Modeling the long-term persistence of neutralizing antibody in children and toddlers after vaccination with live attenuated Japanese encephalitis chimeric virus vaccine

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ABSTRACT

The live-attenuated Japanese encephalitis chimeric virus vaccine JE-CV (IMOJEV®, Sanofi Pasteur) elicits a robust antibody response in children, which wanes over time. Clinical efficacy is based on a correlate of protection against JE infection defined as neutralizing antibody levels equal to or greater than the threshold of 10 (1/dill). Information on the duration of persistence of the JE antibody response above this threshold is needed. We constructed statistical models using 5-year persistence data from a randomised clinical trial (NCT00621764) in children (2–5 years old) primed with inactivated JE vaccine who received a booster dose of JE-CV, and in JE-naïve toddlers (12–24 months) who received a JE-CV single dose primary vaccination. Models were constructed using a Bayesian Monte-Carlo Markov Chain approach and implemented with OpenBugs V3.2.1. Antibody persistence was predicted for up to 10 years following JE-CV vaccination. Findings from a piecewise model with 2 phases (children) and a classic linear model (toddlers) are presented. For children, predicted median antibody titers (77 [2.5th–97.5th percentile range 41–144] 1/dill) remained above the threshold for seroprotection over the 10 years following booster JE-CV vaccination; the predicted median duration of protection was 19.5 years. For toddlers, 10 years after JE-CV primary vaccination median antibody titers were predicted to wane to around the level required for seroprotection (10.8 [5.8–20.1] 1/dill). A booster dose of JE-CV in children is predicted to provide long-term protection against JE. Such data are useful to facilitate decisions on implementation and recommendations for future vaccination strategies.

Introduction

Japanese encephalitis (JE) virus is the most common cause of viral encephalitis, transmitted predominantly by the mosquito Culex tritaeniorhynchus and endemic to many countries across Asia and the Western Pacific. About 25–30% of reported cases are fatal and 50% result in permanent neuropsychiatric sequelae.

Previous estimates of JE incidence in these regions vary. Estimates range from 0.003 per 100,000 in a passive surveillance study in Japan (1992–2004) to 15 per 100,000 among 5–9-year-olds in India. In Thailand, JE incidence varies between the north and south of the country. In northern Thailand huge epidemics occur during the summer months, whereas in southern Thailand JE tends to be endemic, with a peak in the number of cases reported after the start of the rainy season. Reported incidence rates before introduction of routine vaccination against JE in the 1990s were as high as 8.5/100,000 in some northern provinces; with the introduction of routine vaccination to those areas, the highest rates (2/100,000) are now in southern provinces. JE is considered to primarily affect the young. However, in countries that have achieved high vaccine coverage, JE cases are reported mainly in unvaccinated elderly people. In Taiwan, where a vaccine campaign was launched in 1968, over 90% of JE cases are reported in people older than 20 years.

The live attenuated vaccine against JE, SA14-14–2, is available in China and some endemic countries in Asia Pacific. A comparable immune response was observed in infants and toddlers in Thailand who received a single dose of JE-CV versus SA14-14–2. Fewer solicited reactions were reported following JE-CV compared with SA14-14–2 administration.

Newer one-dose primary and booster vaccination with live attenuated JE vaccines are replacing the 3-dose primary immunization and booster vaccination (mouse-brain derived inactivated JE vaccine, MBDV) due to the more favorable reactogenicity profile, improved safety, and a simpler immunization schedule of the live attenuated JE vaccines. JE-CV (IMOJEV®, Sanofi Pasteur) is a live-attenuated Japanese encephalitis chimeric virus vaccine indicated for prophylaxis of JE caused by JE virus in individuals from 9 months of age and over.

