Grading of recommendations, assessment, development, and evaluation (GRADE) for use of inactivated Vero cell culture-derived Japanese encephalitis vaccine in children

Background

Inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC [manufactured as IXIARO]) is the only JE vaccine licensed and available in the United States. JE-VC is manufactured by Intercell Biomedical (Livingston, United Kingdom) and distributed in the United States private market by Novartis Vaccines (Cambridge, Massachusetts). In March 2009, FDA licensed JE-VC for use in adults aged ≥17 years. ACIP recommendations for use of JE-VC in adults were approved in June 2009 and booster dose recommendations were approved in February 2011 [CDC 2010; CDC 2011].

There are no efficacy data for JE-VC. However, a JE virus 50% plaque reduction neutralization test (PRNT50) titer of ≥10 is an established immunologic correlate of protection [Markoff 2000; Hombach 2005]. JE-VC was licensed based on its ability to induce neutralizing antibodies and a non-inferiority comparison to a licensed inactivated mouse brain-derived JE vaccine (JE-MB [manufactured as JE-VAX]). Since JE-VC was licensed in 2009, >375,000 doses have been distributed in the United States for use in adults.

In May 2013, FDA approved JE-VC for use in children aged 2 months through 16 years [FDA 2013]. The FDA-approved primary series for JE-VC is two intramuscular doses administered 28 days apart. For children aged 2 months through 2 years each dose is 0.25mL and for adults and children aged ≥3 years each dose is 0.5mL.

The ACIP JE Vaccine Workgroup evaluated the evidence for use of JE-VC in children using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methods [Ahmed 2011]. The workgroup developed a policy question, identified outcomes of critical importance, performed a systematic review of the available data, and evaluated evidence of benefits, harms, values, and preferences for use of JE vaccine in U.S. children.

Policy question

The primary policy question was "Should inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) be recommended for use in children 2 months through 16 years of age at increased risk of travel-related exposure to Japanese encephalitis virus?"

Population: Children 2 months through 16 years of age traveling to JE-endemic areas
Intervention: JE-VC administered as a 2-dose primary series
Current option: No JE vaccine recommended and available for use in children

Identify and rank relative importance of outcome measures

For the GRADE evaluation of JE-VC in children, the benefits considered critical outcomes for which there were data available included seroprotection at 1 and 6 months after vaccination using the established immunologic correlate of protection (JE virus neutralizing antibodies at a PRNT50 titer ≥10) **(Table 1)**. The harms considered critical outcomes were serious adverse events and systemic adverse events (i.e., fever, rash, hypersensitivity or urticaria, neurologic, and medically attended adverse events). Evidence type for each critical outcome was derived through a review of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations (i.e., publication bias, strength of association, dose response, or opposing plausible residual confounding).

Evidence retrieval

To identify published literature that contained relevant evidence, we conducted PubMed and Embase searches of papers in any language published between January 1, 2006 and April 30, 2013. The date limits were based on known vaccine development history. We used the following search strategy and keywords: "Japanese encephalitis" and "vaccine" and "IXIARO or JESPECT or IC51 or Vero or purified inactivated". The title and abstract of the studies were reviewed to identify relevant articles; if no abstract was provided, the paper itself was reviewed.

Articles that presented data on JE-VC were included if they met the following criteria: 1) Involved human subjects; 2) Reported primary data; 3) Included data relevant to the outcome measures being assessed (i.e., vaccine efficacy, seroprotection at 1 month after vaccination, seroprotection at 6 months after vaccination, serious adverse events, or systemic adverse events); and 4) Included data for an FDA-approved dose (i.e., 0.25mL for children aged 2 months through 2 years and 0.5mL for children and adults aged ≥3 years). Publications that met the above criteria but represented a single case report were excluded.

We identified 67 studies in PubMed using the search strategy. Among these studies, 51 were excluded as they did not include any JE-VC data or did not present primary data. Four studies that included JE-VC human data were also excluded: 1) One study presented data on the impact of pre-existing Tick-borne encephalitis virus antibody on vaccine safety and immunogenicity and so was excluded as not being relevant to the outcome measures and the safety and immunogenicity data from the study subjects were included in a separate publication which was included; 2) One study used only non-recommended vaccine doses; 3) One study presented immunogenicity data in adults at 12 months post-vaccination; and 4) One study was a case report describing an adverse event in one patient. Following these 55 exclusions, 12 studies were included in the GRADE evaluation. The Embase search identified 162 articles but no additional studies meeting the selection criteria were found.

Unpublished data were also considered for JE-VC and another similar inactivated Vero cell culture-derived JE vaccine (JEEV) manufactured by Biological E (Hyderabad, India). JEEV is manufactured with technology licensed from Intercell. JEEV and IXIARO use the same virus strain, adjuvant, and virus purification; however, no process comparability studies have been completed and it cannot be assumed that the two final vaccine products are the same. JEEV is approved in India for use in children aged 1 through 2 years (two 0.25mL doses administered 28 days apart) and adults aged 18 through 49 (two 0.5mL doses administered 28 days apart) [Central Drugs Standard Control Organization 2013]

Summarize relevant evidence for critical outcomes

Seroprotection at 1 month

The evidence used to evaluate seroprotection at 1 month after vaccination with JE-VC was from 10 studies of JE-VC, including three studies in children and seven studies in adults (**Table 2**). Of the 1,259 JE-VC recipients in the 10 studies combined, 1,237 (98%) were seroprotected at 1 month after the 2-dose primary series, including 99% (457/459) of children and 98% (780/800) of adults. When data from the four RCTs (one in children and three in adults) were combined and weighted using a random effects model, there was no difference in seroprotection rates between JE-VC and the other JE vaccines (**Table 3**).

Seroprotection at 5 to 6 months

The evidence used to evaluate seroprotection at 5 to 6 months after vaccination with JE-VC was

from five studies of JE-VC, including two studies in children and three in adults (**Table 4**). Of the 721 JE-VC recipients in the five studies combined, 661 (92%) were seroprotected at 5 to 6 months after the 2-dose primary series was completed, including 92% (376/407) of children and 91% (285/314) of adults. The findings from the two RCTs in adults showed that a higher proportion of JE-VC recipients were seroprotected compared to subjects who received mouse brain-derived JE vaccine (**Table 5**).

Serious adverse events

The evidence used to evaluate serious adverse events following JE-VC was from 13 studies, including 11 clinical trials or observational studies (three in children and eight in adults) and two reviews of post-marketing surveillance data in adults. Serious adverse events within 1 month after either dose were reported in 18 (<1%) of the 4,393 subjects in 10 studies, including 6 (<1%) of 1,519 children and 12 (<1%) of 2,874 adults (**Table 6**). Serious adverse events within 6 to 7 months after the first dose were reported in 63 (1%) of the 5,029 subjects in three studies, including 25 (2%) of 1,471 children and 38 (1%) of 3,558 adults (**Table 7**). Although the relatively small numbers of subjects in the clinical trials limit the ability to detect rare serious adverse events, post-marketing surveillance data from >375,000 doses distributed provide indirect but reassuring data in adults with 1.6 to 3.3 serious adverse events reported per 100,000 doses distributed (**Table 8**). No patterns in the timing or types of serious adverse events were identified in the clinical trials or surveillance data. When data from the seven RCTs (two in children and five in adults) were combined and weighted using a random effects model, there was no difference in serious adverse events within 1 month between JE-VC and the comparison vaccines (**Table 9**). There was also no difference between JE-VC and comparison vaccine recipients in serious adverse events reported within 6 to 7 months post-vaccination in two RCTs (one in children and one in adults) (**Table 10**).

