Vaccines against tick-borne encephalitis (TBE)
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Grading of scientific evidence in support of key recommendations

Table I: Does a primary series of the currently available TBE vaccines protect children and adults of all ages against clinical TBE for ≥3 years?				
			Rating	Adjustment to score
Quality Assessment	No of Studies/Starting Score		7 RCTs[1]	**4**
	Factors decreasing confidence	Limitation in study design	None serous[2]	**0**
		Inconsistency	None serious	**0**
		Indirectness	Serious[3]	**-1**
		Imprecision	None serious	**0**
		Publication bias	None serious	**0**
	Factors increasing confidence	Large effect	Very large effect[4]	**+2**
		Dose-response	Evidence of dose-response[5]	**+1**
		Antagonistic bias and confounding	Not applicable	**0**
	Final Score			6 (Maximum score is 4)
Summary of Findings	Quality			We are very confident that the true effect lies close to that of the estimate of effect on health outcome
	Conclusion			There is strong evidence that a primary series of the currently available TBE vaccines protects children and adults of all ages against clinical TBE for ≥3 years

[1]There are no trials on vaccine efficacy against clinical TBE; indirect evidence of protection is provided by trials using immunogenicity (in this case mainly induction of neutralizing antibodies) as an endpoint. These 7 RCTs show strong antibody induction (high seroconversion rates) following TBE vaccination. In addition, observational studies regularly demonstrate the strong immunogenicity of currently available TBE vaccines. Four observational studies which were followed up for ≥3 years showed persistence of neutralizing antibodies throughout this period; [2] four of the 7 RCTs suffer from inappropriate randomization and/or lack of concealment; no serious limitation in study design for the remaining 3; [3]Immunogenicity rather than clinical protection is used as an endpoint. There is a lack of a standardized serological correlate of protection; [4] Very high seroconversion rates demonstrated in RCTs and observational studies. Where measured, observational studies consistently indicate high levels of protectionfor for at least 3 years; [5]Increasing reduction of clinical TBE with increasing immunization coverage observed through observational studies.

Randomised, controlled trials (RCTs) on immunogenicity

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"). In these 4 trials a total of 5063 children and adults were followed up serologically for 6-12 months; all vaccinees reached seroconversion rates of 92%-100% by ELISA, HI, or NT *(Ehrlich 2003; Loew-Baselli 2006; Schoendorf 2007; Schöndorf 2007)*. 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).*

A recent randomized study compared the immunogenicity in adults 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 single-blind, multi-center, randomized, controlled, phase III clinical study compared the immunogenicity and safety of FSME-IMMUN® Junior and Encepur Children® in 303 children aged 1-11 years. With FSME-IMMUN® Junior, the seropositivity rates as determined by NT 28 days after the second vaccination were 100.0% in all three age groups (1–2, 3–6 and 7–11 years). The corresponding rates with Encepur® Children were 100.0% in subjects aged 1–2 years, 95.5% in children aged 3–6 years and 97.6% in those aged 7–11 years *(Pöllabauer EM et al 2010).*

Observational studies on immunogenicity

Data on on the immunogenicity of Encepur® from 8 clinical trials and post-marketing studies (database 7,500 subjects) showed that following primary immunization all subjects seroconverted or showed a fourfold increase in anti-TBEV antibodies *(Zent O et al 2005).*The seroconversion rate (ELISA) of FSME-IMMUN was 98.5-100% after primary immunization of 412 children aged 1-15 years (pediatric dose); 96% in 64 vaccinees 12-15 year old (also pediatric dose), and 98.2% in 57 vaccinees aged 16-35 years (adult dose) *(Pöllabauer et al 2010).*

In 2001-2002, two studies in Russia involving 200 adults showed that with TBE-Moscow, antibody titers ≥1:80 were detected in 84% and 93%, and with EnceVir® in 82% and 89% of the vaccinees, following two doses, 2 or 5 months apart *(Gorbunov et al, 2002, Krasilnikov et al. 2002)*. Similarly, an evaluation involving 325 individuals stratified into the age groups 3-6 years, 7-14 years and 15-18 years, showed ≥4-fold increase of HI-antibody titres in 96%, 93% and 89%, respectively, using the TBE-Moscow vaccine, as compared to 84%, 97% and 92% with EnceVir® *(Pavlova LI et al 2003).*

Little information is available on immunogenicity and effectiveness of TBE vaccines in cases when the recommended immunization intervals were grossly extended. However, a recent study (*Schosser R et al 2009)* concluded that even the first TBE immunization mounts long lasting immune memory in 94% of vaccinated subjects.

Although vaccine breakthroughs do occur, they are rare *(Stiasny et al 2009; Andersson CR et al 2009).* Direct assessments of the break-through rate require RCTs against clinical outcome measures, which are currently unavailable.

Several observational studies testify to the high effectiveness of current TBE-vaccines in terms of TBE reduction in a population *(Heinz FX et al 2007, Kunz C, 2003, Romanenko VV et al, 2007); Borodina TN et al 2004).*

Observational studies on persistence of neutralizing antibodies ≥3 years after primary TBE-immunization

After the primary 3-dose immunization with FSME-IMMUN®, *Vene S et al (2007)* found persistence of neutralizing antibody activity in 89-95% of 535 adult vaccinees before the first booster (due after 3 years).*Loew-Baselli et al (2009)* showed that following a primary series of 2 doses of Encepur® and one dose of FSME-IMMUN®, initial seropositivity rates by NT were 100%, decreasing to 96.8% in the first two years and to 95.4% after 3 years. With Encepur Adult®, neutralizing TBE antibodies (geometric mean titers) remained on a high level prior to the first booster *(Zent et al 2003).* Protracted surveillance following the three primary doses of EnceVir® demonstrated maintenance of high antibody levels during at least 3 years *(Il'ichenko et al 2009).*

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