THERAPEUTIC ADVANCES in
Infectious Disease

Review

Acute neurologic emerging flaviviruses

Ther Adv Infect Dis

2022, Vol. 9: 1–19

DOI: 10.1177/20499361221102664

Marissa Caldwell*, Abhilasha P. Boruah* and Kiran T. Thakur

***Abstract*:** The COVID-19 pandemic has shed light on the challenges we face as a global society in preventing and containing emerging and re-emerging pathogens. Multiple intersecting factors, including environmental changes, host immunological factors, and pathogen dynamics, are intimately connected to the emergence and re-emergence of communicable diseases. There is a large and expanding list of communicable diseases that can cause neurological damage, either through direct or indirect routes. Novel pathogens of neurotropic potential have been identified through advanced diagnostic techniques, including metagenomic next-generation sequencing, but there are also known pathogens which have expanded their geographic distribution to infect non-immune individuals. Factors including population growth, climate change, the increase in animal and human interface, and an increase in international travel and trade are contributing to the expansion of emerging and re-emerging pathogens. Challenges exist around antimicrobial misuse giving rise to antimicrobial-resistant infectious neurotropic organisms and increased susceptibility to infection related to the expanded use of immunomodulatory treatments. In this article, we will review key concepts around emerging and re-emerging pathogens and discuss factors associated with neurotropism and neuroinvasion. We highlight several neurotropic pathogens of interest, including West Nile virus (WNV), Zika Virus, Japanese Encephalitis Virus (JEV), and Tick-Borne Encephalitis Virus (TBEV). We emphasize neuroinfectious diseases which impact the central nervous system (CNS) and focus on flaviviruses, a group of vector-borne pathogens that have expanded globally in recent years and have proven capable of widespread outbreak.

Keywords: neuroinfectious disease, flavivirus, neurotropism, neurovirulence, CNS

Received: 7 September 2021; revised manuscript accepted: 30 April 2022.

Correspondence to:
Kiran T. Thakur
Division of Critical Care and Hospitalist Neurology, Department of Neurology, Columbia University Irving Medical Center, NewYork-Presbyterian Hospital (CUIMC/NYP), 177 Fort Washington Avenue, Milstein Hospital, 8GS-300, New York, NY 10032, USA.
ktt2115@cumc.columbia.edu

Marissa Caldwell
Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

Abhilasha P. Boruah
Department of Neurology, Columbia University Irving Medical Center, NewYork-Presbyterian Hospital (CUIMC/NYP), New York, NY, USA

Case Western Reserve University School of Medicine, Cleveland, OH, USA

*These authors contributed as the co-first authors for this study.

Introduction

The COVID-19 pandemic has shed light on the challenges we face as a global society in preventing and containing emerging and re-emerging pathogens. Multiple intersecting factors, including environmental changes, host immunological factors, and pathogen dynamics, are intimately connected to the emergence and re-emergence of communicable diseases.[1–3] There is a large and expanding list of communicable diseases that can cause neurological damage, either through direct or indirect routes. Novel pathogens of neurotropic potential have been identified through advanced diagnostic techniques, including metagenomic next-generation sequencing, but there are also known pathogens which have expanded their geographic distribution to infect non-immune individuals. Factors including population growth, climate change, the increase in animal and human interface, and an increase in international travel and trade are contributing to the expansion of emerging and re-emerging pathogens. Challenges exist around antimicrobial misuse giving rise to antimicrobial-resistant infectious neurotropic organisms and increased susceptibility to infection related to the expanded use of immunomodulatory treatments. In this article, we will review key concepts around emerging and re-emerging flaviviruses, a group of vector-borne pathogens that have expanded globally in recent years and have proven capable of widespread outbreak.[4–6] These viruses are transmitted through arthropod vectors, primarily mosquitoes and ticks. Notable mosquito-borne neurotropic flaviviruses include Japanese Encephalitis Virus (JEV), Dengue Virus (DENV), West Nile Virus (WNV), Zika Virus (ZIKV), St Louis Encephalitis Virus (SLE), and Murray Valley Encephalitis

Virus (MVE). Meanwhile, Tick-Borne Encephalitis Virus (TBEV) and Powassan Virus (POWV) are prominent tick-borne neuroinfectious flaviviruses.[7] We highlight several neurotropic flaviviruses of interest and discuss factors associated with neurotropism and neuroinvasion, emphasizing diseases which impact the central nervous system (CNS).

Emergence of neurological infections: the pathogen and the host

Close interactions between humans, animals, and the environment contribute substantially to the emergence of infectious pathogens.[8] Most human infections, including those which are neurotropic, have origins in animals, which are estimated to contribute approximately 60%.[9] To be precise, neurotropic pathogens can directly infect cellular populations of the nervous system including neurons and glial cells.[10] Neurovirulence refers to a pathogen's ability to cause disease specifically in the nervous system.[11,12] More broadly speaking, a pathogen may have 'neurological properties' if causes neurological dysfunction secondary to the infection without directly invading the nervous system.[12] A pathogen's ability to infect the nervous system and ensuring disease course also depends on host factors, primarily the response of the immune system and destruction of vascular and brain parenchyma by both the infection itself and the inflammatory response.[13]

Overview of clinical findings of neurotropic infectious diseases

Encephalitis, or infection of the brain parenchyma, classically presents with acute or subacute onset of fever, headache, altered mental status, personality changes, perceptual changes, and disorientation.[14] Patients will also present with specific neurological signs that localize to the infected region of the brain, which can vary widely.[14] Meningoencephalitis, rhombencephalitis (infection of the brainstem), and encephalomyelitis (infection of the brain and spinal cord) can be seen.[15] Certain neuroinvasive infections may affect the peripheral nervous system (PNS), including the muscle nerve and neuromuscular junction, sometimes in combination with CNS phenomena. Neurological signs and symptoms often are not specific to a particular pathogen, making systemic manifestations important in narrowing the differential diagnosis – for example, upper respiratory symptoms, rash, and history of tick bites.[15] Cerebrospinal fluid (CSF) studies typically show lymphocytic or neutrophilic pleocytosis (10–500 cells/μl), moderately elevated protein (0.5–1.5 g/l), elevated IgG synthesis rate, and elevated CSF: serum oligoclonal bands.[15] Immunocompromised patients may show other abnormalities, such as acellularity or high CSF white blood cell count.[15] Imaging studies are helpful to identify clinical encephalitis but are often nonspecific, such as hyperintensity on FLAIR/T2-weighted images and enhancement with gadolinium.[15] Some viruses are known to cause specific patterns on magnetic resonance imaging (MRI), such as periventricular enhancement seen in infants with Cytomegalovirus (CMV) encephalitis.[15] The hallmark features of viruses that will be discussed in this review are summarized in Table 1. Important considerations based on recent literature related to neurological manifestations of these viruses are also presented.

JEV

General overview

JEV is a vector-borne, enveloped flavivirus that is considered one of the most important encephalitis-causing flaviviruses globally. The severe neurologic sequelae associated with the disease have established JEV as the arthropod-borne virus causing the most disability-adjusted loss of life years annually.[19] JEV is transmitted *via Culex* mosquito vectors and exists in an enzootic cycle in which pigs act as the amplifying host and aquatic birds serve as the maintenance host.[20] Humans with JEV are 'dead-end' hosts as they do not develop a high enough viral load to infect other species.[21] Currently, JEV is endemic in 24 countries across Asia, particularly in rural and agricultural areas of Southeast Asia and the Western Pacific during the summertime and rainy seasons.[21] According to the World Health Organization (WHO), the incidence in these regions ranges from 1 to over 10 cases per 100,000 and outbreaks occur every 2–15 years, with most cases occurring in children less than 14 years of age.[22]

Currently, five different genotypes of JEV have been identified (G1–5) and are thought to derive from a common ancestor in Southeast Asia.

Table 1. Summarized findings of emerging flavivirus neuroinavasive disease.

	Most prevalent regions	Mode of transmission	Neurological complications	Important considerations
JEV	Southeast Asia Western Pacific	• *Culex* mosquito through an enzootic cycle with humans, pigs, and water birds	Severe acute manifestations (1% of cases) • Encephalitis • Aseptic meningitis • Meningoencephalitis Post-acute (10–28 days) manifestations • Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis	• Anti-NDMAR encephalitis should be considered in patients with recent JEV infection and new onset behavior or movement disorders • Vaccine-preventable and recommended in endemic regions

WNV	Africa
	Europe
	Middle East
	West Asia
	Australia
	North America
		• *Culex* mosquitoes through an enzootic cycle with birds and humans
		• Rare: organ transplant, blood transfusion, breast milk, and vertical transmission (one case)
			• West Nile Fever (20–25%)
			• Severe (1%)
			  ○ Encephalitis
			  ○ Meningitis
			  ○ Myelitis
			  ○ Acute flaccid paralysis
				• Neurological sequelae may be permanent, but functional improvement over time has been demonstrated
				• Children appear more likely to present with meningitis than encephalitis

ZIKV	Africa
	Asia
	Outbreaks have occurred in Micronesia, French Polynesia, and Brazil, causing global spread through travel
		• *Aedes* mosquito
		• Blood
		• Sexual encounters
		• Vertical transmission
			Adults
			• Guillain–Barré syndrome
			• Neuropathy
			• Transverse myelitis
			• Encephalomyelitis
			• Meningoencephalitis
			• Encephalopathy
			• Chronic inflammatory demyelinating polyneuropathy
			• Ophthalmic abnormalities
			• Congenital Zika Syndrome
			  ○ Spontaneous abortion
			  ○ Microcephaly
			  ○ Hypertonicity
			  ○ Seizures
			  ○ Irritability
			  ○ Ophthalmic abnormalities
				• Adults with neurological symptoms during acute infection may have long-term sequelae
				• Infants of mothers with ZIKV during pregnancy may develop neurological symptoms several months to years after birth, even if asymptomatic initially
				• Close monitoring of infants with intrauterine ZIKV exposure is recommended

