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Immunogenicity and safety of a single dose of a live attenuated Japanese encephalitis chimeric virus vaccine in Vietnam: A single-arm, single-center study

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ABSTRACT

Objective: To describe the immunogenicity and safety of the Japanese encephalitis chimeric virus vaccine (JE-CV) in children and adults in Vietnam.
Methods: In this prospective, open-label, single-center, single-arm study, 250 healthy participants aged 9 months to 60 years received a single dose of JE-CV (IMOJEV®). JE neutralizing antibody titers were assessed at baseline and 28 days after vaccination using the 50% plaque reduction neutralization test ($PRNT_{50}$). Safety and reactogenicity were assessed through solicited and unsolicited adverse events.
Findings: Seroconversion (titer ≥10 [1/dil] in participants JE seronegative [titer <10] at baseline [per protocol analysis], or a 4-fold rise from a baseline titer ≥10) and seroprotection (titer ≥10 [1/dil]) rates 28 days after vaccination were both 98.5% (132/134) in the per protocol analysis, and 82.4% (201/244) and 98.8% (242/245), respectively, in the full analysis set. Geometric mean titers (GMTs) increased in all age groups from Day 0 to Day 28; Day 28/Day 0 GMT ratios were 55.3 (95% confidence interval [CI] 38.4–79.8), 348 (95% CI 211–572), 296 (95% CI 152–576) and 194 (95% CI 13.1–2870) in those aged 9 months to 4 years, 5–11 years, 12–17 years and 18–60 years, respectively, in the per protocol analysis. There were no safety concerns during the study.
Conclusion: A single dose of JE-CV in children and adults aged 9 months to 60 years in Vietnam elicited a protective immune response and was well tolerated with no safety concerns.
Registered at www.clinicaltrials.gov (NCT02492165).

Introduction

Japanese encephalitis (JE) virus is a mosquito-borne flavivirus epidemic and endemic in a number of countries across Asia and the Western Pacific region; including India, Indonesia, Thailand and Vietnam (Wang and Liang, 2015). Patients with JE present with high fever, and a range of neurological disorders including: coma, seizures and spastic paralysis (Solomon et al., 2000). Mortality from symptomatic JE can be as high as 10–40%, and a large proportion of those who survive suffer from a range of neurological sequelae (Solomon et al., 2000; Sarkari et al., 2012; Hills et al., 2010). An estimated 67,900 clinical cases of JE occur annually in JE-endemic countries, leading to an estimated 13,600–20,400 associated deaths (Campbell et al., 2011).

JE has been recognized as a public health concern in Vietnam since the first reports of JE epidemics in the 1960s and 1970s (Okuno, 1978). Estimated rates for acute encephalitis syndrome (surrogate used for JE surveillance) of 1–8 cases per 100,000 population were reported between 1985 and 1993 (Yen et al., 2010). In 1997, the JE immunization program was launched in Vietnam using locally produced, inactivated mouse brain-derived vaccine (MBDV) initially targeting children 1–5 years old in high-risk areas (Marks et al., 2012), and subsequently expanded nationwide (Yen et al., 2010). JE surveillance data in Vietnam between 1998 and 2007 showed a decreasing trend in the incidence of acute encephalitis during this period, with a mean annual incidence of 2.4 cases per 100,000 population and a case-fatality rate of 3.8% (Yen et al., 2010). In 2006, the World Health

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Organization (WHO) recommended the gradual replacement of MBDV with new generation JE vaccines due to safety concerns (World Health Organization, 2006).

A live attenuated JE chimeric vaccine (JE-CV; IMOJEV®; Sanofi Pasteur) has been developed for protection against JE. The safety and immunogenicity of primary vaccination with a single-dose JE-CV has been demonstrated in toddlers, children and adults in several endemic and epidemic areas (Chokephaibulkit et al., 2010; Feroldi et al., 2012, 2014; Kim et al., 2014; Chotpitayasunondh et al., 2017; Huang et al., 2014). A single-dose JE-CV provides long-term protection that persists for at least 5 years in children (Chokephaibulkit et al., 2016; Kosalaraksa et al., 2016). The vaccine was initially licensed in Australia in 2010, and is now available or approved in a number of countries in South East Asia. The present study investigated the safety profile and immunogenicity of a single dose of JE-CV in healthy participants aged 9 months to 60 years in Vietnam as part of the registration requirements for this country.

