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Post-licensure, phase IV, safety study of a live attenuated Japanese encephalitis recombinant vaccine in children in Thailand ☆

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ABSTRACT

Background: Japanese encephalitis is a mosquito-borne viral disease endemic in most countries in Asia. A recombinant live, attenuated Japanese encephalitis virus vaccine, JE-CV, is licensed in 14 countries, including Thailand, for the prevention of Japanese encephalitis in adults and children.
Methods: This was a prospective, phase IV, open-label, multicentre, safety study of JE-CV conducted from November 2013 to April 2015, to evaluate rare serious adverse events (AEs). JE-CV was administered to 10,000 healthy children aged 9 months to <5 years in Thailand as a primary (Group 1) or booster (Group 2) vaccination. Serious AEs (SAEs), including AEs of special interest, up to 60 days after administration were evaluated. Immediate Grade 3 systemic AEs up to 30 min after JE-CV administration were also described.
Results: The median age of participants was 1.1 years in Group 1 and 3.8 years in Group 2. SAEs were reported in 204 (3.0%) participants in Group 1 and 59 (1.9%) participants in Group 2. Among a total of 294 SAEs in 263 participants, only three events occurring in two participants were considered related to vaccination. All three cases were moderate urticaria, none of which met the definition of AEs of special interest for hypersensitivity. AEs of special interest were reported in 28 (0.4%) participants in Group 1 and 4 (0.1%) participants in Group 2; none were considered related to vaccination. Febrile convulsion was the most frequently reported AE of special interest: 25 (0.4%) participants in Group 1; and 2 (<0.1%) in Group 2. There were no cases of Japanese encephalitis reported. No Grade 3 immediate systemic AEs were reported after any JE-CV vaccination.
Conclusions: Our study did not identify any new safety concerns with JE-CV and confirms its good safety profile.
This study was registered on www.clinicaltrials.gov (NCT01981967; Universal Trial Number: U1111-1127-7052).

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1. Introduction

Japanese encephalitis (JE) is a mosquito-borne viral disease that is endemic in most countries in Asia [1]. JE belongs to the same genus (Flavivirus) as yellow fever (YF) and dengue viruses [2]. The greatest burden of disease occurs in childhood with 66% of cases occurring in those under 15 years of age and an overall case fatality rate of up to 35% [3]. In Thailand during the 1970s and 1980s, 1500–2500 cases of encephalitis were reported annually [3]; following the introduction of a national JE vaccination programme in 1990, the number of cases declined to 297–418 cases per year between 2002–2008, reflecting the large proportion of cases caused by JE virus [4].

There is no specific antiviral treatment for JE. The World Health Organization recommends that JE vaccination should be integrated into national immunisation schedules in endemic areas [5]. A live, attenuated JE vaccine (JE-CV; IMOJEV™, Sanofi Pasteur) has been developed using the YF virus vaccine vector YF17D with the cDNA encoding the envelope proteins of YF virus replaced with that of the attenuated JE SA-14-14-2 virus strain [6,7]. A number of phase II and phase III studies conducted in adults and children have demonstrated the safety and immunogenicity of JE-CV [5,8–13]. The vaccine was first registered in Australia and Thailand in 2010 in children aged 12 months to 5 years and has subsequently been licensed in 12 other countries to date, for the prevention of JE in both children and adults. For children, the current recommended dosing schedule for JE-CV is a single dose as primary vaccination from 9 months of age followed by a booster dose 12–24 months later [14]. In adults, a booster dose is not required for up to 5 years after administration of a single dose of JE-CV [14].

Previous safety evaluation in non-clinical studies showed no evidence of viscerotropism or neurotropism [15]. We undertook this large prospective phase IV post-marketing safety study to further characterise the safety profile of JE-CV to evaluate rare (>1/10,000 and <1/1000) serious adverse events (SAEs) in a large population. Here we describe Grade 3 systemic immediate adverse events (AEs) and SAEs, including AEs of special interest (AESIs), of JE-CV following administration to 10,000 children, 70% of whom received JE-CV for the first time.