TBEV	Europe
	Asia
		• *Ixodes ricinus* and *Ixodes persulcatus*, among other tick species
		• Unpasteurized milk
			• Meningitis
			• Severe encephalitis
			  ○ Chronic, progressive encephalitis found in 3% of cases of the TBEV-Sib strain
			• Spinal paralysis
			  ○ 5–10% of cases: monoparesis, paraparesis, or tetraparesis
			• Asymmetrical cranial nerve dysfunction
			• 40–50% develop post-encephalitic syndrome
				• TBEV typically follows a biphasic course, and patients with monophasic illness may have more severe illness
				• Post-acute cognitive deficits are common and should be monitored
				• Vaccine-preventable and recommended in endemic areas

(Continued)

Table 1. (Continued)

	Most prevalent regions	Mode of transmission	Neurological complications	Important considerations
DENV	Africa North and South America Eastern Mediterranean South-East Asia Western Pacific	• *Aedes* mosquito	• Encephalitis • Encephalopathy • Meningitis • Stroke • Cerebellar syndrome • Transverse myelitis • Acute disseminated encephalomyelitis • Cerebellitis • Ophthalmologic abnormalities	• DENV-associated encephalopathy has a 50% mortality rate • Secondary infection with a different DENV serotype is associated with more severe disease • Vaccination against DENV is recommended only in the setting of a previous DENV infection
POWV[16]	North America	• *Ixodes* and *Dermacentor* ticks • Small/medium mammals are reservoirs	• Headache • Altered mental status • Cerebellar dysfunction • Hemiplegia • Encephalitis	• 50% of infections have long-term neurologic sequelae
SLE[17]	North America (primarily United States) Sporadic cases in Caribbean, Mexico, and Central America	• *Culex* mosquitoes • Enzootic cycle between wild birds • Domesticated animals and humans	• Altered mental status • Headache • Agitation/confusion • Coma • Meningitis • Encephalitis	• Encephalitis is a common cause of death in first 2 weeks of infection • In patients with neurologic disease, approximately 30% develop syndrome of inappropriate antidiuretic hormone secretion (SIADH)
MVE[18]	Australia Papua New Guinea	• *C. annulirostris* & *Aedes normanensis* mosquitoes • Enzootic cycle with waterbirds and humans	• Encephalitis • Spinal cord dysfunction leading to flaccid paralysis • Cranial nerve palsy • Tremor	• 30–50% of survivors have long-term neurological sequelae

DENV, dengue virus; JEV, Japanese Encephalitis Virus; MVE, Murray Valley Encephalitis Virus; NMDAR, anti-N-methyl-D-aspartate receptor; POWV, Powassan Virus; SLE, St Louis Encephalitis Virus; TBEV, Tick-Borne Encephalitis Virus; WNV, West Nile Virus; ZIKV, Zika Virus.

However, with rising global temperatures from climate change, there is growing concern that JEV will become endemic globally with potentially catastrophic effects.[23] Geographic trends have suggested that typical genotype distributions are evolving to become more widespread with infections increasing in non-traditional regions. JEV-G1, which was typically endemic to Southeast Asia, has expanded its regional spread to parts of South, Central, and East Asia, and has now become the most dominant genotype in Asia above the previously dominant G3.[24,25] JEV-G3 RNA has been found in birds in Europe, and the first case of sequence-confirmed JEV-G3 in Africa was reported in Angola during the 2016 Yellow Fever epidemic.[26,27] A 19-year-old male without a history of foreign travel presented with fever, jaundice, headache, and blood sample positive for yellow fever, and was subsequently found to be JEV-positive *via* RNA sequencing. The emerging presence of JEV in non-endemic areas indicates that the strain has potential to amplify the current JEV disease burden in traditionally dormant regions.[27] After a 60-year silent period following the initial detection of JEV-5 in 1952, a novel strain of JEV-G5 emerged in Tibet, China in 2009 and has since been detected in multiple areas of South Korea in following years.[28] With over 3 billion people already at risk for JEV in epidemic areas, these patterns of re-emergence and spread in novel areas emphasize that continual monitoring of JEV in both traditional and non-traditional endemic areas is critical for controlling future disease burden.

Neurotropism of JEV

As with most flaviviruses, the viral glycoprotein E binds to host cell receptors and is endocytosed with clathrin-coated vesicles (endocytosis).[29] Following a bite from an infected mosquito, JEV first enters the epidermis and infects dendritic cells, then travels to lymphoid organs where it replicates, enters circulation, and disseminates to other organs.[29] The mechanism of JEV entry into the CNS remains poorly understood, with recent studies suggesting that inflammatory cytokine and protease-driven breakdown of the blood–brain barrier (BBB) allow for paracellular invasion of neuroinvasive JEV.[30] *In vitro* models suggest that JEV is capable of transcellular migration through endothelial cells allowing it to breech the BBB and may also be able to replicate in the endothelium.[31,32] JEV-specific cellular receptors have been proposed but not clearly identified to date.[29]

JEV infection has been found primarily in the gray matter of the hypothalamus, thalamus, hippocampus, and substantia nigra, including in pericytes, astrocytes, microglia, and developing neurons.[29–31] JEV has been reported to have preference for neuronal cell injury, allowing for virus spread through inhibition of neuronal cell proliferation. On infection, there is an increased production of microglial nodules, and it has been suggested that microglia contribute to the neuronal cell death caused by JEV.[33] Neuropathological features of JEV include neuronal necrosis predominantly of the thalamus and brainstem, cerebral astrocytosis, perivascular cuffing by mononuclear cells, and focal gliosis.[34]

Neurological features of JEV

Most patients are asymptomatic or have limited, mild symptoms including fever, headache, nausea, and vomiting. Before the onset of JEV encephalitis, patients may experience nonspecific symptoms, such as diarrhea or coryza. Neuroinvasive complications develop in an estimated 1% of infected individuals and are associated with a 20–30% mortality rate.[22,35] Of the patients who survive up to 50% experience chronic neurological sequelae of the disease. Patients with encephalitis or meningoencephalitis can present with rapid onset of high fever, headache, altered mental status, seizure, paralysis, speech changes, psychosis, cranial nerve palsies, and parkinsonian features.[36] Damage to the anterior horn cells can cause a poliomyelitis-like flaccid paralysis, while parkinsonian symptoms, such as rigidity, tremors, and mask-like facies, indicate involvement of the basal ganglia.[37] Studies have shown that up to 45–50% of patients have seizure activity during the acute phase of illness, and in children, these rates are even higher.[38]

Unique features of JEV course

While JEV illness is usually monophasic, a secondary phase of immune-mediated anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been reported in children and adults.[39–45] Ma *et al.*[40] reports three cases of unvaccinated children with immunoglobulin M (IgM)-confirmed JEV who developed symptoms of choreoathetosis, irritability, sleep disorders, agitation, mutism, and rigidity 25–29 days after their initial illness phase. The patients were found to

have anti-NDMAR IgG in CSF samples and made full recoveries with immunoglobulin. Pastel *et al.*,[44] Shaik *et al.*,[45] and Tian *et al.*[41] similarly each report a case of pediatric anti-NMDAR encephalitis 10 days and 4 weeks, respectively, after confirmed JEV infection. In a prospective study of 31 pediatric patients with clinically diagnosed JEV, five developed autoimmune encephalitis within 2 weeks to 2 months after their acute infection phase: two with anti-NMDAR antibodies, one with anti-$GABA_BR$ antibodies, and two with other unidentified anti-neuronal surface antibodies.[42] JEV RNA was not found in the CSF of all five patients during their second phase of illness. The study also found that compared to patients who only had one phase of illness, patients with autoimmune encephalitis suffered more long-term neurological deficits. Adult cases of JEV-induced anti-NMDAR encephalitis have also been reported, but the presentation tends to vary from pediatric cases; declining cognition and abnormal behaviors are the most common signs in adults, while chorea is most common in children and adolescents.[43] Importantly, Wang[46] reports an anti-NMDAR encephalitis case in a 2-year-old patient after receiving the JEV vaccine. Patients with a recent history of JEV infection who present with new onset behavioral or movement disorders should be evaluated for anti-NMDAR antibodies.

