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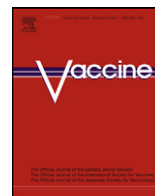
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Immunogenicity of one dose of Vero cell culture-derived Japanese encephalitis (JE) vaccine in adults previously vaccinated with mouse brain-derived JE vaccine

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ABSTRACT

Background: There are no data on the use of inactivated Vero cell culture-derived Japanese encephalitis (JE) vaccine (JE-VC) as a booster among individuals who previously received inactivated mouse brain-derived JE vaccine (JE-MB).

Methods: Military personnel who received ≥ 3 doses of JE-MB or were JE vaccine-naïve were vaccinated with 2 doses of JE-VC on days 0 and 28. Serum neutralizing antibodies were measured pre-vaccination and 28 days after each dose. Non-inferiority was evaluated for seroprotection rate and geometric mean titer (GMT) between previously vaccinated participants post-dose 1 and vaccine-naïve participants post-dose 2.

Results: Fifty-three previously vaccinated and 70 JE vaccine-naïve participants were enrolled. Previously vaccinated participants had significantly higher GMTs pre-vaccination, post-dose 1, and post-dose 2. Sero-protection rates among previously vaccinated participants post-dose 1 (44/44, 100%) were noninferior to those achieved in previously naïve participants post-dose 2 (53/57, 93%). The GMT was significantly higher in previously vaccinated participants post-dose 1 (GMT 315; 95% CI 191–520) compared to previously naïve participants post-dose 2 (GMT 79; 95% CI 54–114).

Conclusions: Among military personnel previously vaccinated with ≥ 3 doses of JE-MB, a single dose of JE-VC adequately boosts neutralizing antibody levels and provides at least short-term protection. Additional studies are needed to confirm these findings in other populations and determine the duration of protection following a single dose of JE-VC in prior recipients of JE-MB.

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1. Introduction

Japanese encephalitis (JE) virus, a mosquito-borne flavivirus, is an important cause of encephalitis in Asia. Among an estimated 67,000 annual cases, 20%–30% of patients die and 30%–50% of survivors have neurologic sequelae [1–3]. There is no specific treatment for JE but the disease is vaccine-preventable. For most travelers to Asia, the risk for JE is very low but varies based on destination, duration, season, and activities [4]. The U.S. Advisory Committee on Immunization Practices (ACIP) recommends JE vaccine for some travelers to Asia and laboratory personnel who work with JE virus [2].

In 2009, the U.S. Food and Drug Administration (FDA) licensed a new inactivated Vero cell culture-derived JE vaccine (JE-VC [manufactured as IXIARO]) for use in persons aged ≥ 17 years [5]. JE-VC was licensed based on its ability to induce JE virus-specific neutralizing antibodies, which are thought to be a reliable surrogate of efficacy [6,7]. The vaccine is administered in a 2-dose primary series at 0 and 28 days with a booster dose recommended ≥ 1 year later for persons who remain at increased risk of JE virus exposure [5,8]. An inactivated mouse brain-derived JE vaccine (JE-MB [manufactured as JE-VAX]) has been licensed in the United States since 1992 for use in persons aged ≥ 1 year [2]. However, JE-MB is no longer being produced and all remaining doses expired in 2011 [9].

There are no data on the interchangeability of JE vaccines or the use of JE-VC in persons who previously received JE-MB. Because both vaccines contain inactivated whole JE virus, it is reasonable to assume that JE-VC might provide adequate boosting after a 3-dose primary series with JE-MB. However, until further data are available, ACIP recommends persons who have previously received JE-MB and require further vaccination against JE virus should

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receive 2 doses of JE-VC [2]. Demonstrating the immunogenicity of a single booster dose of JE-VC for travelers and military personnel who previously completed a primary series with JE-MB would decrease cost and conserve resources, shorten the time required to complete re-vaccination before travel or deployment, and possibly reduce adverse events following immunization. We evaluated the noninferiority of a single dose of JE-VC among persons previously vaccinated with JE-MB compared with the standard 2-dose series of JE-VC in persons who had not previously received any JE vaccine.