Systemic adverse events

The evidence used to evaluate systemic adverse events (i.e., fever, rash, hypersensitivity or urticaria, neurologic, and medically attended adverse events) following JE-VC was from nine studies, including seven clinical trials or observational studies (three in children and four in adults) and two reviews of post-marketing surveillance data in adults. Fever within 7 days after either JE-VC dose was reported in 216 (6%) of the 3,659 subjects in six clinical trials, including 141 (9%) of 1,519 children and 75 (4%) of 2,140 adults (**Table 11**). Rash within 7 days after either JE-VC dose was reported in 79 (2%) of the 3,659 subjects, including 3% of children (51/1,519) and 1% of adults (28/2,140) (**Table 12**). Hypersensitivity or urticaria within 1 month of either dose was reported in 5 (<1%) of 3,635 JE-VC recipients in five studies, including <1% of both children (4/1,519) and adults (1/2,116) (**Table 13**). Neurologic adverse events (excluding headache) within 1 month of either JE-VC dose was reported in 31 (1%) of the 3,635 recipients, including 5 (<1%) of 1,519 children and 26 (1%) of 2,116 adults (**Table 14**). Medically attended adverse events within 1 month after either dose were reported in 524 (14%) of 3,714 subjects overall but varied from 18% of children (259/1,471) to 12% of adults (265/2,243) (**Table 15**). In passive post-marketing surveillance data, the reported incidence of hypersensitivity was 4.5 to 4.7 per 100,000 doses distributed and the incidence of neurologic adverse events was 1.8 per 100,000 doses distributed (**Tables 16 and 17**). When data from the RCTs were combined and weighted using a random effects model, there was no difference in the incidence of any of these systemic adverse events between recipients of JE-VC and comparison vaccines (**Tables 18-22**).

Outcomes for a similar JE vaccine in children

In addition to the studies of JE-VC in children and adults, we reviewed evidence for seroprotection, serious adverse events, and systemic adverse events in one RCT performed using a similar JE vaccine (JEEV) among children aged 1 and 2 years in India [Biological E 2013(b)] (**Table 23**). The findings were similar to those seen with JE-VC.

Summarize quality of evidence across outcomes

For the benefits considered critical outcomes, seroprotection rates were high at both 1 month and 6 months after the 2-dose primary series with JE-VC; evidence type is 2 for the RCTs (downgraded because of indirectness due to majority of data are in adults) and 3 for observational studies (**Table 24**). For harms considered critical outcomes, no safety concerns were identified. Serious adverse events were uncommon; evidence type is 3 for RCTs (downgraded because of inadequate blinding and indirectness due to majority of data are in adults) and 4 for observational studies (downgraded because of indirectness due to majority of data are in adults). Incidence of systemic adverse events was similar to comparison vaccines; evidence type is 2 for RCTs (downgraded because of inadequate blinding) and 3 for observational studies. The overall quality of evidence is type 2 for vaccine safety and effectiveness using seroprotection as the endpoint (**Table 25**).

Assess the values related to management options and outcomes

The risk for JE for most travelers to Asia is very low but varies based on destination, duration, season, and activities. The overall incidence of JE among people from nonendemic countries traveling to Asia is estimated to be less than one case per 1 million travelers [CDC 2010]. However, the risk for JE among expatriates and travelers who stay for prolonged periods in rural areas with active JE virus transmission may be similar to the risk among the susceptible resident population (5–50 cases per 100,000 children per year). Recurrent travelers or travelers on brief trips might be at increased risk if they have extensive outdoor or nighttime exposure in rural areas during periods of active transmission. Short-term travelers whose visits are restricted to major urban areas are at minimal risk for JE.

From 1973–2012, 65 cases of travel-associated JE were reported among persons from non-endemic areas, including 6 (9%) among children <17 years of age [Fischer 2013]. Among 47 recently-reported JE cases among travelers from non-endemic countries, 30 (64%) spent ≥1 month in Asia, 13 (24%) spent 2 to 4 weeks, and 4 (8%) spent 1 to <2 weeks. Of the 17 travelers who spent <1 month in Asia, 4 (24%) spent extensive time in rural areas and 13 (76%) took shorter trips to rural areas or stayed in coastal resorts. No cases were reported among short-term travelers who visited only urban areas. Thirteen (20%) of the 65 reported travel-associated cases were fatal and 28 (43%) of the patients survived with neurologic, cognitive, or behavioral sequelae. Among the six pediatric cases, two were fatal, three survivors had sequelae, and one patient had unknown outcome. Of the 65 reported cases, 19 (29%) occurred in U.S. travelers or expatriates, including three (50%) of the pediatric cases. However, a JE vaccine has been available in the United States since 1992 and it is not known how many cases have been prevented due to vaccination or how many cases are not diagnosed or reported. The denominator of numbers of susceptible travelers to JE-endemic areas is also unknown.

Recommendations regarding the use of JE vaccine for pediatric travelers must weigh the overall low risk for travel-associated JE disease, the lack of treatment, high mortality (20-30%)

and morbidity (30-50% survivors with sequelae) when JE does occur, the low probability of serious adverse events following vaccination, and the high cost of the vaccine (**Table 26**). High value is placed on preventing this life-threatening disease. A survey performed in the United States in 2001 found that both parents and community members were willing to pay a median of $500 to reduce the risk of bacterial meningitis from 21 per 100,000 to 6 per 100,000 [Prosser 2004]. Although the rates of disease used in the survey are higher than the risk for JE among travelers, they establish a willingness to pay to prevent a serious outcome. The workgroup also places a high value on educating healthcare providers to help them counsel travelers about JE and JE vaccine, and inform decisions about JE vaccination based on a traveler's planned itinerary.

Review health economic data

Several studies have demonstrated that using JE vaccine to immunize children in JE-endemic countries is cost saving. However, given the large numbers of travelers to Asia (>5.5 million entries of U.S. travelers into JE-endemic countries in 2004), the very low risk for JE for most travelers to Asia (<1 case per million travelers overall), and the high cost of JE vaccine ($400-500 per 2-dose primary series for JE-VC), providing JE vaccine to all travelers to Asia would not be cost-effective. In addition, for some travelers with lower risk itineraries, even a low probability of vaccine-related serious adverse events might be higher than the risk for disease. Therefore, JE vaccine should be targeted to travelers who, on the basis of their planned travel itinerary and activities, are at increased risk for disease.

The number of U.S. children who travel to Asia and have an itinerary that puts them at increased risk for JE is likely very low. In addition, travel vaccines are usually paid for by the travelers themselves; they are not covered under the Vaccines for Children (VFC) program or by most private insurance plans. As a result, the workgroup decided not to perform a cost-effectiveness study of JE vaccine for U.S. children traveling to JE-endemic countries.

Assess the balance of risks and benefits

JE-VC provides high levels of seroprotection in children following a 2-dose primary series. Serious adverse events are uncommon and rates are similar to those seen with comparison vaccines. Systemic adverse events also occur at rates similar to comparison vaccines. There is high value placed on prevention of a serious disease with no treatment and substantial morbidity and mortality. The overall disease risk is very low and vaccine cost is high.

