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Emerging and Reemerging Viral Diseases

In late spring of 2014, a man from Bourbon County, Kansas, found an engorged tick on his shoulder while working outside on his property. Several days later, he became ill with nausea, vomiting, and diarrhea. The following day, he developed a fever, chills, headache, myalgia, and arthralgia. He was prescribed antibiotics by his doctor for a presumed tickborne bacterial infection. The following morning, his wife found him with reduced consciousness and took him to the hospital, where he was admitted. There they noticed a maculopapular rash and low white blood cell and platelet counts. He continued to decline, dying 11 days after first becoming ill.

A novel virus was isolated from a specimen of the man's blood (Fig. 16.1). The virus, named Bourbon virus after the county in which it was isolated, is in the *Orthomyxoviridae* family and *Thogotovirus* genus. Like influenza virus, another orthomyxovirus, Bourbon virus possesses a segmented –ssRNA genome. This was the first report of a Thogotovirus originating in the Western Hemisphere.

Although all viruses have a source, some viruses seem to randomly appear or reappear in the human population. An **emerging infectious disease (EID)** is defined as a disease caused by a pathogen that has not before been observed within a population or geographic location. Similarly, a **reemerging infectious disease** is caused by an established pathogen that appears in a new geographical location or was once controlled but begins appearing at a higher incidence. A significant number of emerging and reemerging infectious diseases are viral in nature, and they are becoming more frequent. The 2014–16 epidemic of Ebola virus in West Africa, as well as the human immunodeficiency virus (HIV) and past epidemics of yellow fever virus, West Nile virus (WNV), and Nipah virus, among others, emphasize that emerging and reemerging viral diseases can be of great concern for global public health.

16.1 FACTORS INVOLVED IN THE EMERGENCE OF VIRAL INFECTIOUS DISEASES

Many aspects influence the emergence or reemergence of viral diseases by changing the exposure of people to the

virus. These can broadly be divided into human, environmental/ecological, and viral factors (Table 16.1). Three-quarters of emerging or reemerging infectious diseases are **zoonoses**, infectious diseases of animals that are transmitted to humans. Most zoonoses arise from wildlife, although they can also be derived from domesticated animals or through **vectors** such as mosquitoes and ticks. Other viral diseases, such as measles, are reemerging due to the changing susceptibility of the human population to the virus because of reduced immunization rates.

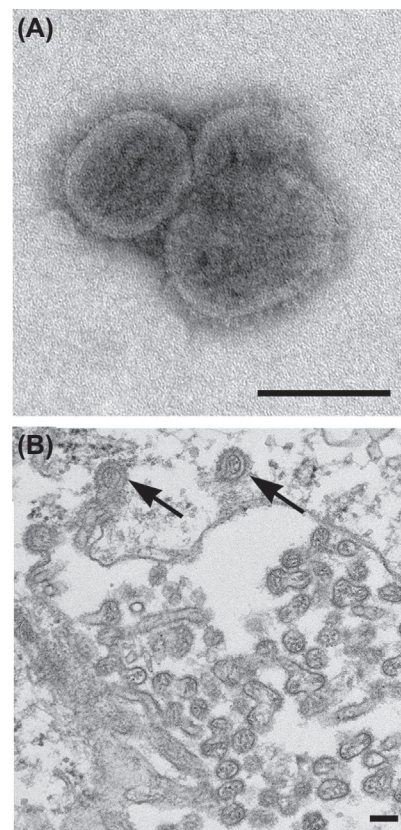


FIGURE 16.1 Bourbon virus, a novel Thogotovirus. Bourbon virus was isolated from a man in Bourbon County, Texas, that had died following a possible tick-borne infection. (A) Electron micrograph of spherical Bourbon virus particles with distinct surface projections. (B) Electron micrographs of cells infected with Bourbon virus show numerous extracellular virions. Arrows indicate virions that have been endocytosed into a cell. Images courtesy of Kosoy, O.I., et al., 2015. *Emerg. Infect. Dis.* 21(5), 760–764.

TABLE 16.1 Factors Involved in the Emergence/ Reemergence of Viral Diseases

Human (including economical, governmental, and societal)	
Population growth	Inadequate public health infrastructures
Urbanization	Lack of access to health care
International travel	Reduced immunization policies
Tourism	Conflicts/wars
Human behaviors	Free trade economies
Human susceptibility to virus	Human invasion of wild animal habitats
Environmental and ecological	
Rainfall accumulation	Wildlife host species richness
Temporary weather patterns	Human encroachment into pristine lands
Long-term climate change	Building of dams, land development
Dew point	Deforestation for farming
Soil moisture	
Viral	
Genomic changes through reassortment, recombination, or mutation	

16.1.1 Human Factors

An abundance of factors related to human behaviors and social systems are pivotal in the emergence or reemergence of viral diseases. Increases in **urbanization**, the process of people living together in towns and cities rather than rural areas, result in denser populations that are subsequently more prone to spreading infectious diseases. This is particularly true in overcrowded urban centers and those that lack adequate sanitary conditions and clean water supplies. **Globalization** is the expansion of economies, populations, and businesses to areas throughout the world. Globalization has facilitated the ability of infectious diseases to spread rapidly between countries through trade and travel. Increased trade between countries can promote the spread of infectious diseases, particularly those found in food or animal products. Illegal activities, such as the trade of bushmeat, also contribute to the spread of infectious diseases. As an example, the U.S. Geological Survey found that bushmeat that had been confiscated at US borders contained novel herpesviruses and retroviruses. The illegal trade of bushmeat is extensive, providing an avenue for zoonoses to be transferred to the human population. In fact, the HIV pandemic may have begun with the acquisition of bushmeat contaminated with simian immunodeficiency viruses.

A notable contribution to globalization is the ability of humans to quickly and easily fly between distant

countries. A person traveling from one country to another can spread infectious diseases in this way, as occurred in the 2003 outbreak of **severe acute respiratory syndrome (SARS)**, which was characterized by severe lower respiratory symptoms, pneumonia, and fever. SARS was later determined to be caused by a novel coronavirus, named **SARS-associated coronavirus (SARS-CoV)**. In this case, the virus initially appeared in November of 2002 in Guangdong Province, China, and was spread by travelers within weeks to over 30 countries in Europe, North America, and other areas of China and Asia. In total, 8098 people were infected, and 774 (9.6%) died. In Guangdong Province markets, the virus was isolated from palm civets, a meat- and fruit-eating mammal with a cat-like appearance that was sold for meat. SARS-CoV was also isolated from civet meat from a restaurant that employed a worker that had contracted SARS. Although the palm civets were the most likely source of SARS-CoV in this outbreak, much higher rates of SARS-CoV were found in palm civets from local markets as compared to palm civets on distant farms. This suggested that the palm civets themselves may have contracted SARS-CoV from another animal source while in the market. The virus has also been identified in horseshoe bats, the likely natural reservoir of this zoonosis.

Imported insects and animals can also carry viruses into new environments. West Nile Virus (Fig. 16.2A) is a mosquito-borne flavivirus that was first identified in Uganda in 1937 and later identified in other parts of Africa, as well as Asia, Europe, and the Middle East. Although mostly asymptomatic, the virus causes fever, body aches, joint pain, vomiting, diarrhea, and rash in about 20% of those infected. Less than 1% of total infected individuals develop encephalitis or meningitis, but 10% of those that develop these neurological effects die.

WNV first emerged in North America in October of 1999, when an outbreak occurred in both humans and birds in New York City. It was found to be most closely related to a strain circulating in geese and humans in Israel. Although the initial source of WNV within the United States is unknown, it is thought that imported birds or mosquitoes—either accompanying their natural avian hosts or as stowaways on international flights—were responsible for introducing the virus to North America. From 1999 to 2014, a total of 41,762 US cases of WNV disease were reported to the Centers for Disease Control and Prevention (CDC). This caused 1765 deaths (4.2% of cases).

WNV normally cycles between mosquitoes (*Culex* species, Fig. 16.2B) and birds, although mosquitoes can also transmit the virus to horses and humans, which are both considered “dead end” hosts because they do not develop high enough viral titers in the bloodstream to continue the transmission cycle to mosquitoes. However, WNV has been found to be transmitted through organ transplantation or

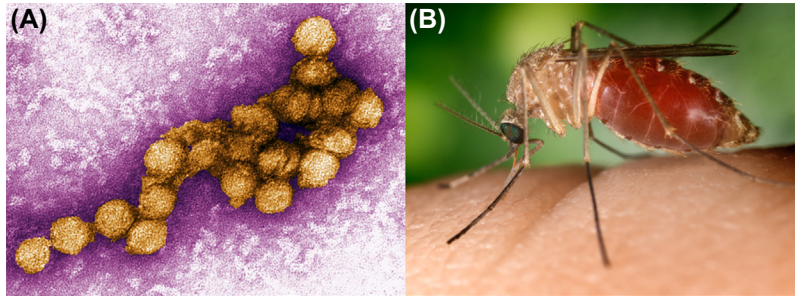


FIGURE 16.2 West Nile virus. West Nile virus (A) is a flavivirus that emerged in the United States in 1999. It is transmitted by *Culex* mosquitoes, such as this engorged female *Culex quinquefasciatus* (B), the primary vector of the virus in southern California and the southeastern United States. Images courtesy of CDC and (A) P.E. Rollin and Cynthia Goldsmith and (B) Games Gathany.

blood transfusions, as well as from mother to child during pregnancy, delivery, or breastfeeding. As a result, nucleic acid testing of the blood supply for WNV began in 2003.

