coli* (**Figure 32.1a**; see also Figure 32.14*c*) to be distinguished from weakly fermentative species such as *Proteus*.



(a) (b) (c)

Figure 32.1 Fecal coliforms and their detection in water samples. *(a)* Colonies growing on a membrane filter. A drinking water sample was passed through the filter and the filter placed on an eosin–methylene blue (EMB) agar plate (EMB is both selective and differential for coliforms; more strongly fermentative species [such as *Escherichia coli*] form colonies with darker centers). *(b)* Total coliforms and *E. coli*. A filter exposed to a drinking water sample was incubated at 35°C for 24 hours on a medium containing special compounds that fluoresce when metabolized. The filter was then examined under ultraviolet light. The single *E. coli* colony in the sample fluoresces dark blue (arrow). Coliforms that do not metabolize the compound form colonies that fluoresce white to light blue. *(c)* The IDEXX Colilert water quality test system. When specific reagents are added to water samples and incubated for 24 h, they develop a yellow color if they contain coliforms (right). Samples containing *Escherichia coli* develop a yellow color but also fluoresce blue (left). Samples negative for coliforms remain clear (center).

Selective media are also available that not only detect total coliforms but also specifically identify *E. coli* simultaneously. These *defined substrate tests* are typically faster and more accurate than EMB-based assays. One popular plate-based test is based on the ability of *E. coli* but not other enteric bacteria to metabolize a combination of two specific chemicals to form a fluorescent blue compound (Figure 32.1*b*). A commonly used liquid method reveals whether coliforms are present and also specifically detects *E. coli* in the water sample (Figure 32.1*c*). In addition to these colorimetric tests, dipsticks have been developed that detect ATP in a water sample. There is a strong correlation between the total number of bacteria in a sample and its ATP content, and the latter can be measured using the luciferase enzyme system in which a flash of light is emitted when ATP is hydrolyzed (Figure 9.4*b*). Using this system, the total microbial load in a water sample can be quickly assessed, and portable kits are available commercially to carry out these analyses in water purification facilities as well as remote field sites.

Reporting Water Purity Data

In properly regulated drinking water supply systems, total coliform and *E. coli* fecal coliform tests should be negative. A positive test indicates that a breakdown has occurred in either the purification or distribution system (or both). In the United States, microbiological standards for drinking water are specified in the *Safe Drinking Water Act* and are administered by the Environmental Protection Agency (EPA). Water utilities must report coliform test results to the EPA monthly, and if they do not meet the prescribed standards, the utilities must notify the public and take steps to correct the problem.

Major improvements in public health in the United States beginning in the early twentieth century were largely due to the adoption of water filtration and chlorination procedures in large-scale wastewater and drinking water treatment plants (Sections 22.7 and 22.8). Where drinking water standards have not reached this level, especially in developing countries, a variety of waterborne diseases are common. We turn our attention to these diseases now, beginning with cholera, the most widespread and devastating of all waterborne diseases.

MINIQUIZ

- Why is *Escherichia coli* used as an indicator organism in microbial analyses of water?
- What procedures are used to ensure the safety of potable water supplies?

II • Waterborne Diseases

32.3 *Vibrio cholerae* and Cholera

Cholera is a severe gastrointestinal diarrheal disease that is now largely restricted to countries in the developing world. Cholera is caused by ingestion of contaminated water containing cells of *Vibrio cholerae*, a gram-negative and motile curved species of

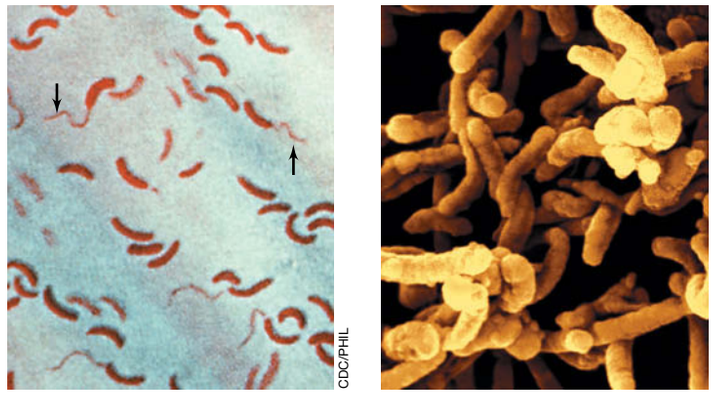


Figure 32.2 *Vibrio cholerae*, the causative agent of cholera. *(a)* Gram-stained preparation shows the typically curved (vibrio-shaped) cells of this bacterium and polar flagella (arrows). *(b)* Colorized scanning electron micrograph of cells of *V. cholerae*. A single cell is about 0.5 × 2 μm.

Proteobacteria (Figure 32.2). Cholera can also be contracted from contaminated food, especially improperly cooked shellfish.

The ingestion of a large number ($>10^8$) of *V. cholerae* cells is required to cause disease. The ingested cells attach to epithelial cells in the small intestine where they grow and release *cholera toxin*, a potent enterotoxin (Figure 25.15). Studies with human volunteers have shown that normal stomach acidity (about pH 2) is why the large inoculum of *V. cholerae* cells is needed to initiate disease. In studies with human volunteers, those given bicarbonate to neutralize gastric acidity develop cholera when given as few as 10^4 cells. Even lower cell numbers can initiate infection if *V. cholerae* is ingested with food, presumably because the food protects the vibrios from destruction by stomach acidity.

Cholera enterotoxin causes severe diarrhea that can result in dehydration and death unless the patient is given fluid and electrolyte therapy. The enterotoxin causes fluid losses of up to 20 liters (20 kg or 44 lb) per person per day, causing severe dehydration. The mortality rate from *untreated* cholera is 25–50% and can be even higher under conditions of severe crowding and malnutrition as often occurs in refugee camps or in areas that have experienced natural disasters such as floods, earthquakes, and the like. In these situations there is often a near-complete breakdown in sanitation leading to the contamination of drinking water with feces and the rapid transmission of cholera.

Diagnosis, Treatment, and Prevention of Cholera

At treatment facilities in large outbreaks of cholera, each cholera patient is placed on a "cholera cot," which is a conventional folding cot containing an opening into which feces can be voided (Figure 32.3*a*). The feces of a cholera patient are more liquid than solid, and confirmation of the disease is straightforward because the pathogen is easily cultured on selective agar media (Figure 32.3*b–d*). Cholera treatment is simple and effective. An oral (or in severe cases, intravenous) liquid and electrolyte replacement therapy is the most effective means of treatment. Oral treatment

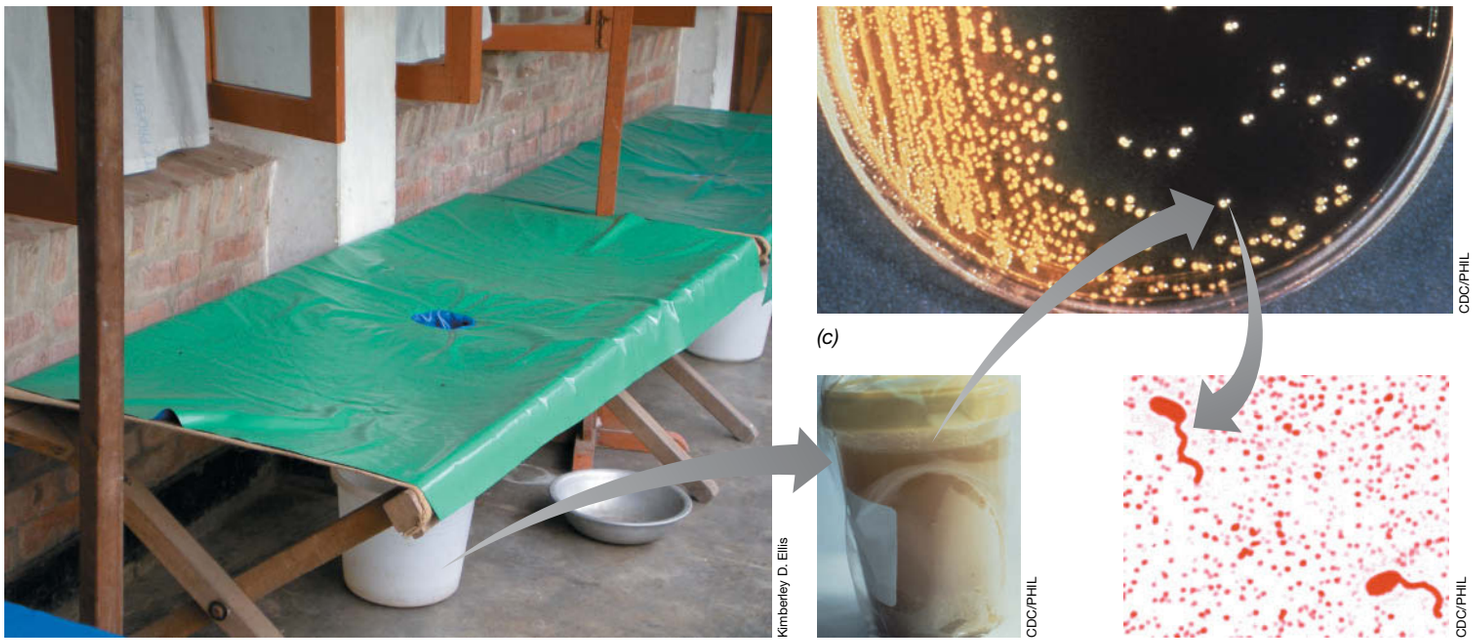


Figure 32.3 Cholera and its diagnosis. *(a)* A cholera cot. The cot allows a person to lie prostrate and void feces directly into a bucket. Cholera cots are used during cholera outbreaks for treating active disease cases with rehydration therapy. *(b)* Feces from a cholera patient. The "rice-water" stool is mostly liquid (the solid material in the bottom is mucus). *(c) Vibrio cholerae* is easily cultured on the medium TCBS, which is both selective and differential. TCBS contains high levels of bile salts and citrate, which inhibit enteric bacteria and gram-positive bacteria, and thiosulfate and sucrose, which cells of *V. cholerae (d)* use as a sulfur and carbon/energy source, respectively.

is preferred because no special equipment or sterile precautions are necessary. The rehydration solution is a mixture of glucose, salt (NaCl), sodium bicarbonate ($NaHCO_3$), and potassium chloride (KCl). If the solution is administered quickly during an outbreak, cholera mortality can be greatly reduced, as rehydration allows patients the time necessary to mount an immune response.

Antibiotics may shorten the course of cholera infection and the shedding of viable cells, but antibiotics are of little health benefit without simultaneous fluid and electrolyte replacement. Public health measures such as adequate sewage treatment and a reliable source of safe drinking water are the keys to preventing cholera. *V. cholerae* is eliminated from wastewater during proper sewage treatment and drinking water purification procedures (Chapter 22). For individuals traveling in cholera-endemic areas, attention to personal hygiene and avoidance of untreated water or ice, raw food, and raw or undercooked fish or shellfish that can feed on phytoplankton contaminated with *V. cholerae* (**Figure 32.4**) can prevent cholera.

Since 1817, cholera has swept the world in seven major pandemics with an eighth pandemic likely already started (↪ Section 29.8 and Figure 29.14). The World Health Organization estimates that only 5–10% of cholera cases are reported, so the total worldwide incidence of cholera probably exceeds 1 million cases per year. Only a handful of cases of cholera are reported each year in the United States, typically from imported shellfish that are eaten raw or after only minimal cooking.

MINIQUIZ

- What organism causes cholera, and what are the symptoms of the disease?
- Why does transmission of cholera usually require a large inoculum? Under what conditions can cholera be transmitted by fewer cells?
- Describe how cholera can be prevented and how it is treated.

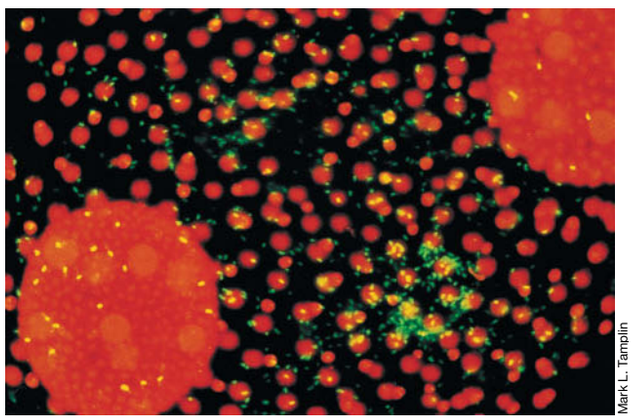


Figure 32.4 Cells of *Vibrio cholerae* attached to the surface of *Volvox*, a freshwater alga. The sample was from a cholera-endemic area in Bangladesh. The *V. cholerae* cells are stained green by a fluorescently labeled antibody against a *V. cholerae* cell surface protein. The red color is from chlorophyll *a* fluorescence of the algae.

32.4 Legionellosis

Legionella pneumophila, the bacterium that causes *legionellosis*, is an important waterborne pathogen whose transmission was originally linked to aerosols from evaporative cooling devices. However, *L. pneumophila* (**Figure 32.5**) is now known to be a major pathogen in residential water systems as well, where the organism persists in biofilms that form on interior surfaces of water distribution pipes and also within the cells of certain microbial parasites. In these sites, *L. pneumophila* is protected from the chlorine present in potable waters, and thus biofilms and infected parasites are reservoirs for transmitting legionellosis by a waterborne route (Section 22.9 and Figure 22.22).

Pathogenesis, Diagnosis, and Treatment

Cells of *L. pneumophila* invade the lungs and grow within macrophages and monocytes. Infections are often asymptomatic or produce only a mild cough, sore throat, mild headache, and fever; these self-limiting cases typically resolve themselves in 2–5 days. However, the elderly, whose resistance may be naturally reduced, and those with compromised immune systems often acquire more serious *Legionella* infections resulting in pneumonia. Prior to the onset of pneumonia, intestinal disorders, followed by high fever, chills, and muscle aches, are common. These symptoms precede the dry cough and chest and abdominal pains typical of legionellosis. Up to 10% of cases that reach this stage are fatal, usually as a result of respiratory failure.

Clinical detection of *L. pneumophila* infection is usually done by culture of the organism from bronchial washings, pleural fluid, or other body fluids or tissues (Figure 32.5*a*). Various serological tests can detect anti-*Legionella* antibodies or *Legionella* cells in these samples and also in patient urine, and this is used to confirm a diagnosis (Figure 32.5*b, d*). Legionellosis can be treated with the antibiotics rifampin and erythromycin, and intravenous administration of erythromycin is the treatment of choice for life-threatening cases.

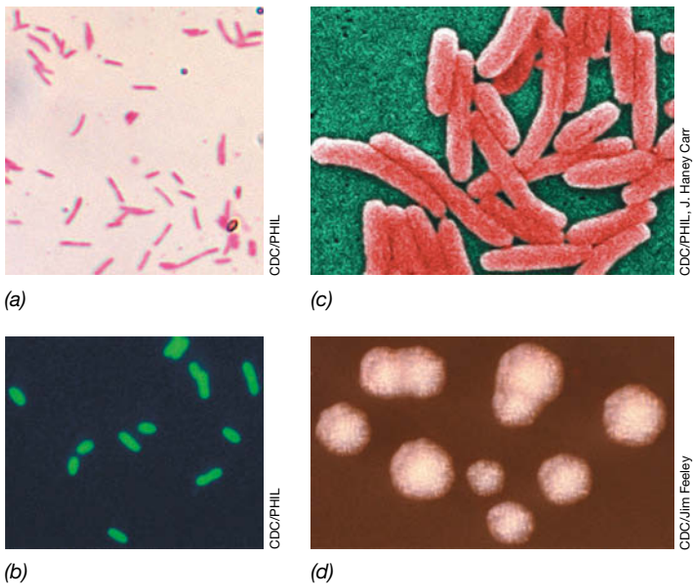


Figure 32.5 *Legionella pneumophila*. *(a)* Gram-stained cells of *L. pneumophila* from lung tissue of a legionellosis victim. *(b)* Cells of *L. pneumophila* can be positively identified using fluorescent anti–*L. pneumophila* antibodies. *(c)* Colorized scanning electron micrograph of *L. pneumophila* cells. Cells are about 0.5 × 2 µm. *(d)* Colonies of *L. pneumophila* grown on a complex enrichment medium showing their typical textured surface.

Epidemiology

L. pneumophila is a gram-negative, obligately aerobic rod-shaped species of the *Gammaproteobacteria* (Figure 32.5), and shows complex nutritional requirements including an unusually high requirement for iron. The organism can be isolated from terrestrial and aquatic habitats as well as from legionellosis patients. *Legionella pneumophila* was first recognized as the pathogen that caused an outbreak of fatal pneumonia at an American Legion convention (thus the name legionellosis) in Philadelphia (USA) in 1976. Besides legionellosis, the same bacterium can also cause a milder syndrome called *Pontiac fever*.

L. pneumophila is present in freshwaters and in soil. It is relatively resistant to heating and chlorination, so it can spread through drinking water distribution systems (Section 22.9). The pathogen is often found in large numbers in improperly sanitized cooling towers and evaporative condensers of large air conditioning systems. The pathogen grows in the water and is disseminated in humidified aerosols. Human infection is by way of airborne droplets, but the infection does not spread from person to person.

Besides its presence in evaporative coolers and domestic water systems, *L. pneumophila* has also been detected in hot water tanks and spas; in the latter, it can reach high cell numbers in warm (35–45°C), stagnant water, especially if chlorine (or other sanitizer) levels are not maintained. Many outbreaks of legionellosis have been linked to swimming pools. *L. pneumophila* can be eliminated from water supplies by hyperchlorination or by heating water to greater than 63°C. Although incidence peaks in the summer months, epidemiological studies indicate that *L. pneumophila* infections can occur at any time of year, primarily as a result of aerosols generated from heating and cooling systems and contaminated premise water (Section 22.9) used for showering or bathing. In the United States, a few thousand cases of legionellosis are typically reported each year.

MINIQUIZ

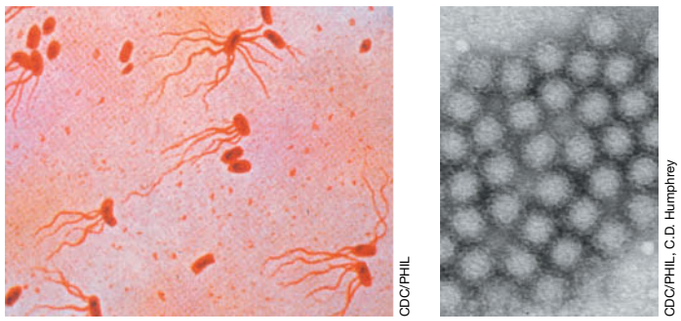
- How is legionellosis transmitted?
- Identify specific measures for control of *Legionella pneumophila*.

32.5 Typhoid Fever and Norovirus Illness

Although cholera remains the most widespread and potentially dangerous of waterborne diseases, other waterborne pathogens also cause serious disease. We focus on two major ones here, the causative agents of typhoid (a bacterium) and norovirus gastrointestinal illness (an RNA virus).

Typhoid Fever

On a global scale, probably the most important waterborne bacterial pathogens are *Vibrio cholerae* (Section 32.3) and *Salmonella*



(a) (b)

Figure 32.6 Bacterial and viral agents of severe gastrointestinal waterborne diseases. *(a)* Flagella-stained cells of *Salmonella enterica* (*typhi*) showing peritrichous flagellation (Section 2.11). A single cell measures about 1 × 2 µm. *(b)* Transmission electron micrograph of virions of norovirus. A single virion is about 30 nm in diameter.

enterica (*typhi*), the organism that causes typhoid fever. *S. enterica* (*typhi*) is a gram-negative, peritrichously flagellated bacterium related to *Escherichia coli* and other enteric bacteria (**Figure 32.6*a***). The organism is transmitted in feces-contaminated water, and thus typhoid fever, like cholera, is primarily restricted to areas where sewage treatment and general sanitation are either absent or poorly maintained. Typhoid today is a well-entrenched endemic disease in sub-Saharan Africa, the Indian subcontinent, and Indonesia, but appears only sporadically in North America, Europe, northern Asia, and Australia.

Typhoid fever progresses in several stages. Cells of the pathogen (Figure 32.6*a*) ingested in contaminated water (or occasionally food) reach the small intestine where they grow and enter the lymphatic system and the bloodstream; from here, the pathogen can travel to many different organs. One to two weeks later, the first symptoms of typhoid appear; these include a mild fever, headache, and general malaise. During this period, the liver and spleen of the typhoid patient become heavily infected. About a week later, the fever becomes more intense (up to 40°C) and the patient typically becomes delirious; diarrhea can occur in this stage and abdominal pain can be severe. Complications can follow, including intestinal bleeding and perforation of the small intestine. The latter releases large numbers of bacterial cells into the abdomen, leading to a condition called *sepsis* (systemic infection and inflammation) and possibly also to septic shock. Both of these conditions are potentially fatal and up to 40% of sepsis cases are fatal. After about a week in this crisis stage, the symptoms of typhoid begin to wane and recovery occurs.

Treatment for typhoid consists of antibiotic therapy and fluid replacement to ward off dehydration. In some cases surgery may be necessary to repair perforated intestines. Although a variety of antibiotics can kill *S. enterica* (*typhi*), resistance to many of these has developed. Isolation of the causative strain and assessment of its antibiotic sensitivity (Section 28.4) is often necessary to ensure that antibiotics will cure the infection.