Formulate recommendations and determine the category

Current ACIP recommendations for JE vaccine were approved in 2009; these recommendations included JE-VC for adults aged ≥17 years and JE-MB (inactivated mouse brain-derived JE vaccine) for adults and children aged ≥1 year. However, JE-MB is no longer available.

The GRADE evaluation found that JE-VC is effective using seroprotection as the endpoint and safe in children aged 2 months through 16 years (Evidence type 2). The workgroup proposes to extend the current recommendations for use of JE-VC in adults to include children ≥2 months of age; no other changes to the existing recommendations are proposed. The current recommendations are as follow:

- JE vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JE virus transmission season. This includes long-term travelers, recurrent

travelers, or expatriates who will be based in urban areas but are likely to visit endemic rural or agricultural areas during a high-risk period of JE virus transmission (Recommendation category A).

- JE vaccine should be considered for short-term (<1 month) travelers to endemic areas during the JE virus transmission season if they plan to travel outside of an urban area and have an increased risk for JE virus exposure (e.g., spending substantial time outdoors in rural or agricultural areas, participating in extensive outdoor activities, or staying in accommodations without air conditioning, screens, or bed nets). JE vaccine also should be considered for travelers to an area with an ongoing JE outbreak and travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel (Recommendation category B).

- JE vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside of a well-defined JE virus transmission season (Recommendation category A).

References

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2. Biological E. Unpublished data presented to the ACIP JE Vaccine Workgroup by Katrin Dubischar-Kastner (Intercell AG). April 2013.
    a. Summary: Randomized, controlled, open-label study in India in which adults aged 18–49 years received two 0.5mL doses of Intercell JE-VC (N=54) or two 0.5mL doses of JEEV (N=108). The seroprotection rate in JEEV recipients was non-inferior to that in JE-VC recipients. Of note, 91% (49/54) of JE-VC recipients and 86% (93/108) of JEEV recipients were seroprotected at baseline prior to vaccination; 65% (35/54) of JE-VC recipients and 54% (58/108) of JEEV recipients had a ≥4-fold rise in neutralizing antibody titers.
    b. Summary: Randomized, controlled, open-label study in India in which children aged 1–2 years received two 0.25mL doses of JEEV (N=304) or three doses of JenceVac (N=152). The seroprotection rate in JEEV recipients was non-inferior to that in JenceVac recipients.

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    Summary: JEEV is approved in India for use in children aged 1–2 years (two 0.25mL doses administered 28 days apart) and adults aged 18–49 (two 0.5mL doses administered 28 days apart).

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    a. Summary: Open-label, uncontrolled study in which adults (≥18 years) enrolled in a previous randomized controlled trial were followed for up to 24 months after receiving two 0.5mL doses of JE-VC (N=116).

7. Dubischar-Kastner K, Kaltenboeck A, Klingler A, Jilma B, Schuller E. Safety analysis of a Vero-cell culture derived Japanese encephalitis vaccine, IXIARO® (IC51), in 6 months of follow-up. Vaccine 2010;28:6463–9.
    b. Summary: Combined safety data from seven clinical trials in which adults (≥18 years) received at least one dose of JE-VC (N=3558), JE-VAX (N=435), or phosphate buffered saline with 0.1% aluminum hydroxide (N=657). The evaluation includes subjects who received JE-VC in alternative doses or schedules or as a booster dose after the 2-dose primary series.

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    a. Summary: Randomized, controlled, open-label study in which children aged 2–11 months received two 0.25mL doses of JE-VC (N=131) or 7-valent pneumococcal conjugate vaccine (Prevnar 7) manufactured by Wyeth (N=64), and children aged 1–17 years received two 0.25mL doses of JE-VC (N=740), two 0.5mL doses of JE-VC (N=540), or hepatitis A vaccine (Havrix) manufactured by GSK (N=394). Immunogenicity data were collected only for a subset of 485 children who received JE-VC.
    b. Summary: Single arm, open-label, dose-range study in which all children aged 2 months through 2 years received two 0.25mL doses of JE-VC (N=5) and all children aged 3–17 years received two 0.5mL doses of JE-VC (N=55).

9. Erra EO, Hervius Askling H, Rombo L, et al. A single dose of Vero cell–derived Japanese encephalitis (JE) vaccine (IXIARO) effectively boosts immunity in travelers primed with mouse brain–derived JE vaccines. Clin Infect Dis 2012;55(6):825–34.
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evaluation, immunogenicity data was only included for subjects who received the licensed regimens of two doses of JE-VC or three doses of JenceVac.

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    Summary: FDA-approved primary series for inactivated Vero cell culture-derived JE vaccine (JE-VC; IXIARO) is two 0.25mL doses administered 28 days apart for children aged 2 months through 2 years and two 0.5mL doses administered 28 days apart for adults and children aged ≥3 years.

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    Summary: Randomized, controlled, observer-blinded study in which adults (≥18 years) received two 0.5mL doses of JE-VC (N=65), two 0.5mL doses of JE-VC and one dose of Havrix (N=62), or one dose of Havrix (N=65). JE virus immunogenicity data were only collected for adults who received JE-VC with or without Havrix. The seroprotection rate in subjects who received JE-VC and Havrix co-administered was non-inferior to JE-VC alone. For this evaluation, these two groups were combined.

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Summary: Randomized, controlled, open-label dose ranging study in which adults (18–49 years) received two 0.5mL doses of JE-VC (N=24), three 0.5mL dose of JE-VC (N=24), two 1.0mL doses of JE-VC (N=25), or three doses of JE-VAX (N=21). For this evaluation, immunogenicity and safety data were included only for subjects who received the licensed regimen of two 0.5mL doses of JE-VC or three doses of JE-VAX.

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Summary: Randomized, controlled, observer-blinded, dose-range study in which adults (≥18 years) received two 0.5mL doses of JE-VC (N=125), one 0.5mL dose of JE-VC (N=124), or one 1.0mL dose of JE-VC (N=124). For this evaluation, immunogenicity and safety data were included only for subjects who received the licensed regimen of two 0.5mL doses of JE-VC.

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Summary: Inactivated Vero cell culture-derived JE vaccine (JE-VC; IXIARO) was licensed in the United States, Europe, and Australia in 2009 for use in adults. Adverse events following vaccination with JE-VC reported to Intercell AG and retrieved from literature searches, VAERS, and domestic pharmacovigilance

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Summary: Randomized, controlled, observer-blinded, non-inferiority study in which adults (≥18 years) received two 0.5mL doses of JE-VC (N=428) or three doses of JE-VAX (N=435). The seroprotection rate in JE-VC recipients was non-inferior to that in JE-VAX recipients.

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Summary: Randomized, placebo-controlled, double-blinded study in which adults (≥18 years) received two 0.5mL doses of JE-VC (N=1,993) or two doses of phosphate buffered saline with 0.1% aluminum hydroxide (N=657).

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Summary: Unpublished data of reports of adverse events received by the Vaccine Adverse Events Reporting System (VAERS) as of May 1, 2013 following immunization with JE-VC administered to persons aged ≥ 17 years over the three years from May 1, 2009 to April 30, 2012, in the United States or among U.S. military personnel stationed abroad. Novartis Vaccines (Cambridge, Massachusetts) provided the estimated 275,848 doses distributed in the United States during this time period. Serious adverse events, hypersensitivity reactions, and neurologic adverse events were actively investigated. Adverse events reported through VAERS and other similar passive surveillance systems may or may not be causally related to the vaccine.

