Immunizing Children Aged 9 to 15 Months with Live Attenuated SA14-14-2 Japanese Encephalitis Vaccine in Thailand

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The authors aimed to evaluate the safety and immunogenicity of a live attenuated SA14-14-2 Japanese Encephalitis (JE) vaccine in healthy Thai infants. One hundred and fifty subjects aged 9-15 months were vaccinated with one dose of this vaccine. Regarding the vaccine safety, during the 28-day post-vaccination follow-up, no vaccine-related serious adverse events were reported. In terms of immunogenicity, the sero-conversion rate of a single dose vaccination was 95% (95% CI, 90.0-97.6%) within 90 days after vaccination and the geometric mean titer (GMT) was 66.1. Eight subjects with JE sero-negative on days 28-35 post-vaccination became sero-positive on day 90. Seven subjects who remained sero-negative during days 28-35 and day 90 post-vaccination were successfully sero-converted after receiving a second dose 3 months later. Thus, two doses of this JE vaccine resulted in a 100% (95% CI, 97.3-100%) sero-conversion rate with the GMT of 260.8. Eight children with GMTs lower than protective level after a single vaccination demonstrated a booster response with GMT of 1237 after the second dose of JE vaccination.

In conclusion, the live attenuated SA14-14-2 vaccine was safe, well tolerated and highly immunogenic with 95% and 100% sero-conversion rate after one and two doses, respectively. Nevertheless, its long-term immune response and possible influences from natural dengue infection requires further evaluation.

Keywords: *Japanese encephalitis, Vaccine, Immunogenicity*

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Japanese encephalitis (JE) is the leading recognized cause of childhood viral encephalitis in Asia. Over 50,000 cases with a case-fatality ratio of 5-35% are estimated to occur annually in this region[1,2]. Japan, Taiwan and Korea have used an inactivated, mouse brain-derived vaccine in their national JE vaccination programs and have been successful in controlling the disease. In other Asian countries, however, the expense and complexity of producing the vaccine with the requirement of having numerous doses in stock have limited its implementation. Typically, 2-3 doses of inactivated mouse brain-derived vaccine are given in the primary JE immunization series, followed by booster doses to maintain immunity[2]. In addition to the limitations posed by multiple doses, as the vaccine has been introduced elsewhere to protect travelers, a high rate of hypersensitivity events has been reported among vaccine recipients in North America, Europe and Australia[2-4].

A live-attenuated JE vaccine made from the SA14-14-2 strain was developed in China. For more than two decades since its licensing in 1988, this live JE vaccine has been safely distributed to more than 100 million children[2]. The vaccine given to infants

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over one year in annual spring campaigns was 98% effective when two doses were administered[5]. The immunogenitic study for Korean children showed that a single primary immunization dose of SA14-14-2 vaccine produced neutralizing antibodies in 96% of the subjects and the geometric mean titer (GMT) was 188[6]. The efficacy of SA14-14-2 vaccine was also demonstrated in Nepal, as a single dose of SA14-14-2 vaccine provided 98.5% protection at one year after vaccination and 96.2% at five years after immunization[8,9]. Here, we conducted an open-label study of immunogenicity, safety, tolerability and possible interference in the immune response to a single dose of SA14-14-2 vaccine in healthy Thai infants.

Material and Method

Vaccines

One lot (Lot. No. 200512A085-2) of SA14-14-2 vaccine (CD. JEVAXTM) produced by the Chengdu Institute of Biological Products, Chengdu, China was used in the present study. Its respective virus titer was 6.10 log PFU/0.5 ml.

Study design and procedures

One hundred and fifty healthy Thai infants aged 9-15 months recruited at the Queen Sirikit National Institute of Child Health (study center), Bangkok, Thailand, were enrolled in the present study from March 6 to December 6, 2006. Exclusion criteria were as follows: had received JE vaccine or any other vaccine within 30 days before enrollment; known allergy to any component of this vaccine; had fever > 37.5°c on day of enrollment; had received blood or blood product transfusion within 3 months prior enrollment, had any chronic medical illness, immuno compromised condition and received systemic steroid therapy; had any medical condition resulting in physician's (investigator's) decision not to enroll because of a safety reason; and known HIV infection. The present study was approved by the ethics committees (EC) of the study center (EC approval No. 82/2548). Written informed consent was obtained from the parents/guardians of all infants before enrollment.

