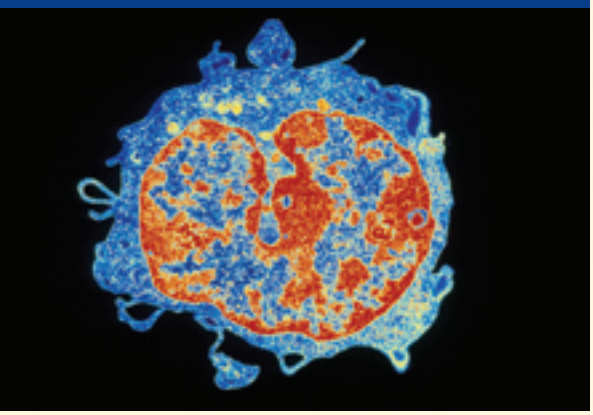
PART 5

Disease and Resistance



False-color transmission electron micrograph image of a T lymphocyte (T cell), which plays a critical role in the human immune response against viruses, bacteria, and tumors.

In past centuries, the spread of disease appeared to be willfully erratic. Illnesses would attack some members of a population while leaving others untouched. A disease that for many generations had taken small, steady tolls would suddenly flare up in epidemic proportions. And strange, horrifying plagues descended unexpectedly on whole nations.

Scientists now know humans live in a precarious equilibrium with the microorganisms surrounding them. Generally, the relationship is harmonious, because humans can come in contact with most microorganisms and develop resistance to them. However, when the natural resistance is unable to overcome the aggressiveness of microorganisms, disease sets in. In other instances, the resistance is diminished by a pattern of human life that gives microorganisms the edge. For example, during the Industrial Revolution of the 1800s, many thousands of Europeans moved from rural areas to the cities. They sought new jobs, adventure, and prosperity. Instead, they found endless labor, unventilated factories, and wretched living conditions—and they found disease.

In Part 5 of this text, we shall explore the infectious disease process and the mechanisms by which the body responds to disease. Chapter 19 opens with an overview of the host-microbe relationship and the factors contributing to the establishment of disease. Epidemiology and diseases within populations also will be explored. In Chapters 20 and 21, the discussion turns to nonspecific and specific methods by which body resistance develops, with emphasis on the immune system. Various types of immunity are explored in Chapter 22, together with a survey of laboratory methods using the immune reaction in the diagnosis of disease. In Chapter 23 the discussion centers on immune disorders leading to serious problems in humans. This includes an extensive discussion of AIDS. Finally, in Chapter 24, we move to treating the patient by discussing antimicrobial drugs, including antibiotics. In these chapters, we uncover the roots of infectious disease and resistance and come to understand the interactions and impact that microorganisms and viruses have on humans at the fundamental level.

Epidemiology

Flying to an impoverished African country on your second day of work to battle Ebola, one of the most deadly viruses, isn't most people's idea of a dream assignment. But it was for Marta Guerra. In fact, the trip to Uganda in 2000 was the assignment she had been coveting. "I wasn't that worried," Guerra says. "This particular strain has only a 65% death rate instead of the Congo strain which is 85%."

Guerra is a disease epidemiologist, popularly known as a "disease detective," with the Epidemic Intelligence Service (EIS) of the Centers for Disease Control and Prevention (CDC) in Atlanta.

Growing up in the multicultural environments of Havana, Cuba, and Washington, D.C., Marta Guerra developed a keen interest in other cultures and teaching people about health risks. She was fascinated by stories her professors told about working overseas. After seeing the movie *Outbreak,* "I thought, that's what I want to do—help contain a deadly epidemic," recalls Guerra. So she obtained a Master's in public health and a Ph.D. in tropical medicine.

Like all EIS officers, Guerra's job is to isolate the cause of an outbreak, prevent its spread, and get out public health messages to people who could have been exposed. When Guerra flew to Uganda in November 2000, the Ebola outbreak had already been identified, so her task was to go from village to village, trying to locate family members and friends, and educate them about symptoms and treatment. "In every corner of Africa people know the word Ebola, and they are terrified of it," Guerra explains. "Sometimes they hide sick family members; sometimes they're frightened of survivors."

The job of a disease detective can be difficult—and dangerous. Although Guerra seldom considered she might acquire a disease she was investigating, she was concerned about political violence. In Uganda, Guerra's team needed military escorts on their travels through villages. In Ethiopia, while on a polio-eradication mission in the summer of 2001, she recalls, "There was rebel activity in all the areas we traveled through—plus land mines. It was pretty scary."

Perhaps you might be interested in a similar career. "You have to be highly motivated, with the ability to think fast on your feet and make quick decisions. You have to be able to walk into a chaotic situation and deal with whatever is thrown at you," Guerra says. "Sometimes I barely drop my bags at home before I'm called out again. Being adaptable is really essential."

To get started, you need a bachelor's degree in a biological science. In addition to required courses in chemistry and biology, undergraduates should study microbiology, mathematics, and computer science. A master of science in epidemiology or public health also is required; many have a Ph.D. or a medical or veterinary degree. Most American disease epidemiologists then apply to EIS's two-year, post-graduate program of service and on-the-job training, where they work with mentors like Marta. She says, "I like the fact that I am contributing to science in the sense that what I do will affect people far into the future."

(Essay modified from *Disease Detective* by Carol Sonenklar in MedHunters.com)

19

Infection and Disease

"Health care matters to all of us some of the time, public health matters to all of us all of the time"

—C. Everett Koop, former Surgeon General of the United States

By late July 1999, crows were literally dropping out of the sky in New York City and dead crows were found in surrounding areas as well. By early September, officials at the Bronx Zoo discovered other birds, including a cormorant, two red Chilean flamingoes, and an Asian pheasant at the zoo had died of the same brain and heart inflammations as found in the crows.

On August 23, 1999, an infectious disease physician at a hospital in northern Queens reported to the New York City Department of Health that two patients had been admitted with encephalitis. In fact, on further investigation, the health department identified a cluster of six patients with encephalitis. Testing by the Centers for Disease Control and Prevention (CDC) of these initial cases for antibodies to common North American **arboviruses**—viruses transmitted by arthropods, such as insects—was positive for St. Louis encephalitis (SLE)—a virus carried by mosquitoes. These findings prompted the health department to begin aerial and ground application of insecticides.

News of SLE and spraying caught the attention of the Bronx Zoo officials. If the birds were dying from the same encephalitis disease as in humans, it could not be caused by the SLE virus because birds do not contract SLE.

So, a reinvestigation by the CDC of virus samples taken from humans, birds, and mosquitoes was undertaken. Results indicated all viral isolates were closely related to West Nile virus (WNV), which had never been isolated in the western hemisphere. It soon became evident that, indeed, the disease in birds and humans was caused by WNV (see Chapter 16).

By early fall, mosquito activity waned and the number of human cases declined (FIGURE 19.1). In all, 61 people would be infected and 7 would die. Although New York City and the surroundings could

Chapter Preview and Key Concepts

19.1 The Host–Microbe Relationship

1. Infection and disease occur when a host–microbe relationship tilts in favor of the microbe.
2. Microbes vary greatly in their pathogenicity.
3. Contact with a potential pathogen can have several outcomes.

19.2 Establishment of Infection and Disease

4. Disease progression involves incubation, prodromal, acute, decline, and convalescent stages.
5. Pathogens gain access to the host through portals of entry.
6. Invasiveness is critical for many pathogens.
7. Virulence factors include enzymes and toxins.
8. Pathogens leave the host through portals of exit.

19.3 Infectious Disease Epidemiology

9. Reservoirs are places in the environment where a pathogen can be found.
10. Diseases have certain behaviors in populations.
11. Disease transmission can involve direct or indirect contact.
12. Diseases are identified as being endemic, epidemic, or pandemic.
    MICROINQUIRY 19: Epidemiological Investigations
13. Nosocomial infections are contracted as a result of being treated for another illness in a hospital or other health care setting.
14. Diseases emerging or reemerging anywhere in the world can become a global health menace.

Epidemiology: The scientific study of the causes and transmission of disease within a population.

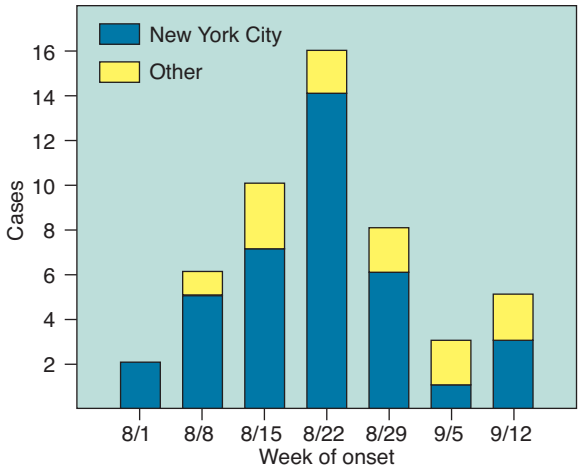


FIGURE 19.1 Positive Cases of West Nile Virus Infection, New York—1999.
Source: www.cdc.gov/mmwr/preview/mmwrthml/mm4839a5.htm. »» What does this graph tell you about the frequency with which WNV occurred?

breathe a sigh of relief, the WNV outbreak was only the beginning of a virus march across the United States. By 2008, human cases of West Nile encephalitis would be reported across America (FIGURE 19.2).

The outbreak of West Nile encephalitis is one example describing the epidemiology of infection and disease; that is, the scientific (and medical) study of the causes, transmission, and prevention of disease within a population. As you remember from Chapter 1, modern epidemiology can trace its origins back to John Snow, the English surgeon who studied a cholera outbreak in the Soho district of London in 1854. His paper, *On the Mode of Communication of Cholera*, is a model of epidemiological detective work that included a map of cholera cases in Soho. By marking with rectangles

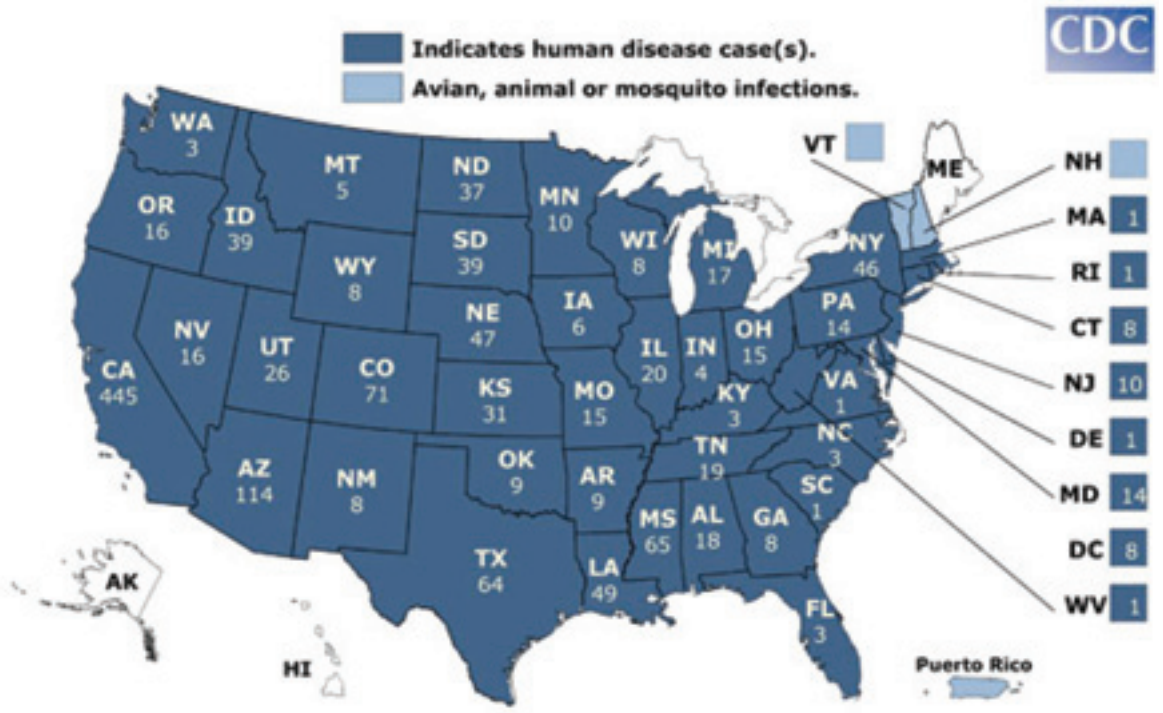


FIGURE 19.2 West Nile Virus Activity, United States—2008. The map indicates the distribution of avian, animal, or mosquito infections in 2008. It also identifies the number of reported human cases in each state (a state is shaded no matter in what area of the state the disease case(s) occurred). *Source:* www.cdc.gov/ncidod/dvbid/westnile/mapsactivity/surv&contol08Maps.htm »» Why is this epidemiological map referred to as a geographical distribution?

where each cholera death occurred, Snow showed they all pointed to the Broad Street pump, which supplied drinking water for the victims and, Snow realized, was the source of the disease. In the end, the outbreak was quelled by simply removing the handle from the pump. Snow's investigation was the classic of epidemiology: what's the source of the outbreak; how is it being transmitted; and how does one prevent further spread?

Today, the CDC, the World Health Organization (WHO), and other agencies throughout the world have built on the historical work of John Snow, Ignaz Semmelweis, Joseph Lister, Louis Pasteur, Robert Koch, and many others. Yet, the epidemiologists employed by these organizations seek the same goals as John Snow: to identify and investigate disease outbreaks; conduct research to enhance prevention; and then devise prevention strategies.

In this chapter, we discuss the mechanisms underlying the spread and development of infectious disease. Our purpose is to bring together many concepts of disease and synthesize an overview of the host–microbe relationship. We summarize much of the important terminology used in medical microbiology and outline some of the factors used by microorganisms to establish themselves in tissues. An understanding of the topics concerning the host–microbe relationship will be essential preparation for the detailed discussion of host resistance (immune) mechanisms in Chapters 20 and 21.

19.1 The Host–Microbe Relationship

By the early 1970s, the Surgeon General of the United States claimed we could "close the books on infectious diseases" (see Chapter 1). The development and use of antibiotics, and vaccines, had made the threat of infectious disease of little consequence. However, antibiotic resistance and new emerging diseases, including Legionnaires' disease, AIDS, Lyme disease, hantavirus pulmonary syndrome, and SARS, have thwarted such optimism. In 2008, of the approximately 57 million humans who died worldwide, more than 25% (15 million) died from infectious diseases, making them the second leading cause of death (behind cardiovascular disease) (FIGURE 19.3). In fact, infectious diseases are the leading cause of death in children under 5 years of age.

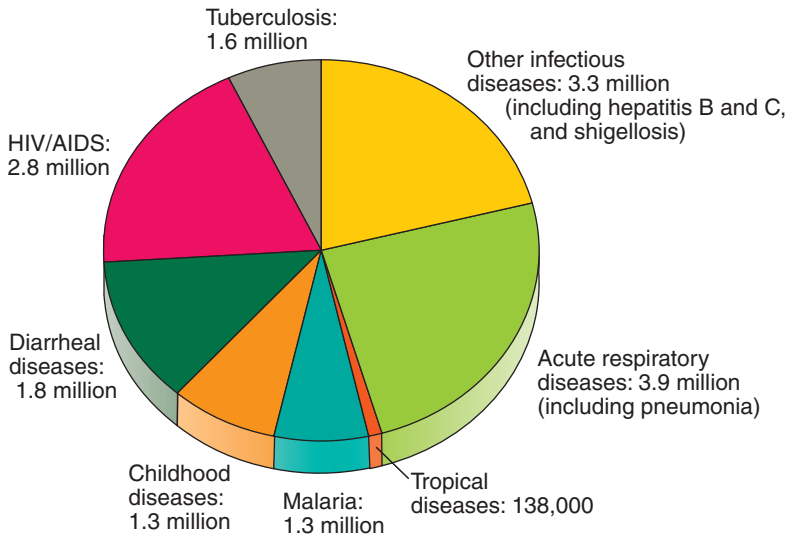


FIGURE 19.3 Infectious Disease Deaths Worldwide. This pie chart depicts the leading causes of infectious diseases and the number of worldwide deaths as reported by the World Health Organization. Tropical diseases: trypanosomiasis, Chagas disease, schistosomiasis, leishmaniasis, filariasis, and onchocerciasis. Childhood diseases: diphtheria, measles, pertussis, polio, and tetanus.
»» Only one of the "pie slices" has grown explosively in mortality numbers since 1993. Identify the disease and explain why that is so.

The Human Body Maintains a Symbiosis with Microbes

KEY CONCEPT

1. Infection and disease occur when a host–microbe relationship tilts in favor of the microbe.

Infection refers to the multiplication of a microbe in a host and the competition for supremacy taking place between them. (Note: in this chapter, for simplicity of discussion, "microbe" includes the viruses.) A host whose resistance is strong remains healthy, and the microbe is either driven from the host or assumes a benign relationship with the host. By contrast, if the host loses the competition, disease develops. The term **disease** refers to any change from the general state of good health. It is important to note that disease and infection are not synonymous; a person may be infected without suffering a disease.

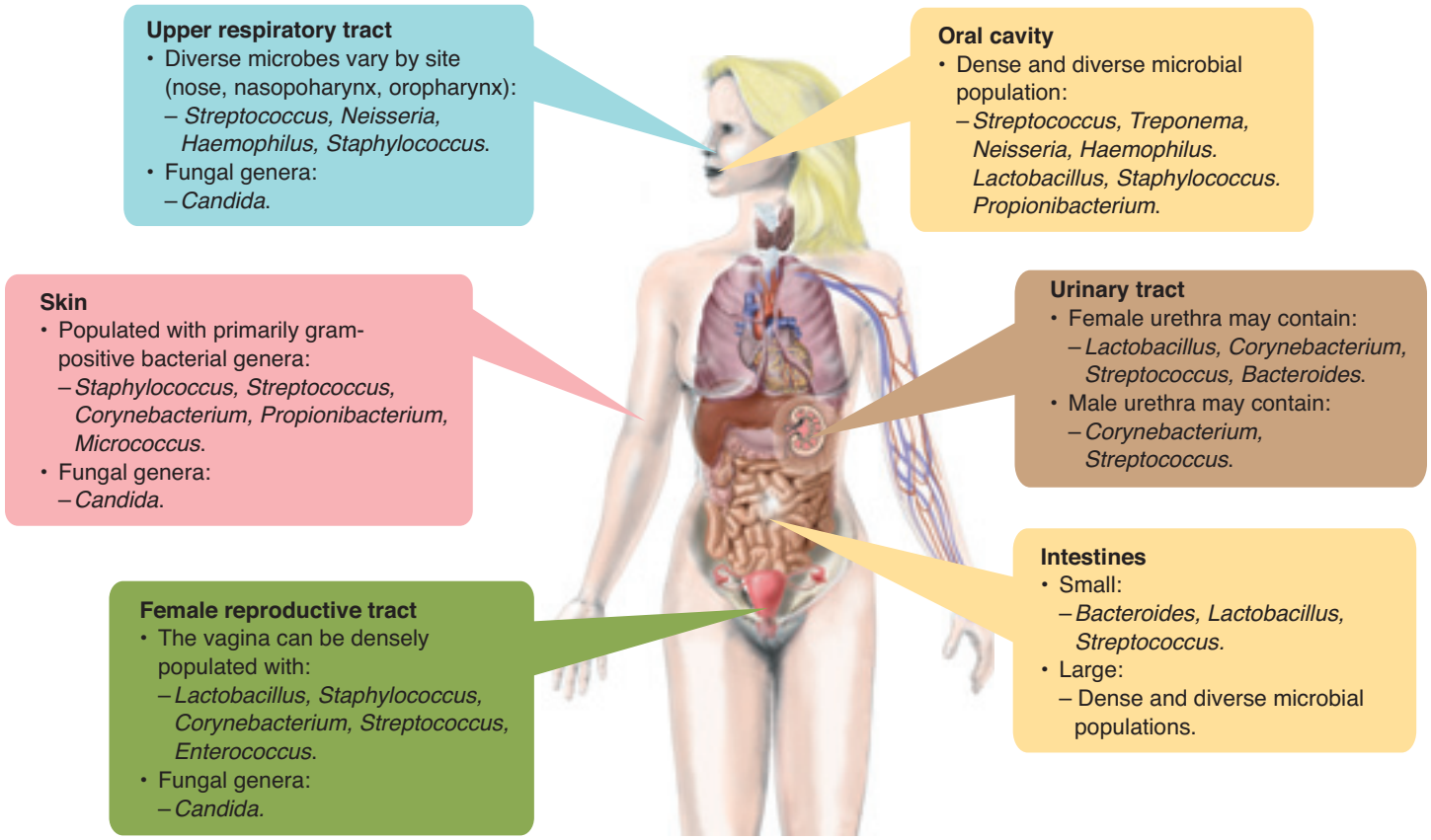


FIGURE 19.4 A Sampling of the Indigenous Microbiota of the Human Body. In reality there are thousands of microbial species and viruses on and within some human body systems. »» Explain why some body systems (e.g., circulatory system, nervous system) normally remain sterile?

