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Japanese Encephalitis Vaccines Recommendations of the Advisory Committee on Immunization Practices (ACIP)



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Japanese Encephalitis Vaccines

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Prepared by

Marc Fischer, MD, Nicole Lindsey, MS, J. Erin Staples, MD, PhD, Susan Hills, MBBS

Division of Vector-Borne Infectious Diseases, National Center for Emerging and Zoonotic Infectious Diseases (proposed), CDC

Summary

This report updates the 1993 recommendations by CDC's Advisory Committee on Immunization Practices (ACIP) regarding the prevention of Japanese encephalitis (JE) among travelers (CDC. Inactivated Japanese encephalitis virus vaccine: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 1993;42[No. RR-1]). This report summarizes the epidemiology of JE, describes the two JE vaccines that are licensed in the United States, and provides recommendations for their use among travelers and laboratory workers.

JE virus (JEV), a mosquito-borne flavivirus, is the most common vaccine-preventable cause of encephalitis in Asia. JE occurs throughout most of Asia and parts of the western Pacific. Among an estimated 35,000–50,000 annual cases, 20%–30% of patients die, and 30%–50% of survivors have neurologic or psychiatric sequelae. No treatment exists. For most travelers to Asia, the risk for JE is very low but varies on the basis of destination, duration, season, and activities.

JE vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JEV transmission season and for laboratory workers with a potential for exposure to infectious JEV. JE vaccine should be considered for 1) short-term (<1 month) travelers to endemic areas during the JEV transmission season if they plan to travel outside of an urban area and will have an increased risk for JEV exposure; 2) travelers to an area with an ongoing JE outbreak; and 3) travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel. JE vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside of a well-defined JEV transmission season.

Two JE vaccines are licensed in the United States. An inactivated mouse brain-derived JE vaccine (JE-VAX [JE-MB]) has been licensed since 1992 to prevent JE in persons aged ≥ 1 year traveling to JE-endemic countries. Supplies of this vaccine are limited because production has ceased. In March 2009, an inactivated Vero cell culture-derived vaccine (IXIARO [JE-VC]) was licensed for use in persons aged ≥ 17 years. JE-MB is the only JE vaccine available for use in children aged 1–16 years, and remaining supplies will be reserved for use in this group.

Introduction

Japanese encephalitis virus (JEV), a mosquito-borne flavivirus, is the most common vaccine-preventable cause of encephalitis in Asia (1,2). Japanese encephalitis (JE) occurs throughout most of Asia and parts of the western Pacific (1,3). Among an estimated 35,000–50,000 annual cases, approximately 20%–30% of patients die, and 30%–50% of survivors have neurologic or psychiatric sequelae (4,5). In endemic countries, JE is primarily a disease of children. However, travel-associated

JE, although rare, can occur among persons of any age (6–9). For most travelers to Asia, the risk for JE is very low but varies based on destination, duration, season, and activities (9,10).

JEV is transmitted in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily pigs and wading birds (11,12). JEV is transmitted to humans through the bite of an infected mosquito, but disease develops in <1% of infected persons. JEV transmission occurs primarily in rural agricultural areas. In most temperate areas of Asia, JEV transmission is seasonal, and substantial epidemics can occur. In the subtropics and tropics, transmission can occur year-round, often intensifying during the rainy season.

This report provides recommendations for use of the two JE vaccines licensed in the United States for prevention of JE among travelers and laboratory workers. An inactivated mouse brain-derived JE vaccine (JE-MB) has been available since 1992 for use in travelers aged ≥ 1 year (13). In March 2009, the Food and Drug Administration (FDA) approved a

This report originated in the National Center for Emerging and Zoonotic Infectious Diseases (proposed), Thomas Hearn, PhD, Acting Director, and the Division of Vector-Borne Infectious Diseases, Lyle Petersen, MD, Director.

Corresponding preparer: Marc Fischer, MD, Division of Vector-Borne Infectious Diseases, National Center for Emerging and Zoonotic Infectious Diseases (proposed), CDC, 3150 Rampart Road, MS P-02, Fort Collins, CO 80521. Telephone: 970-221-6489; Fax: 970-266-3568; E-mail: mfischer@cdc.gov.

new inactivated Vero cell culture-derived JE vaccine (JE-VC) for use in persons aged ≥ 17 years (14).

Methods

The Advisory Committee on Immunization Practices (ACIP) JE vaccine workgroup* first met in October 2006 to review available information on the risk for JE for travelers, begin revising recommendations for the use of the available vaccine, and develop recommendations for the use of a new vaccine. In addition to ACIP members, the workgroup included participants from CDC, FDA, National Institutes of Health, Department of Defense, Public Health Agency of Canada, European Centre for Disease Prevention and Control, American Academy of Pediatrics, International Society of Travel Medicine, American Society of Tropical Medicine and Hygiene, PATH JE Project, American Osteopathic Association, National Association of Pediatric Nurse Practitioners, Association of Immunization Managers, Washington State Department of Health, and the University of Liverpool. Workgroup members included persons with expertise in JE, infectious diseases, travel medicine, public health, biostatistics, immunization safety, and vaccine policy.