2. Methods

2.1. Study participants

We identified active-duty service members belonging to United States Marine Corps (USMC) units undergoing vaccination against JE virus in preparation for deployment. Marines ≥ 17 years of age who had not previously received JE-VC were eligible for enrollment. Enrolled participants were assigned to 1 of 2 study cohorts: (1) individuals who previously received ≥ 3 doses of JE-MB, and (2) JE vaccine-naïve individuals. Persons who had previously received 1 or 2 doses of JE-MB or who received their last dose of JE-MB at <18 months or >11 years prior to the study were excluded from participation. Individuals also were excluded if they were: (1) immunocompromised or had a condition that would pose a health risk or interfere with the evaluation of the vaccine; (2) nursing, pregnant, or planning to become pregnant during the study period; (3) enrolled in another vaccine or drug study; or (4) unable to attend the scheduled visits or comply with the study procedures.

2.2. Study enrollment and procedures

The study was approved by the Institutional Review Boards at the Naval Health Research Center (NHRC) and the Centers for Disease Control and Prevention (CDC). Study enrollment occurred during 2 time periods corresponding to recruitment from 2 different USMC battalions. These battalions did not differ by age, rank, or branch of service but did differ by sex; 1 battalion contributed 4 female participants while the other contributed none.

This was a prospective, observational clinical trial with three study visits. Enrolled participants in both cohorts (previously vaccinated and no previous vaccine) underwent identical study procedures; all received the recommended 2-dose primary series of JE-VC. At study visit 1, after determining eligibility and obtaining informed consent, we recorded participant demographic and medical history data, and collected a blood specimen prior to the administration of a dose of JE-VC. Study visit 2 occurred at 28 days (± 2 days) after the first dose of JE-VC; at that time, we reviewed reactogenicity data from post-dose 1, obtained an interim medical history, and collected a blood specimen prior to the administration of a second dose of JE-VC. At study visit 3, which occurred at 56 days (± 2 days) after the first dose of JE-VC, we reviewed reactogenicity data from post-dose 2, obtained an interim medical history, and collected a final blood specimen. Vaccination screening and administration were not part of study procedures and were conducted by the unit medical personnel as part of predeployment procedures.

2.3. Specimen collection and testing

At each study visit, 10 mL of blood were collected in a serum separator tube from each participant. Blood specimens were maintained on ice until the end of each study day when they were transported to NHRC for processing. Upon arrival, the specimens were centrifuged, and serum was separated, aliquoted, and stored at -20°C . After the completion of all study visits, the serum specimens were shipped frozen to CDC for testing. Each specimen

was tested by a 50% endpoint plaque reduction neutralization test (PRNT₅₀) for neutralizing antibodies against the SA₁₄₋₁₄₋₂ JE virus strain using a standardized protocol as previously described [10]. The PRNT₅₀ is the reciprocal of the highest serum dilution at which 50% of the virus is inhibited. Laboratory personnel were blinded to the subjects' previous JE vaccination status. Seroprotection was defined as a titer ≥ 10 [7]. A titer <10 was considered negative and assigned a value of 5 for geometric mean titer (GMT) calculations.

2.4. Adverse event data collection

Side effect monitoring cards were provided after each vaccine dose and participants were instructed to record the severity (0 = none, 1 = mild, 2 = moderate, 3 = severe, defined according to interference with normal activities) of three common injection site symptoms (redness, pain, and swelling) and five systemic symptoms (fever, headache, rash, vomiting or diarrhea, and muscle aches) on each of the 4 days following vaccination. Participants who did not return the card as requested were queried about these symptoms at the time of next contact. An interim medical history, including hospitalization or medical care received for vaccine-associated events, was solicited at both follow-up visits.

2.5. Statistical analysis

The per-protocol population was defined at each visit as participants who attended the study visits, received all doses of JE-VC vaccine, and provided all blood specimens and safety data requested at the appropriate time intervals up to and including that visit. The immunogenicity population was defined as previous JE vaccine recipients who provided a serum specimen following 1 dose of JE-VC and JE vaccine-naïve participants who provided a serum specimen following 2 doses of JE-VC, regardless of whether the vaccine dose or serum collection occurred at the appropriate time interval. The safety population was defined for each JE-VC dose as all participants who received that dose of vaccine and provided safety data.

