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**RESEARCH ARTICLE**

# BE AWARE OF THE ARTHROPOD-BORNE DISEASE: DENGUE, YELLOW FEVER, AND DISEASES FROM ENCEPHALITIC VIRUSES (WEST NILE, ST. LOUIS ENCE PHALITIS, CALIFORNIA SEROGROUP)

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**ABSTRACT**

Arthropod-borne infectious viral diseases continue to plague mankind and are not causally treatable. The source of infection is often unknown, and the initial symptoms of patients may be vague, merely influenzalike, though progression to severe disease and, potentially, death may follow. This review selects and presents five such diseases, borne by mosquitoes: Dengue and yellow fever of the tropics and subtropics; West Nile virus disease, St. Louis encephalitis virus disease,and disease caused by encephalitic California serogroup viruses, which all three affect inhabitants of temperate zones (but not limited to). These currently relevant diseases are described regarding transmission highlights, viral reservoir animals and mosquito vectors, symptoms, and regions affected, aiming at raising the preventive and early clinical awareness.



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# INTRODUCTION

Viral diseases transmitted by hemophagous, ectoparasitical arthropods cause morbidity and mortality worldwide and are causally untreatable in standard medicine (1,2), including the here presented mosquito-borne diseases of dengue, yellow fever (YF), West Nile virus (WNV) disease, St. Louis encephalitis virus (SLEV) disease (due to flaviviruses), and California serogroup (CSG) encephalitis virus disease (due to orthobunyaviruses). Mosquitoes breed in water, which renders their control challenging. Thus, in developing countries, ecological changes due to agricultural advances (e.g., irrigation, building of dams, deforestation) and urbanization (e.g., wastewater, water storage pots) have favored mosquito density and disease transmission (3,4). In temperate regions, permanent aquatic habitats such as storm drains and wastewater retention ponds are conducive in urban zones, as are flood irrigation and drainage ditches in rural areas (5). In a given area, even if community and personal efforts at limiting aquatic habitats have been made, progress is slow (1,6); a few remaining sites, such as on a private property, will yet sustain larval development and promote disease transmission (1). Moreover, global warming shifts or augments vector distribution (3,4,7). In mainland Europe, it has facilitated the transmission of dengue by the implicated exotic *Aedes albopictus* since 2007. Higher temperatures in Europe and summer droughts requiring flooding/rewetting promote the activity and occurrence of indigenous *Culex* mosquitoes, vectors of the WNV disease (7); a European outbreak was first documented in 1962-1963 in southern France (8).

In the tropics and subtropics, dengue virus (DENV) (9) and YF virus (YFV) trigger infection ranging from asymptomatic to fatal, though YF bypasses Asia and the Pacific countries and territories and is counteracted by an established vaccine (10,11). Dengue causes an estimated 96 million apparent infections annually, mainly in Asia (9). Dengue shock syndrome (DSS) is life-threatening, mostly affecting the young (6). Its resemblance with anaphylaxis has been elucidated (12,13). YF is fatal in up to half of the patients entering the severe phase of the disease characterized by hemorrhages and organ dysfunction (liver, kidney, myocardium) (1). It has been

estimated that 90% of YF cases occur in Africa, with an estimated 78,000 annual fatalities (2).

In temperate zones (and beyond), the general population risks potentially fatal neuroinvasive arthropod-borne viral (arboviral) disease. Infection is mostly asymptomatic (14,15), such as an estimated 70-80% of WNV infections (16). WNV disease, SLEV disease, and CSG encephalitis virus disease occur across larger regions (5,8,17) and co-occur in North America as part of the arboviral neuroinvasive disease burden, which includes Powassan encephalitis and eastern equine encephalitis. In the United States of America (USA), human vaccines are lacking for these diseases, which tend to produce aseptic meningitis or encephalitis; acute flaccid paralysis may co-occur or manifest alone; unspecified neurological presentations are also documented (15). Flaccid paralysis is a manifestation of WNV disease and is described as poliomyelitis-like (16) though only affects a minority of patients (15,16,18), namely 7% (16). It occurs in other arboviral diseases such as in SLEV disease, though is rare (19), and in Powassan encephalitis. In the latter disease, a spastic paralysis is displayed as well, especially in children (20). Notably, during the first WNV disease outbreak in the Western Hemisphere in late summer of 1999 in the New York City area, 6 out of 7 deaths were among patients who suffered encephalitis combined with muscle weakness. The latter, after neurological exams, was defined as flaccid paralysis, decreased muscle strength, or hyporeflexia (18).