Primary vaccination with a single dose of JE-CV elicits a rapid and robust immune response in adults, toddlers and children. In adults, a protective response against JE was documented to persist for at least five years after a single dose of JE-CV. A previous modeling exercise predicted that this protective response in adults would persist for up to 21.4 years.
(95% confidence interval [CI]: 7.3–34.0 years) in a non-endo-
mic setting, with predicted median antibody titers at 10 years of
38 1/dil (95% CI: < 10–174) corresponding to seroprotection
levels at 10 years of 85.5% (95% CI: 72.7–94.9). Single-dose
primary immunization of JE-vaccine-naïve toddlers (12–
24 months old) elicits a seroprotective response that has been
shown to wane to levels of approximately 60% at 5 years after
vaccination. These findings prompted the recommendation
in the product label by the company for use of booster vaccina-
tion at 1 to 2 years after the primary dose in children. Indeed,
a very strong booster response is observed following a single
booster dose in 2–5 year olds primed with JE vaccination, with
high seroprotection levels persisting for at least 5 years
post-booster.

Information on the longer term duration of seroprotection
after single-dose primary and booster JE vaccination in chil-
dren is needed to provide insight into the potential long-term
benefits, and to help make informed decisions about immu-
nization programs. Here, we present the results of statistical
modelling to predict long-term antibody responses based on
previously published observed antibody titers up to 5 years
after vaccination following i) a booster dose of JE-CV in
children (2–5 years old) primed with two doses of MBDV and
ii) a single-dose primary administration of JE-CV in
toddlers (12–24 months old). These data are discussed in the
context of a comprehensive review of the literature on the
long-term persistence of JE neutralizing antibody response
following JE-CV vaccination.

Results
Children – 2 to 5 years old
Model fit
Median parameter estimates and 2.5th–97.5th percentile
ranges based on 97 subjects using each of the models tested
are shown in Table 1A. For children, the piecewise linear
model showed the best fit (Supplementary Figure S1).

Predicted antibody persistence using the piecewise model
Predicted median antibody titers remained well above seropro-
tective levels (≥ 10 [1/dil]) for at least 10 years following JE-CV
booster vaccination, decreasing from 2684 (2.5th–97.5th
percentile range 1778–4056) at day (D) 28 to 539 (357–816) at
year (Y) 1, 225 (145–351) at Y5 and 77 (41–144) at Y10 (Figure 1;
Table 2A). The estimated median duration of the initial period of
rapid antibody decay (from vaccination to the change point) was
0.81 years (2.5th–97.5th percentile range: 0.67–0.98 years), or
9.7 months (8.04–11.8 months) (Table 1A).

Toddlers – 12 to 24 months old
Model fit
For toddlers, following JE-CV single dose primary vaccina-
tion, all tested models showed poor convergence for D28–Y5
data (Table 1B), and so a classical linear model was con-
structed using data from M6 (Supplementary Figure S2). Median parameter estimates and 2.5th–97.5th percentile
ranges based on data from 187 subjects using the linear
model are shown in Table 1B.

Predicted antibody persistence using the linear model
Predicted median antibody titers declined to levels only just
above seroprotective levels (≥ 10 [1/dil]) at Y10, decreasing
from 65.3 (2.5th–97.5th percentile range 44.2–96.2) at M6 to
27.8 (17.8–43.5) at Y5 and 10.8 (5.8–20.1) at Y10 (Figure 2;
Table 2B).

Table 1A: Parameter estimates and fit statistics for the 3 models in children (2–5 Year Olds)

| Parameter                          | Median estimate | 2.5th–97.5th percentiles | DIC    |
|-----------------------------------|-----------------|---------------------------|--------|
| **Linear model**                  |                 |                           |        |
| Intercept (α+αi)                  | 7.235           | 6.94; 7.53                | 1625   |
| Slope (β1+βi)                     | -0.418          | -0.464; -0.373            |        |
| **Piecewise linear model (2 phases)** |               |                           |        |
| Intercept (α+αi)                  | 8.06            | 7.74; 8.38                | 1448   |
| Slope before change point (β1+βi) | -2.15           | -2.64; -1.75              |        |
| Slope after change point (β2+βi)  | -0.215          | -0.27; 0.16               |        |
| Change point (τ)                  | 0.81 years (9.7 months) | 0.67; 0.98 (8.04, 11.8)  |        |
| **Exponential model**             |                 |                           |        |
| Intercept (α+αi)                  | 10.8            | 9.37; 12.6                | 1477   |
| Slope (β+βi)                      | -4.29           | -6.06; -2.85              |        |
| Exponent (γ+γi)                   | 6.85            | 4.04; 12.2                |        |

DIC, deviance information criterion
Predicted proportion of seroprotected subjects

For the toddler (12–24 months old) population, despite a good prediction for the GMT over time, the predicted seroprotection appears to be overestimated (data not presented).