Given the observational nature of this study, in which sampling of individuals from the general population and randomization of treatments were not possible, we used permutation methods as a basis for statistical inference to evaluate the null hypotheses that individuals' responses would be the same whether previously vaccinated or not [11,12]. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC), R version 11.1 (www.r-project.org), and StatXact version 9 (Cytel, Inc., Cambridge, MA). Categorical variables are presented as frequency counts and proportions, and compared using Fisher's exact tests and exact, unconditional 95% confidence intervals (95% CI) for the difference of proportions [13]. Continuous variables are presented using median and range or GMT with 95% CI, and comparisons of GMTs were based on their ratios and 95% CI. When full permutation distributions were computationally unavailable, we used 100,000 random permutations of vaccination status.

Noninferiority was determined by comparing the GMT of post-dose 1 sera in individuals previously vaccinated with JE-MB with that of post-dose 2 sera from JE vaccine-naïve individuals. Noninferiority was defined as the lower bound of the two-tailed 95% CI of the GMT ratio in previously vaccinated to vaccine-naïve participants $>1/1.5$ [5]. The effects of age and rank were evaluated and controlled for by employing permutation tests in linear models and analysis of variance (ANOVA) to compare GMT using the R package lmpm versions 1.1–2. There was insufficient information to control for sex. A secondary immunogenicity assessment was made by comparing the proportion (p) of participants seroprotected in the previously vaccinated group (p_{previous}) post-dose

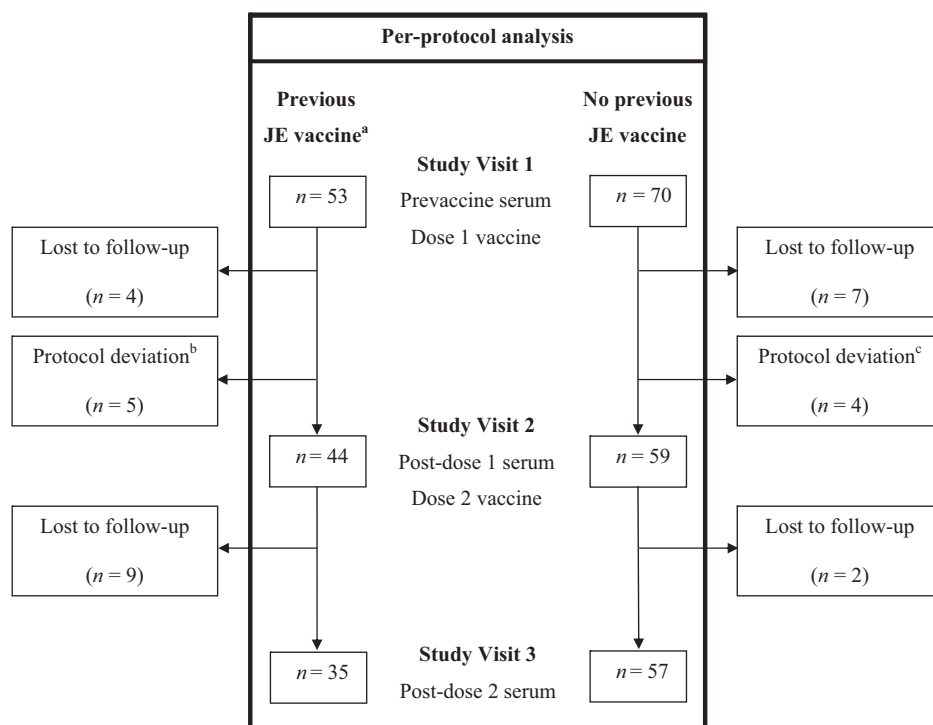


Fig. 1. Study flow and disposition of participants receiving inactivated Vero cell culture-derived Japanese encephalitis (JE) vaccine (IXIARO) by previous JE vaccination status. ^aReceived at least three doses of inactivated mouse brain-derived JE vaccine (JE-MB) at 18 months to 11 years prior to enrollment. ^bTwo subjects provided a post-dose 1 serum at 56 days after the first dose but prior to receiving a second dose of vaccine and did not provide a post-dose 2 serum; three subjects did not provide a post-dose 1 serum, received a second dose of vaccine 32–35 days following the first dose, and provided a post-dose 2 serum 21–24 days after the second dose. ^cTwo subjects did not provide a post-dose 1 serum but received a second dose of vaccine and provided a post-dose 2 serum per protocol; one subject did not provide a post-dose 1 serum, received a second dose of vaccine at 33 days and provided a post-dose 2 serum at 23 days after the second dose; one subject provided a post-dose 1 serum at 56 days after the first dose but prior to receiving a second dose of vaccine and did not provide a post-dose 2 serum.

