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RESEARCH ARTICLE

BE AWARE OF THE ARTHROPOD-BORNE DISEASE: MOSQUITO-BORNE MALARIA AND TICK-BORNE FLAVIVIRUS ENCEPHALITIS

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ABSTRACT

Hemophagous, ectoparasitical arthropod vectors transmit infectious diseases, and local inhabitants and travelers are often unaware of exposure. Early clinical awareness in regard to a possible transmission and to the important, regionally specific or dominant pathogens and vectors aids in the prevention or anticipation of a potentially severe course of illness. Two diseases are reviewed that are endemic over large regions and tend to a regional diversity concerning pathogens, severe disease highlights, and vectors, and this diversity is described: Malaria of the tropics and subtropics, borne by Anopheles mosquitoes, and tick-borne (ixodid-borne) flavivirus encephalitis of the temperate climate zone, specifically the tick-borne encephalitis (Eurasia) and the Powassan encephalitis (North America, Russia).

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INTRODUCTION

The arthropod-borne endemic diseases marked by regionally specific or dominant pathogens and vectors include the curable tropical and subtropical protozoal disease of malaria (borne by *Anopheles* mosquitoes) (1-5) and the not causally treatable flavivirus encephalitis (borne by hard ticks) of the temperate climate zone; specifically, this article selects the tick-borne encephalitis (TBE) of Eurasia and the Powassan encephalitis of North America and Russia (6-10) that are caused by flaviviruses belonging to the TBE serocomplex (10). Early recognition of the regional risks of infectious transmission aids in the clinical management of local inhabitants and travelers. In 2020, malaria caused an estimated 241 million cases globally and 627,000 deaths, of which 47,000 deaths were ascribed to interrupted malaria-related services due to the coronavirus (SARS-CoV-2) pandemic (1). The children in sub-Saharan Africa aged under 5 years and infected with *Plasmodium falciparum* (falciparum malaria) are at a particularly high risk of death (1,4). In 2021, the World Health Organization (WHO) recommended vaccination against *P. falciparum* in children of regions with moderate to high infectious transmission, after a successful pilot introduction of Malawi (1). Chemoprophylaxis (4,11) is recommended for travelers in endemic regions who, when neglecting the prophylactic regimen and subjected to delayed diagnosis or an indistinct early symptomatology, can succumb to falciparum malaria (11). Vaccines exist for TBE of Eurasia (7,9,10), where an estimated 10,000 to 15,000 clinical cases occur annually (7,10). In Europe, up to 75% of infections are asymptomatic. For the year 2019, in Europe, 3,246 confirmed TBE cases (20 deaths) were reported, which occurred mostly between May and November, highlighted in July. Lithuania in eastern Europa was particularly affected (12). The Powassan virus (POWV) causes neuroinvasive disease, often severe, in the United States of America (USA), Canada, and Russia. Vaccination is not available (8,10). The annual numbers of disease cases are low. Apparently, many asymptomatic infections occur and remain unnoticed (10). For the year 2019, in the USA, the reported numbers of arthropod-borne neuroinvasive disease cases (deaths in brackets) were due to the following viruses: West Nile, 633 (60); LaCrosse, 48; Jamestown Canyon, 25 (2); St. Louis encephalitis, 15; Powassan, 39 (9); eastern equine encephalitis, 38 (19). Powassan encephalitis was the second deadliest disease, reported mostly during the second and third, but also fourth quarter of the year. Eight of the 9 deaths were in patients aged

over 60 years (13). (Except for POWV, these viruses are mosquito-borne.) For malaria, TBE, and Powassan encephalitis, this article endeavors to give differentiating and otherwise noteworthy information on the regionally specific or dominant pathogens and their pertaining severe disease highlights and important regional vectors, thus giving an overview and aiding in the preventive and early clinical awareness.