In the United States, fewer than 400 cases of typhoid occur per year, but typhoid fever used to be a major public health threat before drinking water was routinely filtered and chlorinated (Figure 29.7). However, breakdown of water treatment methods, contamination of water during floods, earthquakes, and other disasters, or contamination of water supply pipes with leaking sewer lines can propagate epidemics of typhoid fever, even in developed countries.

In some typhoid patients, the gallbladder becomes infected with the pathogen. If these individuals also have gallstones, these can become colonized with *S. enterica* (*typhi*) cells and serve as a long-term reservoir of the pathogen from which it is continuously shed into feces and urine. Such individuals are otherwise healthy "carriers" of typhoid and can transmit the disease over long periods. The notorious cook "Typhoid Mary," who as a cook for hire spread typhoid throughout the New York City area for nearly 15 years beginning in the early twentieth century, was the classic example of a typhoid carrier.

Norovirus Illness

Viruses can be transmitted in water and cause human disease. Norovirus (Figure 32.6*b*) is one example and a common cause of gastrointestinal illness due to contaminated water (or food, Section 32.14). Norovirus is a single-stranded plus-sense RNA virus (Section 10.8) and is the leading cause of gastrointestinal illnesses worldwide (see Table 32.5).

Norovirus infection causes symptoms of vomiting, diarrhea, and malaise of relatively short duration. The disease is rarely fatal, although in compromised individuals (very young, elderly, or immune deficient), the significant dehydration that accompanies repeated bouts of norovirus-triggered vomiting and diarrhea can be life-threatening. A clinical diagnosis of norovirus gastrointestinal illness is made by a combination of observing symptoms and the direct detection of either viral RNA by RT-PCR (Sections 12.1 and 28.8) or viral antigens by enzyme immunoassay (Section 28.7) in samples of feces or vomit.

Norovirus disease is easily transmitted person to person or to food by the fecal–oral route. The infectious dose is very small, as exposure to as few as 10–20 norovirus virions (Figure 32.6*b*) is sufficient to initiate disease. The most common sources of waterborne norovirus outbreaks are well water or recreational waters that have been contaminated with sewage. Norovirus is also often the culprit when mass common-source gastrointestinal illnesses strike people on cruise ships or in long-term care facilities or other group settings. In these situations, the virus can be transmitted person to person, by contaminated food or water (usually food), or by any combination of these.

MINIQUIZ

- Contrast the causative agents of typhoid and noro gastrointestinal disease.
- What public health conditions allow for outbreaks of typhoid fever?

III • Food as a Disease Vehicle

The foods we eat, whether they are fresh, prepared, or preserved, are rarely sterile. Instead, they are almost always contaminated with spoilage microorganisms of various kinds and occasionally with pathogens. Microbial activities are key to the production of

some foods, such as fermented foods, but most of the microorganisms in or on food are unwelcome and diminish either food quality or safety (or both). In this part, we explore the contrasting processes of food spoilage and food preservation, how food safety is assessed, and the transmission of pathogens in food. In the next two parts we focus on major foodborne diseases.

32.6 Food Spoilage and Food Preservation

Many foods provide an excellent medium for the growth of bacteria and fungi. Properly stored food can still undergo food spoilage but is usually not a vehicle for disease assuming that it was free of pathogens to begin with. This is because with rare exception, organisms responsible for food spoilage are not the same as those that cause foodborne illnesses.

Food Spoilage

Food spoilage is any change in the appearance, smell, or taste of a food product that makes it unacceptable to the consumer, whether or not the change is due to microbial growth. Foods are rich in organic matter, and the physical and chemical characteristics of a food determine its susceptibility to microbial activity. With respect to spoilage, a food or food product falls into one of three categories: (1) **Perishable foods** include many fresh food items such as meats and many fruits and vegetables; (2) **semiperishable foods** include foods such as potatoes, some apples, and nuts; and (3) **nonperishable foods** include items such as sugar and flour. The foods in these categories differ primarily with regard to their *moisture content*, as measured by their water activity (a_w, Section 5.13). Nonperishable foods have low moisture levels and can generally be stored for long periods without spoilage. Perishable and semiperishable foods, by contrast, typically have higher moisture levels and hence these foods must be stored under conditions that inhibit microbial growth.

Fresh foods are typically spoiled by a wide variety of bacteria and fungi (Table 32.3). The chemical properties of foods vary widely, and each food is characterized by its moisture level and the nutrients it contains as well as other factors, such as its acidity or alkalinity. As a result, each susceptible food is typically spoiled by a specific group of microorganisms. The time required for a microbial population to reach a significant level in a given food product depends on both the size of the initial inoculum and the rate of growth during the exponential phase. Microbial numbers in a food product may initially be so low that no measurable effect can be observed, with only the last few cell doublings leading to observable spoilage. Hence, an unconsumed portion of a food product that is palatable and eaten one day can be badly spoiled the next.

The type of food spoilage and the microbial composition of the spoilage community (Table 32.3) are functions of both the food product and the storage temperature. Food spoilage microorganisms are often *psychrotolerant*, meaning that although they grow best at temperatures above 20°C, they can also grow at refrigeration temperatures (3–5°C) (Section 5.10). However, at any given storage temperature, some species grow faster than others, and thus the composition of the microbial spoilage community of the same food product stored at different temperatures can vary significantly.

TABLE 32.3 Microbial spoilage of fresh food[a]

Food product	*Type of microorganism*	*Common spoilage organisms, by genus*
Fruits and vegetables	Bacteria	*Erwinia, Pseudomonas, Corynebacterium* (mainly vegetable pathogens; rarely spoil fruit)
	Fungi	*Aspergillus, Botrytis, Geotrichum, Rhizopus, Penicillium, Cladosporium, Alternaria, Phytophthora*, various yeasts
Fresh meat, poultry, eggs, and seafood	Bacteria	*Acinetobacter, Aeromonas, Pseudomonas, Micrococcus, Achromobacter, Flavobacterium, Proteus, Salmonella, Escherichia, Campylobacter, Listeria*
	Fungi	*Cladosporium, Mucor, Rhizopus, Penicillium, Geotrichum, Sporotrichum, Candida, Torula, Rhodotorula*
Milk	Bacteria	*Streptococcus, Leuconostoc, Lactococcus, Lactobacillus, Pseudomonas, Proteus*
High-sugar foods	Bacteria	*Clostridium, Bacillus, Flavobacterium*
	Fungi	*Saccharomyces, Torula, Penicillium*

[a]The organisms listed are the most commonly observed spoilage agents of fresh, perishable foods. Many of these genera include species that are human pathogens (Chapters 30–33).

Food Preservation and Fermentation

Food storage and preservation methods are designed to slow or stop the growth of microorganisms that spoil food or that can cause foodborne disease. The major methods of food preservation include altering the temperature, acidity, or moisture level of the food, or treating it with radiation or chemicals that prevent microbial growth.

Refrigeration slows microbial growth, but a remarkable number of microorganisms, particularly bacteria, can grow at refrigeration temperatures. Storage in the household freezer reduces growth considerably, but slow growth still occurs in pockets of liquid water trapped within the frozen food. In general, a lower storage temperature results in less microbial growth and slower spoilage, but storage at temperatures below −20°C is too expensive for routine use and also can negatively affect food appearance, consistency, and taste.

Heat reduces the bacterial load and can even sterilize a food product, and is especially useful for the preservation of liquids or high-moisture foods. The limited heat treatment of **pasteurization** (Section 5.15) does not sterilize liquids but reduces microbial numbers and eliminates pathogens. *Canning*, by contrast, typically sterilizes the food but requires careful processing in a sealed container at the correct temperature for the correct length of time. If viable microorganisms remain in a can or glass jar, their growth can produce gas, resulting in bulges or even explosions (Figure 32.7). The environment inside a can or sealed jar is anoxic, and an important

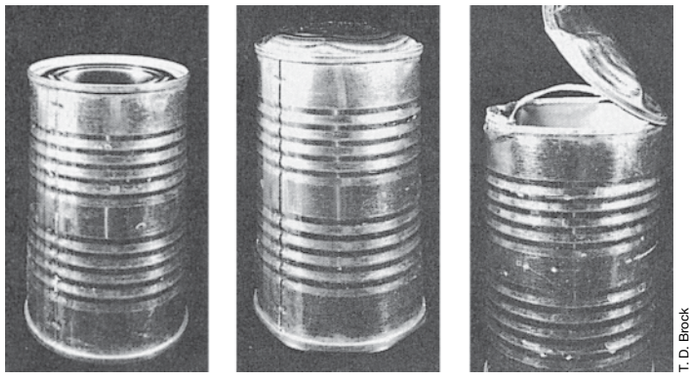


Figure 32.7 Changes in sealed tin cans as a result of microbial spoilage. *(a)* A normal can. The top of the can is pulled in a bit because of the normal slight vacuum inside. *(b)* Swelling due to gas production. *(c)* The can shown in *b* was dropped, and the gas pressure resulted in a violent explosion, tearing the lid apart.

genus of anaerobic bacteria that can grow in canned foods is the endospore-forming *Clostridium*, one species of which causes botulism (Sections 25.6 and 32.9).

Foods can be made drier by either physically removing the water or by adding solutes, such as salt or sugar. Extremely dry or solute-loaded foods help prevent bacterial growth, but spoilage can still occur and when it does, it is typically from fungi. Many foods are preserved by the addition of small amounts of antimicrobial chemicals. These chemicals, which include nitrites, sulfites, propionate, and benzoate along with a few others, find wide application in the food industry for enhancing or preserving food texture, color, freshness, or flavor. Although not widely practiced in many countries, the *irradiation* of food with ionizing radiation is also an effective means for reducing microbial contamination.

Many common foods and beverages are preserved through the metabolic activities of microorganisms; these are *fermented foods* (Figure 32.8 and Table 32.4). The fermentation process (Chapters 3 and 14) yields large amounts of preservative chemicals. The major bacteria important in the fermented foods industry are organic acid–producing bacteria such as the lactic acid bacteria (in fermented milks), the acetic acid bacteria (in pickling), and the propionic acid bacteria (in certain cheeses) (Table 32.4). The yeast *Saccharomyces cerevisiae* produces alcohol as the preservative in the production of alcoholic beverages. The high level of organic acids or alcohol generated from these fermentations prevents the growth of both spoilage organisms and pathogens in the fermented food product.

Figure 32.8 Examples of fermented foods. Bread, sausage meats, cheeses and many other dairy products, and fermented and pickled vegetables are food products that are produced or enhanced by fermentation reactions catalyzed by microorganisms (see also Table 32.4).

TABLE 32.4 Fermented foods and fermentation microorganisms

Food category/ Preservative	*Primary fermenting microorganisms*[a]
Dairy foods/Lactic acid, propionic acid	
Cheeses	*Lactococcus, Lactobacillus, Streptococcus thermophilus, Propionibacterium* (Swiss cheese)
Fermented milk products	
Buttermilk and sour cream	*Lactococcus*
Yogurt	*Lactobacillus, Streptococcus thermophilus*
Alcoholic beverages/Ethanol	*Zymomonas, Saccharomyces*[b]
Yeast breads/Baking	*Saccharomyces cerevisiae*[b]
Meat products/Lactic and other acids	
Dry sausages (pepperoni, salami) and semidry sausages (summer sausage, bologna)	*Pediococcus, Lactobacillus, Micrococcus, Staphylococcus*
Vegetables/Lactic acid	
Cabbage (sauerkraut)	*Leuconostoc, Lactobacillus*
Cucumbers (pickles)[c]	Lactic acid bacteria
Vinegar/Acetic acid	*Acetobacter*
Soy sauce/Lactic acid and many other substances	*Aspergillus,*[d] *Tetragenococcus halophilus*, yeasts

[a]Unless otherwise noted, these are all species of *Firmicutes* except for *Micrococcus*, which is in the *Actinobacteria*, and *Zymomonas* and *Acetobacter*, which are in the *Alphaproteobacteria*.
[b]Yeast. Various *Saccharomyces* species are used in alcohol fermentations. *S. cerevisiae* is the common baker's yeast. To make sourdough bread, species of *Lactobacillus* are used.
[c]Nonfermented pickles are cucumbers marinated in vinegar (5–8% acetic acid).
[d]A mold.

MINIQUIZ

- List the major food groups as categorized by their susceptibility to spoilage.
- Identify physical and chemical methods used for food preservation. How does each method limit growth of microorganisms?
- List some dairy, meat, beverage, and vegetable foods produced by microbial fermentation. What is the preservative in each case?

32.7 Foodborne Diseases and Food Epidemiology

Foodborne illnesses resemble waterborne illnesses in being *common-source* diseases. Most foodborne disease outbreaks are due to

improper food handling and preparation by domestic consumers; these typically affect only a few people and are rarely reported. However, occasional disease outbreaks due to breakdowns in safe food handling and preparation at restaurants or food-processing and distribution plants can affect large numbers of people in geographically widespread regions.

Foodborne Diseases and Microbial Sampling

Foodborne diseases are of two types, *food infections* and *food poisonings*; some foodborne diseases fall into both categories. **Food poisoning**, also called **food intoxication**, results from ingestion of foods containing preformed microbial toxins. The microorganisms that produced the toxins do not have to grow in the host and may not even be alive at the time the contaminated food is consumed; ingestion and activity of the toxin is what causes the illness. We previously discussed some of these toxins, notably the exotoxin of *Clostridium botulinum* and the superantigen toxins of *Staphylococcus* and *Streptococcus* (Sections 25.6 and 27.10). In contrast to food poisoning, **food infection** occurs from the ingestion of food containing sufficient numbers of viable pathogens to cause colonization and growth of the pathogen in the host, ultimately resulting in disease.

Food infections are the most common foodborne illnesses in the United States and account for four of the top five leading foodborne illnesses. Table 32.5 lists the major microorganisms that cause food infections and food poisonings in the United States.

Eight microorganisms account for the great majority of foodborne illness, hospitalizations, and deaths in the United States: *Salmonella* species, *Clostridium perfringens, Campylobacter jejuni, Staphylococcus aureus, Listeria monocytogenes,* and *Escherichia coli* (all bacteria); norovirus; and *Toxoplasma* (a protist) (Table 32.5). Four of these—norovirus, *Salmonella, C. perfringens*, and *Campylobacter*—account for nearly 90% of all foodborne illness, with norovirus (Sections 32.5 and 32.14) being the most common culprit (60%).

Rapid diagnostic methods that do not require culturing an organism have been developed to detect important food pathogens, and many of these were described in Chapter 28. Isolation of pathogens from foods usually requires preliminary treatment of the food to suspend microorganisms embedded or entrapped within. A standard method for this purpose employs a blender called a *stomacher* (Figure 32.9), a device to process food samples sealed in sterile bags. Paddles in the stomacher crush, blend, and homogenize the samples in a fashion resembling the peristaltic action of the stomach but under conditions that prevent contamination. The homogenized samples are then analyzed for specific pathogens or their products.

In addition to identifying pathogens in the food itself, disease investigators must also recover the foodborne pathogen from the diseased patient in order to establish a cause-and-effect relationship between the pathogen and the illness. In fact, identification of the *same strain* of a particular pathogen in patients and the suspected contaminated food is the "gold standard" for linking cause and effect in a foodborne disease outbreak, and a variety of microbiological, immunological, and molecular techniques are available for these purposes (Chapter 28).

Foodborne Disease Epidemiology

An outbreak of foodborne disease can occur in a home, a school cafeteria, a college dining hall, a restaurant, a military mess hall, or anywhere a contaminated food is consumed by many individuals. In addition, central food-processing plants and distribution centers provide opportunities for contaminated foods to cause disease outbreaks far from where the food was originally processed. It is the job of the food epidemiologist to track disease outbreaks and determine their source, often down to the precise location in which the food was contaminated.

A good example of effective foodborne disease tracking is the outbreak caused by *Escherichia coli* O157:H7 (see Section 32.11 and Figure 32.14*b*) in the United States in 2006. Through culturing and molecular studies, this outbreak was linked to the consumption of contaminated packaged spinach and was quickly traced to a food-processing facility in California. The contaminated spinach was distributed nationwide from the California plant, but most disease cases were in the Midwest. In the summer of 2013, another "packaged" outbreak occurred in the Midwest but in this case was

TABLE 32.5 Major foodborne pathogens[a]

Organism	*Disease*[b]	*Foods*
Bacteria		
Bacillus cereus	FP and FI	Rice and starchy foods, high-sugar foods, meats, gravies, pudding, dry milk
Campylobacter jejuni	FI (4)[c]	Poultry, dairy
Clostridium botulinum	FP	Improperly heat-processed nonacidic foods such as home-canned vegetables (beans, potatoes, corn, asparagus)[e]
Clostridium perfringens	FP and FI (3)[c]	Meat and vegetables held at improper storage temperature
Escherichia coli O157:H7	FI	Meat, especially ground beef, raw vegetables
Other enteropathogenic *Escherichia coli*	FI	Meat, especially ground meat, raw vegetables
Listeria monocytogenes	FI	Refrigerated "ready to eat" foods
Salmonella spp.	FI (2)[c]	Poultry, meat, dairy, eggs
Staphylococcus aureus	FP (5)[c]	Meat, desserts
Streptococcus spp.	FI	Dairy, meat
Yersinia enterocolitica	FI	Pork, milk
All other bacteria	FP and FI	
Protists[d]		
Cryptosporidium parvum	FI	Raw and undercooked meat
Cyclospora cayetanensis	FI	Fresh produce
Giardia intestinalis	FI	Contaminated or infected meat
Toxoplasma gondii	FI	Raw and undercooked meat
Viruses		
Norovirus	FI (1)[c]	Shellfish, many other foods
Hepatitis A	FI	Shellfish and some other foods eaten raw

[a]Data from the Centers for Disease Control and Prevention, Atlanta, Georgia, USA.
[b]FP, food poisoning; FI, food infection.
[c]The number in parentheses is the rank of the top five foodborne pathogens in the United States.
[d]All of these protists are discussed in Chapter 33.
[e]See page 973.

Figure 32.9 A stomacher. Paddles in this specialized blender homogenize the food sample contained in a sealed and sterile bag (arrow). The sample is first suspended in a sterile solution to form a uniform mixture.

linked to lettuce instead of spinach and to the parasite *Cyclospora cayetanensis* (Section 33.4) instead of to the bacterium *E. coli.*

To be effective, foodborne disease trackers must work quickly. For example, when the first case in the *E. coli* spinach outbreak appeared in late August, a link to the specific spinach product was made less than a month later. Because *E. coli* O157:H7 has been well studied, public health officials were able to quickly identify the strain contaminating the bagged spinach. Authorities then traced this strain back to the processing plant and eventually identified a specific agricultural field near the processing plant as the source of the pathogen. Although it remains unclear how the spinach was contaminated, domestic animal manure was the likely source. During the outbreak, two foodborne disease surveillance networks, *FoodNet* (Centers for Disease Control and Prevention) and *PulseNet* (an international molecular typing network for foodborne diseases), played important roles in exposing and ending the outbreak.

The spinach *E. coli* epidemic, although serious and even deadly for some, was discovered, contained, and stopped very quickly. However, this incident shows how centralized food-processing facilities can quickly spread disease to distant populations. Because of this, food hygiene standards and surveillance must be maintained at the highest possible level at all times in restaurants and central food-processing and distribution facilities.

MINIQUIZ

- Distinguish between food infection and food poisoning.
- Describe microbial sampling procedures for solid foods such as meat.
- Describe how a foodborne disease outbreak is tracked.

IV • Food Poisoning

Food poisoning can be caused by various bacteria and a few fungi. Here we consider the gram-positive bacteria *Staphylococcus aureus, Clostridium botulinum*, and *Clostridium perfringens*, the most common causes of bacterial food poisoning. Two of these microbes—*S. aureus* and *C. perfringens*—are part of the "top five" causes of foodborne illness (Table 32.5).

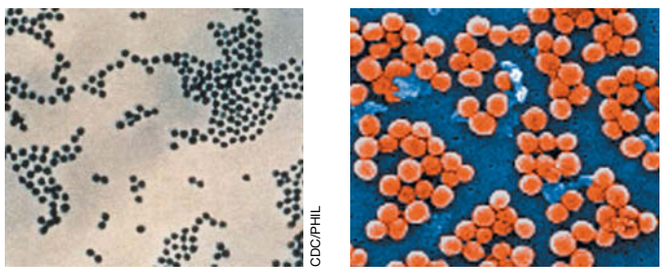
32.8 Staphylococcal Food Poisoning

A powerful form of food poisoning is caused by enterotoxins (Section 25.6) produced by the gram-positive bacterium *Staphylococcus aureus* (**Figure 32.10**; Section 16.7). This organism is commonly associated with the skin and upper respiratory tract and is a frequent cause of pus-forming wounds (Section 30.9 and Figure 30.29). *S. aureus* can grow aerobically or anaerobically in many common foods and produces a suite of enterotoxins. When consumed, the toxins cause gastrointestinal symptoms characterized by one or more of nausea, vomiting, diarrhea, and dehydration. The onset of symptoms is rapid, within 1–6 h of ingestion depending on the amount of enterotoxin consumed, but the symptoms usually pass within 48 h.

Staphylococcal Enterotoxins

Many *S. aureus* enterotoxins are heat-stable and all are stable to stomach acidity. Most strains of *S. aureus* produce only one or two of these toxins, and some strains are nonproducers. However, any one of the staph enterotoxins can cause food poisoning. The toxins pass through the stomach to the small intestine and trigger disease symptoms from there. Besides their normal gastrointestinal activities, staph enterotoxins are also *superantigens* and can lead to potentially lethal toxic shock syndrome (Sections 25.7 and 27.10).