1 to the JE vaccine-naïve group ($p_{\text{no previous}}$) post-dose 2. Noninferiority was supported if the lower-bound of the 2-tailed 95% CI for $p_{\text{previous}} - p_{\text{no previous}}$ was ≥ -0.10 [7].

Solicited side effects reported by each cohort in the 4 days following each JE-VC dose were compared using 2-tailed Fisher's exact tests. Cohort comparisons for each side effect included: (1) presence of the side effect with any severity reported on any day, (2) maximum severity reported for the side effect on any day, and (3) number of days out of 4 that the side effect was reported. Medians were compared by computing permutation-based 95% CI.

3. Results

3.1. Study participant disposition and demographics

A total of 123 study participants completed visit 1, including 53 previously vaccinated and 70 vaccine-naïve individuals (Fig. 1). Due to protocol deviations and loss to follow-up, the per protocol population at the conclusion of visit 2 included 44 previously vaccinated and 59 vaccine-naïve participants, and at visit 3 included 35 previously vaccinated and 57 vaccine-naïve participants.

Nearly all of the participants in both groups were male (Table 1). Participants who had previously received JE-MB were significantly older (median age 26 years; range 21–37 years) than vaccine-naïve participants (median age 21 years; range 19–41 years) (difference 5 years; 95% CI 3–6 years). The majority of participants received only JE-VC at each study visit, with no difference between the cohorts in the proportion of participants who received concomitant vaccines during visit 1 or visit 2. Previously JE-vaccinated participants received their last JE-MB dose a median of 2.9 years (range 1.8–10.2 years) prior to receiving the first dose of JE-VC. The demographics and concomitant vaccine histories of participants who were lost

to follow-up or deviated from the protocol were not significantly different from the per-protocol population.

3.2. Immunogenicity

Among the per-protocol population, 36 (68%) of 53 previously vaccinated had protective JE virus neutralizing antibodies prior to receiving their first dose of JE-VC compared with only 5 (7%) of 70 vaccine-naïve participants ($P < 0.01$) (Table 2). At 28 days after receipt of the first dose of JE-VC, 100% (44/44) of the previously vaccinated participants were seroprotected versus 46% (27/59) of those who had not previously received JE vaccine ($P < 0.01$) (Table 2). At 28 days post-dose 2 of JE-VC, there was no significant difference in the seroprotection rates between the 2 groups. Previously JE-vaccinated participants had significantly higher GMTs than JE vaccine-naïve participants prevaccination, post-dose 1, and post-dose 2 (Table 2; Fig. 2). Seroprotection rates and GMTs of the immunogenicity population were similar to the per-protocol population.

Seroprotection rates among previously vaccinated subjects at 28 days post-dose 1 of JE-VC (44/44, 100%) were noninferior to those achieved in previously naïve subjects at 28 days post-dose 2 of JE-VC (53/57, 93%) (Table 3). The GMT was noninferior and significantly higher in previously vaccinated subjects post-dose 1 (GMT 315; 95% CI 191–520) compared to previously naïve subjects post-dose 2 (GMT 79; 95% CI 54–114). Seroprotection rates and GMTs did not significantly change when adjusted for age in a model with vaccination status by permutation ANOVA.

Among subjects who previously received JE-MB, the time since receiving their last dose did not significantly impact the neutralizing antibody titers achieved following 1 dose of JE-VC (Fig. 3).

Table 1
Characteristics of participants receiving JE-VC.

	Previous JE vaccine (n = 53)		No previous JE vaccine (n = 70)		p value ^a
	No.	(%)	No.	(%)	
Male	52	(98)	67	(96)	0.63
Age group in years					<0.01
<25	22	(42)	60	(86)	
25–29	16	(30)	7	(10)	
30–34	11	(21)	2	(3)	
≥35	4	(7)	1	(1)	
Received 1 or more other vaccines with JE-VC					
Dose 1	10 ^b	(19)	16 ^c	(23)	0.66
Dose 2 ^d	4 ^e	(8)	1 ^f	(2)	0.17
Years since last JE vaccine					
<2	3	(6)	–		
2–3	30	(57)	–		
4–5	11	(21)	–		
6–7	5	(9)	–		
≥8	4	(8)	–		

JE-VC = inactivated Vero cell culture-derived Japanese encephalitis vaccine; JE = Japanese encephalitis.