Whether host or microbe gets the upper hand often is due in part to the 100 trillion microbes found on and in the human body. This remarkable number amounts to almost 3 pounds of human weight! These microbes represent the **microbiota** (*biota* = "life"), a population of microorganisms and viruses residing in the body without causing disease. Some, called the **indigenous microbiota** establish a permanent relationship with various parts of the body, while others, the **transient microbiota**, are more temporary and found only for limited periods of time. In the large intestine of humans, for example, *Escherichia coli* and *Candida albicans* are almost always found, but species of *Streptococcus* are transient.

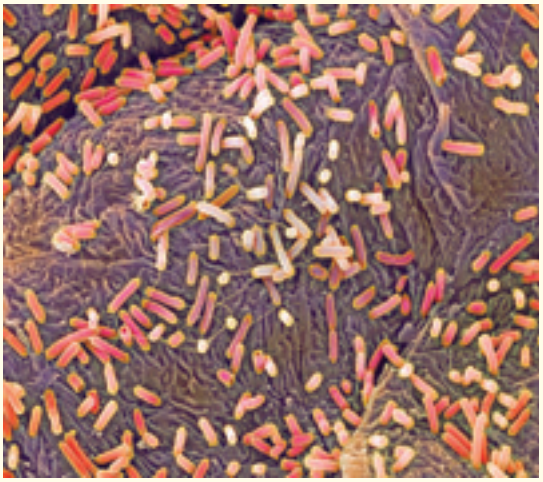
The relationship between the body and its microbiota is an example of a **symbiosis**, or living together. If the symbiosis is beneficial to both the host and the microbe, the relationship is called **mutualism**. For example, species of *Lactobacillus* live in the female vagina and derive nutrients from the environment while producing acid to prevent the overgrowth of other organisms.

A symbiosis also can be beneficial only to the microbe and the host is unaffected, in which case the symbiosis is called **commensalism**. *E. coli* is generally presumed to be a commensal in the human intestine, although some evidence exists for mutualism because the bacterial cells produce nonessential amounts of vitamins B and K. In addition, the microbiota usually will outcompete invading microbial pathogens, thereby protecting the body from dangerous infections.

Microbiota may be found in several body tissues (FIGURE 19.4). These include the skin, the external ears and eyes, and upper respiratory tract. Most of the digestive tract, from oral cavity to rectum, is heavily populated with indigenous microbiota. In fact, many of these are thought to play an important functional role for humans (MICROFOCUS 19.1). Microbiota also make up a population at the urogenital orifices in both males and females.

MICROFOCUS 19.1: Being Skeptical
Can Gut Bacteria Control Human Metabolism?

There is a great diversity of indigenous microbiota present on and within the human body. Adults contain somewhere between 500 and 1,000 different bacterial species in their gut alone. What do all these microbes do? We know *Escherichia coli* can help with water reabsorption and produce some of the vitamin K we use in our diet (see figure). Can these species actually be essential to our metabolism?



False-color scanning electron micrograph of *E. coli* cells on the rat intestinal lining.

Since the 1950s, investigators have manipulated and engineered special strains of mice that have germ-free guts; that is, their guts are sterile. So, one way to determine if various members of the normal microbiota help us in some way is to introduce each species separately into germ-free mice and see what happens. One assumes what happens in a mouse may mirror what happens in a human.

Jeffrey Gordon and colleagues at Washington University School of Medicine in St. Louis studied *Bacteroides thetaiotaomicron,* a gram-negative anaerobe that exists in the human gut at concentrations 1,000 times greater than *E. coli*. At these concentrations, it must be doing something. Gordon's team introduced *B. thetaiotaomicron* into the guts of germ-free mice and monitored what happened. The team quickly discovered the mice synthesized fucose, a monosaccharide sugar, onto the surface of the intestinal cells. Germ-free mice did not. Apparently, *B. thetaiotaomicron* provided a stimulus to the intestinal cells "telling" them to turn on the genes for fucose synthesis. Why fucose? This is the sugar that *B. thetaiotaomicron* uses for energy and metabolism.

Using DNA techniques that allow large numbers of genes to be monitored all at once, Gordon's group realized *B. thetaiotaomicron* actually triggered the intestinal cells to turn on or turn off some 100 of the 25,000 genes in the cell's genome. Some of these genes helped the mice absorb and metabolize sugars and fats. Other genes activated by the bacterial cells produced products helping protect the intestinal wall from being penetrated by other normal microbiota or pathogens. So, the indigenous microbiota may do more than simple commensals. Yet other genes stimulated the growth of new blood vessels, explaining why germ-free mice had to eat 30% more calories to maintain body weight than ordinary mice—germ-free mice have a less well developed blood vessel system and are inefficient at absorbing nutrients. *B. thetaiotaomicron* cells made the human digestive metabolic processes more efficient.

Conclusion: Just from this one bacterial species, the physical development of the normal gut in mice (and extrapolating to the human gut, too) appears to depend on the normal microbiota. Microbes might not only rule the world, they may control our gut physiology and development as well.

Most other tissues of the body remain **sterile**; the blood, cerebrospinal fluid, joint fluid, and internal organs, such as the kidneys, liver, muscles, bone, and brain, are sterile unless disease is in progress.

The first nine months of human development within a mother's womb is the only time when the human body is truly a sterile organism. Indigenous microbiota are introduced when the newborn passes through the birth canal or from a cesarean birth (FIGURE 19.5). Additional organisms enter upon first feeding where nursing or formula can influence what microbes colonize the newborn's gut. During the next weeks, additional contact with the mother and other individuals will expose the infant to additional intestinal microbes. Besides the gut, the skin will be colonized by many different bacterial and fungal species. The upper respiratory tract will be covered with a diverse group of bacterial species while the lower urethra

Sterile: Devoid of living microorganisms, viruses, and spores.

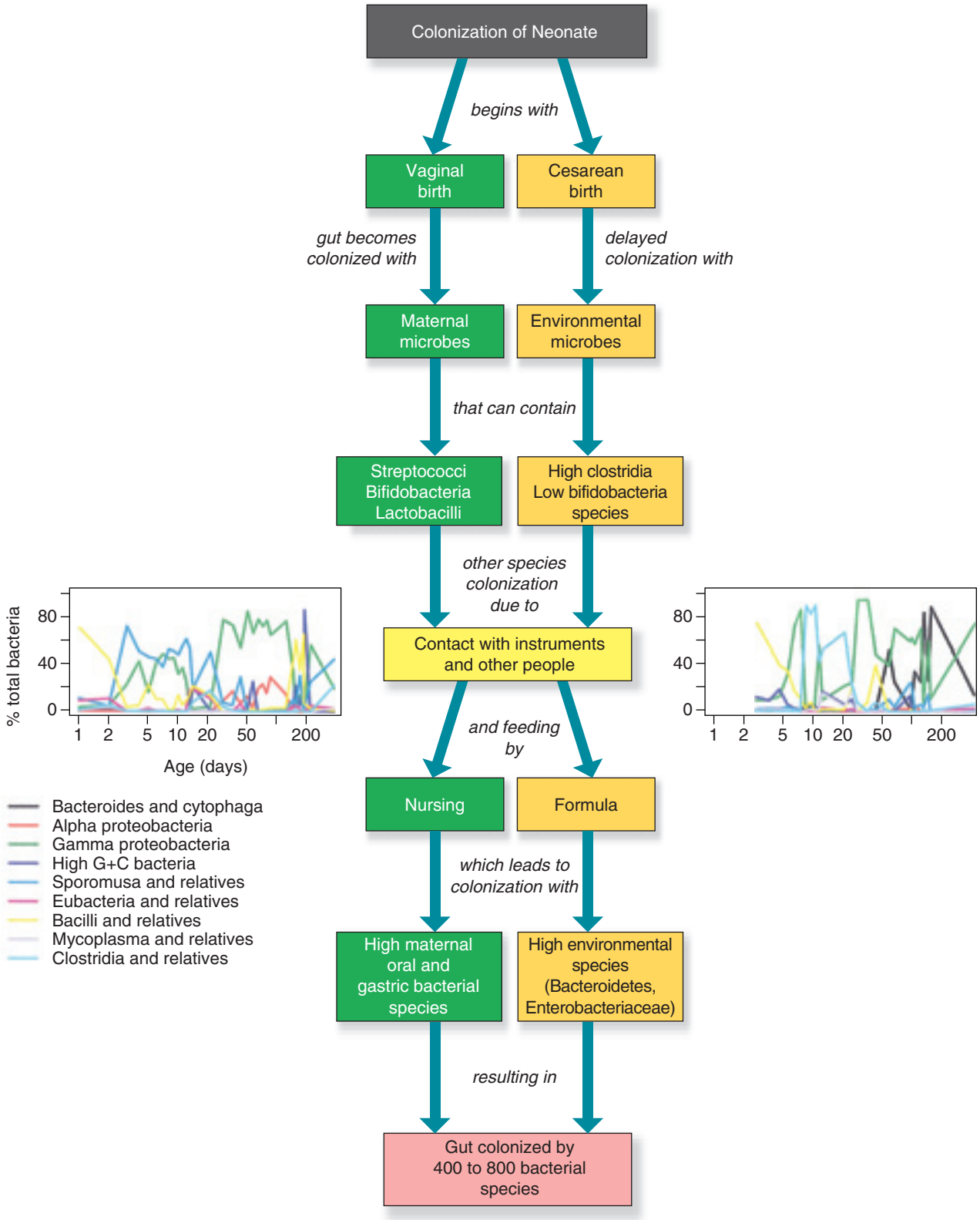


FIGURE 19.5 Colonization of Newborns. This concept map diagrams possible colonization of two newborns based on form of birth (vaginal or cesarean) and feeding (nursing or formula). The graphs (inserts) plot fluctuations in bacterial microbiota (left: vaginal birth; right: cesarean birth) over the first 200 days. »» How would each form of birth and feeding introduce microbiota into the newborn?

Modified from *Development of the Human Infant Intestinal Microbiota*, Palmer C., Bik E.M., DiGiulio D.B., Relman D.A., and Brown P.O., *PLoS Biology* Vol. 5, No. 7, el77 doi:10.1371/journal.pbio.0050177

will be populated by bacterial and fungal organisms, as well as a few potential pathogens.

By one year, the infant's indigenous microbiota is adult-like and remains throughout life, undergoing small changes in response to the internal and external environment of the individual.

CONCEPT AND REASONING CHECKS

19.1 Distinguish between a mutualistic relationship and a commensalistic one.

Pathogens Differ in Their Ability to Cause Disease

KEY CONCEPT

2. Microbes vary greatly in their pathogenicity.

There also are symbiotic relationships, called **parasitism**, where the pathogen causes damage to the host and disease can result. Microbiologists once believed microbes were either pathogenic or nonpathogenic; they either caused disease or they did not. From the previous section, we know that is not true.

Pathogenicity refers to the ability of a microorganism to gain entry to the host's tissues and bring about a physiological or anatomical change, resulting in altered health and leading to disease. Certain pathogens, such as the cholera, plague, and typhoid bacilli, are well known for their ability to cause serious human disease. Others, such as common cold viruses, are considered less pathogenic because they induce milder illnesses. Still other microorganisms are opportunistic.

Whether a disease is mild or severe depends on the pathogen's ability to do harm to the body. Thus, the degree of pathogenicity is called **virulence** (*virul* = "poisonous"). For example, an organism invariably causing disease, such as the typhoid bacillus, is said to be "highly virulent." By comparison, an organism sometimes causing disease, such as *Candida albicans*, is labeled "moderately virulent." Certain organisms, described as **avirulent**, are not regarded as disease agents. The lactobacilli and streptococci found in yogurt are examples. However, it should be noted that any microorganism has the ability to change genetically and become virulent.

In recent years, a new term, **pathogenicity islands**, has been used to refer to clusters of genes responsible for virulence (see Chapter 9). The genes, present on the bacterial cell's chromosome or plasmids, encode many of the virulence factors making a microbe more virulent. These unstable islands are fairly large segments of a pathogen's genome and are absent in nonpathogenic strains. Pathogenicity islands have many of the properties of intervening sequences (see Chapter 8), suggesting they move by horizontal gene transfer. A copy of these blocks of genetic information can move from a pathogenic strain into an avirulent (harmless) organism, converting it to a pathogen. Such horizontal transfer processes show how the evolution of pathogenicity can make quick jumps.

Virulence factors: Pathogen-produced molecules or structures that allow the cell to invade the host (or evade the immune system) and possibly cause disease.

Before examining disease progression, realize that an infection and a resulting disease can be caused by a single microbe. The diseases identified by Pasteur, Koch, and their contemporaries are examples. However, it is now clear that some diseases are caused by two or more microbes acting together or in succession. Such **polymicrobial diseases** include tooth decay, gastroenteritis, urinary tract infections, otitis media, and HIV AIDS.

CONCEPT AND REASONING CHECKS

19.2 Distinguish between pathogenicity and virulence.

Several Events Must Occur for Disease to Develop in the Host

KEY CONCEPT

3. Contact with a potential pathogen can have several outcomes.

For disease to occur, a potential pathogen must first come in contact with exposed parts of the body (FIGURE 19.6). Several outcomes are possible: the pathogen may be lost to the environment or it may colonize the normal microbiota and remain as a transient member. Depending on the nature of the pathogen, it could also become a commensal.

An **exogenous infection** is established if a pathogen from the environment breaches the host's external defenses and enters the host. Likewise, if a microbial member of the normal microbiota should gain access to sterile tissue, an **endogenous infection** ensues. In both cases, the infection may trigger additional host defenses capable of eliminating the invader.

Should the pathogen cause injury or dysfunction to host tissues, then a disease is established. Again, additional host defenses may eliminate the pathogen, in which case the disease declines and the host recovers. In other cases, the pathogen

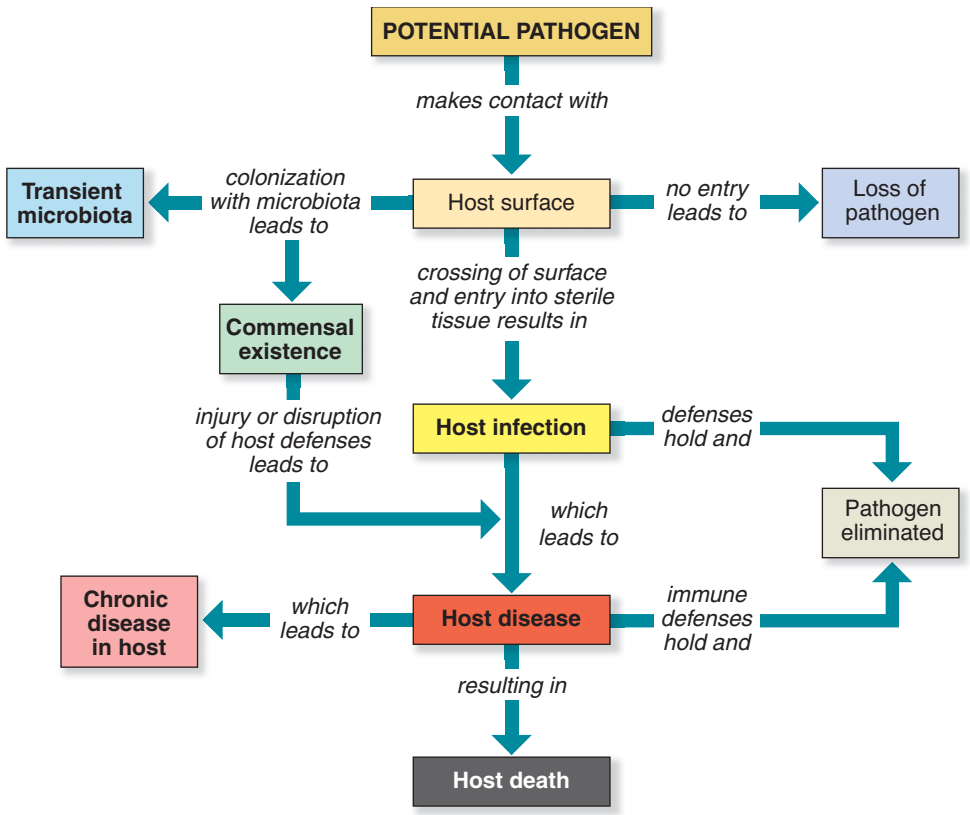


FIGURE 19.6 The Progression and Outcomes of Infection and Disease. A concept map illustrating possible outcomes resulting from the contact between host and pathogen. »» Propose some ways that a pathogen would gain entry into sterile tissue.

and host reach a stalemate where neither has the advantage. Tuberculosis is an example of such a chronic state. Lastly, the inability to eliminate the pathogen may lead to death.

Opportunistic infections often are caused by commensals taking advantage of a shift in the body's delicate balance to one favoring the microbe. If the indigenous microbiota is reduced or the host's immune system is weakened, some commensals seize the "opportunity" to invade the tissues and cause disease. AIDS is an example where crippling of the immune system makes the patient highly susceptible to opportunistic organisms. Thus, an upset in resistance mechanisms or microbiota control may enhance the ability of organisms to establish disease.

Infections may develop in one of two ways. A **primary infection** occurs in an otherwise healthy body, while a **secondary infection** develops in an individual weakened by the primary infection. In the influenza pandemic of 1918 and 1919, hundreds of millions of individuals contracted influenza as a primary infection and many developed pneumonia as a secondary infection. Numerous deaths in the pandemic were due to pneumonia's complications.

As the names imply, **local diseases** are restricted to a single area of the body, while **systemic diseases** are those disseminating to the deeper organs and systems. Thus, a staphylococcal skin boil beginning as a localized skin lesion may become more serious when staphylococci spread and cause systemic disease of the bones, meninges, or heart tissue.

The transient appearance of living bacterial cells in the blood is referred to as **bacteremia**. **Septicemia** refers to an infection of bacterial cells in the blood which can be a life-threatening condition (MicroFocus 19.2). Other microbes also are disseminated. **Fungemia** refers to the spread of fungi, **viremia** to the spread of viruses, and **parasitemia** to the spread of protozoa and multicellular worms through the blood.

CONCEPT AND REASONING CHECKS

19.3 Contrast exogenous, endogenous, and opportunistic infections.

19.2 Establishment of Infection and Diseases

Disease is the result of a dynamic series of events expressing the competition between host and pathogen. To overcome host defenses and bring about the anatomic or physiologic changes leading to disease, the pathogen must possess unusual abilities. Disease therefore is a complex series of interactions between pathogen and host.