Methods

Study design

This study was a prospective, open-label, single-center, single-arm study, of a single dose of JE-CV in healthy children and adults in Vietnam (www.clinicaltrials.gov; NCT02492165). The study was conducted between 27 June and 24 August 2015, in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. The study protocol was approved by the National Institute of Hygiene and Epidemiology Institutional Review Board/Independent Ethics Committee, and the Ministry of Health Ethics Committee, Vietnam. A signed informed consent form was obtained from each participant aged ≥18 years. For participants aged <18 years, the informed consent form was signed by a parent or legal representative; participants aged 12–17 years were additionally required to sign the informed consent form, and those aged 8–11 years were additionally asked to sign an assent form.

Participants

Healthy participants aged 9 months to 60 years were eligible for inclusion. Exclusion criteria included: pregnancy, lactating or of childbearing potential (non-childbearing potential included use of an effective method of contraception or abstinence for at least 4 weeks before and after study vaccination); vaccination against flavivirus disease including JE, dengue and yellow fever; or receipt of any vaccines in the previous 4 weeks, or planned in the 4 weeks following study vaccination. Other main exclusion criteria included: simultaneous participation in another trial investigating a vaccine, drug or medical procedure/device; receipt of blood, or blood-derived products in the past 3 months; known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy within the preceding 6 months, or long-term systemic corticosteroids therapy (for more than 2 consecutive weeks within the 4 weeks preceding vaccination); known or suspected systemic hypersensitivity to any of the vaccine components; history of flavivirus infection confirmed either clinically, serologically or microbiologically; history of central nervous system disorder or disease, including seizures.

Vaccine and procedures

JE-CV (IMOJEV®, Sanofi Pasteur, Government Pharmaceutical Organization — Mérieux Biological Products Co., Ltd., [GPO-MBP], Thailand) was presented as a powder and reconstituted in 0.4% sodium chloride solution immediately before use. Each 0.5 mL dose of vaccine contained between 4.0 and 5.8 $\log_{10}$ plaque forming units of lyophilized virus. Participants received one subcutaneous injection of JE-CV on the day of inclusion (Day 0), into the upper arm. Participants or their parents/guardians received a phone call on Days 1 and 2, and a home visit on Days 3 and 8. Blood samples for immunogenicity were taken on Day 0, before vaccination, and on Day 28.

Immunogenicity assessments and outcomes

JE neutralizing antibody titers were assessed at Day 0 and Day 28 by a JE-CV 50% plaque reduction neutralization assay ($PRNT_{50}$) in Vero cells using 2-fold serial dilutions of serum to be tested and constant challenge dose of JE-CV virus (Focus Diagnostics Inc., San Juan Capistrano, CA, USA), as previously described by Kim et al. (Kim et al., 2014). In brief, the virus-serum test mixtures were incubated at 2–8 °C in 5% CO_2 for 16–20 h to allow neutralization to occur and subsequently inoculated into wells of a 24-well plate of confluent Vero cells and incubated at 37 °C in 5% CO_2 for 1 h. The cell monolayers were then overlaid with methyl cellulose medium, incubated for 5 days and stained with crystal violet/formaldehyde solution. JE-CV infected cells were indicated by the formation of viral plaques that appeared as clear spots on a violet background. The neutralizing antibody (Ab) titer was calculated and expressed as the reciprocal serum dilution reducing the mean plaque count by 50% as compared with mean virus plaque number in the negative control (100% virus load). The assay had a lower limit of quantification titer of 10 (1/dilution). Internal quality control samples, consisting of samples with high, medium or low titers against JE-CV were utilized from serum collected after JE immunization, or a negative control sample from serum collected from JE naïve donors from a non-endemic region (USA).