The workgroup reviewed JE epidemiology, incidence of and risk factors for travel-associated JE disease, measures available to prevent JE disease, and the efficacy, immunogenicity, safety, cost-effectiveness, and availability of JE vaccine. Primary sources were published, peer-reviewed studies; however, unpublished data also were considered. Articles were identified through searches of the PubMed, Global Health, and EMBASE databases, review of relevant bibliographies, and consultation with subject-matter experts.

The workgroup held regular conference calls and met three times. Recommendation options were developed and discussed. When definitive research evidence was lacking, the recommendations incorporated expert opinion of the workgroup members. The workgroup presented progress reports and preliminary recommendations to ACIP during its February 2008 and October 2008 meetings. Proposed recommendations and a draft statement were presented to ACIP and approved at the June 2009 meeting.

ACIP will review additional data as these are made available, particularly regarding any adverse events following receipt of JE-VC that are reported during postmarketing surveillance studies. Recommendations will be updated as needed.

*A list of the members appears on page 27 of this report.

Background

JEV Transmission

JEV is a single-stranded RNA virus that belongs to the genus *Flavivirus* and is closely related to West Nile, St. Louis encephalitis, yellow fever, and dengue viruses (15,16). Four genotypes of JEV have been identified (17). JEV is an arthropod-borne virus (arbovirus) that is transmitted in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily pigs and wading birds (Figure 1) (12,18–22). Because of rapid population turnover with a large number of susceptible offspring and the development of high-titered JEV viremias, domestic pigs are the most important source of infection for mosquitoes that transmit JEV to humans (11,22–26).

JEV is transmitted to humans through the bites of infected mosquitoes. Humans usually do not develop a level or duration of viremia sufficient to infect mosquitoes (12,27). Therefore, humans are dead-end hosts, and human JE cases imported into nonendemic areas represent a minimal risk for subsequent transmission of the virus. Direct person-to-person spread of JEV does not occur except rarely through intrauterine transmission (1,28,29). On the basis of experience with similar flaviviruses, blood transfusion and organ transplantation also are considered potential modes of JEV transmission (30,31).

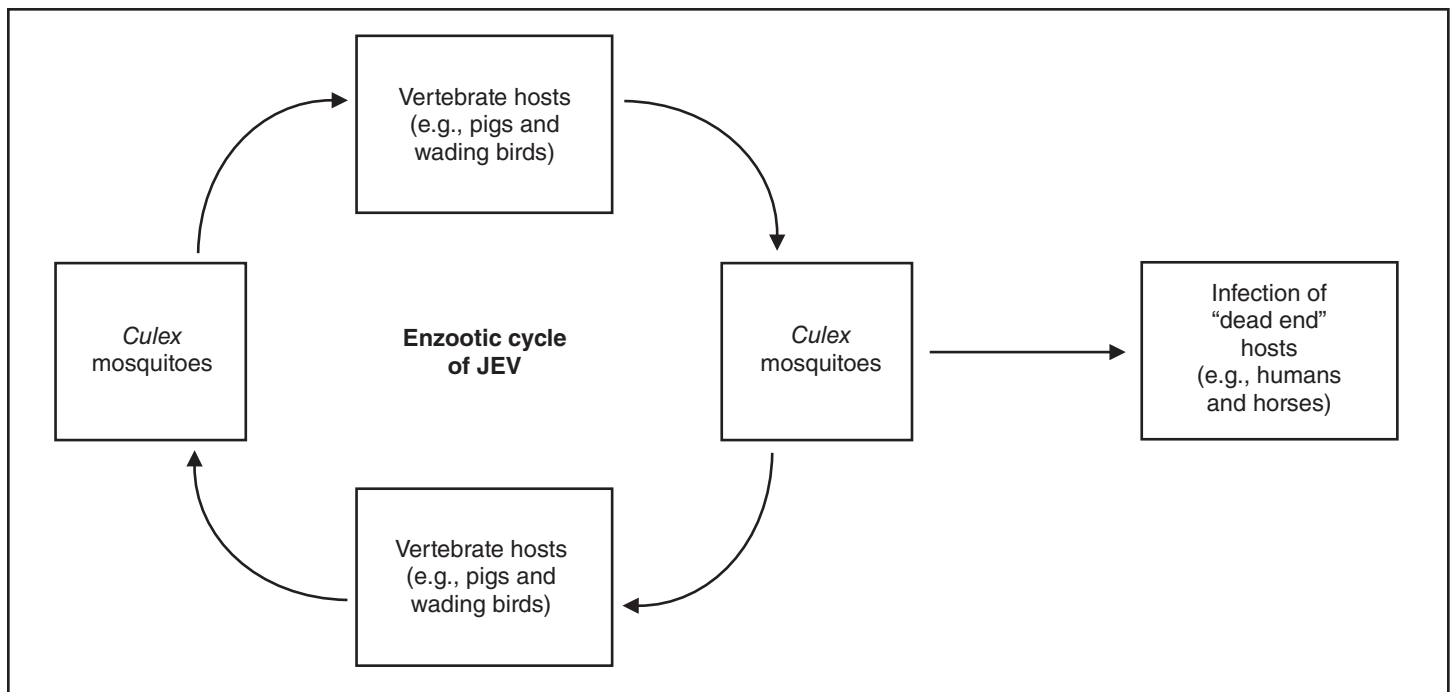
Culex mosquitoes, especially *Cx. tritaeniorhynchus*, are the principal vector for both zoonotic and human JEV transmission throughout Asia (11,12,18,21,32–39). *Cx. tritaeniorhynchus* is an evening- and nighttime-biting mosquito that feeds preferentially on large domestic animals and birds and only infrequently on humans. *Cx. tritaeniorhynchus* feed most often in the outdoors, with peak feeding activity occurring after sunset (20). Larvae are found in flooded rice fields, marshes, and other small stagnant collections of water (37,38). In temperate zones, this vector is present in greatest density from June through November; it is inactive during winter months (20,40,41). In certain parts of Asia, other mosquito species also might be important JEV vectors (12,36,38,40).

