Chapter 5

Virus Transmission and Epidemiology

The previous chapter described how viruses enter, replicate within, and exit host cells. This chapter takes a broader look at how viruses enter a host, spread throughout the body, and exit a host to infect other individuals within a population.

Viral pathogenesis is how viruses cause disease within a host. Several factors must be overcome, however, for a virus to initiate a successful infection. First, sufficient numbers of virions must enter the host. A single virion is theoretically enough to initiate infection, but there are many other factors that make it unlikely that a single virion will be successful in establishing an infection. The host cells must be **accessible** to the virus, and those cells must be **susceptible** to infection, meaning that the cells express the receptors to which the virus can bind. This affinity for susceptible tissues is known as **tropism**. The cells must also be **permissive** to infection, meaning that they contain the proteins and molecules within the cell that are necessary for replication to occur. There are also mechanical, chemical, and microbiological barriers to infection at every site within the body, and the host's immune system is quickly activated to eradicate the virus. The viruses that exist today have evolutionarily been selected for their traits that allow them to circumvent host factors and initiate infection, although the most successful viruses are not the most virulent: an extremely pathogenic virus will kill its host, thereby eliminating its reservoir and interrupting the chain of infection to another susceptible host.
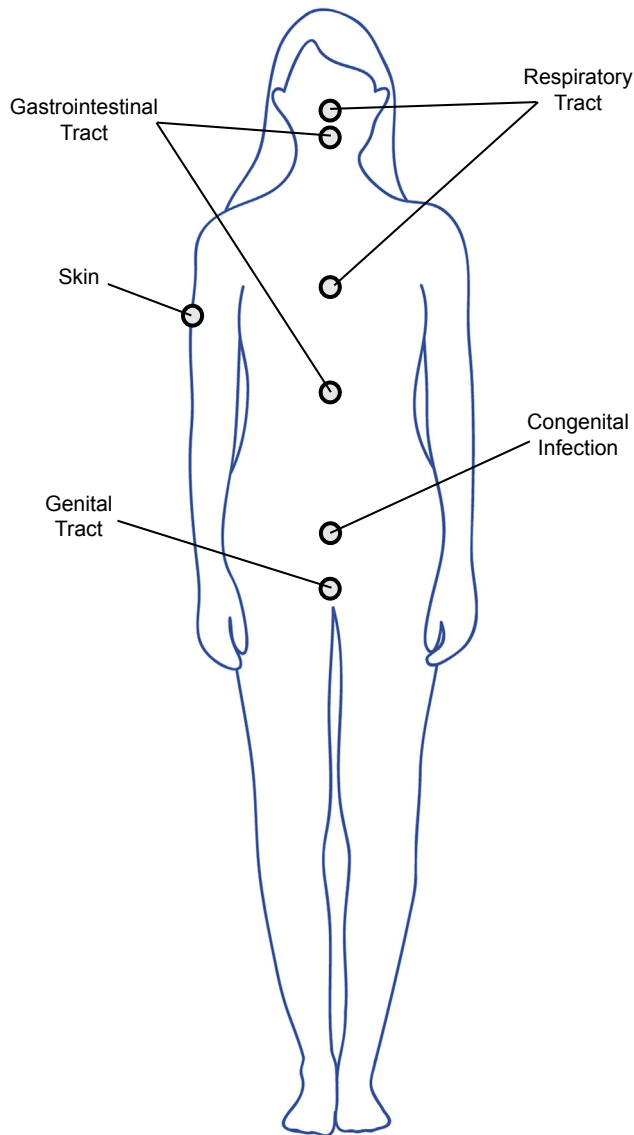
5.1 PORTALS OF VIRUS ENTRY

To establish infection, a virus must come in contact with host cells that are susceptible and permissive to infection. There are several different **portals of entry** that are used by different viruses (Fig. 5.1 and Table 5.1). Most viruses interact with the cells of the host **epithelium**, the layers of cells that line the outside surface and inner cavities of the body. The epithelium acts as the main barrier between the outside world and the internal environment of the body. **Mucosal epithelium**, so named because the epithelium is covered in a protective layer of mucus, lines all the internal surfaces of the body, including the respiratory tract, gastrointestinal tract, and genital tract. The epithelium can be bypassed, however, when viruses are delivered to internal sites through penetration of the skin, as happens with an insect or animal bite, or through transplantation of a virally infected organ.

Several viruses are also able to cross the placenta to a fetus or be transmitted to a child during or after birth.

5.1.1 Respiratory Tract

The **respiratory tract** is the most common portal of entry for viruses into the human body. It is a system of tubes that allows for gas exchange between the body and the external environment. The mucosal surfaces of the respiratory tract translate to a very large surface area with which viruses can interact. A resting human inhales around 2 gallons of air every minute, and within each breath are aerosolized droplets and particles that could contain viruses, such as from a cough or sneeze of an infected individual.

The respiratory tract is subdivided into the upper respiratory tract, which consists of the nose, nasal passages, sinuses, pharynx, and larynx (voice box), and the lower respiratory tract, which consists of the trachea (windpipe), bronchi (singular: bronchus), and lungs (Fig. 5.2A). Within the lungs, the two bronchi branch into smaller-diameter bronchioles that lead to an estimated 300 million alveoli (singular: alveolus), where gas exchange occurs (Fig. 5.2B). Viruses contained in larger droplets are deposited in the upper respiratory tract, while smaller aerosolized particles or liquids are able to travel into the lower respiratory tract. The upper respiratory tract epithelium contains abundant **goblet cells** that produce mucus, a thick fluid that traps inhaled particulate matter. The majority of the upper respiratory epithelium is lined with **cilia**, small hairlike structures that move together like oars to push the mucus and its trapped contents to the throat, where it is swallowed (Fig. 5.2C). Each cell has about 300 cilia. In the lower respiratory tract, mucus-secreting goblet cells become less abundant, and ciliated cells are present at the beginning of the lower respiratory tract but are absent in the alveoli of the lungs. The flow of mucus in the upper and lower respiratory tract traps many viral particles, and antibodies (particularly of the IgA isotype) produced by immune system cells bind to virus particles, preventing them from interacting with the cells of the respiratory epithelium. Within the alveoli of the lung are found many **alveolar macrophages**, another kind of immune system cell that is specialized in **phagocytosis**, a type of receptor-mediated endocytosis that is used by macrophages to endocytose whole cells or pathogens that are then digested by lysosomes within the macrophage.

FIGURE 5.1   Common portals of virus entry. Viruses are able to gain entry into the body through a variety of different portals. These include the respiratory tract, gastrointestinal tract, or genital tract, as well as infection of the skin or underlying subcutaneous tissue. Congenital infections are those that are passed from mother to fetus and present at birth. Other less common pathways to infection, including transplants or infection of the eye, can also occur.

The ciliated epithelial cells of the respiratory tract display receptors for respiratory viruses, such as influenza or rhinovirus (Table 5.1). To initiate infection, however, a virus must avoid being trapped within the mucus lining the epithelium or eliminated by antibodies and macrophages, further emphasizing the importance of having a sufficient number of virions present.

5.1.2 Gastrointestinal Tract

The human digestive or **gastrointestinal tract** is a hollow tube that stretches from the oral cavity (mouth) to the anus

(Fig. 5.3A). Food enters the mouth, where it is chewed and begins being digested by the enzymes found in saliva, provided by the salivary glands. The pharynx moves food via the swallowing reflex into the esophagus, which has several mucus-secreting glands. Muscle contractions by the esophagus move the food into the stomach, which contains numerous pits of cells, all of which produce mucus to protect the cells from the acidic gastric juices secreted by the stomach. From there, food moves to the small intestine, where the food finishes being digested and is absorbed. The small intestine is roughly 6 ft long and is composed of fingerlike projections called **villi** (singular: villus) that increase the surface area of the epithelium (Fig. 5.3B and C). Moreover, the epithelial cells that form the villi have multiple hairlike **microvilli** at their apical (outermost) end, forming what looks like the teeth of a comb. Each cell of a villus has an estimated 3000 microvilli. Together, the total surface area of the small intestine is similar to that of a tennis court. This increases the area of contact for absorption of food, but some viruses also take advantage of this area of exposure for infection (Table 5.1).

Being a mucosal epithelium, the small intestine also contains numerous goblet cells and glands that secrete mucus, which lines the epithelium. Under the epithelium of the small intestine, lymph node–like masses called Peyer's patches contain millions of antibody-secreting lymphocytes (of the IgA antibody variety, as in the lungs), macrophages, and other immune system cells (Fig. 5.3D). Interspersed within the epithelial layer are M (microfold) cells, specialized epithelial cells that constantly survey the contents of the small intestine lumen. These cells transfer the molecules from the lumen to the immune system cells found in the lymphoid tissue below (Fig. 5.3E). However, poliovirus, reovirus, and HIV are thought to exploit M cells to gain entry past the epithelium.

At this point of the gastrointestinal tract, the food has been broken down completely and all nutrients have been absorbed by the small intestine. The food remnants pass into the colon (large intestine), which lacks the villi of the small intestine but has abundant goblet cells for secreting mucus. Although most of the water in the food has been absorbed by the small intestine, absorptive cells in the colon reclaim any remaining water from the digested food, which becomes compacted into feces. At the end of the colon, the rectum stores feces, which are expelled via the anus.

Viruses that enter via the gastrointestinal tract must be able to survive its hostile environment. The flow of food, water, and saliva provides a mechanical barrier to infection, and mucus produced by the stomach, small intestine, and large intestine provides a physical barrier to infection. Macrophages phagocytose virions, and antibodies neutralize virions to prevent their interaction with host cell receptors. Successful viruses must also be resistant to the low pH of stomach acid and the detergent qualities of bile, which is

