E Zoonoses

322 Zoonoses

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SHORT VIEW SUMMARY

Definition

- A zoonosis is an infectious disease of humans that originates in animals.

Epidemiology

- Zoonoses account for more than half of all emerging infectious diseases and include such varied examples as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), Ebola virus, severe acute respiratory syndrome, plague, rabies, influenza, and new-variant Creutzfeldt-Jakob disease.

Diagnosis

- The majority of zoonotic diseases are diagnosed using molecular methods. Many appear in unexpected contexts; thus, a comprehensive travel and exposure history can be critical.

Treatment

- With the notable exception of HIV/AIDS and influenza, most viral zoonoses have not been a focus for drug development. Thus, treatment is primarily supportive. In contrast, many bacterial zoonoses can be treated with antibiotics.

Prevention

- Vaccines are established for only a minority of zoonotic diseases. Thus, prevention is best achieved by limiting exposure to reservoirs and vectors for transmission of infection.

Zoonoses, derived from the Greek words for animal, *zoo,* and the suffix modification indicating a state or condition, *sis,* are infectious diseases of humans that originate in animals. Infectious diseases that originate in humans and move into other animals are commonly described as reverse zoonoses. The majority of emerging viral diseases, up to 70%, represent zoonoses, with such prominent examples as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), influenza, West Nile virus encephalitis, Nipah virus disease, Hendra virus disease, severe acute respiratory syndrome (SARS), Ebola virus disease, Marburg virus disease, hantavirus pulmonary syndrome (Sin Nombre virus), and rabies. Common examples of nonviral zoonoses include Lyme disease (*Borrelia burgdorferi* in North America, *Borrelia afzelii* and *Borrelia garinii* in Europe), cat-scratch disease (*Bartonella henselae*), new-variant Creutzfeldt-Jakob disease, salmonellosis, and toxoplasmosis. Although secondary microbial contamination of agricultural products can cause significant disease, the term zoonosis does not apply unless there is direct transmission to humans from an infected animal.

Many zoonotic diseases can be attributed to anthropogenic changes. Loss of wildlife habitat to development and consumption of bushmeat, necessitated by poverty or resulting from cultural preference, increases opportunities for cross-species jumps. Global warming may also increase the geographic range of phlebotomous arthropod vectors, such as mosquitoes and ticks, that serve as reservoirs and vectors for infectious agents. Because there are more than 50,000 vertebrate species, for example, if we were to assume an average of 20 endemic viruses per vertebrate species, the potential reservoir of vertebrate viruses could be estimated at 1 million. Although it is unlikely that most of them can be transmitted to humans and cause disease, it is sobering to consider the challenge of detecting and responding even to 1% of them—10,000 novel viruses.

ONE HEALTH INITIATIVE

The connection between human and animal microbiology was originally recognized by Virchow and Osler in the 19th century. Nonetheless, the relationship has only recently been emphasized through the One Health Initiative, which promotes coequal collaborations between practitioners and researchers in human and comparative medicine, as well as surveillance programs in wildlife, domestic animals, and humans. An important catalytic event for the Initiative was the West Nile virus outbreak in New York City in 1999, where two independent lines of research investigation converged—one focused on high mortality in native corvids (including crows) and exotic birds in the Bronx Zoo that ultimately led to the culture and identification of the virus by the U.S. Department of Agriculture, and another focused on human encephalitis cases. These were initially attributed to St. Louis encephalitis virus but found to be West Nile virus when brain material of victims underwent DNA sequence analysis by a team composed of investigators at the University of California and the New York State Department of Health.[1] Retrospective analysis indicated that the cause of the human outbreak would have been ascertained earlier if the veterinary and medical practitioners had collaborated in sharing data and samples. A series of national and international meetings culminated in the One Health Resolution signed by the presidents of the American Medical Association and American Veterinary Medical Association, with endorsement by the Centers for Disease Control, the U.S. Department of Agriculture, and the European Union.

