

# INFECTIOUS DISEASES

## An Ongoing Series

### Tick-Borne Encephalitis

#### An Update for the Special Operations Forces Provider

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#### ABSTRACT

Tick-borne encephalitis (TBE) is a severe disease caused by the tick-borne encephalitis virus (TBEV). TBEV is endemic throughout Eurasia and can cause persistent neurologic deficits and death. Special Operations Forces (SOF) participating in field exercises or operations in TBE-endemic countries are at significantly increased risk of infection. Unlike Lyme disease and other tick-borne illnesses, transmission of TBEV can be immediate, and early tick removal does not reduce the risk of infection. While there are no virus-specific treatments available, the US Food and Drug Administration (FDA) recently approved a TBE vaccine that has yet to be incorporated into formal Department of Defense (DoD) recommendations. SOF medical providers should be aware of this disease entity and consider the TBE vaccine when planning exercises and operations in areas of responsibility (AORs) with TBE-endemic countries. This review serves as a refresher and update on the epidemiology, transmission, and management of TBE for the SOF provider.

**KEYWORDS:** *Tick-borne encephalitis; tick-borne disease; vector; biphasic; vaccines; biodefense*

#### Introduction

Tick-borne encephalitis (TBE) is a severe vaccine-preventable disease caused by tick-borne encephalitis virus (TBEV) transmitted by *Ixodes* species ticks.<sup>1</sup> TBEV is among the most prevalent causes of arthropod-borne viral meningitis and encephalitis worldwide.<sup>1,2</sup> Many cases of TBE result in persistent neurologic deficits, and case fatality rates can exceed 20%.<sup>2</sup> Servicemembers, particularly Special Operations Forces (SOF) participating in field exercises or operations in TBE-endemic countries, are at significantly increased risk of infection. Measures to prevent tick bites include standard insect precautions (including use of repellents, long sleeves, permethrin-treated clothing, bed netting, and other gear). However, unlike Lyme disease and other tick-borne illnesses, transmission of TBEV from a tick bite can be immediate, and early tick removal does not reduce risk of infection.<sup>1</sup> Given TBE's potential for significant morbidity and efficient transmission, SOF medical

providers should be aware of this disease entity and strongly consider the newly FDA-approved TBE vaccine when planning exercises and operations in Areas of Responsibility (AORs) with TBE-endemic countries.

#### Military History

TBE was first described in Austria in 1931 with the causative agent later isolated in Russia in 1937.<sup>3</sup> Since that time, TBE has been documented across Eurasia, including many countries housing US troops and DoD beneficiaries.<sup>4</sup> A recent retrospective analysis found eight cases of TBE among servicemembers and their beneficiaries stationed in Germany between 2006 and 2018.<sup>4</sup> Of these eight cases, seven occurred in 2017 or 2018, suggesting an increasing rate of infection. A case report describing three of these infections (a 26-year-old male Soldier, a 17-year-old male dependent, and a 7-year-old female dependent) found that while all three survived, all had persistent headaches and cognitive complaints 3–6 months after diagnosis.<sup>4,5</sup> An updated survey described four additional cases among Military Health System (MHS) beneficiaries from 2019–2021, three of whom were active duty stationed in Germany.<sup>5</sup> These observations are consistent with large-scale studies suggesting a growing number of reported cases overall and that a significant percentage of TBE cases result in long-term neurologic sequelae.<sup>1</sup> There is likely a paucity of data describing the burden of disease among temporary duty (TDY) personnel. While TBE has been a recognized threat to force health protection for decades, US servicemembers had no FDA-approved vaccine options until 2021.