Diagnosis, treatment, and prognosis

A diagnosis of JEV should be considered in patients presenting with encephalitis with a history of recent travel or residence in endemic areas. JEV-specific IgM presence in CSF by enzyme-linked immunosorbent assay (ELISA) is best for diagnostic confirmation because the JEV viral load is typically low in humans, and the test has >95% specificity after 1 week of systemic illness.[21,35,47] Neuroimaging will often show symmetric thalamic, basal ganglia, and brainstem lesions on computed tomography (CT) and MRI. Other reported findings include T2 hyperintensities in the hippocampus, cerebellum, and cerebral hemispheres.[48–50] A recent case study of nine cases of JEV in China revealed that abnormal MRI lesions were most located in the thalamus, hippocampus, midbrain, temporal lobe, basal ganglia, and insula, respectively.[51] However, these findings may not be a sufficient diagnostic tool for JEV encephalitis compared to serological tests: one comparison found that thalamic lesions had 100% specificity for JEV, but only 23% sensitivity.[52]

Treatment of JEV is limited to supportive care as there are no approved antiviral medications. Recent analyses have suggested minocycline may have some clinical efficacy during the acute infectious period; however, these therapies have not been validated for use.[53] Vaccines against JEV are recommended for those who live or plan to travel to endemic regions for longer than 1 month.[22] There are currently four approved vaccines for JEV – the inactivated mouse brain-derived, inactivated vero cell, live attenuated, and chimeric vaccines. Vaccinations have proven to be extremely effective in reducing incidence of JEV and the associated encephalitis syndrome, reducing the morbidity in China by 97% from 1971 to 2005, and reducing incidence in Nepal by 72% just between 2004 and 2009.[54,55] In the United States, the inactivated vero cell-derived vaccine is given as two-dose series 28 days apart with the last dose given at least 1 week prior to travel to a high-risk region. A booster is also recommended in the setting of continued JEV exposure or if the initial series was received more than 1 year prior.[22] JEV vaccination may also provide cross-protection against ZIKV.[56]

Although JEV encephalitis has proven to be vaccine preventable, recent epidemiological shifts in traditional JEV genotype distribution have spurred the development of targeted monoclonal antibody therapies allowing for inhibition of infection from several strains. One study group testing a panel of anti-JEV mAbs on animal models found that antibodies specifically mapped to protein E domains I and III (JEV-31, JEV-169), exhibited the strongest neutralizing activity against multiple JEV genotypes likely as a result of inhibition of viral fusion.[57] These therapies have not been tested in humans but show promise in identifying potent molecular targets for future drug development as prevalence of additional JEV strains rises.

While neurological symptoms typically improve slowly over 6 months to 1 year, 20–50% of patients who develop encephalitis have permanent neurological sequelae, including paralysis, seizures, and difficulty speaking.[21,22,35] A recent 10-year prospective study of Lao patients with severe JEV found that one-fifth of patients died and two-thirds of survivors had neurological sequelae for a

median duration of 4.5 years.[58] Importantly, these sequelae were more common in children than adults.

Neuroinvasive WNV

General overview

WNV is another enveloped flavivirus with single-stranded, positive-sense RNA. Like other flaviviruses, its genome codes for three structural and seven nonstructural proteins and enters cells *via* endocytosis. Current evidence suggests that the viral glycoprotein E infects cells by attachment to cellular glycosaminoglycans, C-type lectins, or integrins, but the direct mechanism is still unknown.[59]

The first known human case of WNV, a vector-borne pathogen occurred in Uganda in 1937.[60] It is currently endemic in Africa, and has spread worldwide to Europe, the Middle East, West Asia, Australia, and North America. The first North American case was reported in 1999, precipitating a US epidemic that lasted through 2010 and is now the most common arboviral infection in the continent.[60–63] While several subtypes of WNV have been identified, Lineages 1 and 2 are most widespread and implicated in severe cases.[62,64] WNV exists in a cycle between mosquitoes and birds, where birds are the primary viral reservoirs and mosquitoes are the primary vector.[65] Humans are infected by the bites of infected *Culex* mosquitoes. Warmer temperatures are associated with increased incidence, with the highest rates of disease occurring between July and September in North America.[66] Humans are dead-end hosts; the viral load is insufficient to transfer back to mosquitoes. WNV transmission has been reported through organ transplant, blood transfusion, and breast milk, but these reports are rare [67–70] (Iwarmoto *et al.*, Pealer *et al.*, Hinckley *et al.*). There has been one single report of vertical WNV transmission.[61]

Neurotropism of WNV

WNV first enters the skin after an infected mosquito bite. It then infects keratinocytes and dendritic cells of the dermis, then reaches the lymph nodes, where it is believed to replicate before traveling to other organs, including the CNS. Infected neurons are most often found in the basal ganglia, thalamus, midbrain, and cerebellum.[71] It is unknown exactly how WNV enters the CNS, but direct invasion of the BBB, endothelial transport, axonal retrograde transport, or 'Trojan Horse' mechanisms through infected immune cells have all been proposed.[72] *In vitro* models of the BBB suggest WNV can cross the barrier without disrupting it, but whether this occurs *in vivo* is still unknown.[73,74] Hussmann *et al.*[75] also demonstrated that WNV can replicate in both endothelial cells and neurons but not well in astrocytes. Transneuronal routes of infection are also under consideration.[71]

Neurological features associated with WNV

An estimated 80% of WNV cases are asymptomatic. 20–25% of patients may develop West Nile Fever, a self-limited condition characterized by high temperature, headache, body aches, maculopapular rash, nausea, and vomiting lasting for 3–6 days.[61,72] About 1% of patients develop serious neurological complications including encephalitis, meningitis, myelitis, and acute flaccid paralysis.[76] In addition to headache and fever, these patients present with neck stiffness, altered mental status, flaccid paralysis, and photophobia. Some patients have also been reported to experience acute respiratory distress secondary to diaphragmatic paralysis caused by WNV.[77] The risk of neuroinvasive disease is greater with advanced age, as individuals above 65 years of age are at least 15 times more likely to develop neurological complications.[78] Neurological presentation of WNV in children is similar to adults. A review of WNV cases from the Centers for Disease Control and Prevention from 1999 to 2009 found that children were more likely to present with meningitis than encephalitis.[79]

Up to 75% of patients with neuroinvasive disease develop encephalitis, with presentation ranging from mild confusion to personality changes to coma.[80] Autoimmune encephalitis, which has been associated with related JEV, may also be triggered by WNV.[71] Karagianni *et al.*[81] report a case of an 84-year-old male who presented with encephalitis during the initial phase of WNV infection, recovered, and then declined at day 10 with worsened mental status, difficulty speaking, extrapyramidal signs, and workup revealing anti-glycine receptor antibodies.

Extrapyramidal signs, such as upper extremity coarse tremor, myoclonus, and bradykinesia, have also been commonly reported. Flaccid

paralysis typically occurs as a result of anterior horn cell destruction typically presenting with proximal asymmetric weakness within 48 h. Progressive paralysis can lead to respiratory failure, and some patients with extensive spinal cord involvement may develop quadriplegia.[80] Notably, Chan *et al.*[82] reported a case of acute flaccid myelitis without altered mental status secondary to WNV that presented similarly with poliomyelitis, suggesting that even without encephalitis, WNV may be an important differential in asymmetric paralysis.

Diagnosis, Treatment, and Prognosis

Diagnosis is confirmed by reverse transcription polymerase chain reaction (RT-PCR), cell culture, or WNV-specific IgG and IgM antibodies in serum or CSF. IgM antibodies are detected with IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) and may be found within 8 days of illness onset with persistence in serum for over a year.[61,83] In immunocompetent hosts, RT-PCR may be insensitive due to the transient viral presence in the CSF, therefore serological IgM is the test of choice.[84] However, it is important to note that in immunocompromised patients, the opposite approach may be more effective due to delayed or absent antibody response causing false seronegative results, and enhanced viral persistence in CSF allowing for prolonged detection by RT-PCR.[85] In patients with neurological complications, lumbar puncture often shows elevated protein levels (<150 mg/dL) and leukocytosis (<500 cells/uL), first with predominantly neutrophils and later lymphocytes. Neuroimaging may exhibit leptomeningeal enhancement, parenchymal spinal cord signal abnormalities, periventricular inflammation, and focal lesions in the pons, basal ganglia, anterior horn, and thalami on MRI.[80,86] Even though MRI is the most useful imaging for WNV, only 20–70% of patients exhibit imaging abnormalities.[87]

Treatment is currently limited to supportive care. Although there have been several investigated therapeutic agents, there are no WNV-specific antiviral medications and no vaccines that are licensed for humans. Some therapies that have shown variable effectiveness against WNV include IVIG, interferon, and ribavirin. While human immunoglobulin with high titers of WNV IgG (Omr-IgG-am) developed by a study team in Israel showed promise in enhancing both prophylaxis and acute treatment of neuroinvasive WNV, a subsequent clinical trial conducted by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group found no statistically significant difference in outcomes between patients receiving treatment with high-titered anti-WNV antibody IVIG compared to standard IVIG or normal saline.[88,89]

Monoclonal antibodies (mAbs) have also emerged as a potential therapeutic against WNV. The developed mAb E16 directed against flavivirus surface E glycoprotein showed *in vitro* and *in vivo* inhibition of viral replication through blockade of WNV release from endosomes into the cytoplasm.[90] Recent work has analyzed the efficacy of monoclonal antibodies against epitopes on envelope E protein domain II (mAb WNV-86), which demonstrates enhanced neutralization against mature virions and a 50% inhibitory concentration three times lower than mAb E16.[91] In addition, antibodies against flavivirus nonstructural protein 1 (NS1), a glycoprotein involved in recruitment of viral replication factors, have shown protection against WNV through triggering complement-mediated clearance of infected cells.[92] Although these targeted therapies have shown initial effectiveness in enhancing clearance of WNV in animal models, there is still concern over effectively mitigating the risk of antibody-dependent enhancement of infection and they have yet to be tested for therapeutic efficacy in humans.[93]

There are vaccines currently authorized for use in veterinary practice in Europe, and emerging research suggests that E protein-based vaccines may be effective.[94] Prevention of the condition is focused on community mosquito control measures and diligent surveillance of vector populations. In the setting of increased vector mosquito populations, low-volume organophosphate or insecticide application may be indicated.[86] Most patients with WNV have an uncomplicated recovery; however, mortality among those with neuroinvasive disease is 10%. Survivors often present with permanent complications from the viral neurological sequelae. Documented chronic deficits include neuropsychological impairment, fatigue, and cognitive decline even years after resolution of the infection.[77,95] Along with chronic deficits, patients with WNV have elevated long-term mortality risk. A cohort study assessing the outcomes of patients hospitalized with WNV found that

there was a twofold increase in mortality of these patients for up to 3 years after illness onset, and factors associated with increased mortality in these patients included older age, encephalitis during acute infection, and need for endotracheal intubation during hospital course.[96] However, a 2018 single-center retrospective review found that on long-term follow-up, most patients who had been hospitalized with neurological WNV manifestations had improved modified Rankin scores (improved from average scores of 3–5 during hospitalization to 0–2), indicating that functional impairment may improve over time.[97] Recent studies suggest there is an association between WNV and future development of neurodegenerative disease due to the impaired BBB causing persistent microglial activation and impaired clearance of amyloid aggregates.[98]