For children (2–5 years old), predicted seroprotection appears better than for the toddlers (closer to the observed seroprotection). The estimated proportion of seroprotected children remained stable between Y1 and Y4, and nearly all children remained seroprotected. After Y5, there was a slight acceleration in decline of overall seroprotection. At Y10, the predicted proportion of seroprotected children was 88% (76–97%) (Figure 3; Table 2A). The predicted median duration of protection was 19.5 years.

Different phases of antibody decay were observed in the 2 populations of children and toddlers; a rapid decay from D28 to year 1 and slower decay after year 1 in children; in contrast to the toddlers with a rapid decay from D28 to month 6 and slower decay after month 6. Following imputation, the observed data showed two distinct periods of antibody decay for both age groups (Supplementary Figure S3). Antibody titers decayed rapidly between D28 and Y1 for the children and between D28 and M6 for toddlers, followed by a slower phase of decay.

Discussion

We constructed statistical long-term models based on real-life antibody persistence data of 5 years to predict the mean geometric titers and duration of seroprotection following immunisation with JE-CV, administered as a single-dose booster in children previously vaccinated with inactivated JE-vaccine, or as a single-dose for primary vaccination in JE-vaccine naïve toddlers. Antibody responses against JE...
were predicted to persist for several years in both age groups. Predicted antibody titers and the median duration of antibody persistence were greater in children who had received an additional booster vaccine as compared to children who received only a single dose.

Primary JE-CV vaccination in JE vaccine-naive toddlers has previously been shown to elicit a robust antibody response that wanes over several years. In the real-life 5-year persistence study in Thailand, JEC01, a single dose of JE-CV elicited a robust immune response in toddlers who had not been previously vaccinated against JE, with protective antibody titers ($\geq 10 \, [1/dil]$) in 96% of toddlers at D28. Follow-up of these toddlers over 5 years showed a decline in geometric mean titers and seroprotection levels. Among toddlers seroprotected on day 28, 64.0% (Kaplan-Meier analysis) were estimated to remain seroprotected at year 5. In another study (JEC02), JE vaccine-naive toddlers in Thailand and the Philippines similarly showed a strong immune response after single dose JE-CV, with 95.0% seroprotection at D28. A subset was then followed for long-term immunogenicity following JE-CV primary vaccination (study JEC05). Among those participants seroprotected at day 28, 68.6% (Kaplan-Meier analysis) were estimated to be still seroprotected at year 5.

### Table 2: Predicted antibody titers and seroprotection rates for up to 10 years following booster vaccination with JE-CV in children (2–5 years old) who had received primary immunization with inactivated JE vaccine, and following primary vaccination with JE-CV in toddlers (12–24 months)

| Timepoint | Median titers, 1/dil (2.5th–97.5th range) | Seroprotection, %* (2.5th–97.5th range) |
|-----------|------------------------------------------|-----------------------------------------|
| **A. Children (2–5 years old)** | | |
| 28 days | 2684 (1778,4056) | 100 (100, 100) |
| 6 months | 1098 (727,1652) | 100 (99, 100) |
| 1 year | 539 (357,816) | 100 (98, 100) |
| 2 years | 430 (286,648) | 100 (98, 100) |
| 3 years | 347 (230,523) | 100 (97, 100) |
| 4 years | 280 (183,426) | 99 (96, 100) |
| 5 years | 225 (145,351) | 98 (94, 100) |
| 6 years | 182 (113,291) | 97 (92, 100) |
| 7 years | 147 (88,242) | 96 (89, 100) |
| 8 years | 118 (69,203) | 94 (85, 99) |
| 9 years | 95 (53,171) | 91 (81, 98) |
| 10 years | 77 (41,144) | 86 (76, 97) |
| **B. Toddlers (12–24 months)** | | |
| 6 months | 65.3 (44.2,96.2) | 65.3 (44.2,96.2) |
| 1 year | 59.3 (40.2,87.4) | 59.3 (40.2,87.4) |
| 2 years | 49.1 (33.1,72.6) | 49.1 (33.1,72.6) |
| 3 years | 40.7 (27.1,60.9) | 40.7 (27.1,60.9) |
| 4 years | 33.6 (22,51.3) | 33.6 (22,51.3) |
| 5 years | 27.8 (17.8,43.5) | 27.8 (17.8,43.5) |
| 6 years | 23 (14.3,37) | 23 (14.3,37) |
| 7 years | 19 (11.4,31.6) | 19 (11.4,31.6) |
| 8 years | 15.8 (9.1,27.1) | 15.8 (9.1,27.1) |
| 9 years | 13.1 (7.3,23.3) | 13.1 (7.3,23.3) |
| 10 years | 10.8 (5.8,20.1) | 10.8 (5.8,20.1) |