Immunogenicity outcomes were summarized using geometric mean titers (GMTs) and by seroconversion and seroprotection rates. Seroconversion at Day 28 was defined as JE virus neutralizing antibody titer ≥10 (1/dil) in participants considered seronegative (titer <10 [1/dil]) at baseline, or a ≥4-fold increase in neutralizing antibody titers in participants seropositive (titer ≥10 [1/dil]) at baseline. Seroprotection was defined as JE-CV neutralizing antibody titers ≥10 [1/dil] (Hombach et al., 2005). GMT ratios (Day 28/Day 0) were also calculated.

Reactogenicity and safety

Participants were observed for 30 min after vaccination to record any immediate adverse events (AEs). Participants or their parents/guardians were provided with diary cards, a flexible ruler and a digital thermometer to record any solicited injection site and systemic reactions. The occurrence and intensity of solicited reactions (prelisted in the participants' diary card and case report form [CRF]) were recorded; injection site reactions (pain, tenderness, erythema and swelling) up to 7 days post-vaccination, and solicited systemic reactions (fever, headache, malaise, myalgia, vomiting, abnormal crying, drowsiness, appetite loss and irritability) up to 14 days post-vaccination.

Unsolicited AEs, including serious AEs (SAEs), were recorded up to 28 days post-vaccination. For each unsolicited AE, study investigators assessed the causal relationship with vaccination and rated seriousness. Unsolicited, non-serious AEs were classified based on the following intensity scale: no interference with activity (Grade 1), some interference with activity (Grade 2) and significant interference that prevents daily activity (Grade 3). All injection site AEs (solicited and unsolicited) and all solicited systemic reactions were considered to be related to vaccination. AEs of special interest (AESI), including hypersensitivity/allergic

reactions, neurological events (including febrile convulsions) and vaccine failure were recorded up to 28 days post-vaccination. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

Statistical analyses

The number of participants enrolled was designed to provide supportive immunogenicity and safety data on the study vaccine when administered as a single dose. A sample size of 250 participants was chosen as this would allow for 225 evaluable participants, with a projected attrition rate of 10%. This sample size would provide 99% power in a one-sided test for non-inferiority with alpha = 0.025 and a 10% clinical non-inferiority margin (Hombach et al., 2005), assuming an underlying seroprotection rate of 94.9% as determined in a large-scale study of JE-CV conducted in 1199 healthy children aged 12–18 months in Thailand and the Philippines (JEC02) (Feroldi et al., 2012). The number of evaluable participants (n = 225) allowed for the detection of adverse events occurring with a frequency of 1.3% or more, at 95% probability, using the rule of three. Power calculations were made for the overall population.

Statistical analyses were performed mainly by age groups: 9 months to 4 years, 5–11 years, 12–17 years and 18–60 years. Immunogenicity analyses were performed on the per protocol (PPS) and full analysis (FAS) sets. Participants included in the PPS were those who: met all inclusion criteria and none of the exclusion criteria, were JE seronegative at baseline, had received JE-CV, had blood samples taken as per-protocol, had valid immunogenicity results and did not receive a protocol-restricted therapy, vaccination or medication during the study. The FAS consisted of all participants who received a dose of JE-CV. Safety analyses were performed on all participants (safety analysis set; SAS) who received a dose of JE-CV and who were assessed for the corresponding safety endpoint (the 9 months to 4 years group was divided into 9–23 months and 2–4 years for the safety analyses, to comply with internal safety guidelines).

Immunogenicity and safety analyses were descriptive with no hypothesis testing. The 95% confidence intervals (CIs) for point estimates were calculated using the exact binomial method (Clopper-Pearson method) (Newcombe, 1998). JE virus neutralizing antibody titers and corresponding 95% CI were calculated on Log_{10} transformed PRNT titers assuming normal distribution for the transformed data, with antilog transformations applied to provide GMTs and their 95% CI on the original scale.

Non-inferiority of the seroprotection rate obtained in this study was tested against the seroprotection rate observed in the large scale JEC02 study in children in Thailand and the Philippines (Feroldi et al., 2012). Non-inferiority was established if the lower limit of the 95% CI for the Day 28 seroprotection rate observed in the current study was higher than the reference value (seroprotection rate observed 28 days post-vaccination in the JEC02 study) minus the clinically acceptable limit for non-inferiority (10%, one-sided equivalence test, alpha = 0.025).