Epidemiology of JE

Geographic Distribution and Spread

JE occurs throughout most of Asia and parts of the western Pacific (Figure 2). During the first half of the 20th century, the disease was recognized principally in temperate areas of Asia including Japan, Korea, Taiwan, and mainland China (42–50). Over the past few decades, the disease appears to have spread south and west with increased JEV transmission reported in Southeast Asia, India, Bangladesh, Sri Lanka, and Nepal (35,44,48,51–62). In the 1990s, JEV spread east and

FIGURE 1. Transmission cycle of Japanese encephalitis virus (JEV)*



*JEV is transmitted in an enzootic cycle between *Culex* mosquitoes and amplifying vertebrate hosts, primarily pigs and wading birds. Humans are a dead-end host in the JEV transmission cycle with brief and low levels of viremia. Humans play no role in the maintenance or amplification of JEV, and the virus is not transmitted directly from person to person.

was recognized for the first time in Saipan and then Australia, initially in the outer Torres Strait islands and subsequently on the northern mainland (63–65). The reasons for this increased geographic distribution are uncertain but might include population shifts or changes in climate, ecology, agricultural practices, animal husbandry, or migratory bird patterns (38,48,65). These factors could contribute to further spread, including potentially beyond Asia and the western Pacific.

Incidence and Burden of Disease

In the early 1970s, more than 100,000 cases of JE were reported each year, with the vast majority from China (49,66). Because of vaccine use, increased urbanization, changes in agricultural practices, and mosquito control, annual JE case counts have declined substantially during the past 30 years (66). Up to 30,000 cases of JE still are reported each year (5). However, as a result of poor diagnostic and surveillance capacity in many endemic countries, this number likely represents an underestimate of the true burden of disease (5,66). Among children in endemic countries, the incidence of laboratory-confirmed JE varies widely from year to year and area to area (range: 5–50 cases per 100,000 children per year) (12,41,42,47,66–70).