TABLE 5.1 Common Portals of Entry and the Viruses That Use Them

Portal	Selected human viruses that use this portal for local or systemic infection
Respiratory tract	Adenovirus, measles, mumps, rubella, enterovirus D68, influenza A virus, influenza B virus, rhinovirus, respiratory syncytial virus, varicella zoster virus, variola
Gastrointestinal tract	Norwalk virus, rotavirus, poliovirus, enteric enteroviruses, hepatitis A virus, hepatitis E virus, sapovirus
Genital tract	Human papillomaviruses, HIV, hepatitis B virus, hepatitis C virus, herpes simplex virus-2 (HSV-2)
Skin	
● Direct contact	Human papillomaviruses, HSV-1, Molluscum contagiosum virus
● Penetration into dermis or subcutaneous tissue	*Injection/cuts*: hepatitis B virus, hepatitis C virus, HIV, Ebola virus
	Mosquito: Dengue virus, West Nile virus, eastern equine encephalitis virus, Chikungunya virus, yellow fever virus
	Ticks: Heartland virus, Powassan virus, Colorado tick fever virus
Through placenta (transplacental)	Cytomegalovirus, variola virus, HSV-1 and -2, measles virus, Zika virus, rubella virus
Eye	Adenoviruses, HSV-1, cytomegalovirus, enterovirus 70, Coxsackievirus A24, rubella virus, measles virus, vaccinia virus
Transplants	
● Solid organs	Hepatitis B virus, hepatitis C virus, HIV, cytomegalovirus, West Nile virus, rabies virus, lymphocytic choriomeningitis virus, HSV, varicella zoster virus
● Blood	HIV, hepatitis B virus, hepatitis C virus, human T-lymphotrophic virus-I and -II, dengue virus, Ebola virus
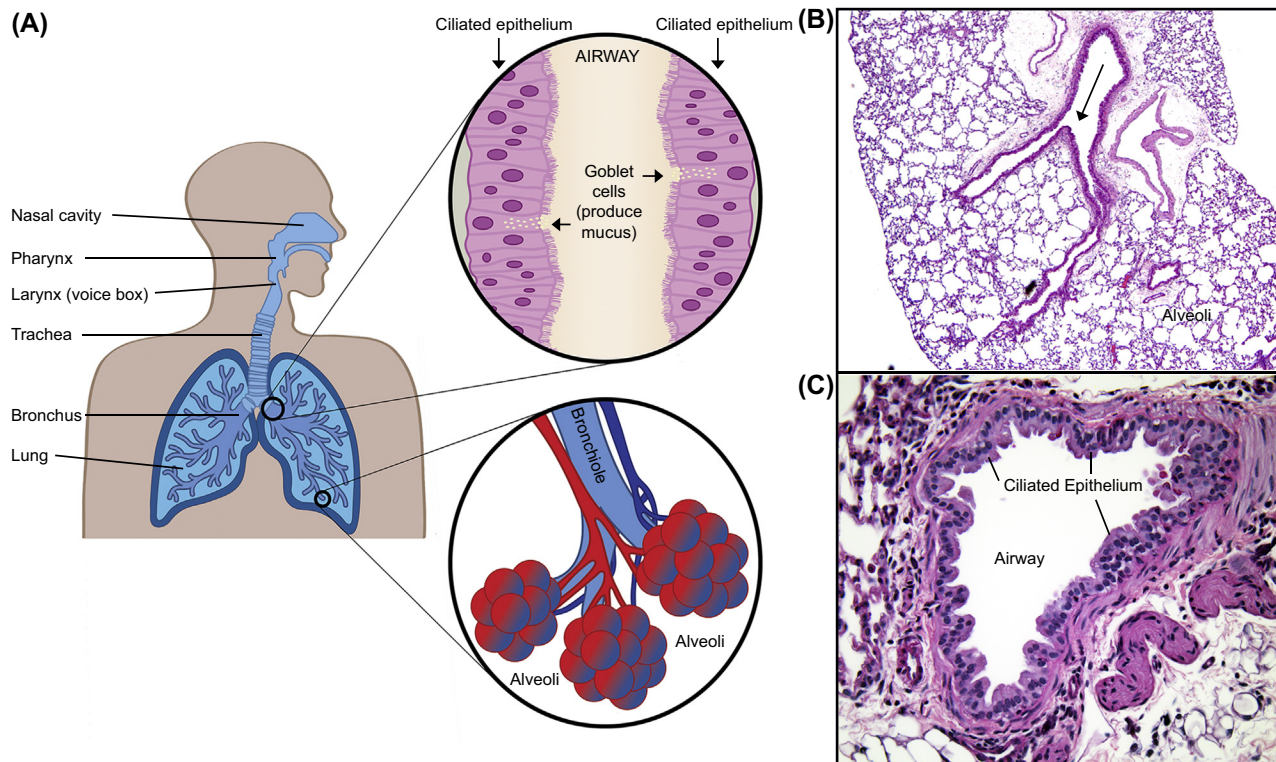
FIGURE 5.2   The respiratory tract. (A) The respiratory tract is subdivided into the upper respiratory tract, which consists of the nose, nasal passages, sinuses, pharynx, and larynx (voice box), and the lower respiratory tract, which consists of the trachea, bronchi, and lungs. The airways of the trachea and bronchi are lined with goblet cells that produce mucus to trap particles and pathogens, and ciliated epithelial cells push the mucus out of the lungs. The two bronchi branch into smaller-diameter bronchioles that lead to an estimated 300 million alveoli, where gas exchange occurs. (B) Cross section of a normal mouse lung at 40× magnification, showing a large bronchus branching into two smaller bronchi, which eventually branch into hundreds of alveoli. (C) Cross section of a normal mouse bronchus at 400× magnification showing the ciliated mucosal epithelium that lines the airways.
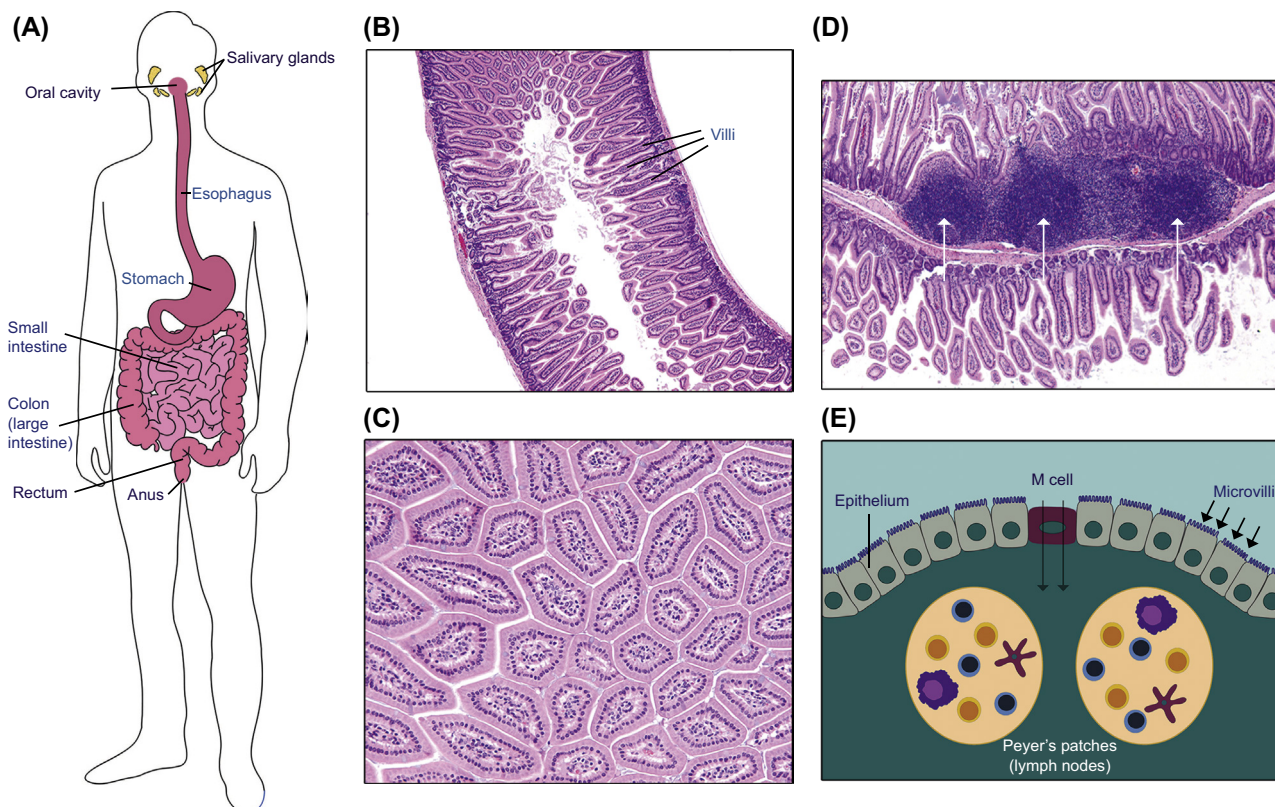
FIGURE 5.3   The gastrointestinal tract. (A) The human gastrointestinal tract, which is used for entry of several viruses into the body, stretches from the oral cavity to the anus. Food is chewed in the mouth and begins being digested by salivary enzymes. The pharynx moves food into the esophagus; muscle contractions here move the food into the stomach, where acidic gastric juices digest the food molecules. It passes into the small intestine, where bile from the gall bladder acts as a detergent. Numerous fingerlike villi (B, mouse tissue at 40× magnification), lined by a layer of epithelium (C, cross section at 200×), increase the surface area of the small intestine for greater absorption (and virus attachment). Lymph nodes called Peyer's patches are found beneath the epithelium in the small intestine (D), Here, specialized epithelial cells called M cells pass molecules from the lumen of the small intestine to immune cells located in the Peyer's patches (E). Some viruses gain entry in this way. After the food has been broken down completely in the small intestine, it passes into the colon and is compacted into feces, stored in the rectum until being expelled by the anus (A).

produced by the liver, stored by the gallbladder, and secreted into the small intestine. The membrane envelopes of most enveloped viruses are disintegrated by bile. **Acid-labile** viruses are unable to withstand the low pH of the stomach, while **acid-resistant** viruses contain capsid proteins that are not denatured by low pH (or their protein denaturation is reversible). Within the *Picornaviridae* family, rhinoviruses are acid labile, whereas poliovirus is acid resistant.

Viruses can be transmitted via the gastrointestinal tract in several different ways. Viruses can be transmitted from mother to child in breast milk, either as free virions or within infected cells; HIV, cytomegalovirus, and West Nile virus are three such viruses. Other viruses enter via the **fecal–oral route**, meaning that virions present in the feces of an infected individual gain entry into the oral cavity of another individual and are ingested. This is a common occurrence in nations without water treatment plants and has been one of the major roadblocks in eradicating polio from undeveloped nations. In developed countries, touching contaminated surfaces or ingesting food or water that has been contaminated

can lead to infection. Norwalk virus, described in Chapter 1, "The World of Viruses," is another virus that is transmitted by the fecal–oral route. It is the leading cause of foodborne illness in the United States, causing roughly 20 million cases of acute gastroenteritis (a sudden stomach illness with vomiting and diarrhea) each year, according to the CDC. Worldwide, acute gastroenteritis caused by viruses is a major cause of death, leading to 1.5 million deaths annually.

> **Study Break**
> What characteristics must a gastrointestinal virus possess in order to effectively infect through this route?

5.1.3 Genital Tract

The genital tract refers to the organs that are involved in reproduction. In males, this includes the penis, testicles, and several associated glands and connecting tubes. The female genital tract includes the vagina, cervix, uterus,

fallopian tubes, and ovaries. Viruses that are transmitted via the genital tract as a result of sexual activity are **sexually transmitted diseases**. Cells can be infected, exhibited by the tropism of human papillomavirus (HPV) for the epithelium of the cervix or penis, or viruses can gain entry into the body through breaks in the genital epithelium or by binding local cell receptors, as occurs with hepatitis B virus or HIV (Table 5.1). Viruses infecting via the genital tract have to overcome local barriers to infection, such as mucus and the low pH of the vagina.

5.1.4 Skin

The skin is a unique organ, a covering to the body that creates $1.5–2\,m^2$ of surface area exposed to the external environment. It is composed of two layers of tissue: the outermost **epidermis** and the underlying **dermis** (Fig. 5.4A and B). **Subcutaneous tissue** is found beneath the skin and contains primarily fat and loose connective tissues.

The epidermis consists of five layers, or strata, of keratin-producing cells (Fig. 5.4C). The innermost layer, the stratum basale, consists of living cells that undergo mitosis. The cells become filled with thick keratin filaments and die as they continue their differentiation through the layers, finally becoming the outermost layer of the skin, the stratum corneum. The cells continuously slough off from the outermost stratum and are reconstituted from the cells progressing through the lower strata.

The epidermis has barrier mechanisms to prevent infection. The flow of fluid or perspiration over the skin makes viral attachment difficult, and the sebum (oil) produced by sebaceous glands creates an acidic environment. In addition, the cells in the outermost strata of skin are not alive and thus cannot support viral replication. Viruses that replicate in the epidermis, such as HPV, gain access through small cuts or abrasions in the skin that allow access to the lower, dividing layers of skin where viral replication can occur.

