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Introduction

Zoonoses are diseases transmissible from vertebrate animals, other than humans, to people. Mammals, birds, reptiles, and probably amphibians are reservoirs or amplifying hosts for viral zoonoses. Frequently, these viruses cause little or no overt disease in their nonhuman vertebrate hosts. Some zoonotic viruses have very limited host ranges; others may infect a wide range of vertebrates. Human infection may vary from unapparent to fatal disease. Both new and old viral zoonoses are especially important in emerging and reemerging virus diseases. Transmission of zoonotic viruses may occur by a variety of routes. They include: "direct" (e.g., rabies virus) or "indirect" (e.g., hantavirus) contact; "nosocomial" (e.g., Ebola virus); "aerosol transmission" (SARS coronavirus); "vertical" (in utero) (Zika virus); and "vector- or arthropod-borne" (e.g., yellow fever virus and West Nile virus). Viral zoonotic diseases occur on every continent except, perhaps Antarctica. Some are found around the world, in a variety of ecological settings. Others are found only in very limited ecological and geographic foci. Although hundreds of viruses are zoonotic, the importance of many of these viruses has not yet been established. Some of the more important viral zoonoses will be discussed briefly.
**Rabies Virus**

Rabies is one of the oldest reported zoonoses. Rabies virus infection causes nervous system disease that ends in death. Animals can become infected without nervous system disease, develop antibodies, and survive, but play no role in transmission. Classical rabies is found all around the world except in Antarctica, Britain, the Hawaiian Islands, Australia, and New Zealand. Transmission occurs by the bite of an infected animal. Aerosol (droplet) transmission is rare. Dogs are the main reservoirs in tropical developing countries where >99% of all human cases occur. In industrialized countries where canine vaccination is often mandated, cats are more likely to be infected than dogs, however, wild mammals remain the main reservoirs. The species involved vary from region to region. The principal species are as follows: in North America, skunks, raccoons, and foxes; in Europe, foxes; and in the Caribbean, mongooses. Bats in all enzootic regions harbor rabies with vampire bats especially important in the Neotropics, where they transmit rabies to cattle, horses, and other domestic animals, and, occasionally, to humans. Rabies virus is classified in the genus *Lyssavirus* of the family *Rhabdoviridae*. Genetic relationships between rabies isolates from different species and geographic areas have been established by genomic sequence analysis (Table 1).

Diagnosis is based on characteristic altered behavior of infected mammals, confirmed by either isolation of virus; demonstration of intracellular antigen by immunofluorescence; or of virus genomic sequences. Postexposure treatment is accomplished by thorough washing of the bite wound, administration of hyperimmune serum or globulin, and administration of antirabies vaccine. Dogs and cats in enzootic areas should be vaccinated. This represents the single most important public health measure that can reduce rabies infection in humans. Other domestic animals and humans at high risk should also be vaccinated. Vaccination campaigns of free-ranging red fox populations in Europe and raccoons and coyotes in the United States have been carried out by oral administration of recombinant vaccinia-vectored vaccines in bait.

**Influenza Viruses**

Influenza viruses are members of the family *Orthomyxoviridae* and consist of four Types. Influenza A viruses are widely distributed in nature and infect humans along with a wide variety of birds, especially waterfowl, and mammals. Virus subtypes are classified on the basis of the antigenicity of their surface glycoproteins hemagglutinin (HA) and neuraminidase (NA). To date, 18 HA and 11 NA genes are known to exist. Of these genes, only three HA (H1, H2, and H3) and two NA (N1 and N2) subtypes have circulated in the human population in the current and last century. The most catastrophic impact of influenza was the pandemic of 1918, also known as the Spanish flu (H1N1), which resulted in the loss of 500,000 lives in the United States and caused about 40 million deaths worldwide. Influenza B circulates among humans and is not considered zoonotic, although recent data suggests it can occur in seals. Influenza C occurs in humans and pigs, but is a very mild illness and is rarely reported. Influenza D occurs in cattle and has not been reported as a human pathogen.

The ability of influenza viruses to undergo antigenic changes is the cause of ongoing significant public health concern. New subtypes emerge when human virus captures genes from animal influenza viruses via reassortment; an event that can occur when both virus types simultaneously infect a host (antigenic shift). Although human strains of influenza A virus replicate poorly in waterfowl, and avian strains generally replicate poorly in human, both replicate well in pigs, making them the ideal "mixing vessel" for emergence of new strains of virus. The threat imposed by influenza virus has been further elevated with the recent introductions of avian influenza viruses into the human population. Avian influenza viruses were initially considered nonpathogenic for humans. However, this perception has changed since 1997, when 18 Hong Kong residents were infected by an avian influenza virus of the H5N1 subtype that resulted in six deaths. Over the next few years, several other cases of direct avian-to-human transmission were reported, including the ongoing outbreak of highly pathogenic H5N1 influenza viruses in several Asian, African, and European countries. More recently, H7N9 strains of avian influenza have emerged and been associated with infections in humans having close contact with commercial poultry.

| Virus name       | Lyssavirus genotype | Location  | Host                                      |
|------------------|---------------------|-----------|-------------------------------------------|
| Rabies           | 1                   | Worldwide | Many wild and domestic mammals           |
| Lagos bat        | 2                   | Africa    | Bats, water mongoose (but no human disease) |
| Mokola           | 3                   | Africa    | Several terrestrial mammals              |
| Duvenhage        | 4                   | Africa    | Bats                                     |
| European bat-1   | 5                   | Europe    | Bats                                     |
| European bat-2   | 6                   | Europe    | Bats                                     |
| Australian bat   | 7                   | Australia | Bats                                     |
| Aravan           | New, proposed       | Kyrgyzstan| Bats                                     |
| Khujand          | New, proposed       | Tajikistan| Bats                                     |
| Irikut           | New, proposed       | Russia    | Bats                                     |
| West Caucasian bat| New, proposed      | Russia    | Bats                                     |
Migratory waterfowl—most notably wild ducks—are the natural reservoir of avian influenza viruses, and these birds are also the most resistant to symptomatic infection. Domestic poultry, including chickens and turkeys, are particularly susceptible to epidemics of rapidly fatal influenza. Direct or indirect contact of domestic flocks with wild migratory waterfowl has been implicated as a frequent cause of epidemics. Live bird markets have also played an important role in the spread of epidemics. Viruses of low pathogenicity can, after circulation for sometimes short periods in a poultry population, mutate into highly pathogenic viruses. Quarantine of infected farms and destruction of infected or potentially exposed flocks are standard control measures aimed at preventing spread to other farms and eventual establishment of the virus in a country's poultry population.