Increased tourism to exotic and pristine areas also puts humans at risk of coming in contact with novel zoonoses. It also exposes native animal populations to human diseases. An **anthroponosis** or **anthroponotic disease** is an infectious disease transferred from humans to other animals. Due to their genetic similarity to humans, great apes such as chimpanzees and gorillas are particularly susceptible to anthroponoses. Chimps have died from human viruses such as respiratory syncytial virus and metapneumovirus, and primatologist Jane Goodall noted in her book *The Chimpanzees of Gombe* that a local outbreak of polio in humans was accompanied by similar symptoms of flaccid paralysis in nearby chimpanzee populations.

Many sociological factors may also contribute to the emergence/reemergence and spread of viral diseases. Some of these factors include inadequate public health infrastructures, a lack of access to vaccinations or reduced immunization policies (see *In-Depth Look*), and political conflict or wars that displace millions of people, creating overcrowded refugee populations without access to basic health care or clean water supplies.

Human behaviors also influence the spread of emerging/reemerging infectious diseases. The popularity of restaurants and partially prepared foods provides an avenue to disseminate foodborne viruses like hepatitis A virus, while importing fruits, vegetables, and nuts from other countries can lead to the widespread distribution of a virus. Sexual activities, body art (tattoos, piercings), and the use of intravenous drugs can spread viruses such as HIV or hepatitis. Religious or spiritual practices can also affect the transmission of viruses. For instance, the touching and handling of deceased individuals has been shown to spread Ebolaviruses, and outbreaks of polio and measles, among others, often occur in religious communities that avoid vaccinations.

Finally, the susceptibility of the human host also plays a role in the ability of a virus to emerge as a human pathogen. The host must possess receptors for the virus and

the intracellular factors required for the virus to replicate. Viruses that are easily combatted by the host immune system will be quickly eliminated, whereas viruses that elicit an internal “cytokine storm” by immune system cells are likely to induce rapid and severe pathology. Immunocompromised individuals, pregnant women, malnourished people, the elderly, and the very young are often more susceptible to infection due to their weaker immune systems.

16.1.2 Environmental and Ecological Factors

Nearly every emerging viral disease can be associated with an environmental or ecological component. The consequences of urbanization and globalization—including but not limited to deforestation, habitat modification, and the use of wild land for farming—impact the emergence and reemergence of potential zoonoses. Increases in the human population have led to the encroachment of humans into animal habitats formerly unoccupied by humans. These circumstances contribute to humans coming in contact with animals with which they would not normally interact, putting them at risk of being exposed to zoonotic viruses that are found in the local wildlife populations. The transfer of zoonotic viruses to humans can occur directly or indirectly. For example, during an outbreak of 276 cases of Nipah virus in Malaysia and Singapore in 1998–99, most infected individuals had contact with sick pigs that were being farmed commercially as livestock and then slaughtered for meat. The pigs contracted Nipah virus from the local bats, which were thought to have spread the virus through urine or by dropping partially eaten fruit, laden with bat saliva, into the pig stalls. The bats may have acquired the fruit from the fruit trees on the farms. Human infection with Nipah virus causes encephalitis, fever, headache, and reduced consciousness. Forty percent of infected individuals died during this outbreak. Interestingly, Nipah virus infection is asymptomatic in bats.

In contrast to the indirect mode of transmission observed in the 1998–99 outbreak in Malaysia and Singapore, transmission of Nipah virus in Bangladesh has occurred directly from bats to humans. The most frequently implicated route

In-Depth Look: Is Measles a Reemerging Disease?

Measles is a respiratory virus (Fig. 16.3A) that causes a fever (as high as 105°F) and a maculopapular rash that covers most of the body (Fig. 16.3B). It is highly contagious, and infection leads to a severe illness that lasts about a week. Infection can cause serious complications, including deafness, encephalitis, blindness, seizures, and pneumonia. Death occurs in 2–3 of every 1000 infected individuals. Worldwide, 20 million people are infected annually, causing over 145,000 deaths each year. It is one of the leading causes of death in young children.

Measles is not a newly emerging disease. The first documentation of infection dates back to the year AD 900 in an account written by a Persian doctor trying to distinguish measles from smallpox. It remains endemic in certain areas of the world, including portions of Europe and Africa. However, vaccination has proven effective in reducing cases of measles and its complications. For example, in the United States, three to four million people contracted measles each year before the vaccine program was initiated in 1963. These infections caused 400–500 deaths, 48,000 hospitalizations, and 4000 cases of encephalitis annually. In 2000, the United States declared that measles had been eliminated from the country, attributable to strong vaccination campaigns.

Unfortunately, measles has been making a comeback in the US in the past decade, imported from foreign countries or from unvaccinated individuals that have visited these countries. Unlike previous occasions when the virus did not meet many susceptible hosts, measles has recently been able to spread locally in the United States because of pockets of individuals that have refused vaccination. Although the vaccine is 97% effective, a small percentage of previously vaccinated individuals have also contracted the disease, further emphasizing the importance of high vaccination rates.

Several large outbreaks have occurred from 2008 to the present (Fig. 16.3C). 2014 saw 668 cases of measles in the United States, the largest number observed since 2000 and more cases than occurred in 1996. As of September 18, 2015, 189 measles cases have occurred in the United States during 2015. Most of these (117) were associated with an outbreak at two Disney theme parks in California. Among 110 infected California residents, 45% were unvaccinated. Twelve were too young to receive the vaccine, but 76% of the unvaccinated individuals declined vaccination due to personal beliefs. The uptick of measles in the United States and other countries in which the virus was previous eradicated emphasize the importance of the measles vaccine and efforts to maintain high immunization rates.

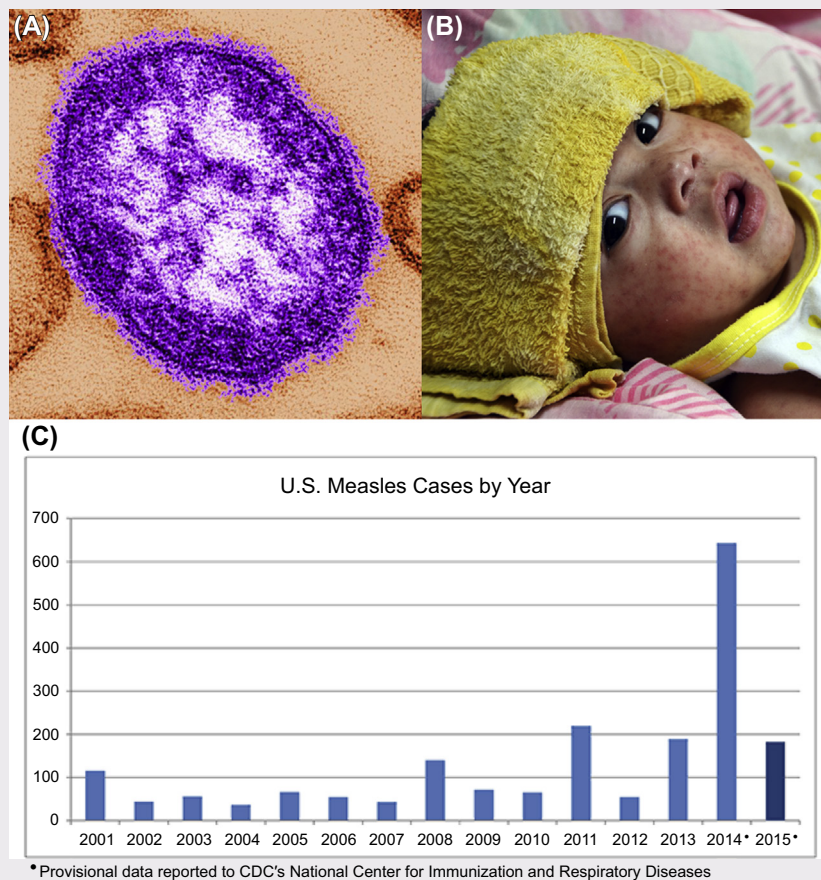


FIGURE 16.3 Reemergence of measles virus. (A) This transmission electron micrograph shows the measles virus, a -ssRNA paramyxovirus. (B) A child in the Philippines capital of Manila in 2014 with the characteristic maculopapular measles rash. (C) Cases of measles have been increasing in the last decade. A record 668 cases of measles were diagnosed in 2014. Images courtesy of CDC and (A) Cynthia S. Goldsmith and William Bellini, PhD (B) Molly Kurnit, MPH and Jim Goodson, MPH, and (C) National Center for Immunization and Respiratory Diseases, Division of Viral Diseases, <http://www.cdc.gov/measles>.

was through the ingestion of fresh date palm sap, which is harvested from date palm trees much in the same way that maple sap is tapped from maple trees to produce maple syrup. Local bat species also visit the pots of date palm sap and lick the sweet sap as it is being collected, thereby contaminating the sap with virus-containing saliva and providing a route of exposure to humans that drink it. Human-to-human transmission of Nipah virus also occurred after the virus entered the human population.

Weather and climate change also play a role in the emergence of novel viral diseases. These can be short-term seasonal and regional changes in weather patterns, or longer-term climate change trends (global warming). For example, increases in rainfall in certain areas lead to growth of the vegetation that supports rodent populations. As a consequence, rodent exposure to humans is increased, concurrent with the frequency of rodentborne viruses. This occurred in the emergence of the Sin Nombre virus, a hantavirus that causes a potentially deadly respiratory syndrome, in the Four Corners region of the Southwestern United States. Preceded by six years of drought, the 1993 spring season was characterized by extremely heavy rains (as a result of an El Niño) that increased 10-fold the population of deer mice (Fig. 16.4A). This resulted in 42 people

contracting Sin Nombre virus, a previously unrecognized hantavirus carried by deer mice. Sixty-two percent of the individuals that contracted Sin Nombre virus died of hantavirus pulmonary syndrome.