2. Methods

2.1. Study design

This study was a prospective, phase IV, open-label, multicentre, safety study of the live attenuated JE vaccine, JE-CV, administered to 10,000 healthy children in Thailand either as a primary vaccination (Group 1) or as a booster ≥1 year after primary immunizaton with inactivated JE vaccine or JE-CV (Group 2). The study was conducted between 03 November 2013 and 09 April 2015 in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on the Harmonization-Good Clinical Practice guidelines. In addition, the study protocol, including any amendments, was approved by each study site's Institutional Review Board and Independent Ethics Committee. Written informed consent was obtained from the parents/guardians of all children before study entry. This trial has been registered at www.clinicaltrials.gov (identifier NCT01981967; Universal Trial Number: U1111-1127-7052).

At study initiation, children aged 12 months to less than 5 years were eligible for inclusion, however, this criteria was later modified in 2014 to include children from 9 months of age, following a change in the age indication for JE-CV. Participants were physically examined to assess general health at the time of inclusion; all participants required vaccination against JE. Children who had received medications such as high dose systemic corticosteroids, antiviral drugs, immunosuppressive drugs (usually chemotherapy) and immunoglobulins/blood products containing immunoglobulins within the last three months were excluded. Other exclusion criteria included: any contraindications to JE-CV vaccination, participation in another clinical trial in the four weeks preceding the vaccination or at any time during the study period, a medical procedure or receipt of any vaccine in the four weeks preceding the study vaccination, planned vaccination in the four weeks following the study vaccination, previous vaccination with another live attenuated JE vaccine (CD-JEVAX®, Chengdu Institute of Biological Products, Chengdu, China) or prior receipt of JE-CV earlier in this study as primary vaccination (Group 2 only).

The proportions of participants included in the study to receive JE-CV either as primary vaccination (Group 1) or as a booster (Group 2) were approximately 70% and 30%, respectively. Group 1 was defined as follows: participants who never received a JE vaccine; participants who received a single dose of inactivated JE vaccine; and participants whose JE vaccination history was unknown or not documented. Group 2 was defined as follows: participants who received at least 2 doses of inactivated JE vaccine (at least 1 year earlier since the last dose); participants who received a single dose of JE-CV as part of the routine vaccination schedule at least 1 year earlier.

2.2. Vaccine

The JE-CV vaccine (IMOJEV™, Sanofi Pasteur) was supplied as powder and solvent for injection. The solvent for reconstitution consisted of sterile 0.4% sodium chloride solution. Two batches of JE-CV (batch numbers 08A1201BF and 08A1305BB) were used in the study. Each 0.5 mL dose of reconstituted vaccine contained 4.0 (batch 08A1201BF) or 5.8 $\log_{10}$ (batch 08A1305BB) plaque forming units of lyophilised vaccine virus. The vaccine was administered subcutaneously into the anterolateral aspect of the thigh or the deltoid region of the upper arm.

2.3. Safety

Participants were kept under observation for 30 min after vaccination to monitor the appearance of any immediate Grade 3 systemic AE. Systemic reactions were graded as follows: for fever, Grade 3 AEs were defined as a body temperature >39.5 °C for participants aged <2 years or ⩾39.0 °C for participants aged ⩾2 years. For any other AE, Grade 3 was defined as a significant AE that prevents normal activity.

Parents/guardians were provided with cards to record information and events during the 60-day follow-up period. Parents/guardians were interviewed by telephone on four occasions during the 60-day follow-up period using a questionnaire to capture SAEs (including AESIs); relevant information was transcribed onto case report forms. A SAE was defined as any untoward medical occurrence following the dose (including overdose) that: resulted in death; was life-threatening; required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; or was an important medical event. AESIs were selected based on events previously reported with licensed JE mouse-brain derived vaccines and related YF17D vaccines, or events typically expected after vaccination with a live-attenuated vaccine. These included: hypersensitivity reactions (severe [Grade 3] allergic reaction, regardless of the relationship to the vaccine, anaphylactic/anaphylactoid reaction); neurological disorders such as convulsions

(including febrile convulsions) or other neurological disorders such as encephalopathy, encephalitis, acute disseminated encephalomyelitis, myelitis, Guillain-Barré syndrome, peripheral neuropathy, facial (Bell's) palsy; and laboratory-confirmed vaccination failure (JE after JE-CV vaccination). Guidelines and Brighton Collaboration case definitions were provided to the Investigator to assist in the assessment of AEs that may have been suggestive of a viscerotropic or neurotropic disease. Parents were instructed to inform the study site and to bring the participant for an unscheduled visit if the participant developed severe fever.