^a For Fisher's exact test comparing counts between the two cohorts defined by previous JE vaccine status.

^b Other vaccines received included influenza (n = 5 subjects), typhoid (n = 2), meningococcal (n = 2), and meningococcal and tetanus, diphtheria, and acellular pertussis (n = 1).

^c Other vaccines received included anthrax (n = 9 subjects), typhoid (n = 3), hepatitis A, hepatitis B, and typhoid (n = 2), anthrax and typhoid (n = 1), and hepatitis A and hepatitis B (n = 1).

^d For dose 2, data regarding other vaccines received with JE-VC were available for 53 previously vaccinated subjects and 65 previously unvaccinated subjects.

^e Other vaccines received included meningococcal (n = 2 subjects), typhoid (n = 1), and tetanus, diphtheria, and acellular pertussis (n = 1).

^f One subject received typhoid vaccine.

Table 2
Seroprotection rates and geometric mean titers in per-protocol participants receiving inactivated Vero cell culture-derived Japanese encephalitis vaccine.

Seroprotection rates ^a	Previous JE vaccine		No previous JE vaccine		<i>p</i> value ^b
	No./ <i>N</i>	(%)	No./ <i>N</i>	(%)	
Prevaccination	36/53	(68)	5/70	(7)	<0.01
Post-dose 1	44/44	(100)	27/59	(46)	<0.01
Post-dose 2	35/35	(100)	53/57	(93)	0.29
Geometric mean titers	GMT	(95% CI)	GMT	(95% CI)	<i>p</i> value ^c
Prevaccination	13	(9, 18)	5	(5, 6)	<0.01
Post-dose 1	315	(191, 520)	11	(8, 15)	<0.01
Post-dose 2	414	(261, 657)	79	(54, 114)	<0.01

JE = Japanese encephalitis; GMT = geometric mean titer; CI = confidence intervals.

^a 50% plaque reduction neutralization test (PRNT₅₀) titer ≥ 10.

^b Fisher's exact test.

^c Permutation test.

However, only 12 (27%) subjects received their first dose of JE-VC at ≥5 years after their last dose of JE-MB.

3.3. Adverse events

Among the safety population, the proportion of participants reporting any of the specific solicited adverse events in the 4 days after dose 1 of JE-VC was similar between the previously vaccinated and vaccine-naïve groups (Table 4). However, after receiving the second dose of JE-VC, participants who had previously received JE-MB were more likely to report injection site pain, redness, and swelling compared with participants who had not received JE-MB. Previously vaccinated subjects also reported significantly greater severity of pain and swelling than vaccine-naïve subjects following the second dose of JE-VC. Among those participants who reported an adverse event, there was no significant difference between previously vaccinated and vaccine-naïve participants in the median number of days that each adverse event occurred. Only 1 participant reported any "severe" reactions (i.e., "unable to perform normal activities"); he had received JE-MB previously and reported severe injection site redness and pain only on the first of the 4 days following the second dose of JE-VC. There were no serious adverse

events or reactions requiring medical care noted among any of the participants.

4. Discussion

We found that among military personnel who were previously vaccinated with ≥3 doses of JE-MB, a single dose of JE-VC resulted in a noninferior neutralizing antibody response compared with a 2-dose primary series of JE-VC in previously unvaccinated individuals. All of the previously vaccinated participants had protective neutralizing antibodies at 28 days after receiving 1 dose of JE-VC, and they had a significantly higher GMT after the first dose when compared with the previously unvaccinated group following two doses of JE-VC. These results suggest that a single dose of JE-VC adequately boosts neutralizing antibody levels and provides at least short-term protection in individuals who previously received ≥3 doses of JE-MB.

All participants in this study received 2 doses of JE-VC at 0 and 28 days according to the licensed regimen. Therefore, we could not evaluate the duration of neutralizing antibodies following 1 dose of JE-VC in the previously vaccinated individuals. In 3 clinical