Increases in rainfall also affect mosquito populations by providing stagnant pools and puddles (Fig. 16.4B) that function as extra breeding grounds for the insects (Fig. 16.4C). The prevalence of dengue virus (DENV) and Rift Valley fever virus, two mosquito-borne viruses, are significantly affected by rainfall. Similarly, WNV is a seasonal epidemic in the United States, appearing in the summer and fall months, the time of the year when rainfall supports mosquito larval habitats.

Depending upon the species, other environmental factors also affect the growth of viral vectors. These include mean temperature, wind speed, dew point, soil moisture, and rain accumulation, among others. Long-term increases in global temperature due to climate change also affect the emergence/reemergence of viral diseases. According to the National Oceanic and Atmospheric Administration, the combined land and ocean surface temperature in 2014 was 1.24°F above the 20th century average, and the 20 warmest years on record have all occurred within the past 20 years. Warmer winter weather allows female mosquitoes to more

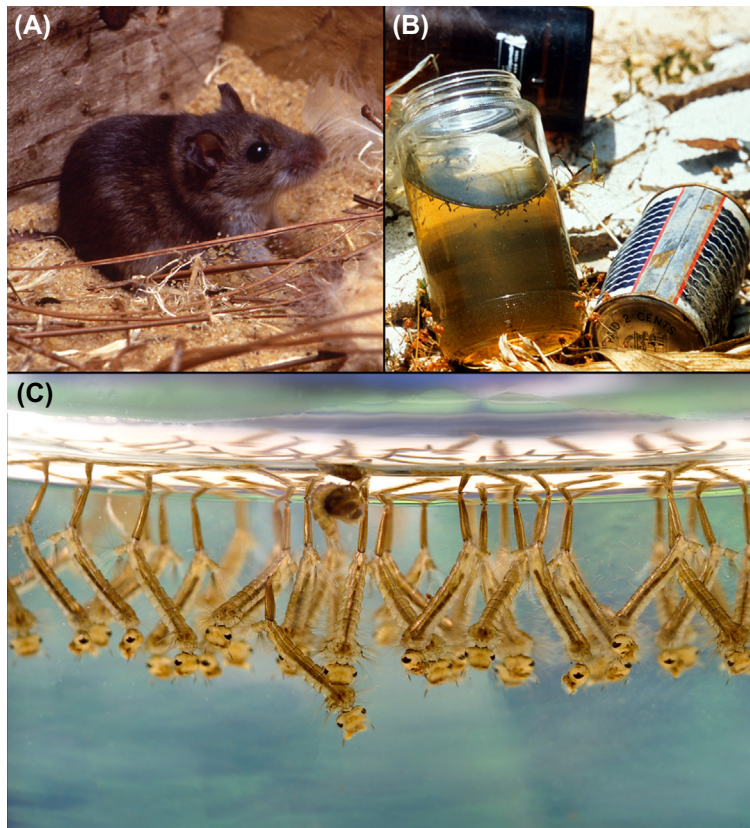


FIGURE 16.4 Factors in the emergence of viral diseases. Changes in rainfall levels can lead to an increase in rodent vectors, such as the deer mouse, *Peromyscus maniculatus* (A), the natural reservoir of Sin Nombre virus. (B) Stagnant water provides breeding grounds for mosquito larvae, as seen in this jar of rainwater. (C) This photograph shows *Culex* mosquito larvae found in standing water just under the surface. A prominent breathing siphon enables the larvae to access their air supply. Photographs courtesy of CDC and (B) Graham Heid and Dr. Harry D. Pratt and (C) James Gathany.

easily overwinter, surviving to the spring. Warmer daily temperatures in an area also expand the habitat for certain mosquito populations, concurrently expanding the populations that can be infected by the viruses they carry. In the United States, mosquito populations in tropical and subtropical Florida support local infections of DENV and Chikungunya virus, the latter of which first emerged in Florida in 2014. As average temperatures increase in states, so will the frequency of zoonotic viruses into states whose climate did not previously support these mosquito species. Similarly, climate changes affect the distribution of ticks and the migratory routes of birds and other animals, changing the locations that are exposed to the zoonoses they carry. In the case of birds, this includes influenza viruses and WNV, among others.

Study Break

Provide four examples of how human or environmental/ecological factors have affected the emergence or reemergence of a viral disease.

16.1.3 Viral Factors

Although human behaviors and environmental/ecological factors are more commonly associated with outbreaks, pathogen characteristics also are involved in the success of emergent/reemergent infectious diseases. For viruses, the molecular makeup of the viral genome often determines whether the virus will successfully integrate into the new population. This generally occurs through reassortment, recombination, or mutation.

Many emerging viruses are unable to establish themselves because their new hosts function as “dead-end” infections that do not sustain person-to-person spread. As described in Chapter 8, “Influenza,” antigenic shift occurs when subtypes of influenza that are circulating in animal populations enter the human population for the first time (see Fig. 6.15B and Section 10.4 of Chapter 8, “Influenza,” for a refresher). The properties of the virus determine whether the antigenic shift will result in a pandemic or will be unable to undergo human-to-human transmission. The 1918 H1N1 virus was able to spread throughout the human population, but H5N1 and H7N9 viruses have only been transmitted to humans through direct contact with birds. However, because influenza viruses are segmented, coinfection of a susceptible host with both avian and human viruses could lead to the reassortment of genetic segments of the two viruses and the creation of a novel human influenza virus subtype. Because of these concerns and the high fatality rate of certain avian influenza strains in the human population, over 45 million chickens, turkeys, and ducks were culled in the Midwestern United States in 2015 in an effort to prevent the further spread of H5N2 in the poultry population and its possible jump to humans.

Another means of acquiring genetic changes is through recombination. As described in Chapter 4, “Virus Replication,” recombination occurs when the RNA or DNA polymerase that is copying the viral genome transfers to the template of another strain of the virus, thereby creating a hybrid genome from two different strains of the virus. Recombination has as much chance of conferring an evolutionarily disadvantageous or neutral result as an advantageous one, but it does contribute to genetic variability within individual virions that could be selected for if beneficial within the environment.

RNA viruses are the most common cause of emerging diseases in humans, attributable to the high mutation rate in RNA viruses compared to DNA viruses. Unlike the DNA-dependent DNA polymerases of living organisms and DNA viruses, RNA-dependent RNA polymerases (including reverse transcriptases) do not possess proofreading ability. This leads to a decrease in enzyme fidelity, inserting an incorrect nucleotide every 10^5 bases (compared to 1 error per 10^9 bases for DNA polymerases). As a result, RNA viruses have some of the highest mutation rates of all biological entities. This ensures a range of genetic diversity that maintains virulence and promotes potential transmission to new hosts.

16.2 NOTABLE EMERGING/REEMERGING VIRAL DISEASES

Within the past 50 years, dozens of viruses have emerged or reemerged within the human population, several of which have been mentioned above (see Table 16.2 for a selection of emerging viruses). It is important to note that other viruses have likely also emerged but are unnoticed because they are not associated with a notable clinical infection. Because the great majority of emerging viral diseases are zoonoses, below we focus on notable zoonotic viruses transmitted by arthropods and by nonhuman mammals to humans.

16.2.1 Arboviruses

Arboviruses (arthropod-borne viruses) are viruses that are transmitted to humans or other mammals by arthropods, invertebrate animals possessing an exoskeleton. The major arthropod vectors for the transmission of viruses are mosquitoes and ticks. In 1930, only six arboviruses had been identified, one of which—yellow fever virus—caused disease in humans. Currently, the CDC arbovirus catalog lists 537 known arboviruses, approximately a quarter of which cause disease in humans. With only a few exceptions, arboviruses are RNA viruses.

Most arboviruses are maintained in a transmission cycle between an arthropod vector and vertebrate hosts, usually birds or small mammals. The virus is acquired by the vector when it feeds upon an infected individual,

TABLE 16.2 Selected Emerging/Reemerging Viral Diseases

Family	Virus	Natural reservoir	Transmitted to humans by:	Mode of transmission	Disease caused
Adenoviridae	Adenovirus 14	Humans	Humans	Respiratory secretions	Acute respiratory disease
Arenaviridae	Guanarito virus	Rodents	Rodents (<i>Zygodontomys</i> sp.)	Urine or feces of infected rodents	Fever, hemorrhagic fever
	Lassa fever	Rodents	Rodents (<i>Mastomys</i> species)	Urine or feces of infected rodents	Fever, hemorrhagic fever
	Machupo virus	Rodents	Rodents (<i>Calomys</i> species)	Urine or feces of infected rodents	Fever, hemorrhagic fever
Bunyaviridae	Crimean–Congo hemorrhagic fever virus	Ticks	Ticks (<i>Hyalomma</i> species)	Tick bite	Fever, encephalitis ^a , hemorrhagic fever
	Rift Valley fever virus	Sheep, cattle	Mosquitoes, infected blood/fluids	Mosquito bite, mucosal infection	Encephalitis, hemorrhagic fever
	Sin Nombre virus	Rodents	Rodents	Urine or feces of infected rodents	Hantavirus pulmonary syndrome
Caliciviridae	Norovirus	Humans	Humans	Fecal-oral	Gastroenteritis, diarrhea, vomiting
Coronaviridae	MERS coronavirus	Camels	Camels, humans	Respiratory secretions	Severe acute respiratory illness
	SARS coronavirus	Horseshoe bats	Civets	Respiratory secretions	Severe acute respiratory illness
Filoviridae	Ebola virus	Bats	Bats, primates, humans	Bodily fluids	Hemorrhagic fever, shock
	Marburg virus	Bats	Bats, primates, humans	Bodily fluids	Hemorrhagic fever, shock
Flaviviridae	Dengue virus	Primates, humans	Mosquitos (<i>Aedes</i> species)	Mosquito bite	Hemorrhagic fever, shock
	Hepatitis C virus	Humans	Humans	Blood products, sexual activity, vertical	Hepatitis, liver cancer
	Powassan virus	Woodchucks, squirrels, mice	Ticks (<i>Ixodes</i> species)	Tick bite	Encephalitis, meningitis
	St. Louis encephalitis virus	Birds	Mosquitoes (<i>Culex</i> species)	Mosquito bite	Encephalitis
	West Nile virus	Birds	Mosquitoes (<i>Culex</i> sp.), birds	Mosquito bite	Encephalitis, meningitis
	Yellow fever virus	Humans, primates	Mosquitoes (<i>Aedes</i> species)	Mosquito bite	Fever, myalgia, hemorrhagic fever
Orthomyxoviridae	Avian influenza viruses	Waterfowl, birds	Poultry	Respiratory secretions	Severe respiratory illness, pneumonia