#### Epidemiology/Transmission

TBE is endemic to countries across the Eurasian continent where the *Ixodes* tick vectors are present, creating the “TBE Belt” (Figure 1). The virus circulates between ticks and various reservoirs: ruminants, birds, rodents, horses, and humans (Figure 2). Three viral subtypes from the family *Flaviviridae* (genus *Flavivirus*) cause TBE: Siberian (TBEV-Sib), Far Eastern (TBEV-FE), and Western (TBEV-Eu). The vector for TBEV-Eu is *Ixodes Ricinus* (Western, Central, and Eastern Europe). The

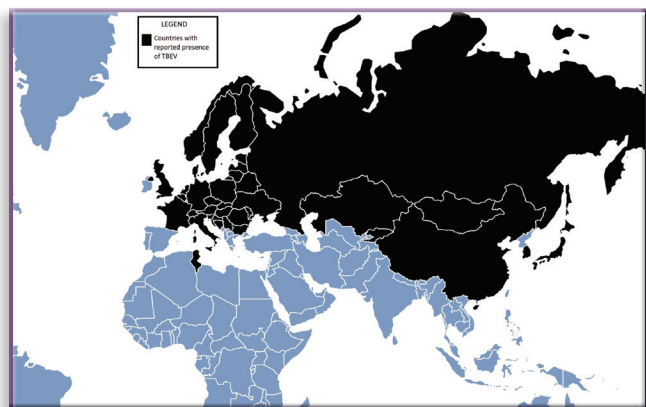
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vector for TBEV-Sib and TBEV-FE is *Ixodes pesiculatus* (Lithuania, Baltic regions, China, Japan) and/or *Ixodes ovatus* (Hokkaido, Japan).<sup>1,6</sup> The infected ticks are predominantly found in the woodland habitats during the months of April through November with July and August as the peak months.<sup>7</sup> During the past few decades, the endemic regions have expanded likely due to social and ecological factors as well as increased awareness and reporting. Tick activity and transmission are dependent on climatic factors—temperature, soil moisture, and humidity. It has been noted that wet summers and mild winters may affect tick populations leading to extended tick feedings and increased risk of TBEV transmission.

**FIGURE 1** Countries with reported presence of tick-borne encephalitis virus (TBEV): Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, China, Croatia, Czech Republic, Denmark, England, Estonia, Finland, France, Germany, Hungary, Italy, Japan, Kazakhstan, Kyrgyzstan, Latvia, Liechtenstein, Lithuania, Moldova, Mongolia, Netherlands, Norway, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, South Korea, Sweden, Switzerland, Tunisia, and Ukraine.<sup>16</sup>

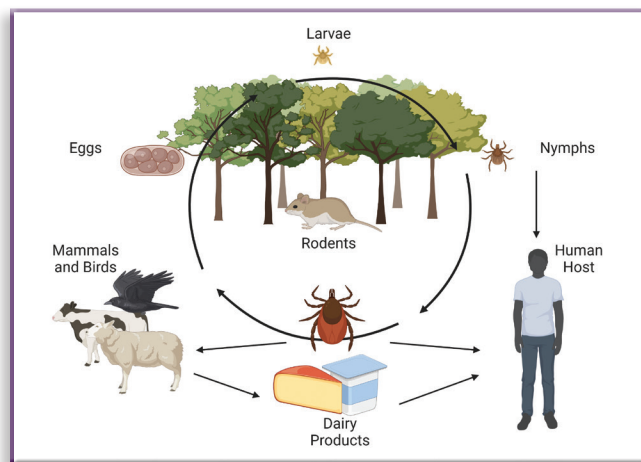


The World Health Organization (WHO) estimates approximately 10,000–12,000 clinical cases are reported annually.<sup>8</sup> TBEV is mainly transmitted from the saliva of an infected tick bite; however, approximately 1% of all TBEV infections can be acquired by consuming unpasteurized milk or dairy products from infected livestock (goats, sheep, or cows).<sup>9</sup> Upon feeding, ticks transmit the TBEV within minutes, and early removal of the tick may not prevent infection. The virus is generally not communicable between humans, though vertical transmission from infected mother to fetus is possible. Additionally, there are case reports of transmission with blood transfusions, breastfeeding, organ transplantation, and laboratory manipulation, or after slaughtering of viremic reservoirs.<sup>1,10</sup> In 2019, per the annual surveillance epidemiological report from European Union/European Economic Area (EU/EEA), there were 3,246 cases of confirmed TBE.<sup>11</sup> The EU/EEA notification rate for 2019 was 0.7 per 100,000, increased from 0.6 from the three previous years.<sup>11</sup> Cases are more frequently reported among men (1.5 male:1 female) within the age group of 45–64 years.<sup>11</sup> This male predominance likely correlates with the higher-risk activities such as hunting, military training, farming, and forestry, which increase the likelihood of tick exposure.