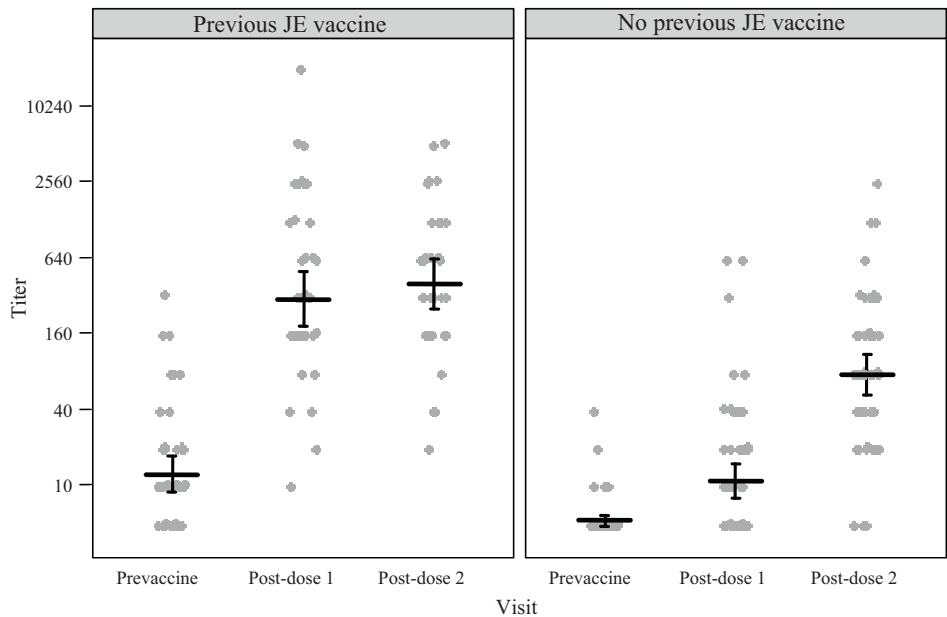


Fig. 2. Geometric mean titers (GMTs) in per-protocol participants receiving inactivated Vero cell culture-derived Japanese encephalitis (JE) vaccine by previous JE vaccination status. Each participant's titer is shown as a grey dot; GMT for the cohort at each time point is shown as a horizontal line with the bars representing the 95% confidence intervals. Dotted lines indicate the noninferiority comparison between previously vaccinated subjects post-dose 1 and naïve subjects post-dose 2.

Table 3
Noninferiority determination among participants receiving inactivated Vero cell culture-derived JE vaccine comparing previous JE vaccine recipients at 28 days after the first dose ($n = 44$) and previous JE vaccine-naïve participants at 28 days after the second dose ($n = 57$).

Noninferiority method	Calculation	Noninferiority threshold ^a	Value	(95% CI)
Seroprotection ^b	$p_{\text{previous}} - p_{\text{no previous}}$	≥ -0.10	0.07	(-0.01, 0.17)
GMT ratio	$\text{GMT}_{\text{previous}} / \text{GMT}_{\text{no previous}}$	$> 1/1.5$	3.99	(2.16, 7.36)

JE = Japanese encephalitis; CI = confidence intervals; GMT = geometric mean titer.

^a Criteria for lower bound of 2-tailed 95% CI to support noninferiority.

^b 50% plaque reduction neutralization test (PRNT₅₀) titer ≥ 10 .

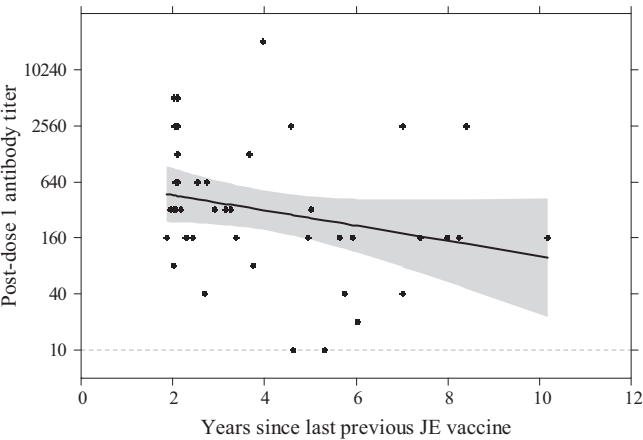


Fig. 3. Relationship between Japanese encephalitis (JE) virus neutralizing antibody titer after one dose of an inactivated Vero cell culture-derived JE vaccine and time since previous JE vaccine among per-protocol participants ($n = 44$). Best-fit regression line with 95% confidence intervals (shaded area) are superimposed on scatter plot of post-dose 1 titer vs. years since previous JE vaccine ($P = 0.097$). Seroprotection (PRNT₅₀ ≥ 10) corresponds to post-dose 1 titer ≥ 10 depicted as a dotted horizontal line.