For 2019, in the USA, the reported numbers of the arboviral neuroinvasive cases (deaths in brackets) were due to the following viruses: West Nile, 633 (60); La Crosse, 48, the most common cause of pediatric arboviral neuroinvasive disease in the USA; Jamestown Canyon, 25 (2); St. Louis encephalitis, 15; Powassan, 39 (9); eastern equine encephalitis, 38 (19). Four unspecified CSG virus cases were also reported. Illness onset was mostly between July and September. All deaths had occurred in patients with neuroinvasive disease (15). Non-neuroinvasive cases have also been fatal; e.g., 45 deaths were reported for WNV disease for the period 2009-2018. Of these deaths, 38 were in patients aged ≥70 years (16). La Crosse virus (LACV), Jamestown Canyon virus (JCV), and snowshoe hare virus (SSHV) belong to the neuroinvasive CSG viruses and are present in the USA (17).

In coping with untreatable, often initially nonspecific and influenzalike arboviral disease, prevention is critical. Studies have emphasized, as preventive efforts: The gaining of ecological information and of biological knowledge of vectors (and reservoir hosts); the exertion of a continued control/surveillance of vectors (1,3,4,6,7,10,11,21). To facilitate disease recognition and preventive awareness, this review describes the symptoms of the five presented arboviral diseases in the context of the pathogens' reservoir hosts, important vectors, and region. Published case histories, recounted in this article for dengue, SLEV disease, and CSG encephalitis virus disease, help to exemplify circumstances of infection and early symptoms, while alerting to a potentially fatal disease progression.

## TRANSMISSION AND PREVENTION

Among arthropod vectors, mosquitoes propel typical sylvatic and urban cycles of infection. They become infected when feeding on an animal host harboring a pathogen and acting as wilderness reservoir (enzootic transmission), or when feeding on an animal host, e.g., a domesticated animal, currently infected (epizootic transmission), or when participating in the human-vector-human infection (urban epidemic transmission) (1). Mosquitoes, to become infected, need highly viremic, "amplifying," hosts (1,5,8). While feeding, they transmit pathogens to another host via saliva containing facilitative antihemostatic and anti-inflammatory ingredients (22).

To prevent mosquito bites in humans, much of the skin should be covered and repellents applied. Bites may cause persistent papular lesions and, if sensitization has occurred, trigger wheals with surrounding edema. Only female mosquitoes, for the ripening of their eggs, have hemophagous habits. Both males and females suck nectar. Eggs are deposited in water, e.g., in discarded containers collecting rainwater (23). The availability of containers is commensurate with disease transmission: For arboviral disease, such as for severe LACV infection in affected areas, risk factors included tree holes, containers, or more than 10 deposited tires in the home environment; also living near a forest edge (24). In 2019, onset months for LACV disease extended from June through October (15). Community awareness of seasonal hazards facilitates the preventive efforts. For inhabitants of the temperate zone, the use of bed nets, common in the tropics, should be considered in regions, where arboviral infections have been reported.

Transmission highlight sand some preventive measures in view of the presented arboviral diseases include:

- Organ and blood donations transmit pathogens, such as observed for WNV (8) and, regarding blood transfusion, for SLEV (19). In the USA, blood donations have been screened since 2003, though infections associated with transfusion have yet occurred (8).
- Human and equine WNV infection (8,25), human LACV infection (24), and human SLEV infection (19) cause low-level viremia hindering transmission to feeding vectors, unlike dengue (6,10) and YF (10,11). Dengue, with a higher epidemic potential than YF, also has a significantly higher level and a longer period of viremia than YF (10). (Keep dengue and YF patients indoors and, generally recommended, install window and door screens.)
- Vaccination in travelers prevents global dissemination of YFV by infected travelers (10,26), who may be asymptomatic (26).
- DENV (27), WNV (8), and YF vaccine virus (11) enter human mammary milk.
- Exposure to maternal dengue antibodies predisposes newborns and minor infants to a severe arthropod-borne infection from a dengue serotype different from the mother's infective serotype (12). This "antibody-dependent enhancement" is generally ascribed to a person's severe secondary dengue infection from a serotype different from the one of the primary infection (1,6,12-14). (Protect this age group, which is vulnerable to severe dengue, from mosquito bites in dengue-endemic regions.)
- In susceptible vertebrate hosts, transmission occurs via the orogastric route, as of YFV (11) and WNV; between birds, WNV can spread via oral or cloacal fluids (8).
- In certain genera of mosquitoes, viruses can pass transovarially to progeny, which is a mechanism enabling

overwintering of a virus (8). The following viruses are included: WNV (8,14), YFV (10,28), DENV (28,29), and encephalitic viruses of the CSG, namely, LACV (28,30), JCV, SSHV, and Tahyna virus (TAHV) (30).

## DENGUE

DENV, genus *Flavivirus* (Flaviviridae), has 4 antigenically distinct serotypes known to cause epidemic disease in humans (6,31). The respective lifelong immunity exists after infection (6,14). Yet, secondary infection with a different serotype predisposes to dengue hemorrhagic fever (DHF) and the progression to DSS, mainly in the young (4,6), due to antibody-dependent enhancement (1,6,12). Yet, other mechanisms may be involved: Immunoglobulin E (IgE), which activates in anaphylactic reactions, was found elevated in dengue patients and suggested to impact pathogenesis and function as a prognostic marker (32). DSS can occur also in a primary infection, and IgE may thus play a role in the escalation to shock. As shown, similarities with anaphylaxis, as from insect sting, exist (13).

Enzootic transmission of DENV involves monkeys (31) and lower primates (6). *Aedes* mosquito species transmit the virus and include:

- The cosmotropical urban *Aedes aegypti* is the principal vector, present also in the southern, mainly humid USA. It tends to feed indoors, mainly in early morning and late afternoon; a nervous feeder, it may probe the skin and infect several persons during one blood meal (6). Climate change facilitates its spreading northward, though British conditions may not be suitable by 2071-2100 (7).
- *Aedes furcifer-taylori* and *Aedes luteocephalus* are sylvatic vectors (31) in Africa (see Yellow Fever).
- The Asian vector *Ae. albopictus* has been imported into the Americas (6,28) (USA included and established in East) (6), into Europe (4,7) and Australia (Torres Strait Islands), and is present in Africa, Middle East, Hawaii (33), Guam, Saipan (6) (and elsewhere).
- *Aedes polynesiensis* (Pacific islands) (6).

The incubation period of dengue is 3-14 days, averaging 4-7 days. The initial fever may reach ~41°C. Beginning suddenly, it may last 2-7 days, with frontal headache, retro-orbital pain, body aches, arthralgia, nausea and vomiting, rash, and, possibly, a relative bradycardia. Bleeding, such as from gums or the gastrointestinal tract, may arise in some patients. After a few days, a remission may occur, lasting 12-24 hours, followed by a short-term fever. Between illness days 2 and 6, a rash ranging in appearance from maculopapular to scarlatiniform may spread and last 2-3 days (6). In some patients, widespread erythema develops with interspersed spots of normal skin (6,34), an apparent immune response (34). In dengue complications, at the closure of the febrile phase, thrombocytopenia and rising hematocrit signal progression to DHF (6,31). During the afebrile critical phase, systemic plasma leakage may cause vascular collapse and shock (escalation to DSS). Mucocutaneous hemorrhages may appear (1,6) that can be cutaneous (petechiae, purpura, ecchymoses), nasal, gingival, gastrointestinal, urinary, uterine (menorrhagia) (6). Patients recover from plasma leakage with volume replacement therapy, which has decreased the case fatality to ≤1% (6,29), from ≥10% (29). The first reported case of DHF from a sylvatic DENV strain documented typical dengue illness, diagnosed as DHF grade II: In January 2008, in Malaysia, a 20-year-old male suffered high fever and chills. On illness day 4, repeated vomiting and diarrheal bouts occurred (temperature 37.5 °C). The next day, facial flush, mild hepatomegaly, and renewed higher fever, 39.6 °C, were noted. Values of thrombocytopenia and hematocrit had worsened from the previous day. The fever abated within 12 hours. Pruritic petechiae appeared on his legs. Signs of plasma leakage, such as ascites, pleural effusion, or circulatory disturbance, were absent (31).