MECHANISMS OF TRANSMISSION

The mechanisms by which zoonotic agents are transmitted to humans vary widely. Many are linked to food collection, processing, or consumption. The most dramatic examples are diseases associated with the slaughter and consumption of wild animals, also known as bushmeat, such as infections caused by Ebola, Marburg, and monkeypox viruses, as well as SARS, and tularemia. However, less exotic meats are associated with transmission of *Salmonella,* highly pathogenic *Escherichia coli,* and prion diseases (e.g., new-variant Creutzfeldt-Jakob disease).

Phlebotomous (blood-sucking) arthropods, such as mosquitoes, ticks, and flies, may also serve as vectors for transmission of viruses and bacteria from birds and mammals to humans. Prominent examples include West Nile virus, St. Louis encephalitis virus, tick-borne encephalitis virus, and *Borrelia* spp. (Lyme disease). Direct transmission can occur through exposure to infected urine or feces, as in leptospirosis, toxoplasmosis, lymphocytic choriomeningitis virus infection, hantavirus pulmonary syndrome, or through wound inoculation as in

KEYWORDS

arthropod vectors; bacterial infections; bats; bushmeat; chikungunya; Ebola virus; emerging infections; encephalitis; foodborne infections; hemorrhagic fever; influenza; livestock; One Health Initiative; pets; plague; prion infections; protozoan infections; rabies; Rift Valley fever; rodents; tularemia; viral infections; wildlife; zoonosis

Bartonella (cat-scratch fever), or rabies—the oldest recorded example of zoonotic disease and the most common one transmitted directly from infected animals to human by bite.

FACTORS IN THE EMERGENCE OF ZOONOTIC DISEASES

Travel and trade are increasingly global, carrying pathogens as well as passengers and products to new locations. John F. Kennedy airport, for example, one of two international airports in the greater New York metropolitan area, receives nonstop flights from more than 100 international destinations and serves annually more than 12 million international passengers.[2] Similar traffic data apply in other major metropolitan areas. Given that an infected individual, mosquito, or other cargo can cross the world in less than 24 hours, clinicians and public health practitioners must be prepared to encounter known and novel agents in virtually any context.

The advent of global agribusiness and urbanization are also important factors in zoonotic diseases. The international food trade has burgeoned by more than 200% since 1975.[3,4] A hundred years ago, most fresh food was produced and consumed within a radius of a few kilometers. It is now not unusual for individuals to consume plants and animals harvested thousands of kilometers away.[5] Contamination of meat by prions, influenza viruses, *Salmonella,* and Rift Valley fever virus has been documented in international trade of livestock.[6] The centralization of food production and processing, particularly of ground meat or raw fruits and vegetables, has resulted in outbreaks of infectious diseases that may be distributed over large geographic areas.

Illegal trafficking in wildlife as pets or food is difficult to monitor. However, annual sales estimates in the United States alone exceed $10 billion for pets and $15 billion for bushmeat.[7] Analysis of bushmeat from bats, rodents, and primates confiscated in major ports has revealed evidence of foamy viruses, herpesviruses, and pathogenic bacteria.[8] Imported pets have been linked to outbreaks of human infection with poxviruses and *Salmonella,* as well other pathogens.[8]

Attention has also increasingly focused on the role of land use dynamics in infectious disease emergence.[9] Deforestation and the expansion of agriculture and the extractive industries, particularly in tropical regions with high wildlife biodiversity, has led directly or indirectly to the emergence of Nipah virus and filoviruses.[10,11] The growth of suburbs in areas that were once only sparsely populated, particularly in the northeastern United States, has been associated with an increase in the incidence of Lyme disease.

Global warming is already extending the geographic range of mosquitoes and ticks that harbor and transmit *Plasmodium* and arboviruses, resulting in outbreaks of malaria, and dengue and yellow fever in new locations.[12] Recent examples in North America include the appearance of dengue fever in Florida in 2010[13,14] and a surge in cases of West Nile encephalitis in Texas in 2012.[15] Mass migration (resulting from war, natural disaster, poverty, and desertification) can lead to increases in the population density, not only of humans, but also of disease vectors, such as rodents and ectoparasites that carry pathogenic viruses and bacteria. In concert, these factors, malnutrition, lack of access to or refusal of vaccines, and exposure to contaminated food and water have enabled the emergence and transmission of zoonoses and other infectious diseases.[16,17]