MALARIA

Protozoans, genus *Plasmodium* (Plasmodiidae), infect man, namely, *P. falciparum, P. vivax,* the 2 dominant worldwide agents, and *P. ovale, P. malariae.* Present in parts of Southeast Asia, *P. knowlesi* infects humans and monkeys (4), specifically long-tailed and pig-tailed macaques (14). The incubation period is, usually, 12-14 days (4,15), but approximately twice as long for *P. malariae* (16,17). Sporozoites, the protozoal life forms inoculated by female *Anopheles* mosquitoes, multiply in human hepatocytes. About a week later, the released merozoites start an asexual cycle by proliferating in erythrocytes, which liberate the newly formed merozoites roughly every 48 hours (*P. falciparum, P. ovale, P. vivax*), 72 hours (*P. malariae*), or 24 hours (*P. knowlesi*); 6-8 days after release of merozoites from hepatocytes, febrile illness occurs with sufficiently high parasitemia, exhibiting the cyclical paroxysms. Headache, aching muscles, and abdominal discomfort may precede the fever (4).

Some erythrocytic parasites develop into sexual gametocytes infectious to feeding anophelines and forming a sporozoite-producing oocyst therein (4,18), at the required external temperatures of 16-33 °C (*P. vivax*) or 18-33 °C (*P. falciparum*); at 27 °C, the production of sporozoites takes ~8-13 days (18). The sporozoites invade the mosquito's salivary glands and are inoculated into the next victim. Untreated parasitemia can linger for months, years, or, in *P. malariae* infection, decades. *P. vivax* and *P. ovale* may remain in the liver for 2 weeks and up to more than a year (as hypnozoites), causing relapses (4), despite initial treatment (4,15). Splenomegaly and thrombocytopenia with unclear fever are diagnostic predictors for malaria (11); the spleen may be palpable during the first symptomatic days (19).

In endemic regions, *P. falciparum* complications have varied according to age group (adapted from 4):

- Advanced hypoglycemia with lactic acidosis and anemia (mostly in children and pregnant women)
- Acidosis, concomitant with convulsions (or coma) and uremia (in children, with 43% mortality)
- Cerebral malaria with coma (when occurring in children, 3-15% have neurological sequelae); acidosis (in all age groups)
- Acute kidney injury, oliguric in 60-70% of cases, often concomitant with jaundice; pneumoedema, progressing to acute respiratory distress syndrome (ARDS), often fatal despite mechanical ventilation (mostly in adults)

Severe disease highlights of malaria plasmodids include: *P. falciparum, P. vivax, P. knowlesi* (4), and *P. ovale* (20) cause the severe pneumoedema (ARDS). *P. ovale* causes complications in 3% of patients, including also jaundice, advanced anemia, and renal impairment (20). *P. knowlesi* triggers, other than ARDS, acute kidney injury and (metabolic) acidosis, but, unlike *P. falciparum* and *P. vivax,* spares children from severity. Hyponatremia (also observed in severe falciparum malaria) and thrombocytopenia accompany the deadly *P. knowlesi* complications. Females, patients aged ≥45 years, and patients with existing cardiovascular disease have highest risks of death (21). Splenic rupture is mostly associated with *P. vivax* and occurs at times, one possible reason being overstraining (19). *P. malariae* causes acute kidney injury (16), also a potentially chronic nephrotic syndrome (membranoproliferative glomerulonephritis) due to glomerular deposits of immune complexes (16,17), which develops some weeks after the initial infection (despite parasite elimination); but other severe disease from *P. malariae* is usually absent (16). *P. vivax* and *P. falciparum* trigger syndromes that are similar, often involving vital organs (brain, lung, liver, kidney), but *P. falciparum* more likely causes more than one syndrome (22).