Afebrile DENV-infected infants have been seen in hospital. In 2015, such a case in a 1-month-old male infant of Yucatán, Mexico, with history of insect bite, resembled anaphylaxis. He lived in a home lacking screens on windows and doors. In hospital, he presented with 2 red papules from insect bites on his left lower leg, crying, irritability, refusal to eat, vomiting (at one occasion), and tachycardia (188 beats per minute). Symptoms and laboratory results included: Generalized erythema, noted hours after admission; delayed coagulation times; hypotension; and hypoalbuminemia. Advanced respiratory distress with expiratory difficulties developed, considered as linked with the anaphylaxis. Thrombocytopenia, leakage of fluid to third space, total absence of peristalsis, and hepatomegaly were noted. The infant developed generalized hypoperfusion, cyanosis, and severe edema in limbs with distal necrosis, dying on the seventh day. Laboratory work clarified: Exposed to maternal dengue antibodies, he had suffered his own arboviral infection, which acted like his "secondary" infection and caused fatal DSS (12). IgE levels were not assessed in this case, but basophil levels, which tend to rise in anaphylaxis, had been found normal.

Regarding the global occurrence of dengue, the tropics and subtropics are affected, with apparent infections occurring mostly in Asia (70%), followed by Africa (16%, though a hidden dengue burden likely), the Americas (14%), and Oceania (<0.2%) (9). For Oceania, regions with occurrence of infections include Hawaii and northeastern Australia (33). India and Indonesia are at particularly high risk; also Pakistan, Bangladesh, China (South), Philippines, Nigeria, and Brazil are highly affected (9). Autochthonous transmission secondary to imported dengue occurs in southern Europe (7) and the USA (6). Locally acquired cases are noted in the southern USA (southern Florida, USA-Mexican border) (23).

## YELLOW FEVER

YFV, genus *Flavivirus* (Flaviviridae), originally from Africa, has geographically diverse genetic lineages. It is pathogenic in nonhuman primates of South America rather than in those of Africa, corresponding to a human case fatality of 40-60% versus ~20% for the respective continents (11). Five viral genotypes circulate in Africa, 2 in South America (10). Infection leads to viral replication in, firstly, the liver, then in other organs such as kidney, spleen, heart, and lung (26).

**Urban and sylvatic vectors in South America and Africa include:**

- *Ae. aegypti* is the urban vector, potentially also *Ae. albopictus* (35,36), which could be a bridge vector, as it tends to reach into sylvatic regions of enzootic transmission (10,28,36). The vectors are present in both

continents; *Ae. aegypti* seeks human blood, *Ae. albopictus* feeds on various hosts (10).

- *Aedes serratus* was found infected in southern Brazil (11).
- *Haemagogus* and *Sabethes* species are sylvatic vectors in South America. *Haemagogus leucocelaenus* and *Haemagogus janthinomys* were the main vectors in the Brazilian outbreak in the coastal Atlantic Forest (2016-2018); evidently, *Ae. aegypti* and *Ae. albopictus* were not involved (36). *Sabethes albiprivus* is implicated in sylvatic transmission in Argentina (11).
- Sylvatic vectors in Africa include *Aedes bromeliae* (East), *Aedes africanus* (central, West), and *Ae. furcifer-taylori*, *Ae. luteocephalus, Aedes metallicus* (West) (11).