PREDICTION AND EARLY DETECTION OF EMERGING AND REEMERGING ZOONOTIC DISEASES

Rapid recognition and response are critical to reducing the mortality, morbidity, and economic and social costs of zoonotic outbreaks. An important factor in early outbreak detection has been the advent of tools for Internet-based infectious disease surveillance. The first of these was ProMED-mail (Programme for Monitoring Emerging Infectious Diseases), created in 1994, which provides continuous, free email updates on new or evolving outbreaks and epidemics[18] in people, domestic animals, and wildlife. Reports submitted by readers are curated by a panel of experts who post submissions with commentary in several languages to a listserve of subscribers in nearly 200 countries. Another program, the fee-based service, GPHIN (Global Public Health Intelligence Network)[19] scans news services worldwide in several languages for information concerning outbreaks.

HealthMap[20] integrates reports from news media, ProMED-mail, and official documents into a user-friendly map that displays real-time updates of disease emergence. HealthMap also allows public submission observations via its website or cellular phone applications.

An ideal surveillance system for zoonotic disease is one that allows identification of potential health threats before they move into the human population. By considering factors implicated as drivers in the emergence of zoonotic diseases, such as human demographics, agricultural production, land-use change, travel and trade patterns, climate and wildlife distribution, risk algorithms can be developed and used to focus surveillance on sites, populations, professions, and species of domestic animals and wildlife where there is an increased probability of known or novel high-threat pathogen emergence.

ZOONOTIC DISEASES

A chapter concerned with infectious agents that share one feature—the capacity to jump host species from domestic animals or wildlife into humans—could be organized by agent, mechanism of transmission, or clinical presentation. I have tried to do all three. The following sections provide an overview of a representative set of zoonotic diseases associated with bats, rodents, and other wildlife as well as domesticated animals. It is illustrative; others might highlight different choices. Nonetheless, it provides a framework for thinking about the range of zoonotic diseases and the factors that contribute to their emergence and control. Table 322-1 indicates routes of transmission and associated syndromes, respectively.

INFECTIONS ASSOCIATED WITH WILDLIFE

Bats, order Chiroptera, comprising more than 1200 species, represent approximately 20% of mammalian species diversity and are found on every continent except Antarctica. They are divided into two suborders: the Megachiroptera, which include fruit bats and flying foxes, and the Microchiroptera, which include insectivorous and vampire bats. Bats are unique among mammals in their ability to fly, tendency to aggregate at high density, and capacity to harbor a wide range of viruses without apparent disease. The physiology of bats is poorly understood, and their tolerance for persistent infection with viruses that cause fatal disease in other mammals is an enigma. However, this puzzle is likely to be solved with recent investments in bat genomic sequencing and systems biology.

A wide range of highly pathogenic RNA viruses have been found in bats: henipaviruses associated with equine and human infections in Australia (Hendra virus), human and pig infections in Malaysia (Nipah virus), and human infections in Bangladesh (Nipah virus), filoviruses associated with human and great ape infections in central Africa (Ebola and Marburg viruses), rabies virus, and the coronaviruses implicated in SARS and the recent outbreak of fatal respiratory and renal disease in the Middle East (see Chapter 157). The route of transmission can vary even for the same virus. Whereas in Malaysia, farm workers became infected with Nipah virus through exposure to pigs that had consumed contaminated droppings of frugiverous bats, in Bangladesh, where pigs are not farmed, human Nipah virus infection has been associated with consumption of palm sap beverages contaminated by bats. In North America, silver-haired bats transmit rabies virus via a bite wound. Humans are typically infected by filoviruses through exposure to infected primate meat; however, there are instances in which infection may have occurred through consumption of infected bats or exposure to bat excreta in close quarters (e.g., caves and abandoned mines). The SARS coronavirus is presumed to have entered the human population through intermediate species (civets) in live-animal markets. We do not yet know the path for human infection of the most recent coronavirus that emerged in the Middle East. Although there are examples of human-to-human transmission of filoviruses and henipaviruses through contact with blood or other bodily fluids, the only bat-associated pathogen that is known to have established efficient transmission within the human population is the SARS coronavirus.