Vaccines were given as 0.5-mL subcutaneous injections into the deltoid muscle. Participants were monitored by study staff for 30 minutes after each injection. Parents were asked to record daily temperatures for 7 days, injection site reactions and systemic adverse events for 28 days post-vaccination in a standardized symptom diary card. Solicited adverse events were measured (fever, erythema, swelling) and categorized as absent, mild, moderate, or severe. Any serious adverse events (SAEs) within 28 days after each vaccination were recorded and reported immediately to the investigator.

Serum samples for JE neutralizing antibody were obtained prior to vaccination (Day 0) and 4-5 weeks (28-35 days) after vaccination. The JE neutralizing antibodies were measured through a plaque reduction neutralization test (PRNT).

All participants who failed to seroconvert (as determined by a titer < 1: 10 by JE PRNT test) were offered the second dose at 3 months after the first dose. Clinical and immunogenetic assessment for the subsequent injections was identical to those of the first dose.

Plaque reduction antibody test

Separated sera were kept under -20°C before testing. The assay was performed according to the method described by Russell et al[10]. The plaque count was determined by using LLC-MK_2 plaque assay single overlay technique. The sera were thawed, diluted and heat-inactivated by incubation at 56°C for 30 minutes. Then, serial four-fold dilutions of serum were made (1: 10, 1: 40 and 1: 160). To contain about 40-50 PFU well, an equal volume of diluted JE virus, Beijing and SA14-14-2 vaccine strain was added to each serum dilution tube. Following incubation at 37°C for 60 minutes, 0.2 ml was removed from each tube and inoculated onto triplicate 6-well plates of confluent LLC-MK_2. Each plate was incubated at 37°C for 90 minutes and monolayers were then overlaid with 4 ml of 3.5% Carboxy Methyl Cellulose/MEM. Finally the plates were incubated at 37°C with 5% CO_2 for 7 days. Plaques were counted and the 50% plaque reduction neutralization titers ($PRNT_{50}$) were determined. The neutralization endpoint in the protocol was a 50% reduction in the plaque formation. Antibody titer above 1:10 was considered positive and protective[11].

Data analysis

The sero-conversion rate and GMT were summarized with the result of PRNT and the corresponding confidence interval was calculated through an interactive procedure based on the binomial probability distribution. The primary endpoint determination of the present study was the proportion of subjects showing sero-conversion for the JE. Sero-conversion was defined as a 50 % reduction in the PRNT at a > 1: 10 serum dilution ($PRNT_{50}$), or a four-fold increase in the JE neutralizing antibody titer if the

subject was JE sero-positive prior to vaccination. The secondary endpoint for immunogenicity was the GMT of JE neutralizing antibody. In addition, local or general adverse events were expressed in percentage as well as number for each reaction. SPSS for Windows version 15.0 (Illinois, Chicago: SPSS Inc, 2006) software was used for statistical analysis.

Results

The reactogenetic analysis was performed on all 150 subjects (males 81, females 69; mean age 10.6 months ± 1.7) (Table 1), whereas the immunogenetic analysis was conducted on 148 subjects as two dropped out due to family relocation. Of the 148 subjects, 140 subjects were sero-negative for antibodies against JE and dengue (PRNT for JE and dengue antibodies was less than 1: 10) before vaccination. Four subjects had antibodies against only dengue virus and another four subjects had antibodies against both JE and dengue viruses before vaccination.

Reactogenicity

A 28-day follow-up for clinical signs and symptoms showed that the SA14-14-2 vaccine was well tolerated. The majority of reported signs and symptoms was mild and of short duration. No serious adverse events were vaccine-related, and no parents withdrew their child from the present study due to a vaccine-related side effect. Less than 3% of vaccines reported signs and/or symptoms at the injection site. Redness was the most frequent local reaction. It would typically start on the first day of vaccination and last until one day after vaccination, causing no functional limitation of the arm. The most frequently reported systemic symptoms were cough (16.0%), runny nose (10.7%) and low-grade fever (9.3%), as shown in Tables 2-1. Six serious adverse events (SAE) occurred during the 28-day post-vaccination period. Six cases who were hospitalized during this period included upper respiratory tract infection with acute diarrhea (1), acute bronchitis (1), acute asthmatic attack (1), pneumonia (2) and pharyngitis (1). All of them recovered completely. These SAEs were common illnesses in this age group and were not considered to be related to vaccination.