**Hantavirus Hemorrhagic Fevers and Pulmonary Syndrome Viruses**

Hantaviruses belong to the genus *Hantavirus* of the family *Bunyaviridae*. In the Americas, hantavirus can cause hantavirus pulmonary syndrome (HPS), an infectious disease typically characterized by fever, myalgia, and headache and followed by dyspnea, non-cardiogenic pulmonary edema, hypotension, and shock. HPS has also been reported and confirmed in seven countries in South America: Argentina, Bolivia, Brazil, Chile, Paraguay, Uruguay, and Panama (Table 2). A more severe clinical syndrome, hemorrhagic fever with renal syndrome (HFRS), shares many of the clinical symptoms of HPS but includes acute renal failure in the final stages. Hantaviruses are harbored by wild rodents which often live in close association with humans. Virus is shed in urine and other excreta. Outbreaks of HPS have been associated with ecological changes and invasion of human habitations by expanding wild rodent populations. More recently, outbreaks of HFRS have been associated with infections in commercial rat colonies. When hantavirus infections were first recognized diagnosis was complicated by the lack of efficient and sensitive isolation and serological methods. However, recent advances in molecular diagnostics has made clinical diagnosis much more efficient and practical. Rodent control and avoidance of exposure to rodent excreta, especially in dust, are the only methods available currently for prevention of transmission to humans.

**Arenavirus Hemorrhagic Fever Viruses**

Arenaviruses are transmitted by the same kind of rodents that carry hantaviruses. They can also cause hemorrhagic fevers and, even though the prototype of this family has been long known (lymphocytic choriomeningitis virus, LCMV), viruses within this family are still being discovered. They produce human diseases in the Old World (Lassa fever in Africa) and New World (Junin, Machupo, and, later on, Guanarito and Sabia in South America). There are about 22 different arenaviruses in the Americas, but only four are associated with significant human disease. These pathogenic arenaviruses establish persistent infection in their rodent hosts, and the virus is shed in urine, infecting humans who live in close contact with these contaminated environments. LCMV has been documented to occur as a result of organ transplantation. Lassa fever is also transmitted nosocomially in rural hospitals to other people in contact with blood from viremic patients. Control of these diseases is attempted mainly by reduction of rodent populations. A live, attenuated vaccine has been developed for Argentine hemorrhagic fever, and a vaccinia-vectored vaccine has been developed for Lassa fever. Ribavirin is effective for treating arenavirus infection if given early in the course of infection and convalescent immune plasma has been administered with some success.

### Table 2 Hantaviruses that cause human disease

| Virus name | Distribution | Rodent host | Human disease                      |
|------------|--------------|-------------|-----------------------------------|
| Hantaan    | Asia, Europe | Apodemus agrarius | Hemorrhagic fever with renal syndrome |
| Seoul      | Worldwide    | Rattus spp.  | Hemorrhagic fever with renal syndrome |
| Dobrava-Belgrade | Europe, Middle East | Apodemus flavicollis | Hemorrhagic fever with renal syndrome |
| Puumala    | Europe, Asia | Clethrionomys glareolus | Hemorrhagic fever with renal syndrome |
| Sin Nombre | North America| Peromyscus maniculatus | Pulmonary syndrome |
| New York   | North America| Peromyscus leucopus | Pulmonary syndrome |
| Bayou      | North America| Oryzomys palustris | Pulmonary syndrome |
| Black Creek Canal | North America | Sigmodon hispidus | Pulmonary syndrome |
| Andes      | South America| Oligoryzomys lanoiicta | Pulmonary syndrome |
| Hu39694    | South America| Unknown       | Pulmonary syndrome |
| Juquitiba  | South America| Unknown       | Pulmonary syndrome |
| Laguna Negra| South America| Calomys laucha| Pulmonary syndrome |
| Lechiguanas| South America| Calomys laucha| Pulmonary syndrome |
| Oran       | South America| Oligoryzomys lanoiicta| Pulmonary syndrome |
| Choclo     | Panama       | Zygodontomys brevicauda| Pulmonary syndrome |
| Monongahela| North America| Peromyscus maniculatus nubetareina| Pulmonary syndrome |
| Bermejo    | South America| Oligoryzomys chacoensis| Pulmonary syndrome |
| Central Plata | South America | Oligoryzomys flavescens| Pulmonary syndrome |
| Araraquara | South America| Bolomys lasiurus| Pulmonary syndrome |
**YF Virus**