Nipah virus, Hendra virus, and SARS coronavirus cause respiratory disease and spread via aerosol. All are associated with high morbidity

TABLE 322-1 Important and Representative Zoonotic Pathogens of Humans

VECTOR		AGENT FAMILY	AGENT	DISEASE
Arthropod	Mosquito	Bunyaviridae	La Crosse encephalitis virus, California encephalitis virus	Encephalitis
			Rift Valley fever virus	Hemorrhagic fever
		Flaviviridae	Japanese encephalitis virus, St. Louis encephalitis virus, West Nile virus	Encephalitis
			Dengue virus, yellow fever virus, Zika virus	Hemorrhagic fever
		Togaviridae	Eastern equine encephalitis virus, western equine encephalitis virus, Venezuelan equine encephalitis virus, chikungunya virus, o'nyong-nyong fever virus	Encephalitis
	Tick	Bunyaviridae	Crimean-Congo hemorrhagic fever virus	Hemorrhagic fever
		Flaviviridae	Tick-borne encephalitis virus, Powassan encephalitis virus	Encephalitis
			Omsk hemorrhagic fever virus, Kyasanur forest virus, Langat virus	Hemorrhagic fever
		Spirochaetaceae	*Borrelia*	Lyme disease
	Flea	Enterobacteriaceae	*Yersinia pestis*	Hemorrhagic fever (plague)
Mammal	Rodent	Arenaviridae	Lassa fever virus, Guanarito virus, Junin virus, Machupo virus, Sabia virus, Lujo virus	Hemorrhagic fever
			Lymphocytic choriomeningitis virus	Meningitis, encephalitis
		Bunyaviridae	Dobrava-Belgrade virus, Hantaan virus, Puumala virus, Seoul virus	Hemorrhagic fever
			Sin Nombre virus	Pulmonary syndrome
		Spirochaetaceae	*Leptospira*	Leptospirosis
	Rabbit	Francisellaceae	*Francisella tularensis*	Tularemia
	Bat	Filoviridae	Ebola virus, Bundibugyo virus, Sudan virus, Tai Forest virus, Marburg virus	Hemorrhagic fever
		Rhabdoviridae	Rabies virus, Chandipura virus	Encephalitis
		Paramyxoviridae	Hendra virus, Nipah virus	Pulmonary, encephalitis
		Coronaviridae	Severe acute respiratory syndrome coronavirus, Middle Eastern coronavirus	Pulmonary
	Cattle	Prions	Bovine spongiform encephalopathy prion	Neurodegeneration
	Cat	Bartonellaceae	*Bartonella*	Cat-scratch disease
		Sarcocystidae	*Toxoplasma*	Toxoplasmosis
Avian	Bird	Orthomyxovirus	Influenza virus	Constitutional illness

and mortality. However, whereas the primary site of pathology in SARS is the lung, Nipah and Hendra viruses cause encephalitis. Ebola and Marburg viruses cause disseminated intravascular coagulation resulting in hemorrhagic shock and multiorgan failure. Ebola virus, Marburg virus, and the arenaviruses and hantaviruses described in the next section are known collectively as *hemorrhagic fever viruses,* in accord with the clinical manifestations of disease. A diagnosis can be made based on clinical presentation in cases in which others with similar presentation, including animals, have had a laboratory diagnosis. Although serology can be definitive, a laboratory diagnosis is typically made by an agent-specific polymerase chain reaction (PCR) assay. There is no established effective therapy for the disease caused by SARS, Nipah, Hendra, Ebola, or Marburg viruses. Vaccines have been effective in preventing disease in animal models of Ebola and Marburg virus infection; monoclonal antibodies may reduce morbidity and mortality in disease caused by Nipah and Hendra viruses. Rabies is typically fatal once the virus enters the central nervous system; however, postexposure prophylaxis is effective, particularly when the exposed individual receives not only vaccine but also rabies immune globulin injected in proximity to the puncture wound.