Among the eight subjects with dengue pre-existing antibody during pre-vaccination (Day 0), there was no local reaction following the SA-14-14-2 vaccination. There was no significant difference of systematic reactions, (except for vomiting) between the subjects with dengue antibody positive and dengue antibody negative at pre-vaccination (Table 2-2). No subjects with pre-existing dengue antibody at pre-vaccination reported severe symptoms after the SA-14-14-2 vaccination.

Immunogenicity

General antibody response among 140 pre-sero-negative (Day 0) for JE and/or Dengue virus subjects

Immunogenicity was evaluated over 140 subjects who were sero-negative for JE and/or Dengue virus at the beginning of the present study. A total of 125 subjects demonstrated JE sero-conversion at 28-35 days after vaccination and 15 subjects did not. The sero-conversion rate was 89.3% (125/140) (95% CI, 83.1-93.4%) at 28-35 days after vaccination and the GMT was 74. However, 8 of the 15 JE sero-negative subjects at day 28-35 post-vaccination had demonstrated sero-conversion at 90 days after the first vaccination whereas 7 subjects remained JE sero-negative at 90 days post-vaccination. The sero-conversion rate for a single dose increased to 95% (133/140) (95% CI, 90.0-97.6%) at 90 days after the primary vaccination (Fig. 1) and the GMT was 66.1 (minimum 11, maximum 654). These 15 subjects had received a second dose 90 days after the first dose. Two doses of vaccine resulted in 100% of JE sero-conversion (95% CI, 97.3-100%) and the GMT was 260.8 (minimum 57, maximum 1,034).

Antibody response after second dose

Fifteen subjects with JE sero-negative at day 28-35 post-vaccination had received a second dose of vaccine 90 days after the first dose. Seven subjects

Table 1. Demographic characteristics of 150 subjects

Gender	Number of subjects	**Min age (Months)**	Max age (Months)	Mean age (Months)	**SD**
Male	81	9	15	10.7	1.79
Female	69	**9**	**14**	**10.5**	**1.60**
All	150	9	15	10.6	1.70

Table 2-1. Summary of reported clinical adverse events-Day 0 to 28 post 1st dose, all 150 subjects

Adverse Events	Day 0-6 (n = 150) No (%)	Day 7-28 (n = 150) No (%)
Local reaction		
Redness	4 (2.7)	0 (0.0)
Swelling	3 (2.0)	0 (0.0)
Induration	2 (1.3)	0 (0.0)
Local pain	2 (1.3)	0 (0.0)
Itching	0 (0.0)	0 (0.0)
Systemic reaction		
Fever (> 38°C)	14 (9.3)	24 (16)
Eruption	10 (6.7)	2 (1.3)
Vomiting	11 (7.3)	15 (10)
Diarrhea	13 (8.7)	16 (10.7)
Anorexia	8 (5.3)	10 (6.7)
Cough	24 (16.0)	42 (28.0)
Fussiness	9 (6.0)	2 (2.3)
Lethargy	5 (3.3)	2 (1.3)
Convulsion	0 (0.0)	0 (0.0)
Runny nose	16 (10.7)	26 (17.3)

with JE sero-negative both at day 28-35 and day 90, had demonstrated JE sero-positive with GMT of 260.8 (minimum 57, maximum 1,031) at 4 weeks after the second dose (day120) (Table 3, Fig. 1). However, eight subjects with JE sero-negative at day 30 who had JE sero-positive at day 90, developed a significant secondary immune response one month after the second dose of the SA-14-14-2 vaccine with GMT markedly increased from 66.1 to 1,237 (minimum 164, maximum 16,229) (Table 3, Fig. 1).

Immune response among different age groups

No significant difference in the JE sero-conversion rate was observed among different age groups (Table 4). It seems that a possible maternal antibody does not interfere with the live JE vaccine at the age of less than 12 months.

