Vaccines against tick-borne encephalitis

WHO Position Paper

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO is issuing a series of regularly updated position papers on vaccines and vaccine combinations against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on the respective diseases and vaccines and conclude with the current WHO position concerning their use in the global context. The papers have been reviewed by a number of experts within and outside WHO and since 2006 they are reviewed and endorsed by WHO's Strategic Advisory Group of Experts (SAGE) on Vaccines and Immunization. The position papers are designed for use mainly by national public health officials and immunization programme managers. However, they may also be of interest to international funding agencies, the vaccine manufacturing industry, the medical community, the scientific media, and the public.

This is the first WHO position paper on vaccines against tick-borne encephalitis. Footnotes provide a limited number of core references; their respective abstracts as well as a more comprehensive list of references are found at http://www.who.int/immunization/documents/positionpapers/en/index.html.

Grading tables assessing the quality of scientific evidence for a few key conclusions are also available at this link and are referenced in the position paper.

Background

Epidemiology

Tick-borne encephalitis virus (TBEV) is an important cause of viral infections of the central nervous system in eastern, central, and northern European countries and in Russia. The endemic areas of tick-borne encephalitis (TBE) cover the southern part of the non-tropical Eurasian forest belt extending from north-eastern France to the Japanese Hokkaido Island (Suss J 2008; Suss J et al 2010). Approximately 10,000-12,000 clinical cases of TBE are reported each year, but this figure is believed to significantly underestimate the actual total number. Even in the most affected areas, TBE is usually limited to certain sylvan foci. Some countries, such as Germany, are defining at risk-areas at district level based on the reported number of clinical cases.

Currently, the highest incidences of clinical TBE are reported from the Baltic states, Slovenia, and from Russia. For example, in 2009, national incidences per 100 000 inhabitants were

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1 References will be provided as footnotes in the final version
10.40, 7.50, and 6.89, respectively, for Estonia, Latvia, and Lithuania, and 9.90 for Slovenia (Stefanoff P et al 2011). In 2006, the average incidence of TBE in the Russian Federation was 2.44 per 100,000 population, but in the Siberian Federal Area, morbidity was more than 5 times higher - in some Siberian areas 10 times higher - than the national average. Similarly, in the Primorsky Territory of the Far Eastern Federal Area, morbidity reached 3.38 per 100,000 population. High incidences of TBE were reported also from the North-Western Federal Area with 3.77 per 100,000 and 2.65 per 100,000, respectively, in the Pskov and Novgorod Provinces (Oniscenko GG et al 2007). Other countries that have reported TBE cases within their territories, or are considered at risk due to focally high TBEV prevalence in ticks, include Albania, Austria, Belarus, Bosnia, Bulgaria, Croatia, Denmark, Finland, Germany, Greece, Hungary, Italy, Mongolia, Norway, Poland, Romania, Serbia, Slovakia, Slovenia, South Korea, Sweden, Switzerland, Turkey, and Ukraine (Stefanoff P et al 2011; Suss J 2008).

TBE may represent an increasing problem as the disease is now reported from previously non-endemic areas for example Scandinavia, Switzerland, Lithuania, Germany, and several regions of Russia (Oniscenko GG et al 2007; Suss J et al 2008). Also, TBE endemic zones are apparently expanding in altitude from below 800 m above sea level to about 1,500 m, as recently reported from Austria and Slovakia (Holzmann H et al 2009; Lukani M et al, 2010).

Three subtypes of the tick-borne encephalitis virus (TBEV) cause human disease (Ecker M et al, 1999; Fauquet CM et al 2005): The European subtype is prevalent in western, northern, central and eastern parts of Europe, and in South Korea; the Far-Eastern subtype occurs in eastern parts of Russia, in Japan and China, and the Siberian subtype in all parts of Russia (predominates in the Asian parts of Russia). All three sub-types co-circulate in the Baltic, the European part of Russia, and in Siberia (Demina et al 2010; Yun et al 2009; Golovljova I et al 2004).

Most TBEV infections result from tick bites acquired through outdoor activities in forested areas, although about one third of confirmed TBE cases may not recall any tick exposure preceding their illness (Kaiser R 1999). Ticks become active at temperatures above 8°C and a relative humidity of 70-80%. The seasonal incidence of TBE coincides with increased tick exposure during spring, summer and fall (Gritsun TS et al 2003).