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Summary: Open-label study in the United States in which adults (≥18 years) received two 0.5mL doses of JE-VC (N=123) to evaluate non-inferiority of one dose of JE-VC in previous JE-VAX recipients compared to two doses of JE-VC in previously unvaccinated subjects. Groups were assigned based on previous history of vaccination with JE-VAX. The seroprotection rate in previous JE-VAX recipients was non-inferior to previously unvaccinated. For this evaluation, immunogenicityand safety data were combined for both groups following two doses of JE-VC.

Table 1. Summary of outcome measure ranking and inclusion for use of inactivated Vero cell culture-derived JE vaccine (JE-VC) in children

Outcome	Importance	Include in evidence profile	Data available
Benefits			
Vaccine efficacy to prevent JE disease	Critical	Yes	No
Seroprotection at 1 month after primary series[1]	Critical	Yes	Yes
Seroprotection at 6 months after primary series[1]	Critical	Yes	Yes
Harms			
Serious adverse events[2]	Critical	Yes	Yes
Systemic adverse events[3]	Critical	Yes	Yes
Injection site reactions	Important	No	--
Interference with response to other vaccines	Important	No	--

JE=Japanese encephalitis

[1]Seroprotection defined as a neutralizing antibody titer ≥10 by 50% plaque reduction neutralization test against the JE virus SA14-14-2 strain [Markoff 2000; Hombach 2005].

[2]Serious adverse event defined as any of the following outcomes: 1) death, 2) life-threatening adverse event, 3) inpatient hospitalization, 4) persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or 5) congenital anomaly/birth defect [FDA. 21 CFR 312.32(a); ICH GCP].

[3]Systemic adverse events evaluated include fever, rash, hypersensitivity/urticaria, neurologic, and medically attended adverse events.

Table 2. Seroprotection at 1 month after a 2-dose primary series of inactivated Vero cell culture-derived JE vaccine (JE-VC) administered according to the FDA-approved dose and schedule

				$PRNT_{50}$ titer ≥10			
				JE-VC		Other JE vaccine[1]	
Study	**Sites**	**Type**	**Age group**	No.	(%)	No.	(%)
Kaltenbock 2010	India	RCT	Children (1–2 yrs)	22/23	(96)[2]	10/11	(91)
Dubischar-Kastner 2013(a)	Philippines	Obs[3]	Children (2 mos–17 yrs)	384/385	(99)[4]	--	--
Dubischar-Kastner 2013(b)	U.S./Europe/Australia	Obs	Children (2 mos–17 yrs)	51/51	(100)	--	--
Tauber 2007	U.S./Europe	RCT	Adults (≥18 yrs)	352/361	(98)	347/364	(95)
Lyons 2007	U.S.	RCT	Adults (18–49 yrs)	21/22	(95)	14/19	(74)
Biological E 2013(a)	India	RCT	Adults (18–49 yrs)	53/54	(98)	107/108	(99)
Schuller 2009	Europe	Obs[3]	Adults (≥18 yrs)	110/113	(97)	--	--
Kaltenbock 2009	Europe	Obs[3]	Adults (≥18 yrs)	126/127	(99)	--	--
Woolpert 2012	U.S.	Obs	Adults (≥18 yrs)	88/92	(96)	--	--
Erra 2012	Europe	Obs	Adults (≥18 yrs)	30/31	(97)	13/15	(87)

JE=Japanese encephalitis; $PRNT_{50}$=50% plaque reduction neutralization test; RCT=Randomized controlled trial; Obs=Observational study

[1]Inactivated mouse brain-derived JE vaccine (JenceVac) manufactured by Green Cross (Korea) [Kaltenbock 2010; Erra 2012], inactivated mouse brain-derived JE vaccine (JE-VAX) manufactured by Biken (Japan) [Tauber 2007; Lyons 2007], or inactivated Vero cell culture-derived JE vaccine adsorbed (JEEV) manufactured by Biological E (India) [Biological E 2013(a)].

[2]Of an additional 21 children aged 1–2 years who received two 0.5mL doses of JE-VC, 20 (95%) were seroprotected at 1 month after the second dose.

[3]RCT with no comparative immunogenicity data.

[4]Of an additional 98 children aged 3–11 years who received two 0.25mL doses of JE-VC, 94 (96%) were seroprotected at 1 month after the second dose.

Table 3. Pooled risk ratios for seroprotection at 1 month after a 2-dose primary series of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) in randomized controlled trials in children or adults

Age group	Number of studies	Number of participants	Weight	Pooled risk ratio	(95% confidence interval)*
Children	1	34	5%	1.05	(0.86, 1.29)
Adults	3	928	95%	1.02	(0.96, 1.07)
All	4	962	100%	1.02	(0.97, 1.06)

*Pooled risk ratios computed using the random effects model (Mantel-Haenszel method). Risk ratio = Seroprotection proportion in JE-VC group / Seroprotection proportion in other Japanese encephalitis vaccine group. Risk ratio >1.0 favors JE-VC versus other Japanese encephalitis vaccine.

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.82$, df = 3 (P = 0.12); $I^2 = 48\%$.

Test for overall effect: Z = 0.70 (P = 0.48).

Test for differences between age groups: $Chi^2 = 0.10$, df = 1 (P = 0.75), $I^2 = 0\%$.

Table 4. Seroprotection at 5 to 6 months after completing a 2-dose primary series of inactivated Vero cell culture-derived JE vaccine (JE-VC) administered according to the FDA-approved dose and schedule[1]

				$PRNT_{50}$ titer ≥10			
				JE-VC		Other JE vaccine[2]	
Study	**Sites**	**Type**	**Age group**	No.	(%)	No.	(%)
Dubischar-Kastner 2013(a)	Philippines	Obs[3]	Children (2 mos–17 yrs)	358/389	(89)[4]	--	--
Dubischar-Kastner 2013(b)	U.S./Europe/Australia	Obs	Children (2 mos–17 yrs)	18/18	(100)	--	--
Lyons 2007	U.S.	RCT	Adults (18–49 yrs)	17/17	(100)	7/13	(54)
Schuller 2008	Europe	RCT	Adults (≥18 yrs)	172/181	(95)	61/82	(74)
Dubischar-Kastner 2010 (a)	Europe	Obs	Adults (≥18 yrs)	96/116	(83)	--	--

JE=Japanese encephalitis; $PRNT_{50}$=50% plaque reduction neutralization test; RCT=Randomized controlled trial; Obs=Observational study

[1]For studies in children, follow-up was at 6 months after completing the 2-dose primary series. For studies in adults, follow-up was at 5 months after completing the 2-dose primary series or 6 months after the first dose.

[2]Inactivated mouse brain-derived JE vaccine (JE-VAX) manufactured by Biken (Japan).

[3]RCT with no comparative immunogenicity data.

[4]Of an additional 96 children aged 3–11 years who received two 0.25mL doses of JE-VC, 74 (77%) were seroprotected at 6 months after the second dose.

Table 5. Pooled risk ratios for seroprotection at 5 to 6 months after completing a 2-dose primary series of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) in randomized controlled trials in children or adults

Age group	Number of studies	Number of participants	Weight	Pooled risk ratio	(95% confidence interval)*
Children	0	0	0%	--	--
Adults	2	293	100%	1.40	(1.03, 1.91)
All	2	293	100%	1.40	(1.03, 1.91)

*Pooled risk ratios computed using the random effects model (Mantel-Haenszel method). Risk ratio = Seroprotection proportion in JE-VC group / Seroprotection proportion in other Japanese encephalitis vaccine group. Risk ratio >1.0 favors JE-VC versus other Japanese encephalitis vaccine.