The incubation period of YF is 3-6 days (35). Fever, chills, headache, myalgia, and nausea occur. Most patients recover after a remission period lasting up to 48 hours (26). In other patients, 15-25% (35), this period is followed by hemorrhagic and hepatic complications, with jaundice, vomiting of dark matter (hematemesis), possibly leading to hepato-renal failure and shock. Renal dysfunction is noted between illness days 5 and 7; anuria with acute tubular necrosis may be fatal. Myocardial lesions occur (26). Likewise, the established severe liver damage, which impedes the production of clotting factors and leads to consumption coagulopathy, heralds death (11). Hemorrhages from the mouth, eyes, and nose may be noted. Often, a slow pulse accompanies the initial high fever, paradoxically (29). Jaundice signals YF yet may not be visible until more than a week from illness onset. Therefore, an earlier diagnosis is considered essential for effective patient care and for the timely control of vectors and outbreaks (35). Regarding regional occurrence, YFV favors hot, humid climates (29). Tropical forests pose high risks (26). Mainly tropical, but also subtropical, regions are affected in South America and Africa (10,11,26). In South America, especially Brazil, Argentina, Paraguay, Bolivia, and Peru are involved (26). From 2015 towards the end of the decade, several outbreaks have occurred in Africa; as in Angola, the Democratic Republic of the Congo (26,35), Uganda, Nigeria (and cases in Chad, Ghana, Guinea, Republic of the Congo) (26). Autochthonous transmission is possible in the southeastern USA via the present *Ae. Aegypti* (29). Another YFV vector, *Ae. albopictus,* occurs in parts of the eastern USA (23).

**WEST NILE VIRUS DISEASE:** WNV, genus *Flavivirus*, family Flaviviridae, and SLEV belong to the Japanese encephalitis serocomplex. WNV was first isolated in 1937 in Uganda from a patient with febrile illness. It has several geographically diverse genetic lineages spreading with migratory birds. Infected horses perish, and certain birds ail or succumb, such as American crows (*Corvus brachyrhynchos*) and blue jays (*Cyanocitta cristata*). Amplifying reservoir hosts include house sparrows (*Passer domesticus*), common grackles (*Quiscalus quiscula*), house finches (*Carpodacus mexicanus*), and American robins (*Turdus migratorius*). Some small mammals and the frog *Rana rinibunda* develop viremia levels that may support vector transmission (8).

**Mosquito vectors of WNV include:**

- In the USA, the main vectors are *Culex* species, namely, *Cx. pipiens* (Northeast, north-central and Mid-Atlantic regions), *Cx. quinquefasciatus* (South, Southwest), and *Cx. tarsalis* (West) (8). Also important are *Cx. nigripalpus* (Southeast) (23) and *Cx. salinarius* (East) (23,29). *Cx. pipiens* and *Cx. restuans* were implicated in the first USA outbreak in 1999 in the New York City area (18).
- *Ae. albopictus* was found infected in the USA (28).
- In Canada, *Cx. pipiens* and *Cx. salinarius* were among the *Culex* species first identified as carriers of WNV, found in Ontario (first sampling also occurred in Quebec and Manitoba). *Cx. restuans* was found infected and was forming pools with *Cx. pipiens*. Both tend to feed on birds and are considered enzootic vectors bridging to humans. *Cx. tarsalis,* a detected carrier, and *Cx. salinarius* choose various hosts. The genera *Anopheles, Aedes, Ochlerotatus, Coquillettidia* yielded infected species (25).
- WNV is present in Mexico, where case numbers are low. Isolated neuroinvasive disease cases have occurred in Central and South America and the Caribbean (8). *Cx. quinquefasciatus* is a known vector for these regions. In the Caribbean (tropical Grenada), where WNV disease occurs rarely, *Cx. quinquefasciatus* was found to parasitize diverse hosts, mainly birds and mammals (including humans) and, to a lesser degree, reptiles; hence, it is considered a potential bridge vector (as it is in other parts of the world) between sylvatic and domestic/peridomestic areas. It was observed to readily enter homes (37).
- In the Eastern Hemisphere, mainly *Culex* species are recognized (Europe, Egypt, South Africa, Australia) (8), including *Cx. modestus* (Europe) (7), *Cx. perexiguus* (Middle East), *Cx. univittatus* (South Africa, Iberian Peninsula) (38), and *Cx. pipiens* (China) (39).
- Infected ticks have been found, as in Kenya and central and eastern Europe (8).