The epidermis lacks blood and lymph vessels, but the underlying dermis and subcutaneous tissue are highly vascularized and contain lymphatic vessels that drain lymph to regional lymph nodes. Viruses can be introduced to these areas through penetration of the epidermis (Table 5.1). Bites of insect vectors (mosquitoes, ticks, mites) can introduce viruses into the dermis, and the subcutaneous tissue can be accessed by viruses through animal bites, needle punctures, or improperly sterilized tattooing or piercing equipment. In the dermis and subcutaneous tissue, viruses can easily gain entry into the bloodstream, either directly or through the draining lymph that eventually empties into the bloodstream. The epidermis primarily supports localized viral infections, but introduction of the virus to the underlying dermis and subcutaneous tissue can result in dissemination of the virus to other locations within the body.
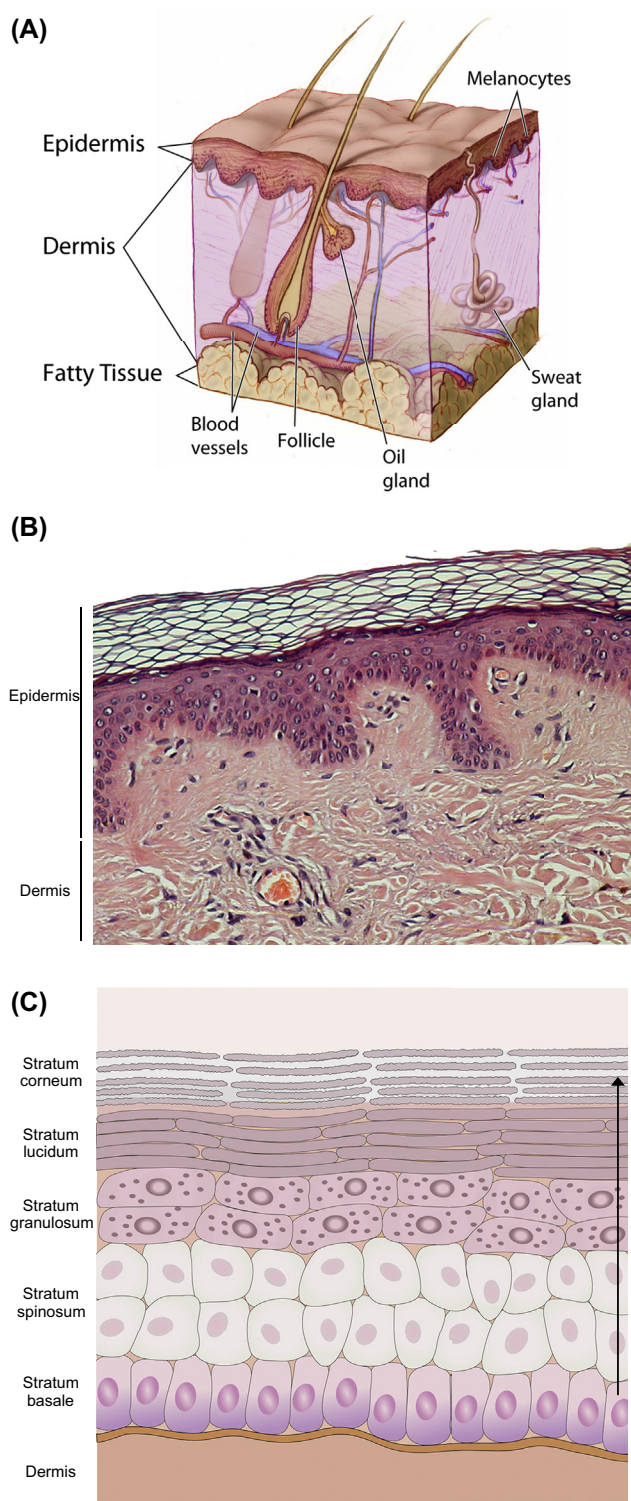
FIGURE 5.4   The skin. The skin is composed of two layers, the epidermis and dermis (A and B). The epidermis is composed of five layers (C); the innermost layer consists of living cells that undergo mitosis. The cells differentiate as they progress through the different layers, eventually dying as they are filled with thick keratin filaments. The cells continuously slough off from the outermost layer, being replenished with cells from the next lower layer. Some viruses, like human papillomaviruses, are able to replicate within the living part of the epidermis, but other viruses must gain entry to the dermis or underlying subcutaneous tissue in order to replicate or disseminate. *Image in Part A by Don Bliss, National Cancer Institute. Magnification of Part B is 100×.*

5.1.5 Eyes

The eye is a complex organ used for perceiving shapes, light, and color. As an interface with the outside world, the eyes can also be a portal of entry for viruses (Table 5.1).

The external layer of the eye is composed of the **sclera** and the **cornea** (Fig. 5.5A). The tough white covering of the eye is the sclera ("whites of the eyes"), which becomes the colorless and transparent cornea in the front and center area of the eye that covers the pupil, lens, and iris. The **conjunctiva** is a thin layer of epithelium that covers the sclera and the part of the eyelid that abuts the eye. An eye blinks every 5 seconds, on average, and tears function to keep the outer surface of the eye moist while washing away any potential pathogens. It is rare to have a viral infection of the eye itself without a traumatic event (a puncture wound, for example) to provide entry into the eye. However, infection of the cornea can occur with herpesvirus exposure, and herpes simplex virus (HSV) infection of the cornea is the most common

infectious cause of corneal blindness in the United States. More often, viruses infect the conjunctiva of the eye or eyelid, causing **conjunctivitis** (Fig. 5.5B). Viral conjunctivitis, also known as "pink eye," is usually caused by adenoviruses.

5.1.6 Placenta

Congenital infections occur when a mother infects a fetus before its birth. Congenital infections occur via **vertical transmission**, meaning that the virus is spread from one generation to the next generation (Fig. 5.6). In contrast, most viral infections exhibit **horizontal transmission**, meaning that direct host-to-host transmission occurs. Viruses with horizontal transmission rely upon a high rate of infection to sustain the virus population, while vertical transmission often leads to long-term persistence of the virus within the child.

Congenital infection can occur when a virus crosses the placenta during pregnancy. The blood of the mother is not mixed with the blood of the fetus; instead, the placenta is the interface between the mother and developing fetus (Fig. 5.7), allowing oxygen, waste products, and nutrients to pass between mother and fetus. Similarly, some viruses are able to pass through the placenta (Table 5.1). Cytomegalovirus, a herpesvirus, is the most common cause of congenital infections, occurring in about 2.5% of live births. Several other viruses can be transmitted transplacentally, including variola (smallpox), rubella, measles, Zika, and parvovirus B19. The effects

(A)

Cornea
Iris
Lens
Vitreous gel
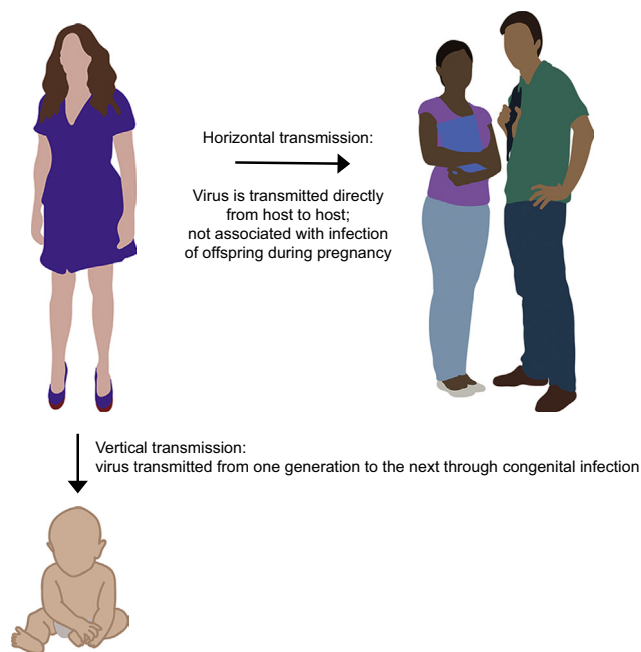Optic nerve
Retina
Sclera
Conjunctiva

(B)

FIGURE 5.5   The eye. (A) The eye is composed of several layers. The white covering of the eye is the sclera, which becomes the transparent cornea in the front of the eye. A thin layer of epithelium, called the conjunctiva, covers part of the sclera and connects to the eyelid. (B) This photograph shows conjunctivitis, the inflammation of the conjunctiva, caused by accidental infection with vaccinia, the virus in the smallpox vaccine. *Courtesy of CDC/Arthur E. Kaye.*

Horizontal transmission:

Virus is transmitted directly from host to host; not associated with infection of offspring during pregnancy

Vertical transmission: virus transmitted from one generation to the next through congenital infection

FIGURE 5.6   Horizontal transmission versus vertical transmission. Horizontal transmission refers to the transmission of an infectious agent among individuals within a population. In vertical transmission, however, an infectious agent is transmitted from one generation to another through congenital infection.

can be severe, including miscarriage, low birth weight, intellectual deficiencies, hearing loss, and death of the infant.

Intrapartum transmission occurs when the child is infected during the birthing process due to contact with the mother's infected blood, secretions, or biological fluids. Vertical transmission of HIV most often occurs by intrapartum transmission, although breastfeeding can also transmit the virus via the gastrointestinal tract. HSV-1 and HSV-2 cause genital warts but are most often asymptomatic in adults. Intrapartum transmission of HSV to the child is highest when the mother has active lesions or contracted a new HSV infection in her third trimester of pregnancy. Antiviral drugs are used to reduce viral load, but a pregnant

mother may be encouraged to deliver the child by C-section if there are active signs of maternal infection.

5.1.7 Transplants

Although the rate is low compared to other portals of entry, transplanted organs and tissues can also harbor viruses that can be transmitted to a new host (Table 5.1). Blood is the most commonly transplanted tissue, and before the advent of sensitive screening tests, **transfusion-transmitted infections** (TTIs) were a low probability but possible result of receiving blood and blood products. Several viruses can be transmitted through blood, including hepatitis A virus, hepatitis B virus, hepatitis C virus, HIV, West Nile virus, and dengue virus. The blood supply is currently screened for many of these, and the current risk of receiving contaminated blood is very low (Table 5.2). However, before tests were developed and screening was instituted, hepatitis B and C viruses contaminated the blood supply. In the early 1980s, when AIDS was reported, blood industry supporters underestimated the risk of HIV having entered the blood supply and were slow to take action. At the time, more than half of the 16,000 people in the United States with hemophilia, a genetic bleeding disease that requires blood plasma transfusions to transfer clotting factors, contracted HIV from contaminated plasma products. Similarly, it is estimated that over 20,000 people contracted HIV from contaminated blood before March 1985, when the U.S. Food and Drug Administration (FDA) approved the first test to detect HIV. Incidents like this one have proven valuable in emphasizing the importance of detecting new viruses in the blood supply. When transfusion-transmitted West Nile virus infections were reported in 2002, a test was rapidly developed and the blood industry began regular testing of donated blood for the virus.

Although infrequent, virus transmission through transplanted organs has also been documented. To prevent the rejection of the transplant, organ recipients are given potent
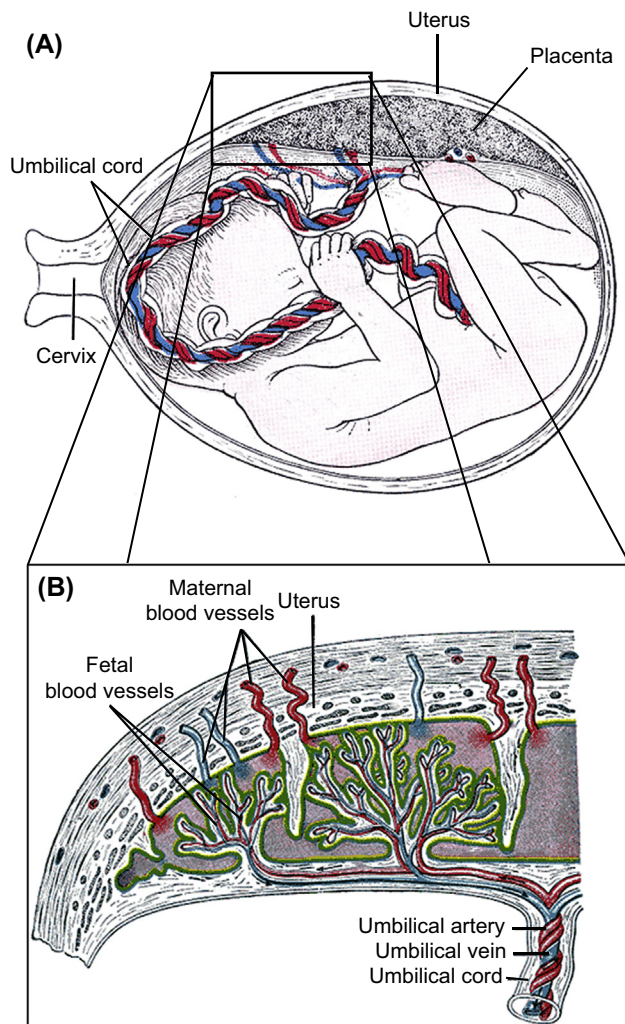
FIGURE 5.7   **The placenta.** The placenta is a fetal tissue that allows the transfer of oxygen, carbon dioxide, waste products, and nutrients between the mother and fetus (A). Although maternal and fetal blood does not mix, the fetal arteries and veins come into close contact with material blood vessels in the placenta, allowing diffusion to occur (B). Several viruses are able to travel from mother to fetus through the placenta. *Illustrations from Henry Gray, Anatomy of the Human Body. Philadelphia and New York, Lea and Febinger, 1918.*

TABLE 5.2 Pathogens for Which the Blood Supply Is Currently Tested

Pathogen type	Specific pathogens tested for
Virus	Hepatitis B virus
	Hepatitis C virus
	Human immunodeficiency virus-1 and -2 (HIV-1/HIV-2)
	Human T-lymphotropic virus-I and -II (HTLV-I/HTLV-II)
	West Nile virus
Bacterium	*Treponema pallidum* (syphilis)

Case Study: Lymphocytic Choriomeningitis Virus Infection in Organ Transplant Recipients—Massachusetts and Rhode Island, 2005

Excerpted from the Morbidity and Mortality Weekly Report, May 26, 2005 54 (Dispatch):1–2.