Untreated falciparum malaria can rapidly lead to multi-organ failure (4,11), largely due to microvascular obstruction by infected erythrocytes (4). From 1988 to 2002, in Switzerland, fatal falciparum malaria contracted in sub-Saharan Africa, mostly in Kenya (15 cases), was documented in 2 immigrants (child and adult) and 23 European travelers (adults), who had not used or had neglected an appropriate chemoprophylactic regimen. The immigrants, with waning semi-immunity due to living in Europe, had visited relatives. Death occurrence, in 23 cases averaging 8 days from symptom onset, was often from vital organ failure. Initial symptoms were non-specific, in some patients interpreted as harmless viral syndrome, and included continuous vomiting and diarrhea for several days (1 case); chills, fever, malaise, myalgia (seen among 13 cases); rhinitis, dry cough, later chills, malaise, also anxiety, confusion, dysarthria (1 case) (11).

Regarding the *Anopheles* vectors: In the USA, autochthonous malaria is known to occur (18); the main vectors are *An. freeborni* (West), *An. quadrimaculatuss.l.* (East), also *An. Pseudopunctipennis* (some southern areas, into Mexico) (3). Globally, important dominant/co-dominant vector species or species complexes can be named for specific regions, in which they are widespread and associated with public health concerns (adapted from 3):

Sub-Saharan Africa: *An. gambiae, An. funestus, An. arabiensis* (widespread; sympatric in western (excepting *An. arabiensis* in forests, e.g., in the Congo Basin) and southeastern regions)

- Americas: *An. albimanus* (Caribbean to Central America); *An. pseudopunctipennis* (Mexico to northwestern edge of South America to northern Argentina); *An. aquasalis* (coastal areas of Central and South America); *An. darlingi* (Amazon basin to northern/northeastern South America); *An. albitarsiss.l.* (savanna (Caatinga, Cerrado))
- Asia: *An. culicifaciess.l., An. fluviatiliss.l., An. stephensi* (sympatric in India); *An. diruss.l., An. minimuss.l.* (sympatric in much of Southeast); *An. sinensis, An. lesteri* (more northern, e.g., China, Korea); *An. sinensis* (Mongolia)
- Other regions: *An. messeae* (western Europe to Asia); *An. stephensi* (Persian Gulf region to India); *An. flavirostris* (Philippines, Lesser Sunda Islands); *An.*

farautis.l. (northern Australian coast to New Guinea, Solomon Islands, Maluku Islands)

For these *Anopheles* species or complexes, some naturally occurring infections with plasmodids are also named, aiding in the global orientation:

- *P. falciparum*: *An. gambiae, An. gambiae s.l.*, *An. funestuss.l., An. arabiensis* (1); *An. funestus* (23); *An. flavirostris* (24)
- *P. vivax*: *An. farauti* (*P. vivax* outbreak) (25); *An. aquasalis* (*P. vivax* epidemic) (2,26); *An. sinensis* (27); (*An. lesteri* (27) and *An. messeae* (28) are susceptible to *P. vivax* infection)
- *P. falciparum, P. vivax*: *An. albimanus, An. pseudopunctipenniss.l., An. darlingi* (29); *An. albitarsiss.l.* (30); *An. stephensi* (1); *An. minimus* (31); *An. fluviatiliss.l.* (32); *An. culicifacies* (species E) (27); *An. culicifacies* (*P. falciparum* and *P. vivax* epidemics) (2); *An. dirus* (27,33)
- *P. ovale*: *An. gambiae, An. gambiae s.l., An. funestus* (15)
- *P. malariae*: *An. darlingi* (29); *An. gambiae s.l., An. funestus* (17)
- *P. knowlesi*: *An. dirus* (co-infection with *P. knowlesi, P. falciparum,* and *P. vivax* detected) (33)

Those species tending to feed and rest indoors are associated with a higher risk of transmission: *An. funestus, An. gambiae* (23), *An. darlingi* (26,29), and *An. stephensi* (27). *An. pseudopunctipennis* (29) and *An. culicifacies* E and *An. fluviatilis* S (species of the *An. culicifacies* and *An. fluviatilis* complexes) (27) readily draw indoors. In coastal areas, the salt-tolerant species of *An. aquasalis* (3,26), *An. farauti* (25), and *An. albimanus* (29) promote malaria transmission. *An. culicifacies*E, an efficient vector, can adapt to variable aquatic habitats, also when containing salinity (27).

