INFORMATION PAPER

DHA-IHD
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Purpose: To describe Tick-borne Encephalitis (TBE) and use of Tick-borne Encephalitis vaccine (TICOVAC) to prevent this infection.

Highlights:

- ✓ TBE is a serious vaccine preventable disease endemic to Europe and Asia.
- ✓ TICOVAC was approved by the FDA in 2021 for use in persons aged ≥1 year. The current formulation has been used effectively internationally for >20 years.
- ✓ TICOVAC is highly effective given in a 3-dose series.
- ✓ Vaccination against Tick-borne encephalitis is **voluntary** but recommended for all persons:
  - with prolonged-stays in highly endemic countries.
  - with any stay that includes outdoor activities especially in forested risk areas.
  - with, in a laboratory setting, are at risk of exposure to Tick-borne encephalitis virus.

Background:
Tick-borne encephalitis is a potentially chronic and fatal neurologic disease due to a virus transmission through a tick bite. Foodborne transmission can also occur from unpasteurized milk consumption, although this is rare. Service Members assigned or traveling to endemic areas in EUCOM are at risk for infection. TICOVAC is an FDA-approved TBE vaccine (TBEV) for use in the United States[1]. It is essentially the same formulation as a highly effective TBEV available for disease prevention in Europe[2,3]. TBE vaccination is not a Force Health Protection requirement, but voluntary receipt of TBE vaccine is strongly recommended for travelers and residents in endemic areas of Europe and Asia. This paper provides an overview for use of TICOVAC for eligible DoD beneficiaries.

1. Facts:

a. Microbiology.
(1) The TBE virus is a single stranded RNA flavivirus from the same virus family which includes yellow fever, Japanese encephalitis and dengue. There are three subtypes of the TBE virus, European, Siberian and Far East, which are genetically and antigenically similar and do not undergo significant antigenic variation in nature. Two or all three subtypes commonly circulate simultaneously. At least eleven transmitting tick species have been identified although most transmission is by I. ricinus (European) or I. persulcatus (Siberian and Far Eastern)[4]. The prevalence of ticks infected with the virus varies with location and time. In Austria and southern Germany 1-3% of ticks were found to carry the virus but the rates in highly affected areas in Russia, Lithuania and Switzerland ranged from 10-30%[5]. The ticks have three distinct life stages and the main transmission is attributed to nymphs. Transmission of TBE virus can occur immediately after tick bite exposure and early removal of the tick may not prevent infection. The saliva of the tick is anesthetizing and 30% of confirmed cases do not recall the bite[4].

b. Disease.
TBE virus is the most prevalent cause of arthropod-borne viral meningitis and encephalitis worldwide[4] although is focally endemic in parts of Europe and Asia. The incubation period ranges from 2-28 days, with a median onset of 8; milk-borne infection is shorter (3-4 days)[4,5,6]. The disease presents with an initial viremic phase characterized by flu-like symptoms (fever, headache, mylagia, fatigue) which resolve in 1-8 days. Approximately a third of patient's progress to serious illness in a biphasic disease pattern with onset of neurologic symptoms typically within 7 days (range 1-21 days) after the viremic phase symptoms have resolved. Clinical presentations include meningitis, encephalitis, myelitis and paralysis. Meningitis is the most frequent presentation in younger persons, while meningo-encephalitis is more prevalent in older individuals. There are no specific treatments options[7,8]. Persistent and chronic progressive forms have occurred. Disease severity and prognosis worsens with age and may vary with viral subtype. Residual neurologic deficits occur in 30-60% of patients and half of these are severe impairments[4,8]. Case fatality rates from European TBE is approximately 0.5-2%, however other subtypes may be above 20%[5,8,9].

c. Epidemiology.
(1) Reservoir
Ticks are both the main vector and the virus reservoir with amplification hosting by small vertebrates, mainly rodents, however, many other species of wild and domestic mammals (bats, cattle, deer, dogs, foxes, goats, hares, sheep, and wild boar) may become infected. Transmission has also been documented via consumption of unpasteurized dairy products, primarily goat's milk, but may include other farm animals such as cows and sheep. Humans are accidental hosts and direct person-to-person spread of TBE virus occurs only rarely, through blood transfusion, solid organ transplantation, or breastfeeding[10]. The disease is highly endemic in Central and Eastern Europe, but overall range may include Northern China and Japan, as far south as Greece and as far west as the United Kingdom[4,8,11]. Forested areas are ideal tick habitats and affected geographical areas have been expanding in recent decades, and has been documented at altitudes up to 2100 meters[4]. Transmission is highest risk in the spring through fall (April through November) when tick activity increases with warmer temperatures above 45F and humidity of 70-80%, however, risk may be present year round.