Ecologic and Seasonal Patterns

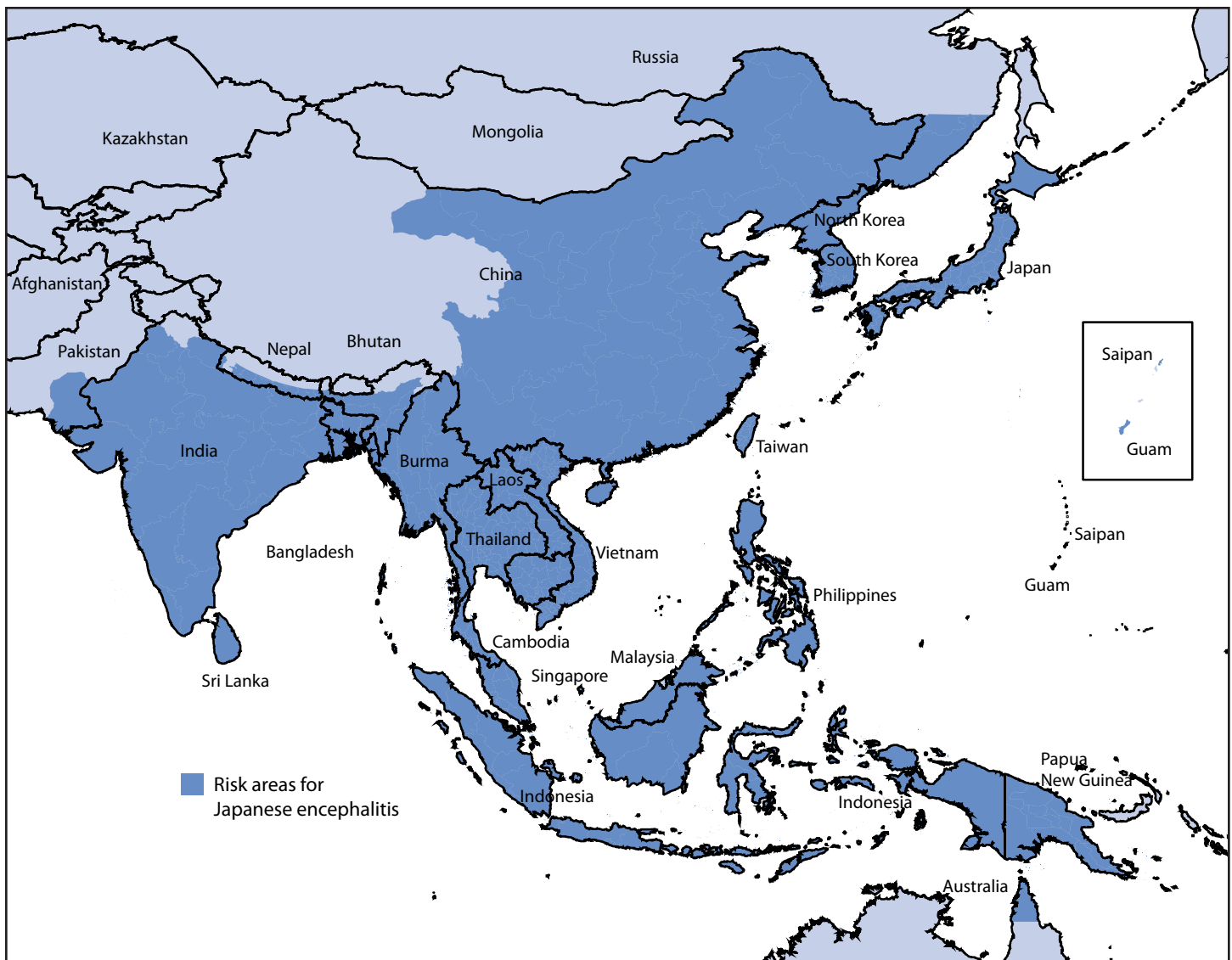
The risk for JE varies by local ecology and season. JEV transmission occurs primarily in rural agricultural areas, often associated with rice production and flooding irrigation, where large numbers of vector mosquitoes breed in close proximity to animal reservoirs (18,21). In some areas of Asia, these ecologic conditions might occur near, or rarely within, urban centers (71).

In temperate areas of Asia, JEV transmission is seasonal, and human disease usually peaks in the summer and fall (41,42,46,47,50,60,62,72). Seasonal epidemics can be explosive, with thousands of JE cases occurring over a period of several months. In the subtropics and tropics, transmission can occur year-round, often with a peak during the rainy season (48,51,56,70).

Age-Specific Patterns

In endemic areas, JE is primarily a disease of childhood, with the vast majority of cases occurring among children aged <15 years (41,46,47,50–52,60,62,70,73–75). However, in areas with childhood JE immunization programs, the overall incidence of JE decreases, and similar numbers of cases are observed among children and adults (42,43,50). In both Japan in 2002 and northern China in 2006, outbreaks were reported in which the majority of cases occurred among older adults

FIGURE 2. Approximate geographic range of Japanese encephalitis



SOURCE: Fischer M, Griggs A, Staples J. Japanese encephalitis. In: Brunette G, ed. Health information for international travel 2010. Atlanta: US Department of Health and Human Services, Public Health Service; 2009:74–81.

(76,77). Because unvaccinated travelers from nonendemic countries usually are immunologically naïve, travel-associated JE can occur in persons of any age.

Clinical Manifestations and Diagnosis

Signs and Symptoms

The majority of human infections with JEV are asymptomatic; <1% of people infected with JEV develop clinical disease (12,67,68,73,77–79). Acute encephalitis is the most commonly identified clinical syndrome with JEV infection (12,72,80–82). Milder forms of disease (e.g., aseptic meningitis

or undifferentiated febrile illness) also can occur but have been reported more commonly among adults (72,83,84).

Among patients who develop clinical symptoms, the incubation period is 5–15 days. Illness usually begins with acute onset of fever, headache, and vomiting (55,85,86). Mental status changes, focal neurologic deficits, generalized weakness, and movement disorders might occur over the next few days (55,82,85–90). Seizures are common, especially among children (85–87,90–92). The classical description of JE includes a parkinsonian syndrome with mask-like facies, tremor, cogwheel rigidity, and choreoathetoid movements (82,93). Acute flaccid paralysis, with clinical and pathological features

similar to poliomyelitis, also has been associated with JEV infection (93,94). Status epilepticus, brain hypoxia, increased intracranial pressure, brainstem herniation, and aspiration pneumonia are the most common complications associated with poor outcome and death (82,85,91,95).

Although information on the burden of JEV infection in pregnancy is limited, miscarriages and an intrauterine infection following maternal JE have been reported. In India, four miscarriages were reported among nine infected pregnant women; all of the women who miscarried were in the first or second trimester of pregnancy (28,29). JEV was isolated in one of the four aborted fetuses, suggesting that intrauterine transmission of JEV can occur (28).