In the event of severe (Grade 3) fever of unknown etiology on at least two consecutive days within 14 days after vaccination, viremia assessments for JE and dengue were undertaken using JE virus isolation techniques. Briefly, laboratory-reared mosquitoes, *Toxorhynchites splendens*, aged 2–4 days, were inoculated intrathoracically with the participant's sera. After incubation for 14 days at 32 °C, the presences of viral antigens was determined by direct fluorescence assay using fluorescein isothiocyanate conjugate anti-flavivirus antibodies. Identification of virus type was confirmed by indirect fluorescence assay.

The site Investigator assessed the causal relationship between each SAE (including AESI) and vaccination as either not-related or related. An AE was defined as not-related when it was clearly or most probably caused by other etiologies such as the participant's underlying condition, therapeutic intervention, or concomitant therapy or the delay between vaccination and the onset of the AE was incompatible with a causal relationship. An AE was defined as related when there was a reasonable possibility that the AE was caused by the vaccination, meaning that there was evidence or arguments to suggest a causal relationship.

2.4. Statistical analysis

The sample size was selected to allow the detection of rare AEs with a frequency >1/10,000 and <1/1000 (>0.01% and <0.1%). The 10,000 participants included in the study provided a probability of approximately 95% of observing any AE with a true frequency of 1/3333. All participants who received JE-CV either as a primary dose or as a booster dose were included in the safety analysis set.

No hypothesis testing was performed in this study. Grade 3 immediate systemic AEs and SAEs (including AESIs) occurring up to Day 60 were summarised in terms of the number and percentage of participants experiencing these events, with participants receiving JE-CV as primary vaccination or as a booster dose summarised separately. For the main parameters, 95% confidence intervals (CIs) of percentages were calculated using the exact binomial distribution for proportions (Clopper-Pearson method) [16].

3. Results

3.1. Study population

10,000 participants received JE-CV either as a primary dose (6851 participants) or as a booster dose (3149 participants) during the study period. There were 28 (0.3%) participants who did not meet all inclusion criteria or met the exclusion criteria; nine had participated in another clinical trial in the four weeks preceding the vaccination; 14 received a vaccine in the four weeks following the study vaccination; four were not aged 9 months to less than 5 years on the day of inclusion; and one had been previously vaccinated with CD-JEVAX®. These participants were not withdrawn but continued to participate in the study and were included in the safety analysis set. 9965 (99.7%) participants completed the trial (up to 60 days after the vaccination). 35 (0.4%) participants withdrew from the trial; 20 voluntarily withdrew from the study for reasons unrelated to AEs, 14 were lost to follow-up and one participant died from leukaemia (unrelated to the administered vaccine).

Table 1
Baseline characteristics of participants.

	Group 1 (N = 6851)	Group 2 (N = 3149)
Sex: n (%)		
Male	3530 (51.5)	1599 (50.8)
Female	3321 (48.5)	1550 (49.2)
Sex ratio: Male/Female	1.1	1.0
Age (year)		
Median	1.1	3.8
Min; Max	0.7; 5.0	1.0; 5.1
Age classification: n (%)		
<1 year	1750 (25.5)	0 (0.0)
⩾1 and <2 years	4807 (70.2)	22 (0.7)
⩾2 years	294 (4.3)	3127 (99.3)
Weight (kg)		
Mean (SD)	9.8 (1.9)	15.5 (3.6)
Min; Max	5.5; 38.0	8.3; 49.0

Max: maximum; Min: minimum; N: number of participants who received the study vaccine; n: number of participants with characteristic; SD: standard deviation.

Participant characteristics, measured at baseline (Study Day 0), are summarised in Table 1. At enrolment, the median age of participants in Group 1, who received a primary vaccination with JE-CV, was 1.1 years which was younger than participants in Group 2 who had a median age of 3.8 years. As the participants in Group 2 were older than in Group 1, they also had a higher body mass (mean 15.5 kg versus 9.8 kg). There were slightly more male participants than female participants at enrolment (51.5% versus 48.5% in Group 1, and 50.8% versus 49.2% in Group 2).

3.2. Safety

There were no Grade 3 immediate (within 30 min) systemic AEs reported after any JE-CV vaccination. A summary of the most frequent and related SAEs (including AESIs) within 60 days after administration of JE-CV is provided in Table 2. A total of 231 SAEs were experienced by 204 (3.0%) participants after JE-CV primary vaccination (Group 1), and 63 SAEs were experienced by 59 (1.9%) participants after JE-CV booster vaccination (Group 2).

