

8.5.14 Flaviviruses excluding dengue 830

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830 section 8 Infectious diseases 8.5.14 Flaviviruses excluding dengue Shannan Lee Rossi and Nikos Vasilakis ESSENTIALS Dengue and dengue haemorrhagic fever (see Chapter 8.5.15) are the most important and widespread human diseases caused by an arbovirus, causing a broad spectrum of illness ranging from asymptomatic to severe and fatal haemorrhagic disease. It is primarily an urban disease transmitted among humans by the highly domesticated *Aedes aegypti* mosquito. Japanese encephalitis virus—has a widespread distribution throughout Asia; is the most important cause of arboviral encephalitis; is maintained in a cycle involving *Culex* mosquitoes and water birds; only about 1% of infections are symptomatic, with manifestations ranging from a febrile illness with headache, through aseptic meningitis, to encephalitis, and death. Many survivors have residual neurological abnormalities. There is no specific treatment. Vaccination should generally be offered to people spending a month or more in endemic areas, especially if travel includes rural areas. Yellow fever virus—found in tropical America and Africa; forest/ jungle transmission cycle involves canopy-dwelling mosquitoes and monkeys, urban cycle involves humans as the vertebrate host and *Aedes aegypti* as the principal vector; 5% of infections present clinically with a viraemic illness, which may be followed after a transient period of remission by relapse with shock, neurological deterioration, jaundice, haemorrhagic manifestations, and renal failure. Treatment is symptomatic. A live, attenuated, single-dose vaccine is highly effective. Zika virus was relatively rare until the last decade but now has a large distribution. In 2015–2016, it was responsible for large outbreaks in South America. Like dengue virus, it is largely spread by the *A. aegypti* mosquito and, in most people is either asymptomatic or causes a febrile illness with a rash and arthralgia. However, it is now known to be associated with congenital defects, particularly microcephaly, and with Guillain-Barré syndrome. There is no specific treatment and no vaccine available. West Nile virus—found in Africa, the Middle East, Asia, Australia (Kunjin is a subtype of West Nile virus), parts of Europe and the Americas; maintained in a cycle involving *Culex* mosquitoes and water birds; most infections are asymptomatic, but 20% develop a febrile illness, and 1% neuroinvasive disease including meningitis, encephalitis, and acute flaccid paralysis. There is no specific treatment. Several equine vaccines are available, and human vaccines are in clinical trials. Other important mosquito-borne flaviviruses include Murray Valley, St Louis encephalitis, and

Rocio virus. Tick-borne flaviviruses Tick-borne encephalitis, louping ill, Powassan encephalitis—geographical distribution determined by that of relevant hard tick vectors; rodents are the principal vertebrate hosts, with occupational and vocational pursuits favouring tick exposure as risk factors for human disease; most infections are subclinical, but a non specific influenza-like illness may be followed, after a few days of apparent recovery, by aseptic meningitis or meningoencephalitis that may lead to permanent paralysis in some cases. Treatment is supportive. Effective inactivated vaccines are available for tick-borne encephalitis. Tick-borne haemorrhagic fevers—these include Kyasanur Forest disease and Alkhumra (strictly Al Khumra) and Omsk haemorrhagic fevers.

Introduction The family Flaviviridae currently consists of four recognized genera: Flavivirus, Pestivirus, Hepacivirus, and Pegivirus. Although members of the family have a large host range that includes both vertebrates and invertebrates, only members of the genus Flavivirus are known as arboviruses, vectored either by mosquitoes or ticks. The remaining genera in the family are exclusively found in mammals, and their diversity has greatly expanded with recent virus discoveries. The genus Flavivirus comprises 92 virus species, of which over 40 can cause human infection (Table 8.5.14.1). Many of these include important human pathogens such as Zika (ZIKV), dengue (DENV), yellow fever, West Nile (WNV), and Japanese encephalitis virus. Flaviviruses are small spherical particles of approximately 40–50 nm in diameter, whose genome is a positive sense single stranded RNA of c.11 kb that encodes three structural proteins and seven nonstructural proteins. Based on epidemiological and phylogenetic analyses (Fig. 8.5.14.1), the flaviviruses are classified into four groups: (1) those that are mosquito-borne, (2) those that are tick-borne, (3) those for which no arthropod vector has been demonstrated, and (4) those with a restricted host range transmission among arthropods (insect-specific) without the involvement of vertebrates. All flaviviruses of human importance belong to the first two groups; the last two groups contain viruses found only in other vertebrates or in arthropods, respectively. Most flaviviruses are maintained in nature within two ecologically and evolutionarily distinct transmission cycles between vertebrates (wild or domestic animals or humans) and one or more hematophagous arthropod vectors. The transmission cycles include: (i) an enzootic, sylvatic cycle, where the virus circulates between arboreal mosquitoes and nonhuman primates; and (ii) and a human or urban cycle, between humans and peridomestic/ domestic mosquitoes. Representative transmission cycles for Zika and yellow fever viruses are depicted in Fig. 8.5.14.2. Humans mostly become infected when infected arthropod vectors feed on them and, for most of the flaviviruses, humans do not develop high enough viremias and are not thought to contribute to the transmission cycle. However, some flaviviruses such as dengue, yellow fever, and Zika viruses do produce high viremias in humans, which allow maintenance through a mosquito-human-mosquito transmission cycle. Transmission of some flaviviruses directly from one person to another through blood transfusion or organ transplantation as well as in utero or via sexual contact has also been documented. The epidemiology and geographical distribution of members of the genus flavivirus depends on several factors including: (i) the

8.5.14 Flaviviruses excluding dengue 831 Table 8.5.14.1 Taxonomy of flaviviruses

Group	Species name	Strain name, synonyms, and tentative species names	Abbreviation
Mosquito-borne viruses	Aroa virus group	Aroa virus	AROAV
	Bussuquara virus	BSQV	
	Iguape virus	IGUV	
	Narajal virus	NJLV	
Dengue virus group	Dengue viruses	Dengue virus 1	DENV-1
	Dengue virus 2	DENV-2	
	Dengue virus 3	DENV-3	
	Dengue virus 4	DENV-4	
Japanese encephalitis virus group	Cacipacore virus	Cacipacore virus	CPCV
	Japanese encephalitis virus	Japanese encephalitis virus	JEV
	Koutango virus	Koutango virus	KOUV
	Murray Valley encephalitis virus	Alfuy virus	ALFV
	Murray valley encephalitis		

virus MVEV St Louis Encephalitis virus St Louis Encephalitis virus SLEV Usutu virus Usutu virus USUV West Nile virus Kunjin virus KUNV West Nile virus WNV Yaounde virus Yaounde virus YAOV Kokobera virus group Kokobera virus Kokobera virus KOKV Stratford virus STRV Ntaya virus group Bagaza virus Bagaza virus BAGV Ilheus virus Ilheus virus ILHV Rocio virus ROCV Israel Turkey meningoencephalitis virus Israel Turkey meningoencephalitis virus ITV Ntaya virus Ntaya virus NTAV Tembusu virus Tembusu virus TMUV Zika virus Zika virus ZIKV Yellow fever virus group Sepik virus Sepik virus SEPV Wesselsbron virus Wesselsbron virus WSLV Yellow fever virus Yellow fever virus YFV Probably mosquito-borne Kedougou virus group Kedougou virus Kedougou virus KEDV Edge Hill virus group Banzi virus Banzi virus BANV Bouboui virus Bouboui virus BOUV Edge Hill virus Edge Hill virus EHV Jugra virus Jugra virus JUGV Saboya virus Potiskum virus POTV Saboya virus SABV Uganda S virus Uganda S virus UGSV Tick-borne viruses Mammalian tick-borne virus group Gadgets Gully virus Gadgets Gully virus GGYV Kyasanur Forest disease virus Kyasanur Forest disease virus KFDV Alkhumra haemorrhagic fever virus AHFV Langat virus Langat virus LGTV (continued)