YF is a flavivirus that causes hemorrhagic disease with severe liver damage and death in up to half of the most acute cases. The virus exists predominately in a jungle (sylvan) cycle between nonhuman primates and mosquitoes. Humans or primates can transport the virus from densely forested regions to grassland (savanna) environments or urban areas, where a variety of mosquito vectors can transmit YF to humans. YF remains a disease of significant public health importance, with an estimated 200,000 cases and 30,000 deaths annually. The disease is endemic in tropical regions of Africa and South America; nearly 90% of YF cases and deaths occur in Africa. It is a significant hazard to unvaccinated travelers to these endemic areas. Reestablishment of the major urban vector, *Aedes aegypti*, the recent spread of the Asian tiger mosquito (*Ae. albopictus*) as well as the rise in air travel has increased the risk of introduction and spread of the disease. YF is an acute infectious disease characterized by sudden onset with a two-phase development, separated by a short period of remission. The clinical spectrum of YF varies from very mild, nonspecific, febrile illness to a fulminating, sometimes fatal disease with pathognomonic features. In severe cases, jaundice, bleeding diathesis, with hepatorenal involvement is common. There is no specific treatment for YF, making the management of YF patients extremely problematic. YF can be diagnosed by virus isolation, detection of circulating antigens, demonstration of a significant rise in specific YF virus antibodies, and microscopic detection of viral inclusion bodies or antigen in tissues taken at postmortem examination. Insecticide spraying and elimination of breeding sites in homes can be used for vector control in epidemic situations. Disease can be prevented in humans by vaccination.

**West Nile Virus**

West Nile virus (WNV) is a flavivirus maintained in nature through a bird–mosquito–bird cycle of transmission. The virus was first discovered in the West Nile District of Uganda in the 1937. Since then it has been found to be widespread throughout parts of Africa, the Middle East and Eurasia, and has been associated with numerous outbreaks among humans and horses. WNV first appeared in North America in 1999 with an outbreak in New York City producing high mortality in crows and other birds. Based on serologic surveys, most human infections are asymptomatic. However, around 20% of infected individuals experience a febrile illness characterized by malaise, myalgia and lymphadenopathy. [<1% of patients show severe neurologic involvement manifested by focal paralysis, encephalitis, coma and death. Severe neurological involvement is most common in young children and the elderly. After 1999 the virus spread rapidly throughout North America, the Caribbean, Mexico, and into South America. WNV is now present in every state except Hawaii, and Alaska. Numerous bird and mosquito species have been are susceptible to infection with WNV but vary dramatically in their competence as reservoir hosts and vectors. *Culex* spp. mosquitoes seem especially important as vectors. There is no vaccine or antiviral therapy currently approved for humans.

**Chikungunya Virus**

Chikungunya (CHIK) is an alphavirus of the family *Togaviridae* that has been responsible for acute febrile disease with rash and severe arthralgia in people in Africa and Asia. The disease can cause significant morbidity due to the severe joint pain and can contribute to mortality, especially in elderly patients. CHIK virus is maintained in sylvan or savanna cycles involving wild primates and arboreal *Aedes* mosquitoes. In both Africa and Asia, the virus also has an urban cycle involving humans and *Ae. aegypti* mosquitoes that is more important from a public health standpoint. An outbreak of CHIK was reported on Reunion Island in March 2005 that resulted in >3,500 confirmed cases and an estimated 250,000 suspected cases, affecting >25% of the island’s inhabitants. Since then the geographic distribution and number of cases has expanded dramatically, with many thousands of cases being documented in the Americas ranging from the southern United States into South America. No vaccine or specific antiviral therapy is currently available.

**Zika Virus**

Zika virus is flavivirus maintained in nature through a mosquito–monkey–mosquito transmission cycle. The virus was discovered in 1947 in the Zika forest in Uganda and, until 2007, was restricted to an equatorial belt across Africa and Asia. Since then there has been significant spread of infection throughout Central and South America and into the southern United States. Infection in humans is through *Aedes* spp. mosquitoes, mostly *A. aegypti* and *A. albopictus*. Sexual transmission can also occur and recent studies indicate that men infected with Zika virus can have viable virus present in their semen for up to 6 months or more. One of the most important complications of Zika virus infection is vertical transmission from mothers to infants either in utero or during delivery. Although most infections are subclinical, when symptoms do occur they mimic a mild form of dengue with fever, arthralgias, conjunctivitis and maculopapular rash. In infants the consequences are much more severe with many of them developing microcephaly and other severe brain malformations. There is no specific antiviral therapy for Zika virus. Prevention is based largely on avoidance of mosquito vectors in endemic areas and reducing sexual transmission to women of child bearing age from men recovering from acute infection. Clinical trials are underway but to date there are no approved vaccines currently available.
Sindbis Virus

Sindbis (SIN) virus is one of the most widely distributed mosquito-borne viruses in the world, being found in Africa, Europe, Asia, and Australia. Disease in humans is usually mild, and is characterized by acute fever, with arthralgia, myalgia, and rash. There have been periodic epidemics in Finland, where it is termed Podosta disease. SIN virus is maintained predominately in wild bird populations and possibly some mammals. Vectors include *Culex* and *Culiseta* spp. mosquitoes. In Africa and the Middle East, SIN is often found in the same ecosystems where WNV virus is transmitted. The virus is an alphavirus of the *Togaviridae*. Phylogenetic analysis indicates that there is one major genetic cluster of western SIN virus strains in Africa and another in Australia and Asia. There is evidence of some geographic mixing of western strains of SIN virus that suggest long-distance transport via migrating birds. There is no vaccine available. Since many of the mosquito vectors breed in extensive rice fields, large-scale control would be expensive.

Crimean-Congo Hemorrhagic Fever Virus

Crimean-Congo hemorrhagic fever (CCHF) virus is very widely distributed, and is found from eastern Europe and the Crimean, southward through the Middle East to western China, and southward to South Africa. CCHF is characterized by severe hemorrhagic fever with hepatitis, with case mortality of 10%–50%. Maintenance of CCHF virus involves horizontal transmission from *Hyalomma* ticks to cattle, goats, sheep and other mammals. Vertical transmission occurs through tick eggs. *Hyalomma* ticks have been found on birds migrating between Europe and Africa—a mechanism for long-distance dispersal of the virus. Transmission can also occur from contact with infected animal blood and nosocomially through infected human blood and body fluids. Human CCHF cases have occurred in workers handling livestock and their products in Saudi Arabia and the United Arab Emirates which have been attributed to importation of infected cattle and their ticks from Somalia and the Sudan. There are no vaccine or tick control measures available. CCHF virus belongs to the genus *Nairovirus* of the *Bunyaviridae*. Genetic analysis indicates that reassortment and recombination occur in nature.