Continued

TABLE 16.2 Selected Emerging/Reemerging Viral Diseases—cont'd

Family	Virus	Natural reservoir	Transmitted to humans by:	Mode of transmission	Disease caused
Paramyxoviridae	Hendra virus	Fruit bats (<i>Pteropodidae</i> sp.)	Horses	Bodily fluids, urine, feces	Respiratory illness, encephalitis
	Measles virus	Humans	Humans	Respiratory secretions	Fever, rash, conjunctivitis
	Nipah virus	Bats	Bats, pigs, humans	Bodily fluids, urine, feces	Encephalitis
Picornaviridae	Poliovirus	Humans	Humans	Fecal–oral	Paralysis
Poxviridae	Monkeypox	Unidentified rodents	Rodents, marsupials, primates	Bodily fluids, respiratory secretions	Fever, rash, encephalitis
Reoviridae	Rotavirus	Humans	Humans	Fecal-oral or respiratory secretions	Gastroenteritis, diarrhea, dehydration
Retroviridae	Human immunodeficiency virus	Chimpanzees	Chimpanzees, humans	Blood products, sexual activity, vertical	Immunodeficiency
Rhabdoviridae	Rabies virus	Bats	Bats, dogs, raccoons, skunks	Animal bite	Encephalomyelitis
Togaviridae	Chikungunya virus	Bats, rodents, primates	Mosquitoes (<i>Aedes</i> species)	Mosquito bite	Arthralgia, rash
	Eastern equine encephalitis virus	Birds, rodents	Mosquitoes (<i>Culex</i> species)	Mosquito bite	Encephalitis
	Venezuelan equine encephalitis virus	Rodents, horses	Mosquitoes (<i>Culex</i> species)	Mosquito bite	Encephalitis
	Western equine encephalitis virus	Birds	Mosquitoes (<i>Culex</i> species)	Mosquito bite	Encephalitis

^aInflammation of the brain.

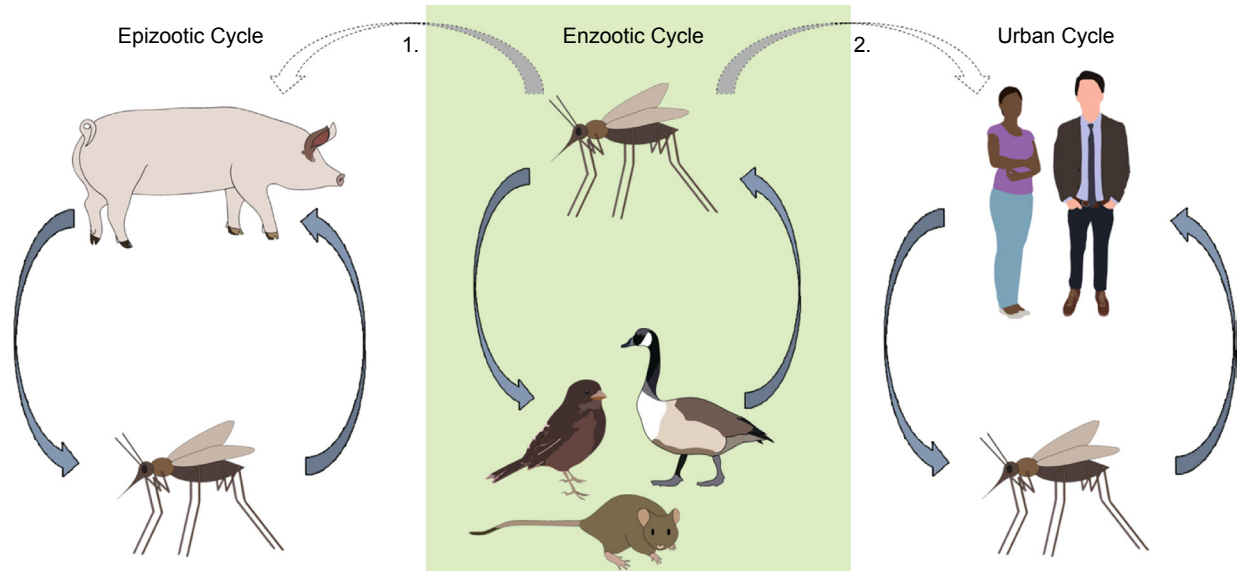


FIGURE 16.5 Arbovirus transmission models. An enzootic cycle occurs when the virus is transmitted between its arthropod vector and its natural reservoir, a wild animal. The vector may infect (1) and cause an epidemic within domestic animals, which can further amplify the virus in an epizootic cycle. Humans may also become infected tangentially from enzootic cycles (2). In the urban cycle, the virus cycles directly between the vector and a human host.

taking a blood meal that contains the virus. Only female mosquitoes feed on blood meals (males feed on flower nectar). Within the infected mosquito, the virus breaches the midgut to infect the salivary glands, becoming transmitted within the saliva of the mosquito when it bites a new individual. On the other hand, ticks attach to the skin of the host and create a feeding pool within the epidermis, becoming engorged with blood. As with the mosquito, the virus enters the tick within the blood meal, replicates within the salivary glands, and is transmitted through saliva to the next host. Once infected, the mosquito or tick can remain infectious for the duration of its life, generally 6–8 weeks for female mosquitoes, and years for ticks. Viruses can also be transmitted vertically from an infected female mosquito or tick to the next generation within eggs, although this is not thought to be the primary means of arbovirus persistence within the population.

Arboviruses are transmitted via several models of transmission (Fig. 16.5). The **enzootic cycle**, also known as the jungle cycle or sylvatic cycle (*sylvatic* means “occurring in wild animals”), occurs when the virus cycles between the arthropod vector and the natural reservoir, a wild animal. Some arboviruses may also possess an **epizootic cycle**, indicating the virus has the potential to cause an epidemic within animals that become infected by the vector. This can occur in wild or domestic animals, such as pigs and horses. For example, Japanese encephalitis virus normally circulates between mosquitoes and birds but can be amplified in pigs, and Venezuelan equine encephalitis virus has an enzootic cycle between mosquitoes and rodents but is capable of initiating a rural epizootic cycle in horses. Both

of these transmission cycles can result in tangential infection of humans if infected by the arthropod vector. On the other hand, an **urban cycle** involves the direct transmission of the virus between mosquitoes and humans. In this case, the viremia that occurs upon human infection is sufficiently large to transmit the virus when the person is bitten by the mosquito. Urban cycles occur with yellow fever virus and DENV, although both of these viruses possess enzootic transmission cycles as well. Intermediate cycles are also possible in which vectors transmit the virus back and forth between human and nonhuman hosts.

The *Flaviviridae* family contains several well-known viruses, including hepatitis C virus. These viruses are enveloped and possess +ssRNA genomes within an icosahedral capsid. Within *Flaviviridae*, the *Flavivirus* genus contains over 50 different species, the majority of which are transmitted by vectors. It includes several notable human pathogens, including yellow fever virus, DENV, Japanese encephalitis virus, WNV, and St. Louis encephalitis virus (see Table 16.2). DENV is currently the most common arboviral disease in the world, infecting around 400 million individuals and causing over 12,000 deaths each year. Dengue-like epidemics have been recorded in tropical areas of the world since the 1600s, and the virus was first isolated in 1943–44 by Albert Sabin and others from soldiers in the Pacific and Asia during World War II. DENV is considered a reemerging virus due to the expansion of the domesticated *Aedes aegypti* mosquito (Fig. 16.6A), the primary vector, and *Aedes albopictus*, a lesser vector for DENV. The spread of these mosquito species is attributable to the factors mentioned above. Currently, the mosquito species live mainly