### Pathogenesis/Clinical Disease

After the initial tick bite, TBEV spreads to the local lymph nodes and later disseminates to other organs including the spleen, liver, and bone marrow.<sup>12</sup> Viremia is persistent for

**FIGURE 2** Lifecycle ticks and transmission of tick-borne encephalitis (TBE).

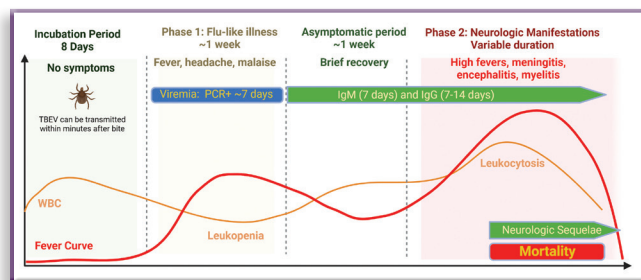


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several days and clinically corresponds to the first phase of the TBE biphasic presentation.<sup>12</sup> During this time, the virus crosses the blood-brain barrier. While the exact mechanism for central nervous system invasion is unknown, hypothesized routes include (1) via peripheral nerves, (2) via olfactory neurons, (3) via vascular endothelial cells of brain capillaries, and (4) via diffusion of virus between capillary endothelial cells.<sup>12</sup>

The TBEV incubation period after a tick bite is approximately eight days.<sup>1</sup> Food-borne transmission shortens the incubation period to approximately four days. While the majority of TBEV infections are asymptomatic, symptomatic cases experience a biphasic illness. Patients initially present with flu-like symptoms: fever, fatigue, general malaise, headache, and myalgia/arthritis.<sup>1</sup> The initial phase is followed by an asymptomatic interval of approximately one week. The second phase then presents with high fevers and central nervous system involvement, to include meningitis, myelitis, encephalitis, radiculitis, or meningoencephalitis (Figure 3). Additional reports suggest the disease can present with alternative phenotypes. These include an abortive form that does not progress to the encephalitic phase and a chronic progressive form resulting in epilepsy, progressive neuritis, and Parkinson-like disease.<sup>9</sup>

**FIGURE 3** Tick-borne encephalitis (TBE) disease progression.



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The long-term outcomes of TBE appear to depend upon the subtype of TBEV infection. TBEV-Eu subtype is associated with milder disease: 20–30% experience the second phase, 10% experience neurological sequelae, and 0.5–2% experience mortality.<sup>13</sup> The TBEV-FE subtype is more severe with

no asymptomatic interval, higher rates of severe neurologic sequelae, and a mortality rate up to 35%.<sup>13</sup> The TBEV-Sib subtype is associated with less severe disease, but still with 1–3% mortality and chronic complications.<sup>13</sup>

## Evaluation and Diagnosis

During the first phase, laboratory evaluation often reveals leukopenia, thrombocytopenia, and slightly elevated transaminases. In the second phase, leukocytosis may occur. Abnormalities on MRI are usually confined to thalamus, cerebellum, brainstem, and caudate in up to 18% of patients; however, MRI and electroencephalogram (EEG) are not specific nor diagnostic.<sup>1</sup>

Diagnosis can be confirmed via blood reverse transcriptase-polymerase chain reaction assay (RT-PCR) during the first phase and serology during the second phase. While viremia is present in the first phase, by the time neurological symptoms develop, the virus has cleared from the blood, and RT-PCR from the blood may be negative (Figure 3). During the second phase, cerebrospinal fluid (CSF) analysis reveals moderate pleocytosis with initial polymorphonuclear cell predominance that may later change to mononuclear cell dominance.<sup>1</sup> The detection of TBE virus IgM/IgG antibodies in serum and/or CSF via enzyme-linked immunosorbent assay can be diagnostic. Notably, there is significant cross-reactivity between the antigenic structures of flaviviruses (West Nile virus, dengue virus, yellow fever virus, Japanese encephalitis virus) and the antibodies induced by their vaccines.<sup>1</sup>