Rodents, like bats, are globally distributed. They are the largest order of mammals, comprising more than 2200 species, and are implicated in transmission of both viruses and bacteria. The rodent-associated arenaviruses (named for their sandy appearance by electron microscopy; *arena* means sand in Latin) that cause human disease include Lassa fever virus, endemic in western Africa; lymphocytic choriomeningitis virus, found in the Eastern and Western Hemispheres; and several South American viruses, including Guanarito, Junin, Machupo, and Sabia (see Chapter 169). Another African arenavirus, Lujo virus, is presumed, but not proven, to have a rodent reservoir. Lassa fever is clinically similar to the infections caused by Ebola and Marburg viruses; however, whereas Lassa fever virus infection may be asymptomatic in up to 80% of cases, asymptomatic filovirus infection is uncommon. The South American arenaviruses can cause hemorrhagic fever but can also be associated with asymptomatic infection. Lymphocytic choriomeningitis virus has been implicated in aseptic meningitis and birth defects, particularly in the central nervous system. Although there is no specific drug for arenavirus infection, the nucleoside analogue ribavirin may have efficacy. Passive immunotherapy with hyperimmune plasma has been useful in Argentinean hemorrhagic fever (Junin virus infection).

Leptospira organisms, named for their morphology (*leptos* is thin in Greek; *spiral* is coil in Latin), are spirochetes that persistently infect rodents, concentrating in the kidneys. Infectious organisms are excreted in urine, collect in standing water, and enter humans and other animals either through breaks in the skin or the alimentary canal. Infection is correlated with potential for exposure; hence, leptospirosis is common year-round in the tropics and during warm wet months in temperate climate zones (see Chapter 241). Food markets, particularly those where rodents congregate and where there is opportunity for blood from infected animals to contaminate standing water, are high-risk environments for contraction of disease. The onset of disease is heralded by nonspecific symptoms, such as fever, malaise, and headache. The illness may progress to meningitis, vasculitis, renal and liver failure, and disseminated intravascular coagulation. Antibiotics (penicillin, amoxicillin, and doxycycline) are effective in prophylaxis as well as for therapeutic intervention. There are vaccines for some serotypes.

The Bunyaviridae family of RNA viruses includes several important human pathogens: hantaviruses, nairoviruses, and phleboviruses. Hantaviruses are transmitted by contact with rodent excreta (see Chapter 168); the other clinically significant bunyaviruses are transmitted through blood exchange by arthropod vectors, including mosquitoes, ticks, and flies. Hantaviruses (named for the Hantaan River in South Korea, where the first hantaviruses were identified) may cause hemorrhagic fever with renal failure (hemorrhagic fever with renal syndrome, HFRS) or an acute respiratory distress syndrome (hantavirus pulmonary syndrome [HPS]). HFRS is more common in Africa, Asia, and Europe. HPS has only been reported in North America. There is no hantavirus-specific drug or vaccine. Recovery from HFRS is not uncommon with supportive care; however, HPS is typically fatal. Crimean-Congo hemorrhagic fever virus, a nairovirus, is distributed throughout Asia and Africa. A wide range of small mammals may serve as reservoirs; domestic sheep, goats, cattle, and horses are typically intermediate hosts. The agent is most commonly transmitted by ticks; however, outbreaks have been linked to preparation or consumption of infected meat. Manifestations of disease range from mild influenza-like illness to hemorrhagic fever.

Tick-borne encephalitis is a meningoencephalitis due to infection with a flavivirus called tick-borne encephalitis virus (TBEV). TBEV is found in Europe and Asia. It is transmitted to humans from a wide range of infected hosts, including sheep, deer, and rodents. Infection is rarely fatal; however, neurologic sequelae are not uncommon. There are effective vaccines but no known antiviral therapy.