(2) Incidence
TBE incidence varies significantly between and within individual countries and the rate estimates have increased as much as 400% in last 30 years[4,9]. Contributing elements include changes in climate, habitat expansion, increase in recreational activities and improvements in surveillance and reporting[5,10]. Overall, the disease is likely underreported, due to variances in

definitions and insufficient routine diagnostics and surveillance in all affected countries[4,5]. The estimated overall risk of TBE is 1 case/10,000 person-months while unvaccinated individuals were estimated at 6 per 100,000[8,12]. Approximately 5,000 to 13,000 clinical cases of TBE are reported each year, although incidence rates widely fluctuate and have been reported as high as 40/100,000 or more in parts of Russia[4,5,8,10]. TBE incidence is highest in people aged 50 years and above. The disease is more common in men (2:1), military members, farmers, and persons who participate in outdoor recreational activities[4]. Geographically, the highest incidence levels are reported in southern Germany (Bavaria and Baden-Württemberg), Austria, western Siberia, Slovenia, Estonia, Latvia, and Lithuania[6,10,13]. Other affected countries include Albania, Belarus, Bosnia, Croatia, Czech Republic, Denmark, Finland, France, Hungary, Italy, Netherlands, Norway, Poland, Romania, Serbia, Slovakia, Sweden, Switzerland, Ukraine China, Japan, Kazakhstan, Kyrgyzstan, Mongolia, and South Korea.

(3) Prevention
Prevention activities include standard insect precautions to include use of insect repellents such as DEET or picaridin, long sleeves and pants and permethrin-treated clothing and gear. However, repellants or insecticides provide unreliable protection against tick bites[7]. Food borne illness is prevented by avoidance of unpasteurized milk and dairy products, which is also a standard precaution[10]. Vaccination is the most effective method of prevention and immunization programs have demonstrated a substantial decrease in TBE incidence in endemic regions[8].

d. Vaccine.
TICOVAC
TICOVAC is manufactured by Pfizer and marketed under the names FSME-IMMUN (Europe) and TICOVAC (Austria, Germany, and the United States). The vaccine is inactivated whole Neudörfl strain European subtype TBE virus cultured in chick cell embryos and alum adjuvated. Each adult dose contains 1.2 mcgs and the pediatric dose is one-half the adult dose. TICOVAC is available in a 0.5 mL adult formulation and a 0.25 mL pediatric formulation.

The excipients include human albumin, sodium chloride, disodium phosphate-dihydrate, potassium dihydrogen, phosphate, sucrose, water, aluminum hydroxide (0.30-0.40mgs Al_3). Formaldehyde, protamine, neomycin, gentamycin, and trace amounts of chicken and egg proteins. TICOVAC is albumin-, preservative- and thimerosal-free. The pre-filled syringe contains no natural rubber latex.

(1) Dosing:
Adult (≥16 years of age; 0.5 mL) & pediatric (1 through 15 years of age; 0.25 mL) formulations.
Route: TICOVAC is administered intramuscularly (IM).

(2) Schedule:
Primary Vaccination: Three doses

Primary Vaccination Schedule		
	1 through 15 years of age	16 years of age and older
First dose	Day 0	Day 0

Second dose	1 to 3 months after the first vaccination	14 days to 3 months after the first vaccination
Third dose	5 to 12 months after the second vaccination	5 to 12 months after the second vaccination

A booster dose (fourth dose) may be given at least 3 years after completion of the primary immunization series if ongoing exposure to tick-borne encephalitis virus is expected.
Notice the potential for an 'accelerated' immunization schedule for adults (only) between the 1st and 2nd doses. This may be of benefit in the pre-deployment setting.

Catch-up dosing: Restarting the series is not required. A single catchup dose is sufficient if the patient has received two doses in the past.