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 1.86$, df = 1 (P = 0.17); $I^2 = 46\%$.

Test for overall effect: Z = 2.15 (P = 0.03).

Test for differences between age groups: Not applicable.

Table 6. Serious adverse events reported within 1 month after either dose of JE-VC

				Serious adverse events			
				JE-VC		Comparison vaccines[1]	
Study	**Sites**	**Type**	**Age group**	No.	(%)	No.	(%)
Kaltenbock 2010	India	RCT	Children (1–2 yrs)	0/48	(0)	0/12	(0)
Dubischar-Kastner 2013(a)[2]	Philippines	RCT	Children (2 mos–17 yrs)	6/1411	(<1)	5/458	(1)
Dubischar-Kastner 2013(b)	U.S./Europe/Australia	Obs	Children (2 mos–17 yrs)	0/60	(0)	--	--
Tauber 2007[3]	U.S./Europe	RCT	Adults (≥18 yrs)	1/428	(<1)	0/435	(0)
Tauber 2008[4]	U.S./Europe/Australia	RCT	Adults (≥18 yrs)	10/1993	(<1)	6/657	(1)
Lyons 2007	U.S.	RCT	Adults (18–49 yrs)	0/24	(0)	0/21	(0)
Biological E 2013(a)	India	RCT	Adults (18–49 yrs)	0/54	(0)	0/108	(0)
Kaltenbock 2009[5]	Europe	RCT	Adults (≥18 yrs)	1/127	(1)	0/65	(0)
Schuller 2009	Europe	Obs[6]	Adults (≥18 yrs)	0/125	(0)	--	--
Woolpert 2012	U.S.	Obs	Adults (≥18 yrs)	0/123	(0)	--	--

[1]Inactivated mouse brain-derived JE vaccine (JenceVac) manufactured by Green Cross (Korea) [Kaltenbock 2010], 7-valent pneumococcal conjugate vaccine (Prevnar 7) manufactured by Wyeth [Dubischar-Kastner 2013(a)], hepatitis A vaccine (Havrix) manufactured by GSK [Dubischar-Kastner 2013(a); Kaltenbock 2009], inactivated mouse brain-derived JE vaccine (JE-VAX) manufactured by Biken (Japan) [Tauber 2007; Lyons 2007], phosphate buffered saline with 0.1% aluminum hydroxide [Tauber 2008], or inactivated Vero cell culture-derived JE vaccine (JEEV) manufactured by Biological E (India) [Biological E 2013(a)].

[2]Six serious adverse events following JE-VC included two febrile seizures (2 days after dose 2 and 20 days after dose 1), cellulitis (9 days after dose 2), gastroenteritis and hematoma (12 days after dose 1), pneumonia (23 days after dose 2), and dengue (24 days after dose 1). Five serious adverse events following comparison vaccines included three febrile seizures (9 days and 4 weeks after Havrix and 4 weeks after Prevnar), dyspnea (14 days after Havrix), and gastroenteritis (20 days after Havrix).

[3]Only serious adverse event following JE-VC was a myocardial infarction at 3 weeks after dose 2.

[4]Ten serious adverse events following JE-VC included one each of rectal hemorrhage, chest pain, limb abscess, appendicitis, facial injury, facial fracture, ulna fracture, adnexal pain, ovarian cyst, and dermatomyositis. Six serious adverse events after placebo included appendicitis (n=2), acute coronary syndrome, proctalgia, urinary calculus, and circulatory collapse.

[5]Only serious adverse event following JE-VC was a seizure in a patient with a history of epilepsy.

[6]RCT with no comparative safety data.

Table 7. Serious adverse events reported within 6 to 7 months after the first dose of JE-VC[1]

				Serious adverse events			
				JE-VC		Comparison vaccines[2]	
Study	**Sites**	**Type**	**Age group**	No.	(%)	No.	(%)
Dubischar-Kastner 2013(a)[3]	Philippines	RCT	Children (2 mos–17 yrs)	23/1411	(2)	11/458	(2)
Dubischar-Kastner 2013(b)[4]	U.S./Europe/Australia	Obs	Children (2 mos–17 yrs)	2/60	(3)	--	--
Dubischar-Kastner 2010 (b)[5]	U.S./Europe/Australia	RCT	Adults (≥18 yrs)	38/3558	(1)	16/1092	(1)

[1]For studies in children, follow-up was at 7 months after the first dose of vaccine. For studies in adults, follow-up was at 6 months after the first dose.

[2]7-valent pneumococcal conjugate vaccine (Prevnar 7) manufactured by Wyeth or hepatitis A vaccine (Havrix) manufactured by GSK [Dubischar-Kastner 2013(a)], inactivated mouse brain-derived JE vaccine (JE-VAX) manufactured by Biken (Japan) or phosphate buffered saline with 0.1% aluminum hydroxide [Dubischar-Kastner 2010 (b)].

[3]Serious adverse events reported in 23 JE-VC recipients included pneumonia (n=6), febrile seizures (n=5), dengue (n=2), gastroenteritis (n=2), and one each with hematoma, cellulitis, hepatitis A, strabismus, car accident, Kawasaki disease, typhoid, upper respiratory infection, urinary tract infection, stillbirth, meningitis, and disseminated intravascular coagulation. One subject had two preferred terms reported (gastroenteritis and hematoma) and two subjects had three preferred terms reported (one with meningitis, pneumonia and disseminated intravascular coagulation, and one with dengue, pharyngitis, and upper respiratory infection). The stillbirth occurred in a subject who became pregnant >4 months after vaccination. One death occurred in a 12 year old male with meningitis, pneumonia, and disseminated intravascular coagulation with onset 4 months after he received dose 2 of JE-VC. Serious adverse events in 11 comparison vaccine recipients included febrile seizures (n=4), pneumonia (n=3), dengue (n=1), gastroenteritis (n=1), familial periodic paralysis (n=1), hyponatremia (n=1), dyspnea (n=1); one subject had two preferred terms reported.

[4]Two serious adverse events in JE-VC recipients included one subject each with diabetes mellitus (3 months after dose 2) and dizziness (4 months after dose 2).

[5]The 38 serious adverse events occurring within 6 months following receipt of JE-VC were not delineated. One death occurred in a 70 year old female with adenocarcinoma of the lung diagnosed 1 month after she received dose 2 of JE-VC.

Table 8. Serious adverse events reported through post-marketing surveillance following receipt of JE-VC in adults[1]

Study	Countries	Reporting Period	Doses distributed	Serious adverse events reported	
				No.	Rate per 100,000 doses distributed
Schuller 2011	U.S./Europe/Australia	Apr 2009–Mar 2010	246,687	4[2]	1.6
VAERS 2013	U.S.	May 2009–Apr 2012	275,848	9[3]	3.3

[1]Adverse events reported through VAERS and other similar passive surveillance systems may or may not be causally related to the vaccine.

[2]One report each of neuritis (9 hours after vaccination), oropharyngeal spasm (day of vaccination), meningismus (1 day after vaccination), and iritis (1 day after vaccination). The patient with iritis had also received typhoid vaccine.