Regarding the global occurrence of the pathogens: *P. vivax* has adapted to a broader ecological and climatic range than *P. falciparum* (5). Generally, *P. malariae*is encountered in areas of *P. falciparum* distribution (17). *P. ovale* occurs naturally in sub-Saharan Africa and islands of the western Pacific; infections are reported from other regions, such as from Southeast Asia (15) and South America (34). The *P. knowlesi*infection is acquired in forests, such as in Malaysian Borneo (14); 2,609 cases (5 deaths) were reported in 2020 in Malaysia (1). As known, cases have occurred elsewhere, e.g., in Myanmar, Thailand, Singapore, the Philippines (14). In 2020, in the WHO regions, *P. falciparum* infections were documented most often, excepting the Region of the Americas (*P. vivax,* 75%), and were ≤100% (4 WHO African Regions (sub-Saharan Africa)); 74% (Eastern Mediterranean Region); 60% (South-East Asia Region, where *P. vivax* dominated in more northern areas); and 70% (Western Pacific Region). (The last 3 percentages included co-infections with other plasmodids.) In 2021, WHO certified the countries of China and El Salvador as malaria-free.

Travelers within WHO regions are to note the countries with the most estimated cases, such as Nigeria, India, and Papua New Guinea (1):

- African Regions: Nigeria (within west Africa) had 55.2% of cases; Democratic Republic of the Congo (within central Africa), 53.1%; Uganda (among countries with high transmission in east and southern Africa), 23.2%; Eritrea (among countries with low transmission in east and southern Africa), 83.6%
- Region of the Americas: Venezuela, 35%; Brazil, 26%; Colombia, 16%
- Eastern Mediterranean Region: Sudan, 56%; Somalia, 15%; Yemen, 14%
- South-East Asia Region: India, 82.5%; Indonesia, 15.6%; Myanmar, 1.6%
- Western Pacific Region: Papua New Guinea, 86.2%; Solomon Islands, 6.7%; Cambodia, 4.1%

TICK-BORNE FLAVIVIRUS ENCEPHALITIS

Neurotropic viruses, genus *Flavivirus* (Flaviviridae), can pass through the blood-brain barrier and attack the central nervous system. TBE virus (TBEV) mainly targets neurons (10). Europe, Siberia, the Far East (which includes eastern Russia) have separate viral subtypes of TBEV (TBEV-Eu, TBEV-Sib, TBEV-Fe), which co-circulate in the Baltic States and Finland due to vector overlap of *Ixodes ricinus* and *Ixodes persulcatus* (7). Tick bites (transmitting pathogens via the tick's saliva (8)) or ingested raw dairy products, often from viremic goats or cows, infect humans (7,35). The handling and crushing of ticks and, thereafter, touching one's mouth area are to be avoided. Infected tick species, even if not known as an efficient vector, can thus cause the alimentary transmission.

Mainly rodents, often parasitized by immature ticks (6), are reservoir hosts for TBEV, significantly *Apodemus*mice (6,9,10). In non-viremic vertebrate hosts, the infected host skin at tick feeding sites can transmit TBEV to uninfected ticks co-feeding with infected ticks (6). In North America, POWV has 2 lineages: POWV, the prototype lineage, is present also in Russia, with groundhogs (*Marmota monax*), red squirrels (*Tamiasciurushudsonicus*), chipmunks (*Tamias amoenus*), mustelids (skunks) (North America) (8), *Apodemus*mice, and *Microtus* voles (Russia) as important reservoirs (6). The deer tick virus (DTV), named after its vector, the deer tick (*Ixodes scapularis*), represents lineage II. White-footed mice (*Peromyscus leucopus*) act as reservoir (8).