832 section 8 Infectious diseases Group Species name Strain name, synonyms, and tentative species names Abbreviation Louping ill virus Louping ill virus LIV British subtype LIV-Brit Irish subtype LIV-IR Spanish subtype LIV-Spain Turkish sheep encephalitis virus subtype TSEV Greek goat encephalitis virus subtype GGEV Omsk haemorrhagic fever virus Omsk haemorrhagic fever virus OHFV Powassan virus Powassan virus POWV Royal Farm virus Royal Farm virus RFV Tick-borne encephalitis virus Tick-borne encephalitis virus TBEV European subtype TBEV-Eu Far Eastern subtype TBEV-FE Siberian subtype TBEV-Sib Seabird tick-borne virus group Meaban virus Meaban virus MEAV Saumarez Reef virus Saumarez Reef virus SREV Tyuleniy virus Tyuleniy virus TYUV Probably tick-borne Kadam virus group Kadam virus Kadam virus KADV Viruses with no known arthropod vector Entebbe bat virus group Entebbe bat virus Entebbe bat virus ENTV Sokoluk virus SOKV Yokose virus Yokose virus YOKV Modoc virus group Apoi virus Apoi virus APOIV Cowbone Ridge virus Cowbone Ridge virus CRV Jutiapa virus Jutiapa virus JUTV Modoc virus Modoc virus MODV Sal Vieja virus Sal Vieja virus SVV San Perlita virus San Perlita virus SPV Rio Bravo virus group Bukalasa bat virus Bukalasa bat virus BBV Carey Island virus Carey Island virus CIV Dakar bat virus Dakar bat virus DBV Montana myotis leukoencephalitis virus Montana myotis leukoencephalitis virus MMLV Phnom Penh bat virus Batu Cave virus BCV Phnom Penh bat virus PPBV Rio Bravo virus Rio Bravo virus RBV Viruses tentatively placed in the Flavivirus genus Mammalian tick-borne Karshi virus KSIV Mosquito-borne Spondweni virus SPOV Insect/Mosquito Specific Flaviviruses Aedes flavivirus AEFV Cell fusing agent virus CFAV Culex flavivirus CXFV Kamiti River virus KRV Table 8.5.14.1 Continued (continued)

8.5.14 Flaviviruses excluding dengue 833 presence of suitable amplifying hosts, (ii) the presence, density and feeding behaviour of suitable arthropod vectors, and (iii) the frequency of exposure of immunologically naive vertebrate reservoir hosts susceptible to infection. Following World War II, globalization of trade and travel, uncontrolled human population growth and urbanization, changes in land and water use, changes in agricultural practices, new irrigation systems and deforestation and unsustainable vector control programmes have produced fertile conditions for the explosive increase in incidence and geographical expansion of the flaviviruses (Fig. 8.5.14.3). Two dramatic examples in the last 20 years are the introduction and subsequent spread of the West Nile and Zika viruses in the western hemisphere. Flavivirus infections in humans can result in a wide spectrum of manifestations ranging from asymptomatic infection or clinical illness ranging

from nonspecific febrile illness, fever with rash or arthralgia or both, haemorrhagic fever, hepatitis, encephalitis, and death. For most flaviviral infections no specific therapy is available, however, prompt supportive treatment and proper management may substantially reduce mortality from some flavivirus infections. Laboratory diagnosis All flaviviruses have common group epitopes on the pre/membrane, envelope, and nonstructural 1 (NS1) proteins that result in extensive cross-reactions in serological tests. The specificity of antibodies ought to be confirmed by the gold standard test of specificity, the plaque reduction neutralization test (PRNT). However, in areas where multiple flaviviruses are hyperendemic/ enzootic, antibody-based assays, including the PRNT assay, are noninformative. The most common diagnostic assay based on serology for acute flavivirus infections is the IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA), which is cost-effective and does not require specialized laboratory settings. IgM-specific antibodies are usually detectable 5 to 8 days after onset of symptoms.

Group	Species name	Strain name	synonyms	tentative species names	Abbreviation
	Nakiwogo virus	NAKV			Quang Binh
	Qinghai virus	QBQV			Mercadeo virus
	MECDV				Hanko virus
	HANKV				Nienokoue virus
	NIEV				Palm Creek virus
	PCV				Ilomantsi virus
	ILOV				Marisma mosquito virus
	MMV				Donggang virus
	DONV				LaTina virus
	LTNV				Long Pine Key virus
	LPKV				Kampung Karu virus
	KKV				Nhumirim virus
	NHUV				Barkedji virus
	BJV				Culiseta flavivirus
	CsFV				Parramatta River virus
	PaRV				Yamadai flavivirus
	YDFV				Yunnan Culex flavivirus
	YNCxFV				Culex theileri flavivirus
	CtFV				Ochlerotatus caspius flavivirus
	OCFV				Xishuangbanna flavivirus
	XFV				Viruses with no known arthropod vector
	Chaoyang virus	CHAOV			Lammi virus
	LAMV				Ngoye virus
	NGOV				Nounané virus
	NOUV				Tamana bat virus
	TABV				

Table 8.5.14.1 Continued

834 section 8 Infectious diseases -Insect-specific viruses -No known vector -Tick-borne -Vectored by 'Old World' Stegomyia Spp. -Vertebrate host unknown -Vectored by Stegomyia Spp. -Vectored by Culex Spp. Fig. 8.5.14.1 Maximum-likelihood phylogenetic tree of representative members of the genus flavivirus. Bootstrap values are shown for most clades. All horizontal branch lengths are drawn to scale; bar, 0.05 nucleotide substitutions per site. The tree is midpoint-rooted for purposes of clarity only.