Neuroinvasive ZIKV infection

General overview

ZIKV is a mosquito-borne flavivirus. While the Aedes mosquito is the primary source of spread, ZIKV also spreads through blood, sexual encounters, and vertical transmission.[99–101] The primary vectors are Aedes aegypti and Aedes albopictus mosquitoes.[102] ZIKV was first detected in monkeys in Uganda in 1947; the first-known spread to humans occurred in 1952. For several decades, ZIKV cases were contained within Africa and Asia, but recent outbreaks in Micronesia (2007), French Polynesia (2013–2014), and most significant, Brazil (2015) spread the virus around the world.[99] In response to the outbreak in Brazil in 2016, the WHO deemed ZIKV a public health emergency of international concern and outlined its potential to spread through sexual transmission.[103]

Like other flaviviruses, viral glycoprotein E and precursor protein M are most implicated in the infection mechanism of ZIKV. Following endocytosis, viral RNA is released into the cytoplasm which serves to both allow the virus to replicate and trigger the host cell's innate immune response.[99,104] The incubation period can last from 3 to 18 days, but most infected individuals never develop symptoms. In those who do, symptoms are usually mild, such as fever, rash, conjunctivitis, myalgia, joint pain, fetal malaise, and headache, and last for 2–7 days, on average.[101] However, in some cases, neurological complications may develop, including Guillain-Barré syndrome (GBS), neuropathy, myelitis, and ophthalmic abnormalities. Furthermore, the neurotropic potential of ZIKV has been confirmed through the detection of the ZIKV and anti-ZIKV antibodies in the CSF of patients with neurological disease. Perhaps most worrisome – especially given the asymptomatic nature of most ZIKV cases – is the association of infection with spontaneous abortion and congenital abnormalities, such as microcephaly (termed 'Congenital Zika Syndrome' or CZS).[101,105]

Neurological complications of ZIKV

Since the Brazil outbreak of 2015, CZS resulting from vertical transmission has become the most well-known neurological manifestation of ZIKV. The most reported neurological signs in affected infants include microcephaly, hypertonicity, seizures, irritability, and ophthalmologic changes, including optic nerve, retinal, and vision abnormalities, nystagmus, and strabismus.[100,106,107] A case–control study of microcephalic infants found higher levels of ZIKV RNA and Zika-specific IgM antibodies in the CSF and serum of cases *versus* non-microcephalic infants.[108] Fetal CNS anomalies were found to be higher in women who had confirmed Zika infections during pregnancy *versus* not.[109] A study comparing CNS and eye defects in infants born in Columbia found abnormalities were more common during a ZIKV outbreak (from 2015 to 2016) than in the period before and after.[110] Interestingly, prior to the Brazil outbreak, most studies showed only 0.3–0.5% of ZIKV-infected mothers gave birth to infants with microcephaly. However, during the epidemic, 46% of infected mothers had children with microcephaly, suggesting that the severity of the infection evolves based on multiple factors.[106] Mortality for infants diagnosed with CZS ranges 4–7%, and surviving children have a variety of chronic neurological impairment, such as hearing loss, developmental delay, and vision difficulty.[111] In addition, within children of mothers infected with Zika that showed no anomalies at birth, up to 9% exhibited some neurodevelopmental delay before the age of 2 years.[112]

In adults, Guillain-Barré syndrome (GBS) is the most frequently reported neurological sequela of Zika infection and has been linked to several outbreaks in different countries. It has been postulated that this autoimmune complication occurs secondary to molecular mimicry between ZIKV structural proteins and gangliosides, which are glycolipids

containing sialic acid found in the nervous system.[113] Patients who develop GBS in the context of Zika usually exhibit symptoms 5–10 days after the onset of acute illness.[114] A case–control study of GBS patients during the ZIKV outbreak in 2013–2014 in French Polynesia found that 100% of cases had Zika antibodies *versus* only 56% of the control group composed of patients presenting to the same hospital with a non-febrile illness.[115] Similarly, 27 out of a sample of 29 patients diagnosed with GBS in Brazil in 2016 were found to be Zika-positive; another prospective study of 71 GBS patients in Brazil from 2014 to 2017 found that half of the patients with recent evidence of an arbovirus infection had ZIKV.[116,117] It has been suggested that individuals with Zika-associated GBS have higher morbidity and more severe chronic neurological sequlae, such as, cranial nerve palsies.[118] Other neurological complications associated with adult Zika infection include encephalomyelitis, meningoencephalitis, transverse myelitis, encephalopathy, and chronic inflammatory demyelinating polyneuropathy (CIDP).[116,119,120]

Diagnosis, treatment, and prognosis

Diagnosis of acute ZIKV is made with RT-PCR or nucleic acid amplification tests. However, since ZIKV is asymptomatic in most patients and often only transiently present in blood and serum samples, RT-PCR is not a consistently reliable diagnostic measure. For this reason, serology testing for Zika antibodies using MAC-ELISA is usually preferred for the detection of Zika in all phases. Zika IgM antibodies usually appear in the CSF 4–7 days after the onset of illness and persist for up to 12 weeks.[121] In addition, Zika can be detected in urine and saliva, as viral shedding in these mediums persists longer than serum and can be found 7–14 days after onset of illness. It is important to recognize that Zika can serologically cross-react with other flaviviruses, which can lead to potential false-positive or equivocal results. For samples exhibiting cross-reactive results, the plaque reduction neutralization test (PRNT) has shown diagnostic utility; however, this test is often limited by the need for more developed infrastructure as it is both time- and resource-intensive. There is still a significant need for accessible and inexpensive testing for Zika despite the major global burden of the disease it causes. Currently, treatment of ZIKV is supportive as there are no FDA-approved treatments or vaccines for the disease.[101]

Long-term outcomes: adults. In the post-acute period, adults with Zika infection may continue to experience neurological complications. In one study of 34 Zika-associated GBS cases, patients with GBS during their acute Zika infection were more likely to report disability and depression after 1 year compared to patients who had uncomplicated ZIKV.[122] *In vitro* studies of human and mouse brain tissue suggest that ZIKV can replicate within human and mouse brain cells and may lead to memory and synaptic changes *via* virus-induced inflammation and disrupted neuronal–glial communication.[123,124] This suggests that patients with a history of Zika infection may be at a higher risk of neurodegeneration and need to be monitored for clinical signs.

Long-term outcomes: children. Recently, it has become clear that congenital neurodevelopmental complications of vertical Zika transmission may manifest later in development, even if infants appear asymptomatic at birth. A study of children with intrauterine Zika infection who were normocephalic at birth performed worse in several neurodevelopmental domains than those without intrauterine infection at 6-month follow-up, in addition to having shorter attention spans and longer processing times of visual stimuli.[125] Data from the Dominican Republic outbreak found that children of women who had been infected during pregnancy developed post-natal developmental abnormalities, including post-natal microcephaly, hypotonia, hypertonia, hearing issues, and transient developmental delay.[105] A 18-month longitudinal study of Columbian mothers with ZIKV during pregnancy and their infants found that newborns without CZS showed declines over time in neurodevelopmental outcomes using two validated assessments of infant development.[126] Hcini *et al.*[127] report similar findings that both symptomatic and asymptomatic children are at risk of neurodevelopmental delay at least as far as 3 years old. A recent study analyzing neuroimaging of children diagnosed with CZS at 3-year follow-up revealed delayed myelination, persistent intracranial calcifications, ventriculomegaly, cerebellar hypoplasia, and cortical abnormalities on CT. All children included in this analysis displayed severe neurodevelopmental impairment.[128]

While the mechanism for these delayed effects is unclear, murine models suggest that Zika infection of oligodendrocytes and subsequent cell death in the post-natal period leads to secondary immune demyelination.[129] It is also possible that ZIKV has

persistent replicating ability in the CNS, which could increase the risk of neurological issues in children with intrauterine Zika exposure.[130] Together, these data present a strong case that clinically normal infants at birth whose mothers had a known Zika infection during pregnancy should be closely followed for the signs of neurodevelopmental delays years after initial diagnosis.

TBEV

General overview

TBEV is a flavivirus common in Europe and parts of Asia. TBEV is typically caused by one of the three strains: European (TBEV-Eu), Siberian (TBEV-Sib), and Far Eastern (TBEV-FE). Recent studies have also shown the emergence of the Baikalian (TBEV-Bkl) and the Himalayan (TBEV-Him) subtypes.[131,132] TBE-FE is associated with the most severe disease course, while TBEV-Eu and TBEV-Sib have been documented to have a milder presentation. The virus can occasionally be transmitted after the intake of unpasteurized milk products from viremic livestock. TBEV-infected ticks are likely to become more abundant as a result of emerging climatic changes.