On May 3, 2005, CDC received a report of severe illness in four patients who had received solid organ transplants from a common donor. All four organ recipients subsequently were found to have evidence of infection with lymphocytic choriomeningitis virus (LCMV), a rodent-borne Old World arenavirus. Preliminary findings from the ensuing investigation indicate the source of infection likely was an infected hamster in the donor's home.

In early April, in Rhode Island, a woman with a medical history remarkable only for hypertension (*high blood pressure*) and 1 week of headache had sudden onset of hemiplegia (*paralysis of one half of the body*) caused by a stroke, followed by brain death within 3 days. A thorough evaluation was not suggestive of infection.

Family members of the woman consented to donation; organs and tissues were recovered, including the liver, the lungs, both the kidneys, both the corneas, and the skin. Within 3 weeks after transplantation, the four persons who received the liver, lungs, and two kidneys had abnormalities of liver function and blood coagulation and dysfunction of the transplanted organ. Signs, symptoms, and clinical laboratory test results varied in these patients and included fever, localized rash, diarrhea, hyponatremia (*low blood sodium*), thrombocytopenia (*low blood platelets*), hypoxia (*low oxygen levels*), and kidney failure. Three of the four organ recipients died, 23–27 days after transplantation. The fourth patient, a kidney recipient, survived.

When the cause of illness among the recipients was not identified through extensive diagnostic testing and suspicion of transplant-transmitted infection arose, tissue and blood samples from the donor and recipients were sent from the Rhode Island Department of Health and the Massachusetts Department of Public Health to CDC. LCMV was identified as the cause of illness in all four organ recipients. Sequencing of the virus genome confirmed its identity as LCMV.

Epidemiologic Investigation

To determine the source of LCMV infection, investigations were conducted at the hospitals involved in organ recovery and transplantation and at the coordinating organ procurement organization. Interviews also were conducted at locations where the donor had spent substantial time in the month preceding her death.

Interviews with hospital and organ bank staff members revealed no likely sources of LCMV infection in the hospital or organ-recovery settings. Environmental assessment at locations the donor frequented (eg, home and work) revealed limited opportunities for exposure to wild rodents; the sole location noted with rodent infestation was a garden shed at her home. Interviews with family members of the donor determined that a pet hamster had been acquired recently. The hamster was cared for primarily by another family member. No illnesses compatible with LCMV had been reported in the donor or family members during the month preceding the donor's death.

Laboratory Investigation

Family members of the donor were tested for LCMV antibodies. The family member who cared for the hamster had specific IgM and IgG antibodies to LCMV. No other family member had detectable IgG or IgM antibodies to LCMV. All available donor tissues were tested, and no evidence of LCMV was determined. However, the pet hamster was determined positive for LCMV.

Reported by Rhode Island Hospital, Providence; Rhode Island Dept of Health. New England Organ Bank, Newton; Massachusetts General Hospital, Brigham and Women's Hospital, Boston; Massachusetts Dept of Public Health. Infectious Disease Pathology Activity, Special Pathogens Br, Div of Viral and Rickettsial Diseases, Div of Healthcare Quality Promotion, National Center for Infectious Diseases; EIS officers, CDC.

drugs to suppress the immune system, which causes the host to become **immunocompromised**. When transferred through organ transplantation, these viruses can reemerge and infect the immunocompromised host. Herpesviruses, which remain in tissues or cells in a dormant state after infecting a healthy host, are common viral pathogens in transplants, although a variety of other viruses have also been transmitted through transplantation, including rabies, West Nile virus, HIV, hepatitis viruses, lymphocytic choriomeningitis virus, and several respiratory viruses. Risk questionnaires and screening of donor tissues are recommended to reduce the transmission of certain of these viruses.

5.2 DISSEMINATION WITHIN A HOST

As we have seen, viruses can gain entry into a host through a variety of ways. Viruses that infect and replicate only within cells at the site of infection cause **localized infections**. Rhinovirus is an example of a virus that causes a localized infection: it infects the epithelial cells of the upper respiratory tract and replicates there. Similarly, papillomavirus strains that infect the skin replicate locally in the epidermis. On the other hand, viruses that initiate infection through one organ but then spread to other sites within the body cause **systemic infections**. These viruses infect cells within the initial organ, where they either replicate locally before spread or use infected local cells to travel to other locations within the body.

Virions spread to other organs through one of two ways. In **hematogenous spread**, viruses spread to target organs using the bloodstream. This can occur through direct injection into the blood, as would happen with animal or insect bites, or it can occur from virions entering the interstitial fluid that bathes all our cells within the tissues. This

interstitial fluid, or lymph, is collected in lymphatic vessels that lead back to lymph nodes (Fig. 5.8). Immune system cells filter the lymph within the lymph nodes, but high virion concentrations can mean that some escape these cells and continue within the lymph, which is eventually returned to the bloodstream. **Viremia** is the term used to describe the presence of virus within the bloodstream. Since blood circulates throughout the entire body, viruses can use the bloodstream to gain access to their cellular targets in organs other than the ones through which they entered the body. **Primary viremia** indicates the first time that the virus is found in the bloodstream. After replicating within the target organ, additional virions may enter the bloodstream. This is known as a **secondary viremia**.

In **neurotropic spread**, viruses spread through the body using neurons. Viruses rarely infect neurons directly because it is difficult for viruses to directly access these cells. Most often, viruses replicate in cells at the local site of infection and then infect neurons located nearby. Several herpesviruses spread in this manner, infecting and replicating within the local epithelium until sufficient virions are present to infect nerves associated with the tissue.

Herpesviruses are dsDNA viruses and must gain entry into the cell's nucleus for replication. However, the nucleus of a neuron, can be quite a distance from the axon terminal where the virus initiated attachment to the cell. As mentioned in Chapter 4, "Virus Replication," herpesviruses have evolved mechanisms to overcome this challenge. Viral proteins bind to dynein, a host cell protein that "walks" vesicles of cargo along microtubules to the nucleus. At the nucleus, the capsid docks at a nuclear pore and its viral DNA is transported into the nucleus for replication or latency.

Viruses first infect neurons of the peripheral nervous system, which can be used to access the central nervous system. Certain viruses can cause devastating results if they reach the central nervous system. For instance, death occurs within days of the rabies virus reaching the brain.

5.3 PORTALS OF VIRUS EXIT

In order to persist within a population, a virus must spread from an infected host to a susceptible host. The **shedding** of virus refers to the release of infectious virions from the host. During localized infections, the virus is shed from the primary site of infection. Viruses that infect the skin are spread through skin-to-skin contact, and respiratory viruses are shed within respiratory secretions, passed along through a cough or sneeze to a new, susceptible host. Gastrointestinal viruses are shed within aerosolized vomit or diarrhea, potentially contaminating food or water that could infect a subsequent individual. Viruses that replicate in the lungs, nasal cavity, or salivary glands can be shed in saliva, and viruses such as HIV and herpesviruses can replicate within genital compartments and be shed in semen or vaginal secretions.

Viremia is a common occurrence of infection with several viruses, including HIV and hepatitis. Consequently, these viruses can be transmitted through blood. **Viruria**,
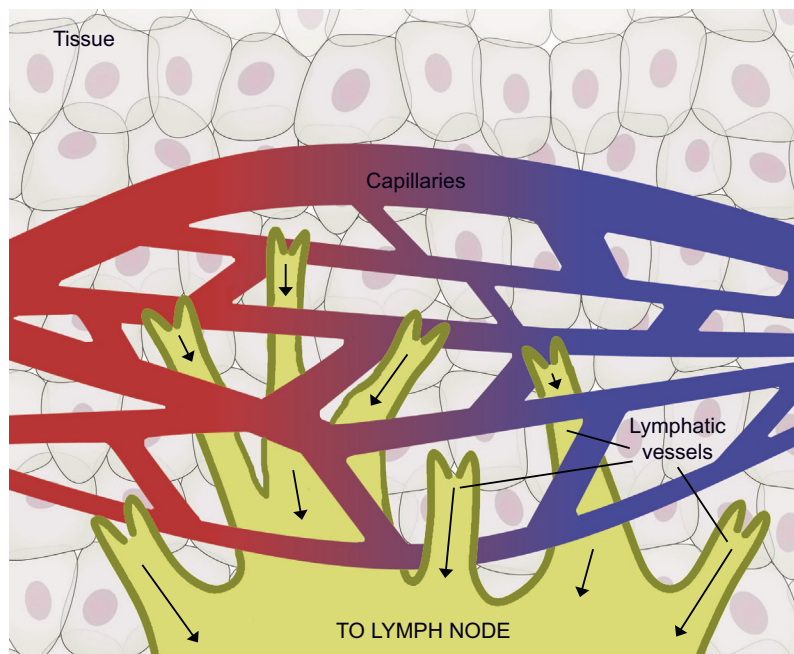
FIGURE 5.8   **The lymphatic system.** Fluid with nutrients and oxygen diffuses through small capillaries within a tissue. This interstitial fluid, or lymph, is collected by one-way lymphatic vessels that drain to lymph nodes, where immune cells filter the lymph. It is eventually returned to the bloodstream. Viruses within tissues can travel within the lymph and enter the blood if not successfully filtered by the lymph node immune cells.

the presence of virus within the urine, occurs with several systemic viral infections, including measles and mumps. Other viruses replicate within and are shed by cells of the urogenital tract, such as JC polyomavirus (JCPyV) and BK polyomavirus. Some viruses that cause severe disease are transmitted to people through aerosolized virions found in rodent urine or droppings (see *In-Depth Look*).

Although viruses cannot replicate independently outside a host, virions can remain infectious outside the body. The stability of virions within the environment, however, depends upon several factors, both of the environment and of the virion itself (Table 5.3). The biochemical characteristics of the virion and its contents, including the type of nucleic acid, the sensitivity of viral proteins to pH changes, and the presence or absence of a lipid envelope, play a role in the sensitivity of the virion to inactivation by environmental factors. Temperature, humidity, moisture content, sunlight, pH, and the presence of organic matter all affect the inactivation of virions within the environment.

Viruses within contaminated feces or urine can be transmitted via the fecal–oral route or shed within feces and urine and then aerosolized and inhaled. The neutral pH of human waste generally protects virions, and organic matter within feces also buffers the chemical makeup and temperature

of the environment. Temperature plays a large part in the persistence of viruses within feces or waste water. Viruses are inactivated within minutes or hours at high temperatures (above 121°F or 50°C), but certain viruses, particularly those that are nonenveloped, can remain infectious for days or months at ambient temperatures.

Airborne viruses can be transmitted within liquid droplets or aerosolized particles that are released when a person sneezes, coughs, speaks, or breathes. Droplets

Study Break
Describe the difference between respiratory droplets and aerosolized particles. How can these affect the dissemination of virions in the environment?

In-Depth Look: Transmission of Serious Diseases Through Rodent Urine and Droppings
Several potentially dangerous viruses replicate primarily in rodent populations and only become problematic when the virus is inadvertently transmitted to humans. One such illness is hantavirus pulmonary syndrome (HPS), caused by a hantavirus known as Sin Nombre virus. This virus causes a fever ≥101°F (38.3°C), chills, muscle aches, headache, and severe respiratory problems. In the United States, an average of 29 people have been infected each year since recording began in 1993. Of these infections, 36% have been fatal.