The European subtype of TBE is transmitted primarily by *Ixodes ricinus*, and the Far Eastern and Siberian subtypes mainly by *Ixodes persulcatus*. The percentage of TBEV-infected ticks varies considerably with time and location; 1-3% of the ticks were found to carry the virus in endemic areas of Austria and Southern Germany, 1.7% in Lithuania, and 14.3% in a heavily affected location in Switzerland (Süss J et al, 1999; Han X et al 2005; Casati et al 2006). In 2006, surveillance of the tick populations in highly endemic areas of the Russian Federation showed rates of TBEV infection that frequently exceeded 10%; in the Penza Province 29.2% of the ticks were TBEV-infected (Onischenko GG et al, 2007). However, the incidence of TBE among inhabitants of an area depends on a variety of factors and is not directly correlated to the prevalence of TBEV in the local tick population (Süss J et al 2006, Stefanoff P et al 2010).
Larvae, nymphs, and adult ticks become infected when ingesting blood from viremic animals, particularly small rodents, and can subsequently infect vertebrate species including humans, during the next blood meal. In addition, ticks may acquire TBEV transovarially or through co-feeding.

More than 100 different species of animals including foxes, voles, deer, dogs, sheep, monkeys and horses can be infected by TBEV and some of these species act as a reservoir for this virus (Barrett P et al 2008). Occasionally, infected cows, goats or sheep may pass the virus in unpasteurized milk or milk products and infect humans through the alimentary route (Holzmann H et al 2009). Person-to-person transmission of TBEV has not been described.

Attempts at eliminating the disease through chemical extermination of the tick population were unsuccessful or were discontinued for ecological reasons; the protective impact of impregnated clothing or the use of repellents have been at best short-lived (Hoffmann G, 1978). However, when staying out-door in endemic areas the risk of exposure to TBEV can be reduced through appropriate clothing and daily inspection of the skin for possible ticks to be removed. The risk of TBEV infection is negligible for persons who remain in urban or non-forested areas and who do not consume unpasteurized dairy products.

**The virus, pathogenesis, and etiological diagnosis**

TBEV is a member of the genus *Flavivirus* of the *Flaviviridae* family, which comprises about 70 viruses including dengue viruses (DV), yellow fever virus (YFV), Japanese encephalitis virus (JEV), West-Nile virus (WNV) and also tick-borne viruses other than TBEV such as Kyasanur Forest disease virus (KFDV), Omsk hemorrhagic fever virus (OHFV), and Powassan virus (POW). The TBEV virion consists of a single-stranded RNA molecule enclosed by the core membrane and the envelope (E) protein. The E-protein contains the antigenic determinants responsible for haemagglutination and neutralization and induces protective immunity in the host. The three genetically and antigenically closely related subtypes of TBEV (Western, Far-Eastern, and Siberian) are not subject to significant antigenic variation (Holzmann H et al 1992; Ecker M et al 1999).

Following the bite of an infected tick, TBEV first replicates in the local dermal cells, subsequently in the regional lymph nodes and the reticuloendothelial system. The virus crosses the blood-brain barrier after infection of the capillary endothelium. In fatal cases, characteristic neuropathologic changes include polioencephalomyelitis which is accentuated in the spinal cord, brain stem and cerebellum (Gelpi E et al 2006).

The etiological diagnosis of TBE requires laboratory confirmation, as the clinical manifestations are relatively non-specific. During the initial viremic phase of the disease, TBEV may be detected by polymerase chain reaction (PCR) tests (Saksida A et al 2005) or recovered through inoculation into suitable cell-cultures or suckling mice. During the second, neurological stage, TBEV can in rare cases be detected in the cerebrospinal fluid or brain. Antibodies against TBEV are normally detectable at the time of neurological symptoms and serodiagnosis is based on a variety of methods including enzyme-linked immunosorbent assays (ELISA), tests for neutralizing antibodies (NT), and haemagglutination inhibition
techniques (HI). In cases of previous exposure to other flaviviruses (e.g. DV, YFV JEV, WNV, KFDV, OHV, or POW, including vaccination against YF or JE), tests for TBEV-specific IgG may show false positive results due to cross-reacting antibodies (Calisher et al 1989). In those cases, the use of a highly specific neutralization assay is required for determination of immunity (Sonnenberg K et al, 2004; Holzmann H 2003).

The disease
The incubation period lasting 2-28 days (most commonly 7-14 days) is followed by 1-8 days of nonspecific signs and symptoms such as fatigue, headache, aches of the back and limbs, nausea, and general malaise, usually combined with fever of 38°C, or more. TBE may run a mono- or a biphasic course: after an asymptomatic interval of 1-20 days about one third of clinical cases experience a second phase of the disease characterized by fever frequently exceeding 40°C and signs of central nervous system (CNS) involvement, such as meningitis, encephalitis (notably cerebellar ataxia), myelitis, or radiculitis. Encephalitic patients may develop stupor, pyramidal tract dysfunction as well as paralyses that frequently involve muscles of the shoulder region. In up to 40% of encephalitic cases TBE results in permanent central nervous sequelae (Kaiser R et al, 1999) including various neuropsychiatric and cognitive complaints characteristic of the postencephalitic syndrome (Haglund M et al 1996). There is no specific treatment for TBE.