Neurological complications of TBEV

The median duration of the first stage of illness is 5 days (range 2–10) with a 7-day symptom-free interval to the second phase (range 1–21). In the first viremic stage, the virus replicates in the Langerhans cells of the skin, travels to draining lymph nodes, and causes common systemic signs of infection as it spreads through the bloodstream.[133] In the second stage, the virus crosses the BBB and replicates in the neurons of the anterior horn, medulla oblongata, pons, cerebellum, dentate nucleus Purkinje cells, and striatum. The clinical spectrum ranges from mild meningitis to severe encephalitis with or without myelitis and spinal paralysis. Importantly, TBEV-Sib is associated in up to 3% of cases with a chronic, progressive encephalitis that is thought to develop over years. A flaccid poliomyelitis-like paralysis may occur as well during the febrile phase of the infection, and in about 5–10% of cases, monoparesis, paraparesis, and tetraparesis can develop, and paralysis of respiratory muscles. Some patients also present with an asymmetrical cranial nerve dysfunction predominantly affecting the ocular, facial, pharyngeal, and vestibular nerves.[134] It has also been suggested that individuals experiencing monophasic rather than typical biphasic presentation have a more severe course of disease.[135]

Diagnosis, treatment, and prognosis

Diagnosis is established by clinical presentation suggestive of meningeal involvement, elevated cell counts in the CSF, and positive serological testing. Positive serum TBEV-IgM typically is positive in diagnosis, with intrathecal IgM and IgG antibody response detectable in CSF, but several days later than in serum. Enzyme immunoassays are usually used for specific serodiagnosis. Neuropathological findings of this include diffuse lymphocytic and neutrophilic infiltrates within the meninges, and gray matter lesions are made up of lymphocytes, glial cells, and necrotic nerve cells.[136]

No specific treatment for tick-borne encephalitis exists, though some patients have been responsive to steroids and intravenous immunoglobulin. Vaccination against TBE with the European vaccines is recommended for all age groups above 1 year in the highly endemic areas ($\geqslant$ 5 cases/100,000/year) and for individuals at risk in areas with a lower incidence.[137] Travelers to endemic areas should be vaccinated if their visits will include extensive outdoor activities. Other preventive techniques include general tick avoidance, protective clothing, and pasteurization of milk.

The prognosis of TBEV is linked to the severity of the acute phase of the infection, as individuals with more severe symptoms have been shown to have a protracted recovery period. In addition, data have shown that up to 40–50% of patients with TBE develop a post-encephalitic syndrome involving deficits in cognition, psychiatric complaints, headache, hearing loss, and vision changes.[138]

DENV

General overview

DENV is one of the most common *Aedes* mosquito-borne viruses worldwide, particularly in tropical and subtropical regions, and is responsible for an estimated 390 million infections yearly – nearly 100 million of which are symptomatic.[4,139] There are four known serotypes, DENV-1 through DENV-4; while infection with one serotype provides lifetime protection against re-infection of that serotype, it provides only mild and

temporary protection against infection with other serotypes. In fact, secondary infection with a different serotype is associated with more severe disease.[4] DENV has spread from just nine countries in 1970 to over 100 today, with the highest burden in Asia. While Europe has not seen a DENV epidemic, cases are now seen regularly, and an epidemic is now considered a possibility.[139]

The disease spectrum of DENV can vary widely, from subclinical to severe dengue characterized by acute capillary leakage, thrombocytopenia, and hemorrhage leading to hypovolemic shock and organ failure.[4,140] Symptomatic cases commonly present first with acute onset of fever with headache, retroorbital pain, rash, myalgia and arthralgia, anorexia, abdominal pain, and nausea. As of 2009, the WHO classifies DENV infection in three ways: dengue (1) with or (2) without warning signs and (3) severe dengue. Warning signs include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, liver enlargement of greater than 2 cm, and increasing hematocrit with rapid and simultaneously decreasing platelets.[140] Severe dengue is defined as severe plasma leakage, severe bleeding, or severe organ involvement.[140] It is associated with secondary DENV infection with a different serotype and time between infections is associated with increased disease severity.[4,141] If untreated, severe dengue has a mortality of up to 20%.[141]

Neurotropism and neurological manifestations of DENV

DENV was initially considered to be non-neurotropic, and neurological sequelae of DENV infection were attributed to systemic, immune-mediated, or metabolic complications. In recent decades, an increasing body of evidence, including the presence of virions within the CSF, suggests that DENV can invade the nervous system, most likely hematogenously *via* the BBB.[142] Infection with DENV has been implicated as the cause of encephalitis and encephalopathy in patients from an endemic region, without evidence of other viruses.[143] Genomic comparison of serologic and CSF samples of DENV patients with neurologic manifestations showed 99.7% similarity, further suggestive of the ability of the virus to cross the BBB.[144] In particular, serotypes DENV-2 and DENV-3 are most commonly associated with neurologic manifestations.[144]

The most common neurological manifestations of DENV infection are encephalitis and encephalopathy. DENV-associated encephalopathy, which is often seen in the cases of severe dengue, has a 50% mortality rate.[145] Other CNS complications include meningitis, stroke, cerebellar syndrome, transverse myelitis, and acute disseminated encephalomyelitis, and cerebellitis.[146–149] Ophthalmologic complications have also been widely reported in association with DENV infection, including retinopathy, maculopathy, and choroiditis.[150–153]

DENV virus in children can manifest differently than adults. Children under the age of 1 year and between 4 and 9 years of age are at the highest risk of developing severe dengue. Mortality ranges 2.5–5% but can be as high as 44% if disease advances to shock.[145] Neurological manifestations reported in children include acute disseminated encephalomyelitis (ADEM), hepatic encephalopathy, parkinsonism, epilepsy, transverse myelitis, subarachnoid hemorrhage, and stroke.[145]

Diagnosis, treatment, and prognosis

DENV has an incubation period of 2–7 days followed by a symptomatic period of 4–10 days. Diagnosis *via* RT-PCR or viral NS1 protein levels is most useful during the febrile phase of infection. Rapid NS1 tests are commercially available and are particularly useful in endemic regions.[139] However, ELISA for dengue-specific antibodies is the preferred method for definitive diagnosis; IgM levels are detectable within 1 week and are at their highest levels 2–4 weeks following infection.[141] In primary infections, IgG antibodies typically appear around day 10 of infection but will rise rapidly within the first week in the setting of secondary infection.[139] Because DENV and JEV are common in similar regions and the virions are serologically cross-reactive, DENV encephalitis can be difficult to distinguish clinically from JEV and careful evaluation is the key.[154]

To date, no specific treatment for DENV infection exists. Severe dengue and hypovolemic shock must be managed carefully with intravenous rehydration. For milder symptoms, acetaminophen and paracetamol are recommended while NSAIDS should be avoided due to the risk of hemorrhage associated with DENV infection.[139]

Effective and safe vaccine development for dengue has proved challenging. To date, one live-attenuated

recombinant tetravalent vaccine, CYD-TVD (Dengvaxia, manufacturer: Sanofi Pasteur) is commercially available. However, it has been associated with an increased risk of severe dengue if the first natural infection of DENV comes after vaccination and is only recommended for those with a confirmed previous infection of DENV.[139,155,156]

Conclusion

Neurotropic infectious diseases are a growing concern to the global population, with significant associated morbidity and mortality. Ongoing environmental changes are increasing the population's susceptibility to emerging and re-emerging flaviviruses. Enhancing early detection of neuroinvasive infections, optimizing prevention strategies and public health surveillance systems in the years ahead will be critical to decrease the impact of neurotropic infectious diseases.

Ethics approval and consent to participate

Ethics approval and consent to participate was not required given the review nature of this manscript.

Consent for publication

Consent for publication was not required due to given the review nature of this manuscript.

Author contribution(s)

Marissa Caldwell: Writing – original draft; Writing – review & editing.

Abhilasha P. Boruah: Writing – original draft; Writing – review & editing.

Kiran T. Thakur: Conceptualization; Writing – original draft; Writing – review & editing.

ORCID iD

Kiran T. Thakur https://orcid.org/0000-0003-0050-0323

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: Dr. Kiran Thakur is supported by NIH K23 Award: K23NS105935-01.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Morens DM and Fauci AS. Emerging pandemic diseases: how we got to COVID-19. *Cell* 2020; 182: 1077–1092.
2. Kojom LP and Singh V. A review on emerging infectious diseases prioritized under the 2018 WHO research and development blueprint: lessons from the Indian context. *Vector Borne Zoonotic Dis* 2021; 21: 149–159.
3. Lee VJ, Aguilera X, Heymann D, *et al.* Preparedness for emerging epidemic threats: a Lancet Infectious Diseases Commission. *Lancet Infect Dis* 2020; 20: 17–19.
4. Pierson TC and Diamond MS. The continued emerging threat of Flaviviruses. *Nat Microbiol* 2020; 5: 796–812.
5. Fauci AS and Morens DM. Zika virus in the Americas – yet another arbovirus threat. *N Engl J Med* 2016; 374: 601–604.
6. Williams DT, MacKenzie JS and Bingham J. Flaviviruses. In: Zimmerman JJ, Karriker L, Ramirez A, *et al.* (eds) *Diseases of swine*. 11th ed. Hoboken, NJ: John Wiley & Sons, 2019, pp. 530–543.
7. Flaviviridae. Viral hemorrhagic fevers (VHFs). *CDC*, 2021, https://www.cdc.gov/vhf/virus-families/flaviviridae.html (accessed 18 January 2022).
8. Thompson A and Kutz S. Introduction to the special issue on 'emerging zoonoses and wildlife. *Int J Parasitol Parasites Wildl* 2019; 9: 322.
9. World Health Organization. *Asia Pacific strategy for emerging diseases*. Geneva: World Health Organization, 2011.
10. Patrick MK, Johnston JB and Power C. Lentiviral neuropathogenesis: comparative neuroinvasion, neurotropism, neurovirulence, and host neurosusceptibility. *J Virol* 2002; 76: 7923–7931.
11. Zhang L, Wei L, Wang Z, *et al.* COVID-19: neuroinvasiveness, neurotropism and neurovirulence. *J Neurol Exp Neurosci* 2020; 6: S24–S31.
12. Desforges M, Le Coupanec A, Brison E, *et al.* Neuroinvasive and neurotropic human respiratory coronaviruses: potential neurovirulent agents in humans. *Adv Exp Med Biol* 2014; 807: 75–96.
13. Dahm T, Rudolph H, Schwerk C, *et al.* Neuroinvasion and inflammation in viral central nervous system infections. *Mediators Inflamm* 2016; 2016: 8562805.
14. Roos KL and Tyler KL. Encephalitis. In: Jameson JL, Fauci AS, Kasper DL, *et al.* (eds)

Harrison's principles of internal medicine. 20th ed. New York: McGraw-Hill Education, 2018, accessmedicine.mhmedical.com/content.aspx?aid=1163580317 (accessed 23 July 2021).