S. aureus enterotoxins are given acronyms beginning with "SE" (for "staphylococcus enterotoxin"): SEA, SEB, SEC, and SED, which are encoded by the genes *sea, seb, sec*, and *sed*. Not all of these genes are on the *S. aureus* chromosome, but their sequences show them to be highly related. The genes *seb* and *sec* are encoded on the bacterial chromosome, *sea* on a lysogenic bacteri-ophage (Section 8.7), and *sed* on a plasmid. The phage- and plasmid-encoded genes can transfer the ability to make toxin to nontoxigenic strains of *Staphylococcus* by horizontal gene transfer (Chapter 11). SEA is the most common cause of staph food poisoning worldwide.



(a) (b)

Figure 32.10 *Staphylococcus aureus*. *(a)* Gram-stained light micrograph showing the typical "cluster of grapes" morphology of staphylococci. *(b)* Colorized scanning electron micrograph of cells of *S. aureus*. A single cell is about 0.8 μm in diameter.

Disease Properties, Treatment, and Prevention

Foods may contain cells of *S. aureus* for several reasons. The organism may have been present on the food source itself, for example, on a meat product. But more commonly, cells of *S. aureus* are introduced to the food by contamination from the food preparer or by contamination of the food product with raw meat or a contaminated sauce or dressing. A common scenario for a staph food poisoning incident is when a food preparer introduces *S. aureus* from nasal secretions or from an uncovered skin wound or leaking bandage into the food during its preparation. If the contaminated food is then stored at room temperature or above, the stage is set for the rapid growth of *S. aureus* and the production of staph enterotoxins.

Each year there are an estimated nearly quarter million cases of staphylococcal food poisoning in the United States. The foods most commonly implicated are custard- and cream-filled baked goods, poultry, eggs, raw and processed meat, puddings, and creamy salad dressings. Salads prepared with mayonnaise-based dressings or those that contain shellfish, chicken, pasta, tuna, potato, egg, or meat, are also common vehicles. Salted foods such as ham can be vehicles because of the ability of *S. aureus* to grow quickly in salty environments (Section 30.9). If any of these foods are contaminated with *S. aureus* but are refrigerated immediately after preparation, they usually remain safe because the organism grows poorly at low temperatures. But if enterotoxin has already been produced, mild heating may not make the food safe, as staph enterotoxins are stable to 60°C.

Treatment of staph food poisoning with antibiotics is not useful because any ingested cells of *S. aureus* have already been killed by the acidity in the stomach and antibiotics have no effect on the enterotoxins. Rest, drinking plenty of fluids, and using antinausea drugs are the best prescription for a rapid recovery. As for any foodborne illness, staphylococcal food poisoning can be prevented by proper sanitation and hygiene in food production, preparation, and storage. In this regard, food preparers should practice thorough and frequent hand washing, prevent foods from coming into contact with nasal tissues and secretions, and routinely wear and frequently change disposable gloves when handling food products, especially if they have a bandaged hand wound.

MINIQUIZ

- Identify the symptoms and mechanism of staphylococcal food poisoning.
- Why does antibiotic treatment not affect the outcome or the severity of disease with staph food poisoning?

32.9 Clostridial Food Poisoning

The endospore-forming anaerobic bacteria *Clostridium perfringens* and *Clostridium botulinum* (Section 16.8) cause serious food poisoning. Canning and cooking procedures kill vegetative cells of these species but may not kill all endospores. If this occurs, viable endospores in the food can germinate and the resulting cells produce toxins.

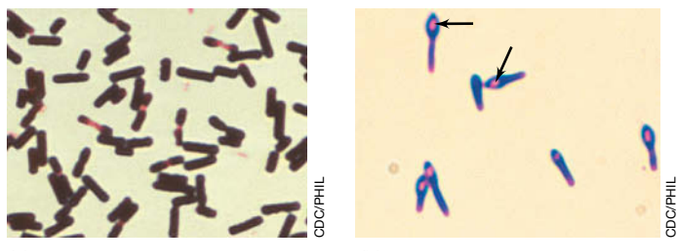
There is a clear distinction in the disease process between perfringens food poisoning and botulism. In the case of botulism, the toxin is a neurotoxin and only the toxin is required for disease. Botulism does not require the growth of *C. botulinum* in the human body but growth may nevertheless occur, particularly in cases of infant botulism. By contrast, with perfringens food poisoning, a large number of cells must be ingested in order for the toxin—in this case, an enterotoxin—to be produced.

Clostridium perfringens Food Poisoning

Clostridium perfringens (**Figure 32.11a**) is commonly found in soil but can also be found in sewage, primarily because it lives in small numbers in the intestinal tract of humans and other animals. *C. perfringens* is the third most often reported cause of foodborne disease in the United States behind norovirus illnesses (Sections 32.5 and 32.14) and *Salmonella* infections (Section 32.10 and Table 32.5). In 2015, about 1 million perfringens cases were estimated to have occurred in the United States.

C. perfringens is a proteolytic bacterium; proteins are catabolized by fermentation (Section 14.21). Perfringens food poisoning requires the ingestion of a large dose ($>10^8$) of *C. perfringens* cells in contaminated cooked or uncooked foods, usually high-protein foods such as meat, poultry, and fish. *C. perfringens* can grow in meat dishes cooked in bulk where heat penetration is often insufficient. *C. perfringens* grows quickly in the food, especially if left to cool at room temperature. It is when sporulation begins that the perfringens enterotoxin is produced. The toxin alters the permeability of the intestinal epithelium, leading to nausea, diarrhea, and intestinal cramps. The onset of perfringens food poisoning typically begins 7–15 h after consumption of the contaminated food and usually resolves within 24 h; for this reason, the disease is sometimes written off as a "stomach flu" or "24-hour flu." Fatalities from perfringens food poisoning are rare, and no specific treatment is necessary other than replacing fluids lost from diarrhea or vomiting (if it occurs).

A diagnosis of perfringens food poisoning is made from isolation of *C. perfringens* from the feces or, more reliably, by an immunoassay that can detect *C. perfringens* enterotoxin in feces. Prevention of perfringens food poisoning requires that cooked foods not be contaminated with raw foods and that all foods be properly heated during cooking and home canning. The perfringens enterotoxin is



(a) (b)

Figure 32.11 Food poisoning clostridia. *(a)* Gram stain of a growing culture of *Clostridium perfringens*, the bacterium that causes perfringens food poisoning. A cell measures about 1 × 3 µm. *(b)* Gram stain of a sporulating culture of *Clostridium botulinum*, the agent of botulism. A cell measures about 1 × 5 µm and endospores (arrows) appear red.

heat-labile and thus any toxin that may have formed in a food product is destroyed by proper heating (75°C). Cooked foods should be refrigerated as soon as possible to rapidly lower temperatures and inhibit the growth of any *C. perfringens* that may have been present.

Botulism

Botulism is a severe and potentially fatal food poisoning caused by the consumption of food containing the exotoxin produced by *C. botulinum* (Figure 32.11*b*). This bacterium normally inhabits soil or water, but its cells or endospores may contaminate raw and processed foods. If viable endospores of *C. botulinum* remain in the food, they may germinate and produce botulinum toxin; ingesting even a small amount of this highly poisonous substance can cause severe illness or death.

Botulinum toxin is a neurotoxin that affects autonomic nerves that control key body functions such as respiration and heartbeat; the typical result is a flaccid paralysis (Section 25.6 and Figure 25.13). At least seven distinct botulinum toxins are known. Because the toxins are destroyed by heat (80°C for 10 minutes), *thoroughly* cooked food, even if contaminated with toxin, is harmless. Much foodborne botulism is from improperly processed home-canned foods, especially nonacidic foods such as corn, potatoes, and beans. Any viable *C. botulinum* endospores that remain in the sealed (and now anoxic) jar may germinate during storage and produce toxin. Many of these foods are used without cooking when making cold salads, and hence any botulinum toxin present is not destroyed (see page 973 for an example). Prevention of foodborne botulism thus requires careful attention to canning and related food preservation practices.

Although infants can be poisoned by toxin-contaminated food, the majority of infant botulism cases occur from toxin produced following actual *infection* of the infant with *C. botulinum*. This occurs most commonly in newborns up to about 2 months of age because they lack a well-developed intestinal microbiota that can outcompete *C. botulinum*. Ingested *C. botulinum* endospores germinate in the infant's intestine, triggering growth and toxin production. Wound botulism can also occur from infection, presumably from endospores in contaminating material introduced via a parenteral route. Wound botulism is most commonly associated with illicit injectable drug use.

All forms of botulism are rare. In the United States about 110 cases are observed each year with about 45% being infant, 30% wound, and 25% foodborne. Botulism, however, is very serious because of the high mortality associated with untreated disease. Because most cases are diagnosed and treated, less than 5% of all botulism cases result in death. Botulism is diagnosed when either botulinum toxin or *C. botulinum* cells are detected in the patient (or in the contaminated food) coupled with clinical observations of localized paralysis (impaired vision and speech) beginning 18–24 h after ingestion of the contaminated food. Treatment for botulism is by administration of botulinum antitoxin if the diagnosis is early, and mechanical ventilation if signs of respiratory paralysis have already appeared. If the dose of toxin is not too high, infant botulism is usually self-limiting, and most infants recover with only supportive therapy, such as assisted ventilation.

MINIQUIZ

- Compare and contrast toxin production and toxemia in botulism and perfringens food poisoning.
- Describe differences in the transmission of botulism in adults versus infants.

V • Food Infection

Recall that food *infection* is not the same thing as food *poisoning* (Section 32.7). Food infection results from ingestion of food containing sufficient numbers of viable pathogens to allow growth of the pathogen and disease in the host. Food infections are very common, and in the United States, the sum total of food infections outnumbers cases of food poisoning by nearly 10-fold. Sections 25.1 and 25.2 reviewed the infection process, summarizing the steps by which microorganisms—friend and foe alike—attach and become established in host tissues.

32.10 Salmonellosis

Salmonellosis is a gastrointestinal disease typically caused by ingesting food contaminated with *Salmonella* or by handling *Salmonella*-contaminated animals or animal products (Figure 32.12). Salmonellosis is the most common bacterial food infection in the United States and second only to norovirus in total number of cases. Symptoms of salmonellosis begin after the pathogen—a gram-negative, facultatively aerobic rod related to *Escherichia coli*

(a) (b) (c) (d)

Figure 32.12 Some sources of *Salmonella*. *(a)* Poultry contain *Salmonella* in their intestines and droppings. *Salmonella* can also be transferred to humans from both *(b)* reptiles and *(c)* amphibians. *(d)* Fresh chicken breasts and eggs.

(↔ Section 16.3 and see Figure 32.13)—colonizes the intestinal epithelium. *Salmonella* species normally inhabit the intestine of warm-blooded and many cold-blooded animals (Figure 32.12) and are common in sewage. Thus, some cases of salmonellosis are waterborne rather than foodborne infections, and this is especially the case for typhoid fever (Section 32.5).

The accepted species epithet for pathogenic *Salmonella* is *enterica*, and there are seven subspecies of *S. enterica*. Most human salmonellas fall into the *S. enterica* subspecies *enterica* group. Each subspecies is also divided into *serovars* (serological variants). Thus, there are *Salmonella enterica* serovar Typhi, or *Salmonella enterica* (*typhi*) for short, and *Salmonella enterica* serovar Typhimurium, and so on. *S. enterica* serovars Typhimurium and Enteritidis are most frequently associated with foodborne salmonellosis.

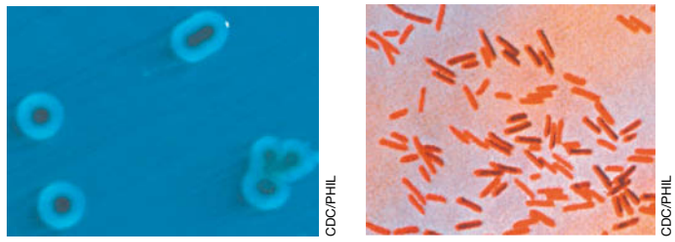
Pathogenesis and Epidemiology

The most common form of salmonellosis is *enterocolitis*. Ingestion of food containing viable cells of *Salmonella* results in colonization of both the small and large intestines. From here, cells of *Salmonella* invade phagocytic cells and grow intracellularly, spreading to adjacent cells as host cells die. After invasion, pathogenic *Salmonella* deploy several virulence factors including endotoxins, enterotoxins, and cytotoxins that damage and kill host cells (Chapter 25). Symptoms of enterocolitis typically appear 8–48 h after ingestion and include a headache, chills, vomiting, and diarrhea, followed by a fever that can last for several days. The disease normally resolves without intervention in 2–5 days. After recovery, however, patients may shed *Salmonella* in their feces for several weeks and some become healthy carriers. A few serovars of *S. enterica* may also cause septicemia (a blood infection) and enteric or typhoid fever, a potentially fatal disease characterized by systemic infection and high fever lasting several weeks (Section 32.5).

The incidence of salmonellosis in the United States has been steady over the last decade, with about a million estimated cases each year. There are several routes by which *Salmonella* may enter the food supply. The bacteria may reach food through fecal contamination from food handlers. Food production animals such as chickens, pigs, and cattle harbor *Salmonella* serovars that are pathogenic to humans, and these may be carried through to fresh foods such as eggs, meat, and dairy products (Figure 32.12*d*). *Salmonella* food infections are often traced to products such as custards, cream cakes, meringues, pies, and eggnog made with uncooked eggs. Other foods commonly implicated in salmonellosis outbreaks are meats and meat products, especially poultry, cured but uncooked sausages and other meats, milk, and milk products. The simple handling of *Salmonella*-contaminated animals (Figure 32.12*b*) can also lead to salmonellosis.

Diagnosis, Treatment, and Prevention

Foodborne salmonellosis is diagnosed from a combination of clinical symptoms, a history of recent consumption of high-risk foods, and culturing of the organism from feces. Selective, differential media are used to isolate *Salmonella* and discriminate it from other gram-negative enteric bacteria (**Figure 32.13**). Tests for the presence of *Salmonella* are commonly carried out on foods of animal origin such as raw meat, poultry, eggs, and powdered milk. Tests include several rapid tests (Chapter 28), but even rapid tests usually rely on enrichment procedures to increase cell numbers of *Salmonella* to testable levels.



(a) (b)

Figure 32.13 Isolation of *Salmonella*. *(a)* Colonies of *S. enterica* (*typhimurium*) on Hektoen agar, which contains inhibitors of gram-positive bacteria and both lactose and peptone as carbon sources. Thiosulfate in the medium is reduced to H_2S by *Salmonella* and complexes with iron to form black FeS. *Salmonella* thus forms white colonies with black FeS centers, a pattern unique among enteric bacteria. The blue color results from the medium turning alkaline because *Salmonella* species do not ferment lactose and instead consume the amino acids in peptone. *(b)* Gram stain of cells of *Salmonella*; an average cell is about 1×3 μm.

Treatment of enterocolitis is usually unnecessary, and antibiotic treatment does not shorten the course of the disease or eliminate the carrier state. Foods containing *Salmonella* but heated to at least 70°C are generally safe if consumed immediately, held at 50°C or above, or quickly refrigerated. Any foods that become contaminated by an infected food handler can support the growth of *Salmonella* if the food is held for a long enough period, especially if it is not kept very warm or refrigerated.

MINIQUIZ

- Describe salmonellosis food infection. How does a food infection differ from food poisoning?
- How might *Salmonella* contamination of food production animals be contained?

32.11 Pathogenic *Escherichia coli*

Most strains of *Escherichia coli* are common microbiota in the human colon and are not pathogenic. However, a few strains are potential foodborne (and occasionally waterborne) pathogens (**Figure 32.14**) and produce potent enterotoxins (↔ Section 25.6). These pathogenic strains are grouped on the basis of the type of toxin they produce and their specific disease syndromes. We focus here on Shiga toxin–producing *E. coli* and briefly consider some other toxigenic *E. coli* strains.

Although not in the "top five" in terms of foodborne infection pathogens (Table 32.5), pathogenic *E. coli* strains cause disease symptoms so severe that they often require hospitalization. Indeed, infections with pathogenic *E. coli* may cause life-threatening diarrheal disease and urinary tract distress.

Shiga Toxin–Producing *Escherichia coli* (STEC)

Shiga toxin–producing *Escherichia coli* (STEC) strains produce *verotoxin*, an enterotoxin similar to the Shiga toxin produced by

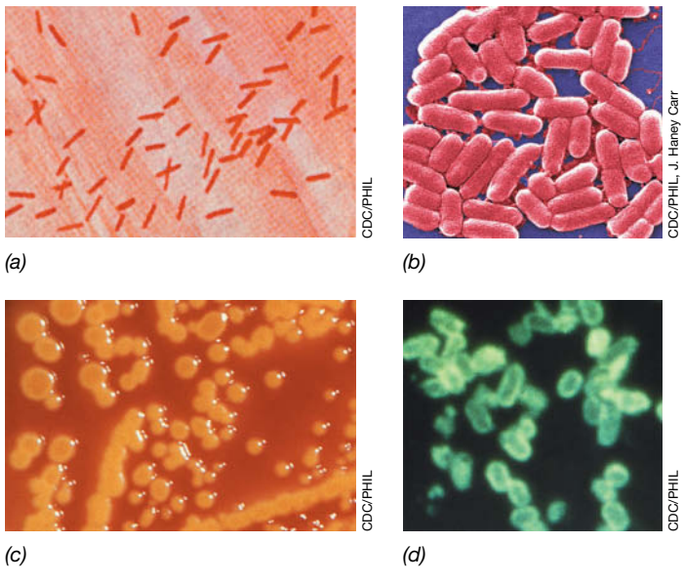


Figure 32.14 Pathogenic *Escherichia coli*. *(a)* Gram-stained cells showing the typical gram-negative, rod-shaped morphology of *E. coli*. *(b)* Colorized scanning electron micrograph of cells of *E. coli* O157:H7. Cells measure about 1 × 3 μm. *(c) E. coli* can be easily isolated on various selective and differential culture media such as Hektoen agar, where colonies of *E. coli* turn yellow because this bacterium ferments lactose and acidifies the medium (compare these with colonies of *Salmonella* on Hektoen agar in Figure 32.13*a*). *(d)* Enteropathogenic strains of *E. coli* can be detected, as in this fecal smear, using a specific fluorescent antibody.

Shigella dysenteriae, a close relative of *E. coli*. This toxin inhibits protein synthesis and induces a bloody diarrhea and kidney failure. STEC strains of *E. coli* are also called *enterohemorrhagic E. coli* (EHEC). The most widely distributed STEC is *E. coli* O157:H7 (Figure 32.14*b*). Following ingestion of food or water containing STEC, the bacteria infect the small intestine where they grow and produce verotoxin, which both causes a bloody diarrhea and initiates signs of kidney failure.

Nearly half of STEC infections are caused by the consumption of contaminated uncooked or undercooked meat, particularly mass-processed ground beef. *E. coli* O157:H7 is normally present in the intestines of healthy cattle and enters the human food chain if meat is contaminated with the animal's intestinal contents during slaughter and processing. STEC strains have also been implicated in food infection outbreaks caused by dairy products (especially raw milk products), fresh fruit, and raw vegetables. Contamination of the fresh foods by fecal material, typically from cattle carrying STEC strains, has been implicated in several of these cases (Section 32.7).

Other Pathogenic *Escherichia coli*

Children in developing countries often contract diarrheal disease caused by *E. coli*, and *E. coli* can also be the cause of "traveler's diarrhea," a common infection causing watery diarrhea (as opposed to the bloody diarrhea of STEC strains) in travelers to developing countries. The primary causal agents here are *enterotoxigenic E. coli* (ETEC, Figure 32.14*d*). These strains infect the small intestine and produce one of two heat-labile, diarrhea-producing enterotoxins.

In studies of United States citizens traveling in Mexico, the infection rate with ETEC is often greater than 50%. The prime vehicles are perishable foods such as fresh vegetables (for example, lettuce in salads) and public water supplies. The local population is typically resistant to the ETEC strains because of long-term contact with the organism. Other pathogenic *E. coli* strains include *enteropathogenic E. coli* (EPEC) strains that cause diarrheal diseases in infants and small children but do not cause invasive disease or produce toxins, and *enteroinvasive E. coli* (EIEC) strains, which invade the colon and cause watery and sometimes bloody diarrhea.

Diagnosis, Treatment, and Prevention

The general pattern established for the diagnosis, treatment, and prevention of STEC infection reflects current procedures used for all pathogenic *E. coli* strains. Laboratory diagnosis requires culture from the feces (Figure 32.14*c*) and identification of the O (lipopolysaccharide) and H (flagellar) antigens and toxins by immunological methods (Figure 32.14*d*). Identification and typing can also be done using various molecular analyses.

Treatment of STEC infections includes supportive care for dehydration and monitoring of renal function, blood hemoglobin, and platelets. Antibiotics may actually be harmful because they may trigger the release of large amounts of verotoxin from dying *E. coli* cells that would otherwise be voided intact in feces. For other pathogenic *E. coli* infections, treatment includes supportive therapy and, for severe cases and invasive disease, antimicrobial drugs to shorten and eliminate infection.

The most effective way to prevent infection with pathogenic *E. coli* of any type is to wash raw foods vigorously and make sure that meat, especially ground beef, is cooked thoroughly, which means that it should appear gray or brown with clear juices and have attained a temperature of greater than 70°C. In general, proper food handling, water purification, and appropriate hygiene also prevent the spread of pathogenic *E. coli*. Travelers can avoid diarrhea from pathogenic *E. coli* by drinking water only from properly sealed bottled water and avoiding any uncooked foods.