Immune response among subjects with pre-existing dengue virus antibody

The authors assessed the antibody response to live, attenuated JE vaccine among children with pre-existing natural antibody against dengue virus. Eight

Table 2-2. Comparison of reported clinical adverse events among dengue naive and pre-existing subjects - Day 0 to 28 post 1st dose

Adverse Events	Day 0~6		Day 7~28	
	Dengue Naive (n=142) No. (%)	Dengue pre-existing antibody (n = 8) No. (%)	Dengue Naive (n = 142) No. (%)	Dengue pre-existing antibody (n = 8) No. (%)
Local reaction				
Redness	4 (2.7)	0	0	0
Swelling	3 (2.0)	0	0	0
Induration	2 (1.3)	0	0	0
Local pain	2 (1.3)	0	0	0
Itching	0 (0.0)	0	0	0
Systemic reaction				
Fever (> 38°C)	12 (8.5)	2 (25)	21 (14.8)	3 (37.5)
Eruption	10 (7.0)	0 (0.0)	2 (1.4)	0 (0.0)
Vomiting	10 (7.0)	1 (12.5)	12 (8.5)	3 (37.5)[a]
Diarrhea	12 (8.5)	1 (12.5)	14 (9.9)	2 (25.0)
Anorexia	7 (4.9)	1 (12.5)	8 (5.7)	2 (25.0)
Cough	23 (16.2)	1 (12.5)	37 (26.5)	5 (62.5)
Fussiness	9 (6.3)	0 (0.0)	1 (0.7)	1 (12.5)
Lethargy	5 (3.5)	0 (0.0)	2 (1.4)	0 (0.0)
Convulsion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Runny nose	16 (11.3)	0 (0.0)	25 (17.6)	1 (12.5)

* a: $p < 0.05$

subjects who had pre-existing natural dengue virus antibody (D 0) were given one dose of SA14-14-2 vaccine. They were included in the safety study, but excluded from the immunogenicity evaluation (Table 5). All of the 4 subjects with pre-existing naturally-acquired dengue virus antibody had demonstrated sero-conversion of JE neutralizing antibody with GMT of 129.2 (minimum 21, maximum 855). Another 4 subjects with very high titer of pre-existing serotype 2 dengue virus antibodies had demonstrated no secondary JE antibody response after the SA 14-14-2 single dose vaccination (Table 5).

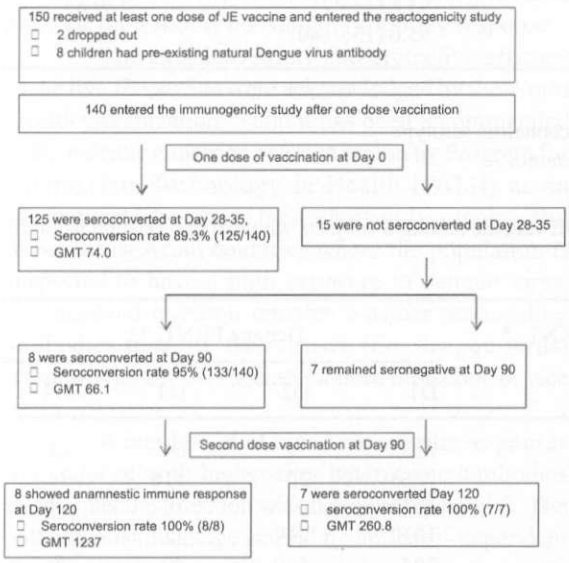

Fig. 1 Flow chart of the vaccination and the results of seroconversion rate of neutralizing antibody against JE virus

Discussion

A live attenuated SA14-14-2 JE vaccine was originally developed in China and further characterized by a group of US scientists under the auspices of the Rockefeller Foundation in the early 1990's. It has been used nationally in China for the past 17 years. Over 200 million doses of live attenuated JE vaccine are estimated to have been administered so far without any serious side effects reported by passive and active surveillance.

The results of the present study, conducted in Bangkok, Thailand, provide evidence to support the safety and immunogenicity of the live JE vaccine when given to healthy Thai infants aged 9-15 months. The sero-conversion rate was 95.0% with one dose and 100% with two doses. This finding is rather similar to other clinical or field study results ranging from 85% to 100% JE sero-conversion rate after one or two doses. In addition, it demonstrated similar findings on neutralizing antibody response to the booster vaccination with a live attenuated JE vaccine as reported in Korean and Nepalese studies[6,7]. Eight

Table 3. Neutralizing antibody response of 15 subjects on Day 120 whom had received 2nd dose on Day 90

Subjectcode	Day 90PRNT$_{50}$	Day 120 PRNT$_{50}$*				
		SA14-14-2	G1	G2	G3	G4
001	<10	136	100	27	67	32
018	<10	57	<10	10	10	<10
041	<10	150	400	210	208	152
068	<10	633	29	56	138	36
069	<10	105	29	121	105	43
089	<10	1030	61	29	123	37
135	<10	1031	169	188	182	52
005	21	436	302	10	119	89
011	19	164	472	283	340	124
056	316	1629	1297	4728	2886	1157
078	17	903	152	524	269	187
094	24	2726	1295	2816	2745	535
099	12	1770	362	1331	1061	289
116	29	1943	542	279	150	131
146	33	558	154	442	118	96