Clinical Laboratory Findings and Neuroimaging

Clinical laboratory findings with JE are nonspecific and might include moderately elevated white blood cell count, mild anemia, and hyponatremia (72,82,85,86,90). Thrombocytopenia and elevated hepatic enzymes have been noted (86). Cerebrospinal fluid (CSF) usually shows a lymphocytic pleocytosis with moderately elevated protein (52,55,72,74,82,85,87,90).

Magnetic resonance imaging (MRI) of the brain is better than computed tomography (CT) for detecting JEV associated abnormalities such as changes in the thalamus, basal ganglia, midbrain, pons, and medulla (96,97). Thalamic lesions are the most commonly described abnormality; although these can be highly specific for JE in the appropriate clinical context, they are not a very sensitive marker of JE (98).

Laboratory Diagnosis

JEV infections are confirmed most frequently by detection of virus-specific antibody in CSF or serum (12,99–103). Because humans have low or undetectable levels of viremia by the time distinctive clinical symptoms are recognized, virus isolation and nucleic acid amplification tests (NAAT) are insensitive and should not be used for ruling out a diagnosis of JE (104,105). In one study in Thailand, of 30 nonfatal cases involving persons with JEV infection of the central nervous system (CNS), none had virus isolated from plasma or CSF (100). By contrast, JEV was isolated from CSF in five (33%) of 15 fatal cases, and from brain tissue in 8 (73%) of 11 fatal cases. More recent studies have shown the utility of NAAT for diagnosing JE in some patients with encephalitis or aseptic meningitis, but this method still lacks the sensitivity needed for routine diagnosis (84,106).

Acute-phase specimens should be tested for JEV-specific immunoglobulin (Ig) M antibodies using a capture enzyme-

linked immunosorbent assay (MAC ELISA) (12,99–103). JEV-specific IgM antibodies can be measured in the CSF of most patients by 4 days after onset of symptoms and in serum by 7 days after onset (99,100). JEV-specific IgM antibodies in CSF indicate recent CNS infection and can help distinguish clinical disease attributed to JEV from previous vaccination (99). With clinical and epidemiologic correlation, a positive IgM test has good diagnostic predictive value, but cross-reaction with arboviruses from the same family can occur. Plaque reduction neutralization tests (PRNT) can be performed to measure virus-specific neutralizing antibodies. A fourfold or greater rise in virus-specific neutralizing antibodies between acute- and convalescent-phase serum specimens collected 2–3 weeks apart may be used to confirm recent infection or to discriminate between cross-reacting antibodies attributed to other primary flaviviral infections. In patients who have been infected previously by another flavivirus or vaccinated with a flaviviral vaccine (e.g., JE or yellow fever vaccine) and who then acquire a secondary flaviviral infection, cross-reactive antibodies in both the ELISA and neutralization assays might make identifying a specific etiologic agent difficult. Vaccination history, date of onset of symptoms, and information regarding other arboviruses known to circulate in the geographic area that might cross-react in serologic assays should be considered when interpreting results. Diagnostic testing for JE is available in select state public health laboratories and at CDC's Division of Vector-Borne Infectious Diseases in Colorado (available at http://www.cdc.gov/ncidod/dvbid/misc/arboviral_shipping.htm; telephone 970-221-6400).

Treatment and Management

JE therapy consists of supportive care and management of complications. No specific antiviral agent or other medication to mitigate the effects of JEV infection is available (107). In controlled clinical trials, corticosteroids, interferon alpha-2a, or ribavirin did not improve clinical outcome (108–110).

Outcome and Sequelae

JE has a case-fatality ratio of approximately 20%–30% (46,47,53,56,62,74,75,82,85–87,111,112). Although some motor deficits and movement disorders improve after the acute illness, 30%–50% of JE survivors have neurologic or psychiatric sequelae even years later (66,74,82,85,87,93,109,111,113–117). These include seizures, upper and lower motor neuron weakness, cerebellar and extrapyramidal signs, flexion deformities of the arms, hyperextension of the legs, cognitive deficits, language impairment, learning difficulties, and behavioral problems (82). Because of the lack of specific antiviral therapy, high case fatality, and substantial morbidity, prevention of JE through vaccination and mosquito precautions is important.

JE Among Travelers

For most travelers to Asia, the risk for JE is very low but varies on the basis of destination, duration, season, and activities (3,9,10,13,118). The overall incidence of JE among persons from nonendemic countries traveling to Asia is estimated to be less than one case per 1 million travelers. However, the risk for JE among expatriates and travelers who stay for prolonged periods in rural areas with active JEV transmission is likely similar to that among the susceptible resident population. 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 (119–121). Short-term (<1 month) travelers whose visits are restricted to major urban areas are at minimal risk for JE. Because JEV is maintained in an enzootic cycle between animals and mosquitoes, in endemic areas where few human cases occur among residents as a result of vaccination or natural immunity, susceptible visitors might be at risk for infection. JE should be suspected in any patient with evidence of a neurologic infection (e.g., encephalitis, meningitis, or acute flaccid paralysis) who has recently returned from a country in Asia or the western Pacific in which JE is endemic.