15. Thakur K and Noble JM. Viral infections of the nervous system. In: Brust JCM (ed.) *CURRENT diagnosis & treatment: neurology*. 3rd ed. New York: McGraw-Hill Education, 2019, accessmedicine.mhmedical.com/content.aspx?aid=1159972608 (accessed 17 June 2021).
16. Birge J and Sonnesyn S. Powassan virus encephalitis, Minnesota, USA. *Emerg Infect Dis* 2012; 18: 1669–1671.
17. Simon LV, Kong EL and Graham C. *St. Louis encephalitis*. Treasure Island, FL: StatPearls, 2022, http://www.ncbi.nlm.nih.gov/books/NBK470426/ (accessed 18 January 2022).
18. Floridis J, McGuinness SL, Kurucz N, *et al.* Murray valley encephalitis virus: an ongoing cause of encephalitis in Australia's North. *Trop Med Infect Dis* 2018; 3: 49.
19. Mathers CD, Ezzati M and Lopez AD. Measuring the burden of neglected tropical diseases: the global burden of disease framework. *PLoS Negl Trop Dis* 2007; 1: e114.
20. de Wispelaere M, Desprès P and Choumet V. European Aedes albopictus and Culex pipiens are competent vectors for Japanese encephalitis virus. *PLoS Negl Trop Dis* 2017; 11: e0005294.
21. Japanese encephalitis, https://www.who.int/news-room/fact-sheets/detail/japanese-encephalitis (accessed 18 January 2022).
22. Japanese encephalitis. *CDC*, 2019, https://www.cdc.gov/japaneseencephalitis/index.html (accessed 16 July 2021).
23. Yun SI, Kim SY, Choi WY, *et al.* Molecular characterization of the full-length genome of the Japanese encephalitis viral strain K87P39. *Virus Res* 2003; 96: 129–140.
24. Solomon T. Flavivirus encephalitis. *N Eng J Med* 2004; 351: 370–378.
25. Gao X, Liu H, Li X, *et al.* Changing geographic distribution of Japanese encephalitis virus genotypes, 1935–2017. *Vector Borne Zoonotic Dis* 2019; 19: 35–44.
26. Platonov AE, Rossi G, Karan LS, *et al.* Does the Japanese encephalitis virus (JEV) represent a threat for human health in Europe? Detection of JEV RNA sequences in birds collected in Italy. *Eurosurveillance* 2012; 17: 20241.
27. Simon-Loriere E, Faye O, Prot M, *et al.* Autochthonous Japanese encephalitis with yellow fever coinfection in Africa. *N Engl J Med* 2017; 376: 1483–1485.
28. Kim H, Cha GW, Jeong YE, *et al.* Detection of Japanese encephalitis Virus genotype V in Culex orientalis and Culex pipiens (Diptera: Culicidae) in Korea. *PLoS ONE* 2015; 10: e0116547.
29. Laureti M, Narayanan D, Rodriguez-Andres J, *et al.* Flavivirus receptors: diversity, identity, and cell entry. *Front Immunol* 2018; 9: 2180.
30. Lannes N, Summerfield A and Filgueira L. Regulation of inflammation in Japanese encephalitis. *J Neuroinflammation* 2017; 14: 158.
31. German AC, Myint KS, Mai NT, *et al.* A preliminary neuropathological study of Japanese encephalitis in humans and a mouse model. *Trans R Soc Trop Med Hyg* 2006; 100: 1135–1145.
32. Patabendige A, Michael BD, Craig AG, *et al.* Brain microvascular endothelial-astrocyte cell responses following Japanese encephalitis virus infection in an in vitro human blood-brain barrier model. *Mol Cell Neurosci* 2018; 89: 60–70.
33. Chen C-J, Ou Y-C, Lin S-Y, *et al.* Glial activation involvement in neuronal death by Japanese encephalitis virus infection. *J Gen Virol* 2010; 91: 1028–1037.
34. Sethi M, Das T, Tomar N, *et al.* Japanese encephalitis virus-induced neuropathology in mouse model infected through the conjunctival route. *Indian J Med Res* 2019; 150: 498–503.
35. Simon LV, Sandhu DS, Goyal A, *et al. Japanese encephalitis*. Treasure Island, FL: StatPearls, 2021, http://www.ncbi.nlm.nih.gov/books/NBK470423/ (accessed 19 July 2021).
36. Kuhn JH and Charrel RN. Arthropod-Borne and Rodent-Borne virus infections. In: Jameson JL, Fauci AS, Kasper DL, *et al.* (eds) *Harrison's principles of internal medicine*. 20th ed. New York: McGraw-Hill Education, 2018, accessmedicine.mhmedical.com/content.aspx?aid=1155971053 (accessed 17 July 2021).
37. Misra UK and Kalita J. Movement disorders in Japanese encephalitis. *J Neurol* 1997; 244: 299–303.
38. Mehta A, Singh R, Mani VE, *et al.* Japanese B encephalitis. *Indian J Crit Care Med* 2021; 25(Suppl 2.): S171–S174.
39. Pradhan S, Gupta RK, Singh MB, *et al.* Biphasic illness pattern due to early relapse in Japanese-B virus encephalitis. *J Neurol Sci* 2001; 183: 13–18.
40. Ma J, Zhang T and Jiang L. Japanese encephalitis can trigger anti-N-methyl-D-aspartate receptor encephalitis. *J Neurol* 2017; 264: 1127–1131.

41. Tian M, Li J, Lei W, *et al*. Japanese encephalitis virus-induced anti-N-methyl-D-aspartate receptor encephalitis: a case report and review of literature. *Neuropediatrics* 2019; 50: 111–115.
42. Liu B, Liu J, Sun H, *et al*. Autoimmune encephalitis after Japanese encephalitis in children: a prospective study. *J Neurol Sci* 2021; 424: 117394.
43. Wang C, Zeng Z, Zhang F, *et al*. Clinical features of adult anti-N-methyl-d-aspartate receptor encephalitis after Japanese encephalitis. *J Neurol Sci* 2020; 417: 117080.
44. Pastel H, Chakrabarty B, Saini L, *et al*. A case of anti- N-methyl-D-aspartate (NMDA) receptor encephalitis possibly triggered by an episode of Japanese B encephalitis. *Neurol India* 2017; 65: 895–897.
45. Shaik RS, Netravathi M, Nitish LK, *et al*. A rare case of Japanese encephalitis-induced anti-N-methyl-d-aspartate receptor encephalitis. *Neurol India* 2018; 66: 1495.
46. Wang H. Anti-NMDA Receptor Encephalitis and Vaccination. *Int J Mol Sci* 2017; 18: 193.
47. Tiwari S, Singh RK, Tiwari R, *et al*. Japanese encephalitis: a review of the Indian perspective. *Braz J Infect Dis* 2012; 16: 564–573.
48. Solomon T, Dung NM, Kneen R, *et al*. Japanese encephalitis. *J Neurol Neurosurg Psychiatry* 2000; 68: 405–415.
49. Meng Q, Zou Y-L, Bu H, *et al*. Imaging and cytological analysis of 92 patients with Japanese encephalitis. *Neuroimmunol Neuroinflammation* 2014; 1: 29–34.
50. Basumatary LJ, Raja D, Bhuyan D, *et al*. Clinical and radiological spectrum of Japanese encephalitis. *J Neurol Sci* 2013; 325: 15–21.
51. Su Q, Xie Z-X, He F, *et al*. Adults with severe Japanese encephalitis: a retrospective analysis of 9 cases in Linyi, China. *Neurol Sci*. Epub ahead of print 9 November 2020. DOI: 10.1007/s10072-020-04867-8.
52. Dung NM, Turtle L, Chong WK, *et al*. An evaluation of the usefulness of neuroimaging for the diagnosis of Japanese encephalitis. *J Neurol* 2009; 256: 2052–2060.
53. Singh DAK, Mehta DA, Kushwaha DKP, *et al*. Minocycline trial in japanese encephalitis: a double blind, randomized placebo study. *Pediatr Rev Int J Pediatr Res* 2016; 3: 371–377.
54. Wang H, Li Y, Liang X, *et al*. Japanese Encephalitis in Mainland China. *Jpn J Infect Dis* 2009; 62: 331–336.
55. Upreti SR, Janusz KB, Schluter WW, *et al*. Estimation of the impact of a Japanese encephalitis immunization program with live, attenuated SA 14-14-2 vaccine in Nepal. *Am J Trop Med Hyg* 2013; 88: 464–468.
56. Tarbe M, Dong W, Hu G, *et al*. Japanese encephalitis virus vaccination elicits cross-reactive HLA-class I-restricted CD8 T cell response against Zika virus infection. *Front Immunol* 2020; 11: 577546.
57. Fernandez E, Kose N, Edeling MA, *et al*. Mouse and human monoclonal antibodies protect against infection by multiple genotypes of Japanese encephalitis virus. *Mbio* 2018; 9: e00008–e00018.
58. Mayxay M, Douangdala P, Vilayhong C, *et al*. Outcome of Japanese encephalitis virus (JEV) infection in pediatric and adult patients at Mahosot Hospital, Vientiane, Lao PDR. *Am J Trop Med Hyg* 2021; 104: 567–575.
59. Martín-Acebes MA and Saiz J-C. West Nile virus: a re-emerging pathogen revisited. *World J Virol* 2012; 1: 51–70.
60. West Nile virus. *CDC*, 2020, https://www.cdc.gov/westnile/index.html (accessed 21 July 2021).
61. West Nile virus, https://www.who.int/news-room/fact-sheets/detail/west-nile-virus (accessed 20 July 2021).
62. Chancey C, Grinev A, Volkova E, *et al*. The global ecology and epidemiology of West Nile virus. *Biomed Res Int* 2015; 2015: 376230.
63. Curren EJ, Lehman J, Kolsin J, *et al*. West Nile virus and other nationally notifiable arboviral diseases – United States, 2017. *Morb Mortal Wkly Rep* 2018; 67: 1137–1142.
64. Fall G, Di Paola N, Faye M, *et al*. Biological and phylogenetic characteristics of West African lineages of West Nile virus. *Plos Negl Trop Dis* 2017; 11: e0006078.
65. Farrar F. West Nile virus: an infectious viral agent to the central nervous system. *Crit Care Nurs Clin North Am* 2013; 25: 191–203.
66. Soverow JE, Wellenius GA, Fisman DN, *et al*. Infectious disease in a warming world: how weather influenced West Nile virus in the United States (2001–2005). *Environ Health Perspect* 2009; 117: 1049–1052.
67. Iwamoto M, Jernigan DB, Guasch A, *et al*. Transmission of West Nile virus from an organ donor to four transplant recipients. *N Eng J Med* 2003; 348: 2196–2203.