MINIQUIZ

- How do STEC strains of *Escherichia coli* differ from other pathogenic *E. coli*?
- Why are meats prime vehicles for pathogenic *E. coli*? How can contaminated meat be rendered safe to eat?

32.12 *Campylobacter*

Along with salmonellosis (Section 32.10) and perfringens food poisoning (Section 32.9), *Campylobacter* infections are in the top three most common bacterial foodborne diseases in the United States (Table 32.5). Cells of *Campylobacter* are gram-negative and motile spiral-shaped *Epsilonproteobacteria* (Section 16.5) that grow best at reduced oxygen tension (microaerophilic). Several species of *Campylobacter* are recognized, but *C. jejuni* and *C. fetus*

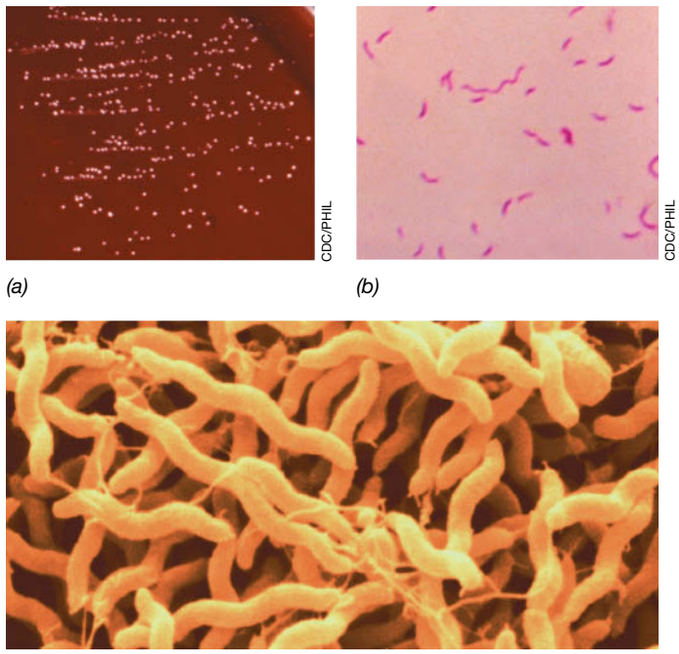


Figure 32.15 *Campylobacter*. *(a)* Colonies of *C. jejuni* grown on *Campylobacter* agar, a selective medium. The medium contains several antibiotics to which *Campylobacter* species are naturally resistant. *(b)* Gram stain and *(c)* scanning electron micrograph of cells of a *Campylobacter* species. Single cells average 0.4 × 2 μm in size.

(**Figure 32.15**) are the most commonly linked to human foodborne illnesses.

Epidemiology and Pathology

Campylobacter is transmitted to humans via contaminated food, most commonly in undercooked poultry or pork, raw shellfish, or occasionally in fecally contaminated water from surface sources. *C. jejuni* is a normal resident of the intestinal tract of poultry, and according to the United States Department of Agriculture, up to 90% of turkey and chicken carcasses are contaminated with *Campylobacter*. Pork can also carry *Campylobacter*, while beef is rarely a vehicle. *Campylobacter* species also infect domestic animals such as dogs, causing a milder form of diarrhea in the animal than that observed in humans. *Campylobacter* infections in infants in particular are often traced to infected domestic animals, especially dogs.

After cells of *Campylobacter* are ingested, the organism multiplies in the small intestine, invades the epithelium, and causes inflammation. Because *C. jejuni* is sensitive to gastric acid, cell numbers as high as 10^4 may be required to initiate infection. However, this number may be reduced to fewer than 500 cells if the pathogen is ingested in food or if the person is taking medication to reduce stomach acid production. *Campylobacter* infection causes a high fever (usually greater than 40°C), headache, malaise, nausea, abdominal cramps, and diarrhea with watery, frequently bloody emissions; symptoms subside in about a week.

Diagnosis, Treatment, and Prevention

Diagnosis of *Campylobacter* food infection requires isolation of the organism from feces and identification by growth-dependent tests, immunological assays, or genomic analyses. Culture media containing multiple antibiotics to which campylobacters are naturally resistant have been developed for selective isolation of this organism (Figure 32.15*a*). Various immunological methods are also available for diagnosing a campylobacter infection.

Antibiotic treatment with the drug azithromycin is widely practiced if a confirmed diagnosis is made from culture or culture-independent evidence. In addition, severe cases of dehydration from a *Campylobacter* infection may require intravenous perfusion and hospitalization. Rigorous personal hygiene, especially by those in food preparation facilities, proper washing of uncooked poultry (and any kitchenware coming in contact with uncooked poultry), and thorough cooking of meat are the major means of preventing *Campylobacter* infections.

MINIQUIZ

- Describe the pathology of *Campylobacter* food infection. What are the major vehicles for this pathogen?
- How might *Campylobacter* contamination of food production animals be controlled?

32.13 Listeriosis

Listeria monocytogenes causes **listeriosis**, a gastrointestinal food infection that may lead to bacteremia (bacteria in the blood) and meningitis. *L. monocytogenes* is a gram-positive, nonsporulating coccobacillus (phylum *Firmicutes*) that is acid-, salt-, and cold-tolerant and facultatively aerobic (**Figure 32.16**) (Section 16.7). Although *Listeria* is a minor foodborne pathogen in terms of the number of cases observed per year, infections can be very severe and cause an estimated 20% of all deaths from foodborne illness in the United States. Listeriosis is primarily seen in the elderly, pregnant women, newborns, and adults with weakened immune systems. In 2014, 660 cases of invasive listeriosis (infection beyond the gastrointestinal tract) were reported in the United States with 107 cases being fatal (16%).

Epidemiology

L. monocytogenes is present in soil and water and although it is not common in foods, virtually no food source is safe from possible

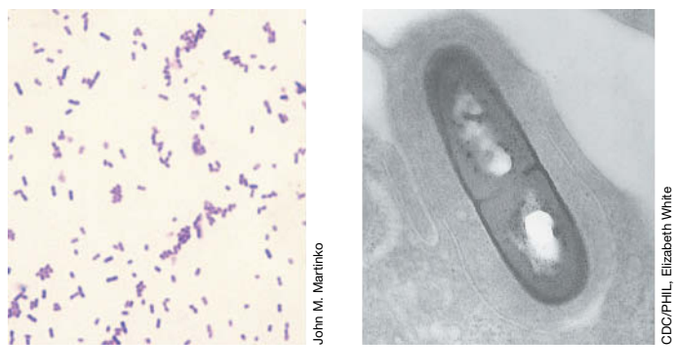


Figure 32.16 *Listeria monocytogenes*. *(a)* Gram stain and *(b)* transmission electron micrograph of cells of *L. monocytogenes*, the cause of listeriosis. The *Listeria* cell in *b* is within host tissues (see Figure 32.17).

L. monocytogenes contamination. Food can become contaminated at any stage during production or processing. Ready-to-eat meats, fresh soft cheeses, unpasteurized dairy products, and inadequately pasteurized milk are the major food vehicles for *Listeria*, even when these foods are properly stored at refrigerator temperature (4°C). Food preservation by refrigeration, which ordinarily prevents the growth of other foodborne pathogens, is ineffective in the case of *Listeria* because the organism is psychrotolerant. Cells of *L. monocytogenes* produce a series of branched-chained fatty acids that keep the cytoplasmic membrane functional at cold temperatures (Section 5.10).

Pathology

Immunity to *L. monocytogenes* is normally conferred by cell-mediated Th1 inflammatory cells (Section 27.8). However, if cells of *Listeria* evade these immune cells, as they can in hosts with compromised immune systems, the organism is taken up by intestinal phagocytic cells. Although one might think that this is good from the standpoint of host defense, it is actually not because phagocytic uptake initiates the *Listeria* infection cycle.

Listeria cells are taken up by host phagocytic cells into a vacuole called the *phagosome*. This triggers production of a major *Listeria* virulence factor, the exotoxin *listeriolysin O*, and this protein lyses the phagosome and releases *L. monocytogenes* into the cytoplasm (**Figure 32.17**). Here the bacterium multiplies and produces a second major virulence factor, *ActA*, a protein that induces host cell actin polymerization; the actin coats the bacterial cell and assists in moving the pathogen to the host cell cytoplasmic membrane. Once there, the bacterium–actin complex pushes out, forming protrusions called *filopods*, which are then taken up by surrounding phagocytic cells (Figure 32.17). Filopod formation allows cells of *L. monocytogenes* to move about host tissues without exposure to the major weapons of the immune system: antibodies, complement, and neutrophils (Chapters 26 and 27).

Cells of *Listeria* in the intestine cross the intestinal barrier and are carried by the lymph and blood to other organs, in particular the liver, and multiply there as they do in intestinal phagocytes (Figure 32.17). From here cells of *L. monocytogenes* can infect the central nervous system, where they grow in neurons and lead to inflammation of the meninges (the tissues covering the brain and spinal cord), causing meningitis. In addition to listeriolysin O, which also allows *Listeria* to establish chronic infections in many host tissues, other major virulence factors include phospholipases that can destroy host cell membranes, antioxidants that counter phagocytic cell oxidants, and an array of "stress proteins" common in many bacteria (Sections 6.9 and 6.10).

Diagnosis, Treatment, and Prevention

Listeriosis is diagnosed by culturing *L. monocytogenes* (Figure 32.16) from the blood or cerebrospinal fluid. *L. monocytogenes* can be identified in foods by direct culture or by several molecular methods. The latter methods are also used to subtype clinical isolates in order to track the source(s) of infection. Intravenous antibiotic treatment with penicillin, ampicillin, or trimethoprim plus sulfamethoxazole is used to treat invasive listeriosis.

Prevention measures include recalling contaminated food and taking steps to limit *L. monocytogenes* contamination at the food-processing site. Because *L. monocytogenes* is susceptible to heat and radiation, raw food and food-handling equipment can be readily decontaminated. However, unless the finished food product is pasteurized (Section 5.15) or cooked, the risk of contamination cannot be eliminated because of the widespread distribution of the pathogen.

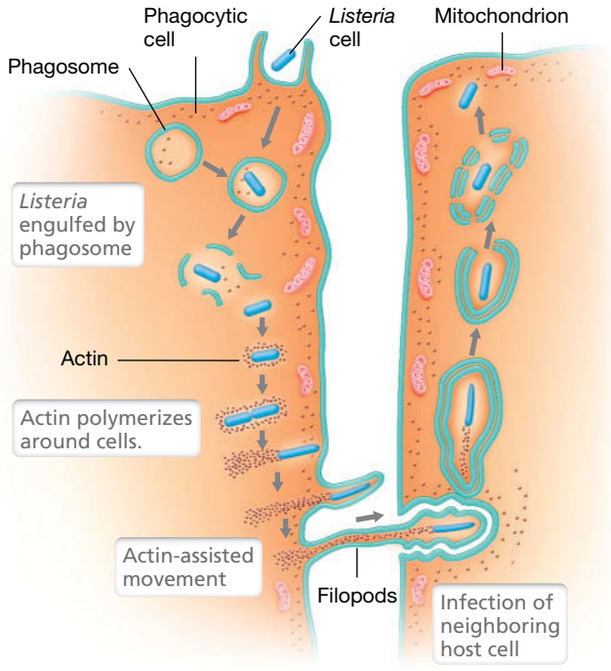


Figure 32.17 Transmission of *Listeria* during listeriosis. Cells of *Listeria* are taken up in phagosomes of phagocytic cells. These are eventually lysed by the virulence factor listeriolysin O to release *Listeria* cells. The bacterial cells then become covered with actin that assists in their movement to the cell periphery. Filopods facilitate transfer of *Listeria* cells to neighboring host cells, where the cycle repeats.

MINIQUIZ

- What is the likely outcome of *Listeria monocytogenes* exposure in normal healthy individuals?
- Which populations are most susceptible to serious disease from *L. monocytogenes* infection?

32.14 Other Foodborne Infectious Diseases

Over 200 microorganisms, viruses, and other infectious agents can cause foodborne diseases, and we have thus far summarized the major ones. Here we consider a few other bacterial pathogens that are rather uncommon compared with the "top five" (Table 32.5), and we take a second look at norovirus (previously considered as a waterborne pathogen, Section 32.5) in its more frequent context as a foodborne pathogen and overall number one cause of gastrointestinal illness in the United States.

Bacteria

Besides the major bacterial foodborne pathogens we have already considered, several other bacteria cause human gastrointestinal

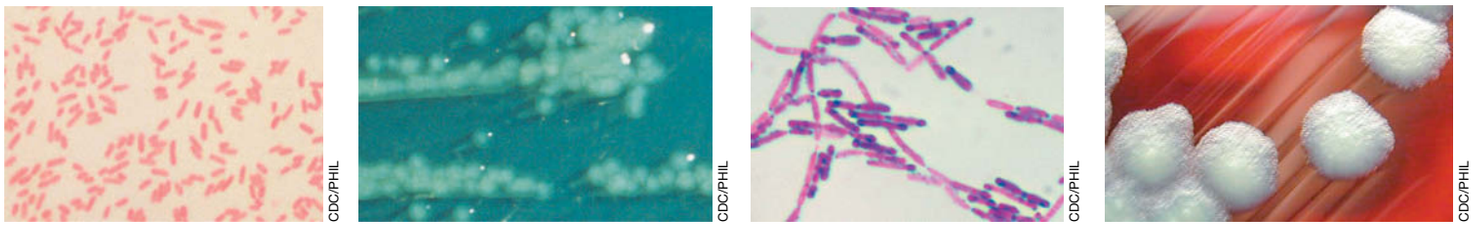


Figure 32.18 Less common foodborne bacterial pathogens: *Yersinia enterocolitica* and *Bacillus cereus*. *(a)* Gram-stained cells of *Y. enterocolitica*. *(b)* Colonies of *Y. enterocolitica* on Hektoen agar, a selective and differential medium. *Y. enterocolitica* forms white colonies because this bacterium does not ferment lactose and does not produce sulfide (compare with colonies of *Salmonella* on Hektoen agar in Figure 32.13*a* and colonies of *Escherichia coli* on Hektoen agar in Figure 32.14c). *(c)* Gram-stained cells of a sporulating culture of *B. cereus*. *(d)* Large crystalline-like colonies of *B. cereus* formed on blood agar. Foodborne illness due to *Y. enterocolitica* or *B. cereus* is much less common than illness due to *Salmonella, Campylobacter*, or *Clostridium perfringens*.

illnesses. *Yersinia enterocolitica* is an enteric bacterium commonly found in the intestines of domestic animals and causes foodborne infections from contaminated meat and dairy products. The most serious consequence of *Y. enterocolitica* infection is *enteric fever*, a severe, life-threatening infection. *Y. enterocolitica* can be isolated on the same selective, differential medium used to isolate *Salmonella* (**Figure 32.18*a, b***) but is easily distinguished from this organism on plates (compare Figures 32.13*a* and 32.18*b*).

Bacillus cereus is responsible for a relatively small number of food poisoning cases. This endospore-producing bacterium (Sections 2.10 and 16.8) produces two enterotoxins that cause different symptoms. In the *emetic form*, symptoms are primarily nausea and vomiting. In the *diarrheal form*, diarrhea and gastrointestinal pain are observed. *B. cereus* grows in foods such as rice, pasta, meats, or sauces that are cooked and left at room temperature to cool slowly. When endospores of this bacterium germinate, toxin is produced. Reheating may kill the *B. cereus* cells, but the toxin is heat-stable and may remain active. *B. cereus* is readily culturable and can be tentatively identified by a combination of microscopy and its typically large, grainy, and spreading colonies (Figure 32.18*c, d*).

The enteric bacterium *Shigella* causes the food infection *shigellosis*, and species of *Vibrio* can also cause food poisoning, primarily from consumption of contaminated shellfish. Most *Shigella* infections are the result of fecal to oral contamination, but food and water are occasional vehicles. We discussed the Shiga-like toxin produced by some pathogenic strains of *Escherichia coli* in Section 32.11.

Viruses

About 70% of annual foodborne infections in the United States are caused by norovirus (**Figure 32.19*a***; Section 32.5). The virus is also known as *Norwalk virus* and is a single-stranded plus-sense RNA virus related to poliovirus (Section 10.8). In general, noroviral foodborne illnesses are characterized by diarrhea, often accompanied by nausea and vomiting. Recovery from norovirus infections is typically spontaneous and rapid, usually within 24–48 h (thus the disease is often nicknamed "the 24-hour bug").

Rotavirus, astrovirus, and hepatitis A make up the bulk of the remaining foodborne *viral* infections. These viruses inhabit the gut and are often transmitted in food or water contaminated with feces. Hepatitis A virus (HAV, Figure 32.19*b*) is an RNA virus that, like norovirus, is related to poliovirus, but replicates in liver cells. We considered hepatitis viruses transmitted primarily by blood in Section 30.11, but HAV is mainly a foodborne virus. HAV usually triggers mild, and in many cases subclinical, symptoms, but rare cases of severe liver disease from HAV can occur. The most significant food vehicles for HAV are shellfish, usually oysters or clams harvested from water polluted by human feces and then eaten raw. In recent years, HAV has also been seen in fresh produce served without cooking.

The general trend for incidence of both foodborne and bloodborne hepatitis has moved steadily downward and is now at record low levels, partly due to the availability of effective vaccines against both hepatitis A and hepatitis B (HBV) viruses (Figure 30.32), but also because of heightened awareness of the potential danger of eating raw shellfish. Nevertheless, widespread and likely mild HAV infections continue to occur because surveys have shown that over 30% of individuals in the United States have circulating antibodies to HAV, indicating past subclinical infections. In 2014, 1239 cases of hepatitis A were reported in the United States.

Protists and Other Agents

Important foodborne protist diseases are listed in Table 32.5. The major pathogens here include *Giardia intestinalis, Cryptosporidium parvum, Cyclospora cayetanensis*, and *Toxoplasma gondii*. *G. intestinalis* and *C. parvum* are spread in foods when contaminated water is used to wash, irrigate, or spray crops. Fresh foods such as fruits are often implicated as vehicles for these protists. *Toxoplasma gondii* is a protist

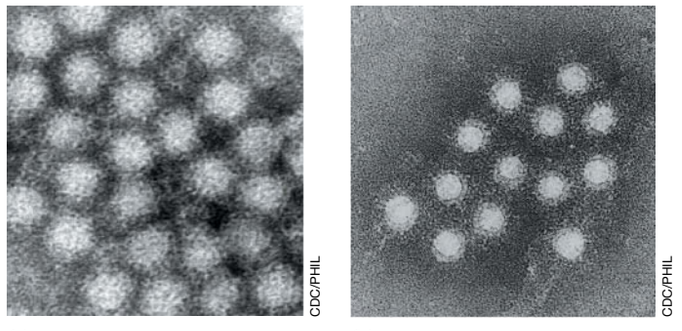


Figure 32.19 Viruses transmitted in contaminated foods. *(a)* Transmission electron micrograph of norovirus; an individual virion is about 30 nm in diameter. *(b)* Transmission electron micrograph of hepatitis A virus; a virion is 27 nm in diameter.

spread primarily through cat feces, but it can also be found in raw or undercooked meat, especially pork. The incidence of foodborne transmission of *C. cayetanensis* has remained low (fewer than 20 cases per year) in recent years, and fresh cilantro and related produce have been the major vehicles of this pathogen in the majority of outbreaks. We discuss the diseases giardiasis, cryptosporidiosis, cyclosporiasis, and toxoplasmosis in Section 33.4.

At least one type of foodborne disease agent is neither cellular nor viral; these are the prions. *Prions* are proteins that adopt novel conformations, inhibiting normal protein function and causing degeneration of host neural tissues (Section 10.16). Human prion diseases are characterized by neurological symptoms including depression, loss of motor coordination, and eventual dementia. A foodborne human prion disease called *variant Creutzfeldt–Jakob disease* (vCJD) has been linked to consumption of meat products from cattle suffering from *bovine spongiform encephalopathy* (*BSE*), a disease caused by a prion. Although several thousand cases of vCJD were diagnosed in Great Britain in the mid-1990s, bans on cattle feeds containing rendered cattle parts and bone meal have greatly diminished the incidence of BSE in Europe and have kept the incidence of this disease very low in the United States.

MINIQUIZ

- In what two forms can *Bacillus cereus* food poisoning manifest itself?
- Compared with all other foodborne or waterborne pathogens, what is unique about prions?

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Chapter Review

I • Water as a Disease Vehicle

32.1 Contaminated drinking and recreational waters are sources of waterborne pathogens. In the United States, the number of disease outbreaks due to these sources is relatively small in relation to the large exposure the population has to water. Worldwide, lack of adequate water treatment facilities and access to clean water contribute significantly to the spread of infectious diseases.

Q What determines whether or not a pathogen present in a water source will lead to a person being infected with a waterborne disease?

32.2 Drinking water quality is determined by counting coliform and fecal coliform bacteria using standardized techniques. Filtration and chlorination of water significantly decreases microbial numbers. Water purification methods in developed countries have been a major factor in improving public health, although in developing countries, waterborne illness is still a significant source of infectious disease.

Q Describe how ATP can be used as a tool for estimating total bacterial numbers in a given water sample.

II • Waterborne Diseases

32.3 The bacterium *Vibrio cholerae* causes cholera, an acute diarrheal disease associated with severe dehydration. Cholera occurs in pandemics, primarily in developing countries where sewage treatment and sanitation is lacking. Oral rehydration and electrolyte replacement can effectively treat cholera and greatly reduce disease mortality.