The incubation periods of the diseases are ~7-14 days (range of 4-28 days) (TBEV-Eu) (36) and 7-35 days (POWV) (8). TBEV-Eu causes a biphasic illness in ~75% of patients, as noted in southern Germany in 656 patients studied between 1994 and 1998: The first phase, influenzalike, lasted 1-7 days, with fever, headache, myalgia, and, at times, involved the upper respiratory tract and/or abdomen. Asymptomatic days (~7, but range of 3-21) followed. Neurological symptoms developed during the first 5 days of the febrile second phase, mainly impaired consciousness, ataxia, paresis of limbs, and paresis of cranial nerves (e.g., hearing impairment, dysphagia, and dysarthria). Patients suffered meningitis (49%), meningoencephalitis (41%), and meningoencephalomyelitis with flaccid paresis of the limbs (10%). Of the 656 patients, 18% needed rehabilitation procedures (36).

The meningoencephalomyelitis did not occur in children and adolescents. Remarkably, it showed the biphasic disease course least often but produced all fatalities (8 patients) and

the most severe residual sequelae, mainly paresis of limbs, as well as produced most cases of limb paresis and of respiratory insufficiency and impaired bowel function (36). TBE patients have shown thalamic lesions (36-38). Such a patient, a 64-year-old male, was afebrile during the second phase of illness, which is atypical, and resembled a victim of stroke (38). TBEV-Fe causes a monophasic (9,37) and often more severe illness, as noted in a 15-year-old female adolescent from the USA traveling in June and July of 2007 in northeastern China, Tianjin. Initially, she had a fever and diarrhea. Acute encephalitis with persistent fever and confusion arose, and she developed seizures, Bell's palsy, hemiplegia, aphasia, and hyperreflexia. Thalamic and basal ganglia lesions were noted. She needed rehabilitation (37). In spring and summer, infected persons in China suffer sudden high fever, severe headache, stiff neck, nausea, and vomiting. The fever lasts 5-7 or up to 12-14 days. Two thirds of the TBE cases are severe, with disturbed consciousness, paralysis, and difficulty in swallowing and verbal communication; myocardial damage has been caused. Long-term disabilities affect nearly 20% of patients. In China, the former fatality rate of >20% has decreased (9). The fatality rate for TBE in Eurasia is known to extend from 1% (TBE-Eu) to 20% (TBE-Fe). It has been estimated at ~10-15% for POWV (10). TBEV-Sib infections may show chronic forms. Thus, progressive neurological disease, without an apparent preceding acute phase, has occurred in Asian-Russian regions, e.g., progressive muscular atrophy, lateral or dispersed sclerosis, and Parkinson-like disease (6).

POWV triggers fever, photophobia, headache, and retro-orbital pain, usually with neurological signs such as lethargy, seizures, paralysis, and paresis (6). Myalgia, neck stiffness, tremors, and ataxia have been noted (10). A sore throat is common during the initial phase. Meningitis, meningoencephalitis, disseminated encephalomyelitis, hemorrhagic encephalitis, and spastic or flaccid paralysis may occur (~10% case fatality in encephalitis). Over 50% of survivors suffer long-lasting neurological sequelae such as hemiplegia, headaches, muscular atrophy, and memory loss (8). DTV, existing in *I. scapularis,* was first reported from New England in 1997 (39), then from Wisconsin in 1999 (40). The first documentation of a fatal DTV case was published in 2009:

In late spring, in New York State, a 62-year-old male with chronic hematological cancer, who often visited wooded areas, died from a widespread necrotizing meningoencephalitis. Initially, the monophasic illness produced fever, a bilateral maculopapular palmar rash, diplopia, dysarthria, and weakened right-sided limbs. The fever, continuing for ~8 days, reached the temperature of 40.3 °C; findings included thalamic lesions. Nymphal *I. scapularis* was the suspected vector (41). It transmits DTV within 15 minutes of attachment, experimentally, while some bacterial or parasitical transfers in ixodids occur, generally, after 12-48 hours of attachment. TBEV, as known, enters the cement plug surrounding *I. persulcatus* mouthparts within 1 hour of attachment (42).