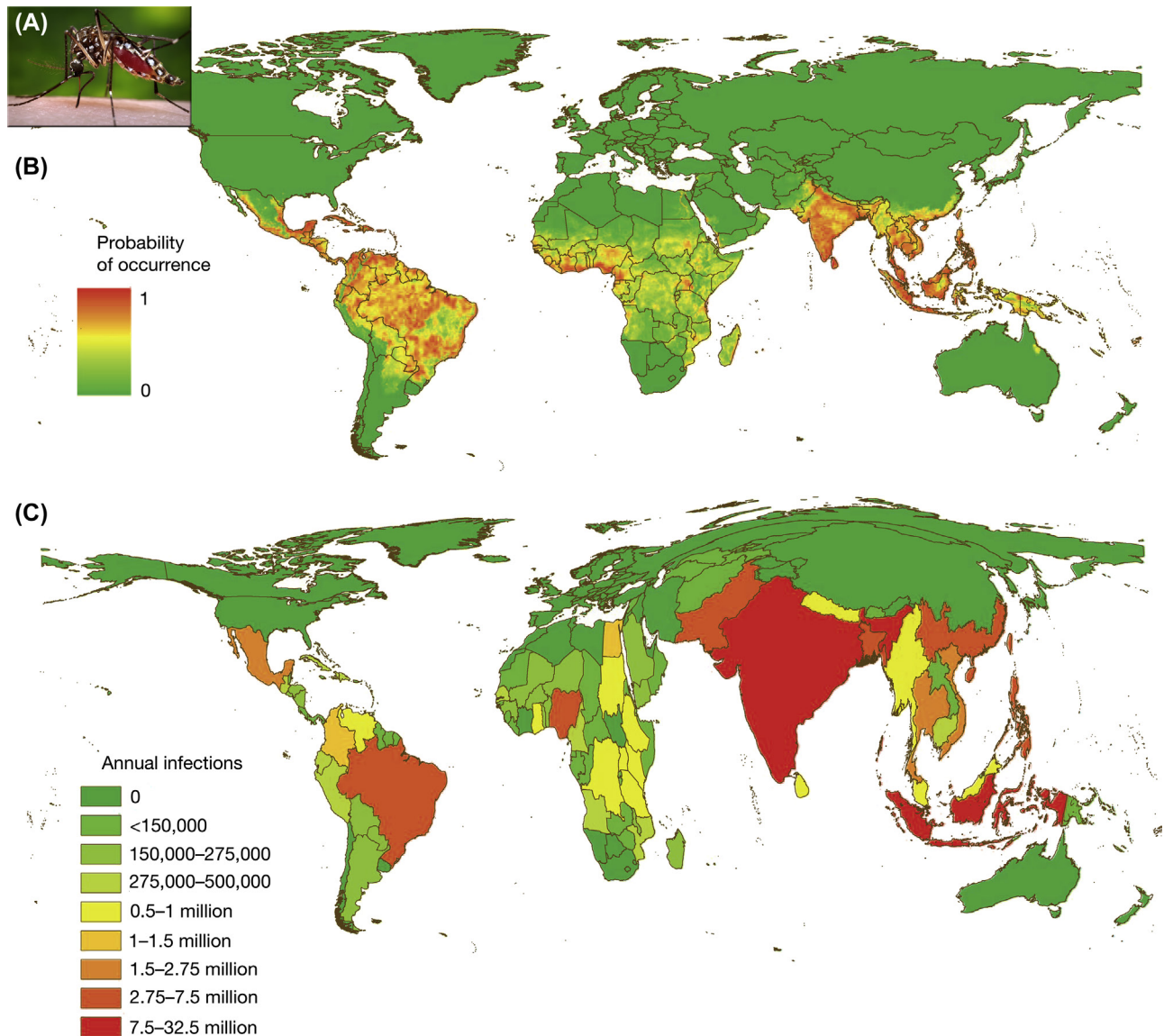


FIGURE 16.6 Geographical distribution of dengue virus. (A) *Aedes aegypti* is a domestic, day-biting mosquito that prefers to feed on humans. It is the most common vector of dengue virus. (Image courtesy of CDC/Prof. Frank Hadley Collins and James Gathany.) (B) Map showing the probability of dengue occurrence. Areas with a high probability of occurrence are shown in red and areas with a low probability in green. (C) A cartogram that has distorted the geographic area to correspond to the annual number of dengue infections for all ages. ((B) and (C) reprinted by permission of Bhatt, S. et al., 2013. *The global distribution and burden of dengue*. *Nature* 496(7446), 504–507. Macmillan Publishers Ltd., copyright 2013.)

between the 35°S and 35°N latitudes and below 3200 feet in areas where the evening temperature does not fall below 50°F (Fig. 16.6B and C). They are associated with human-populated areas and cities, and as such, DENV is communicated primarily via an urban transmission cycle.

Although they cause similar clinical symptoms, the four serotypes of DENV (DENV-1, DENV-2, DENV-3, and DENV-4) are genetically distinct. As such, immunity against one serotype does not provide long-term protection against another serotype, although some short-term

protection may occur. Within 5–7 days of being bit by an infected mosquito, a person develops a viremia that lasts 5–12 days. DENV can be transmitted from human to human through blood transfusions or organ transplants, and perinatal transmission can occur if the mother is infected around the time of delivery. The virus can be transmitted back to a mosquito host if the insect feeds on an infected person during the viremia. Following infection of a mosquito, the virus takes 8–12 days to disseminate to the salivary glands and become transmissible to another human in saliva.

TABLE 16.3 Case Definitions^a of Symptomatic Dengue Illness**Dengue without warning signs**

Fever and two of the following:
 Nausea, vomiting
 Rash
 Aches and pains
 Leukopenia
 Positive tourniquet test

Dengue with warning signs

Dengue as defined above with any of the following:
 Abdominal pain or tenderness
 Persistent vomiting
 Clinical fluid accumulation
 Mucosal bleeding
 Lethargy, restlessness
 Liver enlargement >2 cm
 Laboratory: increase in hematocrit with decrease in platelet count

Severe dengue

Dengue with at least one of the following criteria:
 Severe plasma leakage leading to:
 • Shock
 • Fluid accumulation with respiratory distress
 Severe bleeding as evaluated by clinician
 Severe organ involvement:
 • Liver: AST or ALT \geq 1000
 • CNS: impaired consciousness
 • Failure of heart and other organs

^aMost recent (2009) World Health Organization case definitions.

As many as three-quarters of DENV infections are asymptomatic. Symptomatic illness is divided into non-severe dengue and severe dengue (Table 16.3). Nonsevere dengue is further divided into dengue without warning signs or dengue with warning signs. **Dengue without warning signs** is the less severe form of disease, characterized by fever and at least two of the following symptoms: nausea/vomiting, rash, aches and pains, **leukopenia** (low white blood cell count), or a positive tourniquet test. The tourniquet test is performed by applying a blood pressure cuff on the individual for 5 min at a pressure between the person's systolic and diastolic pressures and then counting the number of **petechiae**, small red spots indicative of capillary **hemorrhages** (bleeds). Dengue is also known as “break-bone fever,” alluding to the extreme bone pain that can be experienced.

During **dengue with warning signs**, individuals display any of the above symptoms with the addition of abdominal pain, mucosal bleeding, lethargy, liver enlargement >2 cm, persistent vomiting, or accumulation of fluid in the abdomen or between the pleural linings covering the lungs. They

may also have an increase in hematocrit (the volume within the blood that is occupied by red blood cells), indicating that plasma is leaving the bloodstream. These symptoms may progress to **severe dengue**, which is characterized by **hemorrhagic fever**. This is a severe multiorgan syndrome that results from increased permeability of the vascular system, leading to petechiae and bleeding within the internal organs or from orifices like the mouth, nose, and eyes. Severe dengue usually occurs after **defervescence**, the abatement of fever. During this 1–2-day “critical period,” plasma leakage can also result in **shock**. The leakage of plasma from major blood vessels causes a loss of blood pressure and subsequent damage to multiple organs due to an inadequate supply of blood and the clotting of blood in small vessels. There are no antivirals approved for use against dengue virus, so treatment is supportive in an attempt to prevent progression to shock. Severe dengue may be fatal for up to 5% of those with the condition, while recovery often takes months in those that survive.

The emergence and spread of arthropod-borne zoonotic viruses are a major concern because many arboviruses cause serious disease—including death—in humans. Besides *Flaviviridae*, arboviruses are also found in the *Bunyaviridae*, *Reoviridae*, and *Togaviridae* families. Major control measures are aimed at eliminating the vector and preventing transmission. For example, mosquito-control measures can reduce vector populations, while public education can lessen the interaction of humans with mosquitoes or ticks by encouraging the use of insect repellents, clothes that cover exposed skin, or bed nets. Currently, yellow fever virus and Japanese encephalitis virus are the only two arboviruses for which human vaccines are available, although vaccines for DENV and WNV are in development.

Study Break

What factors might contribute to the expanding range of dengue virus?

16.2.2 Vertebrate Zoonoses

Although arboviruses are a major cause, wildlife is the primary source of viral zoonoses. The two most species-rich orders are *Rodentia* (rodents) and *Chiroptera* (bats), so it is not surprising that both are host to a variety of high-impact zoonotic viruses. Rodent and bat species are host to 68 and 61 zoonotic viruses, respectively, although bats carry more zoonotic viruses per species. Viruses within the *Arenaviridae* and *Filoviridae* families are transmitted by rodents and bats, respectively. Like dengue virus, both families contain viruses that can cause serious disease, including hemorrhagic fever leading to hypotension, shock, and multiple organ failure.

Word Origin: Arenaviruses

Arenaviruses derive their name from the Latin word *arena*, meaning “sandy.” When viewed with an electron microscope, the interior of an arenavirus virion contains sandy or grainy particles (Fig. 16.7). These are ribosomes that were enclosed within the lipid envelope during assembly. The ribosomes are nonfunctional and not required for replication. Like all viruses, arenaviruses rely upon entry into a host cell for replication.