* Proportion of seroprotected subjects to be interpreted with caution due to limitation of the model.

Figure 3. Observed and predicted seroprotection rates from D28 to Y10 in children, using the piecewise linear model. The red and blue arrows indicate the period of time for which real-life data were collected (red) and the period of time over which the model is extrapolated (blue).
Booster JE-CV vaccination elicits very strong immune responses in children previously vaccinated against JE, irrespective of whether primary vaccination was with inactivated JE vaccine\(^\text{10}\) or JE-CV.\(^\text{18}\) In JEC01, all children aged 2–5 years receiving a JE-CV booster dose 1 to 2 years after JE primary vaccination with MBDV were seroprotected 28 days after JE-CV booster vaccination\(^\text{10}\) and 97% were seroprotected at 5 years post-booster (sensitivity analysis).\(^\text{15}\) No cases of symptomatic JE virus infection were recorded during the 5-year follow-up study\(^\text{15}\); however, given the endemicity of JE in Thailand, it is possible that the children came into contact with circulating JE virus during this time. It cannot be excluded that natural exposure to JE virus or another flavivirus may have caused a natural booster effect in some of these children, and thus may have impacted the findings from the current modeling exercise. In JEC15, among children who received a JE-CV booster dose 2 years after primary vaccination with a single dose of JE-CV, 100% (95% CI 98.9–100%) were seroprotected at D28 and nearly all (99.4% [95% CI 97.9–99.9%]) were seroprotected 1 year later\(^\text{18}\). 98.2% (95% CI, 96.2%–99.3%) of subjects remained seroprotected (Kaplan-Meier analysis) 5 years after booster with GMT of 161, 1/dil (95% CI 141–184).\(^\text{19}\) A further subset of JE-CV primed children from the JEC02/JEC05 study received a JE-CV booster after a longer interval of 5 years following primary vaccination. A strong booster response was elicited, with 100% seroprotection at 28 days after booster; 92.8% had antibody titers ≥ 1,280 (1/dil).\(^\text{20}\)

The observation of strong booster responses very early after JE-CV booster vaccination in children primed with a single dose of JE-CV 2 years earlier suggests that immune memory is induced by the primary dose of JE-CV. Indeed, in JEC15, among JE-CV primed children whose neutralising antibody titers had fallen below levels of protection (< 10 [1/dil]) before booster, 82.4% (95% CI 71.2–90.5%) were seroprotected at only 7 days after booster, when the primary response to vaccination is known to be low. This was compared to seroprotection levels of 15.4% (95% CI 5.9–30.5) in JE-vaccine naïve children 7 days after a JE-CV single dose primary immunization; GMTs (1/dil) were 44.3 and 6.41 for JE-vaccine primed and naïve children, respectively.\(^\text{18}\) These findings suggest that primary JE-CV vaccination may provide additional protective potential for children who are re-exposed to the JE virus, potentially even for those whose neutralizing antibody titers have declined over time to below the threshold of protection. It is conceivable that any exposure to wild-type Japanese encephalitis virus in view of this memory will trigger a prompt and robust response. In such cases, immunological memory induced at primary vaccination may allow sufficient levels of antibody titers to neutralise the virus before undergoing replication cycles and crossing the blood-brain barrier.