The incubation period of WNV disease has been quoted as 3-15 days (18). A surveillance report of the disease in the USA (2009-2018) noted the period of 2-6 days. Illness onset tends to occur during July to September (16). In August and September 1999, during the first USA outbreak, 59 patients presented, of whom some had engaged in evening outdoor activities around the home, such as gardening. The patients' median age was 71 years; almost all had fever (90%). The temperature range among patients was 36.5-40.2 °C. They had been symptomatic before admittance (mean duration of 5.3 days). Presenting symptoms included weakness (56%), nausea (53%), vomiting (51%), headache (47%), altered mental status (46%), stiff neck (19%), and erythematous rash (neck, trunk, limbs in some combination) that was macular, papular, or morbilliform (19%). Other symptoms included diarrhea (27%), myalgia (17%), arthralgia (15%), and seizures (3%) (18). Fifty-four of the 59 presenting patients had neuroinvasive disease, with encephalitis in 37 and meningitis in 17 patients. Six patients exhibiting the unusual combination of encephalitis and muscle weakness died, of 7 fatalities total. Muscle weakness was neurologically documented as flaccid paralysis (neither ascending nor descending), decreased muscle strength, or hyporeflexia (18). Manifestations of WNV disease include ataxia, myelitis, and optic neuritis (29). Sequelae (physical, cognitive) have lasted for over a year post-infection in approximately half of the patients with neuroinvasive disease (8,25), such as headache, muscle weakness, memory loss (25). The case fatality is 3-19% in encephalitis (8) and, in 1999 in

the first USA outbreak, was 30% in encephalitis combined with muscle weakness (18).

WNV disease affects every continent, except Antarctica, mostly North America, eastern Europe to Russia (to Siberia), Mediterranean countries, Africa, Middle East, and Asia (largely India, Pakistan) (8). The neurotropic Kunjin viral subtype and its variant circulate in Australia (8,21). West Nile encephalitis occurs in Xinjiang (northwestern China) (8,39) but may proliferate beyond; endemic in much of China, the similar Japanese encephalitis strikes mostly children and young adults (39). WNV first affected the Eastern Hemisphere only. In 1999, it caused the outbreak in the New York City area (18) and, within 3 years, spread to most of the contiguous USA and to Canada and Mexico (8). In the USA, data on neuroinvasive disease cases included (15,16): In 2019, 40 states and the District of Columbia (DC) reported cases, with highest incidences (cases per 100,000 population), in descending order, in Arizona, New Mexico, DC, and Nevada. Most cases were reported from California (147), Arizona (132), Colorado (52), and Nevada (34) (15). States in the western north-central region show increased WNV activity: During 2009–2018, high average annual incidence had consistently occurred in North Dakota, South Dakota, and Nebraska (16).

## ST. LOUIS ENCEPHALITIS VIRUS DISEASE

SLEV, genus *Flavivirus* (Flaviviridae), has 8 geographically diverse genotypes, apparently dispersing via migratory birds. The virus is amplified in passerine and columbiform avian species, e.g., in the eared dove (*Zenaida auriculata*) and picui ground dove (*Columbina picui*) (Argentina) (5). In the USA, an apparent neutralizing immunity exists in wild birds with previous WNV infection; with host overlap between the viruses, as in *P. domesticus* and *C. mexicanus,* which are amplifying hosts for either virus; *Q. quiscula* has exposure to SLEV (5) and amplifies WNV (8).

**Vectors include:**

*Culex* species are the important vectors; mainly, in the USA, the subtropical and widespread *Cx. nigripalpus* (South)*,* the rural *Cx. tarsalis* (West), and the urban *Cx. pipiens* and *Cx. quinquefasciatus*. The latter is a vector in Argentina (5).