* Plaque reduction neutralizing antibody against Japanese encephalitis serotype

Table 4. Seroconversion rate among different age group at day 90

Age groups	Number of subjects	SCR*	$PRNT_{50}$**
		% (n)	GMT
9-11 month	93	95.7 (89/93)	118.07
12-15 month	47	93.6 (44/47)	129.63
Total	140	95.0 (133/140)	121.78

* Seroconversion rate
** Plaque reduction neutralizing antibody against Japanese encephalitis serotype
*** No significant difference between 9~11 month and 12~15 month

Table 5. Neutralizing antibody response to a live attenuated JE vaccine among 8 subjects who had pre-existing naturally acquired Dengue virus antibody

Subject code	Age (mo)	Day	JE $PRNT_{50}$*	Dengue $PRNT_{50}$**			
				D1	D2	D3	D4
002	10	0	<10	2183	59	64	13
		28-35	19	7258	26	116	<10
		1 Y	15	3049	94	19	<10
064	10	0	<10	101	219	117	112
		28-35	19	294	189	50	70
		1 Y	748	101	359	72	565
143	9	0	<10	30	<10	<10	<10
		28-35	14	19	<10	<10	<10
		1Y	68	17	<10	<10	<10
050	12	0	<10	77	<10	<10	<10
		28-35	2999	12	<10	<10	<10
		1 Y	304	<10	<10	<10	<10
010	11	0	36	33	1953	38	35
		28-35	10	14	880	19	16
		1 Y	382	79	39130	38	<10
062	9	0	27	43	1648	84	40
		28-35	15	15	110	10	<10
		1 Y	203	96	75	<10	<10
072	10	0	23	376	36821	150	45
		28-35	36	326	33573	102	<10
		1 Y	246	52	748	38	67
091	14	0	25	206	6631	89	49
		28-35	83	97	68652	30	0
		1 Y	1009	239	6412	33208	605

* Plaque reduction neutralizing antibody against Japanese encephalitis virus serotype III
** Plaque reduction neutralizing antibody against Dengue virus serotype (D1-D4)

subjects who had vaccine-primed antibody demonstrated the secondary immune response of a more than four-fold rise (GMT 1237; min 164, max 16229).

As for the humoral antibody response to re-vaccination with a live attenuated vaccine, the pre-existing antibodies in the serum may inhibit a strong serologic response to the live attenuated vaccine, or on the other hand, immunological memory may allow for a robust serologic response to vaccination[13]. For example, measles vaccination does not boost the

measles antibody titer in an individual with pre-existing naturally-acquired and high titer antibody. The immune response of MMR re-vaccination in adults demonstrated that only subjects with very low and undetectable measles antibody have a booster effect after re-vaccination[14-16]. However, SA14-14-2 re-vaccination demonstrated that every second dose allowed for a robust boosting of antibody response.

The excellent safety and protective efficacy of the live JE vaccine were acknowledged by the World Health Organization[12] and it has been recommended to JE endemic countries in Asian region by Program for Appropriate Technology in Health (PATH) as an alternative to the mouse brain-derived JE vaccine. But in Southeast Asian countries where the population is suspected to have a high exposure to dengue virus, the unsolved question remains whether pre-existing antibodies to other flaviviruses (*i.e.* dengue virus) interfere with live JE vaccine-induced protection or vice versa.

A rapid onset of broad anamnestic responses was induced with higher-titer heterotypic antibodies after sequential infection with flavivirus species[17]. The potential disadvantage caused by antibody-dependent disease enhancement like secondary infection with dengue virus infection could be considered after live attenuated JE vaccination. In an animal study, mice with sub-neutralizing anti-JEV antibody concentrations have been shown to have a high titer of viremia and increased mortality after sequential infections with another flavivirus[18]. The present study provided preliminary data on vaccination among the subjects with a pre-existing antibody against dengue virus (Table 5). Among 150 subjects, eight were identified with a pre-existing dengue antibody (5.3%); dengue type 2 was the predominant serotype, followed by type 1, which was generally consistent with the previous reports[19,20]. Eight subjects, who had the pre-existing natural dengue virus antibody at the initial test, were given the SA14-14-2 JE vaccine. It was well tolerated without any serious side effects. No boosting of dengue virus antibody titers following the JE vaccination was observed. All 4 subjects without cross-reactive antibody to the JE virus showed sero-conversion after one dose of the SA14-14-2 vaccine. The GMT was 62.7. Another 4 subjects with high pre-existing antibody titer to dengue virus serotype 2 showed a possible cross-reactive antibody response to the other serotypes and the JE virus. However, further study with a larger number of subjects should be performed to evaluate the long-term immune response and a possible influence from naturally acquired dengue infection.