trials performed in participants with no previous JE vaccination, 48% (95% CI 39%–57%) to 83% (95% CI 77%–88%) had protective neutralizing antibodies at 1–2 years after receiving a 2-dose primary series of JE-VC [14–16]. In 2 of these studies, a booster dose was administered between 11 and 23 months after the primary

series and produced an anamnestic response with all subjects seroprotected at 1 month after the booster [15,16]. At 1 year after the booster dose, $\geq 98\%$ of subjects maintained neutralizing antibodies, and a mathematical model predicted that 95% of the vaccinees would still be protected approximately 4 years after the booster dose [16]. Our findings suggest that a single dose of JE-VC produces a similar anamnestic response in people who have received ≥ 3 doses of JE-MB. The GMT achieved in previously vaccinated subjects after 1 dose of JE-VC was significantly higher than that observed after 2 doses in the previously unvaccinated cohort. There was no significant increase in the seroprotection rate or GMT for previously vaccinated participants between their first and second dose of JE-VC, suggesting limited benefit of a second dose in these subjects. However, additional data are needed on the duration of neutralizing antibodies following 1 dose of JE-VC in previously vaccinated individuals.

In the current study, at 28 days after receiving 1 dose of JE-VC, subjects previously vaccinated with JE-MB had a neutralizing antibody GMT of 315 (95% CI 191–520). In previous studies, among subjects who received a 2-dose primary series of JE-VC followed by a booster dose at 11, 15, or 23 months, the neutralizing antibody GMTs at 28 days after the booster dose were 2- to 8-fold higher at 676 (95% CI 365–1252), 900 (95% CI 742–1091), and 2496 (95% CI 1409–4427), respectively [15,16]. These data could suggest that JE-VC is more effective than JE-MB in priming for a subsequent booster dose with JE-VC. However, the observed differences in GMTs between the current and previous studies also might be due to differences in testing procedures. For example, although the

Table 4

Solicited local and systemic adverse events occurring within 4 days after receiving JE-VC.

	Post-dose 1				Post-dose 2			
	Previous JE vaccine (N = 49)		No previous JE vaccine (N = 67)		Previous JE vaccine (N = 39)		No previous JE vaccine (N = 60)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Injection site reactions								
Pain	14	(29)	14	(21)	16	(41)	9	(15) ^a
Redness	5	(10)	6	(9)	5	(13)	1	(2) ^a
Swelling	3	(6)	1	(1)	6	(15)	0	(0) ^a
Systemic reactions								
Fever	3	(6)	1	(1)	2	(5)	0	(0)
Headache	8	(16)	7	(10)	6	(15)	2	(3)
Myalgia	9	(18)	5	(7)	6	(15)	3	(5)
Rash	0	(0)	0	(0)	2	(5)	0	(0)
Vomiting or diarrhea	3	(6)	3	(4)	2	(5)	0	(0)

JE-VC = inactivated Vero cell culture-derived Japanese encephalitis vaccine; JE = Japanese encephalitis.

^a 2-tailed Fisher's exact test $p < 0.05$ for the proportion of participants with previous JE vaccine and no previous JE vaccine who reported pain, redness, or swelling within 4 days after receiving the second dose of JE-VC.

studies used similar methods to measure the PRNT₅₀, including the same JE virus SA₁₄₋₁₄₋₂ target strain, our specimen processing included a 30 min heat inactivation step at 56 °C, whereas the previous studies did not. The importance of differences in the testing methods is supported by the fact that although 93% of the previously unvaccinated cohort in our study were seroprotected at 28 days after receiving their second dose of JE-VC, their neutralizing antibody levels (GMT 79; 95% CI 54–114) were 3- to 4-fold lower than among comparable participants in the prior studies (GMT 311; 95% CI 269–359) [14,17].

In this study, all previously vaccinated persons developed seroprotective antibodies against JE virus following 1 dose of JE-VC regardless of the time since last vaccination with JE-MB. In addition, the GMT achieved was not significantly lower with longer time since previous vaccination. These results suggest that persons who previously received ≥ 3 doses of JE-MB will develop neutralizing antibodies following a single dose of JE-VC administered up to 11 years after their last dose of JE-MB. However, only 12 participants received their last dose of JE-MB ≥ 5 years prior to enrollment. A larger study is needed to confirm that persons who received JE-MB ≥ 5 years previously will achieve adequate neutralizing antibodies and duration of protection following one dose of JE-VC, and to determine if there is a maximum time since the last JE-MB vaccination after which an anamnestic response will no longer occur in response to a single dose of JE-VC. Finally, very few of the study participants received concomitant vaccines, making it difficult to assess if simultaneous administration of other vaccines with JE-VC would affect the JE virus neutralizing antibody response in previously vaccinated individuals.