In this section, we outline the stages of disease from which we can explore the processes and factors determining whether disease can occur.

Diseases Progress through a Series of Stages

KEY CONCEPT

4. Disease progression involves incubation, prodromal, acute, decline, and convalescent stages.

In most instances, there is a recognizable pattern in the progress of the disease following the entry of the pathogen into the host. Often these periods are identified by **signs**, which represent evidence of disease detected by an observer (e.g., physician). Fever or bacterial cells in the blood would be examples. Disease also can be noted by **symptoms**, which represent changes in body function sensed by the patient. Sore throat and headache are examples. Diseases also may be characterized by a specific collection of signs and symptoms called a **syndrome**. AIDS is an example.

Disease progression is distinguished by five stages (FIGURE 19.7). The episode of disease begins with an **incubation period**, reflecting the time elapsing between the entry of the microbe into the host and the appearance of the first symptoms. For example, an incubation period may be as short as 2 to 4 days for the flu; one to two weeks for measles; or three to six years for leprosy. Such factors as the number of organisms, their generation time and virulence, and the level of host resistance determine the incubation period's length. The location of entry also may be a determining factor. For instance, the incubation period for rabies may be as short as several days or as long as a year, depending on how close to the central nervous system the viruses enter the body.

The next phase in disease is a time of mild signs or symptoms, called the **prodromal phase**. For many diseases, this period is characterized by indistinct and general symptoms such as nausea, headache, and muscle aches, which indicate the

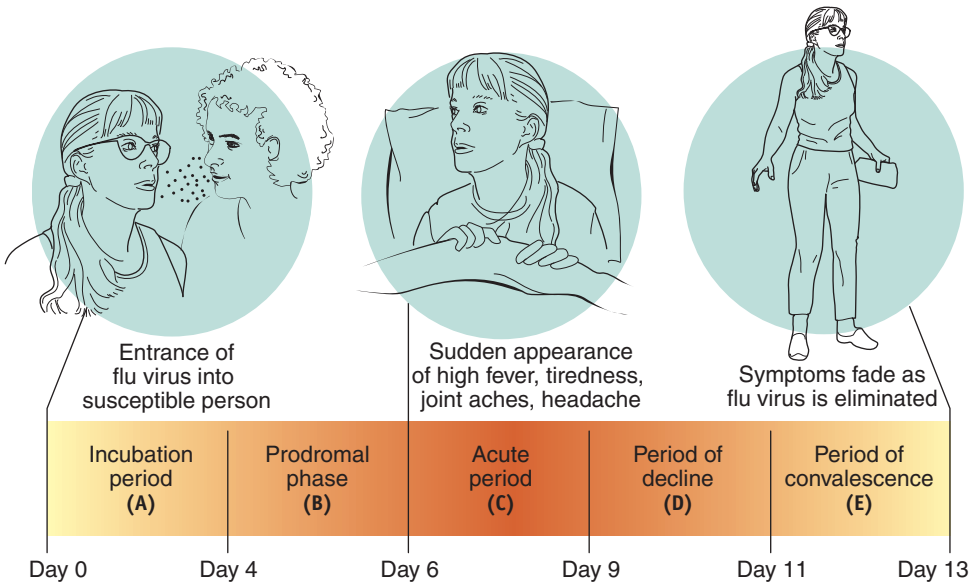


FIGURE 19.7 The Course of an Infectious Disease, as Typified by the Flu. (**A**) A susceptible person could be exposed to flu viruses in respiratory droplets at which time the incubation period begins. (**B**) The prodromal phase is characterized by mild signs and symptoms, such as a headache and fever. (**C**) The acute period is characterized by sudden symptoms of high fever with chills, cough, tired muscles and joint pain, and loss of appetite. (**D**) As the virus is eliminated from the body, the fever breaks and appetite returns as recovery begins. (**E**) With the period of convalescence, the body returns to normal.
»» How would the course of the flu differ from that for a common cold?

MICROFOCUS 19.2: Evolution

Sepsis and Septic Shock

The presence of living bacteria in the bloodstream is called **bacteremia**. Because the blood is sterile, any bacterial cells detected in the blood are cause for alarm. In most situations, however, only a small number of bacterial cells gain entry and no symptoms develop because the invaders are rapidly removed by white blood cells (Chapter 20). Such temporary bacteremia may occur in healthy individuals during dental procedures or tooth brushing, when bacterial species living on the gums around the teeth enter the bloodstream through trauma to the gums. However, in a vulnerable host, such as a person with heart valve disease, prevention of bacteremia may include taking antibiotics prior to surgery or dental procedures to prevent any bacterial cells from colonizing the heart.

If more cells enter the bloodstream than can be effectively removed, an infection will develop. A more serious, but rare condition is **septicemia** (or **sepsis**) that occurs when the bacterial cells multiply and spread throughout the bloodstream. Often sepsis results from another infection in the body or from surgery on an infected area. In the United States, sepsis is the leading cause of death in non-coronary intensive care unit (ICU) patients, and the tenth most common cause of death overall according to data from the CDC. Sepsis affects 750,000 Americans each year of which about 30% die.

Sepsis can be caused by several gram-positive and gram-negative bacterial species (see figure A). Common gram-positive bacteria include *Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus* species that are microbiota of the intestines, and *Streptococcus* pyogenes. Common gram-negative bacteria causing septic shock include opportunistic microbiota of the intestines such as *Escherichia coli, Klebsiella* species, and *Pseudomonas aeruginosa*. The most common obligate anaerobe is *Bacteroides fragilis*.

Sepsis is also called **systemic inflammatory response syndrome (SIRS)** because it involves an exaggerated immune response to released bacterial toxins (see figure B). Such a systemic response is very serious and can be life threatening. The manifestations of SIRS include two or more of the following conditions: high or low body temperature, increased heart rate, rapid breathing, and an elevated leukocyte count. Besides the inflammatory cascade that develops, the bacterial toxins attack the walls of the small blood vessels, causing them to become leaky so that fluid is lost from the blood into the surrounding tissues. Leakage and swelling also can develop in the lungs, causing difficulty breathing (respiratory distress).

Another dangerous effect of bacterial toxins is widespread clotting of the blood within the small blood vessels. This is called **disseminated intravascular coagulation (DIC)**, and can be fatal if not treated quickly. As clotting factors are used up, blood vessel leakage can lead to hemorrhaging. Often the person now has a condition called **severe sepsis**, which is associated with at least one acute organ dysfunction, decreased blood flow, or low blood pressure.

The risk of death now becomes high and requires immediate, aggressive treatment with antibiotics. A delay starting antibiotic treatment greatly decreases the person's chances of survival. Often two or three antibiotics will be given together to increase the chances of killing the bacteria cells.

Without treatment, septicemia often develops into **septic shock**, which is characterized by a dangerously low drop in blood pressure and multiple organ system failure (see figure B). In the United States, septic shock is the number one cause of death in ICUs and the 13th most common cause of death. It occurs most often in newborns and people with a weakened immune system.

The loss of fluid from the blood may be so great that the normal circulation (the rate the heart pumps at) cannot be maintained and blood pressure drops. Persistent hypotension reduces the blood flow and supply of oxygen to major organs such as the heart, kidneys, and brain. Signs of septic shock include a rapid and very weak pulse, reduced urine flow, confusion, and collapse—that is, multiple organ failure.

Septic shock is a medical emergency and is normally treated in an ICU. Large doses of antibiotics, along with infusions of fluids, are given to fight off the infection and maintain blood pressure. Drugs are given to increase blood flow to the brain, heart, and other organs. If the lungs fail, the person may need a mechanical ventilator to help breathing. Despite all efforts, more than 25% of people with septic shock die.

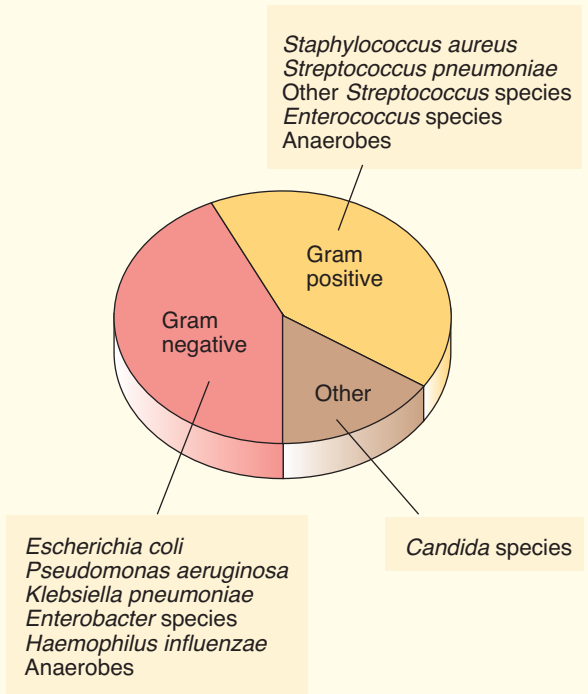


FIGURE A Microbes causing septicemia.

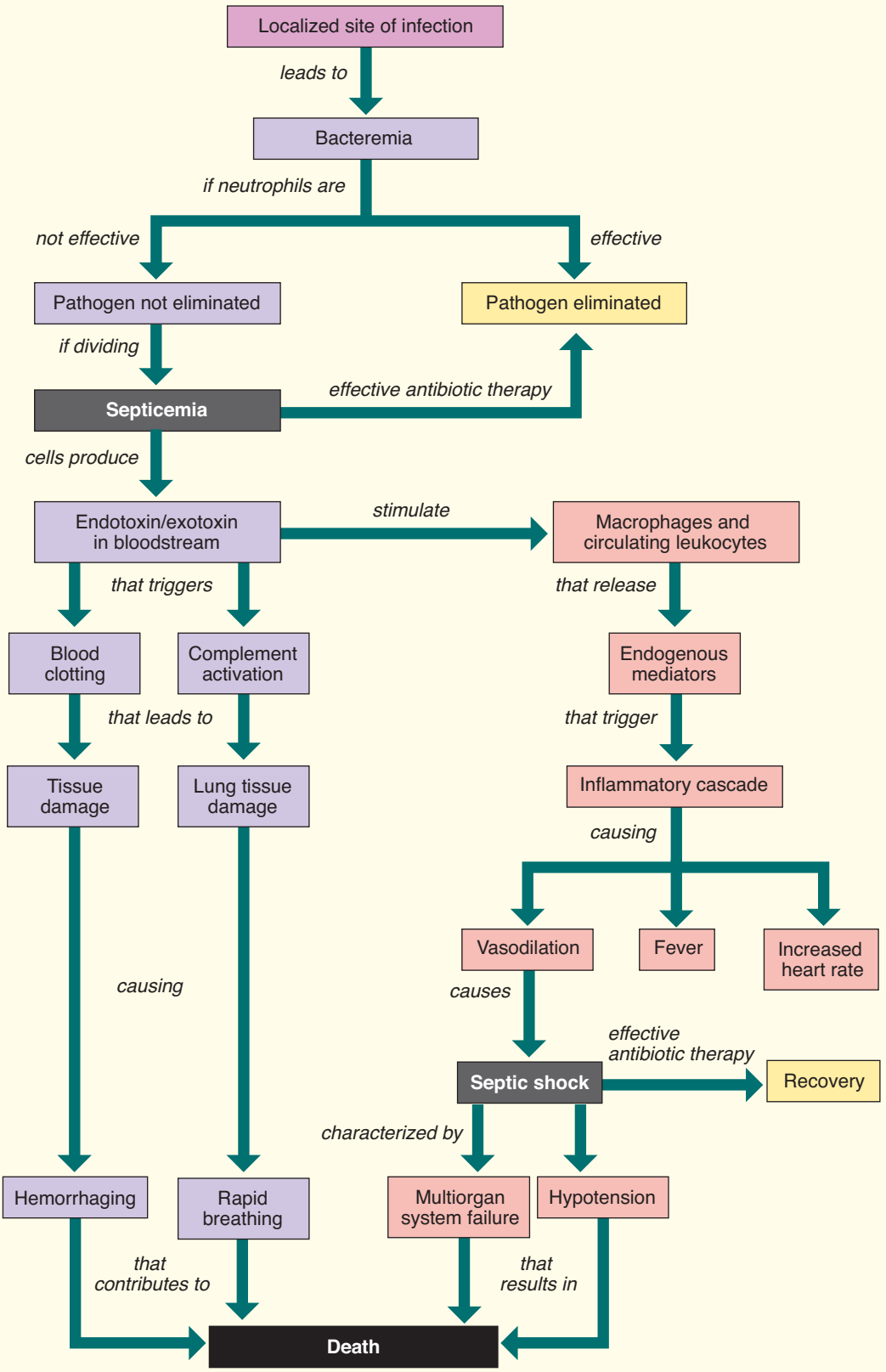


FIGURE B Chain of events leading to sepsis and septic shock.

competition between host and microbe has begun. During the onset and progression of a disease, it can be described as clinical or subclinical. A **clinical disease** is one in which the symptoms are apparent, while a **subclinical disease** is accompanied by few obvious symptoms. Many people, for example, have experienced subclinical cases of mumps or infectious mononucleosis, and in the process developed immunity to future attacks. By contrast, certain diseases are invariably accompanied by clearly recognized clinical symptoms. Influenza is one example.

The **acute period** or **climax** follows. This is the stage of the disease when signs and symptoms are of greatest intensity. Examples are the skin rash in scarlet fever, jaundice in hepatitis, swollen lymph nodes in infectious mononucleosis, and Koplik spots and rash in measles (see Chapter 15). For the flu, patients suffer high fever and chills, the latter reflecting differences in temperature between the superficial and deep areas of the body. Dry skin and a pale complexion may result from constriction of the skin's blood vessels to conserve heat. A headache, cough, body and joint aches, and loss of appetite are common. The length of this period can be quite variable, depending on the body's response to the pathogen and the virulence of the pathogen. Although the patient feels miserable, there is some evidence some signs and symptoms can be beneficial (MicroFocus 19.3).

As the signs and symptoms begin to subside, the host enters a **period of decline**. Sweating may be common as the body releases excessive amounts of heat and the normal skin color soon returns as the blood vessels dilate. The sequence comes to a conclusion after the body passes through a **period of convalescence**. During this time, the body's systems return to normal.

When studying the course of a disease, it often can be defined by its severity or duration. An **acute disease**, like the flu, develops rapidly, is usually accompanied by severe symptoms, comes to a climax, and then fades rather quickly. A **chronic disease**, by contrast, often lingers for long periods of time. The symptoms are slower to develop, an acute period is rarely reached, and convalescence may continue for several months. Hepatitis A,

MICROFOCUS 19.3: Public Health
Illness May Be Good for You

For most of the twentieth century, medicine's approach to infectious disease was relatively straightforward: Note the symptoms and eliminate them. However, that approach may change in the future, as Darwinian medicine gains a stronger foothold. Proponents of Darwinian medicine ask why the body has evolved its symptoms, and question whether relieving the symptoms may leave the body at greater risk.

Consider coughing, for example. In the rush to stop a cough, we may be neutralizing the body's mechanism for clearing pathogens from the respiratory tract. Nor may it be in our best interest to stifle a fever (at least a low grade fever), because fever enhances the immune response to disease. Many physicians view iron insufficiency in the blood as a symptom of disease, yet many bacterial species (e.g., tubercle bacilli) require this element, and as long as iron is sequestered out of the blood in the liver, the bacterial cells cannot grow well. Even diarrhea can be useful—it helps propel pathogens from the intestine and assists the elimination of the toxins responsible for the illness.

Darwinian biologists point out that disease symptoms have evolved over the vast expanse of time and probably have other benefits waiting to be understood. They are not suggesting a major change in how doctors treat their patients, but they are pushing for more studies on whether symptoms are part of the body's natural defenses. So, don't throw out the Nyquil, Tylenol, or Imodium quite yet.

trichomoniasis, and infectious mononucleosis are examples of chronic diseases. Sometimes an acute disease may become chronic when the body is unable to rid itself completely of the microbe. For example, one who has contracted a parasitic disease, such as giardiasis or amoebiasis, may experience sporadic symptoms for many years.

With this understanding of the disease stages, we now can examine several factors required for the establishment of disease, as outlined in FIGURE 19.8.

CONCEPT AND REASONING CHECKS

19.4 Assign the following signs and symptoms of the flu to the appropriate disease stage (fever, headache, chills, and muscle pain).

Pathogen Entry into the Host Depends on Cell Adhesion and the Infectious Dose

KEY CONCEPT

5. Pathogens gain access to the host through portals of entry.

A portal of entry refers to the characteristic route by which an exogenous pathogen enters the host. It varies considerably for different organisms and is a key factor leading to the establishment of disease. Abrasions or mechanical injury to the skin can be a portal of entry. For example, tetanus may occur if *Clostridium tetani* spores on a sharp object in the soil puncture the skin and enter the anaerobic tissue of a wound. Tetanus will not develop if spores are consumed with food because the spores do not germinate in the human intestinal tract.

The ability of a pathogen to establish an infection and possible disease usually depends on the **infectious dose**, the numbers of microbes taken into the body. The consumption of a few hundred thousand typhoid bacilli will lead to disease. By contrast, many millions of cholera bacilli must be ingested if cholera is to be established. One explanation for the difference is the high resistance of typhoid bacilli to the acidic conditions in the stomach, in contrast to the low resistance of cholera bacilli. Also, it may be safe to eat fish when the water contains hepatitis A viruses, but eating raw clams from the same water can be dangerous because clams are filter-feeders, concentrating hepatitis A viruses in their bodies.

Often the host is exposed to low doses of a pathogen and, as a result, develops immunity. For instance, many people can tolerate low numbers of mumps viruses without exhibiting disease. They may be surprised to find they are immune to mumps when it breaks out in their family at some later date.

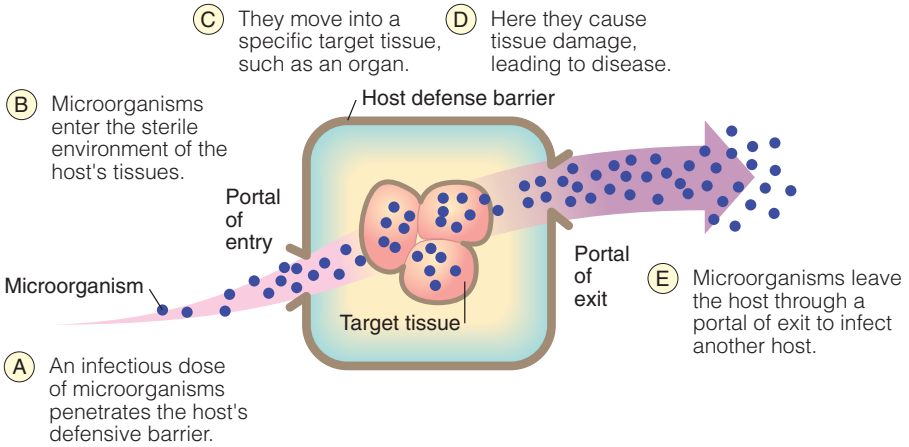


FIGURE 19.8 The Generalized Events on the Establishment of a Local Disease. The infectious dose and adhesion to cells or tissues are required to initiate infection and disease. »» Identify which events would not occur if an infection but not a disease occurred.