68. Pealer LN, Marfin AA, Petersen LR, *et al*. Transmission of West Nile virus through blood transfusion in the United States in 2002. *N Eng J Med* 2003; 349: 1236–1245.

69. Montgomery SP, Brown JA, Kuehnert M, *et al*. Transfusion-associated transmission of West Nile virus, United States 2003 through 2005. *Transfusion* 2006; 46: 2038–2046.

70. Hinckley AF, O'Leary DR and Hayes EB. Transmission of West Nile virus through human breast milk seems to be rare. *Pediatrics* 2007; 119: e666–e671.

71. Shives KD, Tyler KL and Beckham JD. Molecular mechanisms of neuroinflammation and injury during acute viral encephalitis. *J Neuroimmunol* 2017; 308: 102–111.

72. Clark MB and Schaefer TJ. *West Nile virus*. Treasure Island, FL: StatPearls, 2021, http://www.ncbi.nlm.nih.gov/books/NBK544246/ (accessed 21 July 2021).

73. Verma S, Lo Y, Chapagain M, *et al*. West Nile virus infection modulates human brain microvascular endothelial cells tight junction proteins and cell adhesion molecules: transmigration across the in vitro blood-brain barrier. *Virology* 2009; 385: 425–433.

74. Mustafá YM, Meuren LM, Coelho SVA, *et al*. Pathways exploited by flaviviruses to counteract the blood-brain barrier and invade the central nervous system. *Front Microbiol* 2019; 10: 525.

75. Hussmann KL, Samuel MA, Kim KS, *et al*. Differential replication of pathogenic and nonpathogenic strains of West Nile virus within astrocytes. *J Virol* 2013; 87: 2814–2822.

76. Riedel S, Hobden JA, Miller S, *et al*. Arthropod-Borne and Rodent-Borne viral diseases. In: Riedel S, Hobden JA, Miller S (eds) *Jawetz, Melnick, & Adelberg's medical microbiology, 28e*. New York: McGraw-Hill Education, 2019, accessmedicine.mhmedical.com/content.aspx?aid=1163283301 (accessed 27 July 2021).

77. Sejvar JJ, Bode AV, Marfin AA, *et al*. West Nile virus–associated flaccid paralysis. *Emerg Infect Dis* 2005; 11: 1021–1027.

78. Carson PJ, Borchardt SM, Custer B, *et al*. Neuroinvasive disease and West Nile virus infection, North Dakota, USA, 1999–2008. *Emerg Infect Dis* 2012; 18: 684–686.

79. Lindsey NP, Hayes EB, Staples JE, *et al*. West Nile virus disease in children, United States, 1999–2007. *Pediatrics* 2009; 123: e1084–e1089.

80. Jeha LE, Sila CA, Lederman RJ, *et al*. West Nile virus infection: a new acute paralytic illness. *Neurology* 2003; 61: 55–59.

81. Karagianni P, Alexopoulos H, Sourdi A, *et al*. West Nile Virus infection triggering autoimmune encephalitis: pathophysiological and therapeutic implications. *Clin Immunol* 2019; 207: 97–99.

82. Chan V, Minalyan A, Ottman P, *et al*. Falling for a diagnosis: West Nile myelitis without encephalitis. *Cureus* 2019; 11: e5838.

83. Tilley PAG, Fox JD, Jayaraman GC, *et al*. Nucleic acid testing for West Nile virus RNA in plasma enhances rapid diagnosis of acute infection in symptomatic patients. *J Infect Dis* 2006; 193: 1361–1364.

84. Diagnostic testing West Nile virus. *CDC*, 2021, https://www.cdc.gov/westnile/healthcareproviders/healthCareProviders-Diagnostic.html (accessed 18 January 2022).

85. Goates C, Tsuha S, Working S, *et al*. Seronegative West Nile virus infection in a patient treated with rituximab for rheumatoid arthritis. *Am J Med* 2017; 130: e257–e258.

86. Petersen LR, Brault AC and Nasci RS. West Nile virus: review of the literature. *JAMA* 2013; 310: 308–315.

87. Jani C, Walker A, Al Omari O, *et al*. Acute transverse myelitis in West Nile Virus, a rare neurological presentation. *Idcases* 2021; 24: e01104.

88. Ben-Nathan D, Gershoni-Yahalom O, Samina I, *et al*. Using high titer West Nile intravenous immunoglobulin from selected Israeli donors for treatment of West Nile virus infection. *BMC Infect Dis* 2009; 9: 18.

89. Gnann JW Jr, Agrawal A, Hart J, *et al*. Lack of efficacy of high-titered immunoglobulin in patients with West Nile virus central nervous system disease. *Emerg Infect Dis* 2019; 25: 2064–2073.

90. Thompson BS, Moesker B, Smit JM, *et al*. A therapeutic antibody against West Nile virus neutralizes infection by blocking fusion within endosomes. *PLoS Pathog* 2009; 5: e1000453.

91. Goo L, Debbink K, Kose N, *et al*. A potently neutralizing human monoclonal antibody targeting an epitope in the West Nile virus E protein preferentially recognizes mature virions. *Nat Microbiol* 2019; 4: 71–77.

92. Wessel AW, Doyle MP, Engdahl TB, *et al*. Human monoclonal antibodies against NS1 protein protect against Lethal West Nile virus infection. *Mbio* 2021; 12: e02440.

93. Haslwanter D, Blaas D, Heinz FX, *et al.* A novel mechanism of antibody-mediated enhancement of flavivirus infection. *PLoS Pathog* 2017; 13: e1006643.

94. Alli A, Ortiz JF, Atoot A, *et al.* Management of West Nile encephalitis: an uncommon complication of West Nile virus. *Cureus* 2021; 13: e13183.

95. Sadek JR, Pergam SA, Harrington JA, *et al.* Persistent neuropsychological impairment associated with West Nile virus infection. *J Clin Exp Neuropsychol* 2010; 32: 81–87.

96. Lindsey NP, Sejvar JJ, Bode AV, *et al.* Delayed mortality in a cohort of persons hospitalized with West Nile virus disease in Colorado in 2003. *Vector Borne Zoonotic Dis* 2012; 12: 230–235.

97. Hawkes MA, Carabenciov ID, Wijdicks EFM, *et al.* Outcomes in patients with severe West Nile neuroinvasive disease. *Crit Care Med* 2018; 46: e955–e958.

98. Vittor AY, Long M, Chakrabarty P, *et al.* West Nile virus-induced neurologic sequelae – relationship to neurodegenerative cascades and dementias. *Curr Trop Med Rep* 2020; 7: 25–36.

99. White MK, Wollebo HS, David Beckham J, *et al.* Zika virus: an emergent neuropathological agent. *Ann Neurol* 2016; 80: 479–489.

100. Freitas DA, Souza-Santos R, Carvalho LMA, *et al.* Congenital Zika syndrome: a systematic review. *PLoS ONE* 2020; 15: e0242367.

101. Zika virus, https://www.who.int/news-room/fact-sheets/detail/zika-virus (accessed 22 June 2021).

102. Chouin-Carneiro T, David MR, de Bruycker Nogueira F, *et al.* Zika virus transmission by Brazilian Aedes aegypti and Aedes albopictus is virus dose and temperature-dependent. *PLoS Negl Trop Dis* 2020; 14: e0008527.

103. WHO. *Sexual transmission of Zika Virus: Current status challenges and research priorities*. Geneva: WHO, http://www.who.int/reproductivehealth/zika/sexual-transmission-experts-meeting/en/ (accessed 18 August 2022).

104. Agrelli A, de Moura RR, Crovella S, *et al.* ZIKA virus entry mechanisms in human cells. *Infect Genet Evol* 2019; 69: 22–29.

105. Pimentel R, Khosla S, Rondon J, *et al.* Birth defects and long- term neurodevelopmental abnormalities in infants born during the Zika virus epidemic in the Dominican Republic. *Ann Glob Health* 2021; 87: 4.