Q Describe the mode of action of *V. cholerae* on the small intestine in the body.

32.4 *Legionella pneumophila* is a respiratory pathogen that causes Pontiac fever and legionellosis, a more serious infection that may result in pneumonia. *L. pneumophila* grows to high numbers in warm waters and is spread via cooling tower aerosols and in domestic water distribution systems where the bacterium develops in biofilms.

Q How is *L. pneumophila* usually detected, and what are the various means of treating legionellosis in an infected patient?

32.5 Typhoid fever, caused by a *Salmonella* species, and norovirus illness are important waterborne diseases. Typhoid is common in developing countries while norovirus illness is seen worldwide. Both of these diseases can be controlled by good sanitation practices and effective water treatment.

Q How is *S. enterica*, the causative agent of typhoid fever, transmitted? What are the stages of typhoid fever?

III • Food as a Disease Vehicle

32.6 The potential for microbial food spoilage depends on the nutrients and moisture levels of the food. Growth of microorganisms in perishable foods can be controlled by refrigeration, freezing, canning, pickling, dehydration, chemicals, and irradiation. Microbial fermentations can be used to naturally preserve many foods, including dairy products, meats, fruits and vegetables, and alcoholic beverages.

Q Identify and define the three major categories of food perishability. Why is milk more perishable than sugar even though both are rich in organic matter? Identify the major methods used to preserve food and the major categories of fermented foods.

32.7 Food poisoning results from the activities of microbial toxins while food infections are due to the growth of the pathogen within the body. Identification of common characteristics of foodborne pathogens from seemingly isolated foodborne outbreaks can pinpoint the origin of foodborne contamination and track the spread of the disease. The top five foodborne pathogens in the United States in decreasing order of their appearance are: norovirus, *Salmonella* spp., *Clostridium perfringens, Campylobacter jejuni*, and *Staphylococcus aureus*.

Q Distinguish between food infection and food poisoning and give two examples of each.

IV • Food Poisoning

32.8 Staphylococcal food poisoning results from the ingestion of a preformed staphylococcal enterotoxin, a superantigen produced by cells of *Staphylococcus aureus* as they grow in food. Proper food preparation, handling, and storage can prevent staphylococcal food poisoning.

Q What causes the symptoms of staphylococcal food poisoning? Why are cases of staph food poisoning often linked to a food preparer?

32.9 *Clostridium* food poisoning results from ingestion of toxins produced by microbial growth in foods or from microbial growth followed by toxin production in the body. Perfringens food poisoning is quite common and is usually a self-limiting gastrointestinal disease. Botulism is a rare but serious disease, with significant mortality.

Q Identify the two major types of clostridial food poisoning. Which is most prevalent? Which is most dangerous and why?

V • Food Infection

32.10 More than a million cases of salmonellosis occur every year in the United States. Infection results from ingestion of cells of *Salmonella* introduced into food primarily from animal-derived food products or food handlers.

Q What are the possible sources of *Salmonella* spp. that cause food infections?

32.11 Toxigenic *Escherichia coli* cause many food infections, and of these, STEC strains are the most severe. Contamination of foods from animal feces spreads these pathogenic strains of *E. coli*, but good hygiene practices and specific antibacterial measures such as irradiation or thorough cooking of ground beef, a major vehicle, can control disease outbreaks.

Q How does *Escherichia coli* O157:H7 end up in ground beef? To what class of pathogenic *E. coli* does this strain belong? How does this class differ from other classes?

32.12 *Campylobacter* infection is the third most prevalent foodborne bacterial disease in the United States. Poultry is a major vehicle for *Campylobacter* illness, whereas beef and pork are not. Proper poultry preparation and cooking can prevent *Campylobacter* illness.

Q Name a food product that could transmit both *Salmonella* and *Campylobacter* simultaneously. How could this food product be rendered safe to eat?

32.13 *Listeria monocytogenes* is a ubiquitous bacterium, and in healthy individuals, it seldom causes infection. However, in immunocompromised individuals, *Listeria* can cause serious disease as it grows as an intracellular pathogen and invades the central nervous system. Listeriosis is uncommon but shows high mortality.

Q Identify the food sources of *Listeria monocytogenes* infections. How does *Listeria* evade the immune system?

32.14 Viruses, especially norovirus, cause the most foodborne illness while the bacteria *Bacillus cereus, Shigella* species, and *Yersinia enterocolitica* are only occasionally linked to foodborne disease outbreaks. Hepatitis A virus is also a serious foodborne pathogen. Some protists and prions also cause foodborne illness but are far less common foodborne pathogens than are bacteria and viruses.

Q What agent is the number one cause of gastrointestinal illness? What is the causative agent of vCJD? How does the structure of this agent differ from that of the agent of noro foodborne illness?

Application Questions

1. As a visitor to a country in which cholera is an endemic disease, what specific steps would you take to reduce your risk of cholera exposure? Will these precautions also prevent you from contracting other waterborne diseases? If so, which ones? Identify waterborne diseases for which your precautions may not prevent infection.
2. Argue a case for why perfringens foodborne illness can be considered both a food poisoning and a food infection.
3. Improperly prepared or handled potato salads are often the source of both staphylococcal food poisoning and salmonellosis. List some reasons why this might be the case. How do these differ from the foodborne disease incident linked to potato salad described on page 973?

Chapter Glossary

Botulism food poisoning due to ingestion of food containing botulinum toxin produced by *Clostridium botulinum*

Coliforms gram-negative, nonsporulating, facultatively aerobic rods that ferment lactose with gas formation within 48 hours at 35°C

Food infection a microbial infection resulting from the ingestion of pathogen-contaminated food followed by growth of the pathogen in the host

Food poisoning (food intoxication) a disease caused by the ingestion of food that contains preformed microbial toxins

Food spoilage a change in the appearance, smell, or taste of a food that makes it unacceptable to the consumer

Listeriosis a gastrointestinal food infection caused by *Listeria monocytogenes* that may lead to bacteremia and meningitis

Nonperishable foods foods of low water activity that have an extended shelf life and are resistant to spoilage by microorganisms

Pasteurization the use of controlled heat to reduce the microbial load, including both pathogens and spoilage organisms, in heat-sensitive liquids

Perishable foods fresh foods generally of high water activity that have a very short shelf life because of spoilage by microbial growth

Potable in water purification, drinkable; safe for human consumption

Salmonellosis enterocolitis or other gastrointestinal disease caused by any of several subspecies of the bacterium *Salmonella*

Semiperishable foods foods of intermediate water activity that have a limited shelf life because of their potential for spoilage by growth of microorganisms

33

Eukaryotic Pathogens: Fungi, Protozoa, and Helminths

microbiologynow

Environmental Change and Parasitic Diseases in the Amazon

Changes in the environment—from both human and natural causes—can have significant effects on an ecosystem. Besides the obvious changes associated with major shifts in land use, other, more subtle changes can occur, and these can be deadly if they include infectious diseases.

The Amazon is the largest drainage basin on Earth and contains a fifth of all the freshwater and a third of the tropical forests that remain on the planet. The Amazon stretches over nine countries, with the largest part located in Brazil. These are hot and moist areas of the world where major health threats exist from the many parasitic microbes that plague the region. Deforestation is a major activity in the Amazon, as agriculture, mining, ranching, road-building, logging, and oil exploration become ever more common in this ecologically sensitive area (see photo). However, lost among the environmental concern for the shrinking of the Amazon rainforests (nicknamed "the lungs of the world" for their capacity to fix CO_2 and expel O_2) is the influence of deforestation on the burden of human parasitic disease.

A recent review predicts that the incidence of malaria, leishmaniasis, soil-transmitted microscopic worm infections, Chagas disease, and schistosomiasis will increase significantly as deforestation continues in the Amazon. There are at least three reasons for this. First, deforestation leaves in its wake disturbed land loaded with water catchments that provide new habitats for the major parasitic disease vectors—mosquitoes and flies—to reproduce. Second, deforestation greatly reduces both soil and water quality. This generates more exposed soils (making transmission of soil-associated helminthic diseases more likely) and contaminated water (increasing opportunities for schistosomiasis and other waterborne infectious diseases). And third, land clearing inevitably affects demographics; land that was previously heavily forested and sparsely populated quickly transitions to densely settled communities when the trees are gone. Collectively, when numbers of both people and disease vectors increase, increases in disease incidence naturally follow.

Deforestation reaps short-term benefits to miners, ranchers, and oil explorers who descend on recently logged land. But in the long run, such major land use changes are not only ecological disasters; they set the stage for increased transmission of some of the most devastating and chronic infectious diseases known.

Source: Confalonieri, U.E.C., C. Margonari, and A.F. Quintão. 2014. Environmental change and the dynamics of parasitic diseases in the Amazon. *Acta Tropica 129:* 33–41.

In this chapter we focus on *eukaryotic* pathogenic microorganisms. These include several fungi—both molds and yeasts—and various parasitic protists. Some small worms also cause infectious diseases and we consider the most significant of these in the final section.

A common problem in treating diseases caused by eukaryotic pathogens is the fact that their hosts are also eukaryotic. This thwarts many therapeutic strategies and often makes these diseases highly refractory and long-term chronic infections. This is especially true of systemic fungal pathogens.

I • Fungal Infections

Fungi cause a variety of human diseases. Some are mild and self-limiting, whereas others can be firmly entrenched systemic diseases. We begin by considering some of the major fungal pathogens followed by a description of some major fungal diseases, the mycoses.

33.1 Pathogenic Fungi and Classes of Infection

The fungi include the *yeasts*, which normally grow as single cells, and *molds*, which form branching filaments called *hyphae* with or without septa (cross-walls); hyphae eventually intertwine to form visible masses called *mycelia*. The diversity of the molds and yeasts was discussed in Chapter 18.

Common Fungal Pathogens

Fortunately, most fungi are harmless to humans. Most fungi grow in nature as saprophytes on dead organic material; in so doing, fungi are important catalysts in the carbon cycle, especially in oxic environments in soil. Fungi are also important in medicine both as agents of disease and in chemotherapy (antibiotic production). Only about 50 species of fungi cause human diseases, and in healthy individuals, the incidence of serious fungal infections is low, although certain superficial fungal infections (for example, athlete's foot) are fairly common. In those with compromised immune systems, however, fungal infections can be systemic, reaching even the deepest of internal tissues. Such infections can cause serious health problems and be life-threatening.

Common fungal pathogens include both yeasts and molds (**Figure 33.1**). However, many pathogenic fungi are *dimorphic*, meaning that they can exist as *either* a yeast *or* in filamentous form. In *Histoplasma*, for example, cells in laboratory culture form hyphae and mycelia and thus exist in the mold form (Figure 33.1*e*). By contrast, when *Histoplasma* causes histoplasmosis, cells grow in the host in the yeast form (see Figure 33.5*a*). In the mold form, spores are produced, either asexual spores—*conidia*—or sexual spores (↻ Section 18.9). When filamentous fungi are cultured from an infection, the morphology of these spore-bearing structures is observed and is often a major clue in reaching a diagnosis. In addition to microscopy, a variety of clinically useful molecular and immunological tools (including fluorescent antibodies, Figure 33.1*c*) are also available to diagnose fungal

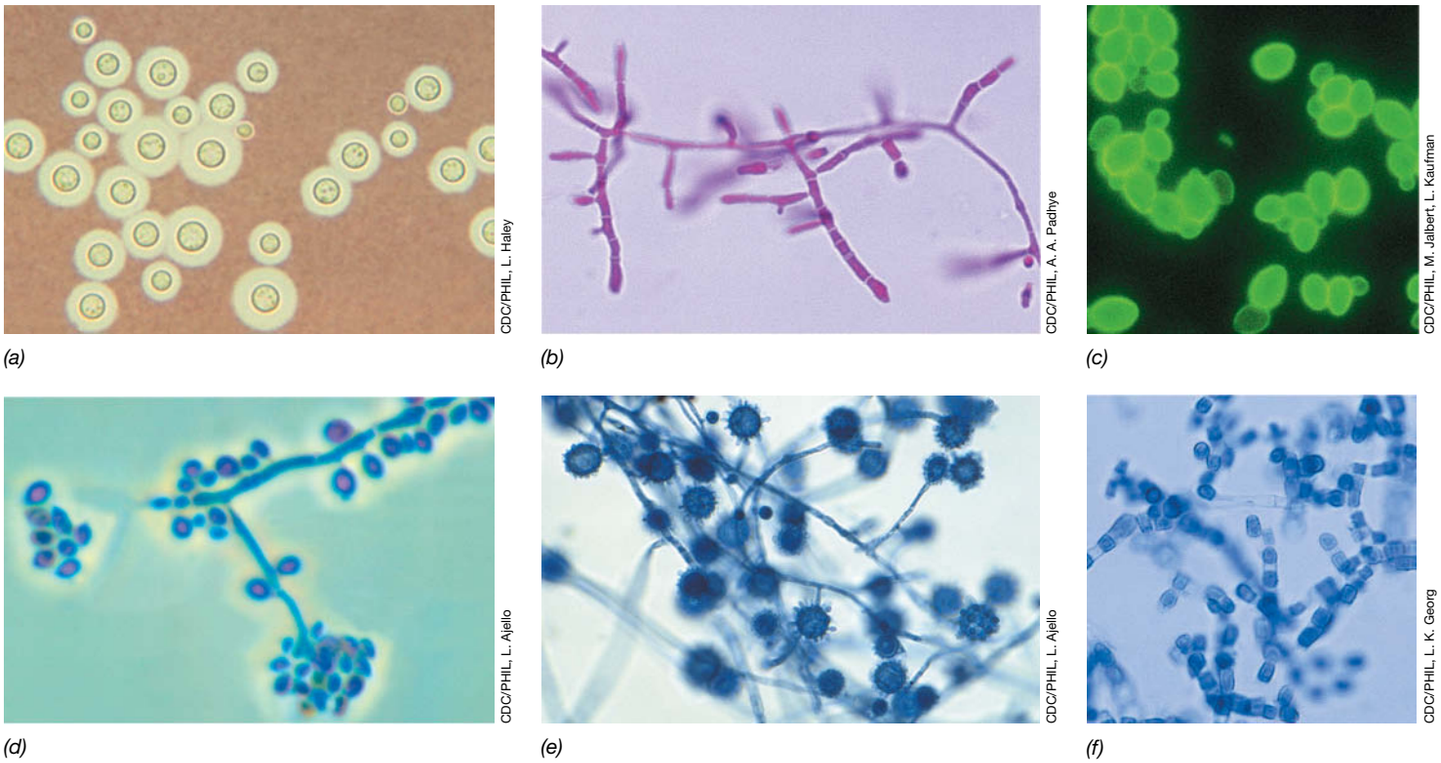


Figure 33.1 Pathogenic fungi. These organisms range from about 4 to 20 μm in diameter. *(a) Cryptococcus neoformans* yeast cells stained to reveal the capsule. *(b) Trichophyton* spp. mycelia and conidia. *(c) Candida albicans* yeast form stained with a fluorescent antibody. *(d) Sporothrix schenckii* mycelia and conidia. *(e) Histoplasma capsulatum* mycelia and large conidia. *(f) Coccidioides immitis* conidia. See fungal disease symptoms in Figure 33.5.

infections. Table 33.1 lists some major fungal pathogens and the types of infections they cause.

Fungal Disease Classes and Treatment

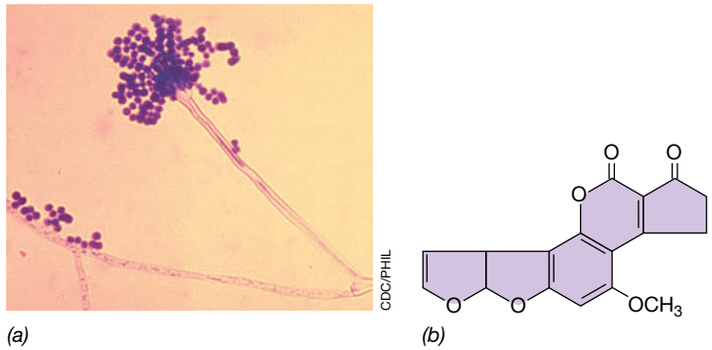
Fungi cause disease through three major mechanisms: inappropriate immune responses, toxin production, and mycoses. Some fungi trigger immune responses that result in allergic (hypersensitivity) reactions following exposure to specific fungal antigens. Reexposure to the same fungi, whether growing on the host or in the environment, may cause allergic symptoms. For example, *Aspergillus* spp. (Figure 33.2*a*), common saprophytes often found in nature as a leaf mold, produce potent allergens, triggering asthma attacks or other hypersensitivity reactions in susceptible individuals.

Fungal disease may occur from the production of *mycotoxins*, a large and diverse group of fungal exotoxins (Section 25.6). The best-known examples of mycotoxins are the *aflatoxins* (Figure 33.2*b*) produced by *Aspergillus flavus*, a species that commonly grows on improperly stored dry foods, such as grain. Aflatoxins are highly toxic and are also carcinogenic, inducing tumors in some animals, especially in birds that feed on contaminated grain. Although aflatoxins are known to cause human liver damage including cirrhosis and even liver cancer, adults are not seriously affected by low-level aflatoxin exposure. However, chronic exposure in children can cause serious liver disease and other health effects.

TABLE 33.1 Major pathogenic fungal diseases[a]

Class and disease	Causal organism	Site
Superficial mycoses		
Athlete's foot	*Epidermophyton*, *Trichophyton*	Between toes, skin
Jock itch	*Trichophyton*, *Epidermophyton*	Genital region
Ringworm	*Microsporum*, *Trichophyton*	Scalp, face
Subcutaneous mycoses		
Sporotrichosis	*Sporothrix schenckii*	Arms, hands
Chromoblastomycosis	*Phialophora verrucosa*, other fungi	Legs, feet, hands
Systemic mycoses		
Aspergillosis	*Aspergillus* spp.[b]	Lungs
Blastomycosis	*Blastomyces dermatitidis*	Lungs, skin
Candidiasis	*Candida albicans*[c]	Oral cavity, intestinal tract, vagina
Coccidioidomycosis	*Coccidioides immitis*[c]	Lungs
Paracoccidioidomycosis	*Paracoccidioides brasiliensis*	Skin
Cryptococcosis	*Cryptococcus neoformans*[c]	Lungs, meninges
Histoplasmosis	*Histoplasma capsulatum*[c]	Lungs
Pneumocystis pneumonia	*Pneumocystis jirovecii*[c]	Lungs

[a]Symptoms of many of these diseases are shown in Figures 33.3–33.5.
[b]*Aspergillus* can also cause allergies, toxemia, and limited infections.
[c]An opportunistic pathogen frequently implicated in the pathogenesis of HIV/AIDS.



(a) (b)

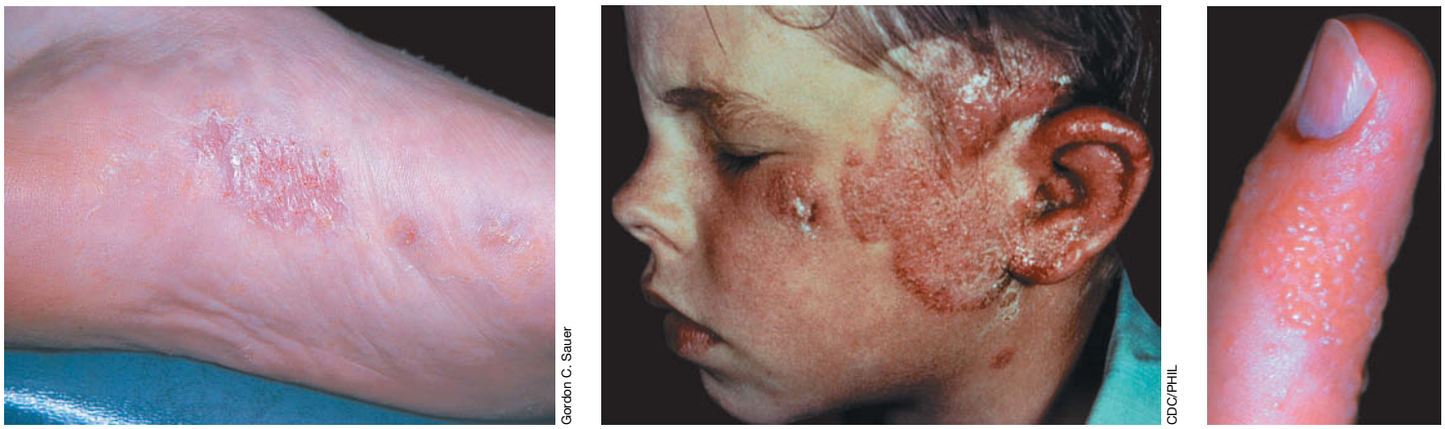
Figure 33.2 *Aspergillus* and aflatoxin. *(a)* Mycelia and conidia of an *Aspergillus* species. *(b)* Structure of aflatoxin B1. This toxin is one of a group of related compounds produced by *Aspergillus flavus*.

The final fungal disease-producing mechanism is through actual host infection. The growth of a fungus on or in the body is called a **mycosis** (plural, mycoses). Mycoses are fungal infections that range in severity from superficial to life-threatening. Mycoses fall into three classes (Table 33.1). **Superficial mycoses** are those in which the fungus infects only the surface layers of skin, hair, or nails (see Figure 33.3). **Subcutaneous mycoses** are infections of deeper layers of skin (see Figure 33.4) and are typically caused by different fungi than superficial infections (Table 33.1). The **systemic mycoses** are the most serious category of fungal infections. These are characterized by fungal growth in internal organs of the body (see Figure 33.5) and can be either primary or secondary infections. A *primary* infection occurs when an otherwise normal, healthy individual is infected with the fungal pathogen; these are rather uncommon. By contrast, a *secondary* infection occurs in a host that harbors a predisposing condition, such as antibiotic therapy or immunosuppression, that makes the individual more susceptible to infection.