The most common tick-borne illness is Lyme disease (see Chapter 243). In North America, the causative agent is the spirochete *Borrelia burgdorferi*, carried by the tick *Ixodes scapularis*. In Europe and Asia, the correlate agents include *Borrelia afzelii and Borrelia garinii*, carried by *Ixodes ricinus* and *Ixodes persulcatus*, respectively. Early signs and symptoms of disease may include fever, lassitude, and headache. Some individuals have a classic "bull's-eye" skin rash known as erythema chronicum migrans, which is characterized by redness in the center and the periphery with central clearing. Later stages of the disease may include facial weakness (Bell's palsy), peripheral neuropathy, and encephalomyelitis. Rodents are the reservoir for the spirochete; however, deer are also important to its life cycle. Thus, human transmission is most common in suburban and rural areas, particularly where the density of vegetation is sufficiently thick to harbor large concentrations of rodents. Diagnosis is straightforward in the presence of the characteristic rash, when there is history of travel or exposure to an endemic area and a tick bite. However, many patients will not recall a tick bite, and up to 20% may not have the rash. Laboratory tests are frequently inconclusive.

Francisella tularensis, the causative agent of tularemia (also known as rabbit fever), infects a wide range of vertebrates and invertebrates (see Chapter 229). The most important reservoirs are rodents, deer, and rabbits. Humans become infected through contact with infected animals or hematophagous vectors, including mosquitoes, ticks, or flies. Thus, hunters, hikers, and farmers are at higher risk. Outbreaks of severe respiratory disease have been described in landscapers. The manifestations of infection vary with the route of exposure. Cutaneous inoculation typically results in a vesicular rash that may ulcerate and regional lymphadenopathy. Ingestion results in oropharyngeal lesions. Inhalation can lead to fatal pneumonia. Ocular inoculation results in conjunctivitis. Without antibiotic treatment, some strains disseminate systemically and are associated with up to 30% mortality. The diagnosis is typically made based on clinical presentation with confirmation by PCR or culture. The agent is sensitive to ciprofloxacin, aminoglycosides, and chloramphenicol. Vaccines are in development because of concerns that *F. tularensis* may become a weapon of bioterrorism.

Yersinia pestis, the causative agent of plague, is found in rodents throughout the world, with the exception of Oceania, and has jumped many times to humans (see Chapter 231). Infection is transmitted to humans primarily by fleas. However, transmission can also occur by ingestion and inhalation. Periodic pandemics, including the Black Death, have cost hundreds of millions of lives. Although outbreaks continue to the present in urban areas in the developing world, the majority of reports represent infections of single individuals in both cities and the countryside. The manifestations of disease can vary from an influenza-like mild fever and lymphadenopathy (buboes) to pneumonia, shock, disseminated intravascular coagulation, and tissue necrosis. The diagnosis is typically made based on clinical presentation with confirmation by PCR or culture. Like *F. tularensis*, *Y. pestis* is sensitive to ciprofloxacin, aminoglycosides, and chloramphenicol. It has the dubious distinction of being one of the first microbes to be used as a biological weapon (in the 14th century) and remains a biosecurity concern.

DISEASES ASSOCIATED WITH AGRICULTURAL AND OTHER DOMESTIC ANIMALS

Zoonotic agents associated with livestock, poultry, and companion animals include bacteria, fungi, parasites, and prions. Industrialization of food production has increased the probability of animal-to-animal infection on feedlots and henhouses, as well as cross-contamination of processed meats and dairy products . Outbreaks of disease caused by *E. coli*, including a potentially fatal hemolytic-uremic syndrome, are commonly linked to contaminated ground beef. Raw poultry is frequently associated with outbreaks of *Salmonella* and sporadic cases of *Campylobacter* infections. The use of antibiotics as growth promoters in agriculture also selects for the emergence of antibiotic-resistant bacteria that contribute to human morbidity and mortality associated with infectious disease.

Variant Creutzfeldt-Jakob disease (vCJD) is a progressive, fatal brain disorder caused by exposure to misfolded proteins (prions) in cattle, with an analogous disease known as bovine spongiform encephalopathy (BSE), that catalyze conformational changes in host proteins. BSE was first identified in the United Kingdom in 1986 and peaked in incidence in 1993. The original infection is presumed to have been introduced when cattle were fed with offal from infected sheep or cows. An estimated 400,000 cows with BSE are estimated to have entered the food chain before the outbreak was terminated by culling cattle with behavior indicative of BSE, reducing the age of slaughter (so that titers would be lower in the event an infected animal was inadvertently used for human consumption), and eliminating the practice of feeding animal products to ruminants in 1997. At least 227 people exposed to BSE contracted vCJD. Susceptibility to this disease is determined at least in part by the prion protein (PrP) genotype. The peak incidence of vCJD was observed in 2000 and tapered thereafter. Some investigators predict that a large wave of new cases is unlikely in the absence of recurrence of BSE. However, others note that the incubation of kuru, a prion disorder associated with ritual cannibalism, may be as long as 27 years. The diagnosis of vCJD is made using brain or tonsillar biopsy based on histology and/or the presence of protease-resistant PrP. There is no effective treatment or vaccine for prion diseases.