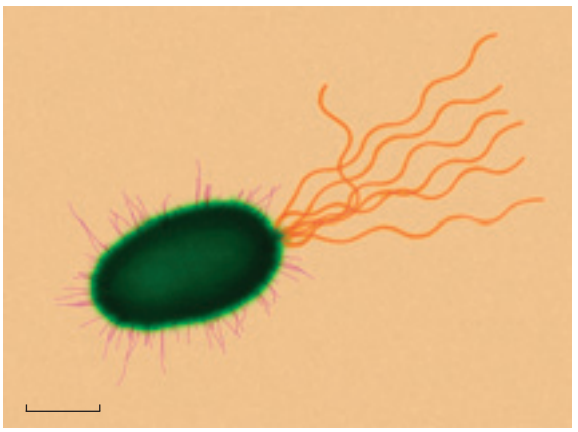


FIGURE 19.9 Pili on *Escherichia coli*. A false-color transmission electron micrograph of *E. coli* displaying the pili used for adhesion to the tissue. Adhesins in pili such as these increase the pathogenicity of the organism by allowing it to localize at its appropriate tissue site. (Bar = 1 μm.) »» What are the long structures projecting from the right side of the cell?

Many pathogens enter at specific, natural portals of entry because these microbes contain on their surface "sticky" factors, called **adhesins**, that allow pathogens to adhere to appropriate tissue sites. A variety of adhesins often are associated with bacterial capsules, flagella, or pili (see Chapter 4) (FIGURE 19.9). For example, the gonococci and some other agents of sexually transmitted diseases often attach by means of pili to specific receptor sites only found on tissues of the urogenital system. The host cell is often an active partner in the adhesion because the pathogen

triggers it to express target receptor sites for adhesin binding. Also, many viruses have spikes on the capsid or envelope, allowing for attachment (see Chapter 14).

Some pathogens have multiple portals of entry. The tubercle bacillus, for instance, may enter the body in respiratory droplets, contaminated food or milk, or skin wounds. The bacterial species causing Q fever can enter by any of these portals, as well as by an arthropod bite. The tularemia bacillus may enter the eye by contact, the skin by an abrasion, the respiratory tract by droplets, the intestines by contaminated meat, or the blood by an arthropod bite.

CONCEPT AND REASONING CHECKS

19.5 Assess the role of the infectious dose and adhesion in establishing an infection.

Breaching the Host Barriers Can Establish Infection and Disease

KEY CONCEPT

6. Invasiveness is critical for many pathogens.

Some pathogens do not need to penetrate cells or tissues to cause disease. The pertussis bacillus, for example, adheres to the surface layers of the respiratory tract while producing the toxins causing disease. Likewise, the cholera bacillus attaches to the surface of the intestine, where it produces toxins.

However, the ability of a pathogen to penetrate tissues and cause structural damage is an important component for the virulence of many pathogens. The ability to penetrate and spread is called **invasiveness** and the bacilli of typhoid fever and the protozoan causing amoebiasis are examples of pathogens that depend on their invasiveness. By penetrating the tissue of the gastrointestinal tract, these microorganisms cause ulcers and sharp, appendicitis-like pain characteristic of the respective diseases.

Actin: A cytoskeletal protein essential for cell movement and the maintenance of cell shape in most eukaryotic cells.

Invasiveness often is facilitated through the pathogen's internalization by immune cells (FIGURE 19.10). These cells, including macrophages, undergo **phagocytosis** by engulfing pathogens, taking them into the cell cytoplasm in vacuoles, and then attempting to destroy them in lysosomes. In addition, some bacterial pathogens are internalized by inducing nonphagocytic cells to undergo phagocytosis. If the pathogen can evade destruction by lysosomes, the cell interior provides a protective niche or a vehicle to pass

Macrophages: Large white blood cells that remove waste products, microorganisms, and foreign material from the bloodstream.

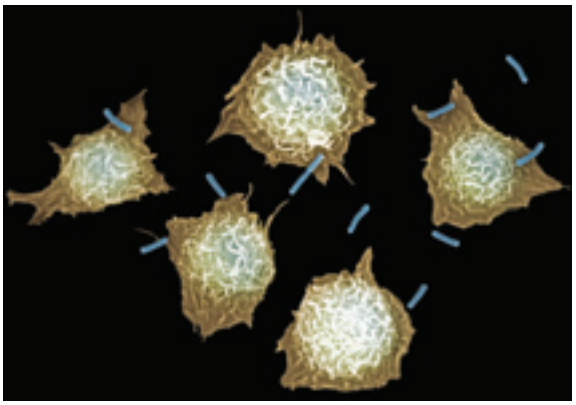


FIGURE 19.10 Macrophages Undergoing Phagocytosis. In this false-color scanning electron micrograph, macrophages, a type of immune cell, are capturing bacterial cells for phagocytosis. »» Why might phagocytosis be an important activity of the human immune system when infection occurs?

through otherwise impenetrable defenses, such as the blood-brain barrier.

Some cytoplasm-invading pathogens, such as *Shigella flexneri* (shigellosis), *Rickettsia prowazekii* (epidemic typhus), and *Listeria monocytogenes* (listeriosis) have cell membrane adhesive proteins that form a zipper-like binding of pathogen to the host cell. As a result of this molecular adhesion and cross-talk, the pathogen triggers the host cell to undergo phagocytosis. Once in the cell, the pathogens escape from the vacuole, eliminating any chance of their destruction by host lysosomes (FIGURE 19.11). In the cytoplasm, the bacterial cells trigger the host cell to synthesize an actin tail on the bacterial cells, which propels the organism through the cell's cytoplasm. When a Listeria cell bumps against the host's plasma membrane, it distorts and indents the adjacent cell, bridges the junction between the two cells, and enters the next cell (somewhat like moving from train car to train car through connecting doors). The system allows bacterial invasion to occur without the bacterial cells leaving the cellular environment.

CONCEPT AND REASONING CHECKS

19.6 Assess phagocytosis as an invasiveness mechanism used by pathogens.

Successful Invasiveness Requires Pathogens to Have Virulence Factors

KEY CONCEPT

7. Virulence factors include enzymes and toxins.

It should be noted that upon entry into a host, a pathogen is confronted with a profoundly dif-

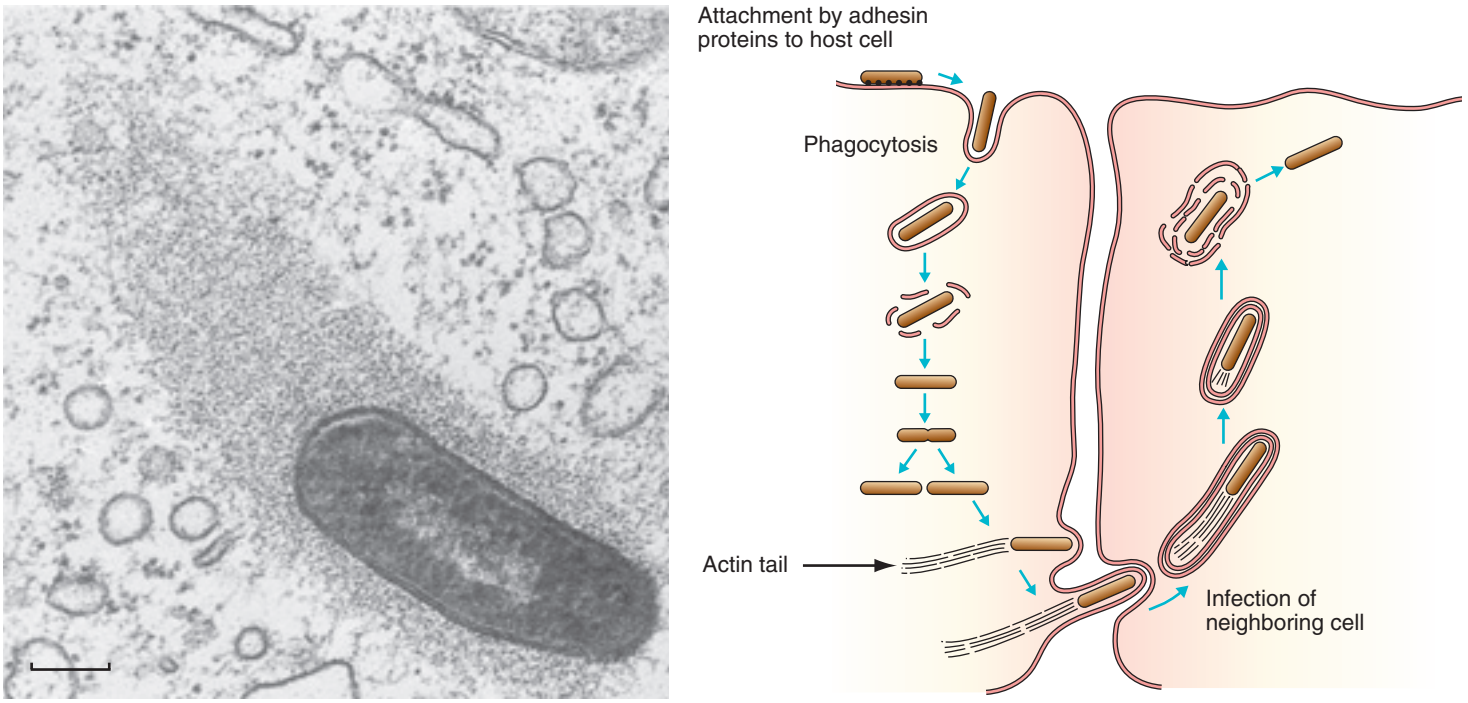


FIGURE 19.11 **Invasion by *Listeria monocytogenes*.** (**A**) A transmission electron micrograph of a *Listeria* cell with its actin tail. (Bar = 0.3 µm.) (**B**) After entering a host cell by phagocytosis, the bacterial cell loses the surrounding membrane and divides to form a larger population. Invasion of neighboring cells uses the actin tail to "drive" the cells into the adjacent cell. In that cell, the cell again loses the surrounding cell membranes and initiates another infection. »» What invasion process is negated by the *Listeria* cell's ability to generate an actin tail?

ferent environment. Adaptation to this environment requires the genetic machinery enabling the pathogen to adapt and withstand the resistance put forward by the host. Several factors may be present to overcome host defenses.

Enzymes. The virulence of a microbe depends to some degree on its ability to produce a series of extracellular enzymes to help the pathogen resist body defenses. A few examples illustrate how bacterial enzymes act on host cells and interfere with certain functions or barriers meant to retard invasion.

One bacterial enzyme is the **coagulase** produced by virulent staphylococci (FIGURE 19.12A). Coagulase catalyzes the formation of a blood clot from fibrinogen proteins in human blood. The clot sticks to staphylococci, protecting them from phagocytosis. Part of the walling-off process observed in a staphylococcal skin boil is due to the clot formation. Coagulase-positive *Staphylococcus aureus* may be identified in the laboratory by combining the cells with human or rabbit plasma. The formation of a clot in the plasma indicates coagulase activity.

Many streptococci have the ability to produce the enzyme **streptokinase**. This substance dissolves fibrin clots used as a defense by the body to restrict and isolate an infected area. Streptokinase thus overcomes an important host defense and allows further tissue invasion by the bacterial cells.

Hyaluronidase is sometimes called the "spreading factor" because it enhances penetration of a pathogen through the tissues. The enzyme digests hyaluronic acid, a polysaccharide that binds cells together in a tissue (FIGURE 19.12B). The term tissue cement is occasionally applied to this polysaccharide. Hyaluronidase is an important virulence factor in pneumococci and certain species of streptococci and staphylococci. In addition, gas gangrene bacilli use it to facilitate spread through the muscle tissues.

Some pathogens also produce enzymes that destroy blood cells. **Leukocidins** are products of staphylococci, streptococci, and pneumococci. The enzymes destroy circulating neutrophils and tissue macrophages, both of which are immune system cells designed to phagocytize and destroy the pathogens. The enzymes attach to the immune

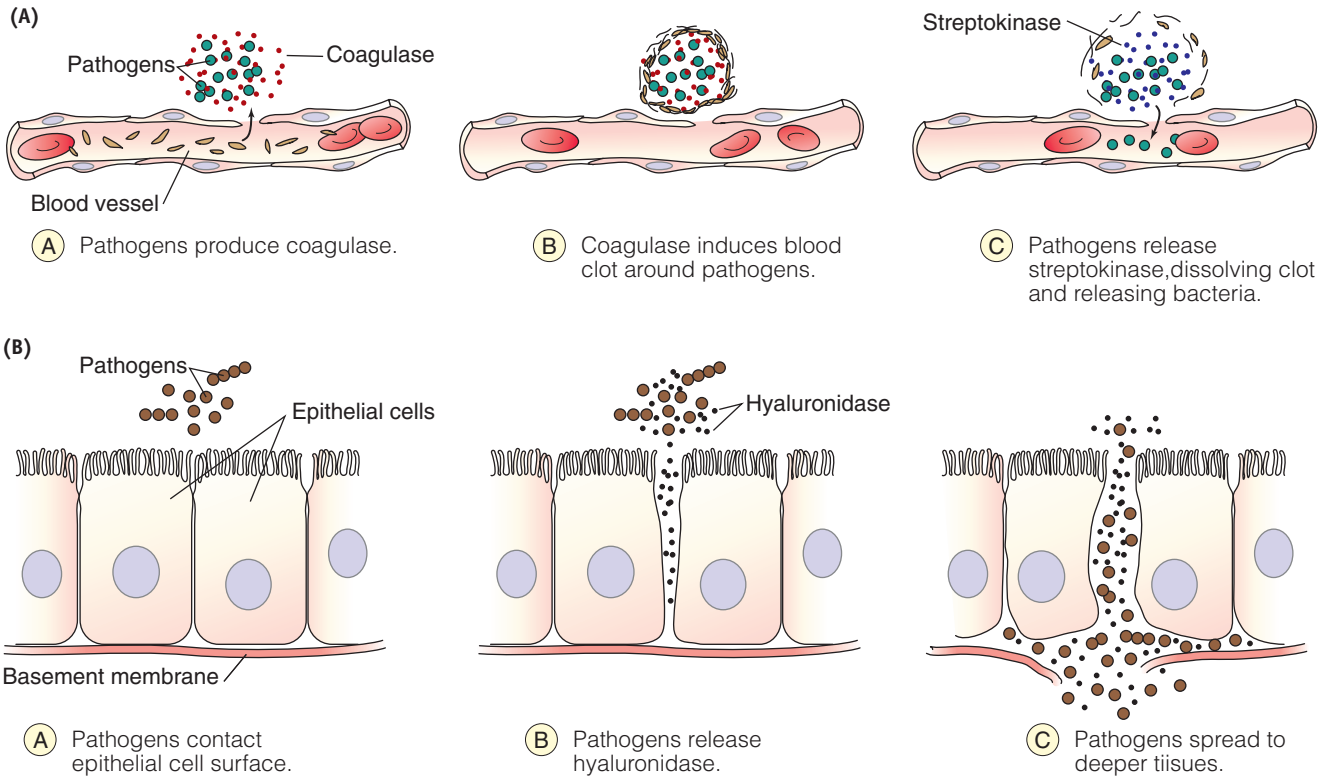


FIGURE 19.12 Enzyme Virulence Factors. (**A**) Some bacterial cells produce the enzyme coagulase, which triggers clotting of blood plasma. Bacterial cells within the clot can break free by producing streptokinase. (**B**) Some invasive bacterial species produce the enzyme hyaluronidase, which degrades the cementing polymer holding cells of the intestinal lining together. »» From these examples, how do virulence factors protect bacterial cells and increase their virulence?

cells' membrane and trigger changes leading to the release of lysosomal enzymes in the cytoplasm. The phagocytes quickly lyse.

Hemolysins combine with the membranes of erythrocytes, causing lysis to take place. Staphylococci and streptococci produce these virulence factors, which, by lysing red blood cells, gives the pathogens the iron in hemoglobin that the bacterial cells need for metabolism. In the laboratory, hemolysin producers can be detected by **hemolysis**, a destruction of blood cells in a blood agar medium (see Chapter 10).

Furthermore, if a pathogen exists in a **biofilm**, its virulence can be enhanced because here it can resist body defenses and drugs. A biofilm is a sticky layer of extracellular polysaccharides and proteins enclosing a colony of bacterial cells at the tissue surface (see Chapter 3). Phagocytes and antibodies have difficulty reaching the microorganisms in this slimy conglomeration of armor-like material. Moreover, microorganisms often survive without dividing in a biofilm. This makes them impervious to the antibiotics that attack dividing cells. (Indeed, the antibiotics do not penetrate the biofilm easily.) CDC officials have estimated that 65% of human infections involve biofilms. TABLE 19.1 summarizes the activities of these enzymes.

Toxins. Microbial poisons, called **toxins**, can profoundly affect the establishment and course of disease. The ability of pathogens to produce toxins is referred to as **toxigenicity**, while toxins present in the blood is called **toxemia** and the person is considered "intoxicated." Two types of toxins are recognized: exotoxins and endotoxins.

Exotoxins are heat-sensitive protein molecules, manufactured during bacterial metabolism.

They are produced by gram-positive and gram-negative bacterial cells and released into the host environment. Alternatively, some gram-negative bacteria inject toxins directly into the host cell. The toxins act locally or diffuse to their site of activity where symptoms of disease soon develop.

The exotoxin produced by the botulism bacillus *Clostridium botulinum* is among the most lethal toxins known (see Chapter 11). Botulism toxin is a neurotoxin that inhibits the release of acetylcholine at the synaptic junction, a process leading to a type of "flaccid" paralysis. Another neurotoxin is produced by the tetanus bacillus, *C. tetani* (see Chapter 12). In this case, the exotoxin blocks the relaxation pathway that follows muscle contraction, thereby permitting volleys of spontaneous nerve impulses and uncontrolled muscular contractions causing a "rigid" paralysis. Other types of exotoxins are identified in TABLE 19.2.

The body responds to exotoxins by producing antibodies called **antitoxins**. When toxin and antitoxin molecules combine with each other, the toxin is neutralized (Chapter 21). This process represents an important defensive measure in the body. Therapy for people who have botulism, tetanus, or diphtheria often includes injections of antitoxins (immune globulin) to neutralize the toxins.

Because exotoxins are proteins, they are susceptible to the heat and chemicals that normally denature proteins. A chemical such as formaldehyde may be used in the laboratory to alter the toxin and destroy its toxicity without hindering its ability to elicit an immune response. The result is a **toxoid**. When the toxoid is injected into the body, the immune system responds with antitoxins, which circulate and provide a measure of defense against disease. Toxoids are used for diphtheria and tetanus immunizations in the diphtheria-tetanus-acellular pertussis (DTaP) vaccine.

Endotoxins all have similar effects and usually are released only upon disintegration of gram-negative cells. They are present in the outer membrane in many gram-negative bacilli and are part of the lipid-polysaccharide (LPS) complex (see Chapter 4). The lipid portion of the LPS is the toxic agent. Endotoxins do not stimulate an immune response in the body, nor can they be altered to prepare toxoids. They function by activating a blood-clotting factor to initiate blood coagulation and by influencing the complement system (Chapter 20). The toxins of plague bacilli are especially powerful.

Endotoxins all have similar toxic effects. At high concentrations, they manifest their presence by certain signs and symptoms. Usually an individual experiences an increase in body temperature, substantial body weakness and aches, and general malaise. Damage to the circulatory system and shock may occur. In this case, the permeability of the blood vessels changes and blood leaks into the intercellular spaces. The tissues swell, the blood pressure drops, and the patient may lapse into a coma. This condition, commonly called **endotoxin shock**, may accompany antibiotic treatment of diseases due to gram-negative bacilli because endotoxins are released as the bacilli are killed by the antibiotic.

Endotoxins usually play a contributing rather than a primary role in the disease process. They may reduce platelet counts in the host and thereby increase hemorrhaging elsewhere in the body. Like exotoxins, endotoxins add to the virulence of a microbe and enhance its ability to establish disease. TABLE 19.3 summarizes the characteristics of the bacterial toxins.