8.5.14 Flaviviruses excluding dengue 835 However, because IgM antibodies can persist for one or more months after infection with most flaviviruses, their presence does not necessarily confirm current infection. Therefore, people with detectable IgM antibodies are considered recent or presumptive cases. Confirmatory laboratory diagnosis of most flaviviruses requires isolation of the virus, detection of specific viral RNA by nucleic acid amplification or of specific antigen in autopsy tissues by immunohistochemistry. Mosquito-borne flavivirus infections of human health importance Japanese encephalitis virus Aetiology and epidemiology Japanese encephalitis virus is the most important cause of arboviral encephalitis with several thousand cases annually. Japanese encephalitis has a widespread distribution throughout Asia, and its distribution has expanded in recent years with outbreaks in the Pacific, Australia, Nepal, and western India, putting at risk of infection close to 3 billion people (Fig. 8.5.14.4). Virus transmission occurs primarily in rural agricultural areas, often associated with rice production and flooding irrigation. Although transmission can occur year-round in the tropics, peaking during the rainy season, in temperate regions, Japanese encephalitis virus transmission is seasonal with disease incidence peaking in the summer and fall. Japanese encephalitis virus is antigenically related to several other flaviviruses that may have similar geographic distribution. The virus is maintained in a transmission cycle involving Culex mosquitoes and wading birds, and is transmitted to humans by Culex mosquitoes, primarily species of the Culex tritaeniorhynchus complex which breed in rice fields. Humans are considered dead-

end hosts, because they do not develop high enough viremia to infect feeding mosquitoes, whereas pigs are considered the primary amplifying host in the peridomestic environment. There are several genotypes of Japanese encephalitis viruses that circulate in distinct geographical areas.

Clinical characteristics Most Japanese encephalitis virus infections are asymptomatic and only about 1% of all infections develop clinical illness, which ranges from febrile illness with headache, aseptic meningitis, encephalitis, and death. The incubation period lasts 6–16 days, before onset of symptoms presented by high fever, change in mental status (lethargy), nausea and vomiting, and headache (prodromal state) lasting several days. The onset of neurological signs, altered state of consciousness and delirium reflects damage to the thalamus, brain stem, and cerebral cortex. In most patients seizures are generalized, although at their onset can be more focal. In 30% of the patients, facial and cranial nerve palsies, and acute flaccid paralysis are observed. This poliomyelitis-like illness may be the only neurological manifestation of the illness or may proceed or accompany encephalitis. Respiratory dysregulation, coma, abnormal plantar reflexes, ZIKV YFV

Sylvatic Zone of emergence Urban TOT TOT ?? Ae. africanus (Africa) Ae. luteocephalus (Africa)* Ae. metallicus (Africa) Ae. opok (Africa) Ae. vittatus (Africa)* Ae. simpsoni complex (Africa) Homo sapiens Ae. aegypti aegypti (global) Alouatta spp (S. America) Colobus spp (Africa) Cercopithecus spp. (Africa) G. senegalensis (Africa) H. janthinomys (S. America) H. leucocelaenus (S. America) S. chloropterus (S. America) Ae. africanus (Africa)* Ae. bromeliae (Africa) Ae. taylori (Africa)* Ae. africanus (Africa)* Ae. dalzieli (Africa) Ae. furcifer (Africa)* Ae. luteocephalus (Africa)* Ae. vittatus (Africa) Rhesus spp (Africa) Chlorocebus sabaeus (Africa) Cercopithecus spp (Africa) Colobus guereza (Africa) Erythrocebus patas (Africa) Pongo borneo (SE Asia) ?? Ae. apicoargenteus (Africa) Ae. furcifer (Africa)* Ae. hirsutus (Africa) Ae. metallicus (Africa) Ae. opok (Africa) Ae. taylori (Africa)* Ae. unilineatus (Africa) Ma. uniformis (Africa) An. coustani (Africa) Cx. perfuscus (Africa) Ae. aegypti aegypti (global) Ae. albopictus?? Ae. polynesiensis (Polynesia) Ae. hensilli (Polynesia) Homo sapiens Ae. Furcifer (Africa)* Ae. Furcifer (Africa)*

Fig. 8.5.14.2 Transmission cycles of Zika and yellow fever viruses, flaviviruses with significant human health impact. ToT, transovarial transmission; *, indicates major vectors; in red: vectors in either transmission cycle; in green: vectors implicated as bridge vectors.

836 section 8 Infectious diseases and prolonged convulsions are associated with a poor prognosis. Defervescence occurs in the second week of the illness and is characterized by gradual improvement of neurologic manifestations and recovery, although long-term sequelae may remain. Overall, up to 70% of survivors have residual neurological abnormalities including behavioural changes, and psychological deficits. Curiously, in some patients clinical relapse has been observed several months following recovery from acute illness, suggesting persistent infection, likely of peripheral mononuclear cells. Laboratory examination during the first week of illness shows modest levels of peripheral leukocytosis and hyponatraemia due to dysregulated antidiuretic hormone (ADH) secretion. Cerebrospinal fluid is clear and elevated pleocytosis is observed. Around 10–40% of cases are fatal usually within the first week of illness. Children less than 10 years of age are more likely to die, and if they survive, are more likely to have residual neurological defects. Congenital infection during the first and second trimester of pregnancy has led to fetal death and spontaneous abortion, whereas infection in the third trimester has been associated with normal fetal outcomes. Common complications during Japanese encephalitis virus infections include concurrent bacterial and parasitic infections, or tuberculosis, which could complicate management of the illness.

Diagnosis The differential diagnosis in Japanese encephalitis virus infections includes other viral encephalitides including arboviruses (e.g. dengue with encephalopathy,

WNV, Murray Valley encephalitis), herpes, and enteroviral infections (mostly enterovirus 71), cerebral malaria, and bacterial infections. Travel history, season, location of residency may provide clues for diagnosis. Nucleic acid testing (NAT) is useful only in the early acute stage of illness. Serology offers accurate and specific diagnosis. MAC-ELISA is nearly 100% sensitive in paired blood and cerebrospinal fluid samples obtained 1–2 weeks after the onset of illness. However, as discussed earlier ('Laboratory diagnosis' section), due to cross-reaction with other flaviviruses, results may be difficult to interpret, especially in patients living in hyperendemic settings, where other related flaviviruses, such as SLEV, WNV, and dengue are cocirculating. Prevention and control There are safe and efficacious vaccines against Japanese encephalitis, ranging from inactivated to attenuated. The formulation offered will depend on the country providing the vaccine. For example, the live attenuated SA14-14-2 has been successfully used in endemic Asian countries. However, an inactivated vaccine derived

Fig. 8.5.14.3 Global geographic distribution of medically important flaviviruses.

