Vaccines against tick-borne encephalitis (TBE)
WHO position paper 10 June, 2011

Grading of scientific evidence in support of key recommendations

Table IV(a). Is protection against clinical TBE waning >3-5 years after one booster in individuals <60 years of age who previously received primary TBE immunization?

(Assessment based on Western TBE-vaccines only)

			Rating	Adjustment to score
Quality Assessment	No of Studies/Starting Score		5 observational[1]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[2]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final Score			**1**
Summary of Findings	**Quality**			We have very little confidence in the estimate of the effect on the health outcome.
	Conclusion			There is no evidence of waning protection > 3-5 years after a booster following the primary series. Available evidence suggests that following a booster dose of TBE-vaccine, protection against clinical TBE persists for at least 6- 8 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. Regardless of which of the two Western TBE vaccine that is used, all long-term serological studies show very low rates of waning of neutralizing antibody titres during the first 3-5 years following the booster. Also, where observation periods of up to 6-8 years have been achieved, neutralizing antibody titres suggesting protective immunity against TBE persist in the vast majority of vaccinees. Although on rare occasions break-through infections occur, (mostly in individuals aged >60 years), the incidence of break-through infections does not increase with time since last vaccination.[2]Immunogenicity rather than clinical protection is used as an endpoint. There is a lack of a standardized serological correlate of protection.

Studies on duration of protection following TBE vaccination.
A total of 222 adults 19-51 years of age were followed up serologically for 3 and 5 years after their first booster dose (Encepur® Adults). High antibody titres were recorded throughout the follow-up period. Neutralization test (NT) titres ≥10 were noted in 99% of subjects 3 and 5 years after the first booster vaccination *(Plentz A et al 2009). Paulke-Korinek et al (2009)* in a 6-year follow up study of 195 vaccinees who had previously received primary TBE vaccination (Encepur® Adults) and at least one booster , all remained seropositive (NT titres ≥1:2) throughout the observation period. In the age group <60 years, 94% had NT titres considered to be protective (≥1:10) six years after the last vaccine dose (86% in subjects aged ≥60 years). *Rendi-Wagner (2007)* found NT titres ≥10 in 96% (187/195) of the Encepur®Adults- vaccinated subjects at year 2, and 97% (232/240) at year 3 post-booster. An analysis by *Wittermann C et al (2009)*, showed that 275 of 278 (99%) and all 190 (100%) of Encepur® Children recipients who completed the follow-up at 3 and 5 years, respectively, had NT titres ≥10. A longitudinal study in Sweden by *Vene S et al (2007)* showed that after the 3 primary doses of FSME-IMMUN®, neutralizing antibody titers of ≥1:5 persisted in 77% of the vaccinees before administration of the first booster dose, and in 89-95% of 535 adult vaccinees before administration of the second and third boosters (about 3 year intervals between doses).

Recent data indicate that in more than 90% of vaccinees, the primary series of TBE vaccination plus one TBE booster induce neutralizing antibody levels that remain stable for at least 8 years and that the occasional break-through infections occurs independent of time since last immunization *(WHO Background paper)*.

Breakthrough infections in vaccinated individuals are rare, but do occur, particularly in elderly individuals (*Stiasnyet 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. (Neither study tries to assess the incidence of break-through infections among vaccinated individuals).

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Table IV (b). Does protection against clinical TBE wane in those who previously received the 3 primary TBE immunizations without booster?

(Assessment based on Western TBE-vaccines only)

			Rating	Adjustment to score
Quality Assessment	No of Studies/Starting Score		8 observational	2
	Factors decreasing confidence	Limitation in study design	Serious[1]	-1
		Inconsistency	No serious	0
		Indirectness	Serious[2]	-1
		Imprecision	No serious	0
		Publication bias	No serious	0
	Factors increasing confidence	Large effect	Large effect	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final Score			1 (total of 0 but lowest score in scale is 1)
Summary of Findings	**Quality**			We have very little confidence in the estimate of the effect on the health outcome.
	Conclusion			There is no evidence showing that in individuals <60 years, protection against clinical TBE wanes after the primary immunization series. However, studies are limited in terms of observation periods and design.

[1] Studies on persistence of antibodies following the primary vaccination series are limited to observation periods of 3 years. [2]There are no trials on persistence of vaccine-induced protection against clinical TBE; indirect evidence of protection is provided by trials using immunogenicity (mainly induction of neutralizing antibodies) as an endpoint.

Most studies on duration of protection are based on the primary 3 doses plus one or more booster doses. However, in a few cases, antibody concentrations have been measured just before administration of the first booster: Three years after the primary 3-dose immunization with FSME-IMMUN®, *Vene S et al (2007)* found persistence of neutralizing antibody activity in about 90% of 535 adult vaccines. *Loew-Baselli et al (2009)* showed that after 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),* and with EnceVir®, high antibody levels were maintained during at least 3 years *(Il'ichenko et al 2009).*

Although break-through infections among vaccinated individuals may occur, the incidence among healthy individuals in particular those < 50 years, is likely to be very low. Of the 25 cases reported from Austria by *Stiasny et al 2009* and the 27 cases reported from Sweden by *Anderson CR et al 2010*, the majority were >50 years of age.

The current requirement for repeated boosters after primary TBE immunization is challenged by the immunological results obtained also with irregular immunizations. Thus, *Heinz et al (2007)* showed that the field effectiveness of Western TBE vaccines was around 95% even in irregularly vaccinated subjects. A recent study by Schosser R et al 2009 concluded that in the majority of cases, an anamnestic antibody response to TBE antigen persisted irrespective of the time elapsed since last vaccination (i.e. up to 20 years) in individuals who had previously received only one TBE-vaccination, and in cases who were sero-negative prior to the booster.

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