TABLE **19.1** A Summary of Some Bacterial Enzymes that Contribute to Virulence

Enzyme	Source	Action	Effect
Coagulase	*Staphylococcus aureus*	Forms a fibrin clot	Provides resistance to phagocytosis
Streptokinase	Streptococci Staphylococci	Dissolves a fibrin clot	Prevents isolation of infection
Hyaluronidase	Streptococci Staphylococci	Digests hyaluronic acid	Allows tissue penetration
Leukocidin	Staphylococci Streptococci Pneumococci	Destroys phagocytes	Limits phagocytosis
Hemolysins	Clostridia Staphylococci Streptococci	Lyses red blood cells	Provides pathogens with source of iron for growth

TABLE

19.2 Characteristics and Effects of Some Bacterial Exotoxins

Exotoxin	Organism	Gene Location	Disease	Effect
Anthrax toxin	*Bacillus anthracis*	Plasmid	Anthrax	Altered host cell communication; cell death
Botulism toxin	*Clostridium botulinum*	Prophage	Botulism	Flaccid paralysis
Cholera toxin	*Vibrio cholerae*	Prophage	Cholera	Water and electrolyte loss
Diphtheria toxin	*Corynebacterium diphtheriae*	Prophage	Diphtheria	Inhibits protein synthesis; cell death
Enterotoxin	*Clostridium perfringens*	Chromosomal	Food poisoning	Permeability of intestinal epithelia
Enterotoxin	*Escherichia coli*	Plasmid	Diarrhea	Water and electrolyte loss
Enterotoxin A	*Staphylococcus aureus*	Prophage	Food poisoning	Diarrhea and nausea
Erythrogenic toxin	*Streptococcus pyogenes*	Prophage	Scarlet fever	Capillary destruction
Exfoliative toxin	*Staphylococcus aureus*	Prophage	Scalded skin syndrome	Massive skin blistering
Exotoxin A	*Pseudomonas aeruginosa*	Chromosomal	Pneumonia (?)	Inhibits protein synthesis; cell death
Perfringens toxin	*Clostridium perfringens*	Chromosomal	Gas gangrene	Hemolysis; membrane lysis
Pertussis toxin	*Bordetella pertussis*	Chromosomal	Whooping cough (pertussis)	Interferes with host cell communication
Pyrogenic toxin	*Staphylococcus aureus*	Prophage	Toxic shock syndrome	Fever, shock
Tetanus toxin	*Clostridium tetani*	Plasmid	Tetanus	Rigid paralysis

TABLE

19.3 A Comparison of Exotoxins and Endotoxins

Characteristic	Exotoxins	Endotoxins
Source	Living gram-positive and gram-negative bacteria	Lysed gram-negative bacteria
Location	Released from cell	Part of cell wall
Chemical composition	Protein	Lipopolysaccharide
Heat sensitivity	Labile (60–80°C)	Stable (250°C)
Immune reaction	Strong	Weak
Conversion to toxoid	Possible	No
Fever	No	Yes
Toxigenicity	High	Low
Representative effects	Interfere with synaptic activity (botulism) Interrupt protein synthesis (diphtheria) Increase capillary permeability Increase water elimination (cholera)	Increase body temperature Increase hemorrhaging Increase swelling in tissues Induce vomiting, diarrhea

CONCEPT AND REASONING CHECKS

19.7 Evaluate the role of enzymes and toxins as important virulence factors in the establishment of disease.

Pathogens Must Be Able to Leave the Host to Spread Disease

KEY CONCEPT

8. Pathogens leave the host through portals of exit.

At the conclusion of its pathogenicity cycle, pathogens or their toxins exit the host through some suitable **portal of exit** (FIGURE 19.13). This is of more than passing importance because easy transmission permits the pathogen to continue its pathogenic existence in the world.

CONCEPT AND REASONING CHECKS

19.8 Are portal of entry and exit always the same? Explain.

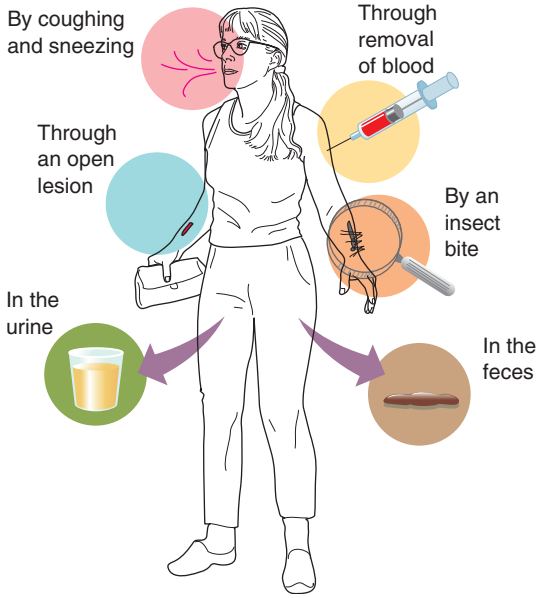


FIGURE 19.13 Six Different Portals of Exit from the Body. »» Why do pathogens need specific portals of exit?

19.3 Infectious Disease Epidemiology

Infectious disease epidemiology is concerned with how infectious diseases are distributed in a population and the factors influencing or determining that distribution. In this final section, we examine the factors putting population groups at risk of contracting infectious disease.

We also look at special environments, such as health care settings, and the public agencies saddled with the job of disease identification, control, and prevention.

Epidemiologists Often Have to Identify the Reservoir of an Infectious Disease

KEY CONCEPT

9. Reservoirs are places in the environment where a pathogen can be found.

To cause an infection, pathogens have to be transferred from a source to a susceptible host (FIGURE 19.14). For many diseases to perpetuate themselves, the disease-causing microbes must exist somewhere in the environment. These ecological niches or sources where a microbe lives and multiplies are called **reservoirs** of infection. Animals are one type of reservoir. A domestic house cat that is infected with *Toxoplasma gondii*, for example, usually shows no symptoms of toxoplasmosis but it can transmit the protozoan to humans, where the disease manifests itself. Water and soil also can be reservoirs because they often are contaminated with disease agents, such as the cholera bacterium or *Giardia* protozoan.

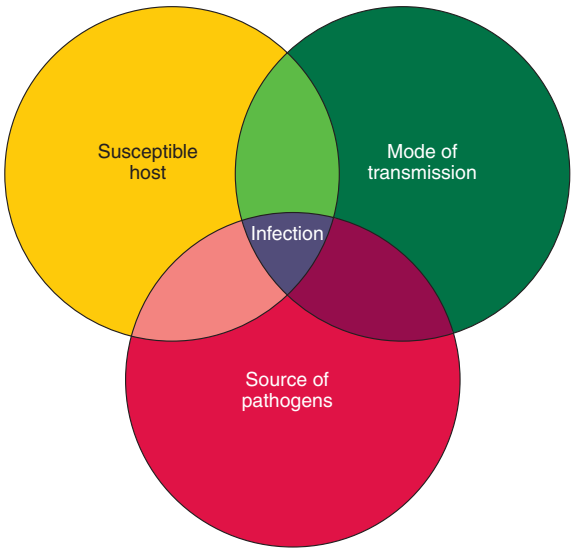


FIGURE 19.14 Infectious Disease Elements. Assuming there is a susceptible host, to cause an infection the pathogenic organism must have a way to be transmitted to that susceptible host. »» What is meant by a susceptible host?

Niches: Environmental areas that ensure an organism's survival.

Not all diseases have a nonhuman reservoir though. The smallpox virus only exists in humans. This is why the World Health Organization (WHO) was able to limit the spread of the virus through vaccination and eradicate smallpox from the world by locating all human reservoirs.

A special type of reservoir is a **carrier**, which is a person who has recovered from the disease but continues to shed the disease agents. For instance, a person who has recovered from typhoid fever or amoebiasis becomes a carrier for many weeks after the symptoms of disease have left. The feces of this individual may spread the disease to others via contaminated food or water.

CONCEPT AND REASONING CHECKS

19.9 Identify the different reservoirs of disease transmission.

Epidemiologists Have Several Terms that Apply to the Infectious Disease Process

KEY CONCEPT

10. Diseases have certain behaviors in populations.

Most diseases studied in this text are **communicable diseases**; that is, infectious diseases transmissible among hosts in a population. Certain communicable diseases are described as being **contagious** because they pass with particular ease among hosts and are highly infectious. Chickenpox and measles fall into this category.

Noncommunicable diseases are singular events in which the agent is acquired directly from the environment and are not easily transmitted to the next host. In tetanus, for example, penetration of soil containing *Clostridium tetani* spores to the anaerobic tissue of a wound must occur before this disease develops. It cannot be spread person-to-person.

CONCEPT AND REASONING CHECKS

19.10 Explain the difference between a communicable and contagious disease. Provide examples beyond the ones mentioned above.

Infectious Diseases Can Be Transmitted in Several Ways

KEY CONCEPT

11. Disease transmission can involve direct or indirect contact.

Diseases can be transmitted by a broad variety of methods involving **direct contact**

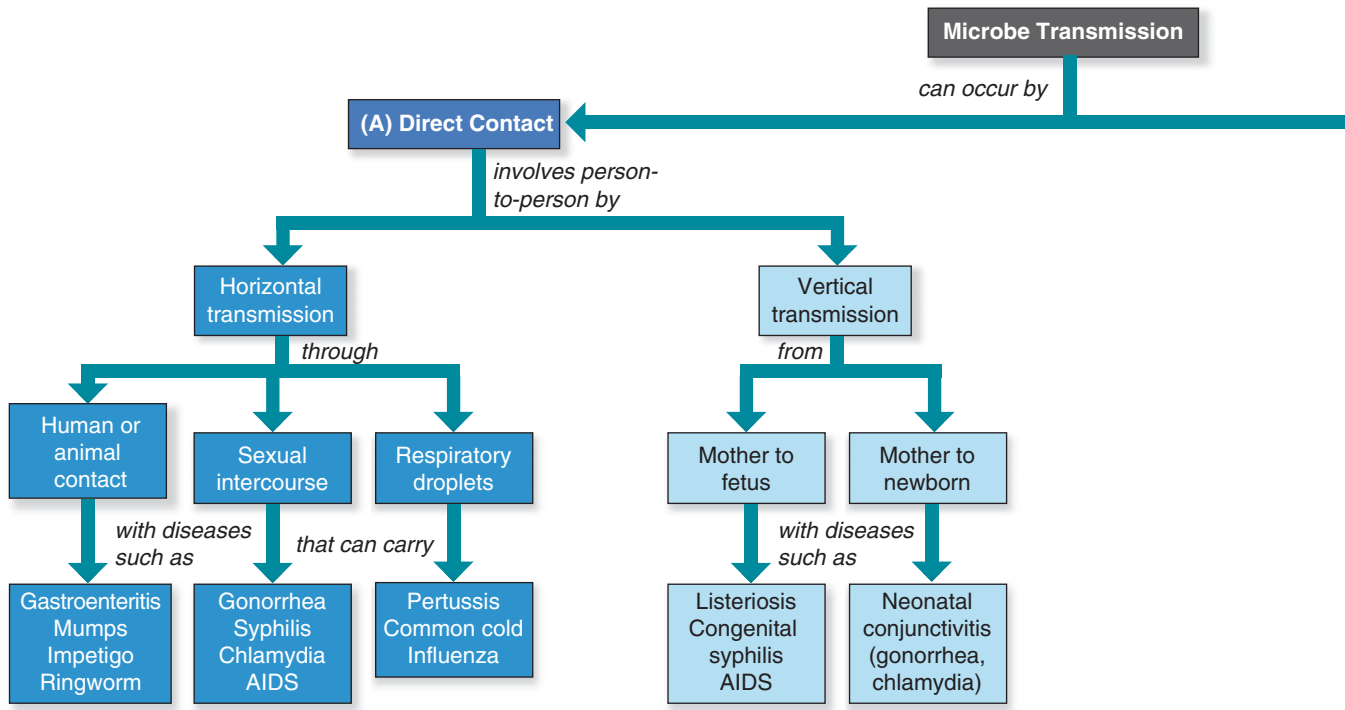


FIGURE 19.15 **Transmission of Microorganisms and Viruses.** **(A)** Pathogens can be transmitted by direct contact involving horizontal or vertical transmission. **(B)** Pathogens also can be transmitted by fomites, contaminated food and water, and vectors. »» Would indirect contact transmission represent horizontal or vertical transmissions? Explain.

(FIGURE 19.15A); that is, close contact that results in exposure to skin or body secretions.

Direct Contact. Person-to-person or **horizontal transmission** implies close or personal contact with someone who is infected or who has the disease. Hand-shaking or kissing an infected person can spread bacterial cells, viruses, or other pathogens to an uninfected person. For some diseases, such as rabies, leptospirosis, and toxoplasmosis, direct contact with an animal is necessary. An animal bite or scratch by an infected animal can spread the disease to an uninfected person. The exchange of body fluids, such as through sexual contact, is another example of direct contact transmission for diseases like gonorrhea and AIDS.

Direct transmission also can involve the violent expulsion of **respiratory droplets** through sneezing, coughing, or simply talking (FIGURE 19.16). **Droplet transmission** through the air requires the "recipient" be close to an infected individual. In a sneeze, the droplets can travel 150 feet per second. However, the droplets are fairly large and fall out of the air within about 1 meter of their source. If an uninfected person is within that distance, the eyes, mouth, or nose may be portals of entry for the airborne pathogens.

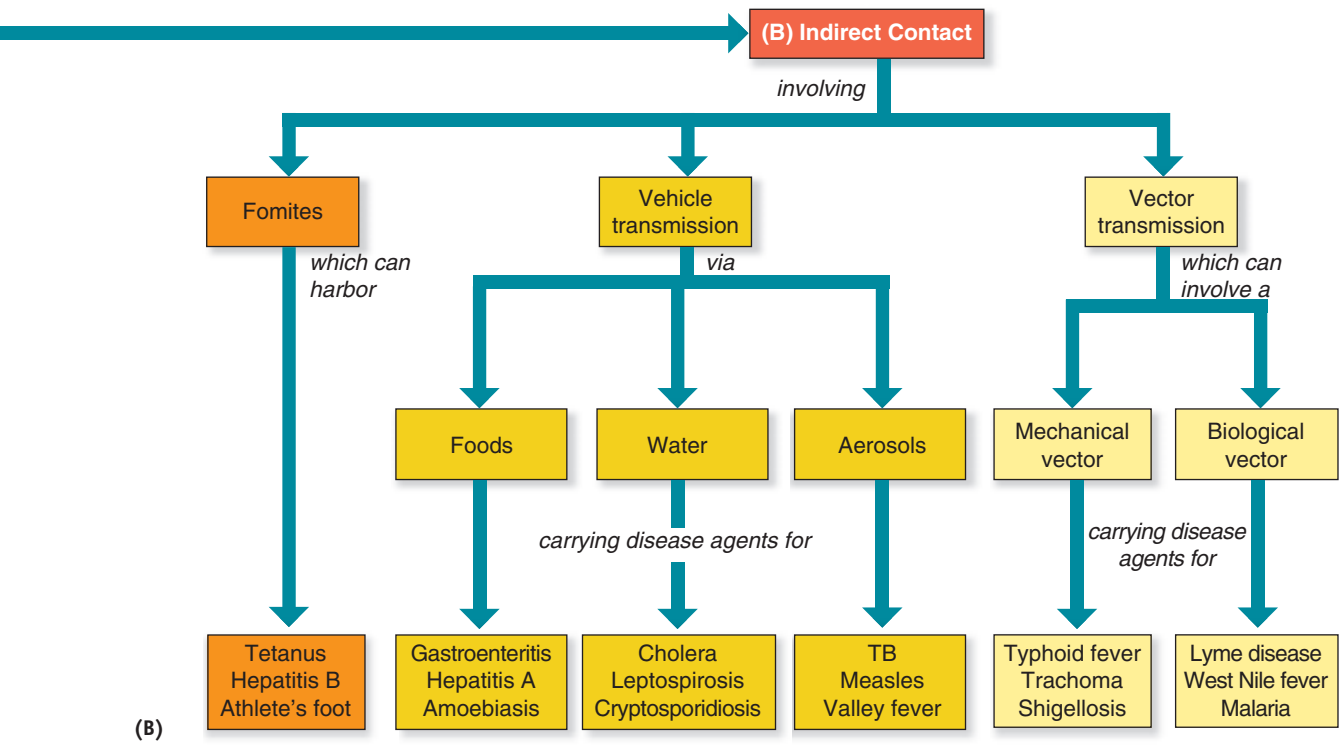
Direct contact called **vertical transmission** includes the spread of pathogens, such as HIV or *Toxoplasma gondii,* from a pregnant mother to her unborn child. Transmission of gonorrhea from mother to newborn can occur during labor or delivery.

CONCEPT AND REASONING CHECKS

19.11A Identify four ways by which infectious disease can be transmitted directly.

Indirect Contact. Indirect transmission can be the result of contact with a non-living object or medium, or a vector (FIGURE 19.15B). **Fomites** are inanimate objects on which or in which disease organisms linger for some period of time. For instance, bed linens may be contaminated with pinworm eggs, and contaminated syringes and needles may passively transport the viruses of hepatitis B or AIDS.

Vehicle transmission involves the indirect spread of disease through contaminated food and water, or air. Foods can be contaminated during processing or handling, or they may be dangerous when made from diseased animals. Poultry products, for example, are often a source of salmonellosis because *Salmonella* species frequently infect chickens, while pork may spread trichinellosis because *Trichinella* parasites may



(B)

FIGURE 19.16 Droplet Transmission. Sneezing or coughing represents a method for airborne transmission of pathogens. »» Identify some portals of entry for pathogen-containing droplets.

live in muscles of the pig. Other examples include the cholera bacterium, *Vibrio cholerae,* which can contaminate many water supplies in developing nations lacking proper water sanitation and the parasite causing giardiasis, *Giardia intestinalis,* which is found in some recreational waters. MicroFocus 19.4 describes two transmission modes: airborne and fomites.

Pathogens also are transmitted through the air on smaller particles called **aerosols**. With **particle transmission**, the particles can remain suspended in the air for longer periods of time and can be moved some distance by air currents. The virus of SARS and the bacterial cells of tuberculosis are two pathogens that can be carried in the air by droplets or aerosols. MicroFocus 19.5 describes long-range effects of airborne transmission.

Arthropods represent another indirect method of transmission. Many pathogens hitch a ride on arthropods, such as mosquitoes, ticks, fleas, and lice, which act as **vectors**, living organisms carrying disease agents from one host to another. **Mechanical vectors** represent arthropods passively transporting microbes on their legs and other body parts. For example, house flies can carry diseases picked up on their feet. In other cases, arthropods represent **biological vectors**, where the pathogen must multiply in the insect before it can infect another host. The malarial protozoan and the West Nile virus infect and reproduce in mosquitoes and accumulate in their salivary glands, from which the pathogens are injected during the next blood meal.

CONCEPT AND REASONING CHECKS

19.11B Identify the methods by which infectious disease can be transmitted indirectly.

Diseases Also Are Described by How They Occur Within a Population

KEY CONCEPT

12. Diseases are identified as being endemic, epidemic, or pandemic.

When epidemiologists investigate an infectious disease, they need to determine if it is localized or spread through a community or region. **Endemic** refers to a disease habitually present at a low level in a certain geographic area. Plague in the American Southwest is an example.