8.5.14 Flaviviruses excluding dengue 837 from cell culture is the only version offered in the United States and requires two doses. It is highly recommended by the Centers for Disease Control and Prevention (CDC) to receive this traveller's vaccine if the stay will be longer than a month or will occur in high transmission areas and times. Typically, short-term stays in highly urbanized areas during a low-transmission time of the year does not warrant traveller's vaccination. As with all vector-borne viral infections, preventing the vector's bite is one of the best ways to prevent infection. Wearing mosquito repellent as well as long-sleeved clothing will work well. Treatment There is no treatment specifically tailored to combat Japanese encephalitis disease. If a patient is in the hospital, supportive care is administered. Fluid and pain medication are typically offered to patients. Yellow fever virus Aetiology and epidemiology Although yellow fever was first described in the 17th century, it remains to this day an important human disease in vast areas of Africa and South America (Fig. 8.5.14.4), with 200 000 infections and 30 000 deaths every year; nearly 90% of these occurring in Africa. Today nearly a billion humans are at risk of infection every year. In 1900, the anthropophilic mosquito *Aedes aegypti* was proven to be involved in the transmission of yellow fever. The virus was isolated in 1927 and a vaccine developed in 1937, leading to the award of the Nobel Prize to its inventor (Max Theiler). The virus is present in tropical America and Africa, but has not been reported in Asia. The transmission cycles of yellow fever include: (i) an enzootic, sylvatic cycle, where the virus circulates between arboreal mosquitoes and nonhuman primates; and (ii) a human or urban cycle, between humans and peridomestic/domestic mosquitoes. Transovarial transmission of mosquitoes had been demonstrated in both transmission cycles and may provide a mechanism for the maintenance of the transmission cycles in interepidemic periods (Fig. 8.5.14.2). The American yellow fever originated from the Old World as a result of sailing ships. Between 1986 and 2016, a series of outbreaks in Nigeria caused an estimated 100 000 cases, with attack rates in affected areas of 30/ 1000 and case fatality rates exceeding 20%. Similar epidemics occur in regular intervals in South America, in what are termed travelling epizootics. The disease affects several hundred people annually, principally young men working in forest areas exposed to arboreal mosquitoes. In the past 10 years, yellow fever was reported in the Democratic Republic of the Congo, Angola, Côte d'Ivoire, Central African Republic, Liberia, Cameroon, Guinea, Uganda, Peru, Brazil, Argentina, and Paraguay. At the time of writing there is another outbreak in central and northern Brazil, resulting in several deaths to date. These events have led to severe vaccine shortages leading to fractional dose vaccine administration. Additionally, as ecotourism has increased in recent years, yellow fever in unvaccinated travellers from Areas with Risk of Japanese

Encephalitis and Yellow Fever Virus Endemic Yellow Fever Virus Transmission Risk Japanese Encephalitis Risk No Known Risk 0 Kilometers N Robinson Projection 2,000 4,000 Fig. 8.5.14.4 Global distribution of Japanese encephalitis virus. Source data from WHO Fact sheet No 386, 'Japanese encephalitis', December 2015. Copyright © WHO 2012.

838 section 8 Infectious diseases North America and Europe has become more common. Furthermore, the recent detection of YF-viremic Chinese workers returning to Asia from Angola raises serious concerns for the establishment of a YFV transmission cycle in Asia. The prospect of such an event will be catastrophic as it will put a third of the world's population at risk who are currently immune-naïve. Clinical characteristics In some patients, yellow fever infection is asymptomatic or presents as a mild, undifferentiated febrile illness. The incubation period lasts 3–6 days, and in its classic form, is characterized by an abrupt onset of chills, fever, headache, viremia, photophobia, lumbosacral pain, nausea, prostration, generalized myalgia, facial flushing, red tongue, and conjunctivitis. The moderately ill begin to recover after a period of 3–4 days. However, in severe cases this recovery is transient, also known as period of remission, only to relapse with jaundice, albuminuria, oliguria, bradycardia (Faget's sign), delirium, stupor, metabolic acidosis, shock, and haemorrhage. The haemorrhagic manifestations are caused by decreased synthesis of clotting factors and may be complicated by disseminated intravascular coagulation, and can vary from petechial lesions to epistaxis, bleeding gums, and haematemesis. This relapse is known as the period of intoxication and the prognosis in such cases is poor, as the case fatality rate is between 20 to 50%. Pathology includes midzonal hepatic necrosis and eosinophilic degeneration of Councilman bodies, and acute renal tubular necrosis, although renal failure has rarely been reported. Focal myocarditis, brain swelling, and petechial haemorrhages contribute to the clinical picture. Diagnosis The differential diagnosis of yellow fever includes typhoid, leptospirosis, tick-borne relapsing fever, typhus, Q fever, malaria, severe viral hepatitis, Rift valley fever, Crimean-Congo haemorrhagic fever, Lassa, Marburg, and Ebola fever. Yellow fever can be diagnosed through serology (haemagglutination inhibition, complement fixation and the PRNT) by virus isolation or NAT. As discussed earlier ('Laboratory diagnosis' section), due to cross-reaction with other flaviviruses, results might be difficult to interpret, especially in patients living in hyperendemic settings. Virus isolation can be attempted from blood, which should be collected within the first 4 days of illness. A variety of techniques are available for virus isolation, such as intracerebral inoculation of newborn Swiss mice or inoculation into susceptible vertebrate or arthropod cell lines. In fatal cases, post-mortem histopathological examination of the liver may provide conclusive diagnosis, with or without immunocytochemical staining for viral antigen, although similar liver pathology has been observed in fatal dengue cases. Liver biopsy is contraindicated as it may lead to severe haemorrhage. Prevention and control Vaccination is recommended by the World Health Organization (WHO) for residents of yellow fever endemic areas; travellers to endemic areas should also be vaccinated. A live attenuated vaccine, known as the 17D vaccine, has been available since 1937 and is delivered as a single 0.5-ml subcutaneous dose with minimal side effects, although mild reactions, such as headache, myalgia and low-grade fever occurring in 5–10% of vaccines have been reported. Vaccination results in lifelong immunity. Until recently official WHO recommendations suggested a booster dose should be given every 10 years, but this changed in 2016. The contraindications to the use of 17D vaccine are altered immune states (e.g. immunosuppressed individuals and pregnancy) and hypersensitivity to eggs. If the vaccine is inadvertently given during pregnancy, recipients should be closely monitored. Vaccination is also contraindicated in children less than 6 months of age, due to increased risk of