During 1973–2008, a total of 55 cases of travel-associated JE among persons from nonendemic countries were reported in the literature (6–8,119–139). A small increase in the number of reported cases occurred in each of the three most recent 10-year periods: 1999–2008 (n = 20), 1989–1998 (n = 17), and 1979–1988 (n = 14). Two cases were reported during 1973–1978, and for two additional published cases, the date of onset was unknown but occurred before 1993. Overall, 33 (60%) cases occurred in tourists, nine (16%) were in expatriates, and six (11%) were in soldiers; the type of travel was unknown in seven (13%) cases. The tourist category included three case-patients who were traveling to visit friends and relatives and two students on study-abroad programs. The case-patients were citizens of 17 different countries. The countries where infection was most commonly acquired were Thailand (n = 19), Indonesia (n = 8), China (n = 7), the Philippines (n = 5), Japan (n = 4), and Vietnam (n = 3). Among the 46 cases for which age was recorded, patients ranged in age from 1 to 91 years (median: 34 years); five (9%) of the 55 cases occurred among children aged ≤10 years and 10 (18%) among adults aged ≥60 years. Overall, 29 (53%) of the 55 case-patients were male, and 22 (40%) were female; sex was unknown for four cases (7%). Ten (18%) of the reported cases were fatal, 24 (44%) patients survived but had sequelae, and 12 (22%) patients recovered fully; outcome was unknown for nine (16%) patients. None of the patients was known to have received JE vaccine.

For 37 (67%) of the travel-associated cases, more complete information on itineraries and activities was available (8). Many reports documented exposures that likely increased risk for infection, including travel to rural areas, living in proximity to farms or in the jungle, staying in unscreened accommodations, or participating in outdoor activities such as trekking. Duration of travel for these cases ranged from 10 days to 34 years and was ≥1 month for 24 (65%) travelers. Of the 13 travelers staying <1 month, 10 (77%) had trip duration of 2–<4 weeks, and three (23%) traveled for 10–12 days. Among these shorter-term travelers, three (23%) travelers spent the majority of their time in rural areas, six (46%) stayed in coastal or nonrural areas but took day trips to rural areas or national parks, and one (8%) stayed in a coastal area and took day trips to unspecified destinations; no exposure-related information was provided for three (23%) travelers. No cases occurred among business or other short-term travelers who visited only urban areas.

Before 1973, >300 cases of JE were reported among U.S. military personnel or their family members (72,79,140–143). Of 15 JE cases reported among travelers from the United States during 1973–2008, only four were reported after 1992, when JE-MB was first licensed in the United States; none of these patients had received JE vaccine (7,122).

In 2004, an estimated 5.5 million entries of U.S. travelers occurred into JE-endemic countries (144). The proportion of these travelers who received JE vaccine or for whom JE vaccine should have been recommended is unknown. However, <30,000 doses of JE vaccine are distributed annually in the U.S. civilian market. A recent survey of adult travelers on direct flights from the United States to Asia determined that 415 (25%) of 1,691 participants described itineraries for which JE vaccination should have been considered according to ACIP recommendations, including 330 (20%) who planned to spend >30 days in a JE-endemic country and another 85 (5%) shorter-term travelers who planned to spend a substantial proportion of their time in endemic rural areas (145). Of these at-risk travelers, only 47 (11%) reported receiving ≥1 dose of JE vaccine. Among 164 unvaccinated at-risk travelers who had visited a health-care provider to prepare for their trip, 113 (69%) indicated that their health-care provider had not offered or recommended JE vaccine. In Europe, an assessment based on the number of JE vaccine doses distributed suggested that <1% of travelers to endemic countries received JE vaccine (118), underscoring the need for health-care providers to understand the risks for JE disease among travelers and the measures available to prevent it.

JE Vaccines

JE Vaccines Licensed in the United States

Two JE vaccines are licensed in the United States; an inactivated mouse brain–derived vaccine (JE-VAX [JE-MB]) and an inactivated Vero cell culture–derived vaccine (IXIARO [JE-VC]) (Table 1). JE-MB has been licensed in the United States since 1992 for use in travelers aged ≥ 1 year (13,146). In 2006, production of JE-MB was discontinued, and the remaining supplies are limited. JE-MB had been manufactured in Japan by The Research Foundation for Microbial Diseases of Osaka University (Biken, Osaka, Japan) and is currently distributed in the United States by Sanofi Pasteur (Swiftwater, Pennsylvania). In March 2009, FDA approved JE-VC for use in persons aged ≥ 17 years (14). JE-VC is manufactured by Intercell Biomedical (Livingston, United Kingdom) and is distributed in the United States by Novartis Vaccines (Cambridge, Massachusetts). Because JE-VC is approved only for use in persons aged ≥ 17 years, JE-MB remains the only JE vaccine approved for use in children in the United States. To meet the JE vaccine needs for children in the United States, Sanofi Pasteur has reserved its remaining JE-MB inventory for use in children aged 1–16 years. Health-care providers should contact Sanofi Pasteur to order doses of JE-MB. Other JE vaccines, including live-attenuated SA₁₄-14-2 JE vaccine, are manufactured and used in Asia but are not licensed for use in the United States (5,147,148).