[3]Includes three reports of seizures (day of, 5 days after, and unknown days after vaccination), three reports of hypersensitivity reactions (two on the day of and one 2 days after vaccination), appendicitis (5 days after vaccination), myocarditis (11 days after vaccination), and encephalomyelitis (39 days after vaccination). Two serious adverse events occurred after administration of JE-VC alone, six events occurred after concomitant administration of JE-VC with other vaccines, and for one event it is unknown if the subject received other vaccines.

Table 9. Pooled risk ratios for serious adverse events within 1 month after either dose of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) in randomized controlled trials in children or adults

Age group	Number of studies	Number of Participants	Weight	Pooled risk ratio	(95% confidence interval)*
Children	2	1,929	38%	0.39	(0.12, 1.27)
Adults	5	3,912	62%	0.69	(0.27, 1.73)
All	7	5,841	100%	0.56	(0.27, 1.15)

*Pooled risk ratios computed using the random effects model (Mantel-Haenszel method). Risk ratio = Serious adverse events proportion in JE-VC group / Serious adverse events proportion in control vaccine group. Risk ratio <1.0 favors JE-VC versus control vaccine.

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.86$, df = 3 (P = 0.60); $I^2 = 0\%$.

Test for overall effect: Z = 1.58 (P = 0.11).

Test for differences between age groups: $Chi^2 = 0.56$, df = 1 (P = 0.45); $I^2 = 0\%$.

Table 10. Pooled risk ratios for serious adverse events within 6 to 7 months after the first dose of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) in randomized controlled trials in children or adults

Age group	Number of studies	Number of participants	Weight	Pooled risk ratio	(95% confidence interval)*
Children	1	1,869	40%	0.68	(0.33, 1.38)
Adults	1	4,650	60%	0.73	(0.41, 1.30)
All	2	6,519	100%	0.71	(0.45, 1.11)

*Pooled risk ratios computed using the random effects model (Mantel-Haenszel method). Risk ratio = Serious adverse events proportion in JE-VC group / Serious adverse events proportion in control vaccine group. Risk ratio <1.0 favors JE-VC versus control vaccine.

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0\%$.

Test for overall effect: Z = 1.50 (P = 0.13).

Test for differences between age groups: $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0\%$.

Table 11. Fever reported as a solicited adverse event within 7 days after either dose of JE-VC

				Fever			
				JE-VC		Comparison vaccines[1]	
Study	**Sites**	**Type**	**Age group**	No.	(%)	No.	(%)
Kaltenbock 2010[2]	India	RCT	Children (1–2 yrs)	1/48	(2)	1/12	(8)
Dubischar-Kastner 2013(a)[2]	Philippines	RCT	Children (2 mos–17 yrs)	136/1411	(10)	52/458	(11)
Dubischar-Kastner 2013(b)[3]	U.S./Europe/Australia	Obs	Children (2 mos–17 yrs)	4/60	(7)	--	--
Tauber 2008[4]	U.S./Europe/Australia	RCT	Adults (≥18 yrs)	64/1993	(3)	20/657	(3)
Lyons 2007[5]	U.S.	RCT	Adults (18–48 yrs)	5/24	(21)	1/21	(5)
Woolpert 2012[6]	U.S.	Obs	Adults (≥18 yrs)	6/123	(5)	--	--

[1]Inactivated mouse brain-derived JE vaccine (JenceVac) manufactured by Green Cross (Korea) [Kaltenbock 2010], 7-valent pneumococcal conjugate vaccine (Prevnar 7) manufactured by Wyeth or hepatitis A vaccine manufactured by GSK (Havrix) [Dubischar-Kastner 2013(a)], phosphate buffered saline with 0.1% aluminum hydroxide [Tauber 2008], or inactivated mouse brain-derived JE vaccine (JE-VAX) manufactured by Biken (Japan) [Lyons 2007].

[2]Fever defined as temperature ≥38.0C.

[3]Fever defined as ≥37.7C.

[4]May include unsolicited adverse events of fever that occurred up to 28 days after either dose of JE-VC.

[5]Fever defined as ≥37.6C.

[6]Fever was subjective as reported by the participant.

Table 12. Rash reported as a solicited adverse event within 7 days after either dose of JE-VC

				Rash			
				JE-VC		Comparison vaccines[1]	
Study	**Sites**	**Type**	**Age group**	No.	(%)	No.	(%)
Kaltenbock 2010	India	RCT	Children (1–2 yrs)	1/48	(2)	0/12	(0)
Dubischar-Kastner 2013(a)	Philippines	RCT	Children (2 mos–17 yrs)	48/1411	(3)	15/458	(3)
Dubischar-Kastner 2013(b)	U.S./Europe/Australia	Obs	Children (2 mos–17 yrs)	2/60	(3)	--	--
Tauber 2008[2]	U.S./Europe/Australia	RCT	Adults (≥18 yrs)	26/1993	(1)	10/657	(2)
Lyons 2007	U.S.	RCT	Adults (18–49 yrs)	0/24	(0)	1/21	(5)
Woolpert 2012	U.S.	Obs	Adults (≥18 yrs)	2/123	(2)	--	--

[1]Inactivated mouse brain-derived JE vaccine (JenceVac) manufactured by Green Cross [Kaltenbock 2010], 7-valent pneumococcal conjugate vaccine (Prevnar 7) manufactured by Wyeth or hepatitis A vaccine (Havrix) manufactured by GSK [Dubischar-Kastner 2013(a)], phosphate buffered saline with 0.1% aluminum hydroxide [Tauber 2008], or inactivated mouse brain-derived JE vaccine (JE-VAX) manufactured by Biken (Japan) [Lyons 2007].

[2]May include unsolicited adverse events of rash that occurred up to 28 days after either dose of JE-VC.

Table 13. Hypersensitivity or urticaria reported as an unsolicited adverse event within 1 month after either dose of JE-VC

				Hypersensitivity or urticaria[1]			
				JE-VC		Comparison vaccines[2]	
Study	**Sites**	**Type**	**Age group**	No.	(%)	No.	(%)
Kaltenbock 2010	India	RCT	Children (1–2 yrs)	0/48	(0)	0/12	(0)
Dubischar-Kastner 2013(a)	Philippines	RCT	Children (2 mos–17 yrs)	4/1411	(<1)	1/458	(<1)
Dubischar-Kastner 2013(b)	U.S./Europe/Australia	Obs	Children (2 mos–17 yrs)	0/60	(0)	--	--
Tauber 2008	U.S./Europe/Australia	RCT	Adults (≥18 yrs)	1/1993	(<1)	1/657	(<1)
Woolpert 2012	U.S.	Obs	Adults (≥18 yrs)	0/123	(0)	--	--

[1]Unsolicited adverse events reported within 28 days after vaccination and classified by the study investigator as hypersensitivity or urticaria.

[2]Inactivated mouse brain-derived JE vaccine (JenceVac) manufactured by Green Cross [Kaltenbock 2010], 7-valent pneumococcal conjugate vaccine (Prevnar 7) manufactured by Wyeth or hepatitis A vaccine (Havrix) manufactured by GSK [Dubischar-Kastner 2013(a)], or phosphate buffered saline with 0.1% aluminum hydroxide [Tauber 2008].