postvaccine encephalitis. Vaccine-associated viscerotropic disease is more common in patients with a history of thymic tumour and thymectomy and is contraindicated in these groups. Fatal outcomes following vaccination have been rarely reported. However, neurological involvement, presenting as encephalitis and Guillain-Barré syndrome and viscerotropic disease have been reported mainly among older vaccinees. Besides vaccination, reducing the densities of the anthropophilic mosquito vector *Ae aegypti* in tropical urban settings through fumigation and other sophisticated vector control approaches are effective methods in controlling epidemics. Treatment There is no specific antiviral therapy available and treatment is supportive. Intensive medical treatment is required for severe cases presenting with acidosis, shock, and metabolic imbalance. Patients with renal failure might require dialysis. Intensive care is a challenge and difficult to provide as many epidemics occur in remote areas of Africa and the Americas. YF disease is regarded a disease of international public health significance, requires quarantine of affected patients and notification of public health officials as soon as possible so that vector eradication and mass immunization can be carried out as promptly to prevent further epidemics. Zika virus Aetiology and epidemiology Zika virus (ZIKV) is a mosquito-borne flavivirus first discovered in the Zika forest of Uganda in 1947 during an investigation of enzootic yellow fever. The transmission cycles of ZIKV include: (i) an enzootic, sylvatic cycle, where the virus circulates between arboreal mosquitoes and nonhuman primates; and (ii) a human or urban cycle, between humans and peridomestic/domestic mosquitoes. Transovarial transmission of mosquitoes had been demonstrated in both transmission cycles and may provide a mechanism for the maintenance of the transmission cycles in interepidemic periods (Fig. 8.5.14.2). Importantly, the recent pandemic documented horizontal transmission through sexual contact, a novel mode of arbovirus transmission. Current studies are assessing the impact of sexual transmission on the epidemic potential of ZIKV, and its contribution to the severity of congenital Zika syndrome. Until 2007, only 14 sporadic human cases were reported, although serological studies and virus isolation from mosquitoes suggested widespread ZIKV circulation in Africa and Asia. The first major ZIKV outbreak was detected in 2007 in Yap Island, followed by another outbreak in same year in Gabon. These outbreaks were followed by 2013–2014 epidemic in French Polynesia which quickly spread to in New Caledonia, the Cook Islands, Easter Island, Vanuatu, and the Solomon Islands. In early 2015, the first ZIKV infections were

8.5.14 Flaviviruses excluding dengue 839 described in Brazil, which quickly became an explosive epidemic spreading throughout the hemisphere. As of January 2017, autochthonous ZIKV infections had been reported in all countries and territories in the Americas, with the exception of mainland Chile and Canada. Many countries in North America and Europe have also reported hundreds of imported cases (Fig. 8.5.14.5). Clinical characteristics It has been reported that up to 80% of ZIKV infections can be asymptomatic. Symptomatic ZIKV infection is characterized by a self-limited illness with mild clinical manifestations, including fever, lethargy, eye pain, conjunctivitis, rash, muscle aches, and arthralgia. In rare instances ocular and auditory abnormalities, brain ischaemia, myelitis, and meningoencephalitis have also been reported. Many of these symptoms are similar to those of DENV and other flavivirus infections, which share geographic distribution range and often have the potential to cocirculate with ZIKV. This has confounded differential clinical diagnosis. Symptoms can last for several days to a week and often patients do not become ill enough to see a medical provider. Infection with Zika very rarely results in fatal outcomes unless there are underlying comorbidities. Infection with Zika leads to lifelong immunity. In some severe cases, ZIKV infection leads to Guillain-Barré syndrome (GBS), an autoimmune polyradiculoneuropathy (see

Chapter 8.5.3). Patients typically present with reduction or absence of deep tendon reflexes and can also develop cranial nerve disorders. A cluster of GBS cases was identified retrospectively during the French Polynesia outbreak of 2013; however, an explosive increase in GBS incidence was documented in several American countries where ZIKV circulation has occurred. The underlying factors that influence the association of GBS and ZIKV infection are not fully understood. However, it has been suggested that sequential arbo- virus infections may exacerbate the immune response and trigger an immunopathogenic process attacking peripheral nerves, thus leading to the onset of GBS. Up to now, ZIKV-induced GBS has been transient in duration and most patients fully recover following intra- venous immunoglobulin therapy. Of greater concern is the large increase of microcephaly cases first reported in Brazil, with about 20-fold increase in incidence from 2014 to 2015. The linkage between ZIKV infection and micro- cephalgy is supported by evidence from clinical, epidemiological, and experimental studies. Microcephaly refers to a head that is smaller than expected. The size of the head is typically defined by the occipito-frontal head circumference, which can be measured Fig. 8.5.14.5 Global distribution of Zika virus.

840 section 8 Infectious diseases in the fetus by ultrasound or in the neonate using a tape. In obstetrical practice, ultrasound measurements for various fetal structures between the 10% and 90% centiles are usually considered within the normal range. The Society for Maternal Fetal Medicine recommends that fetal microcephaly be defined as a fetal head circumference three standard deviations or more below the mean for gestational age, and that the diagnosis be considered certain if the head circumference is five standard deviations or more below the mean. The development of microcephaly depends on an insult that affects brain growth, a dynamic process that may take several weeks to become apparent. An ultrasound close to the time of insult may not show any findings. Birth defects following ZIKV infection in utero include micro- cephalgy, calcium deposits in the brain indicating possible brain damage, excess fluid in the brain cavities and surrounding the brain, absent or poorly formed brain structures, abnormal eye development, or other abnormalities resulting from damage to brain that affects nerves, muscles, and bones, such as arthrogryposis and hearing loss. In rare instances ZIKV infection in utero may lead to hydranencephaly, hydrops fetalis, and fetal demise. The constellation of these congenital abnormalities has now been termed congenital Zika syndrome (CZS). Diagnosis The differential diagnosis includes other arboviruses, such as dengue, chikungunya, and mayaro virus infections. The US Centers for Disease Control and Prevention recommends the Zika MAC- ELISA to be used for the qualitative detection of Zika virus IgM antibodies in serum or cerebrospinal fluid. However, as discussed earlier ('Laboratory diagnosis' section), due to cross-reaction with other flaviviruses, results might be difficult to interpret, especially in patients living in hyperendemic settings. Presumed positive, equivocal, or inconclusive tests must be confirmed by the PRNT assay, which might also be not interpretable in patients living in hyperendemic settings. The most sensitive method of ZIKV detection requires the detection of ZIKV genetic material (virus RNA) by NAT, including the reverse transcription polymerase chain reaction (RT-PCR) or the Triplex assay (described next). Viral RNA can be detected early in the course of illness on serum collected within a narrow window of 5–6 days after symptom onset. NAT testing can also be conducted on urine samples collected, with a patient-matched serum specimen, less than 14 days after symptom onset. Semen samples in infected males have been shown to be positive by NAT up to 6 months postinfection. A negative NAT result does not exclude ZIKV infection and serum should be analysed concurrently with serological tests. Virus isolation can be attempted from blood collected within the first 4 days of illness. A variety of techniques are available for virus isolation, such as

intracerebral inoculation of newborn Swiss mice or inoculation into susceptible vertebrate or arthropod cell lines. For asymptomatic pregnant women, NAT testing is recommended on serum and urine within 2 weeks of the date of last possible exposure (e.g. travel to areas with active ZIKV transmission). Pregnant women who present to their obstetric care provider two or more weeks after exposure, and have been found to be IgM positive, are strongly recommended to be tested by NAT. In areas with active ZIKV transmission, asymptomatic pregnant women should undergo serologic testing (MAC-ELISA) as part of their routine obstetric care in the first and second trimester. Given that the differential diagnosis includes dengue and chikungunya infections, major arboviroses that cocirculate with ZIKV, the Trioplex RT-PCR, a laboratory test designed to detect Zika virus, dengue virus, and chikungunya virus RNA, is highly recommended. The Food and Drug Administration (FDA) has not cleared or approved this test, but it is currently authorized for use under an emergency use authorization.