Correlates of Protection

Because several effective JE vaccines are available in Asia, randomized, controlled efficacy trials to evaluate new JE vaccines would be logistically difficult and potentially unethical. JE-VC was licensed on the basis of its ability to induce JEV-specific neutralizing antibodies, which is thought to be a reliable surrogate of efficacy (149,150). Observations from the 1930s indicated that laboratory workers who had been exposed accidentally to JEV were protected from disease when they had measurable neutralizing antibodies (151). These observations are further supported by passive antibody transfer and active immunization studies in animals using both licensed and experimental JE vaccines. Subsequent studies in mice indicated that passive transfer of neutralizing antibodies protected animals against JEV challenge and established a dose-response relationship between antibody titer and level of protection (69,151–153). These studies also indicated that animals that have been actively primed to respond to JEV antigen but that have no detectable neutralizing antibodies are protected from lethal challenge, demonstrating an effec-

TABLE 1. Composition, storage, dose, and administration of inactivated Vero cell culture–derived Japanese encephalitis vaccine (JE-VC) and inactivated mouse brain–derived JE vaccine (JE-MB)

Characteristic	JE-VC	JE-MB
Trade name	IXIARO	JE-VAX
JEV* strain	SA ₁₄ -14-2	Nakayama-NIH
JEV seed	Attenuated	Wild-type
Substrate	Vero cells	Mouse brains
Adjuvant	Aluminum hydroxide	None
Stabilizer	None	Porcine gelatin
Preservative	None	Thimerosal
Final preparation	Liquid	Lyophilized
Storage	35°–46°F (2°–8°C)	35°–46°F (2°–8°C)
Dose	0.5 mL	1.0 mL [†]
Route	Intramuscular	Subcutaneous
Primary series	2 doses at 0 and 28 days	3 doses at 0, 7, and 30 days
Age group	≥ 17 yrs	≥ 1 yr

* JE virus.

[†] 0.5 mL for children aged 1 and 2 years.

tive anamnestic immune response (153). A more recent study indicated that hyperimmune ascitic fluid raised against two JE vaccines derived from genotype III JEV strains (i.e., JE-MB derived from the Nakayama-NIH strain and a developmental chimeric vaccine derived from the SA₁₄-14-2 strain) protected mice against intracerebral challenge with JEV strains of all four genotypes. These data demonstrate that neutralizing antibodies provide protection against heterologous JEV genotypes (154). In another study, mice were passively immunized with pooled sera with JEV neutralizing antibody titers (range: 20–200 titers) from humans immunized with JE-VC. The mice were challenged 18 hours later with a lethal dose of either a genotype I (KE093) or genotype III (SA₁₄) JEV strain (155). Mice with *ex vivo* JE neutralizing antibody titers of ≥ 10 had survival rates of 86% (6/7) and 100% (10/10) after challenge with the genotype I and III JEV strains, respectively. In mice receiving lower-titer sera, protection against JEV challenge correlated with the anti-JEV neutralizing antibody titer of the immunizing sera. Mice actively vaccinated with varying doses of JE-VC and JE-MB also had dose-dependent protection against intraperitoneal challenge with the JEV SA₁₄ strain (155). Finally, in a study designed to develop a JE animal model in nonhuman primates, 16 rhesus macaques were challenged intranasally with a 90% effective dose of JEV (i.e., a dose that when administered via intranasal challenge would be expected to cause encephalitis in 90% of the animals), including four monkeys that were immunized with 4 doses of inactivated mouse brain–derived JE vaccine, eight monkeys immunized with one of two developmental JE poxvirus vaccines, and four JEV-naïve control monkeys (156,157). The minimum neutralizing antibody titer required to protect the monkeys from lethal challenge was between 30 and 46. The higher titers required

for protection in this study might have been caused by the high challenge dose used to develop the model.

The PRNT is the most commonly accepted test to measure functional antibody able to inactivate or neutralize virus. A World Health Organization (WHO) expert panel accepted a 50% PRNT (PRNT₅₀) titer of ≥ 10 as an immunologic correlate of protection from JE in humans (150). The PRNT₅₀ titer is the reciprocal of the endpoint serum dilution that reduces the challenge virus plaque count by 50%. PRNT is a functional assay that can be performed using various protocols, and the validity and comparability of PRNT results depend on detailed components of the selected assay (e.g., endpoint neutralization, incubation conditions, cell substrate, and target virus) (150,158). JEV PRNTs are performed only at selected reference laboratories, but careful attention must be paid to the characteristics and validation of a PRNT assay that is used to measure and compare JEV neutralizing titers as a surrogate for efficacy.

Inactivated Vero Cell Culture-Derived JE Vaccine (IXIARO [JE-VC])

Vaccine Composition, Storage, and Handling

JE-VC is an inactivated vaccine derived from the attenuated SA₁₄₋₁₄₋₂ JEV strain propagated in Vero cells (Table 1) (14,159,160). Each 0.5-mL dose contains approximately 6 μg of purified, inactivated JEV proteins and 0.1% aluminum hydroxide as an adjuvant. The finished product does not include gelatin stabilizers, antibiotics, or thimerosal.