Results

Study population

Two-hundred and fifty participants were enrolled and vaccinated with a single dose of JE-CV; 100 aged 9 months to 4 years, 60 aged 5–11 years, 60 aged 12–17 years and 30 aged 18–60 years (Table 1). The PPS comprised of 134 participants; of the 116 participants who were not included in the PPS, the most common reason for exclusion was JE seropositivity at baseline (110/116 participants), five participants had serology samples that did not provide valid results, one did not meet the inclusion criteria and one did not have a blood sample taken 28 days post-vaccination. In the FAS 109/250 (43.6%) participants were male, the proportion of males in each age group decreased with increasing age; this trend was also observed for the PPS (Table 1). Mean age was higher in the FAS than in the PPS (10.3 vs. 5.9 years) (Table 1). One participant (in the 5–11 years group) did not attend the Day 28 visit due to voluntary withdrawal from the study, but had complied with all safety assessments.

Immunogenicity

By definition, no participants in the PPS were JE seropositive at baseline. By Day 28 of the study 132/134 (98.5%) participants in the PPS had seroconverted; seroconversion and seroprotection rates by age group are shown in Table 2; the two participants who had not seroconverted were in the youngest age group (aged 17 and 19 months). In the FAS, 110/250 (44%) participants were JE seropositive at baseline; the percentage of those seropositive at baseline increased with increasing age, from 20.0% among the 9 months to 4 years group to 83.3% in the 18–60 years group (Table 2). Seroconversion rates in the FAS at Day 28 decreased with age, from 93.8% (90/96) in the 9 months to 4 years group to 50% (15/30) in the 18–60 years group; however, all participants, except three from the 9 months to 4 years group, had titers $\geq$10 (1/dil) at Day 28.

At baseline GMTs were below the lower limit of quantification (LLOQ) for all participants in the PPS, and increased with increasing age in the FAS. In both the PPS and FAS GMTs increased from baseline to Day 28, and were lowest in the youngest age groups (Table 3). GMT ratios were also highest in the youngest age group, 9 months to 4 years, in both the PPS and FAS. Seroprotection rates in the PPS of this study (98.5% [95% CI 94.7–99.8]) and in the JEC02

Table 1
Baseline characteristics of participants.

	9 months–4 years	5–11 years	12–17 years	18–60 years	Overall
Per protocol analysis set					
Gender, n (%)					
Male	42/76 (55.3)	16/34 (47.1)	7/19 (36.8)	1/5 (20.0)	66/134 (49.3)
Age (years)					
Mean (SD)	0.7 (0.7)	8.7 (1.5)	13.8 (1.3)	35.2 (7.0)	5.9 (7.8)
Full analysis set					
Gender, n (%)					
Male	54/100 (54.0)	29/60 (48.3)	18/60 (30.0)	8/30 (26.7)	109/250 (43.6)
Age (years)					
Mean (SD)	0.7 (0.6)	8.7 (1.5)	13.9 (1.4)	38.7 (10.0)	10.3 (12.3)

n, number of participants with characteristic; SD, standard deviation.

Table 2
Seroprotection and seroconversion rates pre- and post-vaccination with JE-CV.

	9 months–4 years		5–11 years		12–17 years		18–60 years	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
Per protocol analysis set								
Seroprotection on Day 0	0/76 (0.0)	0.0–4.7	0/34 (0.0)	0.0–10.3	0/19 (0.0)	(0.0–17.6)	0/5 (0.0)	0.0–52.2
Seroprotection on Day 28	74/76 (97.4)	90.8–99.7	34/34 (100.0)	89.7–100.0	19/19 (100.0)	(82.4–100.0)	5/5 (100.0)	47.8–100.0
Seroconversion Day 28	74/76 (97.4)	90.8–99.7	34/34 (100.0)	89.7–100.0	19/19 (100.0)	(82.4–100.0)	5/5 (100.0)	47.8–100.0
Full analysis set								
Seroprotection on Day 0	20/100 (20.0)	12.7–29.2	25/60 (41.7)	29.1–55.1	40/59 (67.8)	(54.4–79.4)	25/30 (83.3)	65.3–94.4
Seroprotection on Day 28	93/96 (96.9)	91.1–99.4	59/59 (100.0)	93.9–100.0	60/60 (100.0)	(94.0–100.0)	30/30 (100.0)	88.4–100.0
Seroconversion Day 28	90/96 (93.8)	86.9–97.7	51/59 (86.4)	75.0–94.0	45/59 (76.3)	(63.4–86.4)	15/30 (50.0)	31.3–68.7