By comparison, an **epidemic** refers to a disease that occurs in a community or region in excess of what is normally found within that population. Influenza often causes widespread epidemics. This should be contrasted with an **outbreak**, which is a more contained epidemic. An abnormally high number of measles cases in one American city would be classified as an outbreak. Not only do epidemiologic investigations look at current outbreaks, they also consider future outbreaks, including bioterrorism (MicroFocus 19.6).

A **pandemic** is a worldwide epidemic, affecting populations around the globe. The most obvious example here would be AIDS and the H1N1 flu.

As in the opening quote, "*Health care matters to all of us some of the time, public health matters to all of us all of the time,*" maintaining vigilance against infectious disease is extremely important. For this reason, national and international public health organizations, such as the CDC and the WHO, learn a lot about diseases by analyzing disease data reported to them. The CDC, for example, has a list of infectious diseases that must be reported to state health departments, which then report them to the CDC (TABLE 19.4). These are published in the *Morbidity and Mortality Weekly Report.*

MicroInquiry 19 explores the use of epidemiological data as a tool for understanding disease occurrence.

CONCEPT AND REASONING CHECKS

19.12 Why do you think the term "outbreak" is typically used in news releases rather than epidemic?

MICROFOCUS 19.4: Environmental Microbiology

Riders on the Storm

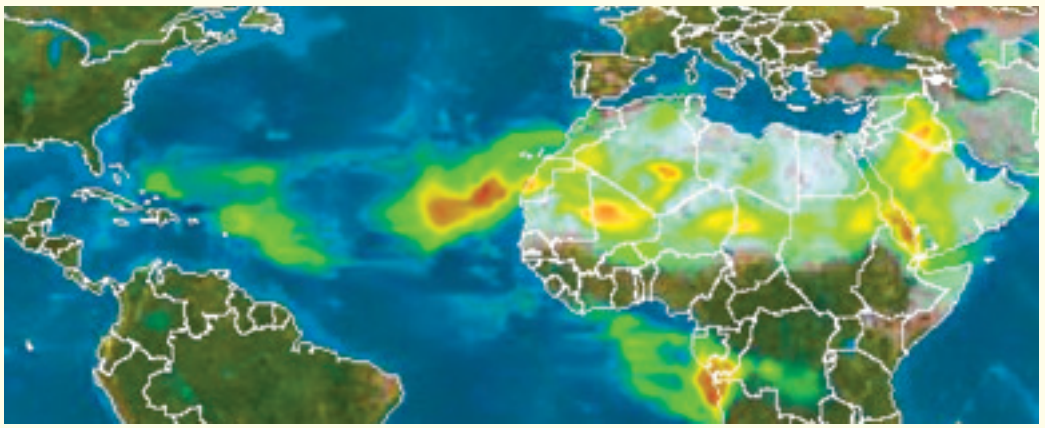
Dust storms can be a relatively common meteorological phenomenon in arid and semi-arid regions of the world. Sometimes called sandstorms, they arise when a gust front passes or when the wind force is strong enough to remove loose sand and dust from the dry soil surface. The result can be an awesome wall of sand that can obscure visibility within seconds. On a more global scale, the major dust storms arise in the Sahara Desert and arid lands around the Arabian Peninsula. In Asia, the Gobi Desert is a major source. Annually, such storms carry more than 3 billion metric tons of dust aloft into the atmosphere.

The long-range movement of dust and suspended particles can certainly have an impact on air quality that often can be observed. Between May and October, strong winds blow off the Sahara Desert and the west coast of North Africa, carrying soil and dust westward across the Atlantic Ocean (see figure). Although much of the dust settles in the ocean, large amounts stay suspended and make the journey to the Caribbean islands and Florida. It is not unusual to wake up in the morning and see a fiery orange sunrise—what the locals call a "tequila sunrise." The orange is the African dust. In fact, traces of such dust have been detected as far west as New Mexico!

Today, these storms are becoming of more concern as worldwide deforestation, overgrazing, and climate change combine to generate massive dust clouds that can carry particles aloft. Besides causing respiratory distress, such as asthma, these storms may have another impact on human health—microbes can be "riders on the storm."

Scientists had believed most of these microbes would be killed by the intense ultraviolet light in the atmosphere and the dry, desiccating conditions of a dust storm. However, recent studies have shown that hundreds of bacterial and fungal species can be cultured from samples of dust clouds moving across the mid-Atlantic Ocean. Exactly what microbes are carried aloft and which might be pathogens is not yet clear. *Pseudomonas aeruginosa* has been detected and many species of *Aspergillus* have been identified. In fact, the researchers suggest that 20% to 30% of the microbes in the dust clouds are animal or plant pathogens.

More research is needed to define the role of dust storms as an indirect transmission mechanism spreading transatlantic pathogens across the globe. Still, these "riders on the storm" might not only renew reservoirs for some plant and animal pathogens in the United States, but also, on occasion, may bring "riders" capable of new diseases.



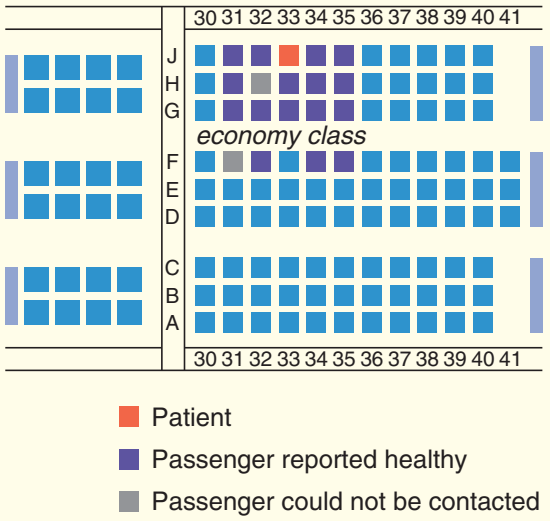
Satellite image of African dust storm spreading westward across the Atlantic Ocean towards Central and North America.

MICROFOCUS 19.5: Public Health

Planes, Trains, and — Ambulances

Vehicles that can take us to great destinations at supersonic speeds, or save our lives, can also harbor and transmit infectious disease.

In August, 2004, a New Jersey man returned home from a trip to West Africa. Within hours after taking the train home from the airport, the man was stricken with fever, chills, a severe sore throat, diarrhea, and back pain. The family rushed him to a local hospital. However, despite intensive care, the gentleman continued to decline and died a few days later. Clinical and postmortem specimens were sent to the Centers for Disease Control and Prevention (CDC) for a specific cause of death. The finding: Lassa fever.



Passenger seating and contact status.

The alarms went off! Lassa fever is an acute viral disease, rarely seen outside West Africa where the disease is endemic (see Chapter 15). In West Africa, the virus, which is carried in rodents, infects 100,000 to 300,000 people every year, and kills 5,000. The case of the New Jersey man was a lethal health risk as the virus can be spread person to person if a susceptible person comes into contact with virus in the blood, tissue, or excretions from infected individuals. Although the virus cannot be spread through casual contact (including skin-to-skin contact without exchange of body fluids), CDC epidemiologists contacted all passengers seated nearby the man (see figure) and others who could have been exposed. These individuals were asked to monitor their body temperatures for fever. Luckily, there were no reported cases.

The scary part is that the man was traveling while ill and potentially exposed some 200 people to the virus: 19 family members, 139 healthcare workers, 16 lab workers, 19 airplane passengers, and numerous commuters on the New Jersey train. This time we dodged the bullet.

From November 2004 to April 2005, a decontamination firm in the United Kingdom examined the ambulances from 12 firms for microbial contamination. They swabbed several fomites, including stretcher rails, the stretcher tracks below the stretcher, the paramedic's utility bag, and five other sites within the vehicle. The swabs were streaked on nutrient agar plates to see what bacterial species would grow.

Examination of the plates indicated the ambulances were heavily contaminated with a diverse group of bacterial species. In fact, in many cases, there were so many bacterial colonies present, they could not be counted. The bacterial species included antibiotic-resistant *Staphylococcus aureus* and a variety of species typically found in the human colon. More surprising, after the ambulances were cleaned by standard procedures, there was little reduction in the numbers of bacterial cells present. In fact, another study showed that cleaning actually spread the bacterial cells onto previously "clean" surfaces. Such contaminated fomites could be dangerous to a person with open wounds in the ambulance.

Since that initial 2005 report, emergency medical services have evaluated and improved their best practices for cleaning and disinfecting surfaces on patient care equipment.

TABLE

19.4 CDC's Summary of Notifiable Diseases in the United States in 2007

Acquired immunodeficiency syndrome (AIDS)
Anthrax
Botulism
Brucellosis
Chancroid
Chlamydia trachomatis, genital infections
Cholera
Coccidioidomycosis
Cryptosporidiosis
Cyclosporiasis
Diphtheria
Domestic arboviral diseases, neuroinvasive and nonneuroinvasive
- California serogroup virus disease
- Eastern equine encephalitis virus disease
- Powassan virus disease
- St. Louis encephalitis virus disease
- West Nile virus disease
- Western equine encephalitis virus disease

Ehrlichiosis
- Human granulocytic
- Human monocytic
- Human, other or unspecified agent

Giardiasis
Gonorrhea
Haemophilus influenzae, invasive disease
Hansen disease (leprosy)
Hantavirus pulmonary syndrome
Hemolytic uremic syndrome, postdiarrheal
Hepatitis A, acute
Hepatitis B, acute
Hepatitis B, chronic
Hepatitis B, perinatal infection
Hepatitis C, acute
Hepatitis C, infection (past or present)
Human immunodeficiency virus (HIV) infection
- Adult (age ≥ 13 yrs)
- Pediatric (age < 13 yrs)

Influenza-associated pediatric mortality
Legionellosis
Listeriosis
Lyme disease
Malaria
Measles
Menigococcal disease
Mumps
Pertussis
Plague
Poliomyelitis, paralytic
Psittacosis
Q fever
Rabies
- Animal
- Human

Rocky Mountain spotted fever
Rubella
Rubella, congenital syndrome
Salmonellosis
Severe acute respiratory syndrome-associated coronavirus (SARS-CoV) disease
Shiga toxin-producing *Escherichia coli* (STEC)
Shigellosis
Smallpox
Streptococcal disease, invasive, group A
Streptococcal toxic-shock syndrome
Streptococcus pneumoniae, invasive disease
- Age <5 yrs
- Drug-resistant, all ages

Syphilis
Syphilis, congenital
Tetanus
Toxic-shock syndrome (other than streptococcal)
Trichinellosis
Tuberculosis
Tularemia
Typhoid fever
Vancomycin-intermediate *Staphylococcus aureus* infection (VISA)
Vancomycin-resistant *Staphylococcus aureus* infection (VRSA)
Varicella infection (morbidity)
Varicella mortality
Yellow fever

MICROFOCUS 19.6: History/Public Health

Bioterrorism: The Weaponization and Purposeful Dissemination of Human Pathogens

The anthrax attacks that occurred on the East Coast in October 2001 confirmed what many health and governmental experts had been saying for over 10 years—it is not if bioterrorism would occur but when and where. Bioterrorism represents the intentional or threatened use of primarily microorganisms or their toxins to cause fear in or actually inflict death or disease upon a large population for political, religious, or ideological reasons.

Is Bioterrorism Something New?

Bioterrorism is not new, and two other MicroFocus boxes in this text (MicroFocus 12.1 and 12.4) mention historical examples. Such bioterrorism agents also have been used as biowarfare agents. In the United States, during the aftermath of the French and Indian Wars (1754–1763), British forces, under the guise of goodwill, gave smallpox-laden blankets to rebellious tribes sympathetic to the French. The disease decimated the Native Americans, who had never been exposed to the disease before and had no immunity. Between 1937 and 1945, the Japanese established Unit 731 to carry out experiments designed to test the lethality of several microbiological weapons as biowarfare agents on Chinese soldiers and civilians. In all, some 10,000 "subjects" died of bubonic plague, cholera, anthrax, and other diseases. After years of their own research on biological weapons, the United States, the Soviet Union, and more than 100 other nations in 1973 signed the Biological and Toxin Weapons Convention, which prohibited nations from developing, deploying, or stockpiling biological weapons. Unfortunately, the treaty provided no way to monitor compliance. As a result, in the 1980s the Soviet Union developed and stockpiled many microbiological agents, including the smallpox virus, and anthrax and plague bacteria. After the 1991 Gulf War, the United Nations Special Commission (UNSCOM) analysts reported that Iraq had produced 8,000 liters of concentrated anthrax solution and more than 20,000 liters of botulinum toxin solution. In addition, anthrax and botulinum toxin had been loaded into SCUD missiles.

In the United States, several biocrimes have been committed. **Biocrimes** are the intentional introduction of biological agents into food or water, or by injection, to harm or kill groups of individuals. The most well known biocrime occurred in Oregon in 1984 when the Rajneeshee religious cult, in an effort to influence local elections, intentionally contaminated salad bars of several restaurants with the bacterium *Salmonella*. The unsuccessful plan sickened over 750 citizens and hospitalized 40. Whether biocrime or bioterrorism, the 2001 events concerning the anthrax spores mailed to news offices and to two U.S. congressmen only increases our concern over the use of microorganisms or their toxins as bioterror agents.

What Microorganisms Are Considered Bioterror Agents?

A considerable number of human pathogens and toxins have potential as microbiological weapons. These "select agents" include bacterial organisms, bacterial toxins, fungi, and viruses. The seriousness of the agent depends on the severity of the disease it causes (virulence) and the ease with which it can be disseminated. The pathogens of most concern, called the Category A Select Agents, are those that can be spread by aerosol contact, such as anthrax and smallpox, and toxins that can be added to food or water supplies, such as the botulinum toxin (see the table below).

Why Use Microorganisms?

At least 15 nations are believed to have the capability of producing bioweapons from microorganisms. Such microbiological weapons offer clear advantages to these nations and terrorist organizations in general. Perhaps most important, biological weapons represent "The Poor Nation's Equalizer." Microbiological weapons are cheap to produce compared to chemical and nuclear weapons and provide those nations with a deterrent every bit as dangerous and deadly as the nuclear weapons possessed by other nations.

TABLE

Category A Select Agents and Perceived Risk of Use

Type of Microbe	Disease (Microbe Species or Virus Name)	Perceived Risk
Bacteria	Anthrax (*Bacillus anthracis*)	High
	Plague (*Yersinia pestis*)	Moderate
	Tularemia (*Francisella tularensis*)	Moderate
Viruses	Smallpox (Variola)	Moderate
	Hemorrhagic fevers (Ebola, Marburg, Lassa, Machupo)	Low
Toxins	Botulinum toxin (*Clostridium botulinum*)	Moderate

With biological weapons, you get high impact and the most "bang for the buck." In addition, microorganisms can be deadly in minute amounts to a defenseless (nonimmune) population. They are odorless, colorless, and tasteless, and unlike conventional and nuclear weapons, microbiological weapons do not damage infrastructure, yet they can contaminate such areas for extended periods. Without rapid medical treatment, most of the select agents can produce high numbers of casualties that would overwhelm medical facilities. Lastly, the threatened use of microbiological agents creates panic/anxiety, which often is at the heart of terrorism.

How Would Microbiological Weapons Be Used?

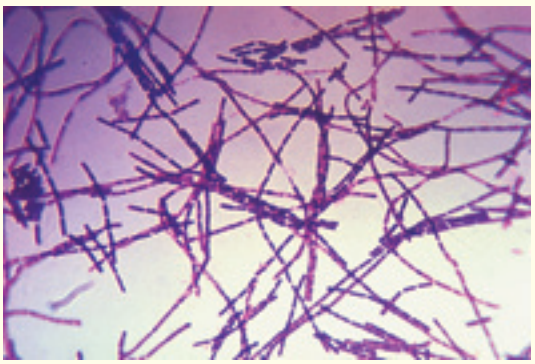
All known microbiological agents (except smallpox) represent organisms naturally found in the environment. For example, the bacterium causing anthrax is found in soils around the world (see left figure). Assuming one has the agent, the microorganisms can be grown (cultured) easily in large amounts. However, most of the select agents must be "weaponized"; that is, they must be modified into a form that is deliverable, stable, and has increased infectivity and/or lethality. Nearly all of the microbiological agents in category A are infective as an inhaled aerosol. Weaponization, therefore, requires the agents be small enough in size so inhalation would bring the organism deep into the respiratory system and prepared so that the particles do not stick together or form clumps. Several of the anthrax letters of October 2001 involved such weaponized spores.

Dissemination of biological agents by conventional means would be a difficult task. Aerosol transmission, the most likely form for dissemination, exposes microbiological weapons to environmental conditions to which they are usually very sensitive. Excessive heat, ultraviolet light, and oxidation would limit the potency and persistence of the agent in the environment. Although anthrax spores are relatively resistant to typical environmental conditions, the bacterial cells causing tularemia become ineffective after just a few minutes in sunlight. The possibility also exists that some nations have developed or are developing more lethal bioweapons through genetic engineering and biotechnology. The former Soviet Union may have done so. Commonly used techniques in biotechnology could create new, never before seen bioweapons, making the resulting "designer diseases" true doomsday weapons.

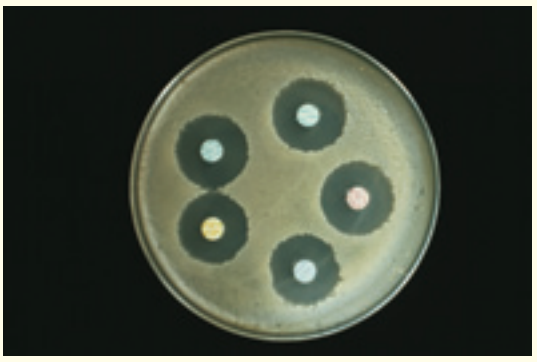
Conclusions

Ken Alibek, a scientist and defector from the Soviet bioweapons program, has suggested the best biodefense is to concentrate on developing appropriate medical defenses that will minimize the impact of bioterrorism agents. If these agents are ineffective, they will cease to be a threat; therefore, the threat of using human pathogens or toxins for bioterrorism, like that for emerging diseases such as SARS and West Nile fever, is being addressed by careful monitoring of sudden and unusual disease outbreaks. Extensive research studies are being carried out to determine the effectiveness of various antibiotic treatments (see right figure) and how best to develop effective vaccines or administer antitoxins. To that end, vaccination perhaps offers the best defense. The United States has stated it has stockpiled sufficient smallpox vaccine to vaccinate the entire population if a smallpox outbreak occurred. Other vaccines for other agents are in development.

This primer is not intended to scare or frighten; rather, it is intended to provide an understanding of why microbiological agents have been developed as weapons for bioterrorism. We cannot control the events that occur in the world, but by understanding bioterrorism, we can control how we should react to those events—should they occur in the future.



Light micrograph of gram-stained *Bacillus anthracis*, the causative agent of anthrax. There is concern that terrorists could release large quantities of anthrax spores in a populated area, which potentially could cause many deaths.



Antibiotic drugs in paper discs are used to test the sensitivity of anthrax bacteria (*Bacillus anthracis*) cultured on an agar growth medium. The clear zone surrounding each disc indicates the bacterial cells are sensitive to the antibiotic.

MICROINQUIRY 19

Epidemiological Investigations

Infectious disease epidemiology is a scientific study from which health problems are identified. In this inquiry, we are going to look at just a few of the applications and investigative strategies for analyzing the patterns of illness. Answers can be found in **Appendix D**.

One of the important measures is to assess disease occurrence. The **incidence** of a disease is the number of reported cases in a given time frame. **Figure A** is a line graph showing the number of new cases of AIDS per year in the United States.

The **prevalence** of a disease refers to the percentage of the population that is affected at a given time.

19.1a. What was the incidence of AIDS in 1993 and 2003?

19.1b. Assuming that 264,000 were living with AIDS in 1993 and 380,000 in 2003, how has the prevalence of AIDS changed between 1993 and 2003? (Assume the population of the United States has remained at 290 million).