Sandfly Fever Viruses

Sandfly fever (Sicilian, Naples, and Toscana) viruses are endemic in the Mediterranean area. They cause acute febrile disease in humans, with occasional aseptic meningitis. In central Italy, Toscana virus (TOSV) caused one-third of previously undiagnosed cases of aseptic meningitis. There are at least two genetic lineages of TOSV—Spanish and Italian. The viruses are members of the genus *Phlebovirus* of the *Bunyaviridae*. They are transovarially and horizontally transmitted by phlebotomine sandflies. Wild mammals are presumed, but unproven, reservoirs and recent serological surveys suggest that domestic dogs may be an important component of the transmission cycle.

Viruses Occurring in the Americas

Encephalitis Viruses

Venezuelan equine encephalitis (VEE) viruses are made up of a closely related complex of subtypes with several varieties, which have differing epidemiology, geographic distributions, and disease importance. The epizootic/epidemic (VEE, IAB, and IC) virus variants are of greatest concern. In equines (horses, donkeys, and mules), the virus causes acute encephalitis, and case fatality may approach 80%. Survivors may have serious neurological deficits. Although the case-fatality rate in humans is low (<1%), the large numbers of acutely infected people that occur during an epidemic may completely overwhelm the local healthcare system. VEE, IAB, and IC viruses are maintained in northern South America, where they have periodically swept through Venezuela and Colombia in epidemic waves, with occasional extensions into Ecuador and massively through Central America into Mexico and South Texas. Epidemic spread depends on the availability of susceptible equine populations (the amplifying host) and abundant mosquito vectors of several species. The interepidemic maintenance systems remain undefined but is probably through infected birds, rodents and other mammals in forests and marshlands. There is evidence that the epizootic strains may arise by mutation of subtype ID enzootic virus. The enzootic strains are maintained in limited foci involving rodents and *Culex* (*Melanconion*) spp. mosquitoes from Florida to Argentina. With the exception of subtype IE, which has caused epizootics in horses in Mexico, these enzootic virus strains do not cause disease in equine animals, but can cause acute febrile illness in humans. The VEE complex viruses are in the genus *Alphavirus* of the *Togaviridae*. There is an effective live, attenuated vaccine for both human and equine use. Because the maintenance of equine herd immunity is costly, most animal health agencies do not carry out ongoing, intensive vaccination campaigns. Thus, the risk of reoccurrence of explosive outbreaks remains.

Eastern (EEE) and western (WEE) equine encephalitis viruses occur in epidemic form in North America, but have also been found in Central and South America. Generally, EEE is maintained in eastern North America but has caused scattered epizootics and cases in the Caribbean, and in Central and South America. Both viruses are maintained in nature through bird-mosquito-bird cycles of infection but can infect humans and horses sporadically and during epidemics. The most important vector for EEE is *Culiseta*
*Vesicular Stomatitis Virus*

Vesicular stomatitis (VS) virus is endemic in Central and northern South America and in the southeastern United States, causing an acute, febrile vesicular disease in cattle, horses, and pigs. Vesicles appear mostly on the lips, tongue and lower extremities of infected animals and can be difficult to distinguish clinically from similar illnesses such as Foot and Mouth disease. Humans are at risk from close contact with infected animals and develop a nonspecific influenza-like illness that is not associated with vesicle formation.

Recently, VS epidemics have been documented in the southwestern United States. The VS viruses comprise a complex of related serotypes and subtypes in the Americas, with related vesiculoviruses (family *Rhabdoviridae*) in Africa and Asia. Many of these viruses are transmitted horizontally and transovarially by phlebotomine sandflies. Blackflies, mosquitoes, and other biting insects are also implicated in transmission. There is evidence for infection in wild rodents and other small mammals. However, the role of these mammals in the epidemiology of VS viruses is unclear because they do not develop viremia.
**Other Neotropical Viruses**

Oropouche virus, a Simbu serogroup bunyavirus, causes epidemics, occasionally severe, or acute febrile disease with arthralgia and occasional aseptic meningitis in humans in the Brazilian and Peruvian Amazon as well as Surinam and Panama. During rainy season epidemics, the virus is transmitted by *Culicoides paraensis* biting midges. Enzootic maintenance cycles are believed to involve forest mammals and arboreal mosquitoes.

Mayaro (MAY) virus occurs epidemically in the Brazilian and Bolivian Amazon Basin, and has also been associated with human febrile disease in Surinam and Trinidad. In humans, the acute, nonfatal, febrile disease with rash is clinically similar to CHIK, an alphavirus to which it is antigenically and taxonomically related. MAY virus appears to be maintained in nature in a cycle similar to that of YF, with arboreal mosquito vectors and primate hosts, but also involving other mammals and birds.

Una virus is a close relative of MAY virus and causes human febrile disease also, but its natural history is not known. Una virus has been isolated from several mosquito species, and has been found at scattered sites from northern South America to Argentina. Antibodies have been found in humans, horses, and birds. Genetic analysis suggests that Una virus is maintained in discrete foci.

Rocio virus was first isolated from fatal human encephalitis cases during an explosive outbreak of acute febrile disease in coastal Sao Paulo State, Brazil in 1975, after which sporadic outbreaks have continued. This virus is an ungrouped flavivirus in the *Togaviridae* and is serologically related to Murray Valley encephalitis virus from Australia. The epidemiology is unclear but probably involves wild birds, and several mosquito species are suspected vectors.