Three SAEs (including AESIs), reported in 2 participants in Group 1, were considered related to vaccination by the Investigator. One participant developed urticaria 4 h after receiving JE-CV and recovered 2 days later. The other participant experienced 2 events of urticaria (2 days after vaccination, lasting 7 days, and 16 days after vaccination, lasting 5 days). The three events were considered as moderate hypersensitivity which did not lead to hospitalisation, and therefore did not meet the case definition of AESI limited to severe (Grade 3) or serious (hospitalised) hypersensitivity.

Table 3 summarises the AESIs reported within 60 days after vaccination with JE-CV. There were no AESIs that were considered related to vaccination by the Investigator. Febrile convulsion was the most frequently reported AESI, occurring mainly in Group 1 (Table 3). 20 of 27 participants reporting febrile convulsion had an alternative etiology (pneumonia, influenza, bacterial pharyngitis or other infections). In the remainder, the time to onset of febrile convulsion was not consistent with a potential role of administered vaccine. Indeed, there was an equal distribution of febrile convulsions throughout the 60-day study period (Fig. 1). Two participants had blood samples taken for assessment of JE, and dengue viremia and were confirmed to have viral pneumonia and viral nasopharyngitis. There were no cases of JE reported. In addition, a single episode of convulsion without fever was reported

Table 2
Most frequent serious adverse events within 60 days after vaccine injection.

	Group 1 (N = 6851)						Group 2 (N = 3149)					
	All SAEs			Related SAEs			All SAEs			Related SAEs		
	n	% (95% CI)	n SAEs	n	% (95% CI)	n SAEs	n	% (95% CI)	n SAEs	n	% (95% CI)	n SAEs
Participants experiencing ⩾ 1:												
SAE	204	3.0 (2.6; 3.4)	231	2	<0.1 (0.0; 0.1)	3	59	1.9 (1.4; 2.4)	63	0	0.0 (0.0; 0.1)	0
Infections and infestations	161	2.4 (2.0; 2.7)	174	0	0.0 (0.0; 0.1)	0	46	1.5 (1.1; 1.9)	47	0	0.0 (0.0; 0.1)	0
Gastroenteritis	28	0.4 (0.3; 0.6)	29	0	0.0 (0.0; 0.1)	0	8	0.3 (0.1; 0.5)	8	0	0.0 (0.0; 0.1)	0
Pneumonia	24	0.4 (0.2; 0.5)	24	0	0.0 (0.0; 0.1)	0	7	0.2 (0.1; 0.5)	7	0	0.0 (0.0; 0.1)	0
Bronchitis	17	0.2 (0.1; 0.4)	17	0	0.0 (0.0; 0.1)	0	10	0.3 (0.2; 0.6)	10	0	0.0 (0.0; 0.1)	0
Pneumonia viral	10	0.1 (0.1; 0.3)	11	0	0.0 (0.0; 0.1)	0	1	<0.1 (0.0; 0.2)	1	0	0.0 (0.0; 0.1)	0
Pharyngitis	10	0.1 (0.1; 0.3)	10	0	0.0 (0.0; 0.1)	0	0	0.0 (0.0; 0.1)	0	0	0.0 (0.0; 0.1)	0
Influenza	4	<0.1 (0.0; 0.1)	4	0	0.0 (0.0; 0.1)	0	5	0.2 (0.1; 0.4)	5	0	0.0 (0.0; 0.1)	0
Nervous system disorders*	28	0.4 (0.3; 0.6)	31	0	0.0 (0.0; 0.1)	0	2	<0.1 (0.0; 0.2)	2	0	0.0 (0.0; 0.1)	0
Febrile convulsion	25	0.4 (0.2; 0.5)	28	0	0.0 (0.0; 0.1)	0	2	<0.1 (0.0; 0.2)	2	0	0.0 (0.0; 0.1)	0
Gastrointestinal disorders†	18	0.3 (0.2; 0.4)	18	0	0.0 (0.0; 0.1)	0	6	0.2 (0.1; 0.4)	6	0	0.0 (0.0; 0.1)	0
Diarrhoea	8	0.1 (0.1; 0.2)	8	0	0.0 (0.0; 0.1)	0	0	0.0 (0.0; 0.1)	0	0	0.0 (0.0; 0.1)	0
Gastritis	8	0.1 (0.1; 0.2)	8	0	0.0 (0.0; 0.1)	0	4	0.1 (0.0; 0.3)	4	0	0.0 (0.0; 0.1)	0