No serious adverse events were reported in either group and none of the participants sought medical care for vaccine-related events during the 28 days following vaccination. Rates of systemic symptoms within 4 days of vaccination were similar between the 2 groups following either dose of vaccine, with headache and myalgia being the most commonly reported symptom. Injection site reactions also were similar in frequency, severity, and duration following the first dose of vaccine. However, following the second dose of JE-VC, previously vaccinated subjects reported a higher rate of injection site pain, redness, and swelling than subjects who had not received JE-MB. Only 1 subject reported a severe injection site reaction and all of the reactions resolved. These data suggest that persons previously vaccinated with ≥ 3 doses of JE-MB are more likely than vaccine-naïve persons to experience injection site reactions following the second dose of a JE-VC primary series.

Given the need to enroll both a JE-vaccine-naïve and previously vaccinated study cohort to determine noninferiority and to provide the recommended 2-dose JE-VC primary series to all participants, we were unable to randomize participants into study groups. This lack of randomization and the performance of the study in active duty and predominantly male military personnel limit the ability to extrapolate these findings to the general population of potential JE vaccine recipients. However, the seroprotection and adverse events among JE-vaccine-naïve participants after each dose of JE-VC were similar to those reported in previous studies [14,17,18], suggesting that it is reasonable to assume that healthy adult travelers or laboratory personnel will have a similar response as was found in this observational trial, including the differences in immunogenicity and reactogenicity identified among previously vaccinated individuals.

In summary, we report that among military personnel who were previously vaccinated with ≥ 3 doses of JE-MB, a single dose of JE-VC resulted in noninferior seroprotection rates compared with a 2-dose primary series of JE-VC in previously unvaccinated individuals. All of the previously vaccinated participants had protective neutralizing antibodies at 28 days after receiving one dose of JE-VC, and they had significantly higher GMTs after the first dose when compared with the previously unvaccinated group following 2 doses of JE-VC. These results suggest that a single dose of JE-VC will provide at least short-term protection in individuals who previously received ≥ 3 doses of JE-MB. Eliminating the second dose of JE-VC for adults who previously completed a primary series with JE-MB would decrease cost and conserve resources, shorten the time required to complete revaccination before travel or deployment, and reduce the number of local adverse events following immunization. Additional studies are needed to confirm these findings in other populations, including older adults, women, travelers, and laboratory personnel, and to determine the duration of protection following a single booster dose of JE-VC among individuals who previously received JE-MB.

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Background. There are no data on the use of inactivated Vero cell culture-derived Japanese encephalitis (JE) vaccine (JE-VC) as a booster among individuals who previously received inactivated mouse brain-derived JE vaccine (JE-MB). Methods. Military personnel who received ≥ 3 doses of JE-MB or were JE vaccine-naïve were vaccinated with 2 doses of JE-VC on days 0 and 28. Serum neutralizing antibodies were measured prevaccination and 28 days after each dose. Noninferiority was evaluated for seroprotection rate and geometric mean titer (GMT) between previously vaccinated participants post-dose 1 and vaccine-naïve participants post-dose 2. Results. Fifty-three previously vaccinated and 70 JE vaccine-naïve participants were enrolled. Previously vaccinated participants had significantly higher GMTs prevaccination, post-dose 1, and post-dose 2. Seroprotection rates among previously vaccinated participants post-dose 1 (44/44, 100%) were noninferior to those achieved in previously naïve participants post-dose 2 (53/57, 93%). The GMT among previously vaccinated participants post-dose 1 (GMT 315, 95% CI, 191-520) also was noninferior to that of previously naïve participants post-dose 2 (GMT 79, 95% CI, 54-114). Conclusions. Among military personnel previously vaccinated with ≥ 3 doses of JE-MB, a single dose of JE-VC resulted in a noninferior neutralizing antibody response compared with a 2-dose primary series of JE-VC in previously unvaccinated personnel.					
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