**Cowpox-Like Viruses**

Cantagalo and related viruses are orthopoxviruses newly reported in Brazil. They can cause vesiculopustular lesions on the hands, arms, forearms, and face of dairy milkers. Virus particles can be detected by either direct electron microscopy (DEM) in vesicular fluids and scab specimens or isolated in cell culture and embryonated chicken eggs. The epidemiological significance of these new vaccinia viral strains and their origins remains unknown.

**Viruses Occurring in Europe**

Tahyna (TAH) virus is widely distributed in Europe and has been reported in Africa. TAH virus produces an influenza-like febrile disease, with occasional central nervous system involvement. The virus is a bunyavirus of the California serogroup, in the *Bunyaviridae*. Like LAC virus, small forest mammals are TAH virus reservoirs, and the virus is horizontally and transovarially transmitted by *Ochlerotatus* mosquitoes. There are no effective control measures.

Tick-borne encephalitis (TBE) virus has been classified into three subtypes: European, far eastern, and Siberian. Because recreation in wooded areas has increased in recent years, TBE has become the most frequent arthropod-borne disease in Europe. The virus occurs in deciduous forests in Western Europe from the Mediterranean countries, westward to France, and northward to the Scandinavian countries, and eastward to Siberia. It is maintained in a transmission cycle involving small mammals and *Ixodes* spp. ticks. Human infection also occurs through the consumption of unpasteurized milk from infected cows and goats. Infection can be prevented by an inactivated vaccine and avoidance of tick bites.

Omsk hemorrhagic fever occurs in a localized area of western Siberia. Disease can be severe, with up to 3% case fatality, and sequelae are common. This virus is a member of the TBE complex of the flaviviruses. The virus is epizootic in wild muskrats, which had been introduced into the area, and is associated with *Ixodes* ticks. Muskrat handlers are at highest risk of infection. Water voles and other rodents are also vertebrate hosts of the virus. TBE virus vaccine is used in high-risk individuals to provide protection.

Cowpox virus is an orthopoxvirus in the *Poxviridae*. It has a wide host range. Domestic cats and occasionally rats are the most important sources of human infection, transmitting the virus from wild rodent reservoirs to people. In addition to cattle, this virus has produced severe, generalized infections in a variety of incidental animal hosts in zoos and circuses, including elephants and large cats, which may die. Humans develop typical poxvirus lesions (vesicle and pustule formation), usually on the hands, but otherwise experience a mild illness. Laboratory diagnosis (characterization of isolated virus) is required to differentiate cowpox from other nodule-forming zoonotic poxviruses such as orf virus, bovine papular stomatitis virus, and pseudocowpox virus, which are worldwide in distribution.

**Viruses Occurring in Africa and the Middle East**

**Rift Valley Fever Virus**

Rift Valley fever virus (RVF) is among the most serious arbovirus infections in Africa today. Repeated RVF epidemics in sub-Saharan Africa cause serious disease in small ruminant animals and humans. RVF disease has expanded its historical geographic range in the livestock--raising areas of eastern and southern Africa and into the Middle East (Saudi Arabia and Yemen) over the past 25 years, causing massive epidemics in Egypt, along the Mauritania–Senegal border and in Madagascar. A major outbreak in East Africa began in 2006 in northeastern Kenya, and spread into southern Somalia and Tanzania. Cattle, sheep, and humans are affected. Abortion storms with febrile disease and bloody diarrhea occur in ruminant animals, and mortality may be heavy in young stock. Most
infected humans develop febrile disease, with prolonged convalescence. A few individuals develop more severe disease, with liver necrosis, hemorrhagic pneumonia, meningoencephalitis, and retinitis with vision loss. The human case-fatality rate is <1%. RVF virus is in the genus Phlebovirus of the Bunyaviridae. In sub-Saharan Africa, RVF virus is closely tied to its Aedes mosquito vectors. RVF vectors transmit the virus transovarially and horizontally. The virus persists in mosquito eggs laid around seasonally flooded pools and depressions. When these pools flood, the eggs hatch and infected mosquitoes emerge and begin transmission. The vertebrate reservoir hosts of RVF virus are unknown. Field and laboratory workers need to exercise caution to avoid becoming infected by exposure to the virus during postmortem examination of animals or processing materials in the laboratory. Both live, attenuated and inactivated vaccines are available for animals, but the unpredictability of scattered, sporadic RVF outbreaks across sub-Saharan Africa has been a major obstacle for triggering implementation of extensive, cost-effective vaccination programs. More recently, predictive ecologic models using climate data from earth-orbiting satellites along with geographic information systems has made it more feasible to anticipate RVF outbreaks in time to intervene with vaccination programs.

Marburg and Ebola Viruses

Marburg and Ebola are hemorrhagic fever viruses associated with high mortality in humans and nonhuman primates. Marburg virus was discovered in 1967 in association with a laboratory outbreak in Germany among workers exposed to cell cultures from green monkeys (Chlorocebus sabaeus) imported from Africa. Ebola virus infection in humans was first documented in 1976 near the Ebola River, in what is now the Democratic Republic of Congo. Since then, both viruses have caused sporadic outbreaks in dozens to hundreds of persons throughout central and western Africa. This changed in 2014 when a very large outbreak involving nearly 30,000 people erupted in the countries of Guinea, Sierra Leone and Liberia. The outbreak continued into 2016 and resulted in over 11,000 deaths.

Marburg and Ebola are RNA viruses in the family Filoviridae and have a bizarre filamentous and pleomorphic morphology. Both cause a severe hemorrhagic shock syndrome with visceral organ necrosis. Other than rabbies, they have the highest case-fatality rate (30%–90%) in humans of all known viruses. They are known to be zoonotic because of their close association with primates, but the severe disease it causes makes it unlikely that primates are the main reservoir of infection in nature. Based on serologic surveys and other data, fruit bats seem to be an important reservoir for Marburg virus, and possibly Ebola virus. Whether or not other important animal reservoirs exist in nature is unclear and the subject of intense investigations.

