

# WHO position paper on vaccines against tick-borne encephalitis (TBE)

Geneva, Switzerland

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## Background information

- TBE is endemic in most of the southern non-tropical Eurasian forest belt. About 10 000–12 000 clinical cases are reported annually (probably underreported). TBE may be an increasing public health problem.
- The highest incidences are reported from the Baltic States, Slovenia and the Russian Federation with annual national incidences reaching 2-10 per 100 000 inhabitants.
- TBE-virus (of genus *Flavivirus*) includes the closely related Western-, Far- Eastern- and Siberian subtypes, all of which cause TBE.
- Blood-feeding ticks (*Ixodes* species) transmit the virus among many animal species and occasionally to humans. The proportion of infected ticks varies considerably with time and location.
- TBE-virus is mostly acquired through tick-bites when visiting forested areas, but infections caused by unpasteurized dairy products from virus-infected cows or goats also occur.
- The virus is not transmitted directly between humans.

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### Clinical features of TBE

- Incubation period: 7–14 days (range 2–28 days).
- Mono- or biphasic clinical course: The first phase with uncharacteristic, non-neurological symptoms; after an asymptomatic interval, about 1/3 of cases enter the second phase, characterized by a variety of CNS manifestations, often including encephalitis.
- Case-fatality rates of TBE vary between 1% ->10% depending upon local conditions and possibly viral subtype; up to 40% of encephalitic cases suffer from permanent CNS sequelae.
- TBE tends to be more severe in elderly people.
- There is no specific treatment for TBE.

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TBE vaccines (a)

- Immunization offers the most effective protection against TBE.
- Currently, there are four widely used vaccines of assured quality, all based on cell-cultured, formalin-inactivated strains of the TBE virus:
- FSME-Immun and Encepur (including FSME-Immun Junior and Encepur-Children) are based on the Western subtype of the TBE virus and manufactured in Austria and Germany, respectively.
- TBE-Moscow and EnceVir, based on the Far-Eastern subtype, are manufactured in the Russian Federation.

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TBE vaccines (b)

- The Western vaccines are licensed for use in adults and with pediatric formulation, children aged  $\geq 1$  year.
- Primary immunization consists of 3 doses; the recommended intervals between doses 1 and 2 are usually 1-3 months and between doses 2 and 3, usually 5-12 (9-12) months. For rapid protection, the former interval may be reduced to 1–2 weeks.
- The Russian vaccines are licensed for adults and children  $\geq 3$  years. Their 3-dose schedule requires the first 2 doses to be given at intervals of 1-7 (5-7) months, the third dose 12 months after the second.

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## TBE vaccines (c)

- Transient local reactions are commonly associated with TBE vaccines, but severe adverse reactions are rarely described\*.
- No contraindications to vaccination except allergy to vaccine components and severe acute infections. Pregnant women at risk of TBE should be vaccinated.
- So far, no interference is observed between TBE vaccines and simultaneously administered vaccines.
- No randomized, controlled trials on vaccine efficacy against clinical TBE have been conducted, but numerous observational studies in Austria and other endemic areas provide evidence for high vaccine effectiveness in preventing the disease.
- Presence of a minimum concentration of circulating antibodies to the virus (e.g.  $\geq 10$  in the neutralization test) is commonly considered as a surrogate marker of protection.

\*Recently, some lots of EnceVir have been frequently associated with high fever and allergic reactions, in particular in children

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TBE vaccines (d)

- Following the primary series of 3 doses, all TBE vaccines induce antibody responses considered to be protective in 90%-100% of vaccinees.
- With the Western vaccines, healthy individuals aged <50 years and considered to be at continued risk of TBE, are conventionally offered booster doses at intervals of 3–5 years. In some endemic areas (Switzerland), booster intervals up to 10 years are now recommended for this age group.
- With the Russian vaccines, 3-year intervals between boosters are recommended, regardless of age.

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## WHO recommendations (a)

- Since the incidence of TBE varies considerably between and within regions, public immunization strategies should be based on careful risk assessments and cost–effectiveness analyses.
- WHO recommends vaccination of all individuals  $\geq 1$  (or  $\geq 3$ ) years of age where TBE is highly endemic (average annual pre-vaccination incidence  $\geq 5$  cases/100 000 population).
- Where the pre-vaccination incidence is moderate or low, or limited to particular locations or outdoor activities, the most severely affected groups should be targeted for immunization.
- People travelling from non-endemic to endemic areas should be offered vaccination if their visits will include extensive outdoor activities.



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## WHO recommendations (b)

- Pending more information on the duration of protection, when using Western TBE vaccines, booster intervals of 3 years should be maintained for individuals 50-60 years of age, or more, who are considered to be at continued risk of TBE.
- For healthy individuals aged <50 years extended booster intervals (5-10 years) may be considered for those receiving Western vaccines.
- For the Russian vaccines, the current recommendations of a booster dose every 3 years should be maintained pending further studies.

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WHO recommendations (c)

- Post-exposure vaccination following a tick bite is not recommended.
- Administration of specific immunoglobulin for passive post-exposure prophylaxis is not recommended in Western Europe, but is sometimes used in the Russian Federation.
- Improved TBE surveillance and reporting is critical.
- Standardization is required for clinical disease definitions as well as for laboratory reagents and methods.