GRADE Table 4. Is there a need for a booster dose following immunization with the primary series of inactivated Vero cell-derived JE vaccine in individuals living in JE-endemic areas?

Population : Immunocompetent individuals living in JE-endemic areas
Intervention: Two doses (primary series) of inactivated Vero cell-derived vaccine administered ≥12 months previously
Comparison: Placebo/no vaccination/other JE vaccine
Outcome : JE disease (immunogenicity accepted)

Is there need for a booster dose following immunization with the primary series of inactivated Vero cell-derived JE vaccine in individuals living in JE-endemic areas?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		4 RCTs[1]	4
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[3,4]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[5]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports limited confidence in the estimate of the effect on the health outcome.**
	Conclusion			**A primary series of inactivated Vero cell-derived JE vaccines administered to children in endemic settings elicits seroprotective neutralizing antibody titres for at least 3 years after the primary immunization.** ***Based on a review of data on IXIARO***

[1]Five clinical studies following participants 12 months post-primary series, 2 years, or 3 years are available, limiting the full assessment of long-term protection. Data in adults from non-endemic settings suggest a decline in seroprotection rates and GMTs in the 24 months following primary immunization. One study in Austria, Germany, and Romania found seroprotection rates dropped from 99% (95% CI: 96.1-99.7) at one month following the primary series to 82% two years later and 84.9% (95% CI: 78.3-89.7) three years later (Schuller 2008; CDC 2011); however, these results were obtained from a study population among which some had previously been exposed or vaccinated against Tick-Borne Encephalitis (TBE). Another study in Germany and Northern Ireland (without TBE) found seroprotection rates dropped from 97.3% (95% CI: 94.4-100.0) to 48.3% (95% CI: 39.4-57.3) (Schuller 2009; Dubischar-Kastner 2010). A booster dose is indicated >12 months after the primary series in non-endemic settings for longer protection. There are limited data in children and in endemic settings. In a study in the Philippines among children aged 2 months – 16 years, the seroprotection rate among 150

children at 3 years was 90%. The GMT decreased between month 2 and month 7, but then was relatively stable through the 3 years of follow up (49-52). (Dubischar-Kastner 2014 and unpublished, quoted with permission from Valneva)

[2]The limited duration of follow up (three years post primary series) of participants in endemic areas (300 children ages 2 months to 17 years) limits the ability to assess the duration of protection in these settings.

[3]Clinical study outcomes are based on an accepted immunological correlate of protection (Hombach 2005).

[4]Data are available from one endemic country (Philippines), with only 150 participants. Other data from adults in non-endemic settings is less applicable (not downgraded twice, as the small population and limited duration of follow up was downgraded under study design).

[5]Data from one study in the Philippines do support a high level (>80%) of effectiveness, a defined threshold in the WHO Guidance for the Development of Evidence-Based Vaccine-Related Recommendations. However, due to the other reasons for downgrading, it was not felt appropriate to upgrade.

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