Rift Valley fever virus, a bunyavirus transmitted by mosquitoes, chiefly affects livestock but can cause human disease (Rift Valley fever), ranging from mild febrile illness to meningitis or hemorrhage and multiorgan failure. Originally reported in Kenya, the virus has expanded in distribution across sub-Saharan Africa and the Arabian Peninsula. Here the domesticated livestock serve as an important geographically proximate reservoir for the infection.

A detailed discussion of influenza virus is beyond the scope of this chapter (see Chapter 167), yet it is a classic zoonotic disease. Influenza is not typically considered a zoonotic disease because human-to-human transmission is efficient; however, both birds and pigs play key roles in the maintenance of existing strains and the emergence of new ones. Only influenza A viruses are associated with pandemic disease, presumably because they have a higher propensity to evolve toward antigenic diversity and thus evade host immune surveillance than influenza B and C viruses. Wild aquatic birds are the natural hosts of the classic seasonal influenza viruses H1N1 and H3N2. Infection of free-range pigs by migrating aquatic birds or in live-animal markets, where they may be housed near aquatic birds, can lead to genetic reassortment (when more than one type of influenza virus is present) and adaptation to humans. H5N1, popularly known as avian influenza, only rarely results in human disease but is frequently fatal when it does. A wide range of diagnostic assays is available for detection of influenza viruses. Vaccines are designed twice each year to reflect strains predicted to predominate during the influenza season in the Southern and Northern Hemisphere. Their efficacy fluctuates with the accuracy of those predictions but, as a rule, is less effective in inducing a protective immune response in the elderly. Efforts are underway to create universal influenza vaccines based on conserved regions of the virus hemagglutinin, rather than those that evolve to evade the immune system. The drug oseltamivir is effective for many strains.

Up to 30% of the world's population may have been exposed to the protozoan parasite *Toxoplasma gondii*, including more than 60,000,000 people in the United States. Infection is contracted through ingestion of contaminated food or contact with feces of domestic cats, the natural host (see Chapter 280). In most instances, infection is asymptomatic or associated with a transient influenza-like illness; however, with immunosuppression in the context of HIV/AIDS, chemotherapy, or pregnancy, the parasite can present as a mass lesion in the brain, causing focal deficits and seizures. Infection of the fetus during pregnancy can result in miscarriage and abnormal brain development. Both house cats and foods of animal origin play roles in the transmission of the agent to humans, where it may remain latent for decades.

A common form of zoonosis concerns natural infections in birds, with arthropod-borne (accidental) transmission to humans. Eastern, western, and Venezuelan equine encephalitis viruses (EEEV, WEEV, VEEV) are mosquito-borne alphaviruses that infect a wide range of vertebrates (see Chapter 153). Birds are the natural reservoirs. The nomenclature reflects the observation that horses with encephalitis are frequent sentinels for risk of human disease and roughly approximates the geographic distribution of the virus. EEEV is found throughout North, Central, and South America but is concentrated in the United States east of the continental divide. WEEV is found in the western United States. VEEV is found primarily in Central and South America. All are associated primarily with an influenza-like illness but may, in a small proportion of cases, progress to encephalitis. West Nile virus (WNV) is a mosquito-transmitted flavivirus that was associated with only mild, sporadic disease until the 1990s, when virulent strains appeared first in Europe and then in North America. Many vertebrate species are susceptible to infection; however, the primary reservoir is birds. Although most infections are asymptomatic or associated with mild influenza-like illness (West Nile fever), encephalitis and poliomyelitis can occur in individuals who are immunologically compromised because of advanced age or underlying medical conditions.

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