Once human infection is established, person-to-person transmission of Marburg and Ebola viruses occurs frequently. An extraordinary level of patient isolation and biosafety containment is needed to avoid hospital and laboratory acquired infection. Laboratory diagnosis is accomplished by enzyme-linked immunoassays (ELISA) and RT-PCR. Both methods have been adapted for use in underdeveloped countries where outbreaks are likely to occur. Treatment is largely supportive, however, a number of other therapies have been used or under development. Immune serum from recovered patients has been used successfully, but is hard to obtain and of insufficient quantity to be effective during outbreaks. Chimeric antibodies to Ebola antigens are under development along with a number of specific antiviral drugs to critical viral replication pathways. During the 2014 outbreak, a candidate vaccine was developed that proved effective in clinical trials.

Monkeypox Virus

Human monkeypox is a smallpox–like illness characterized by fever, lymphadenopathy and vesicular skin eruptions. Monkeypox belongs to the genus Orthopoxivirus in the family Poxviridae. Monkeypox virus (MPXV) is endemic in rodents in West and Central Africa, and is associated with sporadic infections in humans. Human infections occur from close contact with reservoir hosts, and less commonly from person-to-person contact. Two genetic clades of MPXV exist; a western African clade associated with low mortality and minimal risk of person-to-person transmission and a central African clade with higher mortality and significant risk of nosocomial transmission. The largest epidemic of human monkeypox ever documented occurred in the Kato-Kombe area of the Democratic Republic of the Congo (formerly Zaire) in 1996–97, with over 500 people becoming ill and five deaths. Rodent-to-human transmission occurred, as did subsequent secondary human-to-human spread. In 2003, monkeypox emerged for the first time in the Western Hemisphere and caused an outbreak in the Midwestern United States. There were 37 laboratory-confirmed cases and dozens of other probably or suspect cases. The virus entered the United States by importation of infected rodents from western Africa and subsequent exposure of native prairie dogs that were being kept or sold as pets. Molecular analysis showed that the virus was the less virulent western African clade of MPXV and there were no deaths.

Semliki Forest Virus

Semliki Forest (SF) virus caused an extensive epidemic of human disease in Bangui, Central African Republic, in 1987. SF virus is an alphavirus in the Togaviridae. It occurs across East, Central, and West Africa, and has been isolated from various mosquitoes and from wild birds. Antibodies have also been found in wild mammals. The SF virus maintenance cycle probably involves Ae. africanus mosquitoes and vervet monkeys.
**Orungo Virus**

Orungo (ORU) virus caused mild epidemic disease (fever, nausea, headache, and rash) in Nigeria. The virus occurs in a band across Africa from Uganda to Sierra Leone. It is probably mosquito transmitted, but the species that transmit it in nature are not known. Although the vertebrate reservoir hosts are unknown, wild primates have antibody and are suspected to be involved in virus maintenance.

**Alkhurma Virus**

Alkhurma virus (a variant of Kyasanur Forest disease virus, family *Flaviviridae*, genus *Flavivirus*) is an emerging pathogen responsible for hemorrhagic fever in the Middle East. This virus was isolated from hemorrhagic fever patients in Saudi Arabia in 1995. Transmission can occur from tick bites, handling carcasses of infected animals, or drinking unpasteurized milk. The case–fatality rate is 25%.

**Viruses Occurring in Asia**

**Severe Acute Respiratory Syndrome**

In February 2003, a new and previously unknown disease, severe acute respiratory syndrome (SARS), was reported to the World Health Organization (WHO). SARS originated in the province of Guangdong in southern China in November 2002 where it initially was thought to cause atypical pneumonia. However, within a short time the virus spread to Hong Kong, Singapore, Vietnam, Canada, the United States, Taiwan, and several European countries. A novel coronavirus (CoV) was identified as the etiological agent. The SARS-CoV affected >8000 individuals worldwide and was responsible for over 700 deaths during the first outbreak in 2002–03. For reasons unknown the SARS virus is less severe and the clinical progression a great deal milder in children younger than 12 years of age. In contrast, the mortality rate was highest among patients >65 years and can exceed 50% for persons at or above the age of 60 years. Farmed masked palm civets (*Paguma larvata*) and two other mammals in live animal markets in China were sources of SARS-CoV human infection. Three species of horseshoe bats (*Rhinolophus* spp.) are probable wildlife reservoirs in China.

**Kyasanur Forest Disease**

Kyasanur Forest disease (KFD) was first recognized in India in 1957, when an acute hemorrhagic disease appeared in wild monkeys and people frequenting forested areas. KFD has been slowly spreading in India. Human cases have increased from 1999 to 2005, with peak incidence in January and February. The cause of this increase is unknown. KFD virus is a member of the TBE complex of flaviviruses. The basic virus maintenance cycle involves forest mammals (primates, rodents, bats, and insectivores) and ixodid ticks, mainly *Haemaphysalis spinigera*. The virus can be isolated in mice and cell cultures, including tick cells. An inactivated vaccine provides some protection to people at risk of infection.

**Japanese Encephalitis Virus**

Japanese encephalitis (JE) virus is found in a broad area from far eastern Russia, northeastern Asia through China and Southeast Asia to Papua New Guinea and the Torres Strait Islands of Australia and westward into India. JE virus causes the greatest number of clinical human cases, thousands annually, predominantly in children. It produces encephalitis in humans and horses, and acute febrile disease with abortion in swine, an amplifying host. Herons and egrets are wildlife amplifying hosts. The virus is transmitted by *Culex* spp. mosquitoes. The over-wintering mechanism in temperate Asia is unknown. JE virus is a member of a complex of four related flaviviruses in the family *Flaviviridae*. Prevention of disease is mainly through vaccination of humans, horses, and swine. Insecticides and integrated pest control measures that include natural compounds (*Bacillus thuringiensis* toxins), larvicidal fish, and larval habitat modification have been successfully used in China. Use of permethrin-impregnated bed netting can also prevent transmission.