106. Brasil P, Pereira JP, Moreira ME, *et al.* Zika virus infection in pregnant women in Rio de Janeiro. *N Engl J Med* 2016; 375: 2321–2334.

107. Melo AS, de O, Aguiar RS, *et al.* Congenital Zika virus infection: beyond neonatal microcephaly. *JAMA Neurol* 2016; 73: 1407–1416.

108. de Araújo TVB, Ximenes RAA, Miranda-Filho DB, *et al.* Association between microcephaly, Zika virus infection, and other risk factors in Brazil: final report of a case-control study. *Lancet Infect Dis* 2018; 18: 328–336.

109. Pomar L, Malinger G, Benoist G, *et al.* Association between Zika virus and fetopathy: a prospective cohort study in French Guiana. *Ultrasound Obstet Gynecol* 2017; 49: 729–736.

110. Ospina ML, Tong VT, Gonzalez M, *et al.* Zika virus disease and pregnancy outcomes in Colombia. *N Engl J Med* 2020; 383: 537–545.

111. Musso D, Ko AI and Baud D. Zika virus infection – after the pandemic. *N Engl J Med* 2019; 381: 1444–1457.

112. Rice ME. Vital signs: Zika-associated birth defects and neurodevelopmental abnormalities possibly associated with congenital Zika virus infection – U.S. territories and freely associated states, 2018. *MMWR Morb Mortal Wkly Rep* 2018; 67: 858–867.

113. Anaya J-M, Ramirez-Santana C, Salgado-Castaneda I, *et al.* Zika virus and neurologic autoimmunity: the putative role of gangliosides. *BMC Med* 2016; 14: 49.

114. Muñoz LS, Parra B, Pardo CA, *et al.* Neurological implications of Zika virus infection in adults. *J Infect Dis* 2017; 216(Suppl. 10): S897–S905.

115. Cao-Lormeau V-M, Blake A, Mons S, *et al.* Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *The Lancet* 2016; 387: 1531–1539.

116. da Silva IRF, Frontera JA, Bispo de Filippis AM, *et al.* Neurologic complications associated with the Zika virus in Brazilian adults. *JAMA Neurol* 2017; 74: 1190–1198.

117. Leonhard SE, Halstead S, Lant SB, *et al.* Guillain-Barré syndrome during the Zika virus outbreak in Northeast Brazil: an observational cohort study. *J Neurol Sci* 2021; 420: 117272.

118. Dirlikov E, Major CG, Medina NA, *et al.* Clinical features of Guillain-Barré syndrome

with vs without Zika virus infection, Puerto Rico, 2016. *JAMA Neurol* 2018; 75: 1089–1097.

119. Muñoz LS, Barreras P and Pardo CA. Zika virus–associated neurological disease in the adult: Guillain–Barré syndrome, encephalitis, and myelitis. *Semin Reprod Med* 2016; 34: 273–279.

120. Mehta R, Soares CN, Medialdea-Carrera R, *et al*. The spectrum of neurological disease associated with Zika and chikungunya viruses in adults in Rio de Janeiro, Brazil: a case series. *PLoS Negl Trop Dis* 2018; 12:e0006212.

121. Landry ML and St. George K. Laboratory diagnosis of Zika virus infection. *Arch Pathol Lab Med* 2016; 141: 60–67.

122. Walteros DM, Soares J, Styczynski AR, *et al*. Long-term outcomes of Guillain-Barré syndrome possibly associated with Zika virus infection. *PLoS ONE* 2019; 14: e0220049.

123. Figueiredo CP, Barros-Aragão FGQ, Neris RLS, *et al*. Zika virus replicates in adult human brain tissue and impairs synapses and memory in mice. *Nat Commun* 2019; 10: 3890.

124. Bobermin LD, Quincozes-Santos A, Santos CL, *et al*. Zika virus exposure affects neuron-glia communication in the hippocampal slices of adult rats. *Sci Rep* 2020; 10: 21604.

125. Familiar I, Boivin M, Magen J, *et al*. Neurodevelopment outcomes in infants born to women with Zika virus infection during pregnancy in Mexico. *Child Care Health Dev* 2021; 47: 311–318.

126. Mulkey SB, Arroyave-Wessel M, Peyton C, *et al*. Neurodevelopmental abnormalities in children with in utero Zika virus exposure without congenital Zika syndrome. *JAMA Pediatr* 2020; 174: 269–276.

127. Hcini N, Kugbe Y, Rafalimanana ZHL, *et al*. Association between confirmed congenital Zika infection at birth and outcomes up to 3 years of life. *Nat Commun* 2021; 12: 3270.

128. Alves LV, Hazin AN and Alves JGB. Neuroimaging in children born with congenital Zika syndrome: a cohort study. *J Child Neurol* 2021; 36: 1066–1070.

129. Schultz V, Barrie JA, Donald CL, *et al*. Oligodendrocytes are susceptible to Zika virus infection in a mouse model of perinatal exposure: implications for CNS complications. *Glia* 2021; 69: 2023–2036.

130. Ireland DDC, Manangeeswaran M, Lewkowicz AP, *et al*. Long-term persistence of infectious Zika virus: inflammation and behavioral sequela in mice. *PLoS Pathog* 2020; 16: e1008689.

131. Kozlova IV, Demina TV, Tkachev SE, *et al*. Characteristics of the Baikal subtype of tick-borne encephalitis virus circulating in eastern Siberia. *Acta Biomed Sci* 2018; 3: 53–60.

132. Dai X, Shang G, Lu S, *et al*. A new subtype of eastern tick-borne encephalitis virus discovered in Qinghai-Tibet Plateau, China. *Emerg Microbes Infect* 2018; 7: 1–9.

133. Ruzek D, Avšič Županc T, Borde J, *et al*. Tick-borne encephalitis in Europe and Russia: review of pathogenesis, clinical features, therapy, and vaccines. *Antiviral Res* 2019; 164: 23–51.

134. Kaiser R. Tick-Borne encephalitis. *Infect Dis Clin North Am* 2008; 22: 561–575.

135. Lindquist L and Vapalahti O. Tick-borne encephalitis. *The Lancet* 2008; 371: 1861–1871.

136. Bogovic P and Strle F. Tick-borne encephalitis: a review of epidemiology, clinical characteristics, and management. *World J Clin Cases* 2015; 3: 430–441.

137. WHO and Publication. Vaccines against tick-borne encephalitis: WHO position paper – Recommendations. *Vaccine* 2011; 29: 8769–8770.

138. Kaiser R. Tick-borne Encephalitis – still a serious disease? *Wien Med Wochenschr* 2012; 162: 229–229.

139. Dengue severe dengue, https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue (accessed 4 January 2022).

140. World Health Organization. *Dengue: guidelines for diagnosis, treatment, prevention and control*. Geneva: World Health Organization, 2009, 159p.

141. Guzman MG and Harris E. Dengue. *The Lancet* 2015; 385: 453–465.

142. Calderón-Peláez MA, Velandia-Romero ML, Bastidas-Legarda LY, *et al*. Dengue virus infection of blood–brain barrier cells: consequences of severe disease. *Front Microbiol* 2019; 10: 1435.

143. Solomon T, Dung NM, Vaughn DW, *et al*. Neurological manifestations of dengue infection. *The Lancet* 2000; 355: 1053–1059.

144. Ngwe Tun MM, Muthugala R, Nabeshima T, *et al*. Complete genome analysis and characterization of neurotropic dengue virus

2 cosmopolitan genotype isolated from the cerebrospinal fluid of encephalitis patients. *PLoS ONE* 2020; 15: e0234508.

145. Li G-H, Ning Z-J, Liu Y-M, *et al*. Neurological manifestations of dengue infection. *Front Cell Infect Microbiol* 2017; 7: 449.

146. Li F, Wang Y, Yu L, *et al*. Viral infection of the central nervous system and neuroinflammation precede blood-brain barrier disruption during Japanese encephalitis virus infection. *J Virol* 2015; 89: 5602–5614.

147. Khoo CS. Dengue cerebellitis: a case report and literature review. *Am J Case Rep* 2018; 19: 864–867.

148. Singh H, Pannu AK, Bhalla A, *et al*. Dengue: uncommon neurological presentations of a common tropical illness. *Indian J Crit Care Med* 2019; 23: 274–275.

149. Ngwe Tun MM, Muthugala R, Nabeshima T, *et al*. Unusual, neurological and severe dengue manifestations during the outbreak in Sri Lanka, 2017. *J Clin Virol Off Publ Pan Am Soc Clin Virol* 2020; 125: 104304.

150. Somkijrungroj T and Kongwattananon W. Ocular manifestations of dengue. *Curr Opin Ophthalmol* 2019; 30: 500–505.

151. Yadav HM, Dutta Majumder P and Biswas J. Dengue associated choroiditis: a rare entity. *J Ophthalmic Inflamm Infect* 2017; 7: 14.

152. Lima LH, Vianello S, Pimentel S, *et al*. Dengue fever presenting as purtscher-like retinopathy. *Ocul Immunol Inflamm* 2018; 26: 660–665.

153. Carod-Artal FJ. [Neurological complications associated with dengue virus infection]. *Rev Neurol* 2019; 69: 113–122.

154. Sivamani K, Dhir V, Singh S, *et al*. Diagnostic dilemma – dengue or Japanese encephalitis? *Neurol India* 2017; 65: 105.

155. Prevention | Dengue | CDC, 2021, https://www.cdc.gov/dengue/healthcare-providers/hc-providers-prevention.html (accessed 9 January 2022).

156. Dengue vaccines: WHO and position paper, September 2018, https://www.who.int/publications-detail-redirect/WER9335-457-476 (accessed 9 January 2022).