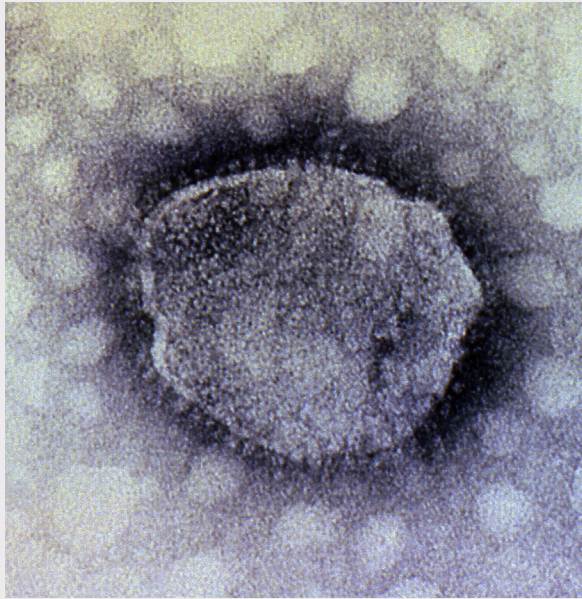


FIGURE 16.7 Arenaviruses. Arenaviruses derive their name from the Latin word *arena*, meaning “sandy,” in reference to the appearance of the interior of the virion when viewed with an electron microscope. Several arenaviruses are transmitted by rodent vectors and are capable of causing severe disease, including hemorrhagic fevers. Image courtesy of CDC and E.L. Palmer.

Arenaviruses are enveloped, ambisense viruses with a bisegmented genome. Viruses within the *Arenaviridae* family are transmitted by rodents and are capable of causing hemorrhagic fever, including Junin virus, Machupo virus, Lassa virus, and Guanarito virus (Table 16.4). The first arenavirus, lymphocytic choriomeningitis virus, was isolated in 1933 and found to be a cause of viral meningitis. Since the 1950s, new arenaviruses have been discovered every few years.

Each of these viruses is limited to the geographical area in which its rodent host is found (Table 16.4). The animals become infected through fighting and bites, although some arenaviruses are transmitted vertically to offspring, thereby maintaining the infected population. The rodents are unaffected by the virus but remain

chronically infected, shedding virus into the environment through urine and feces. Humans become infected when abraded skin comes in contact with rodent excretions, or when they ingest contaminated food or inhale aerosolized particles. Some arenaviruses have been shown to be transmitted from person-to-person, including Lassa virus and Machupo virus, through infectious droplets or bodily secretions. Fatality rates for the arenaviruses that cause hemorrhagic fever range from 5% to 35%, although rates up to 50% have been documented in certain outbreaks.

Whereas rodents transmit arenaviruses to humans, bats are thought to be the natural reservoir of viruses within the *Filoviridae* family (*filo* is Latin for “thread,” referring to the threadlike appearance of these enveloped helical $-ssRNA$ viruses) (Fig. 16.8). The first filovirus was discovered in 1967 when 31 cases of hemorrhagic fever were documented in German and Yugoslavian laboratory workers who had been handling tissues obtained from African green monkeys imported from Uganda. Of these individuals, seven died (22.5%). The virus was named **Marburg virus**, after the location of one of the outbreaks.

The second filovirus was discovered 9 years later, in 1976. Two outbreaks of a hemorrhagic disease simultaneously struck in Africa, one in northern Zaire (currently the Democratic Republic of the Congo) and one in southern Sudan. The disease was found to be spread through close personal contact and shared syringes in hospitals and clinics. Eighty-eight percent of the 318 infected in Zaire succumbed to the disease, while 53% of those infected in Sudan died.

The virus was soon determined to be a filovirus unique from the Marburg virus. The novel virus was named after a river 60 miles from the site of the Zaire outbreak: the Ebola River. The two outbreaks were found to be caused by different species of *Ebolavirus*, *Zaire ebolavirus* and *Sudan ebolavirus*. Since that time, three additional species have been identified: *Reston ebolavirus* in 1989, *Tai Forest ebolavirus* in 1994, (formerly Côte d’Ivoire EBOV), and *Bundibugyo ebolavirus* in 2007. The viruses within these five species are known as Ebolavirus (EBOV), Sudan virus (SUDV), Reston virus (RESTV), Tai Forest virus (TAFV), and Bundibugyo virus (BDBV), respectively (Table 16.5). RESTV is the only ebolavirus that has not shown any symptoms in humans, thus far only being seen in monkeys from the Philippines (being held in quarantine facilities in the United States and Italy) and on a pig farm in the Philippines.

Other than accidental laboratory infections or imported cases, all of the human ebolavirus outbreaks have originated in Africa (Fig. 16.9A). In fact, before 1994, all known natural cases of ebolaviruses were in

TABLE 16.4 Arenavirus Infections of Humans

Arenavirus	Possible disease	Natural host	Geographic range	Year isolated
LCMV ^a	Aseptic meningitis	House mouse (<i>Mus musculus</i>)	Europe, Americas	1933
Junin virus	Argentinian hemorrhagic fever	Drylands vesper mouse (<i>Calomys musculinus</i>)	Argentina	1958
Machupo virus	Bolivian hemorrhagic fever	Large vesper mouse (<i>Calomys callosus</i>)	Bolivia	1963
Lassa	Lassa fever	Multimammate rat (<i>Mastomys natalensis</i>)	West Africa	1969
Guanarito virus	Venezuelan hemorrhagic fever	Short-tailed cane mouse (<i>Zygodontomys brevicauda</i>)	Venezuela	1989
Sabia virus	Brazilian hemorrhagic fever	Unknown	Brazil	1993
Chapare virus	Chapare hemorrhagic fever	Unknown	Bolivia	2008
Lujo virus	Lujo hemorrhagic fever	Unknown	Zambia	2008

^aLymphocytic choriomeningitis virus.



FIGURE 16.8 Marburg virus. The first filovirus, Marburg virus, was discovered in 1967 and named after the location of one of the outbreaks (Marburg, Germany). This electron micrograph shows the threadlike appearance that is characteristic of these helical –ssRNA viruses. Image courtesy of CDC/Frederick Murphy.

TABLE 16.5 Taxonomy of Ebolaviruses^a

Order <i>Mononegavirales</i>
Family <i>Filoviridae</i>
Genus <i>Ebolavirus</i>
Species <i>Tai Forest ebolavirus</i>
Virus: Tai Forest virus (TAFV)
Species <i>Reston ebolavirus</i>
Virus: Reston virus (RESTV)
Species <i>Sudan ebolavirus</i>
Virus: Sudan virus (SUDV)
Species <i>Zaire ebolavirus</i>
Virus: Ebola virus (EBOV)
Species <i>Bundibugyo ebolavirus</i>
Virus: Bundibugyo virus (BDBV)

^aInternational Committee on Taxonomy of Viruses, EC 46, July 2014 (MSL #29).

five countries in Central Africa: Democratic Republic of Congo (formerly Zaire), South Sudan (previously part of Sudan), Uganda, Republic of the Congo, and Gabon. In 1994, a scientist became ill after conducting a necropsy (animal autopsy) on a wild chimpanzee that had succumbed to a viral hemorrhagic fever in the Tai Forest of the Côte d'Ivoire (Ivory Coast). The virus was identified