Descriptive epidemiology describes activities (time, place, people) regarding the distribution of diseases within a population. Once some data have been collected on a disease, epidemiologists can analyze these data to characterize disease occurrence. Often a comprehensive description can be provided by showing the disease trend over time, its geographic extent (place), and the populations (people) affected by the disease.

Characterizing by Time

Traditionally, drawing a graph of the number of cases by the date of onset shows the time course of an epidemic. An epidemic curve, or "epi curve," is a histogram providing a visual display of the magnitude and time trend of a disease.

Look at the epi curve in **Figure B** for an Ebola outbreak in Africa. One important aspect of a bar graph is to consider its overall shape. An epi curve with a single peak indicates a single source (or "point source") epidemic in which people are exposed to the same source over a relatively short time. If the duration of exposure is prolonged, the epidemic is called a continuous common source epidemic, and the epi curve will have a plateau instead of a peak. Person-to-person transmission is likely and its spread may have a series of plateaus one incubation period apart.

19.2a. Identify the type of epi curve drawn in Figure B and explain what the onset says about the nature of disease spread.

19.2b. Is there more than one plateau? Explain the significance that multiple plateaus might have in interpreting the spread of the Ebola hemorrhagic fever outbreak.

Characterizing by Place

Analysis of a disease or outbreak by place provides information on the geographic extent of a problem and may show clusters or patterns that provide clues to the identity and origins of the problem. It is a simple and useful technique to look for geographic patterns where the affected people live, work, or may have been exposed. A geographic distribution for Lyme disease is shown in **Figure C**. This is a spot map, where each reported case of a disease in a county or state may be shown to reflect clusters or patterns of disease. Figure C identifies cases of Lyme disease by county, where each dot represents one reported case in that county in 2007.

19.3a. From this spot map, what inferences can you draw with regard to the reported cases of Lyme disease?

Characterizing by Person

Populations at risk for a disease can be determined by characterizing a disease or outbreak by person. Persons also refer to populations identified by personal characteristics (e.g., age, race, gender) or by exposures (e.g., occupation, leisure activities, drug intake). These factors are important because they may be related to disease susceptibility and to opportunities for exposure.

Age and gender often are the characteristics most strongly related to exposure and to the risk of disease. For example, **Figure D** is a histogram showing the incidence of pertussis (whooping cough) in the United States in 2003.

19.4a. Look at the histogram and describe what important information is conveyed in terms of the majority of cases and relative incidence in 2003.

19.4b. As a health care provider, what role do you see for vaccinations and booster shots with regard to this disease?

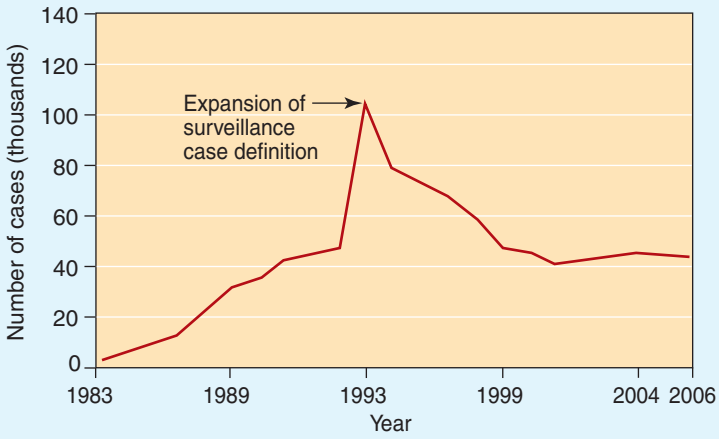


FIGURE A **Acquired Immunodeficiency Syndrome (AIDS).** Number of cases reported by year in the United States and U.S. territories for the years 1983 to 2006. *Source:* CDC.

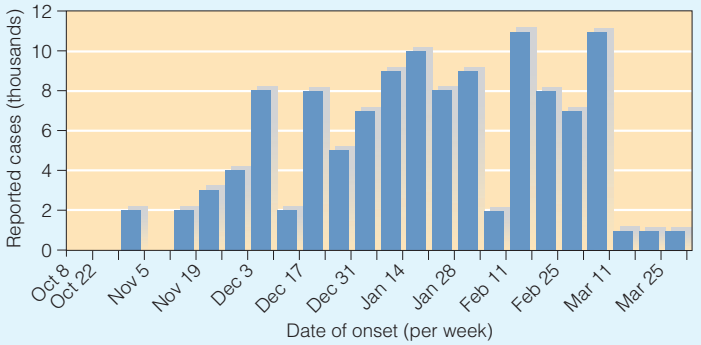


FIGURE B **Ebola Hemorrhagic Fever (Congo and Gabon).** Number of cases of Ebola hemorrhagic fever by week from October 2001 to March 2002. *Data from: Weekly Epidemiological Record,* No. 26, June 27, 2003.

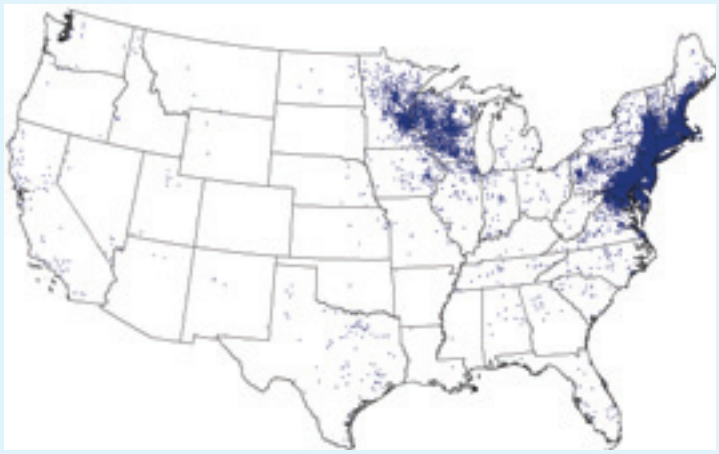


FIGURE C **Lyme Disease.** Each dot represents one reported case of Lyme disease in 2007. *Source:* CDC.

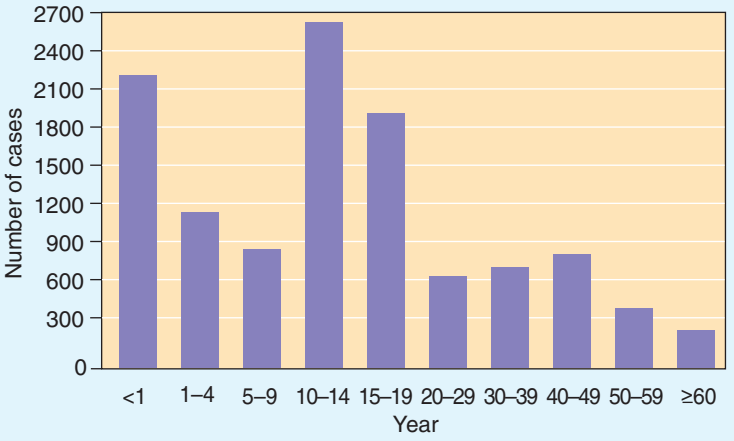


FIGURE D **Pertussis.** The reported number of cases of pertussis by age group in the United States in 2003. *Source:* CDC.

Nosocomial Infections Are Serious Health Threats within the Health Care System

KEY CONCEPT

13. Nosocomial infections are contracted as a result of being treated for another illness in a hospital or other health care setting.

Nosocomial infections represent that portion of **healthcare-associated infections** (**HAIs**) associated with hospitals and account for an estimated 1.7 million infections (more than 1 million were outside intensive care units) and, according to the CDC, some 99,000 deaths each year in the United States. Like all infections, nosocomial infections involve three elements: a compromised host (the hospital patient), a source of hospital pathogens, and a chain of transmission (FIGURE 19.17).

The Compromised Host. Most hospital patients have some form of physical injury, such as a surgical wound, some form of skin trauma like a burn, or the breakdown of another physical barrier through which a pathogen could enter the body. In addition, many hospital patients are **immunocompromised**, so if a pathogen does enter the body, the patient's immune system may be unable to mount an attack and eliminate it. The most common sites of infection are listed in FIGURE 19.18.

The Hospital Pathogens. Hospital personnel attempt to maintain a sanitary and clean hospital environment. Still, the facility can be a reservoir for human pathogens. Although some pathogens come from other patients being treated for an infectious disease—or by healthcare staff—the majority of nosocomial infections are caused by **opportunistic** agents, microbes that do not normally cause illness in healthy individuals, but, given the "opportunity," can infect an immunocompromised patient. The most common microorganisms responsible for nosocomial infections are listed in TABLE 19.5. By examining this table, note that there is now another dimension to the virulence of these potential pathogens—antibiotic resistance. With the patient's immune system compromised, the use of antibiotics often is necessary to fight an infection. Unfortunately, many of these hospital pathogens are becoming resistant to several generations of antibiotics, meaning more toxic and expensive drugs must be used (see Chapter 24).

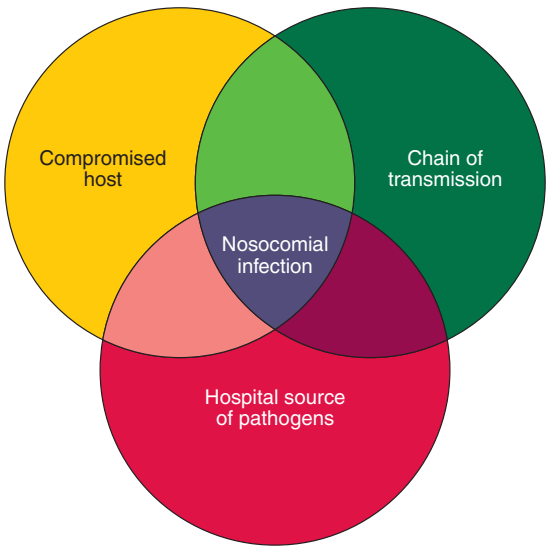


FIGURE 19.17 Nosocomial Infection Elements. For a nosocomial infection to occur, there needs to be a susceptible (compromised) host, pathogenic organisms within the hospital setting, and a chain of transmission. »» How does this nosocomial infection figure compare to that for an infectious disease (see Figure 19.14)?

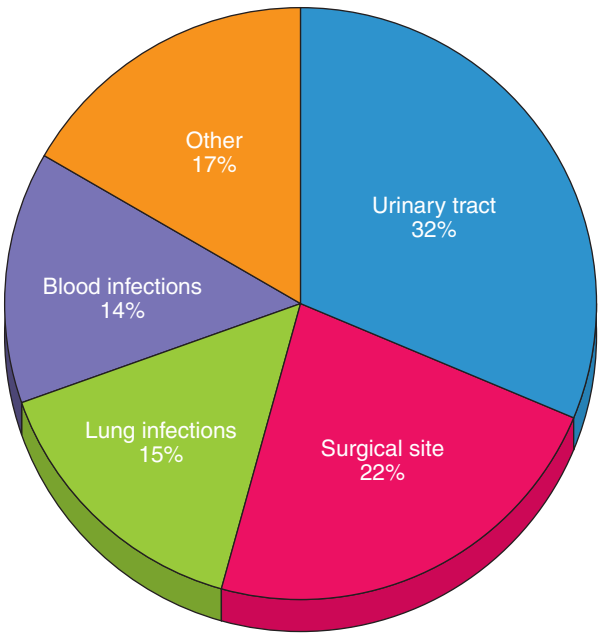


FIGURE 19.18 Sites of Nosocomial Infections. This pie chart shows the sites for the estimated 1.7 million healthcare-associated infections in American hospitals. »» What might be the primary source for the infections for the top four sites? *Source:* CDC. Division of Healthcare Quality Promotion (DHQP).

TABLE

19.5 Top 10 Infectious Agents Involved in Nosocomial Infections

Microorganism	% of Total Infections	% Antibiotic Resistant[1]	Nosocomial Infections
Coagulase-negative staphylococci	15.3%	Not reported (historically greater than 80%)	Blood infections
Staphylococcus aureus	14.4%	56%	Urinary, blood, lung, and surgical site infections
Enterococcus species	12.1%	3–90%	Urinary tract, blood, and surgical site infections
Candida species	10.7%	Not reported	Urinary tract infections
Escherichia coli	9.6%	1–30%	Urinary and surgical site infections
Pseudomonas aeruginosa	7.9%	6–33%	Urinary, blood, and surgical site infections
Klebsiella pneumoniae	5.8%	3–27%	Lung, blood, and surgical site infections
Enterobacter species	4.8%	Not reported	Urinary and surgical site infections
Acinetobacter baumannii	2.7%	26–37%	Urinary, blood, lung, and surgical site infections
Klebsiella oxytoca	1.1%	3–17%	Urinary, blood, lung, and surgical site infections

[1]Means for different species and different nosocomial infections.

Source: CDC. National Healthcare Safety Network Annual Update (2008).

The Chain of Transmission. The key to nosocomial disease and its prevention stems from the way the agents are transmitted to the patient. These chains of transmission may involve direct contact between patients or between healthcare staff and patient. Indirect contact can also be part of the chain of transmission (FIGURE 19.19). Perhaps one of the most common chains of transmission is through the use of indwelling instruments that are not sterile or have not been cleaned thoroughly. Intravenous catheters, respirators, and other medical instruments can be the source.

Therefore, the key to reducing nosocomial infections is to break the chain of transmission. Besides the use of **standard precautions** when working with blood or other body fluids (Figure 19.19), the CDC has published preferred methods for cleaning, disinfecting, and sterilizing patient-care medical devices and general methods for cleaning and disinfecting the healthcare environment. The proper use of chemical disinfectants is essential. This includes alcohols, glutaraldehyde, formaldehyde, hydrogen peroxide, iodophors, phenolics, quaternary ammonium compounds (quats), and chlorine—all chemical methods described in Chapter 7. The sterilization methods recommended include steam sterilization, ethylene oxide, hydrogen peroxide gas, and liquid peracetic acid. The CDC stresses that these chemical and physical methods must be used properly to reduce the risk for infection associated with both invasive and noninvasive medical and surgical devices. And, importantly, it all starts with good hand hygiene on the part of healthcare providers and visitors while in the hospital.

CONCEPT AND REASONING CHECKS

19.13 How do standard precautions limit the chains of transmission?

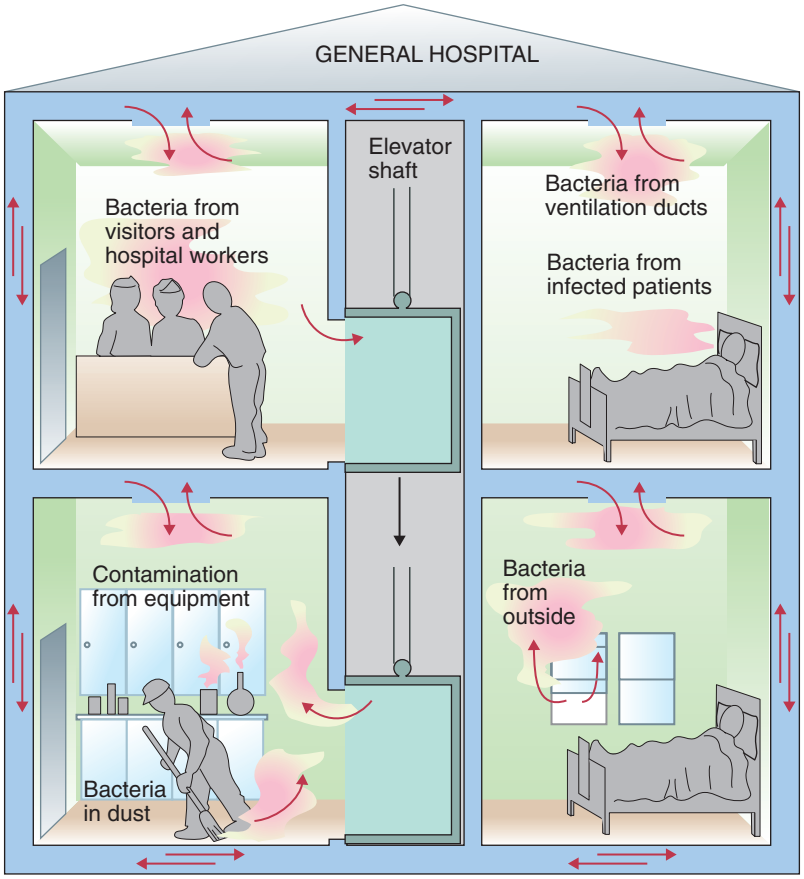


FIGURE 19.19 Microbe Transmission in a Hospital and Standard Precautions. Potential pathogens can be spread through several means within the hospital or health care environment. Protecting patients and other health care workers also means using standard precautions if working with a patient who may be infected. The precautions when handling blood or other body fluids that may harbor pathogens (HIV, hepatitis B or C) include:

- Washing hands
- Wearing personal protective equipment (gloves, mask, and eye protection).
- Handling and disposing of sharps (hypodermic needles) properly.
- Disposing of all hazardous and contaminated materials in approved and labeled biohazard containers.
- Cleaning up all spills with disinfectant or diluted bleach solution to kill any pathogens present.

»» Why is hand washing always at the top of the list for preventing disease transmission?

Infectious Diseases Continue to Challenge Public Health Organizations

KEY CONCEPT

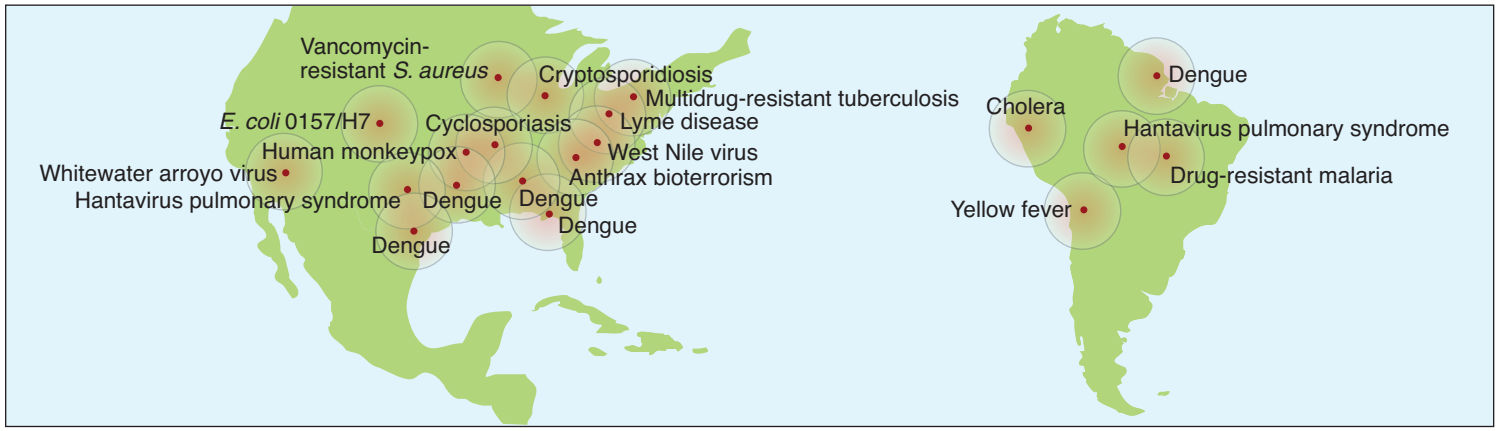
14. Diseases emerging or reemerging anywhere in the world can become a global health menace.

In an era of supersonic jet travel and international commerce, it is not possible to adequately protect the health of any nation without focusing on diseases and epidemics elsewhere in the world. In 2009, we only have to look at H1N1 (swine) flu and the potential bird flu to realize the seriousness of infectious diseases and their threats to global health.