Clinical observations have suggested an association between severity of TBE and the involved viral subtype, whereby the Far-Eastern variety seems to cause more severe disease than its European counterpart, and the Siberian subtype to occupy an intermediate position. Case-fatality rates (CFRs) of ≥20%, 6-8%, and 1-2%, respectively, have been reported for the Far Eastern, the Siberian, and the European subtypes (for references, see Gritsun TS et al 2003). However, CFRs are difficult to compare; recent unpublished estimates in Russia for these subtypes were 12%, 2%, and 1%, respectively (Platonov A et al, 2011). Subtype-associated differences in terms of age preference and disease manifestation are also reported. Thus, compared with the European subtype the Far-Eastern variety of TBEV seems to be characterized by more gradual onset and by affecting children more severely than adults (Barrett PN et al 2008). With the Western TBEV, the CFR seems higher and sequelae more common in the adult and elderly population than observed in younger individuals (Kunze U et al, 2005). Fatal haemorrhagic fever has been associated with the Far-Eastern subtype of the TBEV (Ternovoi VA et al, 2003) whereas rare cases of chronic TBE, characterized by slow progression of the disease for ≥6 months, have been reported mainly with the Siberian subtype (Pogodina VV et al 2004).

Different criteria for patient selection and access to medical services as well as differences of age-specific exposure could account for part of these subtype associated discrepancies.
TBE vaccines

The first vaccine against TBEV was developed in 1937 in the Soviet Union where outbreaks of TBE (then called Russian Spring and Summer Encephalitis) were of considerable public health concern. The first generation mouse-brain derived viral vaccine was efficacious, but resulted in frequent adverse events. Modern, less reactogenic TBE vaccines are based on formalin inactivated strains of TBEV produced in cell cultures. Currently, four different TBE vaccines are licensed: FSME-Immune® and Encepur® are manufactured in Austria and Germany, respectively, and are based on European strains of the virus whereas TBE vaccine Moscow (TBE-Moscow) and EnceVir® are manufactured in Russia based on Far Eastern strains.

Although numerous observational studies, in particular on the Western vaccines, testify to their safety and effectiveness, no randomized, controlled trials have been conducted to demonstrate the efficacy of these vaccines in protecting against clinical TBE. Given their excellent public health record, randomized controlled trials of effectiveness of these vaccines would now be considered unethical.

Immunogenicity is assessed using methods such as ELISA, NT, or HI. Presence of circulating TBEV-antibodies at or above locally agreed concentrations (e.g. an NT titer of $\geq 10$) is commonly considered as surrogate markers of protection against TBE (Holzmann H et al 1996). However, systematic clinical studies to substantiate this assumption are not available. Data on the immunogenicity of different TBE vaccines are not directly comparable, since the manufacturers use different tests and independent head to head comparisons are rare.

Western TBE vaccines

The Western TBE vaccines are marketed as FSME-IMMUN® (new formulation post 2001) and Encepur adults®; their respective pediatric formulations are FSME-IMMUN(Junior)® and Encepur-K®. Children are defined as 1-15 years old with FSME-IMMUN (Junior)®, and as 1-11 years old with Encepur-K®. FSME-IMMUN® (new) is based on the Neudörfl strain of the European TBEV subtype, Human albumin is used as stabilizer. The antigen content per dose is 2.4 µg for adults and 1.2 µg for children. Encepur® is based on the K23 strain of TBEV. Sucrose is used as stabilizer. The antigen content is 1.5 µg per dose for adults and 0.75 µg for children 1-11 years old. Both vaccines are produced according to WHO’s Good Manufacturing Practice guidelines (TRS No 889, 1999). They are produced on chick embryonic fibroblast cells, inactivated by formaldehyde, and use aluminium hydroxide as adjuvant. The vaccines do not contain polyethylene or thiomersal, but traces of formaldehyde, protamine sulfate, gentamicin, and neomycin may be found in the final products. Both vaccines have a shelf-life of 24 months when stored at 2°C to 8°C. They are supplied in prefilled syringes for intramuscular administration, each syringe containing 0.5 ml for adults and 0.25 ml for children.
According to the manufacturers, both FSME-IMMUN® and Encepur® require 3 doses for a complete primary course of immunization. For the “conventional” vaccination schedules the dose intervals are 1-3 months between doses one and two, and 9-12 months between doses two and three. For the “accelerated” schedule of FSME-IMMUN®, the recommendation is vaccination on days 0 and 14, and a third dose after 6-12 months whereas for Encepur® the recommended “rapid” schedule entails vaccination on days 0, 7, and 21, followed by a fourth dose 12 to 18 months later. With both vaccines the manufacturers recommend a booster 3 years after completion of the primary series and subsequent boosters at intervals of 5 years (3 year intervals for individuals aged >60 years).