Therefore, in regions endemic for tick-borne flavivirus encephalitis, the prompt removal of attached ticks is important. Primary vectors for TBEV are *I. ricinus* (occurrence concentrated in Europe) for TBEV-Eu and *I. persulcatus* (occurrence in eastern Europe, Siberia to China, Japan) for TBEV-Sib and TBEV-Fe (7), noting also *Haemaphysalisconcinna* in Russia (6,43). In North America, the important vectors are *Ixodes cookei* for POWV and *I. scapularis* for DTV (8). Vectors in Russia are *I. persulcatus* and *Haemaphysalis*spp. for POWV (6,10); also*Dermacentor silvarum* is referred to (10). It is to be noted: TBEV-Eu is the viral subtype found in South Korea (9); TBEV-Fe is increasingly being detected in Europe (44); in far-eastern Russia, POWV was found in mosquitoes (*Aedes togoi*) (10).

The following ixodids are TBEV vectors with Eurasian range:

- *Ixodes persulcatus*: Eastern, including northeastern, Europe (7) to China, Japan (9); this principal vector tends to parasitize in spring/summer (7)
- *Dermacentor reticulatus*: Europe, not northern regions; from Portugal to western Siberia and the provinces of Xinjiang, Shaanxi, Shanxi in China) (35)
- *Haemaphysalis concinna:* Europe, not northern regions; Atlantic coast of Spain to far-eastern Russia (Kamchatka), China, Japan, Jeju Island (South Korea) (43)
- *Haemaphysalis punctata:* Native of Palearctic region, adapts to variable climate; found in 2010 in the USA (Block Island, State of Rhode Island) (45)

Ticks infected with pathogens in designated regions can be named:

- TBEV-Eu: *Ixodes persulcatus* (Finnish Lapland) (46); *Ixodes ricinus, Dermacentor reticulatus* (Saxony, Germany) (47); *Dermacentor reticulatus* (Poland) (48); *Haemaphysalis longicornis, Haemaphysalis flava, Ixodes nipponensis* (South Korea) (9)
- TBEV-Sib: *Ixodes persulcatus* (western Finland (49); Siberia (Irkutsk) (50); northwestern China (9))
- TBEV-Fe: *Ixodes persulcatus* (Latvia (51); far-eastern Russia (Vladivostok and Khabarovsk) (50)); *Ixodes ricinus, Dermacentor reticulatus, Haemaphysalis punctata* (Moldova in southeastern Europe) (44); *Ixodes persulcatus*, *Haemaphysalis concinna, Dermacentor silvarum, Haemaphysalis japonica* (northwestern and northeastern China) (9); *Ixodes ovatus* (southwestern China) (9); *Ixodes persulcatus* (northern Hokkaido, Japan), *Ixodes ovatus* (southern Hokkaido, Japan) (9)
- POWV: *Ixodes cookei, Ixodes marxi* (near Powassan, Ontario, Canada, where a 5-year-old boy, in 1958, contracted the hitherto unknown viral encephalitis) (8); *Ixodes spinipalpis* (North Dakota, USA) (52); *Ixodes persulcatus, Haemaphysalis japonica, Haemaphysalis longicornis, Dermacentor silvarum* (far-eastern Russia) (10)
- DTV: *Dermacentor andersoni* (Colorado, USA, 1952; not known as an important vector) (10); *Ixodes scapularis* (New England (39) and Wisconsin, USA (40)); *Ixodes cookei* (southern Ontario, Canada, where human DTV infections are increasing) (53)

Apparently, migratory birds participate in spreading TBEV geographically (9,10,44). Regarding global occurrence, TBE affects particularly central and eastern Europe and Russia (7). It is present in Scandinavia though almost absent in Denmark (7,12) and is similarly absent in the British Isles and the Iberian Peninsula (12). In Russia, cases tended to occur in the

Ural regions and Siberia, especially western Siberia. In the Novosibirsk region of western Siberia, a variant of TBEV-Fe has caused a fatal hemorrhagic syndrome with particularly strong gastrointestinal bleeding (6,54), concomitant with viral encephalitis (54). In China, TBEV is endemic in northeastern and southwestern forests (and spreading beyond), as well as in the Northwest and the Inner Mongolia Autonomous Region. The "forest encephalitis" was first noted in forest workers. The virus is endemic in various regions of Japan, mainly in southern Hokkaido, though TBE is rare. Countries affected include Kazakhstan, Kyrgyzstan, and Mongolia. In South Korea, TBEV-endemic regions may be underestimated (9).