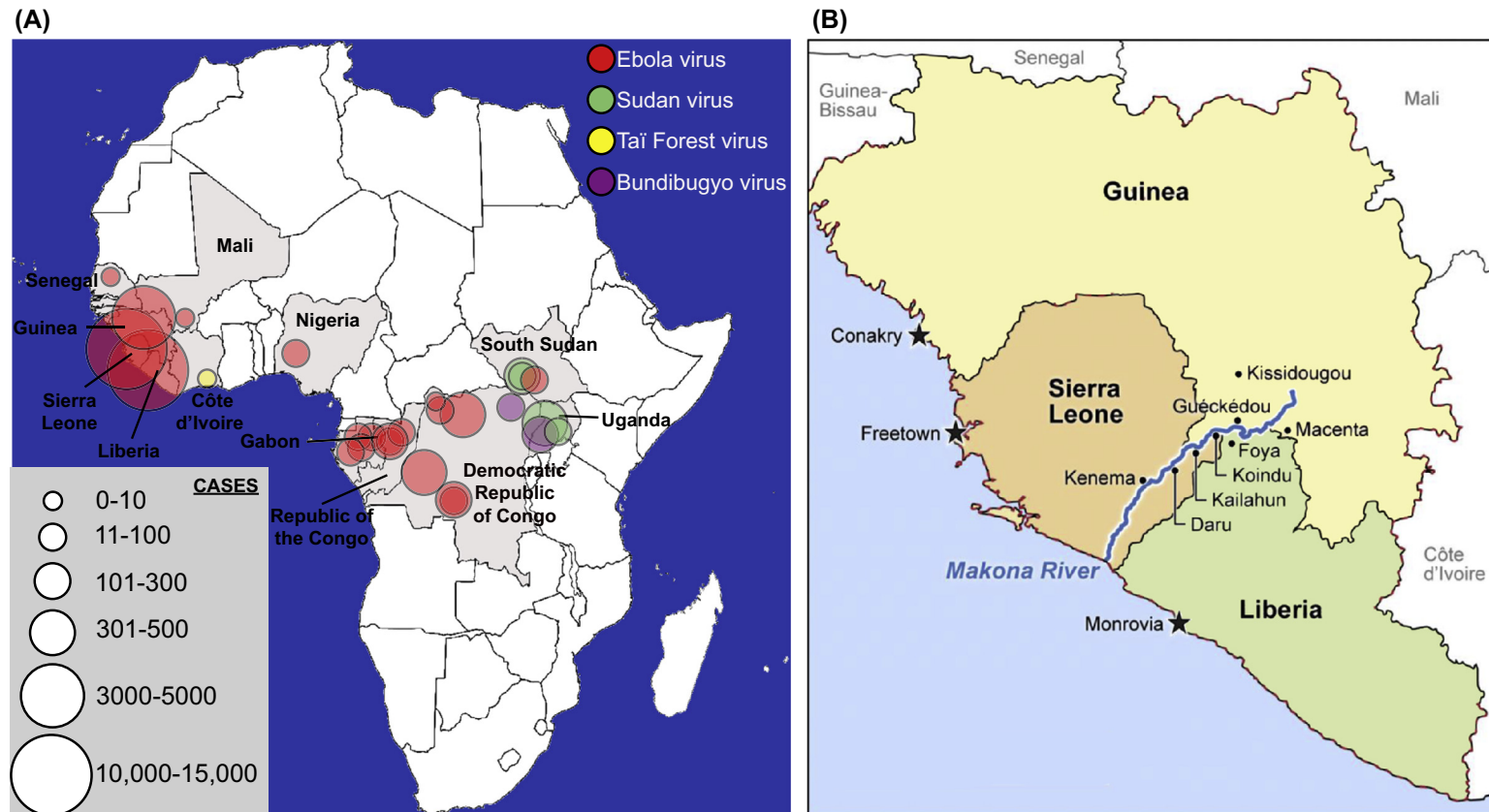


FIGURE 16.9 Ebolavirus outbreaks. (A) Other than accidental or laboratory-acquired infections, all human Ebolavirus infections have originated in Africa. Before 1994, when Taï Forest virus was discovered in Côte d'Ivoire (Ivory Coast), all Ebolavirus infections had occurred in five Central African countries: Democratic Republic of Congo, South Sudan, Uganda, Republic of the Congo, and Gabon. The 2014–15 outbreak that originated in Guinea was 10-times larger than all others combined. Note that the circles are representative of the number of cases and not to scale. (Data derived from CDC (*Ebola Virus Disease*, <http://www.cdc.gov/ebola>) and WHO (*Ebola virus disease outbreak*, <http://who.int/ebola>.) (B) Map showing Guinea, Sierra Leone, and Liberia, the three major countries involved in the 2014–15 Ebolavirus outbreak in West Africa. The village of Meliandou is just northeast of Guéckédou in Guinea. (Updated from Kuhn, J.H., et al., 2014. *Viruses* 6, 4760–4799.)

as a new species of ebolavirus, the first and only ever observed outside of Central Africa.

The geographic history of ebolaviruses in Central Africa is part of why world health authorities were caught off guard by an outbreak that began in March of 2014 in the West African country of Guinea (Fig. 16.9B). The etiologic agent was determined to be Ebola virus (EBOV, of the *Zaire ebolavirus* species), the ebolavirus with historically the highest fatality rates.

Thus far, the virus is thought to have originated in Meliandou, Guinea, a small village with 31 houses, one school, and one medical center (Fig. 16.10A). On December 26, 2013, a 2-year-old boy developed a fever, vomiting, and black stools; he died 2 days later. It is thought that he may have contracted EBOV while he was playing in a hollow tree (Fig. 16.10B) known to be inhabited by insectivorous free-tailed bats (*Mops condylurus*), a species in which EBOV has previously been reported. It is thought that a **spillover event**, the infection of a human by an infected animal, could have occurred through close contact with infectious animal blood, urine, or bodily fluids. The child's 3-year-old sister died on January 5, 2014, and his mother succumbed 6 days later. By February 1, 2014, an infected member of the boy's family had traveled to and died within a hospital in the capital of Conakry. Without suspecting EBOV, no precautions were taken, and the virus soon spread to other areas of Guinea and into nearby countries of Liberia, Sierra Leone, Nigeria, Senegal, and Mali.

Declared over in January 2016, this was the largest ebolavirus outbreak in history. In total, 28,639 cases with 11,316 deaths (39.5%) occurred. All but 36 cases occurred in Guinea, Sierra Leone, and Liberia. Although Guinea was the origin of the outbreak and sustained high fatality rates, Liberia and Sierra Leone bore the brunt of the toll

(Fig. 16.11A). The outbreak was exacerbated by the weak public health systems and lack of resources within these countries (Fig. 16.11B and C). Doctors, laboratories, and governments had never experienced an outbreak and were unprepared to orchestrate an appropriate response. Additionally, in contrast to previous outbreaks in rural Central African villages, the capital cities of Guinea, Sierra Leone, and Liberia were epicenters of the 2014–15 outbreak, providing the human population to allow for rapid transmission. A plethora of other factors contributed to the spread, including mistrust of hospitals, lack of compliance, and denial of the virus.

EBOV is able to spread from person to person, but it is *not* a respiratory virus. It is transmitted through direct contact of broken skin or mucous membranes with infectious blood or bodily fluids, including urine, saliva, sweat, feces, vomit, breast milk, or semen. It can also be transmitted through injection with contaminated syringes. Transmission events occur most often while a person is caring for an infected individual or via direct contact with the body of a deceased individual. The incubation period for EBOV is 2–21 days (average of 8–12 days), and people are not infectious until symptoms develop. Ebola virus disease (EVD) begins with the sudden onset of fever, fatigue, chills, myalgia, headache, and loss of appetite. After about 5 days, this is followed by vomiting, severe watery diarrhea, and abdominal pain. A diffuse maculopapular rash may also develop. Internal and external bleeding is not always present but may occur in some cases, noticeable as bleeding of the gums, blood within the stool, oozing from injection sites, and petechiae. In the 2014–15 outbreak, bleeding was associated with 18% of patients, most often as blood in the stool (6% of patients).

As no antivirals or vaccine exists for EVD, treatment is supportive in an attempt to prevent dehydration, multiorgan



FIGURE 16.10 The possible origin of the 2014–15 Ebolavirus outbreak in Guinea. A young boy in the village of Meliandou, Guinea (A), is the earliest infected individual to be identified in the 2014–15 Ebolavirus outbreak. He was known to play around a tree that was inhabited by insectivorous free-tailed bats (B). Courtesy of Saéz et al., 2015. *EMBO Mol. Med.* 7, 17–23.

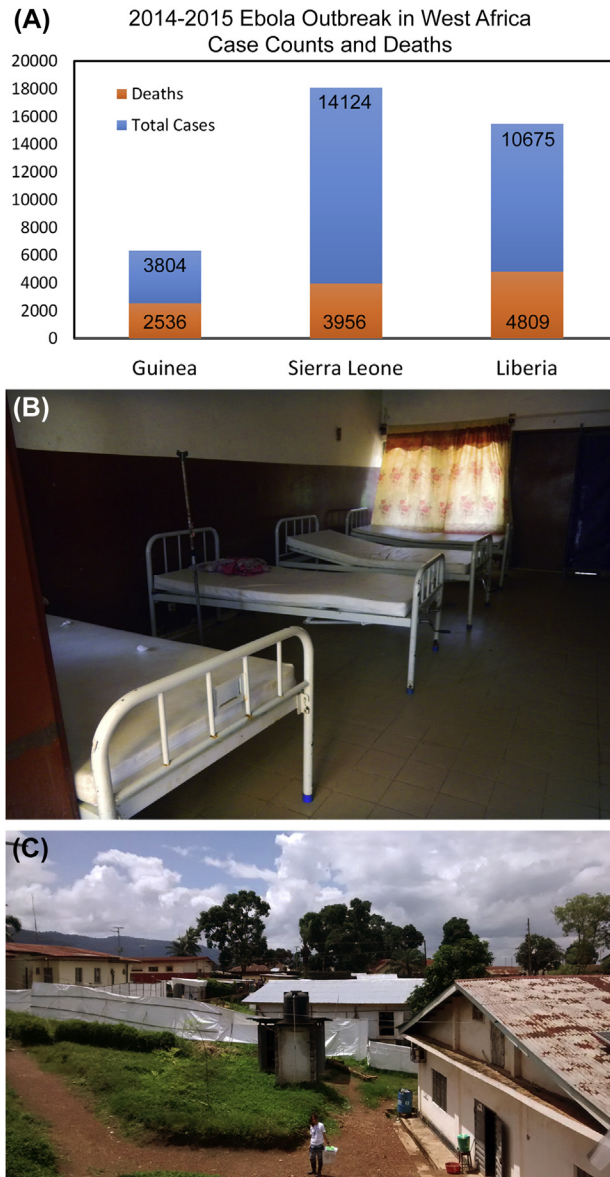


FIGURE 16.11 The 2014–15 Western Africa Ebolavirus outbreak. (A) In total, 28,639 cases of Ebola virus disease were diagnosed – primarily in Sierra Leone, Liberia, and Guinea – accounting for 11,316 deaths. (Data derived from CDC (*Ebola Virus Disease*, <http://www.cdc.gov/ebola>) and WHO (*Ebola virus disease outbreak*, <http://who.int/ebola>.) Weak public health systems and lack of resources contributed to the spread of Ebola, as illustrated by photographs of the Infectious Disease ward at Donka Hospital in Guinea’s capital of Conakry (B) and one of the region’s isolation wards used to accommodate patients ill with Ebola (C). Photos courtesy of CDC and (A) Dr. Heidi Soeters and (B) Daniel DeNoon.

failure, shock, hemorrhages, and other complications. Patients with fatal disease die of these conditions typically between day 6 and 16 after the onset of symptoms. In the 2014–15 outbreak in West Africa, the average was 7.5 days. Individuals that survive typically improve around day 6 and

are thought to cease being infectious when virus is no longer detectable in the bloodstream or in urine. Interestingly, EBOV has been found in the semen of men that have recovered from EVD long after virus was undetectable in other fluids.

Case Study: Chikungunya Fever Diagnosed Among International Travelers—United States, 2005–06

Excerpted from Morbidity and Mortality Weekly Report, September 29, 2006/55(38);1040–1042.