To identify the most suitable schedule for Encepur adults® and Encepur children®, respectively, two randomised, controlled studies were conducted that compared the immune responses (by ELISA and NT) obtained by 4 different schedules; one study included 398 individuals aged ≥12 years (Schöndorf I et al 2007a), the other 294 children aged 1 to 11 years (Schöndorf I et al 2007b). Both studies concluded that the rapid immunization schedule prescribing vaccination on days 0, 7 and 21 compared favorably with vaccination on days 0, 28 and 300; days 0, 21 and 300; and days 0, 14 and 300, respectively, both in terms of fast induction of an immune response and stable NT titers for at least 300 days. Similar studies are not available for FSME-IMMUN®.

**Vaccine immunogenicity and effectiveness**

With both Encepur® and FSME-IMMUN® several studies have been published on the immunogenicity following primary immunization (Zent O et al 2003; Schoendorf I et al 2007a and 2007b; Wittermann C et al 2009; Ehrlich HJ et al 2003; Loew-Baselli A et al 2006; Pöllabauer EM et al 2006 a and b). A recent Cochrane review (Demicheli et al, 2009) summarized seroconversion data obtained from 11 vaccine trials including 4 RCTs of currently licensed Western vaccines (Encepur children, Encepur Adults, and FSME-IMMUN® "new"). A total of 5063 children and adults were included in these 4 trials, and with each of the vaccines, seroconversion by ELISA, HI, or NT were obtained in 92%-100% of the respective vaccinees. Similar high immunogenicity was achieved both with conventional (days 0, 28, and 300) and rapid (days 0,7 and 21) immunization schedules. In a subsequent RCT, >95% of the enrolled 334 children achieved neutralization titres ≥10 following 2 doses of Encepur Children or FSME-IMMUN® Junior (Wittermann C et al. 2009).

Little information is available on immunogenicity and effectiveness of TBE vaccines in cases when the recommended immunization intervals were grossly extended. A recent study on the persistence of immune memory in individuals who had not followed the regular schedule for TBE vaccination (Schosser R et al 2009). In the majority of cases, evidence of immunological priming as reflected by an anamnestic antibody response to TBE antigen, persisted irrespective of the time elapsed since the last vaccination (i.e. up to 20 years), even in individuals who had previously received only one TBE-vaccination, and in cases who were sero-negative prior to the booster. This finding suggests that extended intervals between the first two or three vaccinations is not a critical parameter for the success of subsequent immunizations. Further support for this conclusion is provided by an earlier study showing that the field effectiveness of Western TBE vaccines was around 95% even in irregularly
vaccinated subjects (Heinz et al, 2007). On the other hand, the demonstration of immunological priming alone is likely to an insufficient surrogate marker for protection in the case of TBE (Stiasny et al 2009).

Vaccine breakthroughs are rare, but they do occur, particularly in elderly individuals (Stiasny et al 2009, Andersson et al 2010). Thus, 25 breakthrough cases were reported in Austria between 2002-2008, 8 of whom vaccinated according to the regular vaccination scheme, and during the period 2000-2008, 27 break-through cases were described in Sweden, of whom 21 had received ≥2 doses according to schedule.

Studies on field-effectiveness in Austria for the years 1994-2001 showed protection rates against clinical TBE of 96.4% -100% following two doses and 96% - 98.7% following three doses of FSME-IMMUN® (Kunz C, 2003). These studies were based extensive post-licensure surveillance and the assumption that the whole Austrian population is at risk of infection. In similar studies covering the period 2000-2006, the overall effectiveness of the vaccine was about 99% in those with a documented history of at least three vaccinations within the recommended schedule (Heinz FX et al 2007). The Austrian experience shows that with current vaccines, high vaccination coverage can lead to a dramatic decline of the incidence of TBE.

**Duration of protection and the need for booster doses**

Longitudinal studies show that the annual decline in geometric mean titres (GMT) of neutralizing antibody is less following the primary series plus at least one booster than following the primary series only and also that in general, immunity following at least one booster dose lasts longer than the previously expected 60 months (Paulke-Korinek et al, 2009, Rendi-Wagner, 2007, Rendi-Wagner et al, 2004; Rendi-Wagner P et al, 2006; Loew-Baselli A et al, 2009; Wittermann C et al 2009, Plentz A et al 2009).