Hantaviruses are transmitted by infected deer mice (*Peromyscus maniculatus*) present throughout the western and central United States, cotton rats (*Sigmodon hispidus*) and rice rats (*Oryzomys palustris*) in the southeastern states, and white-footed mice (*Peromyscus leucopus*) in the northeast. The rodents shed the virus in their urine, droppings, and saliva. When fresh rodent urine and droppings are disturbed, particles containing the virus get into the air, and the virus is transmitted to people when they breathe in the virus-containing particles. The virus can also be transmitted when the person inadvertently touches rodent urine or droppings and then touches the mucous membranes of their nose or mouth. Cases of HPS most often occur in rural areas where forests, fields, and farms offer a suitable habitat for these rodents. No human-to-human transmission of hantaviruses has yet occurred.

The *Arenaviridae* family of viruses is also associated with rodent-transmitted diseases of humans (see case study). The first arenavirus discovered was lymphocytic choriomeningitis virus, in 1933. Since that time, seven other arenaviruses have been isolated. As with hantaviruses, rodents are the natural reservoirs of the arenaviruses. The viruses do not cause disease in the rodents but can be transmitted to humans by contact with infected rodent urine or droppings, either by inhaling infected particles or ingesting contaminated food. Lassa virus, Machupo virus, and Lujo viruses have been associated with person-to-person spread.

TABLE 5.3 Characteristics That Affect Virion Stability

Factor	Characteristic
Virion	Type of nucleic acid (DNA is more stable than RNA)
	Sensitivity of viral proteins to pH changes
	Presence/absence of envelope (envelope is susceptible to detergents)
	Sensitivity to damage from ultraviolet light
	Strain of virus
	Adsorption to other materials
	Particle size
	Aggregation of virions
Environment	Temperature
	pH
	Humidity
	Seawater/freshwater/distilled water
	Amount and type of organic matter
	Presence of other organisms
	Salinity
	Presence of enzymes or degrading factors
	Type of surface/medium

are larger in size, about 20 µm, and therefore tend to only be spread short distances before they succumb to gravity and fall out of the air (Fig. 5.9). At 5 µm or less, aerosolized particles remain airborne for much longer periods of time, and the evaporation of liquid from aerosols creates smaller particles that can persist in the air for an extended period of time. Some viruses are better protected from inactivation within droplets. Aerosols, being smaller, generally have greater success in reaching the lower respiratory tract.

For airborne viruses, humidity and temperature often play a role in the persistence of the virion in the environment. It has been shown for several enveloped respiratory viruses, including influenza A virus, measles virus, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome (MERS)-CoV, that lower temperature and humidity are more conducive to maintaining airborne vir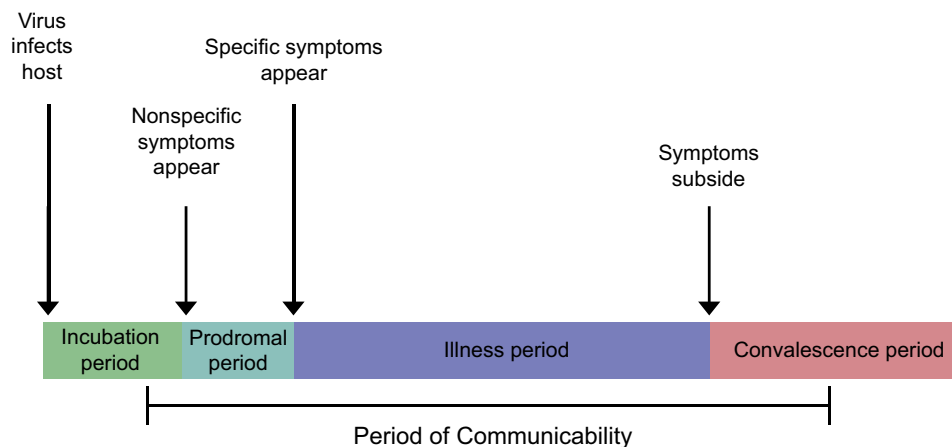ions. Virions are inactivated faster at higher temperatures and humidity, and droplets tend to fall out of the air more readily with higher humidity. On the other hand, nonenveloped viruses like rhinovirus and adenovirus remain infectious longer in higher-humidity environments. Organic matter, such as proteins and carbohydrates derived from mucus or aerosolized fecal matter, can also slow the inactivation of viruses within droplets or aerosols. Other viruses are sensitive to light, primarily the ultraviolet component.

5.4 PATTERNS OF INFECTION

A host typically goes through four stages of disease development when it is infected with a virus (Fig. 5.10). The **incubation period** is the time between when the virus initially infects the host and when symptoms appear. For example, the incubation period of rhinovirus, a cause of the common cold, tends to be about 1–3 days. The incubation periods of well-known viruses are listed in Table 5.4.

The **prodromal period** occurs after the incubation period and is when symptoms first appear. These tend to be nonspecific, mild symptoms that are not clinically indicative of the type of virus, such as malaise, muscle aches, or a low-grade fever. During this period, however, the virus is replicating quickly within the host. The **illness period** occurs when specific symptoms of the disease occur. At this point, the virus is multiplying to high levels and the immune system has been activated, but the response takes time. In **immunocompetent** hosts with functioning immune systems, infected cells will eventually be eliminated and the amount of virus within the host will decline. At this point, the symptoms of the disease subside as the host begins feeling better, having entered into the **convalescent period**. This period may last for days or months, depending upon the severity of the infection.

FIGURE 5.9   **Respiratory droplets.** A sneeze transmits liquid droplets, seen here, that can directly transmit viruses from person to person. *Photo courtesy of CDC/James Gathany.*

FIGURE 5.10   **Stages of disease development.** It takes time for symptoms to appear after a virus infects a host. This period is known as the incubation period. The prodromal period begins when nonspecific signs of illness appear. The appearance of infection-specific symptoms marks the beginning of the illness period. The convalescence period begins when specific symptoms subside. The period of communicability is the range in which a person is infectious and can transmit the virus to a new host. This may include before symptoms appear or after they have subsided.

TABLE 5.4 Incubation Period and Period of Communicability for Selected Human Viruses

| Virus	Average incubation period (range)	Period of communicability
Rhinovirus	~24 h (1–3 days)	24 h before to 5 days after symptoms begin
Influenza A virus	2 days (1–4 days)	24 h before to 5–10 days after symptoms begin
Variola virus (smallpox)	7–17 days	24 h before fever begins until disappearance of all scabs
Ebola virus	8–10 days (2–21 days)	Infectious as long as blood or secretions contain the virus
Measles virus	10–12 days	5 days before to four days after onset of rash
Rubella virus	14 days (12–23 days)	1 week before until at least 4 days after rash appears
HIV	2–4 weeks	Early during infection and continues indefinitely
Mumps virus	16–18 days (12–25 days)	1–2 days before until 5 days after salivary gland swelling
Hepatitis A virus	28 days (15–50 days)	Last half of the incubation period to a week into jaundice (skin yellowing)
Hepatitis C virus	6–9 weeks (2 weeks–6 months)	1+ week before symptoms and continues indefinitely
Hepatitis B virus	~4 months (1.5–6 months)	Weeks before onset of symptoms and continues indefinitely

The duration of each period of disease can vary depending upon the virulence of the pathogen, the site of infection, and the strength of the host immune system. The period of **communicability**, when a person is contagious and able to spread the virus to new hosts through virion shedding, will also vary depending upon the virus and can even include part of the incubation period, when symptoms are not yet present, all the way into convalescence (Table 5.4). For example, influenza is contagious from 1 day *before* symptoms arise until about a week after becoming sick. Ebola virus is communicable in breast milk and semen for weeks to months during the convalescent period.

The replication and persistence of a virus within a host generally follow one of two different patterns of disease. In an **acute infection**, the virus replicates rapidly within the host and is spread to other individuals, but the immune system clears the virus, generally within 7–10 days. Epidemics are most often caused by viruses that cause acute infection. Some acute infections are **inapparent** or **subclinical**, meaning that they produce no symptoms of disease, although the virus still replicates and activates the immune system. Spread to other hosts can still occur with inapparent acute infections. This is different from an unsuccessful infection in which the virus is not able to successfully replicate within a host and does not establish infection, or an abortive infection in which the virus enters susceptible cells but cannot complete replication, usually due to the absence of a protein in the infected cell required for replication.

On the other hand, **persistent infections** occur when the host immune system is unable to effectively clear the virus, but the virus does not replicate to levels that kill the host. Persistent infections often last for the lifetime of an individual and occur for a variety of reasons. Viral proteins can modulate the immune response, and certain viruses, including HIV, infect immune cells and interfere with their proper functioning. Persistent infections can also result from the production of **defective interfering (DI) particles**. DI particles are virions that are created during the replication process but contain incomplete or deleted genomes. Although these are defective, they are still released from the cell and act as a sponge to sequester antibodies. Although the mechanism is unknown, they also interfere with the apoptosis of infected cells, which can lead to a persistent state. The production of DI particles is more common in RNA viruses. Finally, certain organs of the body, including the brain, have highly controlled mechanisms to safeguard against cellular damage caused by inflammation. Viral infection of these tissues may lead to persistent infections due to the protection of these cells against apoptosis.

Persistent infections can also result from viral **latency**, a state in which the virus becomes dormant within host cells. A hallmark of all herpesviruses is that they establish latency. For example, varicella zoster virus causes chickenpox upon primary infection of an individual, but the virus is never completely cleared by the immune system. Instead, it becomes latent in the sensory neurons of the individual. Although the genome persists in the neurons, new virions are not made, and a separate latency gene program is expressed. The virus is largely undetected by the immune system during latency. Later in life, **reactivation** from latency may occur, at which point the virus switches on a productive infectious cycle. Varicella zoster virus reactivation causes the painful skin rash known as shingles. Latency and reactivation will be discussed in more detail in Chapter 13, "Herpesviruses."
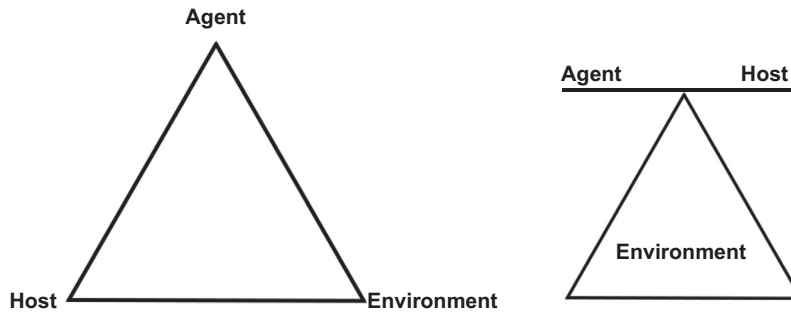
FIGURE 5.11 **Epidemiologic triad model.** The epidemiologic triad model is used to represent how infectious diseases are caused and spread. It illustrates that for infection to occur, an external agent and susceptible host must be brought together by the environment. This can also be thought of as a balance between agent and host factors within an environment.

An unusual variation of persistent infection occurs with **slow infections**. As the name suggests, these viruses can take years to reach a symptomatic phase (if one ever occurs). HIV establishes a slow infection: without antiretroviral drugs, it takes around 8–10 years for an individual to progress to a stage of disease where symptoms are apparent. In this case, symptoms arise as a result of opportunistic infections due to immunosuppression. JCPyV is a very common virus, infecting around half of the general population. JCPyV establishes a slow (and possibly latent) infection in kidney cells. It can reactivate in immunosuppressed individuals to cause progressive multifocal leukoencephalopathy, a brain disease with a high mortality rate that damages the white matter of the brain.