Table 14. Neurologic adverse events reported as an unsolicited adverse event within 1 month after either dose of JE-VC

				Neurologic adverse events[1]			
				JE-VC		Comparison vaccines[2]	
Study	**Sites**	**Type**	**Age group**	No.	(%)	No.	(%)
Kaltenbock 2010	India	RCT	Children (1–2 yrs)	0/48	(0)	0/12	(0)
Dubischar-Kastner 2013(a)[3]	Philippines	RCT	Children (2 mos–17 yrs)	5/1411	(<1)	3/458	(<1)
Dubischar-Kastner 2013(b)	U.S./Europe/Australia	Obs	Children (2 mos–17 yrs)	0/60	(0)	--	--
Tauber 2008	U.S./Europe/Australia	RCT	Adults (≥18 yrs)	26/1993	(1)	8/657	(1)
Woolpert 2012	U.S.	Obs	Adults (≥18 yrs)	0/123	(0)	--	--

[1]Unsolicited adverse events reported within 28 days after vaccination and classified by the study investigator as nervous system disorder other than headaches. No cases of meningitis, encephalitis, acute disseminated encephalomyelitis, or Guillain Barré syndrome were reported among JE-VC or comparison vaccine recipients.

[2]Inactivated mouse brain-derived JE vaccine (JenceVac) manufactured by Green Cross [Kaltenbock 2010], 7-valent pneumococcal conjugate vaccine (Prevnar 7) manufactured by Wyeth or hepatitis A vaccine (Havrix) manufactured by GSK [Dubischar-Kastner 2013(a)], or phosphate buffered saline with 0.1% aluminum hydroxide [Tauber 2008].

[3]Five neurologic events reported following JE-VC included three febrile seizures in children aged 1–2 years (2 days after dose 2, 8 days after dose 2, and 2 weeks after dose 1), one child aged 1–2 years with drooling, and one child aged 3–11 years with dizziness. Three neurologic adverse events in the comparison group were all febrile seizures, including an infant aged 2–11 months at 4 weeks after Prevnar, a child aged 1–2 years at 9 days after Havrix, and a child aged 1–2 years at 4 weeks after Havrix. Two of the febrile seizures in JE-VC recipients and all three febrile seizures in the comparison group were reported as serious adverse events.

Table 15. Medically attended adverse events within 1 month after either dose of JE-VC

				Medically attended adverse events			
				JE-VC		Comparison vaccines[1]	
Study	**Sites**	**Type**	**Age group**	No.	(%)	No.	(%)
Dubischar-Kastner 2013(a)	Philippines	RCT	Children (2 mos–17 yrs)	256/1411	(18)	83/458	(18)
Dubischar-Kastner 2013(b)	U.S./Europe/Australia	Obs	Children (2 mos–17 yrs)	3/60	(5)	--	--
Tauber 2008	U.S./Europe/Australia	RCT	Adults (≥18 yrs)	254/1993	(13)	80/657	(12)
Kaltenbock 2009	Europe	RCT	Adults (≥18 yrs)	11/127	(9)	11/65	(17)
Woolpert 2012	U.S.	Obs	Adults (≥18 yrs)	0/123	(0)	--	--

[1]7-valent pneumococcal conjugate vaccine (Prevnar 7) manufactured by Wyeth or hepatitis A vaccine (Havrix) manufactured by GSK [Dubischar-Kastner 2013(a)], hepatitis A vaccine (Havrix) manufactured by GSK [Kaltenbock 2009], or phosphate buffered saline with 0.1% aluminum hydroxide [Tauber 2008].

Table 16. Hypersensitivity reactions reported through post-marketing surveillance following receipt of JE-VC in adults[1]

Study	Countries	Reporting Period	Doses distributed	Hypersensitivity reactions No.	Hypersensitivity reactions Rate per 100,000 doses distributed
Schuller 2011	U.S./Europe/Australia	Apr 2009–Mar 2010	246,687	11[2]	4.5
VAERS 2013	U.S.	May 2009–Apr 2012	275,848	13[3]	4.7

[1]Adverse events reported through VAERS and other similar passive surveillance systems may or may not be causally related to the vaccine.

[2]Eleven reports of possible hypersensitivity, including five reports of rash, and one report each of urticaria, glossodynia, oral hypoaesthesia, oropharyngeal spasm, pruritus, and swollen tongue. One (oropharyngeal spasm) was classified as a serious adverse event.

[3]The 13 events included occurred within 14 days after vaccination. Seven hypersensitivity reactions reported occurred after administration of JE-VC alone and six events occurred after concomitant administration of JE-VC with other vaccines. Three reports were classified as serious adverse events.

Table 17. Neurologic adverse events other than headaches reported through post-marketing surveillance following receipt of JE-VC in adults[1]

Study	Countries	Reporting Period	Doses distributed	Neurologic adverse events No.	Neurologic adverse events Rate per 100,000 doses distributed
VAERS 2013	U.S.	May 2009–Apr 2012	275,848	5[2]	1.8

[1]Adverse events reported through VAERS and other similar passive surveillance systems may or may not be causally related to the vaccine.

[2]Includes one report of encephalitis at 39 days after vaccination with JE-VC and four other vaccines, and four reports of seizures within 5 days after vaccination; three of the subjects with seizures had received other vaccines and for one there was no information available. Four of the reports were classified as serious adverse events.

Table 18. Pooled risk ratios for fever as a solicited adverse event within 7 days after either dose of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) in randomized controlled trials in children or adults

Age group	Number of studies	Number of participants	Weight	Pooled risk ratio	(95% confidence interval)*
Children	2	1,929	63%	0.84	(0.62, 1.13)
Adults	2	2,695	37%	1.49	(0.45, 4.94)
All	4	4,624	100%	0.94	(0.66, 1.32)

*Pooled risk ratios computed using the random effects model (Mantel-Haenszel method). Risk ratio = Proportion with fever in JE-VC group / Proportion with fever in control vaccine group. Risk ratio <1.0 favors JE-VC versus control vaccine.

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.67$, df = 3 (P = 0.30); $I^2 = 18\%$.

Test for overall effect: Z = 0.37 (P = 0.71).

Test for differences between age groups: $Chi^2 = 0.84$, df = 1 (P = 0.36); $I^2 = 0\%$.

Table 19. Pooled risk ratios for rash as a solicited adverse event within 7 days after either dose of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) in randomized controlled trials in children or adults

Age group	Number of studies	Number of participants	Weight	Pooled risk ratio	(95% confidence interval)*
Children	2	1,929	61%	1.03	(0.59, 1.80)
Adults	2	2,695	39%	0.81	(0.40, 1.64)
All	4	4,624	100%	0.94	(0.61, 1.46)

*Pooled risk ratios computed using the random effects model (Mantel-Haenszel method). Risk ratio = Proportion with rash in JE-VC group / Proportion with rash in control vaccine group. Risk ratio <1.0 favors JE-VC versus control vaccine.

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.72$, df = 3 (P = 0.87); $I^2 = 0\%$.

Test for overall effect: Z = 0.28 (P = 0.78).

Test for differences between age groups: $Chi^2 = 0.27$, df = 1 (P = 0.61); $I^2 = 0\%$.

