# Is a Primary Series Adequate to Protect Against Japanese Encephalitis?

## Literature Watch Review

C. Taucher, H. Kollaritsch, K. L. Dubischar. **Persistence of the immune response after vaccination with the Japanese encephalitis vaccine, IXIARO, in healthy adults: a five- year follow-up study**. *Vaccine*. https://doi.org/10.1016/j.vaccine.2019.03.030.

## Conclusions

- The percentage of vaccinees with protective neutralizing antibody titers against Japanese encephalitis (JE) virus decreased from 99% at 4 weeks post primary vaccination with Ixiaro (Valneva) to 83.4% by month 12 and then remained stable, with 82% protected at month 60.
- This finding suggests strong immune memory and scope for flexibility in the timing of the booster dose, which is currently scheduled at 12 to 24 months in most national guidelines.
- Infrequent travelers to endemic areas of Asia could benefit from this flexibility.
- Vaccination against tick-borne encephalitis (TBE) enhances the antibody response to JE vaccination.

## Abstract

The long-term protective effect of primary vaccination with the inactivated JE vaccine, Ixiaro, is unknown. This article presents the third follow-up of the manufacturer's uncontrolled, multicentric phase 3 follow-up study, whose aim was to document the persistence of Japanese encephalitis virus (JEV)-neutralizing antibodies after primary vaccination with Ixiaro in a group of healthy European travelers.

The article reports the levels of protective neutralizing antibodies against JE at 12, 24, 36, 48, and 60 months after primary vaccination (days 0 and 28 with no further boosters); a subgroup evaluates the effect of vaccination against European TBE on these levels. Immunogenicity assessments were performed by a JEV-specific plaque reduction neutralization test (PRNT) and included seroprotection rates and geometric mean titers (GMTs) in the evaluation. TBE vaccination was recorded as prior to JE vaccination or concomitant with the JE vaccination follow-up period. Safety data were collected at each visit. Statistical methods and data handling are described in the article.

- Of the original 181 participants, 152 were available for assessment at months 24, 36, 48, and 60.
- Demographic data: mean age was 32.1 years (range: 18-74 years); 53% were females; 98.3% were Caucasian.
- The percentage of subjects with protective neutralizing antibody titers had decreased from 99% at 4 weeks post vaccination to 83.4% by month 12 and then remained stable, with 82% (95% CI, 74.7%–86.9%) protected at month 60.
- GMT values remained virtually unchanged (44.3–43.4) from months 24 through 60.
- TBE recipients vaccinated at any time prior to or during the study had higher seroconversion rates (SCRs) at most time-points (with nonoverlapping 95% CIs) from month 24 onwards.
- At month 12, the SCR was 75% in the subgroup of subjects without previous TBE vaccination (N = 92) compared to 92.1% for TBE vaccinated subjects (N = 89). By month 60, the SCRs had declined to 63.8% in the subjects without TBE vaccination (N = 47) and 85.9% in TBE vaccinated subjects (N = 78).
- Safety: All of the 76 adverse events and all the 16 serious adverse events reported during the 5-year follow up were considered unrelated to the study vaccine.

## Commentary

The inactivated JE vaccine was introduced in 2009, and the booster dose at ≥ 1 year was added to the regimen in 2011. A mean 76 months after that booster, 96% of vaccinees were shown to have neutralizing antibody titers ($PRNT_{50}$ ≥ 1:10), which is the titer generally considered to be protective (see *Literature Watch Review* Long-Term Persistence of Antibodies and Need for Second JE Vaccine Booster). This new 5-year follow-up study in healthy European travelers suggests that the primary schedule itself (days 0 and 28) induces immunity lasting for at least 60 months in over 60% of travelers and points to the

induction of a robust immune memory, such that the duration of the interval between the primary series and booster may not be important for obtaining an adequate postbooster immune response. Prior or subsequent vaccination against TBE enhances the response to JE but would not be relevant to travelers from the U.S. This new understanding may have some practical implications; for example, many travelers who make a (seemingly) one-off trip to Asia do not return for the 12-month booster and then 5-years later find themselves going to Asia again. Although a booster dose would be recommended, those unable or unwilling to receive a booster have a significant chance of ongoing protection.

*Editorial note:* This follow-up study was designed and funded by Valneva Austria GmbH, the vaccine manufacturer of Ixiaro. Two authors are employees of the company and the third has received speaking fees.

---

*Published April 19, 2019*