In conclusion, the live attenuated SA14-14-2 vaccine is safe, generally well tolerated and highly immunogenic, showing a 95% sero-conversion rate with one dose and 100% with two doses in healthy Thai infants aged 9-15 months.

Potential conflict of interest

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การศึกษาวัคซีนไข้สมองอักเสบเจอี ชนิดเชื้อเป็นสายพันธุ์ SA-14-14-2 ในเด็กไทยอายุ 9 - 15 เดือน

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วัตถุประสงค์ของการศึกษานี้ เพื่อประเมินความปลอดภัยและการสร้างภูมิคุ้มกันของวัคซีนไข้สมองอักเสบเจอี ชนิดเชื้อเป็นสายพันธุ์ SA-14-14-2 ในเด็กไทยที่แข็งแรงดี เด็กอายุ 9-15 เดือนจำนวน 150 คน ได้รับการฉีดวัคซีนนี้เพียงเข็มเดียว ผลการประเมินความปลอดภัยช่วง 28 วัน หลังฉีดวัคซีนพบว่าไม่มีอาการไม่พึงประสงค์รุนแรงที่เกี่ยวข้องกับวัคซีน ผลการประเมินทางด้านภูมิคุ้มกันต่อไวรัสเจอี พบว่ามีอัตรา seroconversion เท่ากับ 95% (95%CI, 90.0-97.6%) และมีระดับภูมิคุ้มกัน Geometric Mean Titer (GMT) เท่ากับ 66.1 ในช่วง 90 วันหลังฉีดวัคซีนเพียงเข็มเดียว พบเด็ก 8 คนที่ตรวจไม่พบภูมิคุ้มกันต่อไวรัสเจอี เมื่อวันที่ 28-35 หลังฉีดวัคซีนแต่กลับพบภูมิคุ้มกันต่อไวรัสเจอี ในช่วงวันที่ 90 หลังฉีดวัคซีนนี้เข็มเดียว นอกจากนี้พบว่ามีเด็ก 7 คน ที่ไม่พบภูมิคุ้มกันต่อไวรัสเจอี เมื่อวันที่ 28-35 วันและ 90 วัน หลังฉีดวัคซีนเพียงเข็มเดียวนั้นพบว่ามีภูมิคุ้มกันต่อไวรัส เจอี หลังฉีดวัคซีนเข็มที่สองทุกราย ดังนั้นวัคซีนไข้สมองอักเสบเจอี ชนิดเชื้อเป็นสายพันธุ์ SA14-14-2 เมื่อฉีดวัคซีนนี้ 2 เข็มพบการสร้างภูมิคุ้มกันถึง 100% (95% CI, 97.3-100%) และมีระดับ GMT 260.8 อย่างไรก็ตามเด็ก 8 คน ที่มีระดับภูมิคุ้มกันต่ำหลังฉีดวัคซีนเข็มแรกจะพบการกระตุ้นภูมิคุ้มกันต่อไวรัสเจอี อย่างสูงหลังฉีดวัคซีนเข็มที่สอง และมีระดับ GMT 1237

สรุป วัคซีนไข้สมองอักเสบเจอี ชนิดเชื้อเป็นสายพันธุ์ SA14-14-2 มีความปลอดภัยสูง เด็กทนวัคซีนได้ดี และมีการสร้างภูมิคุ้มกันสูงถึง 95% และ 100% ภายหลังฉีด 1 เข็มและ 2 เข็มตามลำดับ อย่างไรก็ตามการติดตามระดับภูมิคุ้มกันต่อไวรัส เจอี ระยะยาวและความเป็นไปได้ของผลกระทบจากการติดเชื้อเดงกี่ตามธรรมชาติควรจะมีการศึกษาต่อไปในอนาคต