The incubation period of the SLEV disease is 4-21 days (40,41); ~5-15 days are also reported (19). During the St. Louis epidemic of 1933 (Missouri), the case fatality was ~20% in the St. Louis area (40), and the virus was first identified as a cause of encephalitis (19). From 2003 to 2017, in the USA, the disease presented as encephalitis (60%), febrile illness (18%), meningitis (13%), and acute flaccid paralysis (3%). Only patients aged >45 years and suffering from neuroinvasive disease died (overall fatality rate of 6%) (19). In the first Latin American SLEV outbreak, in 2005 in Córdoba City, Argentina, symptoms pointing to neuroinvasive disease included headache, tremors, mental changes, sensory depression, and temporal-spatial disorientation. In 47 probable and confirmed cases, 9 deaths occurred, 8 in patients aged >50 years. Additional Argentinian outbreaks followed (5). In 2006, the first Brazilian SLEV outbreak was recorded, arising during a dengue outbreak; 3 of the 6 patients exhibited signs of hemorrhagic disease inviting the misdiagnosis of dengue. It was speculated that these patients may have had a previous dengue infection. The other 3 patients had the diagnosis of viral meningoencephalitis (42). In Arizona, USA, in July to October 2015, 23 confirmed SLEV cases occurred. Thereafter, isolated cases were detected in California (5), as the following: In 2016, SLEV caused meningoencephalitis in a 68-year-old immunocompromised male from Bakersfield, Kern County, California, who liked sitting outside though apparently had not noted mosquito bites. In late August, he reported of 2 days of fever, up to 39.4 °C, chills, confusion, and lethargy. He mentioned dizziness (with 2 falls), dyspnea, cough, and new-onset urinary incontinence. In hospital days later, inflammatory pneumonitis (soon causing hypoxia), possibly from chemical aspiration, was discovered and was fatal ~3 weeks later. Deaths from SLEV were noted as usually occurring during the first 2 weeks. The identified virus was related to a local strain (mosquito pool in Kern County), was apparently the genotype of the 2015-2016 viral reemergence in the Southwest (USA), and was rooted by Argentinian strains of 1978 and 2005 (41).

The region from southern Canada to southern Argentina is affected; isolated cases may occur. In the 21st century, outbreaks arose in Argentina, Brazil, and the USA (Arizona, 2015). Larger epidemics were recorded in the USA in the 20th century, including in 1975 along the Mississippi and Ohio River basins. Several epidemics occurred in southern Florida, up to 1990 (5). Data on neuroinvasive disease cases in the USA included (15,19): In 2019, Arizona, California, and Oklahoma reported cases (15). From 2003 to 2017, 148 cases were reported. The highest average annual incidence (cases per million population) of reported cases was, in descending order, in Arkansas, Arizona, and Mississippi (19).

## CALIFORNIA SEROGROUP ENCEPHALITIS VIRUS DISEASE

Five important neurotropic viruses, genus *Orthobunyavirus* (Peribunyaviridae), of the CSG are (17): North America experiences JCV, with white-tailed deer as reservoir; SSHV, with hares and rodents (such as chipmunks, squirrels) as reservoirs (17,43), and LACV, with chipmunks, squirrels as reservoirs (17). SSHV is present also in Russia. TAHV and Inkoo virus (INKV) are Old World viruses, mainly of Europe. Small mammals are reservoirs for TAHV (rodents, hedgehogs, hares) and INKV (hares) (17). Among the 5 viruses, neuroinvasive cases are caused most often by LACV (~50-100 reported cases annually), least frequently by INKV (reflecting the pathogens' neurological disease pattern in experimental mice). The viruses target children, excepting JCV. TAHV infection is influenzalike, rarely encephalitic (17). INKV causes neuroinvasive cases also in adults, but the disease appears to be more severe in children (30).