Similar rates of decline were observed irrespective of age, but those aged ≥60 years were more likely than younger individuals to become seronegative because they achieve lower antibody titers following boosters (Hainz et al 2004; Loew-Baselli et al, 2009, Paulke-Korinek et al, 2009, Rendi-Wagner et al, 2004b, Rendi-Wagner et al, 2007, Weinberger B et al 2010). In particular, those who started their primary course only at the age of ≥60 years showed reduced ability to respond to recall antigens. On the other hand, elderly persons who received primary TBE immunization when they were young responded to boosting similar to young people (Weinberger B et al, 2010).

Data from Austria indicate that in more than 90% of vaccinees, a TBE booster induce protective antibody levels that remain stable for at least 6 years and that the occasional break-through infections occur independent of time since last immunization (Paulke-Korinek et al 2009). Subsequent data from Austria show that in >90% of vaccinees protective antibody titers persist for at least 8 years following last booster immunization (WHO Background document).

As extended booster intervals will reduce costs and improve compliance, recommendations for TBE vaccine boosters are under revision in several countries. Currently, Switzerland
recommends 10 year intervals between the primary series and the first booster, as well as between subsequent booster doses (Bull BAG 2006; Nr. 13: 225-231).

**Safety of Encepur® and FSME-IMMUN®**

With pre-2001 formulations of these vaccines, adverse events were relatively frequent. Current formulations of FSME-IMMUN® and Encepur® represent considerable improvements in this regard and these vaccines are considered very safe (Zent O et al, 2005a). The above mentioned Cochrane review (Demicheli et al, 2009) summarized also safety data obtained from the 4 RCTs on Encepur children, Encepur Adults, and FSME-IMMUN "new". A total of 5063 children and adults were included in these trials. Although adverse events were commonly reported (transient redness and pain at the site of injection in up to 45% of the cases and fever in up to 5-6%), none of these events were serious or life threatening. In a single-blind, multi-center, randomized, controlled, phase III clinical study comparing the immunogenicity and safety of FSME-IMMUN Junior® and Encepur Children® in 303 children aged 1-11 years, systemic reaction rates were few and similar between the vaccines (Pöllabauer EM et al et al 2010).

Adverse events following booster doses of TBE vaccine were investigated in adults aged 18-67 years whose primary series had consisted of two doses of either FSME-IMMUN® or Encepur adults® and a third vaccination with FSME-IMMUN®. Adverse events associated with the booster given 3 years later were predominantly mild and occurred with a low frequency (Loew-Baselli A et al 2009). In another study, a second Encepur® booster 3 years after the first booster vaccination was well tolerated by all vaccinees (Beran J et al 2004).

Post-marketing studies confirm the absence of severe adverse events following administration of these vaccines. Thus, in 2002 an independent postmarketing sentinel study reported 0.413% adverse events following 25,905 vaccinations (Encepur® and FSME-IMMUN®); mild to moderate fever (<40°C), local reactions, and pain at the injection site were the most common complaints (Weinzettel et al., 2007). Similarly, post marketing surveillance following the distribution of more than five million vaccine doses did not disclose any potential safety risk (Zent O 2005). More recently, The safety of FSME-IMMUN® and Encepur® were compared also in a post licensure, randomized, controlled, single-blind, multi-centre trial that included a total of 334 children (Wittermann et al 2009). Both vaccines were well tolerated, with comparable safety profiles; no vaccine-related serious adverse events were reported. There are no reports indicating impaired immunogenicity or safety when Western TBE vaccines are administered simultaneously with other vaccines, for example in travelers.

**Russian TBE vaccines**

The TBE vaccine Moscow (TBE-Moscow) was approved for use in adults in 1982 and in 1999, following further improvement of the purification process, approved also for children ≥3 years of age. Since 1982, more than 25 million people in Russia and neighboring countries have received this vaccine (Vorob’eva MS et al, 2007).
TBE-Moscow is based on the Sofjin strain of the Far Eastern TBEV subtype. Following passages in mouse brain the virus is further propagated in primary chicken embryo cells. Harvested virus is inactivated by formalin, filtrated, concentrated, treated with the excipient protamine sulfate, stabilized through the addition of human albumin and gelatin, and finally lyophilized. The concentration of viral protein per dose is 0.50-0.75 µg, and immunogenicity is adjusted to preset standards. Before use, lyophilized vaccine is dissolved in fluid containing the adjuvant aluminum hydroxide. EnceVir® was licensed in the Russian Federation in 2001. This vaccine is based on the TBEV-Fe strain 205. The development steps of EnceVir® are nearly identical with those used for the production of the TBE-Moscow vaccine; the concentration of viral protein per dose is 2.0-2.5 µg, aluminum hydroxide is used as adjuvant, but EnceVir® is not lyophilized.