5.5 EPIDEMIOLOGY

Epidemiology is the study of how diseases, including those caused by viruses, spread throughout a population. In fact, the word "epidemiology" means "the study of what falls upon a people." Epidemiology is the field that studies the spread of noninfectious and infectious diseases, with a goal of identifying how diseases occur and can be controlled. Epidemiologists are the detectives of the public health world: during a disease outbreak, they determine how a disease is being transmitted from person to person and establish **control measures** that interrupt the continued transmission of the pathogen.

Within a population, infections can be classified based upon their frequency of occurrence. A **sporadic** disease occurs infrequently and without a consistent pattern. A single case of hantavirus in Nevada would be considered sporadic in nature. **Endemic** refers to the usual presence of a disease in a population at any given time. It is not necessarily a desired level, but it is the norm for a particular area. For example, during a normal September, 3.5 out of every 1000 people in the United States present with symptoms of rhinovirus. An **epidemic** occurs when there are clearly more cases of disease in a particular area than are expected during endemic periods. This is also referred to

as an **outbreak**. From August 2014 through January 2015, 1153 people in 49 US states and the District of Columbia contracted enterovirus D68; only small numbers had been previously reported each year. When an epidemic spreads throughout several countries or the world, it is referred to as a **pandemic**. A major pandemic caused by viruses was the 1918 "Spanish Flu," which is estimated to have killed 50 million people worldwide in the course of months.

5.5.1 Causation of Disease

Assuming that diseases do not occur completely randomly, models are helpful in understanding how viral diseases are caused and spread. The **epidemiologic triad** model consists of three factors: an external **agent**, a susceptible **host**, and an **environment** that brings the host and agent together. This can be represented as a triangle or as a balance (Fig. 5.11).

In this model, *agent* refers to the pathogen and its characteristics that could affect its ability to be spread throughout a population. For instance, how is the pathogen transmitted? How stable is it in the environment? Does it have enhanced virulence factors? Is it susceptible to current antiviral drugs? On the other hand, *host* refers to the human that may come into contact with the agent. The presence of the agent is required for disease to occur, but coming into contact with the agent does not necessarily mean that disease will occur in the host. There are often intrinsic host factors that impact whether disease will occur, including the age and sex of an individual; the immune status of an individual (immunocompetent or immunocompromised); whether or not the person is malnourished; and if the person's behaviors are more likely to expose them to the agent. The *environment* refers to the extrinsic factors that affect whether or not the host will come into contact with the agent. These include socioeconomic factors (proper sanitation, crowding, availability of health services), biological factors (presence of vectors that transmit the agent, other animals that spread the virus), and physical factors (climate, physical environment). For disease to occur, the environment brings together the agent and a susceptible host.

5.5.2 Chain of Infection

The specific details of the epidemiologic triad model can be elaborated upon by examining the factors found within the **chain of infection**: transmission of the *agent* to the host occurs when the agent leaves its *reservoir* through a *portal of exit*, is conveyed by a *mode of transmission*, and enters a *susceptible host* through a *portal of entry* (Fig. 5.12).

Since viruses cannot reproduce outside of a host, humans are most often the reservoirs of human viruses. Some viruses replicate exclusively in humans, including smallpox or polio, while other viruses are able to infect humans and other animals. An example is influenza A viruses, which can infect humans, waterfowl, pigs, and other animals. A **zoonosis** is an infectious disease that can be transmitted from an animal to a human. HIV, Ebola virus, MERS-CoV, and SARS-CoV are examples of viruses that are thought to have been initially transmitted into the human population from animal hosts.

A **carrier** is a reservoir that can transmit the pathogen but shows no symptoms of the infection. This can occur with healthy hosts that are asymptomatic, or because a person has been infected but is still within the incubation period of the illness, before symptoms appear. Similarly, people in the convalescent period may also be capable of transmitting the disease, even though their symptoms have subsided.

Within the chain of infection, the agent leaves its reservoir through a portal of exit. As described in detail in Section 5.3, viruses commonly leave their reservoir hosts in respiratory secretions, urine, feces, or blood. The virus is conveyed through a **mode of transmission**, which can be through direct or indirect means. **Direct transmission** refers to the transfer of the virus by direct contact or droplet spread. Skin-to-skin contact, sexual intercourse, or kissing would be considered direct contact, while droplet spread includes the transmission of virions in respiratory droplets that are sneezed or coughed out of one person and immediately enter the respiratory tract of another person. **Indirect transmission**, on the other hand, requires the presence of an intermediary between hosts. In comparison to droplet spread, which passes directly from one person to another, airborne transmission of viruses carried by dust or aerosolized particles that remain suspended in the air for long periods of time are considered indirect modes of transmission (see Section 5.3 for a review of droplets vs aerosolized particles). **Vehicles** refer to nonliving physical substances—such as food, water, blood, or inanimate objects (fomites)—that can indirectly transmit virions. **Vectors** are living intermediaries that can also transmit viruses. Mosquitos, fleas, and ticks are examples of vectors. Since these are arthropods, the terms **arbovirus** is used to denote **ar**thropod-**bo**rne viruses. "Arbovirus" is a general categorization term, however, and is not a taxonomical term (eg, Flaviviridae).

The agent (virus) is transmitted to and enters a subsequent host through a portal of entry. As described in Section 5.1, examples of portals of entry include the respiratory system,
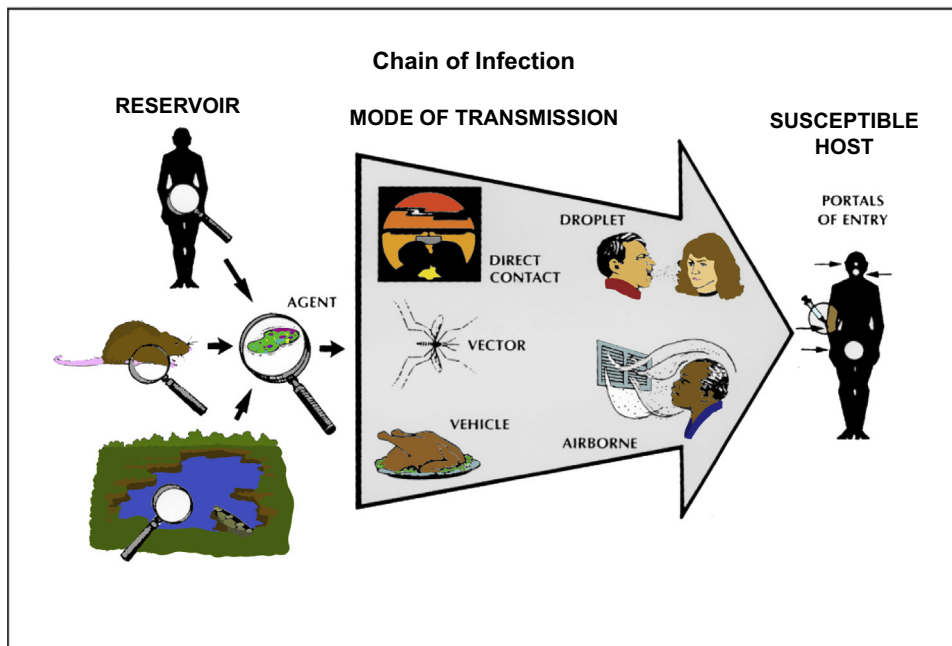
FIGURE 5.12 Chain of infection. The chain of infection represents that an infectious agent leaves its reservoir through a portal of exit, is conveyed by a mode of transmission, and enters a susceptible host through a portal of entry. Epidemiologists identify and examine each step in order to institute control measures that prevent further transmission of the virus. *Reproduced from Centers for Disease Control and Prevention, Updated May, 2012. Principles of Epidemiology in Public Health Practice, third ed. Department of Health and Human Services, Atlanta, GA, US.*

gastrointestinal system, or skin. The susceptibility of the host will depend upon those host factors described above, including age, sex, nutritional status, and immune status.

Identifying the factors involved at each step within the chain of infection allows epidemiologists to devise **control measures** that interfere with the transmission of the virus from the reservoir to a susceptible host (Table 5.5). These measures can be instituted at any point in the chain but are most often directed at controlling/eliminating the virus at the source, preventing the transmission of the virus, protecting portals of entry, and increasing host defenses.

The spread of a virus can be interrupted immediately by preventing the virus from leaving the infected individual. Antiviral drugs are available against HIV, HSV, and certain strains of influenza, and the use of antiviral drugs can be effective in reducing viral load and transmission of the virus, even if the host is not cured of the disease. Those coming into direct contact with infected individuals, such as hospital employees, must also be diligent about handwashing and sterilization measures. For some zoonotic infections, infected animal hosts can be removed or relocated. In other cases, infected patients can be isolated from other individuals to control the direct transmission of the virus. During the 2014 Ebola outbreak, infected individuals were quarantined in an attempt to prevent further transmission of the virus.

Other control measures attempt to interrupt the indirect transmission of the virus. For example, ventilation systems can be modified to prevent airborne transmission, waste water can be treated to kill viruses, clean drinking water can be provided, or insect spraying programs can be instituted to reduce vector populations. For viruses that are transmitted through the fecal–oral route, the environment can be rearranged to prevent transmission.

If the reservoir and environment cannot easily be modified, portals of entry can be protected to prevent infection of the host. Appropriate precautions and proper personal protective equipment (PPE), such as gloves or safety glasses, can be used to protect portals of virus entry. Other physical barriers can be instituted: bed nets can protect infection by mosquitos, and wearing long pants and using insect repellent can prevent interaction with mosquitos, fleas, and ticks.

The epidemiologic triad model requires the interaction of the agent and host in an environment that brings the two into contact, but this does not mean that infection will necessarily occur. A susceptible host is required, and control measures to increase host immune defenses can interrupt the chain of infection. Decreasing malnutrition can positively affect the immune system, but the majority of viruses that cause disease have evolved mechanisms to infect individuals with perfectly functional immune systems. Vaccination is by far the most effective means of preventing susceptibility to these pathogens. As will be discussed in more detail in Chapter 6, "The Immune Response to Viruses," vaccination works by exposing an individual to noninfectious parts of a pathogen to prepare the immune system for infection with the actual pathogen. Vaccination can protect the individual, but it can also protect a population through **herd immunity** (Fig. 5.13). If a large enough

TABLE 5.5 Examples of Some Recommended Control Measures for Preventing MERS-Coronavirus Transmission in U.S. Hospitals

Component	Recommendation
Patient placement	Room for isolating airborne infections
Personal protective equipment (PPE)	• Gloves • Gowns • Eye protection (goggles or face shield) • Fitted respiratory face mask (respirator)
Hand hygiene	• Healthcare personnel should perform hand hygiene frequently, including before and after all patient contact, contact with potentially infectious material, and before putting on and upon removal of PPE, including gloves. • Healthcare facilities should ensure that supplies for performing hand hygiene are available.
Environmental infection control	Follow standard procedures, per hospital policy and manufacturers' instructions, for cleaning and/or disinfection of environmental surfaces and equipment, textiles and laundry, and food utensils and dishware.
Monitoring and management of potentially exposed personnel	Healthcare personnel who care for patients with MERS-CoV should be advised to monitor and immediately report any signs or symptoms of acute illness to their supervisor or a facility designated person (eg, occupational health services) for a period of 14 days after the last known contact with the sick patient.