JE-CV, Japanese encephalitis chimeric virus vaccine; n, number of participants experiencing the endpoint; N, number of participants with available data; CI, confidence interval.
Seroprotection against JE was defined by JE-CV neutralizing antibody titers ≥10 (1/dil).
Seroconversion was defined by JE virus neutralizing antibody titers ≥10 (1/dil) in participants considered seronegative (<10 [1/dil]) at baseline, or a ≥4-fold increase in neutralizing antibody titers in participants observed to be seropositive at baseline.

Table 3
Geometric mean titers for anti-JE antibodies pre- and post-vaccination in the per protocol analysis and full analysis sets.

	9 months–4 years			5–11 years			12–17 years			18–60 years		
	n	GMT	95% CI	n	GMT	95% CI	n	GMT	95% CI	n	GMT	95% CI
Per protocol analysis set												
Pre-vaccination, Day 0	76	5.00	5.00–5.00	34	5.00	5.00–5.00	19	5.00	5.00–5.00	5	5.00	5.00–5.00
Post-vaccination, Day 28	76	277	192–399	34	1738	1055–2862	19	1481	762–2878	5	970	65.6–14,352
Day 28/Day 0	76	55.3	38.4–79.8	34	348	211–572	19	296	152–576	5	194	13.1–2870
Full analysis set												
Pre-vaccination, Day 0	100	9.08	6.77–12.2	60	26.7	14.8–48.3	59	92.1	48.7–174	30	474	199–1128
Post-vaccination, Day 28	96	344	238–498	59	2276	1596–3247	60	2128	1571–2883	30	1796	1055–2965
Day 28/Day 0	96	37.0	25.8–52.9	59	82.9	44.2–155	59	23.0	12.6–42.3	30	3.73	1.65–8.42

JE, Japanese encephalitis; n, number of participants with available data; GMT, geometric mean titer; CI, confidence interval.

Table 4
Safety overview by age group within 28 days after vaccine injection (safety analysis set).