Superficial and subcutaneous mycoses are for the most part easily treatable with topical drugs, including tolnaftate (applied topically), various azole drugs (applied either topically or orally), and griseofulvin, a relatively nontoxic drug that can be taken orally but passes through the bloodstream to the skin where it inhibits fungal growth. Chemotherapy against systemic fungal infections is more difficult because of issues with host toxicity (Section 28.11). For example, one of the most effective antifungal agents, amphotericin B, is widely used to treat systemic fungal infections but can also reduce kidney function and have other unwanted side effects. Hence, effective treatment of the most serious of the mycoses is sometimes very difficult.

MINIQUIZ

- Differentiate between superficial, subcutaneous, and systemic mycoses.
- What is a dimorphic fungus?
- Distinguish between a primary and a secondary fungal disease. Why do those suffering from HIV/AIDS often show secondary fungal infections of major internal organs?



(a) (b) (c)

Figure 33.3 Superficial mycoses caused by *Trichophyton* spp. *(a)* Athlete's foot. *(b)* Ringworm on a child's face and *(c)* on an adult index finger. "Jock itch" (ringworm of the groin) is another common *Trichophyton* infection and can occur in females as well as males. *Tricophyton* is a filamentous fungus (see Figure 33.1*b*).

33.2 Fungal Diseases: Mycoses

The two extremes of fungal infection are the superficial mycoses and the systemic mycoses. *Superficial mycoses* are quite common, and most individuals experience at least one in their lifetime. By contrast, *systemic mycoses* are far less common, and primarily affect the elderly or otherwise immune compromised. As people age, cell-mediated immunity slowly declines as a result of surgeries, transplantations, immunosuppressive drug treatments for rheumatism and autoimmune diseases, and the onset of other conditions, such as pulmonary decline, diabetes, and cancer. Any of these can predispose the elderly to disease. Systemic mycoses also target those of any age whose immune systems have been impaired or destroyed, for example, by HIV/AIDS (Figure 30.45). Systemic mycoses are thus diseases of *opportunistic pathogens*, microbes that cause disease only in those whose immune defenses can no longer fight them off (Sections 25.4 and 30.15).

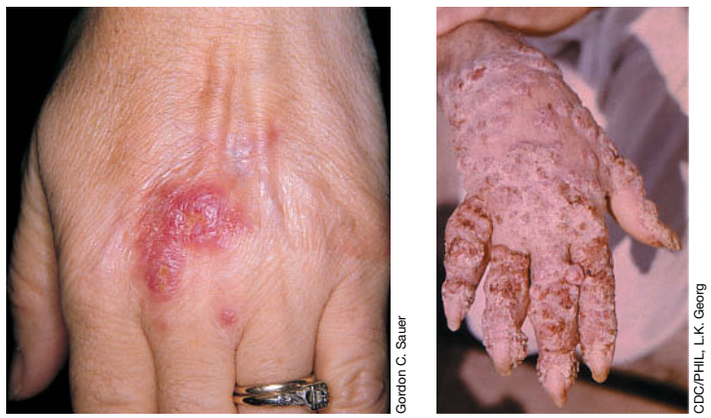
Superficial Mycoses

Table 33.1 listed some of the fungi that cause superficial mycoses; collectively, these pathogens are called *dermatophytes*. In general, superficial mycoses can be bothersome and often recurrent infections, but are not serious health concerns. Fungi such as *Trichophyton* (Figure 33.1*b*) cause infections of the feet (athlete's foot) and other moist skin surfaces, and are quite common (**Figure 33.3*a***). These infections cause flaking and itchy skin and are easily transmitted by cells or spores of the pathogen present in contaminated shower stalls, gymnasium and locker room floors, contaminated shared articles such as towels or bed linens, or from close person-to-person contact. Superficial mycoses can be treated with topical antifungal creams or liquid aerosols, although prophylactic application on a long-term basis may be necessary if constant exposure to the pathogen (for example, to *Trichophyton* on a locker room floor) is unavoidable.

Related surface mycoses include "jock itch," an itchy infection of the groin, skin folds, or anus, and *ringworm* (Table 33.1). Despite the name, ringworm is a fungal infection, typically localized to the scalp or the extremities; the infection causes hair loss and inflammation-like reactions (Figure 33.3*b, c*). These more severe superficial mycoses are usually treated topically with either miconazole nitrate or griseofulvin.

Subcutaneous Mycoses

Subcutaneous mycoses are fungal infections of deeper layers of skin than those of the superficial mycoses (Table 33.1). One disease in this class is *sporotrichosis* (**Figure 33.4*a***), an occupational hazard of agricultural workers, miners, gardeners, and others who come into close and continual contact with the soil. The causal organism, *Sporothrix schenckii* (Figure 33.1*d*), is a ubiquitous soil saprophyte whose spores can enter through a cut or abrasion and infect subcutaneous tissues (Figure 33.4*a*). *Chromoblastomycosis* is due to pathogenic fungal growth in both surface (cutaneous) *and* subcutaneous skin layers, forming crusty, wartlike lesions on the hand (Figure 33.4*b*) or leg. The disease is primarily one of tropical and subtropical countries and occurs when the fungus becomes



(a) (b)

Figure 33.4 Subcutaneous mycoses. *(a)* Sporotrichosis, a subcutaneous infection due to *Sporothrix schenckii*. *(b)* Chromoblastomycosis on the hand caused by the fungus *Phialophora verrucosa*. Chromoblastomycosis can also be caused by species of the fungal genera *Fonsecaea* and *Cladosporium*.

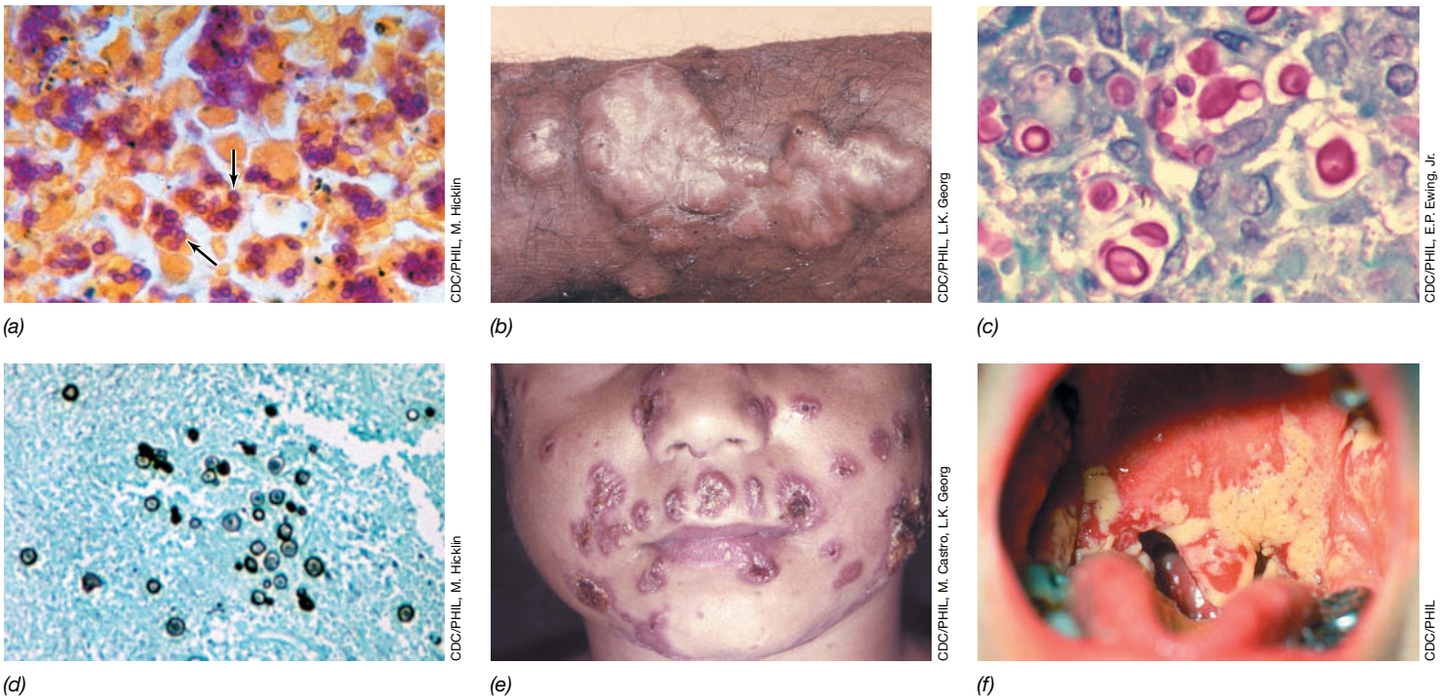


Figure 33.5 Systemic mycoses. *(a)* Histoplasmosis; yeast-form cells of *Histoplasma* (arrows) in spleen tissue. *(b)* Cutaneous blastomycosis on the arm. *(c)* Cryptococcosis; yeast-form cells (stained red) in lung tissue. *(d)* Coccidioidomycosis; yeast-form cells (stained blue-black) in lung tissue. *(e)* Paracoccidioidomycosis lesions on the face. *(f)* Oral thrush. Masses of *Candida albicans* cells (yellow) line the back of the throat. See photomicrographs of cultures of the pathogens causing most of these mycoses in Figure 33.1.

implanted under the skin from a puncture wound. Both sporotrichosis and chromoblastomycosis can be treated with oral administration of azoles.

Systemic Mycoses

Systemic fungal pathogens normally live in soil, and humans become infected by inhaling airborne spores that later germinate and grow in the lungs. From there the organism migrates throughout the body, causing deep-seated infections in the lungs and other organs and in the skin. In the United States, the three major systemic mycoses are, in order of decreasing incidence: histoplasmosis, coccidioidomycosis, and blastomycosis. Mortality from these is high, about 10%.

Histoplasmosis (**Figure 33.5*a***) is caused by *Histoplasma capsulatum* (Figure 33.1*e*), and *coccidioidomycosis* (San Joaquin Valley fever, Figure 33.5*d*) is caused by *Coccidioides immitis* (Figure 33.1*f*). Histoplasmosis is primarily a disease of rural areas in midwestern states of the United States, especially in the Ohio and Mississippi River valleys, whereas coccidioidomycosis is generally restricted to the desert regions of the southwestern United States. In more tropical climates *blastomycosis*, caused by *Blastomyces dermatitidis*, is prevalent (Figure 33.5*b*). *Paracoccidioidomycosis*, caused by the fungus *Paracoccidioides brasiliensis*, is primarily a subtropical disease with lesions forming on the face (Figure 33.5*e*) or other extremities.

Cryptococcosis (Figure 33.5*c*), caused by the dimorphic yeast *Cryptococcus neoformans* (Figure 33.1*a*), can occur in virtually any organ of the body and is the major mycosis seen in HIV/AIDS patients. The dimorphic yeast *Candida albicans* (Figure 33.1*c*) is often present as a minor component of the human microbiota. However, this fungus can cause a variety of diseases including mild vaginal infections, more serious oral infections such as thrush (Figure 33.5*f*), and systemic infection of virtually any organ in those with HIV/AIDS. Like *Histoplasma* and *Coccidioides, Candida* and *Cryptococcus* are primarily opportunistic pathogens and rarely cause life-threatening infections except in immune-compromised people.

Our discussion transitions now from fungi to pathogenic parasites. Like fungi, parasites are eukaryotic microorganisms, but the pathogenic parasites typically attack quite different body tissues and organs than do the pathogenic fungi.

MINIQUIZ

- Give an example of a superficial, a subcutaneous, and a systemic mycosis.
- Why are systemic fungal pathogens called opportunistic?

II • Visceral Parasitic Infections

Parasitism is a symbiotic relationship between two organisms, the parasite and the host (Chapters 23 and 24). The parasite derives essential nutrients from the host and may have little or no harmful effect on the host. However, in most cases, the parasite causes disease in the host. Many different phylogenetic groups of protists (Chapter 18) cause parasitic human diseases and we examine some of the key ones here.

Parasitic infections can be either visceral—inducing vomiting, diarrhea, and other intestinal symptoms—or infections of blood and internal tissues. Some of the major diseases of human history, malaria for example, are parasitic diseases. We begin here with the visceral parasites and then consider blood and tissue parasites. Table 33.2 summarizes some major parasitic human diseases.

33.3 Amoebae and Ciliates: *Entamoeba*, *Naegleria*, and *Balantidium*

The genera *Entamoeba* and *Naegleria* belong to a large group of protists that move by extending lobe-shaped pseudopodia, the *Amoebozoa* (Section 18.7). Both parasites can cause serious, even fatal infections, although *Naegleria* infections are very rare. *Balantidium* is a ciliated species of the alveolate group (Section 18.4) and is mainly a disease of tropical countries.

Amebic Dysentery

Entamoeba histolytica (Figure 33.6*a*) is transmitted by contaminated water or occasionally through contaminated food. *E. histolytica* is an anaerobe, and the organism's *trophozoites* (the active, motile, feeding stage of the parasite) lack mitochondria. Like another common waterborne pathogen, *Giardia* (Section 33.4), the trophozoites of *E. histolytica* produce cysts, which are the means of transmission. Ingested cysts germinate to form amoebae that grow both on and in intestinal mucosa. This leads to tissue invasion and ulceration that triggers diarrhea and severe intestinal cramps.

With further growth, the amoebae can invade the intestinal wall—a condition called *dysentery*, characterized by intestinal inflammation, fever, and the passage of intestinal blood and mucus. If the infection is not treated, *E. histolytica* can invade the liver, the lungs, and even the brain. Growth in these tissues causes abscesses that can be fatal. Nearly 100,000 people, primarily from developing countries where untreated sewage is allowed to enter surface waters, die each year from invasive amebic dysentery. *E. histolytica* amebiasis can be treated with a variety of drugs, but the host immune system plays a significant role in recovery as well. However, protective immunity is not conferred from a primary infection, and reinfection is common.

TABLE 33.2 Major parasitic human diseases

Parasitic diseases by site	*Causal organism*[a]
Gastrointestinal	
Amebiasis	*Entamoeba histolytica*
Giardiasis	*Giardia intestinalis*
Cryptosporidiosis	*Cryptosporidium parvum*
Toxoplasmosis	*Toxoplasma gondii*
Blood and tissue	
Malaria	*Plasmodium* spp.
Leishmaniasis	*Leishmania* spp.
Trypanosomiasis (African sleeping sickness)	*Trypanosoma brucei*
Chagas disease	*Trypanosoma cruzi*
Schistosomiasis	*Schistosoma mansoni*

[a]All are protists (Chapter 18) except for *Schistosoma*, a helminth.

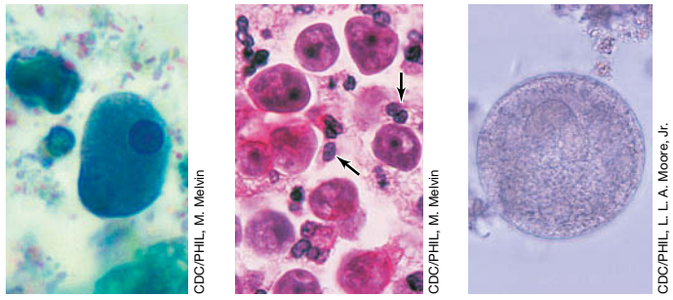


Figure 33.6 Parasitic amoebae and ciliates. *(a)* The growing stage (trophozoite) of *Entamoeba histolytica*; these can be up to 60 µm in length. *(b)* Trophozoites (arrows) of *Naegleria fowleri* in sectioned and stained brain tissue; the parasites are 10–25 µm in length. *(c) Balantidium coli* cyst (about 50 µm wide) present in a fecal sample.

Naegleria and *Balantidium* Infections

Naegleria fowleri can cause amebiasis, but in a very different form from that of *E. histolytica*. *N. fowleri* is a free-living amoeba present in soil and in runoff waters. *N. fowleri* infections result from swimming or bathing in warm, soil-contaminated waters such as warm springs or lakes and streams in summertime. *N. fowleri* enters the body through the nose and burrows directly into the brain. There the organism propagates, causing extensive hemorrhage and brain damage (Figure 33.6*b*), a condition called **meningoencephalitis**. Diagnosis of an *N. fowleri* infection requires observation of the amoebae in cerebrospinal fluid. If a definitive diagnosis is made quickly, which is often not the case because the incidence of *Naegleria* meningoencephalitis is so low and the symptoms resemble those of meningitis, the drug amphotericin B can save the patient; untreated infections are almost always fatal. Thus, although incidence of *Naegleria* meningoencephalitis is very low, mortality of untreated cases is very high, which makes this parasitic infection extremely dangerous. In the United States only 37 cases of *Naegleria* meningoencephalitis were reported in the 10-year period between 2006 to 2015 and virtually all were from recreational waters.

Balantidium coli is a ciliated intestinal human and swine parasite that alternates between the trophozoite and cyst (Figure 33.6*c*) stages; only the cysts are infective. *B. coli* is the only known ciliated parasite of humans. Cysts, typically transmitted in fecally contaminated water, germinate in the colon and infect mucosal tissues, leading to symptoms that resemble those of amebiasis, for which the disease is sometimes mistaken. An infected patient usually experiences a spontaneous recovery or may become an asymptomatic carrier, continuously shedding *B. coli* cysts in the feces. Compared with amebiasis, *B. coli* infections are uncommon, and cases are rarely fatal.

MINIQUIZ

- Contrast an *Entamoeba* and a *Naegleria* infection in terms of tissues infected and symptoms.
- Describe a scenario for contracting a *Naegleria* infection.

33.4 Other Visceral Parasites: *Giardia, Trichomonas, Cryptosporidium, Toxoplasma*, and *Cyclospora*

The protists *Giardia intestinalis* and *Trichomonas vaginalis* are flagellated anaerobic parasites that contain either mitosomes or hydrogenosomes in place of mitochondria (Sections 2.15, 18.1, and 18.3); the parasites cause intestinal and sexually transmitted infections, respectively. The protist *Cryptosporidium* is related to *Toxoplasma*, but unlike *Toxoplasma*, which is primarily transmitted by infected food, as is the pathogenic protist *Cyclospora, Cryptosporidium* is transmitted primarily by contaminated water. We consider all five of these major human parasites here.

Giardiasis

Giardia intestinalis (also called *Giardia lamblia*) is typically transmitted to humans in fecally contaminated water and causes an acute gastroenteritis, *giardiasis*. The trophozoites of *Giardia* (**Figure 33.7*a, c***) produce highly resistant cysts (Figure 33.7*b*) that function in transmission. Ingested cysts germinate in the small intestine to form trophozoites, and these travel to the large intestine where they attach to the intestinal wall and cause the symptoms of giardiasis: an explosive, foul-smelling, watery diarrhea, intestinal cramps, flatulence, nausea, weight loss, and malaise. The foul-smelling diarrhea and the absence of fecal blood distinguish giardiasis from diarrheas due to bacterial or viral intestinal pathogens.

G. intestinalis causes a significant number of drinking water infectious disease outbreaks in the United States (Section 32.1). The thick-walled cysts are resistant to chlorine, and most outbreaks have been associated with water systems that used only chlorination as a means of water purification. Water subjected to proper clarification and filtration followed by chlorination or other disinfection (Section 22.8) should be free of *Giardia* cysts. Most surface water sources (lakes, ponds, and streams) contain *Giardia* cysts, as beavers and muskrats are carriers of this pathogen. This is why surface waters should never be drunk untreated but instead should be filtered and disinfected with iodine or chlorine or alternatively, filtered and boiled. The drugs quinacrine, furazolidone, and metronidazole are useful for treating acute giardiasis.

Trichomoniasis

Trichomonas vaginalis (**Figure 33.8**) causes a sexually transmitted infection, *trichomoniasis*. *T. vaginalis* does not produce resting cells or cysts and as a result, *Trichomonas* transmission is typically from person to person, generally by sexual intercourse. However, unlike most sexually transmitted bacterial pathogens, cells of *T. vaginalis* can survive for several hours on moist surfaces and up to a day in urine or semen. Hence, in addition to disease transmission by intimate contact, trichomoniasis can be transmitted by contaminated toilet seats, sauna benches, and towels.

T. vaginalis infects the vagina in women, the prostate and seminal vesicles of men, and the urethra of both males and females. Trichomoniasis is often asymptomatic in males. By contrast, trichomoniasis in females is characterized by a yellowish vaginal discharge that causes a persistent vaginal itching and burning. The infection is more common in females; surveys have shown that up to 25% of sexually active women are infected with *T. vaginalis* while only about 5% of males are infected. Trichomoniasis is diagnosed by observation of the motile protists in a wet mount of fluid discharged from the patient (Figure 33.8*b*). The antiprotozoal drug metronidazole is effective for treating trichomoniasis.