From Interim Infection Prevention and Control Recommendations for Hospitalized Patients with Middle East Respiratory Syndrome Coronavirus (MERS-CoV). 2014, Centers for Disease Control and Prevention. http://www.cdc.gov/coronavirus/mers/infection-prevention-control.html.
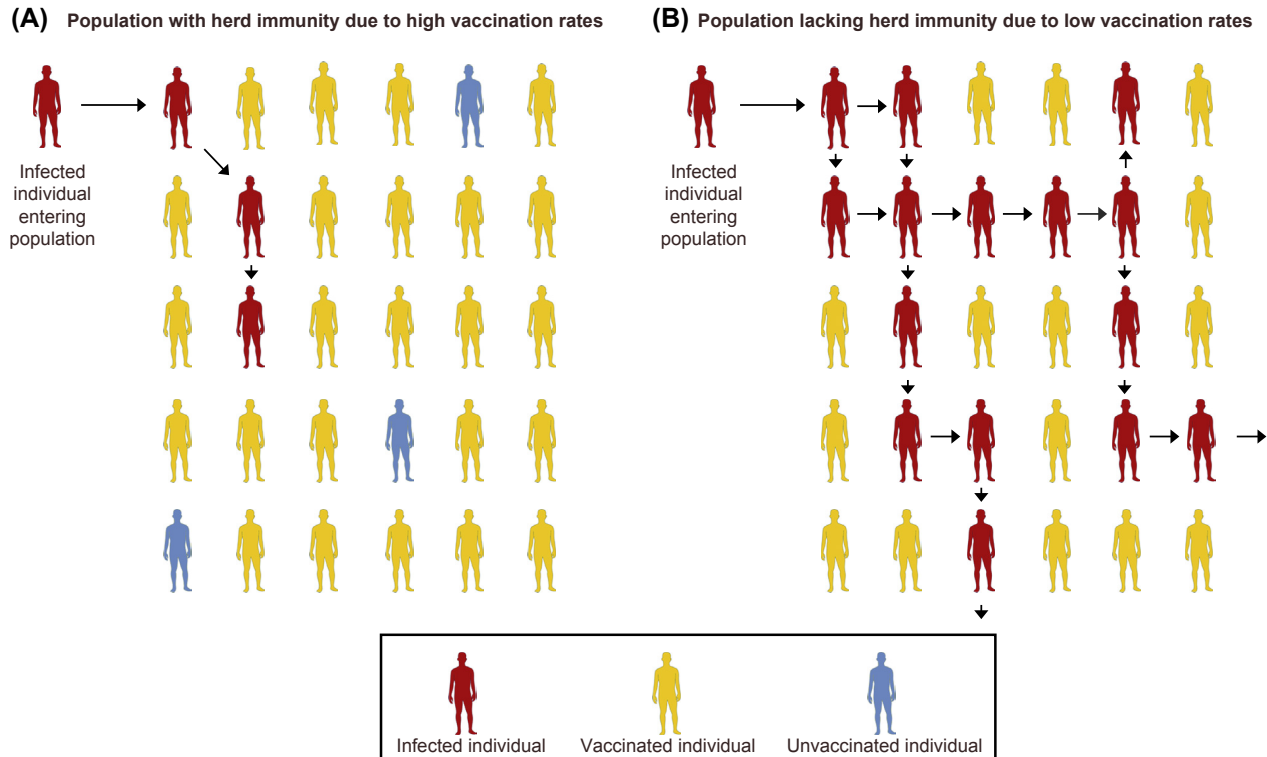
FIGURE 5.13   Herd immunity. (A) If a high proportion of the population is vaccinated against a pathogen, then transmission of the pathogen will soon cease due to lack of susceptible hosts. Note that herd immunity is able to protect those individuals who are unable to be vaccinated because they are too young or immunocompromised (in blue). (B) If a population does not have high vaccination rates, however, then the pathogen continues to easily spread throughout the population.

proportion of the population is vaccinated, then an infected individual may not come into contact with any susceptible hosts and the chain of infection will be terminated. Smallpox, caused by the variola virus, was eradicated from the human population by vaccinating any individuals that came into contact with an infected person. Eventually there were no new susceptible hosts for the virus, and it died out. Herd immunity is effective in preventing epidemics, but a virus is still able to cause an outbreak if a specific population within the herd chooses to not vaccinate its individuals. This also compromises the individuals within the herd that were unable to receive the vaccine due to medical reasons, such as allergy or immunosuppression.

5.6   EPIDEMIOLOGICAL STUDIES

An orderly examination of all the facts surrounding an outbreak is required for epidemiologists to accurately investigate the variables within the chain of infection. Epidemiologists also determine the **morbidity** (rate of illness) and **mortality** (rate of death) associated with an illness. The **incidence** of the disease refers to the number of *new* cases within a population during a specified time, while the **prevalence** of a disease refers to the total number of individuals with the disease at that time. For example, the US CDC

reports that in 2012, the incidence of HIV in the United States was 18.4 cases per 100,000 people, while the prevalence of the disease was 342.1 cases per 100,000. In other words, 18.4 new cases were diagnosed and 342.1 people were living with HIV in 2012, per 100,000 people.

Before counting cases, however, an epidemiologist must determine what qualifies as a case of the illness. Epidemiological studies rely upon a **case definition** to determine whether or not a person has a particular disease. The case definition is a set of clinical and laboratory criteria that rely upon the symptoms the person presents with and the results of virus-specific blood tests. For a specific outbreak, limitations on the time and location may also be included within the case definition. Nationally and internationally, use of a standard case definition allows for proper diagnosis and also ensures comparability among different hospitals and locations. Classification of results can categorize the case as suspected, probable, or confirmed (Fig. 5.14).

Case definitions can change over time and often do so as more information about the illness becomes available. Case definitions can also possess "loose" or "strict" requirements. A sensitive ("loose") case definition is used for containment of viruses with potentially serious effects upon public health; this type of case definition is not

Measles (Rubeola): 2013 Case Definition

Clinical Description
An acute illness characterized by
  • Generalized, maculopapular rash lasting ≥3 days;
  • Temperature ≥101°F or 38.3°C; **and**
  • Cough, coryza, or conjunctivitis.

Case Classification
Probable
In the absence of a more likely diagnosis, an illness that meets the clinical description with:
  • No epidemiologic linkage to a laboratory-confirmed measles case; **and**
  • Noncontributory or no measles laboratory testing.

Confirmed
An acute febrile rash illness with:
  • Isolation of measles virus from a clinical specimen; or
  • Detection of measles virus-specific nucleic acid from a clinical specimen using polymerase chain reaction; or
  • IgG seroconversion or a significant rise in measles IgG antibody; or
  • A positive serologic test for measles IgM antibody not explained by MMR vaccination during the previous 6-45 days; or
  • Direct epidemiologic linkage to a case confirmed by a method above.

FIGURE 5.14 **Measles (Rubeola) case definition.** A case definition is a set of clinical and laboratory criteria to classify an potentially infected person. In this CDC case definition, a probable case of measles virus is an illness that meets the clinical criteria but has not been confirmed with laboratory testing. A confirmed case occurs when a person has a rash and one of several confirmatory laboratory tests showing the presence of the measles virus or a recent immune response against it.

very specific, in an attempt to include all possible cases of the virus even if other viral infections may fall within the case definition. When trying to determine the specific cause of an outbreak, however, epidemiologists employ a strict case definition that will only confirm those infected with the particular pathogen. For instance, an epidemiologist studying the cause of a Norwalk virus outbreak, which is a fecal–oral disease that causes diarrhea, will not want to include diarrhea as the only requirement—many other infectious and noninfectious diseases also cause diarrhea as a symptom. Loose and strict case definitions may overestimate and underestimate the total number of cases, respectively, but are necessary for containing serious viral outbreaks or determining the definitive source of an infection.

In the United States and in many countries around the world, state and national public health departments must be notified when a patient is diagnosed with certain infectious and noninfectious conditions. This surveillance system is used to monitor disease trends, identify populations at high risk, formulate control measures, and create public health policies. The list of notifiable viral diseases is listed in Table 5.6.

Just like reporters, epidemiological studies seek to identify the 5 W's of the epidemiological story: What (the agent), Who (the person infected), Where (the location), When (the time), and Why/How (the causes and modes of transmission). These are also known as **epidemiological variables**. Epidemiological studies are divided into **descriptive** and **analytic studies**. Both types of study start with the agent,

TABLE 5.6 Notifiable Infectious Viral Diseases

Viruses
Arboviral diseases
Chikungunya virus
Eastern equine encephalitis virus
Powassan virus
St. Louten encephalitis virus
West Nile virus
Western equine encephalitis virus
Dengue virus
Hantavirus
Hepatitis A, acute
Hepatitis B, acute
Hepatitis B, chronic
Hepatitis C, acute
Hepatitis C, past or present
HIV
Influenza-associated pediatric mortality
Measles (Rubeola)
Mumps
Novel influenza A virus infections
Poliovirus infection
Rabies (animal)
Rabies (human)
SARS coronavirus
Variola (smallpox)
Varicella (chickenpox)
Varicella deaths
Viral hemorrhagic fevers
Crimean–Congo hemorrhagic fever virus
Ebolavirus
Lassa virus
Lujo virus
Marburg virus
Guanarito virus
Junin virus
Machupo virus
Sabia virus
Yellow fever virus
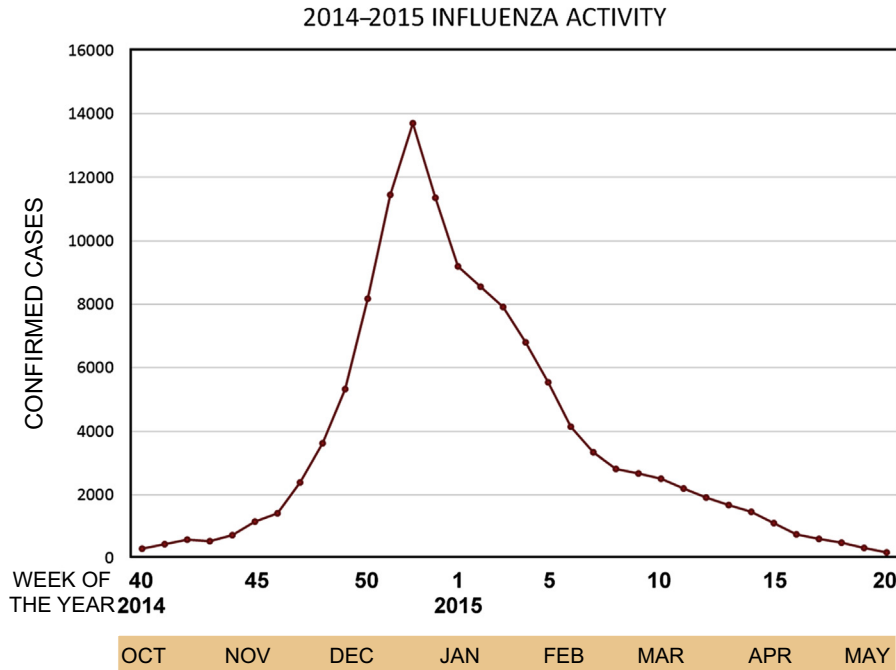
FIGURE 5.15 2014–15 Confirmed cases of seasonal influenza. Many epidemiological variables affect the transmission of viral infection and are worthwhile to consider while analyzing disease transmission. This graph shows that in 2014–15, laboratory-confirmed cases of influenza were at their highest in the United States from November to March, peaking in December of 2015. *Data obtained from FluView (internet), Centers for Disease Control and Prevention, 2015. Available at: http://www.cdc.gov/flu/weekly.*

defined by the case definition, and identify the who, where, and when (host, location, and time). In addition, analytic studies try to determine the cause and transmission.

Time refers not only to the hour and minute of the day, but also to the season and time of year. Some diseases occur more frequently during a particular time of the year; for example, influenza viruses peak during the winter months (Fig. 5.15), when drier weather supports the increased dissemination of aerosolized particles in the environment and people congregate inside more often. In contrast, the incidence of diseases transmitted by mosquitoes, such as West Nile virus or eastern equine encephalitis virus, is higher at the end of the summer when mosquito populations are highest. Other viral infections show no association with season or time of year, such as hepatitis B virus, HIV, or HPV. Determining the typical yearly or seasonal pattern of viral infections is important in creating a baseline that can be used to compare future occurrence of the disease or monitor the effectiveness of control measures. Graphing the time of the incident versus the occurrence of symptoms can also be useful in assessing the incubation period of the virus, which can be helpful in identifying the specific virus.

Place refers to the local location of the case as well as the larger geographic location. A gastrointestinal virus outbreak may occur at a restaurant (the place), suggesting that the food may have been involved in the transmission of the virus. A person presenting with neurological manifestations

in a rural location may suggest different viruses than in a big city—for example, rabies transmission is much more likely in areas where wildlife is prevalent. It would also be important to note that a patient presenting with hepatitis recently traveled to a remote location in South America. This also highlights that, because of viral incubation periods, the location and timing of symptoms does not always correlate with when infection occurred (Fig. 5.16).