Chikungunya virus (CHIKV) is an alphavirus indigenous to tropical Africa and Asia, where it is transmitted to humans by the bite of infected mosquitoes, usually of the genus *Aedes*. Chikungunya (CHIK) fever, the disease caused by CHIKV, was first recognized in epidemic form in East Africa during 1952–53. The word “chikungunya” is thought to derive from description in local dialect of the contorted posture of patients afflicted with the severe joint pain associated with this disease. Because CHIK fever epidemics are sustained by human–mosquito–human transmission, the epidemic cycle is similar to those of dengue and urban yellow fever. During 2005–06, 12 cases of CHIK fever were diagnosed serologically and virologically at CDC in travelers who arrived in the United States from areas known to be epidemic or endemic for CHIK fever. This report describes four of these cases.

Case Reports

Minnesota. On May 12, 2005, an adult male resident of Minnesota returned from a 3-month trip to Somalia and Kenya. He had onset of illness hours after arrival in the United States, including fever, headache, malaise, and joint pain mainly in a shoulder and a knee. Serum obtained on May 13 was tested at CDC and determined to be equivocal for CHIKV RNA by reverse-transcription polymerase chain reaction (PCR), consistent with low-level viremia. A recent CHIKV infection was confirmed by demonstration of IgM antibody in this acute-phase serum specimen and neutralizing antibody in convalescent-phase serum (collected 214 days after illness onset). Arthralgias resolved after several weeks.

Louisiana. On January 15, 2006, an adult female resident of India had onset of an illness characterized by fever, joint pain (in the knees, wrists, hands, and feet), and muscle pain (in the thighs and neck). In March 2006, she traveled to Louisiana, where she sought medical attention for persistent joint pain. At CDC, tests of a single serum sample collected on March 30 (74

days after illness onset) were positive for IgM and neutralizing antibodies to CHIKV.

Maryland. An adult female resident of Maryland visited the island of Réunion in the Indian Ocean from October 2005 through mid-March 2006. On February 18, 2006, during an ongoing CHIK fever outbreak in the island, she had onset of fever, joint pain (in the hands and feet), and rash. A local physician clinically diagnosed CHIK fever, but no laboratory tests were conducted. After returning to the United States, the patient sought medical attention for persistent joint pain. At CDC, tests of a single serum sample collected on March 22 (32 days after illness onset) were equivocal for IgM and positive for neutralizing antibody to CHIKV, consistent with a recent CHIKV infection in which IgM antibody was waning. At 5 months after onset, the patient had persistent joint pain (in the hands and feet).

Colorado. An adult male resident of Colorado visited Zimbabwe during April 17–May 29, 2006. On April 29, he had onset of illness with fever, chills, joint pain (in the wrists and ankles), and neck stiffness; a rash appeared a few days later. All symptoms resolved within 2 weeks, except for joint pain, which persisted for approximately 1 month. At CDC, tests of a single serum sample collected on June 12 (44 days after illness onset) were positive for IgM and neutralizing antibody to CHIKV.

Reported by: E Warner, Denver, Colorado. J Garcia-Diaz, MD, Ochsner Clinic Foundation, New Orleans; G Balsamo, DVM, Louisiana Dept of Health and Hospitals. S Shranatan, DO, Johns Hopkins Community Physicians at Hager Park, Hagerstown; A Bergmann, MS, Maryland Dept of Health and Mental Hygiene. L Blauwet, MD, M Sohail, MD, L Baddour, MD, Mayo Clinic College of Medicine, Rochester, Minnesota. C Reed, MD, H Baggett, MD, Div of Global Migration and Quarantine, National Center for Preparedness, Detection, and Control of Infectious Diseases (proposed); G Campbell, MD, T Smith, MD, A Powers, PhD, N Hayes, MD, A Noga, J Lehman, Div of Vector-Borne Infectious Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases (proposed), CDC.

SUMMARY OF KEY CONCEPTS

Section 16.1 Factors Involved in the Emergence of Viral Infectious Diseases

- An emerging infectious disease is a disease caused by a pathogen that has not before been observed within a population or geographic location.
- A reemerging infectious disease is caused by an established pathogen that appears in a new geographical location or was once controlled but begins appearing at a higher incidence.
- 75% of emerging/reemerging diseases are zoonoses, infectious diseases of animals that can be transmitted to humans. Most zoonoses are transmitted by wildlife or arthropod vectors.
- Many human factors are involved in the emergence of infectious diseases. These include urbanization, globalization, travel advances that allow global travel, inadequate public health-care systems, and human behaviors that facilitate transmission. The susceptibility of the human host is also a factor in viral emergence.
- Nearly every emerging viral disease is associated with an environmental/ecological component. The encroachment of humans into pristine environments for farming or land modification puts them in contact with new wildlife and the viruses they carry. Weather and climate, including human-induced changes, also play a role in the emergence of viruses from their natural reservoirs.
- The molecular make-up of the virus determines whether or not an emerging virus will successfully infect and spread within a population. Reassortment of genetic segments, such as with influenza virus, can lead to antigenic shift and the emergence of a novel human virus. Recombination and mutation are two other means of acquiring genetic change.
- RNA viruses are the most common cause of emerging diseases in humans, attributable to the high mutation rate resulting from the low fidelity of their RNA polymerases.
- Arboviruses can be transmitted through several transmission models. The virus cycles between the arthropod vector and a wild animal in the enzootic cycle. In the rural epizootic cycle, the virus causes an epidemic within domestic animals when they are infected by the vector. An urban cycle involves the direct transmission of the virus between mosquitoes and humans.
- Flaviviruses include several notable vector-transmitted human pathogens, including yellow fever virus, WNV, Japanese encephalitis virus, St. Louis encephalitis virus, and dengue virus, the most common arboviral disease in the world.
- Dengue virus is transmitted by *Aedes* mosquitoes, whose range has been increasing due to climate change. Three-quarters of dengue infections are asymptomatic, but dengue virus can cause dengue without warning signs, dengue with warning signs, and severe dengue, a serious condition characterized by hemorrhagic fever leading to shock and multiorgan failure.
- *Rodentia* (rodents) and *Chiroptera* (bats) are the two most species-rich orders, and both are host to high-impact zoonotic viruses. Arenaviruses are transmitted by infected rodent urine and feces, and several can lead to hemorrhagic fever.
- Bats are thought to be the natural reservoir of Filoviruses, enveloped helical –ssRNA viruses that are capable of causing hemorrhagic fever. Marburg virus and ebolaviruses are filoviruses. Five species of ebolaviruses have been identified, four of which infect humans and cause high mortality rates.
- Until the 2014–15 EBOV epidemic in West Africa, all ebolavirus outbreaks (with the exception of a researcher infected with TAFV) had occurred in Central Africa.
- The 2014–15 West African EBOV outbreak is thought to have originated with the infection of a 2-year-old boy in Meliandou, Guinea, by a spillover event from an insectivorous free-tailed bat. The virus quickly spread to the capital of Conakry and nearby countries of Liberia, Sierra Leone, Nigeria, Senegal, and Mali.
- The 2014–15 EBOV outbreak was declared over in January 2016. In total, 28,639 cases were documented, accounting for 11,316 deaths (39.5%).
- EBOV is spread from person to person through direct contact of broken skin or mucous membranes with infectious blood or bodily fluids or from contaminated syringes. The incubation period averages 8–12 days, at which point a person develops symptoms and is infectious. EVD begins with the sudden onset of fever, fatigue, chills, myalgia, headache, and loss of appetite. After about 5 days, this is followed by vomiting, severe watery diarrhea, and abdominal pain. Internal and external bleeding occurs in about a fifth of patients.

Section 16.2 Notable Emerging and Reemerging Viral Diseases

- The great majority of emerging viral diseases are zoonoses transmitted by arthropods or nonhuman mammals.
- Arboviruses are viruses that are transmitted to humans or other mammals by arthropods, primarily mosquitoes and ticks. The virus is acquired when the arthropod takes a blood meal that contains the virus, which then replicates within the arthropod and is transmitted within infectious saliva to a new host.

- No antivirals or vaccine exists for EVD. Treatment is supportive in an attempt to prevent dehydration, multiorgan failure, shock, hemorrhages, and other complications. Patients with fatal disease die of these conditions typically between day 6 and 16 after the onset of symptoms.

FLASH CARD VOCABULARY

Emerging infectious disease (EID)	Rural epizootic cycle
Reemerging infectious disease	Urban cycle
Zoonosis	Dengue without warning signs
Vector	Dengue with warning signs
Urbanization	Severe dengue
Globalization	Hemorrhagic fever
Severe acute respiratory syndrome (SARS)	Defervescence
SARS-CoV	Shock
Anthroponosis/anthroponotic disease	Arenaviruses
Arbovirus	Marburg virus
Enzootic cycle	Ebola virus
Sylvatic	Spillover event

CHAPTER REVIEW QUESTIONS

1. What are the major causes of emerging or reemerging infectious diseases?
2. How does urbanization lead to an environment that is more conducive to the spread of an emerging virus?
3. What aspects of globalization are involved in the spread of EIDs?
4. What kinds of human or societal factors contribute to the emergence or spread of an emerging virus?
5. Why is measles reemerging in the United States and elsewhere in the world?
6. How do deforestation, habitat modification, and the increased use of wild land for farming contribute to the emergence of viral diseases?
7. Give at least two examples of how weather or climate change can increase viral emergence.
8. Why are EIDs often RNA viruses?
9. Explain the process by which a virus is acquired by an arthropod and then transmitted to a new host.
10. Which arboviral mode of transmission is most likely to occur in a rural area where jungle has been cleared for farming purposes? Why?
11. What is hemorrhagic fever? Explain how hemorrhagic fever can lead to death.
12. You are an expert in emerging arboviral diseases and have been asked to suggest control measures to prevent the emergence or spread of new viruses. What measures would you suggest?
13. Explain how rodents transmit arenaviruses to humans. In which sorts of scenarios do you think transmission would be most likely to occur?
14. What factors contributed to the spread of EBOV in West Africa? Describe at least five.

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