Prevention and control Controlling the Zika pandemic is a major challenge, as the cornerstone of its success is based solely on interrupting its transmission cycle. Recent attempts to control dengue, which shares a similar or identical urban transmission cycle, by relying on controlling its arthropod vectors has largely failed. However, some sophisticated vector control approaches, such as release of genetically modified, or Wolbachia-infected mosquitoes have shown promise to reduce mosquito populations, but these campaigns take months if not years to implement. The potential for prolonged presence of the virus in semen indicates the potential existence of alternative routes of human-human transmission. The risk of being infected with ZIKV can be reduced by using mosquito repellents, wearing long sleeves and trousers while spending time outdoors. Although there is no licensed vaccine currently available, several approaches that have successfully led to efficacious flavivirus vaccines are currently pursued, including but not limited to live attenuated, inactivated, and chimeric virus vaccines, as well as subunit vaccines representing ZIKV proteins, DNA vaccines expressing viral proteins, and other viral vectors expressing viral antigens. It should be noted that each vaccine approach has its pros and cons, complementary approaches should be explored simultaneously to advance effective vaccines for ZIKV. Additionally, no clinically approved antiviral drug therapy is currently available for treatment of ZIKV. However, two recent studies suggested that several repurposed FDA-approved drugs previously shown to have ant Flavivirus activity (e.g. bortezomib, ivermectin, and mycophenolic acid), showed promise in inhibiting ZIKV infectivity. While there are several approaches being considered, effective countermeasures (vaccines and antivirals) may take years for final approval.

Treatment No specific therapy is available, but supportive treatment can reduce morbidity and mortality.

St. Louis encephalitis (SLEV) Aetiology and epidemiology St. Louis encephalitis virus (SLEV) is a mosquito-borne virus that is found throughout the Americas. In 2005, an outbreak in Argentina was the first confirmed case of St. Louis encephalitis disease (SLE) outside of North America. A year later, an outbreak was observed in Brazil. However, on an annual basis, most SLEV cases occur in the United States, mostly in the eastern and central states, where urban-centred outbreaks have recurred since the 1930s; in the western states

8.5.14 Flaviviruses excluding dengue 841 transmission is more of an endemic nature. While only a handful of cases are reported annually in the United States, the largest epidemic of SLEV ever recognized in the United States took place in 1975, with nearly 2000 cases reported. SLEV is maintained in nature within a mosquito-avian cycle. The species of Culex mosquitoes that transmits SLEV depends upon the geographic location. Within the United States, Culex pipiens, Culex quinquefasciatus, Culex nigripalpus, and Culex tarsalis are the main vectors. These mosquitoes prefer feeding from avian species, but will nondiscriminately feed from other

mammals, reptiles, and amphibians. As a result, many nonreservoir or amplifying hosts can seroconvert to SLEV infection. However, both wild and peridomestic birds can develop viremia sufficient to maintain the transmission cycle. This allows the virus to travel along avian migration patterns, which may help to explain the large geographic range of this virus. Although the geographic range of the virus extends from Canada to Argentina, human cases have almost exclusively occurred in the United States.

Clinical characteristics The incubation period for St. Louis encephalitis disease (SLE) is between 5 to 15 days. Of those infected, less than 1% produce symptomatic illness. Patients develop rapid onset of symptoms including fever, headache, malaise, dizziness, and nausea. Approximately a week later, patients can recover completely or progress to a neurologic disease characterized by meningism, tremor, abnormal reflexes, ataxia, cranial nerve palsies, convulsions (especially in children), stupor, and coma. The disease burden is highest for older people where c.90% of symptomatic patients develop encephalitis. The overall case fatality rate is between 5–15% and increases with patient age. Underlying diseases such as hypertension, diabetes, and alcoholism affect the outcome. Diagnosis SLE can be confirmed during the viraemic phase by collecting serum and testing for the presence of viral RNA by NAT. Isolations from tissues aside from cerebrospinal fluid and brain are difficult to make, so direct virus isolation may not be useful. Serum and cerebrospinal fluid IgM tests are available through the CDC and for purchase from commercial vendors. SLE is a reportable disease in the United States. Other evidence, such as a history of mosquito bites or even the time of year, may be useful.

Prevention and control There is no licensed vaccine to protect against SLE. The most effective course of action is to prevent mosquito bites by wearing mosquito repellents and avoiding peak mosquito biting times.

Treatment There is no antiviral or treatment for SLE. Only supportive care can be offered to patients.

West Nile virus (WNV) Aetiology and epidemiology West Nile virus (WNV) can be found worldwide and across every continent except Antarctica. It was first isolated in Africa and was responsible for small outbreaks there and across the Middle East and India. In 1999, the virus caused an epidemic in New York City and eventually became endemic in North America. Other outbreaks in the 1990s also expanded the virus' range across Europe and into Asia. A cluster of infections in Argentina were also observed. A variant of WNV, Kunjin virus, is found in Australia. Like SLEV, WNV is maintained between *Culex* species mosquitoes and birds. The virus is quite unique in that it is vectored by many species of mosquitoes and has been found in mosquitoes from the *Aedes*, *Anopheles*, *Coquillettidia*, *Culiseta*, *Deinocerites*, *Mansonia*, *Orthopodomyia*, *Psorophora*, and *Uranotaenia* genera. Likewise, although the major disease and mortality burden is placed on corvids, WNV has been found in hundreds of bird species in the United States alone. This promiscuousness has allowed WNV to become endemic worldwide. The wide range of feeding preferences from infected *Culex* mosquitoes has resulted in many other vertebrates becoming infected and seroconverting to WNV. Horses and humans can be infected and succumb to illness, but cannot produce a high enough viremia to contribute to the transmission cycle, and are considered 'dead-end' hosts. Human infection can occur through a variety of mechanisms. The most common cause of infection is via an infected mosquito bite. Babies can be infected from the mother in utero, during birth or by breastfeeding. Furthermore, any transplantation of infected tissues, such as organ transplantation and blood transfusion can result in infection. West Nile disease is also a reportable disease in the United States.