Details concerning the *person* (host) can affect the chain of infection and are important to consider in epidemiological studies. Almost every health-related event varies with age because it is a factor in exposure, immune status, and physiological response. For example, older individuals are much more likely to reactivate varicella zoster virus, leading to shingles, whereas children are most likely to show symptoms of the "childhood diseases" to which adults have already become immune. Influenza A virus causes higher morbidity and mortality rates in young children and the elderly.

Many other personal attributes can contribute to infection. The sex of the individual can sometimes be a consideration—cervical cancer caused by HPV will not occur in men—and being part of different genetic, cultural, or social groups can contribute to the exposure of an individual to a particular virus. The socioeconomic status of an individual (income, education, and occupation) can also play a role in exposure to the virus and access to medical care.

(A) Reported cases of SARS in the United States through 11/3/2004: by case definition and state of residence

Location	Total Cases Reported	Total Suspect Cases Reported	Total Probable Cases Reported
Alaska	1	1	0
California	29	22	5
Colorado	2	2	0
Florida	8	6	2
Georgia	3	3	0
Hawaii	1	1	0
Illinois	8	7	1
Kansas	1	1	0
Kentucky	6	4	2
Maryland	2	2	0
Massachusetts	8	8	0
Minnesota	1	1	0
Mississippi	1	0	1
Missouri	3	3	0
Nevada	3	3	0
New Jersey	2	1	0
New Mexico	1	0	0
New York	29	23	6
North Carolina	4	3	0
Ohio	2	2	0
Pennsylvania	6	5	0
Rhode Island	1	1	0
South Carolina	3	3	0
Tennessee	1	1	0
Texas	5	5	0
Utah	7	6	0
Vermont	1	1	0
Virginia	3	2	0
Washington	12	11	1
West Virginia	1	1	0
Wisconsin	2	1	1
Puerto Rico	1	1	0
Total	**158**	**131**	**19**

(B) Reported cases of SARS in the United States through 11/3/2004: by high-risk area visited

Area	Count*
Hong Kong City, China	45
Toronto, Canada	35
Guangdong Province, China	34
Beijing City, China	25
Shanghai City, China	23
Singapore	15
China, mainland	15
Taiwan	10
Anhui Province, China	4
Hanoi, Vietnam	4
Chongqing City, China	3
Guizhou Province, China	2
Macoa City, China	2
Tianjin City, China	2
Jilin Province, China	2
Xinjiang Province	1

FIGURE 5.16 **2004 United States cases of severe acute respiratory syndrome (SARS) by location of diagnosis and travel area.** In the 2004 outbreak of SARS, caused by the SARS coronavirus, case patients were distributed throughout the United States (A). A clearer correlation with *place* could be determined when looking at the location to which each individual recently traveled: the majority of infected individuals traveled to areas of China, Singapore, or Taiwan (B). *Modified from Tables 1.3 and 1.4 of Centers for Disease Control and Prevention, Updated May, 2012. Principles of Epidemiology in Public Health Practice, third ed. Department of Health and Human Services, Atlanta, GA, US.*

Descriptive studies are effective in chronicling patterns and developing hypotheses as to the cause of an illness or outbreak. In addition to the *what, when, where*, and *who* epidemiological variables, analytic studies are also concerned with the *why/how* of the illness. A hallmark of analytic studies is the presence of a comparison (control) group that can be used to generate baseline data to which the outbreak or illness can be compared. With a comparison group, statistical analyses can be performed to determine a cause with good certainty.

Epidemiological studies fall into two general categories: **experimental** and **observational**. Experimental studies are planned, controlled studies; a clinical trial to test new vaccines that enrolls participants into the study, randomly assigns them into one of three groups (vaccine A, vaccine B, or placebo), and then gathers data is an experimental study. As the name implies, observational studies involve the observation of subjects and subsequent recording of data. In comparison to experimental studies, the epidemiologist does not have any influence over what exposure the participant receives. Observational studies are more common in epidemiology than experimental studies.

Observational studies fall into three categories: **cohort studies**, **case-control studies**, and **cross-sectional studies**. Cohort studies are similar to experimental studies in that two groups are compared in real time, except that, being an observational study, the epidemiologists do not assign participants to **cohorts**, or groups. Instead, they allow the natural course of things to proceed, tracking whether or not the two cohorts have different results. An example of a cohort study would be to observe consistent users of hookah pipes, a water pipe used to smoke flavored tobacco. One cohort of participants uses individual disposable plastic mouthpieces on their pipes, while the other group uses the attached metal mouthpiece. This study might observe whether HSV-1 transmission is more common in those using the metal, shared mouthpieces compared to those who each have their own disposable plastic mouthpiece. If this were an experimental study, the epidemiologists would have assigned each participant to a specific group, either the group that uses the shared mouthpiece or the disposable plastic mouthpiece.

A second type of observational study, the case-control study, is always retrospective, meaning that it analyzes past events. A case-control study happens after an event (for example, a viral outbreak) has occurred. Being that the outbreak has already happened, a control group is assembled retroactively with a group of similar people

in a similar place as the outbreak to see if, in fact, the "outbreak" was different from the norm. An example of a case-control study would involve the infection of several people with hepatitis C virus at a tattoo parlor. After noting that all the **case patients** received their tattoos from one tattoo artist, epidemiologists retroactively enrolled a group of people that received tattoos from the other tattoo artist at the parlor. The control group allows them to have a baseline group to determine the typical infection rate. In this case, it was determined that one of the tattoo artists, but not the other, was improperly sterilizing tattoo equipment.

The final type of observational study is the cross-sectional study. In this type of study, data are gathered from a random sample of individuals at one time (a "cross section" of the population) and correlations are made. For example, a cross-sectional study might find that a high proportion of those individuals that have liver scarring have hepatitis C infection. Although the obvious conclusion seems to be that the liver scarring must be caused by the virus, it is also possible that the scarring makes the liver more susceptible to hepatitis C infection, and that is why these individuals have high rates of both liver scarring and hepatitis C. Because the study compares individuals at only one point in time, cause and effect (causation—the how/why) are difficult to determine. *Correlation does not equal causation*! Therefore, a cross-sectional study is not effective as an analytic study, but they are used routinely for descriptive studies.

Since both the cohort and case-control study have comparison groups, they would be considered analytic studies. Cross-sectional studies often do not have a comparison group as a control and are therefore most often carried out as descriptive studies.

SUMMARY OF KEY CONCEPTS

Section 5.1 Portals of Virus Entry

- For successful infection to occur, a host must come in contact with the virus (accessibility). The cells must express the cell surface receptors used by the virus (susceptibility), and they must also contain all the internal requirements for viral replication to proceed (permissivity).
- Portals of entry are the locations through which viruses gain entry into the body. Unless delivered directly into the tissues through a mosquito bite or needle, most viruses first interact with the epithelium at the site of entry.
- The majority of viruses enter humans through inhalation into the respiratory tract. The gastrointestinal tract, genital tract, skin, blood, and eyes are also points of entry.
- Acid-labile viruses break down within the low pH of the stomach, while acid-resistant viruses are resistant.
- Some viruses are able to be transmitted through organ transplants or through the placenta to a developing fetus.

Section 5.2 Dissemination Within a Host

- Localized viral infections replicate at the initial site of infection. Systemic infections spread to additional areas throughout the body, generally through hematogenous or neurotropic spread.

Section 5.3 Portals of Virus Exit

- Viruses are shed through portals of exit to infect new hosts. For localized infections, this is generally at the same location through which the virus entered: viruses that infect the skin are spread through skin-to-skin contact, respiratory viruses are shed within respiratory secretions, and gastrointestinal viruses are shed within aerosolized vomit or diarrhea.
- The stability of virions within the environment is dependent upon many factors, including the type of nucleic acid; the presence of a viral envelope; and the sensitivity of virions to pH, humidity, moisture content, and sunlight.
- Respiratory droplets are larger in size (~20 μm) and are spread only short distances before falling to the ground. Smaller aerosolized particles (<5 μm) can travel extended distances within the air.

Section 5.4 Patterns of Infection

- Upon infection, a host generally passes through four stages of disease: the incubation period, prodromal period, illness period, and convalescent period.
- Acute infections, during which viruses multiply and spread quickly, are often the cause of epidemics.
- Persistent infections result when the immune system is unable to clear the virus from the body. Persistent infections can also result from viral latency or slow infections.

Section 5.5 Epidemiology

- Epidemiology is the study of how disease occurs in populations. Sporadic diseases occur irregularly, while endemic refers to the normal rate of infection. An epidemic occurs when there are more cases than the normal endemic rate. A pandemic is an epidemic that spreads throughout several countries or the world.
- The epidemiologic triad model represents the factors that bring an agent and susceptible host together in a particular environment. There are many factors that affect each component of the model.
- The chain of infection represents how an agent leaves its reservoir through a portal of exit, is conveyed via a mode of transmission, and enters a susceptible host through a portal of entry. Epidemiologists identify the factors involved at these stages in an effort to institute control measures.

Section 5.6 Epidemiological Studies

- Epidemiological studies are divided into descriptive and analytic studies. Both types use a case definition to confirm persons with a case of the disease. Both also analyze the time, place, and persons involved in the chain of infection, but analytic studies use a comparison group to determine the cause of the outbreak.
- Experimental studies are planned ahead of time and participants are randomly assigned to predetermined groups. Observational studies—which fall into cohort, case-control, and cross-sectional studies—acquire data and track cohorts as they occur within normal situations.

FLASH CARD VOCABULARY

Accessibility	Mode of transmission
Susceptibility	Portal of exit
Permissivity	Epithelium
Tropism	Mucosal epithelium
Portal of entry	Respiratory tract
Goblet cells	Neurotropic spread
Alveolar macrophages	Viremia
Phagocytosis	Primary/secondary viremia
Gastrointestinal tract	Shedding
Villi	Viruria
Microvilli	Incubation period
Acid labile	Prodromal period
Acid resistant	Illness period
Fecal–oral route	Convalescent period
Sexually transmitted diseases	Immunocompetent

Continued

FLASH CARD VOCABULARY—Cont'd

Epidermis	Immunocompromised
Dermis	Period of communicability
Subcutaneous tissue	Acute infection
Conjunctiva/conjunctivitis	Persistent infection
Congenital infection	Defective interfering particles
Vertical transmission	Latency/reactivation
Horizontal transmission	Slow infection
Intrapartum transmission	Epidemiology
Transfusion-transmitted infections	Sporadic
Localized infection	Endemic
Systemic infection	Epidemic/outbreak
Hematogenous spread	Pandemic
Epidemiologic triad model	Mortality
Agent	Incidence
Host	Prevalence
Environment	Case definition
Chain of infection	Epidemiological variables
Carrier	Descriptive studies
Zoonosis	Analytic studies
Vehicles	Experimental studies
Vectors	Observational studies
Direct transmission	Cohort studies
Indirect transmission	Case-control studies
Control measures	Cross-sectional studies
Herd immunity	Case patient
Morbidity	

CHAPTER REVIEW QUESTIONS

1. Make a table listing each portal of entry. What defenses does the host have at each location and how are viruses able to successfully bypass them?
2. Norwalk virus causes significant morbidity in developed nations, despite that these countries have clean water supplies. How do you think the virus is transmitted, and why it is so successful?
3. Describe the architecture of the skin and how viruses gain access to each layer and the subcutaneous tissue.
4. How are vertical and horizontal transmission of viruses different from each other?

5. Which viruses are capable of initiating transplacental or intrapartum infections?
6. How do localized infections become systemic infections?
7. Describe how different factors could affect the inactivation of virions within the environment.
8. Draw out the stages of infection after a person is infected with a virus.
9. Your friend walks into class, still sniffling occasionally from a respiratory viral illness. She reassures you that she's "not infectious anymore." You have your concerns. Why?
10. How can persistent infections arise?
11. Describe the difference between endemic and epidemic.
12. Make a list of the three major aspects of the epidemiologic triad model and what factors could affect each aspect in promoting infection.
13. Create a list of control measures that interfere with each variable within the chain of infection.
14. Design a case-control study that attempts to determine the precise food product that was the cause of a viral gastrointestinal illness.

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