N: number of participants who received the study vaccine; n: number of participants experiencing the endpoint; n SAEs: number of SAEs.
Group 1: participants received JE-CV as a primary vaccination; Group 2: participants received JE-CV as a booster vaccination. CI: Confidence interval; SAEs: serious adverse events.
* Nervous system disorders, other than febrile convulsions, included convulsion without fever (n = 1) and epilepsy (n = 2), which were reported only in Group 1.
† Gastrointestinal disorders, other than diarrhoea and gastritis, included enteritis (n = 1) and mouth ulceration (n = 1) in Group1; and dyspepsia (n = 1) and food poisoning (n = 1) in Group 2.

Table 3
Adverse events of special interests within 60 days after vaccine injection.

	Group 1 (N = 6851)			Group 2 (N = 3149)		
	n	% (95% CI)	Number of AESIs	n	% (95% CI)	Number of AESIs
Participants experiencing ⩾ 1:						
AESI	28	0.4 (0.3; 0.6)	31	4	0.1 (0.0; 0.3)	4
Nervous system disorder	28	0.4 (0.3; 0.6)	31	2	<0.1 (0.0; 0.2)	2
Febrile convulsion	25	0.4 (0.2; 0.5)	28	2	<0.1 (0.0; 0.2)	2
Convulsion	1	<0.1 (0.0; 0.1)	1	0	0.0 (0.0; 0.1)	0
Epilepsy	2	<0.1 (0.0; 0.1)	2	0	0.0 (0.0; 0.1)	0
Skin and subcutaneous tissue disorder	0	0.0 (0.0; 0.1)	0	2	<0.1 (0.0; 0.2)	2
Urticaria	0	0.0 (0.0; 0.1)	0	2	<0.1 (0.0; 0.2)	2

AESIs: adverse events of special interest; CI: Confidence interval; N: number of participants who received the study vaccine; n: number of participants experiencing the endpoint.
Group 1: participants received JE-CV as a primary vaccination; Group 2: participants received JE-CV as a booster vaccination.

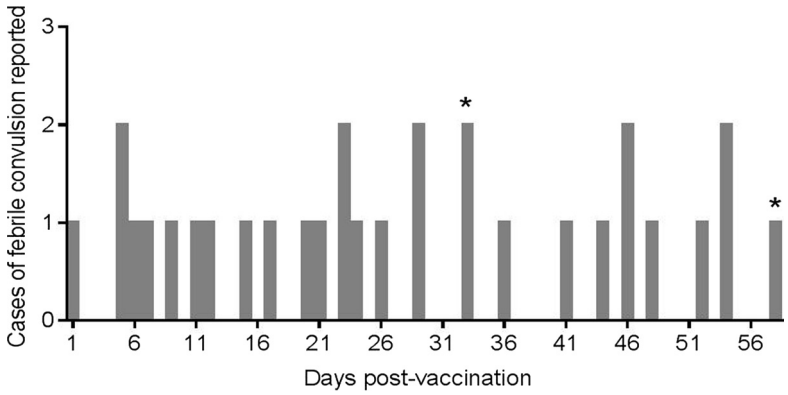

Fig. 1. Distribution of febrile convulsions by days post-vaccination. Data show the distribution of febrile convulsions in group 1 (28 events) and group 2 (2 events). *Group 2 events (33 and 58 days post-vaccination, respectively).

by 1 participant in Group 1, 49 days after vaccination. Severe (Grade 3) or serious (hospitalised) urticaria was reported by 2 participants in Group 2, with a latency of 24 and 28 days after vaccination, respectively. Two cases of epilepsy were reported during the study; both in Group 1, with a latency of 20 and 28 days after vaccination. No cases suggestive of vaccine-associated neurotropic or viscerotropic diseases were reported during the trial for either group.