Clinical characteristics The incubation period for WNV varies between 2 days to 2 weeks. Infection results in clinical symptoms in only 20% of individuals. Of those showing West Nile disease, symptoms include fever, headache, malaise, body aches, and vomiting. Some present with a rash. Most patients recover fully but the recovery time can vary greatly and even last months. Less than 1% of patients will have neurologic

complications, including meningitis and/or encephalitis, seizures, paralysis, and coma. Acute flaccid paralysis and Guillain-Barré syndrome have also been associated with WNV infection. Disease severity is age dependent and increases substantially after the age of 60 yrs. Long-term sequelae are not uncommon following resolution of symptoms, including memory loss, muscle weakness, depression, and other neurological defects. The case fatality rate among patients with neurological disease is c.10%. Interestingly, Kunjin disease is generally subclinical and progression to encephalitis is rare. Diagnosis Diagnostics tests to confirm WNV infection are similar to most other flaviviruses. During the viraemic phase, serum can be used to culture the virus and viral RNA genomes can be detected by NAT. In neurologic cases, cerebrospinal fluid may also be used in lieu of serum. The presence of IgM in the serum or cerebrospinal fluid can also be used to confirm recent infection, although this type of antibody may be long-lived (>30 days) in some patients, so caution must be used when trying to determine the date of infection. IgG testing by ELISA and PRNT to measure total antibody and

842 section 8 Infectious diseases neutralizing antibody titres, respectively, are also useful for confirming previous WNV infection. It is best to compare the titres taken at two different times after infection to look for an increase in WNV-specific titres since flaviviruses exhibit strong cross-reactivity with one another. Prevention and control There is no currently licensed vaccine for human use, despite over a dozen years' worth of direct research to develop one. Several candidates are currently in clinical trials. A horse vaccine has been useful in preventing equine disease. Infection via tissue transplantation has been dramatically reduced due to intensive screening. As most WNV infections occur via mosquito bites, vector control has been a main priority of many individuals and governments. Using mosquito repellent and avoiding mosquito bites at peak biting times are the best ways to prevent infection. Mosquito spraying and destruction of breeding sites have been strategies employed by local communities. Treatment There is no effective and licensed countermeasure for West Nile disease. Supportive care is offered to hospitalized patients, particularly those with neurologic complications, and may require respiratory and rehydration support. Other mosquito-borne infections Ilheus virus (ILHV) Aetiology and epidemiology Ilheus virus (ILHV) was first isolated in 1944 from mosquitoes of the genera *Ochlerotatus* and *Psorophora* collected near the town of Ilheus, Bahia, Brazil. ILHV was also isolated from other mosquito species, including the genera *Culex*, *Sabethes*, *Haemagogus*, and *Trichoprosopon*, and from a variety of birds in different countries in Latin America. ILHV is believed to be maintained in zoonotic cycles between birds and mosquitoes in Central and South America. Human infection with ILHV has been reported in Trinidad, Panama, Colombia, French Guyana, Brazil, Ecuador, and Bolivia. Clinical characteristics Ilheus virus causes mainly asymptomatic infections in human. In mild cases patients present with malaise, asthenia, conjunctival injection, vesicular rash, facial oedema, arthralgia, myalgias, bone pain, abdominal pain, headache, earache and gastrointestinal or respiratory symptoms lasting $\approx$ 1 week. In severe cases, either the central nervous or cardiac system can be affected. However, long-term sequelae or deaths have not been described. Diagnosis Differential diagnosis includes dengue, St. Louis encephalitis, yellow fever, or influenza. Laboratory diagnosis of ILHV infections is through serological based assays, such as MAC and IgG ELISA and testing of serum to detect virus-specific antibodies. Virus may be detected by NAT during the viraemic phase of illness. Prevention and control The risk of infection can be reduced with ILHV by using mosquito repellents, wearing long sleeves and trousers while spending time outdoors. Treatment There is no specific treatment for ILHV and patients are maintained by supportive care. Anti-inflammatory drugs may be effective under certain conditions. Tick-borne

infections of the CNS Tick-borne encephalitis virus Aetiology and epidemiology Tick-borne encephalitis viruses (TBEV) are endemic across Europe and Asia, affecting dozens of countries. There are three antigenically similar viruses that comprise the TBEV subtypes: European (TBEV-Eu), Siberian (TBEV-Sib), and Far Eastern (TBEV-FE). The Far Eastern subtype is also known as Russian spring-summer encephalitis virus. Each subtype may also have coevolved with a specific vector which has restricted its geographic range. TBEV-Eu is transmitted primarily by the hard tick *Ixodes ricinus* whereas TBEV-Sib and TBEV-FE use *Ixodes persulcatus* ticks. Ticks in the *Dermacentor* and *Haemaphysalis* genera may also contribute to TBEV maintenance in nature. These ticks serve as both the reservoir and vector for TBEV as transtadial and transovarial transmission has been observed. These ticks feed from small rodents as well as livestock. Humans become infected following the bite from an infected tick or by consuming tainted milk and milk-based products. Transmission from mother to fetus in humans has been observed. It is estimated that thousands of people are infected by TBEV each year. Clinical characteristics The incubation period of tick-borne encephalitis (TBE) is typically 1–2 weeks. Many of the patients infected with TBEV have mild and nonspecific symptoms, which in some cases may be biphasic. The initial viraemic phase is characterized by nonspecific illness including fever, headache, muscle aches, malaise, and nausea with or without vomiting. Leukopenia and thrombocytopenia are also common. About 8 days later, approximately one-third of patients will progress to the neurologic phase, accompanied by meningitis, encephalitis, or meningoencephalitis. Long-term sequelae are not uncommon. In general, all subtypes of TBEV result in similar clinical disease (resulting in a case fatality rate c.1–2%) but the TBEV-FE subtype can result in more severe symptoms and a higher case fatality rate (5–20%). Most of these deaths occur if severe neurologic disease is present. Diagnosis Virus may be detected by direct isolation or indirectly by RT-PCR during the viraemic phase of illness. IgM, indicative of a

8.5.14 Flaviviruses excluding dengue 843 recent infection, can also be used to confirm infection and is detected by ELISA. The cerebrospinal fluid may also contain virus and antibodies and should be tested in addition to serum. A patient history of a recent tick bite might also help, but is not always noticed. Prevention and control Inactivated vaccines are available in several parts of the world, but not the United States. Immunization is recommended for those who live in endemic areas. Multiple doses are often required to reach vaccine efficacy, and boosters may be required to maintain immunity. Each country has its own guidelines for initial dose and booster times. Evading tick bites by wearing repellents, wearing appropriate clothing, and avoiding tick-infested areas is recommended. It is also advised to avoid unpasteurized milk. Treatment There is no specific treatment for TBEV and patients are maintained by supportive care. Anti-inflammatory drugs may be effective under certain conditions. Powassan virus Aetiology and epidemiology The virus was first isolated from the brain of a patient who died in Powassan, Ontario. The virus is transmitted between *Ix. cookei* (*Ix. ricinus* complex) ticks and rodents. Humans are infected when they come into contact with ticks during outdoor activities. Many people who become infected with Powassan virus remain asymptomatic. Approximately 60 cases of Powassan virus disease were reported in the United States in the past 10 years. Most cases have occurred in the Northeast and Great Lakes region. However, documented Powassan virus cases have also occurred in Russia where the primary vector is *Ix. persulcatus*. Clinical characteristics The incubation period (time from tick bite to onset of illness) ranges from about 1 week to 1 month. Signs and symptoms of infection can include fever, headache, vomiting, weakness, confusion, loss of coordination, speech difficulties, seizures, and memory loss. Powassan virus can infect the central nervous system and

cause encephalitis and meningitis with a 10% fatality rate. Approximately 50% of the infected patients have permanent neurological symptoms, such as recurrent headaches, muscle wasting, and memory problems.