The current study provides further insight into the potential long-term benefit of JE-CV booster vaccination in children. For children 2–5 years old, the piecewise linear model predicted long-term persistence of antibody titers following booster vaccination with JE-CV, with a median titer at 10 years (77 [41–144] 1/dil) that exceeds the threshold for protection.

In toddlers (12–24 months), our linear model starting from 6 months showed that the predicted level of antibody titers in toddlers decreased over 10 years to levels lower than for children who had been primed by JE vaccination 1 to 2 years before receiving a booster dose; the predicted median titers at 10 years for toddlers did remain just above the threshold for protection (10.8 [5.8–20.1] 1/dil).

The need for a booster dose of JE-CV in JE-naïve children was recommended as 1 to 2 years due to a continued risk of exposure in endemic countries; a booster vaccine at a later stage however still demonstrated a memory immune response. This is different to the recommendation in adults (age ≥ 18 years), both naïve and previously vaccinated, whereby only a single dose was recommended, and no booster doses up to five years after administration.\(^\text{17}\) Adults had an initial stronger immune response with higher GMT levels and a lower rate of antibody loss over time.\(^\text{14}\) Thus, a single dose was considered an effective long-term preventive intervention in adults.

The parameters of the model in the present study differed from the ones utilized to predict GMTs and seroprotection in adults up to 25 years after one dose of JE-CV. The intercept of the piecewise linear model was higher in children compared with adults (8.06 [7.74–8.38 for 2.5–97.5 percentiles] vs. 5.81 [5.36–6.58 for 5–95th percentiles], respectively).\(^\text{14}\) These differences were reflected in the higher GMTs at D28 in children in the present study compared with adults in Desai et al.\(^\text{22}\). In addition, a more rapid decline in GMTs was predicted in children than adults by the piecewise linear model, with slope after \(S (b_2 + b_3)\) of – 0.215 (– 0.27, – 0.16) and – 0.109 (– 0.172, – 0.034), respectively.

A number of limitations of this study must be considered. Two different models were used for the different age groups. The piecewise linear model, which provided a good fit with observed titers for children, did not give a good fit for the toddlers age group because of the limited number of time points between D28 and Y1 and a more rapid decrease in titers between D28 and M6. Therefore, a linear model using data from M6 was used for toddlers. Our predictions should be interpreted with caution given the fact that they are based on the assumption that the observed linear trend continues beyond five years. In particular, it should be highlighted that seroprotection estimates were derived from the predicted antibody titers; these derived seroprotection estimates appeared to be overestimated in the linear model used for toddlers (for Y2–Y5), and is not presented here.

Modeling approaches have been used to estimate the duration of protection for a number of other vaccine-preventable diseases. A recent modeling exercise, using piecewise and modified power law models based on real-life 5-year immunogenicity data following immunization with the human papillomavirus-16/18 AS04-adjuvanted vaccine predicted persistence of HPV antibodies above natural infection levels in girls (9–14 years) for over 20 years;\(^\text{21}\) mixed effects models have also been used to predict long-term seroprotection against hepatitis A for at least 20–30 years after vaccination;\(^\text{22,23}\) and to support the need for booster doses of 5-component acellular pertussis vaccine every 10 years.\(^\text{24}\) Predictions of the duration of protection against such vaccine-preventable diseases are highly valuable for decision-making on future vaccination strategies. In the absence of real-life data beyond 5 years, the current modeling exercise supports growing evidence suggesting that primary immunization with a JE-CV single dose in toddlers may elicit a protective response that persists over 5 years despite a decrease in the Ab titers (and
so justifying the booster dose to be administered 1 to 2 years after primary single dose immunization), and JE-CV booster vaccination in children confers protection without the need for further doses for at least 10 years.

**Methods**

**Study data**

Source data (observed individual JE antibody titers) were obtained from a phase 2 randomized controlled immunogenicity study (cross-over design) in Thailand, in which 100 children (2–5 years old) received 1 dose of JE-CV as a booster JE vaccination after primary immunization with the inactivated JE vaccine MBDV and 200 toddlers (12–24 months old) received a single dose of JE-CV as primary immunization. All participants received the control hepatitis A vaccine, administered either 28 days before or 28 days after the study vaccine JE-CV in a cross over design; both groups were treated with both products assuming no effect of hepatitis A vaccination on JE vaccination. Antibody titers were measured before JE-CV administration, then on D28, M6, and Y1, 2, 3, 4 and 5 after vaccination.