One death was reported during the study but was not considered related to vaccination: a 24-month-old male participant developed fever, cough and runny nose and was diagnosed with pharyngitis 2 days after receiving JE-CV as a booster vaccination. Four days later the fever persisted and petechiae appeared. The participant was admitted to the hospital and diagnosed with acute myeloid leukaemia. The participant died from pulmonary haemorrhage 3 days after admission. Blood samples to assess

vaccine viraemia were not taken during hospitalisation and there were no remaining samples available for additional tests. An autopsy was not performed, as requested by the participant's family. High level abnormalities in blood counts discovered 6 days after vaccination suggested that the leukemia had been evolving for several weeks before vaccination.

4. Discussion

This phase IV post-marketing study was designed to further characterise the safety profile of JE-CV, with an objective of identifying any rare AEs. It is the largest study to date to assess the safety profile of JE-CV. Although the sample size of this study was large enough (n = 10,000) to detect rare events, no new risks were identified. Among 294 SAEs reported in 263 participants, only three cases of moderate urticaria reported in two participants were considered related to vaccination. Furthermore, no Grade 3 immediate systemic AEs were reported in the current study after vaccination with JE-CV as a primary dose or as a booster dose.

Since JE-CV is a chimeric vaccine with a YF17D vaccine virus backbone and antigenic determinants of a live, attenuated JE vaccine strain, we selected AESIs to be monitored in our study based on events that have already been reported following vaccination with licensed JE mouse-brain derived and YF17D vaccines, and events typically expected after vaccination with a live-attenuated vaccine. Events meeting AESI definitions were classified as such, irrespective of the relationship to the vaccine. In our study, overall rates of AESI were very low and no AESI was considered related to vaccination. The most frequently reported AESI was febrile convulsion, mainly following primary JE-CV vaccination. The rate of febrile convulsions (0.4%) in the current study following administration of JE-CV as a primary vaccination was similar to that observed in another study (0.3%) where JE-CV was administered as a primary dose to toddlers aged 12–18 months in Asia [10]. Post-marketing surveillance studies of other live attenuated JE vaccines reported similar rates of febrile convulsions (0.33%) [17] and urticaria (0.2%) [18], as observed in the current study. Febrile convulsions are also associated with other live and inactivated vaccines [19]. However, it should be noted that febrile convulsions are common in childhood in the absence of vaccination, affecting 2–5% of children less than 5 years of age, with a peak incidence at approximately 18 months of age [20]. Moreover, febrile convulsions have been reported to occur more frequently in children in Asian countries [20].

A total of two cases of epilepsy were reported during the study; both occurred in children less than 1 year of age. Although previous concerns of a possible association between vaccination and epileptic seizures have caused controversy in the literature, epidemiological evidence does not support a causal relationship between vaccination and childhood epilepsy [21,22]. The World Health Organization reports the incidence of epilepsy to be 25–840 cases per 100,000 children annually, with a higher incidence in developing countries than in industrialized countries [23]. Age-specific incidence of epilepsy is consistently high in the youngest age groups, with highest incidence occurring during the first year of life [24]. As the current trial included 10,000 participants followed for 2 months, the expected number of epilepsy cases derived from background incidence was between 0.4 and 14; therefore, the reported incidence of epilepsy in the current study is within the expected background range. In addition, the time to onset (20 days and 28 days for the two cases in our study) was beyond the usual risk window for AEs related to live attenuated vaccines.

One of the main strengths of the current study is its large sample size, enabling the detection of rare AEs with a frequency as low as 1/3333. In addition, all participants in our study were actively monitored to capture all serious adverse events, in contrast to some post-marketing studies that rely on voluntary reporting of events by patients and healthcare professionals. Our study included participants aged 9 months to <5 years of age living in Thailand, however, it is not known how generalisable our study findings are to other age groups and geographic locations. It should also be noted that, although unlikely in participants of a young age, we cannot rule out a possible impact of prior exposure to dengue virus or other flavivirus on the safety profiles observed for these children.

In conclusion, our study did not reveal any new safety concerns following primary or booster vaccination with JE-CV, confirming its good safety profile.

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Role of funding source

This study was sponsored by Sanofi Pasteur. The sponsor participated in all operational aspects of the study, including data collection, statistical analyses, and writing of this report.

Competing interests

AT, CP, CT, OP, PKe, PO, PP, ST, TC and TP have no competing interests. GH, JK and SC are employees of Sanofi Pasteur. PKo was supported by Sanofi Pasteur to attend the "Conference on Encephalitis" in Siem Reap, Cambodia, February 2015.

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