Table 20. Pooled risk ratios for hypersensitivity or urticaria as an unsolicited adverse event within 1 month after either dose of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) in randomized controlled trials in children or adults

Age group	Number of studies	Number of participants	Weight	Pooled risk ratio	(95% confidence interval)*
Children	2	1,929	62%	1.30	(0.15, 11.59)
Adults	1	2,650	38%	0.33	(0.02, 5.26)
All	3	4,579	100%	0.77	(0.14, 4.27)

*Pooled risk ratios computed using the random effects model (Mantel-Haenszel method). Risk ratio = Proportion with hypersensitivity or urticaria in JE-VC group / Proportion with hypersensitivity or urticaria in control vaccine group. Risk ratio <1.0 favors JE-VC versus control vaccine.

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.58$, df = 1 (P = 0.44); $I^2 = 0\%$.

Test for overall effect: Z = 0.30 (P = 0.76).

Test for differences between age groups: $Chi^2 = 0.58$, df = 1 (P = 0.45); $I^2 = 0\%$.

Table 21. Pooled risk ratios for neurologic adverse events other than headache within 1 month after either dose of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) in randomized controlled trials in children or adults

Age group	Number of studies	Number of participants	Weight	Pooled risk ratio	(95% confidence interval)*
Children	2	1,929	23%	0.54	(0.13, 2.25)
Adults	1	2,650	77%	1.07	(0.49, 2.35)
All	3	4,579	100%	0.91	(0.46, 1.82)

*Pooled risk ratios computed using the random effects model (Mantel-Haenszel method). Risk ratio = Proportion with neurologic adverse events in JE-VC group / Proportion with neurologic adverse events in control vaccine group. Risk ratio <1.0 favors JE-VC versus control vaccine.

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.68$, df = 1 (P = 0.41); $I^2 = 0\%$.

Test for overall effect: Z = 0.26 (P = 0.80).

Test for differences between age groups: $Chi^2 = 0.67$, df = 1 (P = 0.41); $I^2 = 0\%$.

Table 22. Pooled risk ratios for medically attended adverse events within 1 month after either dose of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) in randomized controlled trials in children or adults

Age group	Number of studies	Number of participants	Weight	Pooled risk ratio	(95% confidence interval)*
Children	1	1,869	48%	1.00	(0.80, 1.25)
Adults	2	2,842	52%	0.81	(0.41, 1.59)
All	3	4,711	100%	0.97	(0.79, 1.21)

*Pooled risk ratios computed using the random effects model (Mantel-Haenszel method). Risk ratio = Proportion with medically attended adverse events in JE-VC group / Proportion with medically attended adverse events in control vaccine group. Risk ratio <1.0 favors JE-VC versus control vaccine.

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.97$, df = 2 (P = 0.23); $I^2 = 33\%$.

Test for overall effect: Z = 0.23 (P = 0.81).

Test for differences between age groups: $Chi^2 = 0.35$, df = 1 (P = 0.56); $I^2 = 0\%$.

Table 23. Seroprotection, serious adverse events, and systemic adverse events following receipt of JEEV[1,2]

Outcome	JEEV No.	JEEV (%)	JenceVac[3] No.	JenceVac[3] (%)
Seroprotection (PRNT50 titer ≥10) at 1 month after a 2-dose primary series	258/280	(92)	140/142	(99)
Serious adverse events within 1 month of any dose	1/304	(<1)	1/152	(1)
Solicited systemic adverse events within 7 days after any dose				
Fever	34/304	(11)	24/152	(16)
Rash	4/304	(1)	2/152	(1)

[1]JEEV is manufactured by Biological E (Hyderabad, India) with technology licensed from Intercell. JEEV and JE-VC (IXIARO) use the same virus strain, adjuvant, and virus purification; however, no process comparability studies have been completed and it cannot be assumed that the two final vaccine products are the same [Central Drugs Standard Control Organization 2013].

[2]Randomized, controlled, open-label study in India in which children aged 1–2 years received two 0.25mL doses of JEEV (N=304) or three doses of JenceVac (N=152). The seroprotection rate in JEEV recipients was non-inferior to that in JenceVac recipients.

[3]Inactivated mouse brain-derived JE vaccine (JenceVac) manufactured by Green Cross (Korea).

Table 24. Evidence type for benefits and harms for JE-VC in children

Outcome	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other[1]	Evidence type[2]
Benefits							
Seroprotection at 1 month	RCT (4)	No serious	No serious	Yes[3]	No serious	None	2
	Obs (6)	No serious	No serious	No serious	No serious	None	3
Seroprotection at 6 months	RCT (2)	No serious	No serious	Yes[3]	No serious	None	2
	Obs (3)	No serious	No serious	No serious	No serious	None	3
Harms							
Serious adverse events	RCT (8)	Yes[4]	No serious	Yes[5]	No serious	None	3
	Obs (5)	No serious	No serious	Yes[5]	No serious	None	4
Systemic adverse events	RCT (5)	Yes[4]	No serious	No serious	No serious	None	2
	Obs (4)	No serious	No serious	No serious	No serious	None	3

RCT = Randomized controlled trial with JE-VC; Obs = Observational study, RCT without comparative data for the outcome measure, or post-marketing surveillance data.

[1]Publication bias, strength of association, dose response, or opposing plausible residual confounding.

[2]Evidence type:
1 = RCTs or overwhelming evidence from observational studies
2 = RCTs with important limitations, or exceptionally strong evidence from observational studies
3 = Observational studies, or RCTs with notable limitations
4 = Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

[3]Indirectness due to different population (majority of data are in adults). No efficacy data are available but there is a well-established immunologic correlate of protection.

[4]Risk of bias due to inadequate blinding of study participants and personnel.

[5]Indirectness due to different population (majority of data are in adults).

Table 25. Overall quality of evidence for JE-VC in children

Outcome	Study design (# studies)	Finding	Evidence type[1,2]	Overall quality of evidence
Seroprotection at 1 month	RCT (4)	High (>95%) at 1 month	2	2
Seroprotection at 6 months	RCT (2)	Maintained (85-90%) at 6 months	2	
Serious adverse events	RCT (8)	Low incidence; similar to comparison vaccines	3	
Systemic adverse events	RCT (5)	Similar to comparison vaccines	2	

RCT = Randomized controlled trial.

[1]Evidence type:
1 = RCTs or overwhelming evidence from observational studies
2 = RCTs with important limitations, or exceptionally strong evidence from observational studies
3 = Observational studies, or RCTs with notable limitations
4 = Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

[2]Body of evidence for each outcome includes both RCTs and observational studies; the study design that provides higher quality of evidence was selected.

Table 26. Considerations for formulating recommendations for use of JE-VC in children 2 months through 16 years of age at increased risk of travel-related exposure to Japanese encephalitis virus

Key factors	Comments
Evidence type for benefits and harms	• Overall evidence type 2 for vaccine safety and effectiveness using seroprotection as the endpoint • Downgraded due to indirectness (majority of data in adults) and risk of bias (inadequate blinding of study participants and personnel)
Balance between benefits and harms	• JE-VC provides high levels of seroprotection in children following a 2-dose primary series • Serious adverse events are uncommon and rates are similar to those seen with comparison vaccines • Systemic adverse events also occur at rates similar to comparison vaccines
Value	• Prevent a serious disease with no treatment and poor outcomes • Inform decisions about JE vaccination based on a traveler's planned itinerary
Cost-effectiveness	• Not evaluated • Low risk of disease and high vaccine cost • Number of U.S. children who travel to Asia and have an itinerary that puts them at increased risk for JE is likely very low. • Travel vaccines are usually paid for by the travelers themselves; JE-VC is not covered under the Vaccines for Children program or most insurance plans.