Diagnosis Diagnosis is often based on the patient's clinical presentation, travel history, activities, and epidemiologic history of the location where infection likely occurred. Laboratory diagnosis of Powassan virus infections is through serological based assays, such as MAC-ELISA, MIA (microsphere-based immunoassay), and IgG ELISA, testing of serum and/or cerebrospinal fluid to detect virus-specific antibodies. In fatal cases, NAT, histopathology with immunohistochemistry and virus culture of autopsy tissues can be conclusive.

Prevention and control The risk of Powassan virus infection is greatly reduced by using tick repellents, wearing long sleeves and trousers, avoiding bushy and wooded areas, and doing thorough tick checks after spending time outdoors.

Treatment There is no specific treatment or vaccine available at present. People with severe Powassan virus illness often require hospitalization to receive respiratory support, intravenous fluids, or medications to reduce swelling in the brain.

Louping ill virus (LIV)

Aetiology and epidemiology This virus, isolated in 1931, is primarily of veterinary importance, mainly affecting sheep, but sometimes other animals. It is a member of the tick-borne encephalitis virus complex and is predominantly found in Ireland, western Scotland, northern England, and Norway. The usual vector is *Ix. ricinus*. Naturally occurring human infections are relatively rare but infection via laboratory exposure is not unknown. Most infections relate to human contact with animals or with sheep blood.

Clinical features Clinical disease in humans is relatively mild and might just present as an influenza-like illness. Neurological disease, either presenting as a lymphocytic meningitis or encephalitis, with ataxia and stupor, is the most commonly reported syndrome. Cases resembling poliomyelitis have also been reported. Rare fatal infections have occurred.

Diagnosis Detection of specific IgM or demonstration of a rise in titre of IgG over time can aid in the diagnosis but molecular tests are more sensitive and specific.

Prevention and control Most control measures focus on vector control, reducing tick density. There is a vaccine for sheep as well. For humans, appropriate clothing and tick avoidance are important, along with care in handling diseased animals.

Treatment There is no known treatment other than symptomatic relief.

Tick-borne infections with haemorrhagic manifestations

Kyasanur forest disease virus (KFDV)

Aetiology and epidemiology Kyasanur Forest disease virus (KFDV) is endemic to the southern part of India as the name hails from the Kyasanur Forest from which it was originally isolated from in 1957. The virus is transmitted in a tick-rodent cycle. The hard-bodied forest tick, *Haemaphysalis spinigera* is the primary vector. Small animals like mice, rats, and shrews maintain the virus. Monkeys are extremely susceptible to

844 section 8 Infectious diseases KFDV infection, which is typically lethal and associated with large epidemics. Dead-end livestock hosts like cattle, goats, and sheep may become infected but are not thought to influence human disease. Human infections occur when they are bitten by an infected tick or come into contact with a KFDV-infected animal.

Clinical characteristics Kyasanur Forest disease (KFD) is similar to Omsk haemorrhagic fever in that the disease presents nonspecifically with fever, headache, myalgia, cough, hypotension, and dehydration. This lasts for a few days (3–4) after the incubation period (3–8 days). A biphasic illness is observed in some patients (c.10–20%), which appears in the third week of illness and is characterized by fever and signs of encephalitis. The case fatality rate is c.3–5%. Unlike Omsk haemorrhagic fever, no major sequelae are observed.

Diagnosis Blood taken during the viraemic phase (between days 3–12 of symptoms) can be amplified by RT-PCR to detect viral RNA. After this phase, antibodies against KFDV can be detected by ELISA or PRNT assays.

Prevention and control A formalin-inactivated vaccine for KFDV is available. This vaccine is provided in endemic areas and requires multiple doses; two doses will

provide c.62% efficacy whereas three doses increases to 83% efficacy. Avoidance of tick bites by applying repellants and checking for ticks when in the forest, as well as avoiding sick animals, is advised. Treatment No specific treatment is available. Supportive care for patients including maintaining hydration and preventing excessive bleeding. Alkurma haemorrhagic fever Aetiology and epidemiology Relatively little is known about Alkurma haemorrhagic fever virus (ALKV). It was first observed in 1995 in Saudi Arabia. The full geographic range of ALKV is not fully known but serology is limited to within the countries of the Persian Gulf. The transmission cycle is also unknown. A recent study has shown *Ornithodoros savignyi* ticks contained the ALKV viral RNA. The vertebrate host has not yet been determined. Clinical characteristics A clear clinical picture of this disease is limited based upon the small number of documented cases. Alkurma haemorrhagic fever presents with fever, headache, joint, muscle and retro-orbital pain, and vomiting. Low platelets and white blood cells are observed and some patients progress to haemorrhagic fever or encephalitis. The low number of cases may obscure the actual case fatality rate, which currently is c.30%. Diagnosis Diagnosis is made by detecting the viral RNA in the blood by RT-PCR. The presence of anti-ALKV antibodies can be made by ELISA or neutralization assays. Prevention and control There is no vaccine for ALKV. The best method of prevention is avoiding tick bites. As more is known about the life cycle of ALKV, this may change. Treatment Treatment is supportive with no specific countermeasure currently available. Omsk haemorrhagic fever virus Aetiology and epidemiology Omsk haemorrhagic fever virus is a member of the TBE serogroup and as such is transmitted by ticks. The virus is endemic to a few regions of the Russian Federation, including Kurgan, Tyumen, Omsk, and Novosibirsk. Transmission can occur with or without the tick vectors. *Demacentor reticulatus*, *Demacentor marginatus*, and *Ixodes apronophrus* ticks are the primary vectors of transmission. Small rodents, like muskrats and voles, are the vertebrate hosts for Omsk haemorrhagic fever virus. Humans become exposed to the virus upon the feeding of an infected tick, or by the direct physical exposure to the bodily fluids of an infected rodent. The latter infection route is often associated with hunting. Interestingly, Omsk haemorrhagic fever virus can also be transmitted via the milk of infected goats and sheep. No human-to-human transmission has been described. Clinical characteristics Omsk haemorrhagic fever presents with a Kyasanur Forrest-like disease, with nonspecific signs and symptoms including fever, headache, chills, muscle pain, and bleeding. This can last up to 3–4 days after the incubation period of approximately 3–8 days. During this time, low blood pressure is observed along with low RBC, WBC, and platelet counts. After this initial phase, some patients may continue onto the second phase of illness characterized by fever and/or encephalitis. Some patients develop long-term sequelae including hearing and hair loss. The case fatality rate is between 0.5 to 3%. Diagnosis The best diagnostics tests for confirming infection are like other flavivirus infections. Testing the blood early during the disease allows for the detection of live virus by plaque assay/virus isolation and/or PCR. After viraemia, detection of antibodies by ELISA or PRNT are the best assays to confirm infection. Prevention and control There is no vaccine specifically targeting Omsk haemorrhagic fever. However, the TBE vaccines may provide sufficient cross-reactivity. Infection is best controlled by avoiding tick bites and hunting muskrats, especially in the winter. Treatment The only treatment for Omsk haemorrhagic fever is supportive care, including the administration of fluids for hydration in the case of a haemorrhagic disease.