The manufacturing process of both TBE vaccine Moscow and EnceVir® follows WHO’s Manufacturing requirements (TRS No 889, 1999) and is controlled by the national Russian authorities (Vorob’eva MS et al, 2007). When stored at 2-8°C, the shelf life is 2 years for EnceVir® and 3 years for TBE vaccine Moscow. Both vaccines are stable for 2 days at 9-25°C.

The Russian vaccines are not licensed for children below 3 years of age. Above this age, all vaccinees receive 0.5 mL of either vaccine administered intramuscularly. According to the manufacturers, the standard primary immunization schedule consists of two doses given at an interval of 1-7 months. For EnceVir, a rapid schedule for emergency situations prescribes 5-7 days between the first two doses. Both schedules require a booster 12 months after the second dose, and further booster doses are recommended at 3-year intervals.

**Immunogenicity and effectiveness**

The immunogenicity (defined by HI) of TBE vaccine Moscow and FSME-IMMUN® was compared in children aged 7-17 years. Four weeks after the second vaccine dose, 91.5% of those receiving TBE vaccine Moscow and 98.7% of the FSME-IMMUN® recipients had seroconverted. Comparative immunogenicity studies of TBE vaccine Moscow and EnceVir® vaccines were carried out in 2001-2002 (Gorbunov et al, 2002, Krasilnikov 2002). Using HI tests, the immune response following two doses of either TBE-Moscow or EnceVir® was assessed in 200 adults, of whom half the number received the second dose after 2 months, the other half after 5 months. With TBE-Moscow antibody titers ≥1:80 were detected in 84% and 93% of subjects, respectively; with EnceVir® the corresponding results were 82% and 89%. Similarly, in 2003, the Russian National Regulatory Authority conducted a comparative evaluation of the TBE-Moscow and EnceVir® vaccines in 325 children and adolescents (Pavlova LI et al 2003). The participants were stratified into three age groups (3-6 years, 7-14 years and 15-18 years). After two doses of the respective vaccine administered 2 months apart, TBE-Moscow showed ≥4-fold increase of HI-antibody titres in 96%, 93% and 89% of the vaccinees, respectively, whereas the corresponding results with EnceVir® were 84%, 97% and 92%.
A recent study involving a total of 290 adults compared the immunogenicity of TBE-Moscow, EnceVir®, and the two Western vaccines FSME-IMMUN® (new) and Encepur® adults (Leonova GN et al 2009). Immunogenicity was measured 2-5 months and 2 years following the administration of 3 doses of the respective vaccine. All vaccines induced neutralizing antibody against the Far Eastern subtype strain P-73. With TBE-Moscow, antibody was detected in 100% and in 94% of the vaccinees after 2-5 months and two years, respectively. With EnceVir® the corresponding figures were 88% and 84%, with FSME-IMMUN® 88.2% and 78.1%, and with Encepur® 100% and 100%.

A mass immunization programme that was initiated in 1996 in the Sverdlovsk Region, Russia demonstrated high effectiveness of TBE. By 2005, 2.7 million people had received three doses of TBE vaccine, in most cases TBE-Moscow (Pogodina et al, 2006; Romanenko et al 2007). Vaccination coverage increased from 35% at the beginning of the programme to 55% in 2000 and to 72% in 2006. In this region, the incidence of TBE cases per 100 000 inhabitants decreased from 42.1 in 1996 to 9.7 in 2000 and to 5.1 in 2006. The number of cases was reduced in all age groups. Comparison of the number of TBE cases in vaccinated and non vaccinated groups suggested that vaccine effectiveness increased from 62% in 2000 to 89% in 2006. In part, this increase may be a consequence of more stringent diagnostic criteria (Romanenko et al, 2007). Following routine immunization of children in the Russian Krasnoyarsk Region, the incidence of TBE decreased from 48.5/100 000 in 1999 to 6.1/100 000 in 2003 (Borodina TN et al 2004).

Protracted surveillance following the three primary doses of EnceVir® showed persistence of high antibody levels during at least 3 years (Il’ichenko et al 2009). In the Sverdlovsk Region, the incidence of TBE breakthrough cases in fully immunized persons was in 2006 calculated at 1.5/100 000 (incidence of TBE in non-vaccinated individuals 13.0/100 000). Both Russian and Western vaccines were used, but TBE-Moscow accounted for about 80% of all TBE-vaccinations in this area (Romanenko VV et al, 2007). With the Russian vaccines there are currently no details available on the induction and persistence of immunity in elderly persons.