**Chandipura**

Chandipura virus is ubiquitous across the Indian subcontinent. It is a *Vesicularivirus* in the *Rhabdoviridae*. Chandipura has caused epidemics of febrile diseases, sometimes with encephalopathy. An outbreak occurred in 2004 with a case–fatality rate of 78.3% in children in India (Gujarat State). The virus is transmitted by *Phlebotomus* spp. Sergentomine sandflies and infects a variety of mammals. The virus has also been isolated in West Africa.

**Nipah**

Nipah virus (NiV) was first recognized in peninsular Malaysia in 1998, where it caused mild encephalitis and respiratory disease in commercially raised pigs. Nearly 300 humans were infected resulting in over 100 deaths. The outbreak was halted after nearly a
million pigs were euthanized, resulting in severe economic losses for the region. The virus was found in five species of giant fruit bats (Pteropus spp.) and an onion-like virus (NiV) was isolated from partially eaten fruit. Subsequently, there were five NiV outbreaks recognized in Bangladesh, also associated with Pteropus bats. Transmission in Bangladesh was directly from bats, via contaminated fruit and date palm sap.

**Viruses Occurring in Australia**

**Murray Valley Encephalitis Virus and Kunjin Virus**

Murray Valley encephalitis (MVE) virus and the closely related Kunjin virus are flaviviruses that cause encephalitis, although Kunjin virus more commonly produces a nonencephalitic illness with polyarthralgia. MVE virus is endemic in avian species and is found in humans in northern Western Australia, the Northern Territory, and Queensland. MVE virus is endemic in northern areas of Western and Northern Australia, and in New Guinea. Kunjin virus occurs over a much wider area, including most of tropical Australia, Sarawak, Borneo, Papua New Guinea, and Saibai Island in the Torres Strait. There is some evidence that infection with these viruses is increasing in incidence. In northern Australia, MVE cases occur predominantly between February and July, corresponding to the end of the monsoon season, when the mosquito vector (Culex annulirostris) proliferates in flooded environments. MVE and Kunjin viruses are flaviviruses, family Flaviviridae, of the Japanese encephalitis complex. Kunjin is a subtype of WNV. RNA sequencing indicates that the Australian strains of MVE virus are similar to, but different from Papua New Guinea isolates. No vaccine is available. Control is achieved through application of larvicides.

**Ross River Virus**

Ross River (RR) virus has caused annual epidemics of febrile disease with polyarthritis and rash with most cases occurring in November through April. It is the most commonly reported arthropod-borne virus disease in Australia. RR virus occurs in all Australian states and territories, but is most commonly found in the northern states and coastal areas. Within the past two decades, RR virus has spread through several Pacific Islands in epidemic form and appears to have become endemic in New Caledonia. Convalescence can be long. RR virus is an alphavirus of the family Togaviridae. The enzootic maintenance cycles of RR virus in Australia are not well defined, but wild and domestic mammals appear to be the reservoir hosts, and the principal mosquito vectors are salt marsh Aedes spp. and freshwater Culex spp. In the Pacific Islands outbreaks, the virus was probably transmitted from person to person by Aedes mosquitoes.

**Barmah Forest Virus**

Barmah Forest virus is the second most common mosquito-borne disease in Australia. It causes subclinical and clinical infections in humans, including fever, myalgia, polyarthralgia, and rash. It is an alphavirus in the Togaviridae. The virus appears to be endemic in eastern Australia. It has been isolated from 25 different mosquito species in five genera. Ochlerotatus vigilax (previously known as Aedes vigilax), is considered a major vector. Its vertebrate hosts have not been established, although marsupials are suspected.

**Control**

Real-time disease surveillance supported by rapid and accurate laboratory diagnosis is the basis for recognition and control of zoonotic diseases. Standard diagnostic approaches such as acute and convalescent serology, virus isolation and antigen detection, along with nucleic acid amplification techniques are increasingly available in developed countries, but not always can be implemented on short notice in geographic areas that need them the most. Where laboratory testing is available, it is equally important that the results reach clinicians treating infected individuals and become incorporated into epidemiological databases and early warning systems to assure rapid response by public health authorities to control outbreaks appropriately.

Control of zoonotic virus diseases is accomplished by breaking the cycle of transmission. This is usually achieved by eliminating or immunizing vertebrate hosts, and reducing vector populations. Reduction of reservoir host populations is usually not accomplished because it is too expensive, not environmentally safe, and not technically or logistically feasible. In some cases, reduction of reservoir hosts populations can have the opposite effect and actually increase transmission risk. This has been shown to be the case for WNV where mathematical models clearly show vector reduction, rather than reservoir host reduction, is the critical component for decreasing disease transmission to human. However, there have been some notable exceptions. Bolivian hemorrhagic fever, caused by Machupo virus, was controlled by reduction of its rodent hosts through intensive rodenticiding. The principal vampire bat reservoir of rabies, Desmodus rotundus, is being controlled by the application of warfarin-type anticoagulants. Control programs like these have to be continuous to be effective. Their reduction or discontinuation results in host population recovery through reproduction and immigration, which may result in reemergence of disease sweeping through the increasing, susceptible cohort. Immunization of hosts is another control approach. Safe and effective rabies vaccines are being used for immunization of humans, domesticated animals, and some wildlife species. The human diploid cell vaccine is extremely effective, free of adverse effects, and widely available but at a cost too high for use in many developing countries. Safe, effective animal vaccines of cell culture
origin are on the market. After some initial public resistance, raccoon populations in the eastern United States and wild foxes in Europe are being successfully immunized by means of an oral, vaccinia-vectorized recombinant vaccine. This experience illustrates the need for public understanding, in order to counteract fear of dispersal of a genetically engineered virus. However, vaccines will not be developed for many zoonotic viral diseases that affect relatively few people and are of very limited concern geographically.