	≤23 months (n = 94)		2–4 years (n = 6)		5–11 years (n = 60)		12–17 years (n = 60)		18–60 years (n = 30)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Immediate unsolicited AE[a]	0 (0.0)[b]	0.0–3.8[b]	0 (0.0)	0.0–45.9	0 (0.0)	0.0–6.0	0 (0.0)	0.0–6.0	0 (0.0)	0.0–11.6
Solicited reaction	63 (67)	56.6–76.4	2 (33.3)	4.3–77.7	21 (35.0)	23.1–48.4	28 (46.7)	33.7–60.0	15 (50.0)	31.3–68.7
Injection site reactions[c]	34 (36.2)	26.5–46.7	1 (16.7)	0.4–64.1	9 (15.0)	7.1–26.6	11 (18.3)	9.5–30.4	8 (26.7)	12.3–45.9
Injection site tenderness/pain	34 (36.2)	26.5–46.7	1 (16.7)	0.4–64.1	8 (13.3)	5.9–24.6	11 (18.3)	9.5–30.4	8 (26.7)	12.3–45.9
Injection site erythema	6 (6.4)	2.4–13.4	0 (0.0)	0.0–45.9	3 (5.0)	1.0–13.9	0 (0.0)	0.0–6.0	0 (0.0)	0.0–11.6
Injection site swelling	1 (1.1)	0.0–5.8	0 (0.0)	0.0–45.9	1 (1.7)	0.0–8.9	0 (0.0)	0.0–6.0	0 (0.0)	0.0–11.6
Systemic reactions[d]	49 (52.1)	41.6–62.5	2 (33.3)	4.3–77.7	16 (26.7)	16.1–39.7	23 (38.3)	26.1–51.8	12 (40.0)	22.7–59.4
Fever	14 (14.9)	8.4–23.7	2 (33.3)	4.3–77.7	7 (11.7)	4.8–22.6	2 (3.3)	0.4–11.5	1 (3.3)	0.1–17.2
Vomiting	12 (12.8)	6.8–21.2	–	–	–	–	–	–	–	–
Abnormal crying	20 (21.3)	13.5–30.9	–	–	–	–	–	–	–	–
Drowsiness	12 (12.8)	6.8–21.2	–	–	–	–	–	–	–	–
Appetite loss	38 (40.4)	30.4–51.0	–	–	–	–	–	–	–	–
Irritability	21 (22.3)	14.4–32.1	–	–	–	–	–	–	–	–
Headache	–	–	0 (0.0)	0.0–45.9	9 (15.0)	7.1–26.6	14 (23.3)	13.4–36.0	10 (33.3)	17.3–52.8
Malaise	–	–	1 (16.7)	0.4–64.1	8 (13.3)	5.9–24.6	16 (26.7)	16.1–39.7	9 (30.0)	14.7–49.4
Myalgia	–	–	0 (0.0)	0.0–45.9	5 (8.3)	2.8–18.4	9 (15.0)	7.1–26.6	5 (16.7)	5.6–34.7
Unsolicited AE	22 (23.4)	15.3–33.3	1 (16.7)	0.4–64.1	5 (8.3)	2.8–18.4	2 (3.3)	0.4–11.5	1 (3.3)	0.1–17.2
Unsolicited AR	0 (0.0)	0.0–3.8	1 (16.7)	0.4–64.1	0 (0.0)	0.0–6.0	0 (0.0)	0.0–6.0	0 (0.0)	0.0–11.6
AE leading to study discontinuation	0 (0.0)	0.0–3.8	0 (0.0)	0.0–45.9	0 (0.0)	0.0–6.0	0 (0.0)	0.0–6.0	0 (0.0)	0.0–11.6
SAE	1 (1.1)	0.0–5.8	0 (0.0)	0.0–45.9	0 (0.0)	0.0–6.0	1 (1.7)	0.0–8.9	0 (0.0)	0.0–11.6

n, number of participants experiencing at least one of the AEs specified; CI, confidence interval; AE, adverse event; AR, adverse reaction; SAE, serious adverse event.
[a] Occurring within 30 min of vaccination.
[b] After database lock and statistical analysis, 2 unsolicited AEs for a participant in the ≤23 months age group were reported as immediate AEs when they actually occurred approximately 7 h after vaccination.
[c] Collected daily over 7 days after vaccination.
[d] Collected daily over 14 days after vaccination.

study (94.9% [95% CI 93.2–96.3]) (Feroldi et al., 2012) were both high, and the non-inferiority criterion was met. Similar results for non-inferiority were found in the FAS (data not shown).

Safety

Safety data are summarized in Table 4. There were no immediate AEs reported within 30 min of injection. There were no deaths or withdrawals from the study due to AEs. Over 28 days of the study two SAEs were reported, dermatitis and syncope, but were considered unrelated to the vaccine and did not result in discontinuation. No AESI were reported.

Solicited injection site and systemic reactions were most frequently reported in the 9–23 months age group. Pain (or tenderness, for those in the 9–23 months group) was the most frequently reported injection site reaction across all age groups. All solicited injection site reactions were Grade 1, except for Grade 2 pain/tenderness in two participants in both the 9–23 months and the 12–17 years age groups. The most frequently reported systemic reactions were appetite loss for the 9–23 months group (40.4%), fever for the 2–4 years group (33.3%), headache for the 5–11 years group (15.0%), malaise for the 12–17 years group (26.7%) and headache for the 18–60 years group (33.3%). Most solicited systemic reactions were Grade 1; Grade 3 reactions were reported for three participants in the 9–23 months age group (two cases of fever and one appetite loss) and one participant in the 5–11 years age group (fever).

Unsolicited AEs up to 28 days after vaccination were also most frequently reported in the 9–23 months group. All unsolicited non-serious AEs were Grade 1 or Grade 2. No unsolicited AEs were considered to be related to the vaccination, except one Grade 1 diarrhea case.