Regarding vectors, *Ochlerotatus triseriatus* (syn.: *Aedes triseriatus*) is the primary vector for LACV (17,30). Known as the tree hole mosquito, it breeds in tree holes filled with water (24). Vectors for the 5 CSG viruses include:

- *Oc. triseria*tus (17,30); *Oc. canadensis* (30) and *Ae. albopictus* (28,30) (LACV);
- *Oc. canadensis, Oc. cantator* (JCV) (17);
- *Oc. communis, Oc. punctor, Oc. hexodontus* (INKV) (17);
- *Aedes vexans, Aedes* (*Oc.*) *cantans* (TAHV) (30);

- *Ae. vexans, Aedes cinereus, Culiseta* (SSHV, TAHV) (17);
- *Aedes, Culex, Anopheles, Culiseta* (TAHV, JCV) (17);
- The genera *Aedes, Anopheles,* and *Culiseta* yield vectors in Canada (43).

The incubation period is 3-7days (43), 5-15days for LACV (24). In July 2015, a 73-year-old Canadian male of Grand Manan Island (New Brunswick), who often visited the woods and had exposure to feral cats, suffered fever, purposeless movements, incoherent speech, confusion, headache, and neck pain. Viral encephalitis was diagnosed 1 week from disease onset. Confusion and delirium persisted beyond the fever phase, leading to chronic dependence on assistance in a nursery home, with the diagnosis of postencephalitic dementia. Laboratory work indicated a previous infection with a CSG virus. Tests were positive for both JCV and SSHV (43). For severe LACV infection, reported general signs and symptoms are altered mental status, fever, headache, vomiting, encephalopathy, seizures, and focal neurological deficits linked with muscle and mobility. Mostly children aged <16 years are affected (>90% of cases). Death is rare (<1%). Complications from infection include neurological sequelae (possibly lifelong), behavioral problems, coma, brain herniation, and seizures (24).

LACV is limited to the USA, found in the East (15,17), often in hardwood forests (24). In 2019, the virus caused neuroinvasive disease cases in, primarily, eastern north-central and eastern south-central regions and the South Atlantic states, mostly affecting Ohio, Tennessee, and North Carolina (15). SSHV circulates in USA regions (North, West), in Canada and into Russia. JCV occurs in USA regions (East, West) and in Canada (17). In 2019, in the USA, neuroinvasive disease from JCV affected mainly New England and eastern and western north-central regions (15). INKV occurs in northern Europe (Scandinavia) and Russia. TAHV circulates in Europe, Russia, Asia, and Africa (17,30).

## CONCLUDING REMARKS

Arboviral disease is often difficult to recognize clinically during the early influenzalike stages. This article, reviewing selected arboviral diseases, highlights the early and developing symptoms, shows aspects and ways of transmission and prevention, important vectors, and regional disease occurrence. Alerts in the timely awareness, shown in this article, include the anaphylactic-like nature of DHF progressing to DSS, with advised awareness of IgE levels; the potentially quick progression to death in YF once jaundice appears, which is yet often used as an important diagnostic sign; and the muscle weakness of WNV disease, which, when combined with encephalitis, can indicate death. Critically, the public burden of arboviral disease is diminished by a continually upheld vector control and education of the public in the affected regions. Shielding from mosquitoes is the personal contribution in the global efforts at overcoming disease.

**Keypoints:** Arboviral disease, currently causally untreatable in standard medicine, warrants early clinical awareness. Awareness of early symptoms, regional vectors, aspects of transmission and prevention, also in view of global climate change, is facilitative in clinical and public health management. Alerts in disease progression are given: The anaphylactic-like nature of severe dengue; in yellow fever, the late diagnostic sign of jaundice, which can be followed by death in a short time; and the potentially fatal combination of muscle weakness and encephalitis in West Nile virus disease.

**Abbreviations**

(Related to Diseases and Viruses)

CSG: California Serogroup
DENV: Dengue Virus
DHF: Dengue Hemorrhagic Fever
DSS: Dengue Shock Syndrome
INKV: Inkoo Virus
JCV: Jamestown Canyon Virus
LACV: La Crosse Virus
SLEV: St. Louis Encephalitis Virus
SSHV: Snowshoe Hare Virus
TAHV: Tahyna Virus
WNV: West Nile Virus
YF: Yellow Fever
YFV: Yellow Fever Virus

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