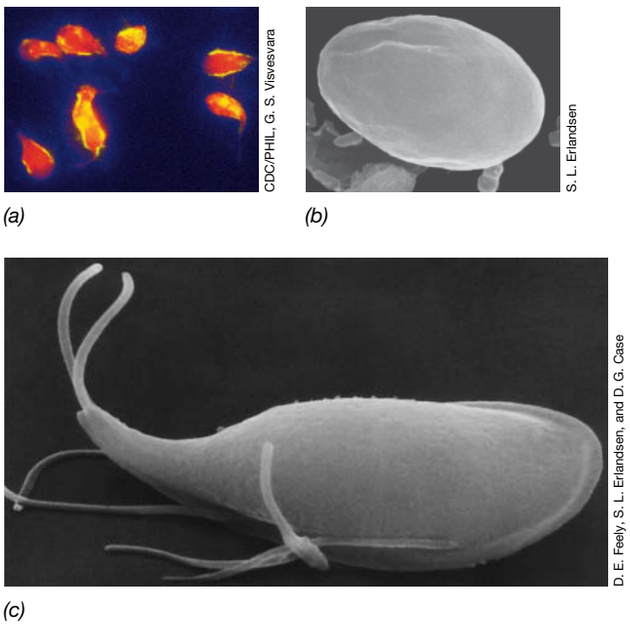


Figure 33.7 *Giardia*. *(a)* Fluorescently stained cells of *Giardia intestinalis*. *(b, c)* Scanning electron micrographs of *(b)* a giardial cyst and *(c)* a motile *G. intestinalis* trophozoite. The trophozoite is 15 μm long and the cyst about 11 μm wide.

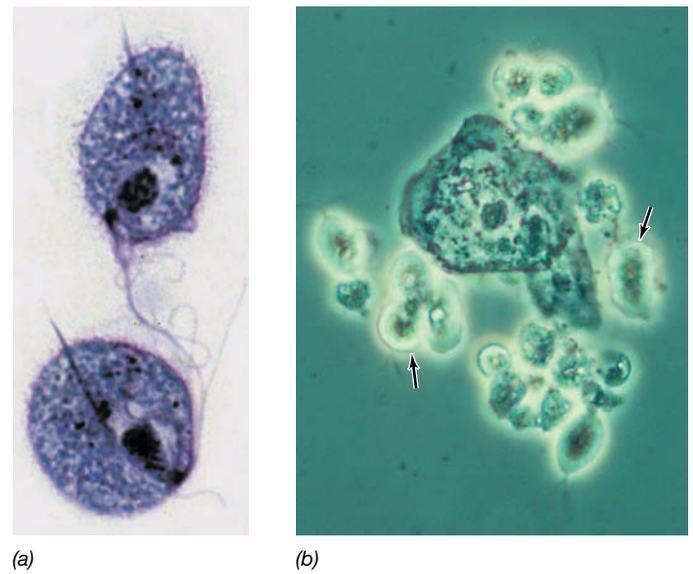


Figure 33.8 *Trichomonas vaginalis*. *(a)* Light micrograph of stained cells; cells vary from 10 to 20 μm in diameter. *(b)* Vaginal discharge from a female with trichomoniasis. *T. vaginalis* cells (arrows) are present along with vaginal secretions and epithelial cells.

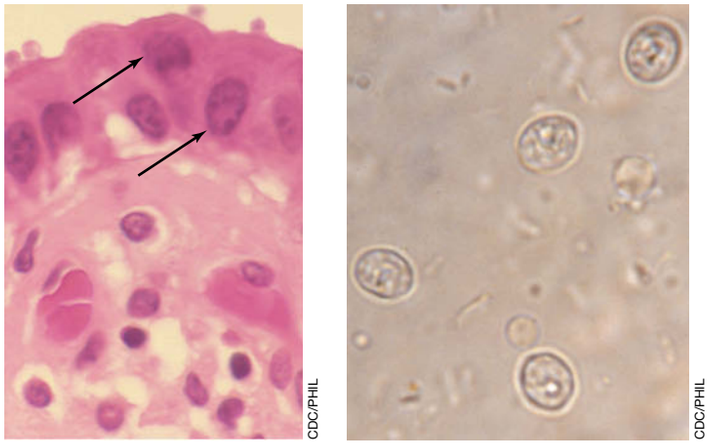


Figure 33.9 ***Cryptosporidium parvum.*** *(a)* Arrows point to intracellular trophozoites of *C. parvum* embedded in human gastrointestinal epithelium. The trophozoites are about 5 µm in diameter. *(b)* Thick-walled *C. parvum* oocysts are about 3 µm in diameter in this fecal sample.

Cryptosporidiosis, Toxoplasmosis, and Cyclosporiasis

Cryptosporidium, Toxoplasma, and *Cyclospora* are genera of parasitic coccidia (which group among the alveolates, ↪ Section 18.4). These parasites are transmitted to humans in fecally contaminated food or water and can trigger serious bouts of diarrhea, or in the case of *Toxoplasma*, serious internal organ damage.

Cryptosporidium parvum infects many warm-blooded animals, in particular cattle. The organism forms small, coccoid cells that invade and grow intracellularly in mucosal epithelial cells of the stomach and intestine (**Figure 33.9*a***), resulting in the gastrointestinal illness *cryptosporidiosis*. *C. parvum* produces thick-walled, highly resistant cysts called *oocysts* (Figure 33.9*b*), which enter water from the feces of infected animals. The infection is then transmitted to other animals and humans when they consume the fecally contaminated water.

Cryptosporidium oocysts are highly resistant to chlorine, and because of this, sedimentation and filtration are the only reliable way to remove them from water supplies. In an average year, *Cryptosporidium* is responsible for the majority of recreational waterborne disease outbreaks in the United States (Chapter 32) but is only occasionally associated with drinking water outbreaks. Nevertheless, *C. parvum* was responsible for the largest single outbreak of disease associated with drinking water ever recorded in the United States. In the spring of 1993, one-quarter of the population of Milwaukee, Wisconsin (USA), developed cryptosporidiosis from consuming water from the municipal water supply. Heavy spring rains and runoff from cattle manure on farmlands had drained into Lake Michigan (the water supply for the city) and overburdened the water purification system, leading to contamination by *C. parvum*.

Cryptosporidiosis typically causes only a mild, self-limiting diarrhea, making treatment unnecessary. However, individuals with impaired immunity, such as that caused by HIV/AIDS, or the very young or old can develop serious complications from a *C. parvum* infection. The primary laboratory diagnostic method for cryptosporidiosis is the demonstration of oocysts in feces (Figure 33.9*b*). Immunological and molecular tools are also available for more precise identification of strains of the pathogen when such tracking is necessary.

As for *C. parvum*, the parasite *Cyclospora cayetanensis* also forms oocysts and causes a mild to occasionally severe gastroenteritis, which is called *cyclosporiasis*. However, unlike *C. parvum, C. cayetanensis* is primarily transmitted by fecally contaminated food products—typically fresh foods—rather than by contaminated water. Most cases of cyclosporiasis have been linked to contaminated fruits or vegetables. A major outbreak in the United States in the summer of 2013 was linked to packaged lettuce (↪ Section 32.7). Another major *C. cayetanensis* outbreak occurred in 2015 and affected persons in 31 states. At least some (and perhaps most) of these illnesses were caused by contaminated fresh cilantro (coriander) imported from Mexico.

Toxoplasmosis is caused by *Toxoplasma gondii* (**Figure 33.10**). This parasite infects many warm-blooded animals, and roughly half of all adults in the United States are infected but asymptomatic because their immune system keeps the organism in check. *T. gondii* is typically transmitted to humans in the form of cysts present in undercooked beef, pork, or lamb; by direct infection from cats, which are major carriers of *T. gondii*; and occasionally from contaminated water. A key step in the *T. gondii* life cycle is completed in felines and thus they are obligate hosts; humans and other animals are only incidental hosts. Most transmission to humans is thus probably from cats.

Toxoplasmosis can be associated with mild to severe symptoms. When cysts of *T. gondii* are ingested, they penetrate the wall of the small intestine. From this initial infection, symptoms can be inapparent or apparent but indistinguishable from those of a mild case of influenza (headache, muscle ache, general malaise). However, in some infected persons, *T. gondii* cysts migrate from the small intestine and circulate throughout the body. Subsequently, the parasite can penetrate nerve cells and infect tissues of the brain and eyes. Although disease symptoms in healthy adults are uncommon, in immune-compromised individuals, toxoplasmosis can damage the eyes, brain, and other internal organ systems.

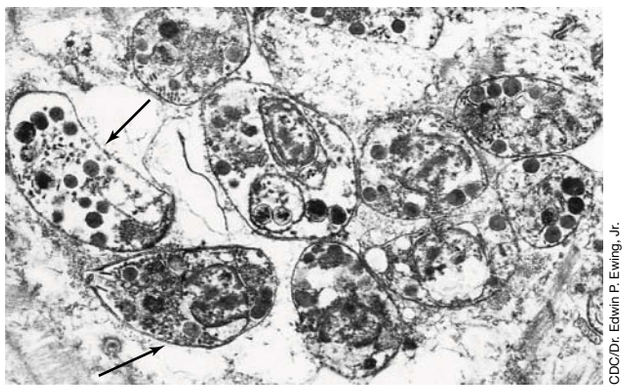


Figure 33.10 ***Toxoplasma.*** Tachyzoites (rapidly growing cells) of *Toxoplasma gondii*, an intracellular parasite. In this transmission electron micrograph, the tachyzoites (arrows) form a cystlike structure in a host cardiac cell. The *Toxoplasma* tachyzoites are 4–7 µm long. For a photo of *T. gondii* sporozoites (the infective phase of the parasite's life cycle), see Figure 18.11*b*.

In addition, a first-time infection with *T. gondii* in expectant mothers can lead to birth defects in newborns; thus pregnant women who have not been in contact with cats should avoid cats until after giving birth.

MINIQUIZ

- What symptoms of giardiasis would suggest that your gastroenteritis was not due to a bacterial pathogen?
- How does one contract a case of trichomoniasis? A case of toxoplasmosis?
- What is unusual about the oocysts of *Cryptosporidium* that facilitates its transmission by a water route?

III • Blood and Tissue Parasitic Infections

Several human parasites infect organs and tissues other than the gastrointestinal tract and are typically transmitted by insect vectors. We begin our consideration of these with malaria, the most devastating and widespread of parasitic diseases and one that remains a major global health problem today.

33.5 *Plasmodium* and Malaria

Malaria is caused by protists of the alveolate group (Section 18.4). Several species of the protozoal genus *Plasmodium* cause malarial diseases in warm-blooded hosts; up to 500 million people worldwide contract malaria annually and about 1 million die from the disease. Malaria is thus one of the most common causes of death worldwide from infectious disease and certainly the most prevalent of parasitic diseases.

In malaria, the complex parasite life cycle requires a mosquito vector. Four species of *Plasmodium*—*P. vivax, P. falciparum, P. ovale*, and *P. malariae*—cause most human malaria. The most widespread disease is caused by *P. vivax*, whereas the most serious disease is caused by *P. falciparum*. Humans are the only reservoirs for these four species. The protists carry out part of their life cycle in the human and part in the female *Anopheles* mosquito, the only vector that transmits *Plasmodium* spp. The vector spreads the protist from person to person.

Malarial Life Cycle

The life cycle of *Plasmodium* is complex and involves a number of stages (Figure 33.11). First, the human host is infected by plasmodial *sporozoites*, small, elongated cells produced in the mosquito that localize in the salivary gland of the insect. The mosquito (Figure 33.11 inset) injects saliva containing the sporozoites into the human when obtaining a blood meal. The sporozoites travel to the liver where they infect liver cells. Here they can remain quiescent for indefinite periods but eventually replicate and become enlarged in a stage called the *schizont* (see Figure 33.12*b*). The schizonts then segment into a number of small cells called *merozoites*, which exit the liver into the bloodstream. Some of the merozoites then infect red blood cells (erythrocytes).

The plasmodial life cycle in erythrocytes proceeds with repeated division, growth, and release of merozoites (Figure 33.12); this results in destruction of the host red blood cells. Plasmodial growth in red cells typically repeats at synchronized intervals of 48 h. During this 48-h period, the host experiences the defining clinical

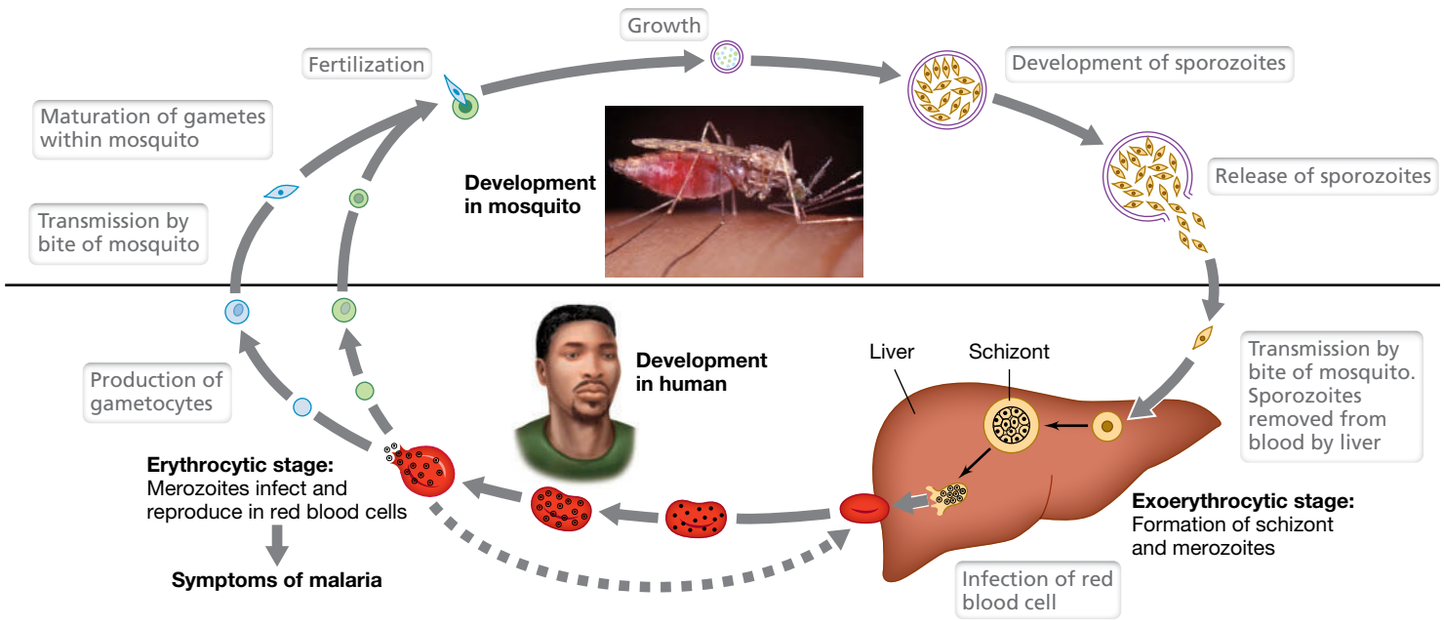


Figure 33.11 The life cycle of *Plasmodium*. The life cycle of *Plasmodium* requires both a warm-blooded host and the mosquito vector. Transmission of the protist to and from the warm-blooded (endothermic) host is done by the bite of an *Anopheles gambiae* mosquito (inset) or certain other *Anopheles* species. Mosquito photo courtesy of CDC/PHIL, J. Gathany.

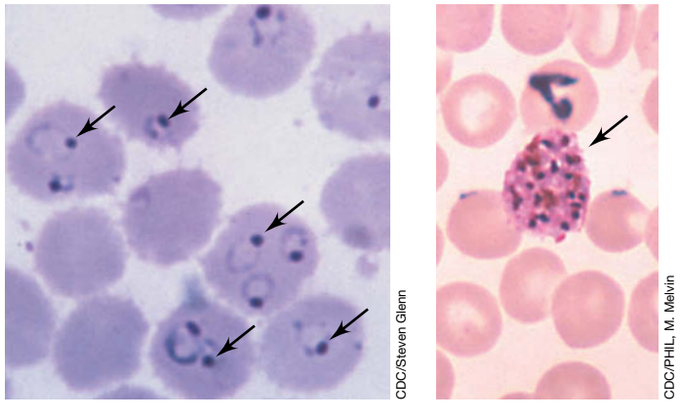


Figure 33.12 *Plasmodium* and malaria. *(a)* Merozoites of *Plasmodium falciparum* (arrows) growing within human red blood cells. *(b)* A schizont of *P. vivax* (arrow) along with red blood cells. When released from the schizont, the merozoites infect erythrocytes (Figure 33.11). Red blood cells are about 6 µm in diameter.

symptoms of malaria: chills followed by fever of up to 40°C (104°F). The chill–fever pattern coincides with the release of merozoites from the erythrocytes during the synchronized reproduction cycle. Vomiting and severe headache may accompany the chill–fever cycles, and over the longer term, characteristic symptomatic malaria can alternate with asymptomatic periods. Because of the destruction of red blood cells, malaria typically causes anemia and some enlargement of the spleen (splenomegaly).

Plasmodial merozoites eventually develop into *gametocytes*, cells that infect only mosquitoes. The gametocytes are ingested when an *Anopheles* mosquito takes a blood meal from an infected person, and they mature within the mosquito into *gametes*. Two gametes fuse to form a zygote, and the zygote migrates by amoeboid motility to the outer wall of the insect's intestine where it enlarges and forms several sporozoites. These are released and reach the salivary gland of the mosquito from where they can be inoculated into another human, and the cycle begins anew (Figure 33.11).

Epidemiology, Diagnosis, Treatment, and Control

Anopheles mosquitoes (Figure 33.11 inset) live predominantly in the tropics and subtropics and are the vector for malaria. Diagnosis of malaria requires the identification of *Plasmodium*-infected erythrocytes in blood smears (Figure 33.12). Fluorescent nucleic acid stains, nucleic acid probes, PCR assays, and various antigen-detection methods (Chapter 28) are also used to verify *Plasmodium* infections or to differentiate between infections with various *Plasmodium* species.

Treatment of malaria is typically accomplished with *chloroquine*. Chloroquine kills merozoites within red cells but does not kill sporozoites. The related drug *primaquine* eliminates sporozoites of *P. vivax* and *P. ovale* that may remain in liver cells. Thus treatment with both chloroquine and primaquine effectively cures most malaria. However, in some individuals, malaria recurs years after the primary infection when a few sporozoites not eliminated from the liver release a new generation of merozoites. Quinine-resistant strains of *Plasmodium* are now widespread and so *combination therapy*, where the malaria patient is treated with several antimalarial drugs at once, is now a common form of treatment.

Malaria can be controlled by either draining swamps and other breeding areas or by eliminating the mosquito with insecticides. Together, these measures have all but eliminated malaria in the United States, with most cases being imported. Several malaria vaccines are also in development, including synthetic peptide vaccines, recombinant particle vaccines, and DNA vaccines (Sections 12.8 and 28.9), but thus far no highly effective and reliable malaria vaccine has emerged for use in mass vaccination programs.

MINIQUIZ

- Which stages of the *Plasmodium* life cycle occur in humans, and which in the mosquito?
- What are the natural reservoirs and vectors for *Plasmodium* species? How can malaria be prevented or eradicated?
- What drugs are used to treat malaria?

33.6 Leishmaniasis, Trypanosomiasis, and Chagas Disease

Parasites of the genera *Leishmania* and *Trypanosoma* are transmitted by bloodsucking insect vectors. These parasites are *hemoflagellates*, organisms that reside in blood or related tissues such as the liver and spleen, and they cause major human diseases, primarily in tropical and subtropical countries.

Leishmaniasis

Leishmaniasis is a parasitic disease of various forms caused by species of the genus *Leishmania*, a flagellated protozoan related to *Trypanosoma*. The disease is transmitted to humans by a bite from the sand fly. *Cutaneous leishmaniasis*, caused by either *L. tropica* or *L. mexicana*, is the most common form of leishmaniasis. Following transmission of the parasite in a blood meal (**Figure 33.13*a, b***),

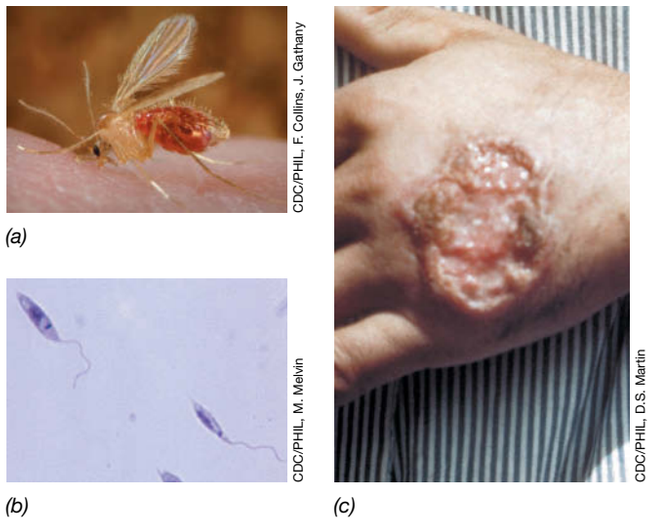


Figure 33.13 Leishmaniasis. *(a)* The sand fly (genus *Phlebotomus*) transmits leishmaniasis in a blood meal. *(b) Leishmania* spp. are flagellated protozoans and the cause of leishmaniasis. *(c)* Cutaneous leishmaniasis showing an open ulcer on the hand. Secondary bacterial infections of these ulcers are common. Leishmaniasis exists in over 88 tropical and subtropical countries. Occasional cases of cutaneous leishmaniasis are reported in the United States, primarily from the state of Texas.

the parasite infects and grows within human macrophage cells (Section 26.4), leading eventually (weeks or months later) to the formation of a small nodule on the skin. The nodule then becomes ulcerated and can enlarge to form a major skin lesion (Figure 33.13*c*) that contains active parasites. In the absence of secondary bacterial infections, which are common if the ulcerated tissue is left open, the lesions heal spontaneously over a period of several months but can leave a permanent scar.