FIGURE 19.20 identifies recent emergent and resurgent (re-emergent) infectious diseases. Globally, there have been more than 40 new diseases and at least 20 resurgent diseases identified since 1980.

There are more than 1,400 known human pathogens (FIGURE 19.21). However, less than 100 are specialized within humans. Over half of the 1,400 represent **zoonoses** (*zoo* = "animal"; *noso* = "disease"), diseases transmitted from animal reservoirs to humans. Some 177 (13%) represent emerging or resurgent diseases, with the largest single number (65%) being RNA viruses (see Chapter 14).

Emerging and re-emerging infectious diseases in North, Central, and South America



Emerging and re-emerging infectious diseases in Europe, Africa, Asia, and Australia

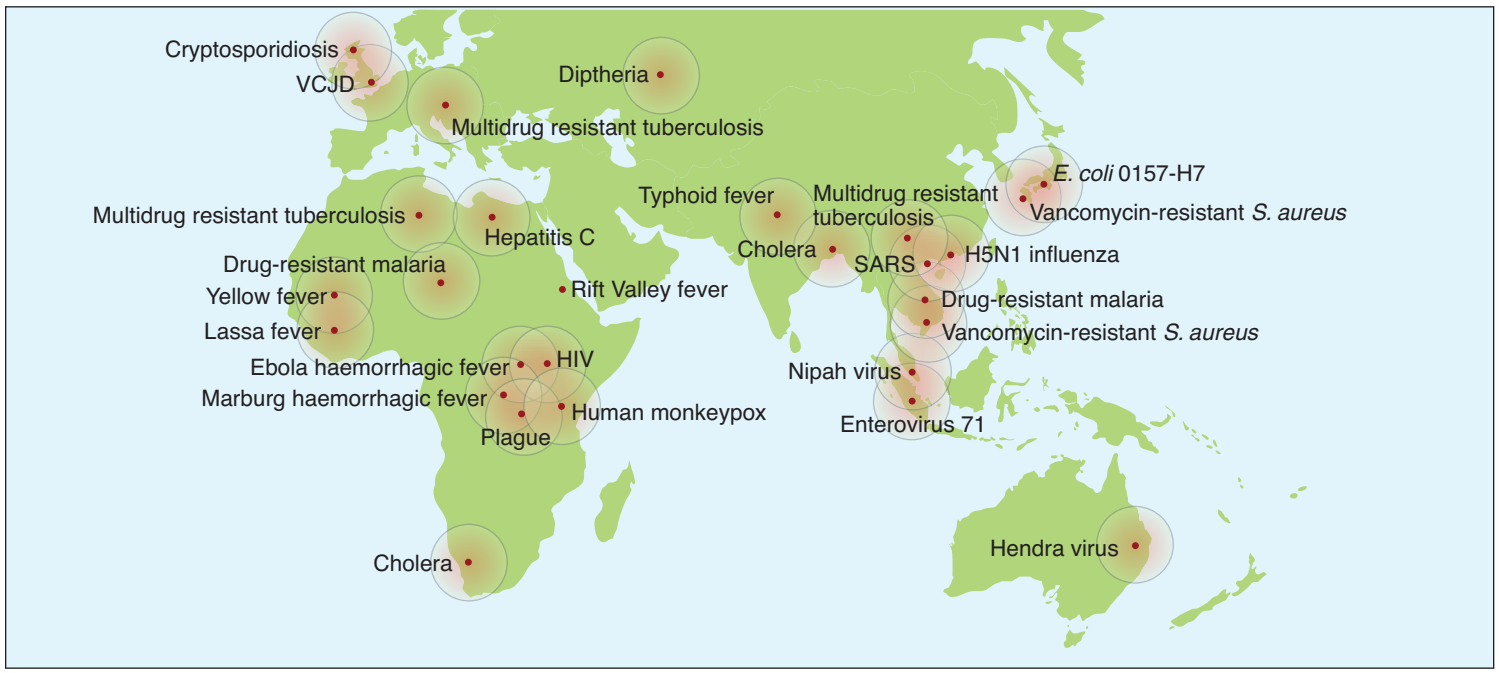


FIGURE 19.20 The Global Occurrence of Emerging and Re-emerging Disease. »» Can you suggest a reason why many of the diseases have appeared in North America?
Modified from American College of Microbiology. *Clinical Microbiology in the 21st Century: Keeping the Pace.* ASM Press, 2008, Washington, D.C.

Numerous reasons help explain how disease emergence and resurgence are driven (in decreasing rank of disease involvement).

1. **Changes in land use or agriculture practices.** Urbanization, deforestation, and water projects can bring new or re-emergent diseases, such as Dengue fever and schistosomiasis.
2. **Changes in human demographics.** The migration of many peoples or whole societies from agrarian to urban lifestyles has brought new diseases to a susceptible population (malaria).
3. **Poor population health.** In many developing nations, large numbers of people suffer from malnutrition or poor public health infrastructure, making disease eruption much more likely (cholera).
4. **Pathogen evolution.** Pathogens have developed resistance to antibiotics and antimi-

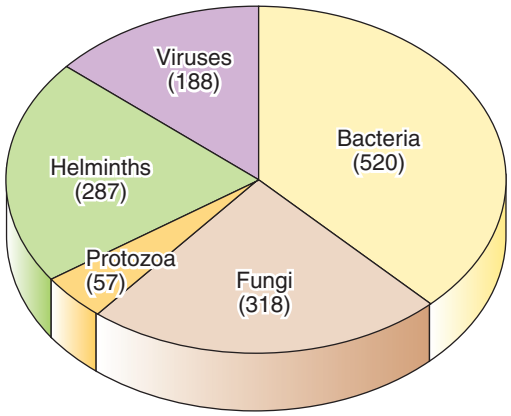


FIGURE 19.21 Known Species of Human Pathogens. The pie chart shows the relative proportions of diseases caused by bacteria, fungi, protozoa, helminths, and viruses. The numbers in parentheses are the known number. »» Name several prominent infections or diseases caused by each group of human pathogens.

crobial drugs, typical of many resurgent diseases (tuberculosis, yellow fever).

5. **Contamination of food sources and water supplies.** Substandard application of, or lapses in, sanitation practices can bring a resurgence of disease (cryptosporidiosis).
6. **International travel.** The number of people traveling internationally can spread diseases to other parts of the globe quickly (SARS, West Nile fever, H1N1 [swine] flu).
7. **Failure of public health systems.** Failure of immunization programs can bring a resurgence of disease (diphtheria).
8. **International trade.** The global movement of produce can introduce new or resurgent diseases (hepatitis A, cyclosporiasis). Likewise, wildlife trade (legal and illegal) provides new mechanisms for disease transmission (monkeypox).
9. **Climate change.** Global changes in weather patterns bring new diseases to new latitudes and elevations (hantavirus pulmonary syndrome).

By understanding these drivers, health organizations such as the CDC and WHO can develop plans to limit or stop emerging disease threats. The CDC has had a history of serving American public health. Regarding emerging and resurgent diseases, the CDC's priority areas include:

- International outbreak assistance to host-countries to maintain control of new pathogens when an outbreak is over.
- A global approach to disease surveillance by establishing a global "network of networks" for early warning of emerging health threats.
- Applied research on diseases of global importance.
- Global disease control through initiatives to reduce HIV disease/AIDS, malaria, and tuberculosis.
- Public health training that supports the establishment of International Emerging Infections Programs in developing nations.

However, a new global health movement requires the involvement of more governmental and non-governmental organizations. Happily, today there is an array of new organizations committed to this cause, including: the Bill and Melinda Gates Foundation; The Global Fund to Fight AIDS, Tuberculosis, and Malaria; President's Emergency Plan for AIDS Relief; and the Global Alliance for Vaccines and Immunization.

CONCEPT AND REASONING CHECKS

19.14 How might climate change alter the occurrence of emerging and re-emerging diseases?

SUMMARY OF KEY CONCEPTS

19.1 The Host–Microbe Relationship

1. **Infection** refers to competition between host and microbe for supremacy, while **disease** results when the microbe wins the competition. However, the human body contains large resident populations of **indigenous microbiota**, which usually out-compete invading pathogens. **Transient microbiota** are temporary residents of the body.
2. **Parasitism** is the symbiotic relationship occurring when the microbe does harm to the host. **Pathogenicity**, the ability of the pathogen to cause disease, and resistance go hand-in-hand. **Virulence** refers to the degree of pathogenicity a microbe displays.
3. Infections may come from an exogenous or endogenous source. If the immune system is compromised, microbes normally acting as commensals may cause **opportunistic infections**. A **primary infection** is an illness caused by a pathogen in an otherwise healthy host, while a **secondary infection** involves the development of other diseases as a result of the primary infection lowering host resistance. **Local diseases** are restricted to a specific part of the body while **systemic diseases** spread to several parts of the body and deeper tissues.

19.2 Establishment of Infection and Disease

4. Most diseases have certain **signs** and **symptoms**, making it possible to follow the course of a disease.
5. To cause disease, most pathogens must enter the body through an appropriate **portal of entry**. The **infectious dose** represents the number of pathogens taken into the body that can cause a disease.
6. The possibility of disease is enhanced if a microbe can penetrate host tissues. The pathogen's ability to penetrate tissues and cause damage is referred to as **invasiveness**. Virulence and invasiveness are strongly dependent on the spectrum of **virulence factors** a pathogen possesses. Bacterial **adhesins** or viral spikes allow bacterial cells or viruses to adhere to specific cells. Adhesion or attachment usually leads to **phagocytosis** of the pathogens.
7. Many bacterial species produce enzymes to overcome the body's defenses. These include **coagulase**, **streptokinase**, and **hyaluronidase** enzymes. In addition, some species produce lytic enzymes, such as **leukocidins** and **hemolysins**. **Exotoxins** are proteins released by gram-positive and gram-negative cells. Their effects depend on the enzyme produced and host system affected. **Endotoxins** are the lipopolysaccharides released from dead gram-negative cells. Their effects on the host are more universal.
8. To efficiently spread the disease to other hosts, the pathogen also must leave the body through an appropriate **portal of exit**.

19.3 Infectious Disease Epidemiology

9. **Reservoirs** include humans, who represent carriers of a disease, arthropods, and any food and water in which some parasites survive.
10. A disease may be **communicable**, such as measles, or **noncommunicable**, such as tetanus.
11. Diseases may be transmitted by **direct** or **indirect** methods. Indirect methods include consumption of contaminated food or water, contaminated inanimate objects (**fomites**), and arthropods. Arthropods can be **mechanical** or **biological vectors** for the transmission of disease.
12. The occurrence of diseases falls into three categories: **endemic**, **epidemic**, and **pandemic**. An "**outbreak**" is essentially the same as an epidemic, although usually an outbreak is more confined in terms of disease spread.
13. **Nosocomial infections**, or **healthcare-associated infections**, are infections acquired as a result of being treated for some other injury or medical problem. **Standard precautions** limit the **chain of transmission**.
14. Public health organizations, such as the CDC, are charged with the duty of limiting or stopping disease threats, including **emerging** and **resurgent diseases**.

LEARNING OBJECTIVES

After understanding the textbook reading, you should be capable of writing a paragraph that includes the appropriate terms and pertinent information to answer the objective.

1. Distinguish between **infection** and **disease**, and between **indigenous** and **transient microbiota**.
2. Contrast **pathogenicity** and **virulence**, explaining how each affects the establishment of disease.

3A. Discuss the consequences of **exogenous** and **endogenous** (including opportunistic) infections on the progression and outcomes of infection and disease.

3B. Distinguish between (a) **primary** and **secondary infections**, (b) **local** and **systemic diseases**, and (c) **bacteremia** and **septicemia**.

4A. Explain the differences between **signs**, **symptoms**, and **syndromes**.

4B. Identify the characteristics that compose the five stages in the course of disease development.

5. Assess the role of the **infectious dose** and pathogen **adhesion** to establishing an infection and disease.
6. Discuss the importance of **invasiveness** to the establishment of an infection.

7A. Name five enzymes and describe their roles as **virulence factors**.

7B. Summarize the differences between **exotoxins** and **endotoxins** as virulence factors associated with disease.

8. Identify six **portals of exit** from the human body.
9. Summarize the characteristics of **reservoirs** as applied to infectious disease.
10. Distinguish between a **communicable**, **contagious**, and **noncommunicable disease** and give an example of each.

11A. Identify the **direct contact** methods of disease transmission.

11B. Evaluate the **indirect contact** methods of disease transmission.

12. Discuss the three types of disease occurrence within populations.
13. Explain how **nosocomial infections** can be controlled or eliminated through using the **standard precautions** to break the **chain of transmission**.
14. Identify the drivers responsible for **emerging** and **resurgent infectious diseases**.

STEP A: SELF-TEST

Each of the following questions is designed to assess your ability to remember or recall factual or conceptual knowledge related to this chapter. Read each question carefully, then select the ***one*** answer that best fits the question or statement. Answers to even-numbered questions can be found in **Appendix C**.

1. A newborn
   - **A.** contains indigenous microbiota before birth.
   - **B.** remains sterile for many weeks after birth.
   - **C.** becomes colonized soon after conception.
   - **D.** is colonized with many common microbiota within a few days after birth.
2. Factors affecting virulence may include
   - **A.** the presence of pathogenicity islands.
   - **B.** their ability to penetrate the host.
   - **C.** the infectious dose.
   - **D.** All the above (**A–C**) are correct.
3. A healthy person can be diagnosed as having a _____ infection with _____, the multiplication of bacterial cells in the blood.
   - **A.** primary; bacteremia
   - **B.** primary; viremia
   - **C.** primary; septicemia
   - **D.** secondary; parasitemia
4. Changes in body function sensed by the patient are called
   - **A.** symptoms.
   - **B.** syndromes.
   - **C.** prodromes.
   - **D.** signs.
5. Adhesins can be found on
   - **A.** host cells.
   - **B.** viruses.
   - **C.** bacterial pili and capsules.
   - **D.** cells at the portal of entry.
6. In the body, bacterial invasiveness can be limited by
   - **A.** fever.
   - **B.** phagocytosis.
   - **C.** enzyme production.
   - **D.** toxic production.
7. Which one of the following is NOT true of exotoxins?
   - **A.** They are proteins.
   - **B.** They are part of cell wall structure.
   - **C.** They are released from live bacterial cells.
   - **D.** They trigger antibody production.
8. A portal of exit would be
   - **A.** the feces.
   - **B.** an insect bite.
   - **C.** blood removal.
   - **D.** All of the above (**A–C**) are correct.
9. If a person has recovered from a disease but continues to shed disease agents, that person is a
   - **A.** vector.
   - **B.** fomite.
   - **C.** vehicle.
   - **D.** carrier.
10. All of the following are examples of communicable diseases *except:*
    - **A.** chickenpox.
    - **B.** measles.
    - **C.** the common cold.
    - **D.** tetanus.
11. Which one of the following is an example of an indirect method of disease transmission?
    - **A.** Coughing
    - **B.** Droplet transmission
    - **C.** A mosquito bite
    - **D.** An animal bite
12. Fifty cases of hepatitis A during one week in a community would most likely be described as a/an
    - **A.** outbreak.
    - **B.** pandemic.
    - **C.** endemic disease.
    - **D.** epidemic.
13. The most common nosocomial infection involves
    - **A.** blood.
    - **B.** lungs.
    - **C.** urinary tract.
    - **D.** a surgical site.
14. A zoonosis is a disease
    - **A.** transmitted from humans to animals.
    - **B.** spread from animals to humans.
    - **C.** transmitted between wild and domestic animals.
    - **D.** spread between wild animals.

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The site features eLearning, an online review area that provides quizzes and other tools to help you study for your class. You can also follow useful links for in-depth information, read more MicroFocus stories, or just find out the latest microbiology news.

STEP B: REVIEW

Test your knowledge of this chapter's contents by determining whether the following statements are true or false. If the statement is true, write "True" in the space. If false, substitute a word for the underlined word to make the statement true. The answers to even-numbered statements are listed in **Appendix C**.

____ **15.** An epidemic disease occurs at a low level in a certain geographic area.

____ **16.** Among the microbial enzymes able to destroy blood cells are hemolysins and leukocidins.

____ **17.** The term disease refers to a symbiotic relationship between two organisms and the competition taking place between them for supremacy.

____ **18.** Organs of the human body lacking a normal microbiota include the blood and the small intestine.

____ **19.** Commensalism is a form of symbiosis where the microbe benefits and causes no damage to the host.

____ **20.** A biological vector is an arthropod that carries pathogenic microorganisms on its feet and body parts.

____ **21.** Organisms causing disease when the immune system is depressed are known as opportunistic organisms.

____ **22.** The human body responds to the presence of exotoxins by producing endotoxins.

____ **23.** The term bacteremia refers to the spread of bacteria through the bloodstream.

____ **24.** A toxoid is an immunizing agent prepared from an exotoxin.

____ **25.** Few symptoms are exhibited by a person who has a subclinical disease.

____ **26.** Indirect methods of disease transmission include kissing and handshaking.

____ **27.** A chronic disease develops rapidly, is usually accompanied by severe symptoms, and comes to a climax.

____ **28.** The acme period is the time between the entry of the pathogen into the host and the appearance of symptoms.

____ **29.** An organism with high virulence generally is unable to cause disease.

____ **30.** Symptoms are changes in body function detected by a physician.

STEP C: APPLICATIONS

Answers to even-numbered questions can be found in **Appendix C**.

31. The transparent covering over salad bars is commonly called a "sneeze guard" because it helps prevent nasal droplets from reaching the salad items. As a community health inspector, what other suggestions might you make to prevent disease transmission via the salad bar?

32. While slicing a piece of garden hose, your friend cut himself with a sharp knife. The wound was deep, but it closed quickly. Shortly thereafter, he reported to the emergency room of the community hospital, where he received a tetanus shot. What did the tetanus shot contain, and why was it necessary?

33. After reading this chapter, you decide to make a list of the ten worst "hot zones" in your home. The title of your top-ten list will be "Germs, Germs Everywhere." What places will make your list, and why?

34. As a state epidemiologist responsible for identifying any disease occurrences, would an epidemic disease or an endemic disease pose a greater threat to public health in the community? Explain.

STEP D: QUESTIONS FOR THOUGHT AND DISCUSSION

Answers to even-numbered questions can be found in **Appendix C**.

35. In 1840, Great Britain introduced penny postage and issued the first adhesive stamps. However, politicians did not like the idea because it deprived them of the free postage they were used to. Soon, a rumor campaign was started, saying that these gummed labels could spread disease among the population. Can you see any wisdom in their contention? Would their concern "apply" today?

36. In 1892, a critic of the germ theory of disease named Max von Pettenkofer sought to discredit Robert Koch's work by drinking a culture of cholera bacilli diluted in water. Von Pettenkofer suffered nothing more than mild diarrhea. What factors may have contributed to the failure of the bacilli to cause cholera in von Pettenkofer's body?

37. A man takes a roll of dollar bills out of his pocket and "peels" off a few to pay the restaurant tab. Each time he peels, he wets his thumb with saliva. What is the hazard involved?

38. When Ebola fever broke out in Africa in 1995, disease epidemiologists noted how quickly the responsible virus killed its victims and suggested the epidemic would end shortly. Sure enough, within three weeks it was over. What was the basis for their prediction? What other conditions had to apply for them to be accurate in their guesswork?

39. A woman takes an antibiotic to relieve a urinary tract infection caused by *Escherichia coli*. The infection resolves, but in two weeks, she develops a *Candida albicans* ("yeast") infection of the vaginal tract. What conditions may have caused this to happen?