**Safety of TBE vaccine Moscow and EnceVir®**

Large-scale, randomized, controlled safety trials of these vaccines have not been published so far. Small-scale studies on systemic and local adverse events suggest a moderate reactogenicity profile with no significant differences between the two vaccines. In 2002-2003, the Tarasevich State Institute for Standardization and Control of Medical Biological Products assessed the local and systemic reactogenicity of TBE-Moscow and EnceVir® in a trial that included 325 children and 400 adults (Pavlova LI et al 2003). No severe adverse events were recorded. Both vaccines were found to be moderately reactogenic without statistically significant differences between the two. Similar conclusions on the safety of TBE-Moscow were reached in other studies (Pavlova et al 1999, Krasilnikov et al, 2002). Furthermore, post-marketing surveillance of EnceVir® did not reveal any severe adverse events (Il’ichenko TE et al 2009) and no vaccine-associated residual complications have been reported to the national control authorities (MichailovI, personal communication 2010; Romanenko VV et al 2007). There are no indications of impaired immunogenicity or safety when the Russian TBE...
vaccines are administered simultaneously with other vaccines, for example in travelers. There are presently no reports available to us on the immunogenicity and safety of Russian TBE vaccines when administered simultaneously with other vaccines.

**Cross-protection by current TBE-vaccines**

There is limited clinical evidence that the two Western TBE vaccines induce protective immunity not only against the homologous subtype, but also against the Far Eastern and Siberian subtypes of the virus. The genetic and antigenic similarity between these subtypes, as well as evidences from non-clinical studies, makes such cross protection likely, however. Immunization of adults with Encepur® induced antibodies with high neutralizing capacity against strains of both the Western and the Far Eastern subtypes of TBEV (Leonova GN et al, 2007). Similarly, all four TBE vaccines induce neutralizing antibodies against Far eastern subtype virus (Leonova 2009). Furthermore, a recent study using FSME IMMUN® post immunization sera showed identical neutralization titers against the European, Siberian, and Far Eastern TBE virus (Orlinger KK et al, 2011). Further support for cross-protective immunity is provided by preclinical studies showing that immunization of mice with vaccine of the European subtype protected against lethal challenges with a variety of eastern TBEV isolates (Holzmann H et al, 1992; Hayasaka D et al, 2001).

Several studies suggest that existing TBE vaccines can be used interchangeably (Broker M 2006; Leonova et al 2009, Wittermann et al 2009; Loew-Baselli et al 2006).

**Contraindications and precautions**

Although currently licensed TBE vaccines are produced in chicken embryo cells, mild allergy to egg protein are not considered a contraindication.

The induction of protective immunity may be inadequate in individuals undergoing immunosuppressive therapy. In such cases, the antibody response should be assessed and, if necessary, an additional dose of TBE vaccine be administered. In general, TBE vaccination should be postponed during acute feverish infection (temperature >38.5°C) and should be administered to pregnant or nursing women only after a careful risk-benefit analysis.

Persons who have been exposed to flaviviruses other than TBEV may develop flavivirus cross-reactive antibodies that not only could interfere with serological tests (Holzmann H, 1996). Given that TBE-immunization programmes are likely to be organized in settings where TBEV and related flaviviruses co-exist, the possible implications of exposure to cross-reacting antigens should be further explored scientifically.

**Post-exposure prophylaxis**

Based on the assumption that vaccination after a tick bite is unlikely to induce immunity in time before possible onset of disease and considering the theoretical risk of antibody-dependent enhancement, no post-exposure prophylaxis is currently recommended after a tick bite in non-vaccinated patients (Bröker M et al, 2008).
In Western Europe, the injection of immune globulins containing high concentrations of antibodies against TBEV showed no beneficial effect when used for post-exposure prophylaxis and this approach is no longer recommended (Arras et al 1996). In contrast, a recent review of Russian experiences in this field indicates some protective effect of early post-exposure administration using Russian immunoglobulin preparations (Pen’efskaya et al, 2010).

Cost-effectiveness of TBE vaccination

Where TBE is prevalent, the disease causes high costs both at the individual and societal levels, in particular due to its frequent long-term neurological sequelae (Donoso Mantke et al., 2008, Kaiser, 1999, Kaiser, 2008). The immunization campaigns in Austria 1991-2000 were estimated to save an equivalent of US$ 80 million by reducing TBE-associated patient care, loss of productivity, and premature retirement (Schwarz B, 1993). In Sweden, the cost-effectiveness ratio for immunisation was estimated to be 1:68, if hypothetically 75% of cases were averted by vaccination of 42% of the Stockholm population (Haglund M et al 1996).