## Management and Prevention

Prevention is the primary countermeasure for TBE. Military personnel should be counseled on risk factors, transmissibility, and signs and symptoms prior to deployment to endemic areas. SOF providers should be familiar with the geographic distribution to be aware of high-risk endemic areas when possible and to enforce standard insect-control measures when operating in these endemic areas. Standard preventative measures include insect repellent, treated clothing, bed netting, tents, and other gear with 0.5% permethrin, daily whole-body tick checks with prompt removal, and avoiding consumption of unpasteurized dairy products. However, as mentioned previously, TBEV can be transmitted within minutes, and tick removal may not prevent infection. Therefore, vaccination of high-risk personnel should be a critical component to health protection of the Force.

In August 2021, the FDA approved the TBE vaccine TICOVAC manufactured by Pfizer.<sup>14</sup> In February 2022, the Centers for Disease Control's (CDC) Advisory Committee on Immunization Practices (ACIP) recommended TBE vaccine for any persons moving or travelling to a TBE-endemic area and are expected to have significant tick exposure.<sup>15</sup> TICOVAC is prepared from TBEV grown in chick embryo cells that is inactivated by formaldehyde.<sup>15</sup> There have been no prospective studies to evaluate the TBE vaccine efficacy; however, protection is assumed based on studies demonstrating the generation of neutralizing antibodies and retrospective population data from endemic countries.<sup>15</sup> The vaccine is generally well-tolerated, with the most common adverse reactions being local tenderness (30%), pain (13%), fatigue (6.6%), headache (6.3%), and muscle pain (5.1%).<sup>15</sup> Initial studies suggested no severe vaccine adverse events in adults, though post-marketing

data have included rare reports of severe immunologic reactions such as Guillain-Barre syndrome, myelitis, and nerve palsies.<sup>15</sup> The vaccine is administered to adults in a three-dose series on day 0, 14 days to 3 months after the first dose, and 5 to 12 months after the second dose.<sup>15</sup>

While the ACIP has recommended the TBE vaccine, formal publication of the recommendation in the Morbidity and Mortality Weekly Report (MMWR) is pending. Therefore, at the time of this review's publication, TBE vaccination in DoD servicemembers is strongly recommended in certain AORs, but it is voluntary, and additional policy is pending publication of the ACIP's recommendations.<sup>2</sup> We recommend any Soldiers participating in field exercises or operations in countries within the "TBE Belt" be vaccinated.

With regard to management, no virus-specific therapeutics exist. Early identification and supportive care remain the critical components for management. Patients with neuromuscular paralysis and respiratory failure may require intubation and ventilatory support, while those with seizures require anticonvulsants. Any soldiers suspected of having TBE should be immediately evacuated to a Role 3 treatment facility. The risk of nosocomial transmission to healthcare providers is minimal, so no special precautions are required other than visibly inspecting the patient for remaining ticks.

## Conclusion

With the recent pivot in attention toward the US European Command (EUCOM) AOR and increasing troop presence throughout Eurasia, SOF providers should become familiar with the infections endemic to the region that propose a significant threat to force health protection. While relatively rare in occurrence, tick-borne diseases such as TBE and Crimean-Congo Hemorrhagic Fever (CCHF) pose important medical threats to US SOF operating in endemic regions and may not be familiar to most US-trained providers. Vigilant insect control and awareness remain cornerstones in prevention, while the newly FDA-approved TBE vaccine provides a valuable countermeasure to SOF providers bound for a TBE-endemic region. The TBE vaccine has yet to receive a formal DoD policy, but is recommended for all persons with prolonged stays in endemic countries. General information and further guidance about TBE is available at <https://www.health.mil/Military-Health-Topics/Health-Readiness/Immunization-Healthcare/Vaccine-Preventable-Diseases/Tick-Borne-Encephalitis/TBE-Resource-Center>.

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## Conflict of Interest

The authors have no conflicts of interest to disclose.

## Author Contributions

HK drafted original manuscript. AS added additional sections, references, and images.

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