Powassan encephalitis typically occurs in northeastern and north-central regions of the USA, in eastern Canada and far-eastern Russia (province of Primorsky Krai). POWV endemicity exists across North America (10). For the year 2019, neuroinvasive POWV cases were reported in the USA from New England (mainly) and Mid-Atlantic states, also from eastern and western regions of the north-central states (13).

CONCLUDING REMARKS

Arthropod-borne infectious disease may cause loss of life due to an often indistinct, usually influenza like, symptomatology and/or delayed diagnosis and treatment; and patients may not recall a bite. As observed in 23 travelers returning to Switzerland, who appeared to lack or not sufficiently display the distinct malarial paroxysms of fever (or other diagnostic signs), death from falciparum malaria ensued, on average, 8 days from symptom onset (11). Early diagnosis and treatment is also crucial in *P. knowlesi* infection; the parasite's daily multiplication cycle yields a quickly increasing and life-threatening parasitemia (14). *P. ovale* (20), *P. falciparum, P. vivax,* and *P. knowlesi* can cause the escalation to ARDS, which is lethal despite mechanical ventilation in over 50% of *P. falciparum* patients, among whom pregnant women are at high risk (4).

Similarly, in Europe, a rapidly developing viral meningoencephalomyelitis may proceed to death; paralysis and respiratory insufficiency can be established within 24-48 hours. More often than other neuroinvasive TBE manifestations in Europe, this disease presents without the biphasic disease course, which, with ataxia, is considered indicative for neuroinvasive TBEV-Eu infection (36). Thus, this severe disease may not receive the required clinical attention during the early stages.

The increasing resistance of malarial pathogens to drugs, e.g., artemisinin resistance (1,4) and *P. vivax* resistance to chloroquine (4), and of mosquito vectors to insecticides, e.g., pyrethroids and organophosphates (1), has hindered the global malaria control. It is of interest that antimalarial plants used in alternative medicine (homeopathy) also happen to be plants used as herbal gastric tonics, including *Cinchona* bark (yielding quinine) and *Artemisia* (*contra*), as well as *Menyanthes trifoliata* and *Erythraea chilensis* (55). The latter two plants could offer a new curative potential also for allopathy, while other herbal gastric tonics may benefit as well and can be explored in alternative and standard medicine.

This article, aiming at arthropod-borne infectious diseases, is to aid in the early clinical awareness and, by focusing on vectors and some of their biological aspects, also preventive awareness regarding transmission. Globally, for malaria, TBE, and Powassan encephalitis, the article facilitates the regional appreciation of circulating pathogens, their symptoms and complications, and of the pertaining vectors and their natural susceptibility to certain pathogens. Personal use of repellents, public vector control, education of the public and of travelers in endemic regions, and continued efforts toward and support for antimalarial and antiviral research are always advised.

Keypoints: Malaria and tick-borne flavivirus encephalitis are endemic over large regions, with diverse pathogens and vectors. Knowledge of the pathogens and vectors aids in the public and clinical disease management. Early clinical awareness regarding the pathogens' severe disease highlights helps to prevent death in patients.

Abbreviations

ARDS: Acute Respiratory Distress Syndrome
DTV: Deer Tick Virus
POWV: Powassan Virus
TBE: Tick-borne Encephalitis
TBEV: Tick-borne Encephalitis Virus
TBEV-Eu: Tick-borne Encephalitis Virus Europe
TBEV-Sib: Tick-borne Encephalitis Virus Siberia
TBEV-Fe: Tick-borne Encephalitis Virus Far East
USA: United States of America
WHO: World Health Organization

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