Leishmaniasis has historically been treated with injections of pentavalent antimony (Sb^{5+}) compounds. Although the mode of action of these compounds is unknown, it is thought that Sb^{5+} in some way stimulates or activates the immune response to better attack the *Leishmania* parasites. At present, however, many *Leishmania* species are resistant to antimony compounds, but a variety of other drugs are available for treating resistant cutaneous forms of the disease. Estimates of cutaneous leishmaniasis prevalence worldwide are about 1 million.

Visceral leishmaniasis is caused by *Leishmania donovani* and is the most severe form of the disease. In visceral leishmaniasis, the parasite travels from the site of infection to internal organs, in particular the liver, spleen, and bone marrow. If left untreated, the visceral disease is almost always fatal. Common symptoms of visceral leishmaniasis include a cycling of fever and chills, a slow reduction in both red and white blood cell numbers, and significant enlargement of the spleen and liver that can lead to major distention of the abdomen. Treatment includes injections of antimony (as for the cutaneous disease), long periods of bed rest, and blood transfusions in acute cases if blood cell counts become dangerously low. Estimates of visceral leishmaniasis prevalence worldwide are about 300,000, causing about 20,000 deaths annually. In addition, because the range of the sand fly is already broad and is increasing as climate change and tropical and subtropical deforestation proceed (see page 994), it is estimated that worldwide nearly 400 million people (over 5% of the world's humans) could be at risk of some form of leishmaniasis.

Trypanosomiasis and Chagas Disease

Flagellated protozoans of the genus *Trypanosoma* (Section 18.3) cause two related forms of **trypanosomiasis**. Two subspecies of *Trypanosoma brucei* native to Africa, *T. brucei gambiense* (**Figure 33.14a**) and *T. brucei rhodesiense*, cause *African trypanosomiasis*, better known as *African sleeping sickness*. The species *T. cruzi* causes *Chagas disease*, also known as *American trypanosomiasis*. These diseases are transmitted by insect bites from either a fly or a bug.

Sleeping sickness is transmitted by the tsetse fly (genus *Glossina*), an insect similar in dimensions to a housefly and native only to tropical regions of Africa; sleeping sickness is therefore endemic only in countries of sub-Saharan Africa. The disease begins with intermittent fever, headache, and malaise. The parasite multiplies in the blood and later infects the central nervous system and grows in spinal fluid. Neurological symptoms soon begin, including sleep patterns that are no longer diel. The parasite produces the aromatic alcohol *tryptophol*, a derivative of the amino acid tryptophan, which triggers a sleep response. Without treatment, the infection gradually progresses to a coma, multiple organ failure, and eventually death after months or years depending on the case. A variety of anti-trypanosomal drugs are available for treating sleeping sickness; some are used primarily for treating the blood infection while others are used if the disease has progressed to the neurological stage. About 10,000 new cases of sleeping sickness are reported annually, but most cases are thought to go unreported.

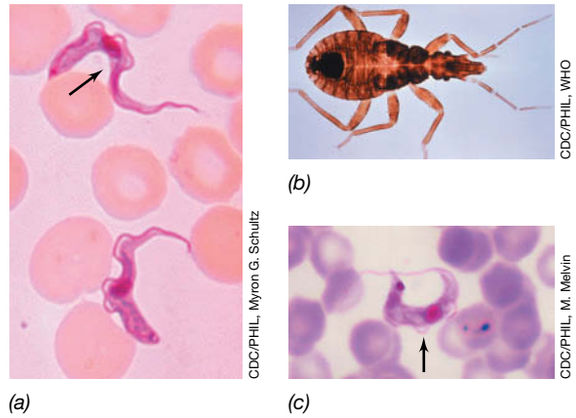


Figure 33.14 African trypanosomiasis and Chagas disease. *(a)* Two cells of *Trypanosoma brucei* (arrow), the causative agent of African sleeping sickness (African trypanosomiasis), in a blood smear. *(b)* The "kissing bug" (*Triatoma infestans*), the vector for Chagas disease (American trypanosomiasis). *(c)* A cell of *Trypanosoma cruzi* (arrow), the causative agent of Chagas disease, in a blood smear.

Chagas disease, named for its discoverer, is caused by *T. cruzi*, a close relative of *T. brucei*, and is transmitted by the bite of the "kissing bug" (Figure 33.14*b, c*). Chagas disease mainly occurs in Latin American countries. The parasite affects several organs including the heart, gastrointestinal tract, and central nervous system, causing inflammatory reactions and tissue destruction. The acute illness is usually self-limiting, but if chronic illness develops, heart damage is significant and is the eventual cause of premature death. About 20,000 deaths due to Chagas disease occur annually in endemic Latin American countries.

Currently no vaccines are available for prevention of African or American trypanosomiases.

MINIQUIZ

- How are trypanosome diseases similar to malaria and how do they differ?
- How do the symptoms of cutaneous and visceral leishmaniasis differ?
- How are sleep patterns altered in cases of African trypanosomiasis?

33.7 Parasitic Helminths: Schistosomiasis and Filariases

Some parasitic diseases are caused by helminths, tiny worms that burrow into the human host and cause debilitating diseases and death. We consider the most widespread of these, schistosomiasis, along with brief coverage of other, less common helminth infections.

Schistosomiasis

Schistosomiasis, also called *snail fever*, is a chronic parasitic disease caused by species of trematodes (flatworms) of the genus

Figure 33.15 Schistosomiasis. *(a)* Adult worm of *Schistosoma mansoni*; the worm is about 1 cm in length. *(b)* An *S. mansoni* egg, about 0.15 mm long. The lateral spine is characteristic of the eggs of this species. *(c)* Fluorescently stained cercaria, the infective form of *S. mansoni*. From the head (top) to the bifurcated tail is about 1 mm. *(d)* Cercarial infection of the forearm. Five infection sites (arrows) are apparent.

Schistosoma; the major species is *S. mansoni* and adult worms can be up to a centimeter in length (**Figure 33.15*a***). The life cycle of the parasite requires both snails and humans (or other mammals) as hosts. Schistosome eggs (Figure 33.15*b*) released into a freshwater aquatic environment hatch to generate *miracidia*, the form of the worm that infects snails. In the snail, miracidia are transformed into *cercariae* (Figure 33.15*c*), the motile stage of the parasite that is released and infects humans.

A cercaria burrows into the skin, leaving a small surface lesion (Figure 33.15*d*), and then migrates to the lungs and liver; in the process, the worm establishes a long-term infection in the blood vessels. From the liver, the parasite infects the bladder, kidneys, and urethra, and the female worm produces large numbers of eggs. The eggs are shed in the urine and also pass through the intestinal wall and are shed in the feces. Large egg masses also become trapped along with fluids in the bladder, liver, and other organs, triggering an inflammatory response and a major distention of the abdomen, a condition commonly seen in infected children (**Figure 33.16*a***). Other symptoms include bloody urine, diarrhea, and abdominal pain. Eggs as well as adult worms can live in the body for years, causing chronic symptoms that can last from youth into adulthood.

Schistosomiasis is a disease of tropical countries, primarily those in Africa, but some cases also occur in subtropical countries such as Latin America and the Caribbean region; poverty, poor sanitation, and land use changes are typically associated with widespread infection (see page 994). Schistosomiasis can be effectively treated with the drug praziquantel, and the diagnosis is made relatively easily by assessing symptoms and observing parasite eggs in the urine and feces. Mortality from schistosomiasis is low, about 0.1%, but schistosomiasis is second only to malaria in terms of total parasitic infections worldwide. In 2014, over 258 million cases of the disease were treated and many others probably went untreated.

Filariases

Several other parasitic helminth infections are known, and chief among these are the *filariases*, infections by parasitic nematodes (roundworms). Unlike the schistosomiasis parasite, these worms are clearly macroscopic in the adult stage (several centimeters in length, depending on the filariasis).

Bancroft's filariasis (also called "elephantiasis") is a chronic infection of the lymphatic system by the roundworm *Wuchereria bancrofti*. The worm is transmitted to humans as tiny *microfilariae* in a mosquito bite. Once in the host, microfilariae develop into adult worms and these interrupt lymph flow, leading to major accumulation of fluids (edema). Fluid accumulation in lower regions of the body can cause massive enlargement of the legs (Figure 33.16*b*). Over 120 million people in the tropics suffer from *W. bancrofti* infection, but the microfilarial stage of the disease is readily treatable with antihelminthic drugs or the drug diethylcarbamazine, which kills both microfilariae and adult worms. Even simpler treatment may be available by administering antibacterial antibiotics. Although the worm itself is not sensitive to these drugs, the worm harbors an endosymbiotic bacterium, *Wolbachia* (*Alphaproteobacteria*, Section 16.1), which is. If *Wolbachia* is eliminated by antibiotic treatment, the worms die, and so antihelminthic treatments often include antibiotics such as doxycycline (Section 28.10) to accelerate the removal of worms from the patient.

Onchocerciasis (also called *river blindness*) is due to a chronic infection by the large parasitic roundworm *Onchocerca volvulus*

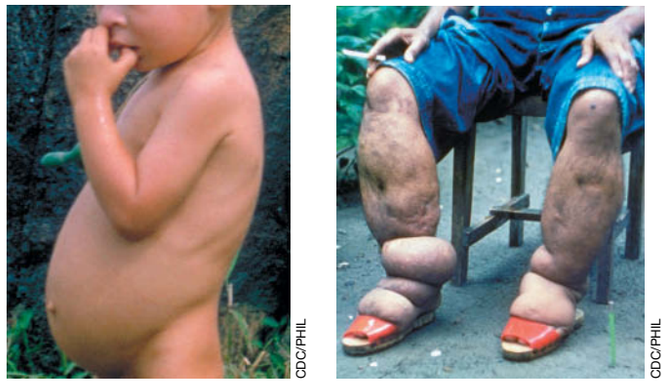
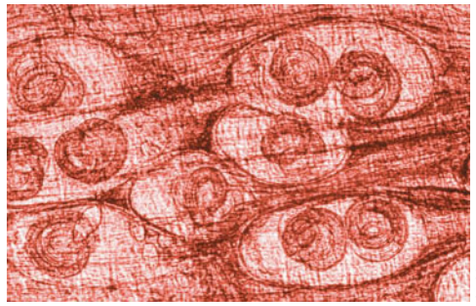


Figure 33.16 Symptoms of parasitic helminth infections. *(a)* Schistosomiasis in a small child. The swollen abdomen from the accumulation of fluids and worm eggs is characteristic of the infection. *(b)* Bancroft's filariasis (elephantiasis). The swollen legs are the result of edema from infection of lymph tissues by the roundworm *Wuchereria bancrofti*.

(a)



(b)

Figure 33.17 The roundworms of river blindness and trichinosis. *(a)* A worm larva of *Onchocerca volvulus*, the causative agent of river blindness. The microfilarial worm is about 0.3 millimeter long, but adult worms can be several centimeters in length. *(b)* Cysts of *Trichinella spiralis* containing worm larvae in muscle tissue. Unlike *O. volvulus*, adult worms are microscopic, just a few millimeters long.

(**Figure 33.17*a***). Humans are the only known host for this parasite, but flies are vectors when they become infected with microfilariae in a blood meal and transmit them to uninfected humans in a bite. Blackflies of the genus *Simulium* are the major means of transmission. The microfilariae invade the cornea and from there the iris and retina, triggering an inflammatory response that causes scarring and partial to total loss of vision. *O. volvulus* infection is second only to trachoma (Section 30.14) as a cause of infectious blindness. It is estimated that about 20 million people are infected with this parasite, primarily in equatorial Africa.

The disease *trichinosis* (also called *trichinellosis*) is caused by species of the parasitic roundworm *Trichinella* (Figure 33.17*b*). This worm commonly infects the muscle tissues of wild mammals and can occasionally infect domestic animals, especially swine; about 20 cases of human trichinosis are reported in the United States each year, usually from the consumption of undercooked wild game or undercooked pork. Human infection with *Trichinella* begins when worm larvae enter intestinal mucosal cells, leading to either an asymptomatic condition or mild gastroenteritis. As the larvae mature and reproduce, new larvae circulate throughout the body and lead to systemic inflammatory reactions such as malaise, facial swelling, and fever. Untreated cases of trichinosis can progress to more severe organ-specific symptoms including heart damage, encephalitis, and even death. However, if properly diagnosed, usually by immunological assays on biopsied muscle tissue, trichinosis is treatable with a variety of drugs, in particular the benzimidazole class of antihelminthics.

MINIQUIZ

- How does the pathogen causing schistosomiasis differ from all other pathogens considered in this chapter?
- From what source are most cases of human trichinosis contracted?

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Chapter Review

I • Fungal Infections

33.1 Fungi include the molds and yeasts, and some fungi are dimorphic, meaning that both mycelial and yeast phases can occur. Superficial, subcutaneous, and systemic mycoses refer to fungal infections of the skin surface, skin subsurface, and internal organs, respectively. Fungal infections can be mild or serious, depending on the health and immune status of those infected.

Q What are the major mechanisms through which fungi cause disease?

33.2 Superficial mycoses such as athlete's foot or jock itch are mild and easily treatable infections, whereas subcutaneous mycoses, such as sporotrichosis, or especially systemic mycoses, such as histoplasmosis, are more difficult to treat effectively. The ability of fungi that cause systemic mycoses to infect internal organs makes these pathogens particularly dangerous to the elderly or those otherwise immune compromised.

Q How are systemic mycoses characterised? What is the difference between a primary and a secondary infection caused by systemic mycoses?

II • Visceral Parasitic Infections

33.3 The genera *Entamoeba* and *Naegleria* are amoebic human parasites that cause gastrointestinal and brain infections, respectively. *Entamoeba* is transmitted in fecally contaminated waters, whereas *Naegleria* inhabits warm, soil-contaminated waters. *Balantidium* is a ciliated intestinal parasite transmitted by fecally contaminated water.

Q If you were to contract one or the other, which would you rather have, an *Entamoeba* infection or a *Naegleria* infection, and why?

33.4 The protists *Giardia intestinalis* and *Cryptosporidium parvum* are major waterborne pathogenic parasites, whereas *Toxoplasma gondii* is primarily a foodborne or cat-transmitted parasite and *Trichomonas vaginalis* is a

sexually transmitted parasite. The pathogenic parasite *Cyclospora* is primarily transmitted by fresh vegetables such as lettuce and spinach contaminated with animal feces. None of these parasites cause life-threatening diseases in otherwise healthy individuals, although *T. gondii* can trigger severe and even fatal infections in immune-compromised hosts.

Q In contrast to disease caused by *Trichomonas*, what do giardiasis and cryptosporidiosis have in common?

III • Blood and Tissue Parasitic Infections

33.5 Infections with *Plasmodium* spp. cause malaria, a widespread, mosquito-transmitted disease of the blood that causes significant morbidity and mortality in tropical and subtropical regions of the world. Malaria is treatable with quinines and other drugs but is not yet preventable by vaccination.

Q Malaria symptoms include chills followed by fever. These symptoms are related to activities of the pathogen. Describe the growth stages of *Plasmodium* spp. in the human host and relate them to the chill–fever pattern.

33.6 Leishmaniasis is a parasitic disease caused by *Leishmania* species; the cutaneous form of the disease is most common. *Trypanosoma brucei* causes African trypanosomiasis (African sleeping sickness), while the related species *Trypanosoma cruzi* causes Chagas disease. All of these diseases are transmitted by insect bites from an insect vector, either a fly or a bug.

Q Contrast leishmaniasis with the two types of trypanosomiasis in terms of causative agents, symptoms, and transmission vectors.

33.7 Schistosomiasis is a major parasitic disease caused by a microscopic worm, *Schistosoma mansoni*. The life cycle of the parasite requires both snails and mammals. The worm infects the liver and kidneys and produces large egg masses that accumulate in the body, leading to systemic inflammation and abdominal distention. Other parasitic worm diseases, such as elephantiasis and river blindness, also leave readily visible signs of infection. Trichinosis is caused by a roundworm that infects the intestine and muscle tissues and is a threat from the consumption of undercooked pork or wild game.

Q Contrast schistosomiasis with all other parasitic infections covered in this chapter. In what major way does it differ?

Application Questions

1. Malaria eradication has been a goal of public health programs for at least 100 years. What factors preclude our ability to eradicate malaria? If an effective vaccine was developed, could malaria be eradicated?
2. In terms of public health, what is a common problem that unites many of the visceral parasitic infections covered in this chapter? How could this problem be attacked? Why are these diseases rare in developed countries?
3. Explain why the diseases malaria, leishmaniasis, and trypanosomiasis are primarily diseases of tropical regions. How could humans be affecting the future geographical ranges of these diseases?
4. Explain why systemic fungal infections are typically seen only in certain individuals even though many people have contact with the pathogen, whereas an outbreak of giardiasis affects virtually everyone that has come in contact with the pathogen.

Chapter Glossary

Leishmaniasis a disease of the skin or viscera caused by infection with species of a parasitic flagellated protozoan, *Leishmania*

Malaria a disease characterized by recurrent episodes of fever and anemia, caused by the protist *Plasmodium* spp., usually transmitted between mammals through the bite of the *Anopheles* mosquito

Meningoencephalitis the invasion, inflammation, and destruction of brain tissue by the amoeba *Naegleria fowleri* or a variety of other pathogens

Mycosis (plural, mycoses) any infection caused by a fungus

Schistosomiasis a chronic disease caused by a parasitic worm that leads to internal organ damage and accumulation of fluids and worm egg masses

Subcutaneous mycoses fungal infections of deeper layers of skin

Superficial mycoses fungal infections of the surface layers of skin, hair, or nails

Systemic mycoses fungal growth in internal organs of the body

Trypanosomiasis any parasitic disease of the blood and internal tissues caused by species of the flagellated protozoan *Trypanosoma*; African sleeping sickness and Chagas disease are two major trypanosomiases

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Chapter 4 4.3a: Stephen P. Edmondson and Elizabeth Parker; 4.3b: A. Pyne, B. Thompson, C. Lueng, D. Roy, B.W. Hoogenboom. 2014 Small 10:3257-3621; 4.4e: S. Yoshimura, Kyoto Unviversity; 4.4f: Steven B. Zimmerman, Journal of Structural Biology; 4.5, b: Andrzej Stasiak. Modified fom G. Witz and A. Stasiask. 2010. *Nucleic Acids Research* 38:2119-2133.; 4.7a: Somenath Bakshi and James Weisshaar; 4.9: Huntington Potter and David Dressler; 4.19b: Sarah French; 4.20: Katsuhiko Murakami; 4.43a: Thomas C. Marlovits and Lisa Konigsmaier; 4.43b: Misha Kudryashev, Henning Stahlberg, and Marek Basler.

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Chapter 6 Chapter Opener: Schwarzer, C., Fischer, H., and Machen, T.E. 2016. Chemotaxis and binding of Pseudomonas aeruginosa to scratch-wounded human cystic fibrosis airway epithelial cells. *PLoS ONE* 11(3): e0150109.; 6.3b.1: Stephen P. Edmondson, Southern Illinois University at Carbondale; 6.3b.2: Fenfei Leng; 6.9: Reprinted with permission from S. Schultz et al., Crystal structure of a CAP-DNA complex: The DNA is bent by 90 degrees. *Science* 253:1001-1007 (1991). Copyright (c) 1991 by the American Association for the Advancement of Science. Photo by Thomas A. Steitz and Steve C. Schultz.; 6.21: Timothy C. Johnston, Murray State University; 6.28: Jingyi Fei.

Chapter 7 7.2a: T. Doan, R. Losick, and D. Rudner; 7.2b: Conrad L. Woldringh; 7.2c: Fabai Wu and Cees Dekker Lab; 7.2d: Martin Loose/IST Austria; 7.3a: S. Uphoff and A. Badrinarayanan; 7.3a: Alexander von Diezmann, Andreas Gahlmann, and W.E. Moerner, Stanford University; 7.7: R. Reyes-Lamothe; 7.8b: T. den Blaauwen and Nanne Nanninga, University of Amsterdam, The Netherlands; 7.10b.1: Alex Formstone; 7.10b.2: Alex Formstone; 7.10c: Christine-Jacobs Wagner; 7.12b: Akiko Umeda and K. Amako; 7.16: C. Fernandez-Fernandez and Justine Collier; 7.17a: Alicia M. Muro-Pastor; 7.18b: Rodney M. Donlan & Emerging Infectious Diseases; 7.20a: CDC/Janice Haney Carr; 7.20b: Olga E. Petrova, Karin Sauer.

Chapter 8 Chapter Opener: Campos, R. K. et al. 2014. Samba virus: a novel mimivirus from a giant rain forest, the Brazilian Amazon. *Virology Journal* 11:95.; 8.3a: John T. Finch, Medical Research Council/Laboratory of Molecular Biology, Cambridge, U.K.; 8.4c: W.F. Noyes; 8.4d: Timothy S. Baker and Norman H. Olson, Purdue University; 8.5: M. Wurtz; 8.6a, b: Timothy Booth; 8.6c: P.W. Choppin and W. Stoeckenius; 8.6d: CDC; 8.9b: Jack Parker; 8.10.1: Paul Kaplan; 8.10.2: Thomas D. Brock; 8.12 top: Bo Hun, Jun Liu, and Ian Molineux, Univ. Texas Science Center, Houston.; 8.15b: Lei Sun and Michael G. Rossmann; 8.17a: A. Dale Kaiser, Stanford University; 8.18: Courtesy of Lanying Zeng; 8.19a, b, c: Stephen C. Harrison.

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