Sensitivity analyses were carried out to account for the disconmpliance of subjects with low neutralizing antibody titers (i.e. below the threshold considered for protection), and who may have received another JE vaccination during the 5-year follow-up period, as previously described. Briefly, for all follow-up visits between year 1 and year 5, missing values occurring after negative values were replaced by negative values; from M6 to Y5, positive values occurring after negative values were replaced by negative values. Titers increasing with a ratio ≥ 8 at Y4 or Y5 in comparison to previous values were deleted (other values were kept for those participants affected). Data from at least two time points had to be available for inclusion.

All data were anonymized such that no patient identifiers were present in the data files received for analysis.

**Statistical models**

Statistical models were developed to predict antibody titers over time for up to 10 years following JE-CV vaccination. It was also expected that the models could estimate the proportions of participants remaining seroprotected against JE from the predicted antibody titers (protective antibody titers ≥ 10 [1/dil]). Observed antibody titers from D28 to Y5 were used to construct models for children. For toddlers, as only limited data were available for the initial decay phase, models with data from D28 to Y5 didn’t fit the data, so models were constructed with data from M6 to year 5 only. Three mixed effect models were fitted to the data for each age group, to account for variation at the population level (fixed effects) and at the individual level (random effects).

**Linear model**

The first model (linear) estimated linear antibody decay and contained fixed and random effects for both slope and intercept parameters:

\[ Y_{ij} = (a + a_i) + (b + b_i) \cdot t_j + \epsilon_{ij} \]

where \( Y_{ij} \) is the log of the neutralizing antibody titer for subject \( i \) observed at time \( t_j \).

\( a \) and \( b \) are the population-level (fixed) effects for the intercept and slope respectively and \( a_i \) and \( b_i \) are the individual-level (random) effects for the intercepts and the slope.

\( \epsilon_{ij} \) is the residual error.

**Piecewise model**

The second model was a 2-period piecewise linear model with fixed and random effects for the intercept \((a,a_i)\), 2 slope parameters \((b,b_i)\) and a change point \(S_h\), representing the point in time when the change in the rate of antibody decay occurs.

\[ Y_{ij} = (a + a_i) + (b + b_i) \cdot t_j + \epsilon_{ij}, \text{ for } t \leq S_h \]

and

\[ Y_{ij} = (a + a_i) + (b + b_i) \cdot S_h + (b_2 + b_{2i}) \cdot (t_j - S_h) + \epsilon_{ij}, \text{ for } t > S_h \]

**Exponential model**

The third model was an Exponential model with fixed and random effects for the intercept \((a,a_i)\), the slope parameters \((b,b_i)\) and a Exponent \((c,c_i)\).

\[ Y_{ij} = (a + a_i) + (b + b_i) \cdot t_j^{(c + ci)} + \epsilon_{ij} \]

**Model construction and validation**

All models were constructed using a Bayesian Monte-Carlo Markov chain approach and were implemented with OpenBugs V3.12. Models were constructed with three chains of 60,000 iterations, excluding the first 30,000 ‘burn-in’ estimates. Models were validated based on the convergence of various parameters: parameter iteration histories (the trace), the auto-correlation and the Gelman Rubin statistics. Models were compared using the Deviance Information Criterion (DIC), The DIC is a generalization of the Akaike Information Criterion and is suitable for assessing mixed-effects models.

**Estimation of seroprotection rates**

Selected models were used to try to predict at each time point the proportion of subjects considered to be seroprotected (i.e. JE antibody titers ≥ 10 [1/dil]). Estimates were based on the distribution of the predicted antibody titers.

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Author contributions
AB, FB and EF were involved in the design, analysis and interpretation of the analysis. All authors contributed to this publication and approved the final manuscript for submission. All authors had access to the study data and are responsible for the veracity and completeness of the data reported.

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