Vector control is another promising but difficult area of zoonoses reduction or elimination. Insecticide application has become more problematic because both vectors themselves, as well as public opinion, have become more resistant to their use. Integrated pest management techniques, well developed for the control of many crop insects, along with the use of natural pesticides such as Bacillus thuringiensis toxin, offers promise for the effective, environmentally safe control of dipterous vectors. Control of tick vectors is likely to remain a problem for some time to come.

**Emerging and Reemerging Zoonoses**

**Ecological Change**

Human disturbance has become a feature of nearly every part of the planet. All too often these disturbances create habitats that favor increases in populations of key hosts and vectors, with subsequent increased transmission of viral zoonoses. Nowhere are ecological changes happening more rapidly and profoundly than in the world’s tropics. Conversion of tropical forests to agricultural ecosystems simplifies diverse ecosystems and provides either native or introduced host or vector species the conditions necessary to become more abundant, and sustain intensified virus transmission in areas where people live and work. In Africa, recent YF epidemics have been increasing dramatically in agricultural areas. Some agricultural irrigation development projects have created extensive vector breeding habitats, with an increase in mosquito-transmitted disease. The extensive dams constructed in Senegal were followed by epidemics of RVF, with numerous cases of disease in humans and small ruminant animals. The public health consequences of development projects must never be overlooked.

Global climate change will also bring ecological changes and shifts of human populations that will affect the occurrence of viral zoonoses. There is general consensus that changes in the global climate will happen with unprecedented speed. With those changes will come alterations in the geography of natural and agricultural ecosystems, with corresponding changes in the distribution of zoonotic diseases and the intensity of their transmission. It is clear that El Niño southern oscillation phenomena have increased rainfall, with resulting increases in rodent populations and occurrence of HPS in the Southwestern United States, and increased breeding sites for mosquito vectors of RVF virus in Africa. While it is not possible to predict accurately what the world will be like in 100 years or what zoonotic diseases are likely to be most troublesome, it is certain that things will be different, and constant surveillance will be essential to avoid serious problems or deal promptly and effectively with the ones that arise.

Movement of zoonotic viruses can result from the displacement of infected animals, contaminated animal products, and virus-carrying arthropod vectors. Pets, sport, laboratory, and agricultural animals are moving around the world as never before. Although international and national regulations have been established to prevent movement of infected individuals, it is not possible to test for all possible zoonotic viruses, and prevent them from crossing international boundaries. Moreover, significant numbers of animals of high commercial value move illegally. The importation of highly virulent Newcastle disease (ND) virus has been occasionally linked to smuggled birds.

Zoonotic viruses may be transported by movement of arthropod vectors, too. Just as the YF mosquito, Ae. aegypti, moved around the world in water casks aboard sailing vessels, mosquitoes are transported around the world in international commerce. Ships still transport mosquito vectors. The Asian tiger mosquito, Ae. albopictus, has become established in the Western Hemisphere after multiple introductions in eggs deposited in used tires. This mosquito is capable of transmitting YF, VEE, JC, and LAC encephalitis viruses. Perhaps of greater concern, modern transport aircraft have been shown to move vector mosquitoes internationally.

Human activity alters animal populations, contact between wild and domestic animals, and human–animal interactions, changing the occurrence of zoonotic diseases and the risk of infection to humans. For example, emergence of new influenza strains is related to the interaction of populations of people, pigs, and aquatic birds.

**Social Change**

Increasing human populations place great demands on the public health and other government services, especially in developing countries where needs for zoonoses diagnosis, control, and prevention are greatest and resources are most limited. Some preventive measures could be implemented by the people who live in the affected areas themselves, and at minimal costs, if they knew why and how they needed to do it. Public education and information is essential for control and prevention of zoonotic diseases; however, it takes more than civic action to deal with them. Delivery of public education, disease surveillance and diagnosis, and the technical materials and logistical support for control or preventive programs depend on national or international scientific and financial support. International technical cooperation and financial support are imperative.

**Summary**

Zoonoses are diseases transmissible from animals, other than humans, to people. Both new and old viral zoonoses are important in emerging and reemerging virus diseases. Some zoonotic viruses occur worldwide, in a variety of ecological settings. Others are found
only in limited ecologic and geographic foci. Important worldwide zoonotic viruses include rabies, hantaviruses, arenaviruses, yellow fever virus, chikungunya virus, Sindbis virus, Crimean-Congo hemorrhagic fever virus, and the sandfly fever viruses. In the Americas, common zoonotic viruses include the encephalitis viruses, Colorado tick fever virus, vesicular stomatitis, Zika virus and others. Zoonotic viruses in Europe include Tahyna virus, the tick-borne encephalitis viruses, and cowpox virus. There are several zoonotic viruses in Africa and the Middle East, including Rift Valley fever virus, Marburg and Ebola filoviruses, monkeypox virus, Semliki Forest virus, Orungo virus, and Alkhurma virus. Zoonotic viruses occurring in Asia include the influenza viruses, SARS coronavirus, Kyasanur Forest virus, Japanese encephalitis virus, Chandipura virus, and Nipah virus. Zoonotic viruses occurring in Australia include Murray Valley encephalitis virus, Kunjin virus, Ross River virus, and Barmah virus. The human and animal health importance of these viruses and their control are discussed. Because rapid ecological change is occurring worldwide, additional zoonotic viruses will emerge.

Further Reading
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