Cost-effectiveness calculations are critically dependent on how well the target group can be defined.

WHO policy on the use of TBE vaccine

Immunization offers the most effective protection against TBE (see Grading table I: immunogenicity/protective immunity). The two TBE vaccines that are manufactured in Western Europe are considered safe and efficacious for individuals ≥1 year of age. Favorable safety and efficacy profiles for individuals ≥3 years of age are reported also for the two Russian TBE vaccines, although for the latter products the published safety and effectiveness data are more limited (see Grading table II: safety). Current TBE vaccines seem to protect against all TBEV subtypes circulating in endemic areas of Asia and Europe (see Grading table III: cross protection within subtypes).

As the incidence of TBE may vary considerably between and even within geographic regions, public immunization strategies should be based on careful risk assessment even at district level and be appropriate to the local endemic situation. Therefore, establishing case reporting of TBE is essential before deciding on the most appropriate preventive measures. Similarly, health authorities are encouraged to conduct a cost-effectiveness analysis before possibly recommending programmatic TBE vaccination.

In areas that are highly endemic for TBE (average pre-vaccination incidence of clinical TBE ≥5/100 000/year), implying a high individual risk of infection for the entire population, WHO recommends to offer TBE vaccination for all age groups either through regular immunization programmes or immunization campaigns. Where a large
percentage of children is likely to be exposed to TBEV infected ticks, inclusion of TBE vaccination into the national or regional immunization programmes should be considered. Routine TBE vaccination of children is likely to result in high coverage and to facilitate monitoring the immunization status of individual vaccinees.

As the disease tends to be most serious and the immune response following primary immunization tends to be relatively low in individuals >60 years of age, elderly people at risk of infection constitute an important target group for TBE immunization.

Where the pre-vaccination incidence of TBE is moderate (>1 to <5/100,000/year, or low (annual average over a 5-year period of about 1/100 000) and/or is limited to particular geographic locations or certain out-door activities, TBE immunisation should be targeted at individuals of the most affected locations and those at highest risk of exposure according to live-style and occupation. This may include travelers from non-endemic to endemic areas.

TBE vaccination requires a primary series consisting of 3 doses and for those at continued risk, one or more booster doses. However, the duration of protection is poorly defined and the scientific evidence for the manufacturers’ choice of the primary immunization schedules is relatively weak. Within the considerable range of acceptable dose intervals, programme managers should select the most rational schedule according to the respective national, regional or district immunization programmes.

With the Western vaccines an interval of 1-3 months is recommended between the first two doses, and 5-12 months between the second and third doses. When rapid protection is required, for example for travelers to TBE endemic areas, the interval between the first two doses may be reduced to 1-2 weeks. The first booster dose should be given 3-5 years after the primary series. WHO recommends that the intervals of subsequent boosters are extended from the current 3-5 years to 10 years in children and adults. However, for those having received their primary immunization beyond the age of 60 years, boosting every 3-5 years appears prudent (see Grading table IV: duration of protection).

With the Russian vaccines, the recommend intervals are 1-7 months between the first two doses, and 6-12 months between the second and third doses. Booster doses are recommended every 3 years for those at continued risk of TBEV exposure. The currently recommended booster interval should be practiced until more data have been generated on the duration of protection induced by Russian TBE vaccines.

Regardless of duration of the delay, interrupted schedules should be resumed without repeating previous doses.

Although there is no experience to suggest any interference between existing TBE vaccines and simultaneously administered vaccines, the issue of potential immunological interactions needs to be addressed by appropriate studies. In addition,
more information is needed on the immune response to TBE vaccine in individuals who have received previous YF or JE immunization.

Post-exposure TBE 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 practiced in Russia.

Standardized case definitions and reporting requirements across endemic countries are greatly needed to better define the burden of disease, to develop evidence-based vaccination recommendations, and to measure the impact of vaccination. This also entails endorsement of standard diagnostic procedures for patients with suspected TBE and well as standardized measurement and follow-up processes to identify long-term sequelae after TBE. Similarly, standardized reagents are needed to allow comparison of test results across laboratories.

In all endemic areas information on the disease, its vector and transmission patterns as well as on available prophylactic measures should be readily available, for example in schools, doctors’ offices and in tourist information leaflets.

**Literature** (in WER, the 40-50 finally selected references will occur as footnotes)


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Grading table of scientific evidence: Table I immunogenicity/protective immunity, with key references.

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