Discussion

This study demonstrates that a single dose of JE-CV elicits a high protective immune response, irrespective of baseline JE serostatus, and is well tolerated in Vietnamese children and adults aged 9 months to 60 years. The immunogenicity and safety profile observed in the current study are consistent with those reported in other studies with JE-CV in children in other endemic Asian countries (Thailand, the Phillipines, Taiwan and the Republic of Korea) (Chokephaibulkit et al., 2010; Feroldi et al., 2012; Kim et al., 2014; Chotpitayasunondh et al., 2017; Huang et al., 2014) and in adults in non-endemic settings (USA and Australia) (Nasveld et al., 2010; Torresi et al., 2010). Long-term studies have shown that the majority of JE-CV recipients remain protected for up to 5 years after a single primary dose (Chokephaibulkit et al., 2016; Kosalaraksa et al., 2016).

In this study, a large number of participants were seropositive for JE at Day 0 (44% of the FAS) and limited the number of participants eligible for the PPS. It was particularly high for those in the older age groups (83% of those in the 18–60 years group), which is probably due to high levels of natural exposure to the JE virus in North Vietnam. Previous studies of JE-CV in endemic and epidemic countries have seen baseline seropositivity for JE in vaccination-naïve children and toddlers of between 2 and 15%, attributed to natural infection and residual maternal antibodies (Chokephaibulkit et al., 2010; Feroldi et al., 2012, 2013, 2014; Kim et al., 2014); in this study 20% of the 9 months to 4 years group were JE seropositive. JE-CV elicited a robust antibody response regardless of baseline JE serostatus, with almost all FAS participants (242/245) having seroprotective levels of antibody titers post-vaccination.

We also retrospectively demonstrated the non-inferiority of the immune response in a Vietnamese population in terms of seroprotection versus that previously observed in a large immunogenicity study conducted in children in Thailand and the Philippines (JEC02) (Feroldi et al., 2012), confirming the robustness of our results in a relatively small study population.

Although we have presented the immunogenicity and safety data by age subgroups, this study was not powered for subgroup analysis since the analysis performed on subgroups was descriptive only, and no retrospective power calculation was undertaken. No new safety concerns were identified with JE-CV in our study. The safety results support those from other JE-CV studies, which have also demonstrated a good safety profile when administered as a single dose to toddlers and children in other endemic Asian countries (Chokephaibulkit et al., 2010; Feroldi et al., 2014; Kim et al., 2014) and adults in non-endemic countries (Nasveld et al., 2010; Torresi et al., 2010), and as a booster dose in children following primary vaccination with JE-CV or other JE vaccines (Chokephaibulkit et al., 2010, 2016; Chotpitayasunondh et al., 2017; Kosalaraksa et al., 2016; Feroldi et al., 2013; Janewongwirot et al., 2016). In this study AEs most frequently occurred in the youngest age group, 9 months to 2 years, when compared to the older age groups. However, as this was a single-arm study these data may reflect age-related background rates for these events.

In conclusion, a single dose of JE-CV elicited a protective immune response in toddlers, children and adults aged 9 months to 60 years in Vietnam. All but three participants were seroprotected at Day 28, and the vaccination was well tolerated with no safety concerns. The results obtained in this study align with similar studies of single-dose JE-CV conducted in other JE endemic countries.

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Competing interests

NDQ, employee of National Institute of Hygiene and Epidemiology, Vietnam, and TTAH, employee of Hoa Binh Provincial Preventive Medicine Centre, Hoa Binh Province, Vietnam, declare no conflict of interest. VDT, employee of National Institute of Hygiene and Epidemiology, Vietnam, received funding from Sanofi Pasteur to conduct the study and present the study findings at the National Foundation for Infectious Diseases 20th Annual Conference on Vaccine Research. VBC, CZ and GH are employees of Sanofi Pasteur.

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VDT, VBC, CZ, and GH participated in the design of the study; VDT, NDQ, and TTAH were involved in data acquisition; VBC, CZ, and GH were involved in data analysis. All authors contributed to the critical revision of the manuscript, final approval and are responsible for the accuracy and integrity of the manuscript.

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