(3) Recommendations
TBE vaccination is recommended for all persons with prolonged-stays in endemic countries, due to the likelihood of occasional travel to forested risk areas or exposure in the outskirts of urban areas. It is also recommend for all persons with any length stay that include hiking, camping, or other outdoor activities in forested risk areas with more than minimal risk. Although not specifically identified as a risk in FDA package insert, clinical studies have identified risk for TBE in those who regularly engage in consumption of unpasteurized dairy products (milk and cheese) from cows, goats, or sheep. Ideally, the vaccine series should be started in winter to ensure full protection before the peak tick season has begun. The goal should be to complete the primary immunization series at least 1 week prior to potential exposure to the TBE virus.

(4) Immunogenicity
Seroconversion is expected no earlier than 14 days after the second vaccination dose with near 100% at 3 weeks after dose 3. When the baseline immunization schedule is completed, antibody titers are maintained for at least 3 years, after which a single booster is recommended[1,2,3].

TICOVAC vaccine effectiveness for preventing hospitalized TBE was estimated to be between 96.3% and 98.7%, following at least 3 doses of TBE vaccine administered according to the recommended schedule. Three years after the primary series of TICOVAC, seropositivity in follow-up studies ranged from 82.9% to 100% depending on age. Following a booster dose the seropositivity rates were 100%.
There is no data for efficacy following 1 dose, but immunogenicity data suggests that at 28 days after 2 doses seroconversion is > 95%[14]. However, for complete, long-lasting protection, completion of the full primary series is recommended.

f. Precautions and Contraindications
(1) Precautions.
Consider postponing vaccination in persons with moderate or severe illness (with or without fever) until recovery, to minimize potential adverse effects. Some individuals with altered immunocompetence may have reduced immune responses to TICOVAC.

(2) Contraindications.
Anaphylactic reaction to a previous dose or a vaccine constituent contraindicates further vaccination with that vaccine or any vaccine containing that constituent.

g. Adverse Events
The vaccines are overall well-tolerated. The most common adverse reactions in individuals 1 through 15 years of age were local tenderness (18.1%), local pain (11.2%), headache (11.1%), fever (9.6%), and restlessness (9.1%). The most common adverse reactions in those 16 through 65 years of age were local tenderness (29.9%), local pain (13.2%), fatigue (6.6%), headache (6.3%), and muscle pain (5.1%).Rare neurological reactions have occurred[1]. Severe allergic reactions such as anaphylaxis can occur, but have been very rare.

h. Special Populations:
(1) Immunocompromised
TICOVAC may not provide complete protection for persons who are immunocompromised. If an immunocompromised person is at risk for TBE, it may be appropriate to determine immune response after the primary series by serologic testing, where available. Previous exposure to other flavivirus vaccines or infection may interfere with serology testing accuracy. Persons with household and other close contacts whom are immunocompromised may receive TBEV.

(2) Pregnancy and breast feeding
There are no adequate and well-controlled studies of TICOVAC in pregnant women. Available human data are insufficient to establish the presence or absence of vaccine-associated risk during pregnancy. Any consideration to provide TBEV to pregnant women is an individual risk-benefit assessment by their provider. There are no specific recommendations to defer pregnancy after vaccine receipt.
Human data are not available to assess the impact of TICOVAC on milk production, its presence in breast milk, or its effects on the breastfed. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TICOVAC and any potential adverse effects on the breastfed child from TICOVAC or from the underlying maternal condition. Per the package insert, receipt of TBE vaccine is not a contraindication to breastfeeding and is not known to affect the safety of breastfeeding for women or their infants. However, any consideration to provide TICOVAC to breastfeeding women or their infants is an individual risk-benefit assessment by their provider.

i. DoD Policy
DOD policy is pending publication of the ACIP's recommendations regarding this FDA-approved vaccine. Awaiting FHP policy, DHA-IHD is prepared to support Service members, beneficiaries, and leaders who have questions regarding the vaccine and its indications.

j. Specific Considerations:
TBE vaccines can be administered intramuscularly with (or at any time before or after) other vaccines.
There is no data on post-exposure prophylaxis and immunization with TICOVAC is not indicated for this use. TICOVAC does not provide protection against any other tick-borne infections.

References

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