The vaccine should be stored at 35°–46°F (2°–8°C); it should not be frozen. The vaccine should be protected from light. During storage, the vaccine might appear as a clear liquid with a white precipitate. After agitation, it forms a cloudy white suspension.

Immunogenicity of JE-VC

Noninferiority of Immunogenicity Compared with JE-MB

No efficacy data exist for JE-VC. The vaccine was licensed on the basis of its ability to induce JEV neutralizing antibodies as a surrogate for protection and safety evaluations in approximately 5,000 adults. The pivotal noninferiority immunogenicity study compared 2 doses of JE-VC given on days 0 and 28 to 3 doses of JE-MB given on days 0, 7, and 28 to adults aged ≥ 18 years in the United States, Austria, and Germany (161). In the “per protocol” analysis, 352 (96%) of

365 JE-VC recipients developed a PRNT₅₀ ≥ 10 compared with 347 (94%) of 370 JE-MB recipients at 28 days after the last dose (Table 2) (14,161). The proportion of recipients who seroconverted differ slightly between the package insert and published manuscript because of the inclusion of four additional JE-VC recipients and six additional JE-MB recipients in the per protocol analysis provided in the package insert (14,161). Most subjects in each group had a PRNT₅₀ > 40 (Figure 3). The PRNT₅₀ geometric mean titer (GMT) for JE-VC recipients was 244 compared with 102 for JE-MB recipients. However, the target JEV strain in the neutralizing antibody assay was SA₁₄₋₁₄₋₂, which is the JEV strain used in JE-VC, whereas JE-MB is produced from the Nakayama JEV strain. In a subset of these specimens that were evaluated using Nakayama as the target JEV strain, the PRNT₅₀ GMT for JE-VC recipients (n = 88) was 240 compared with 1,219 for the JE-MB recipients (n = 89) (Intercell Biomedical, unpublished data, 2007). In another smaller subset of specimens, PRNT₅₀ GMTs against other JEV strains were variable (Figure 4) (Intercell Biomedical, unpublished data, 2007).

Immunogenicity Data Supporting the 2-Dose Primary Series

The licensed vaccine schedule was derived in part on the basis of a study that compared two 6- μg doses of vaccine administered 28 days apart to a single dose of either 6 μg or 12 μg (162). At 28 days after receiving 1 dose of the standard 6- μg regimen, only 95 (41%) of 230 JE-VC recipients had seroconverted with a PRNT₅₀ ≥ 10 (Figure 5). At 56 days after receiving their first dose of vaccine, 97% (110/113) of the subjects who had received 2 doses had a PRNT₅₀ ≥ 10 compared with only 26% (30/117) and 41% (47/114) of the subjects who received a single 6- μg or 12- μg dose, respectively. All of the 2-dose recipients who seroconverted had protective antibodies as early as 7 days after receiving the second dose of vaccine.

Immunogenicity in Persons with Preexisting Flavivirus Antibodies

A study that evaluated the effect of pre-existing antibodies against tick-borne encephalitis virus (TBEV), another flavivirus, determined that TBEV antibodies enhanced the response to JE-VC after the first dose but had no effect following the 2-dose primary series (163). Following 1 dose of JE-VC, 62 (77%) of 81 subjects with preexisting TBEV IgG antibodies developed protective antibodies against JEV compared with only 166 (49%) of 339 JE-VC recipients with no preexisting TBEV antibodies (Table 3). However, after the second dose of JE-VC, subjects with and without TBEV antibodies had similarly high rates of seroconversion against JEV at 96% (78/81)

TABLE 2. Seroconversion rates and geometric mean titers for inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) and inactivated mouse brain-derived JE vaccine (JE-MB) recipients at 56 days after the first dose*

Measure	JE-VC† (N = 365)		JE-MB§ (N = 370)		Rate difference (CI)
	SCR (%)	(95%CI¶) (%)	SCR (%)	(CI) (%)	
Seroconversion rates (SCR)** ††	96	(94–98)	94	(91–96)	2.6 (-0.5–6.0)§§
	(N = 361)		(N = 364)		
	GMT	(CI)	GMT	(CI)	GMT ratio (CI)
Geometric mean titers (GMT)††	244	(216–274)	102	(90–115)	2.3 (2.0–2.8)¶¶

SOURCES: Food and Drug Administration. Product approval information [package insert]. Ixiaro (Japanese encephalitis virus vaccine inactivated). InterCell Biomedical, Livingston, United Kingdom. Washington, DC: Food and Drug Administration; 2009. Available at <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm179132.htm>. Tauber E, Kollaritsch H, Korinek M, et al. Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. *Lancet* 2007;370:1847–53.

* Per-protocol analysis; prevaccination plaque reduction neutralization test (PRNT) <10 for all subjects.

† Two doses administered at days 0 and 28 with 1 placebo dose at day 7.

§ Three doses administered at days 0, 7, and 28.

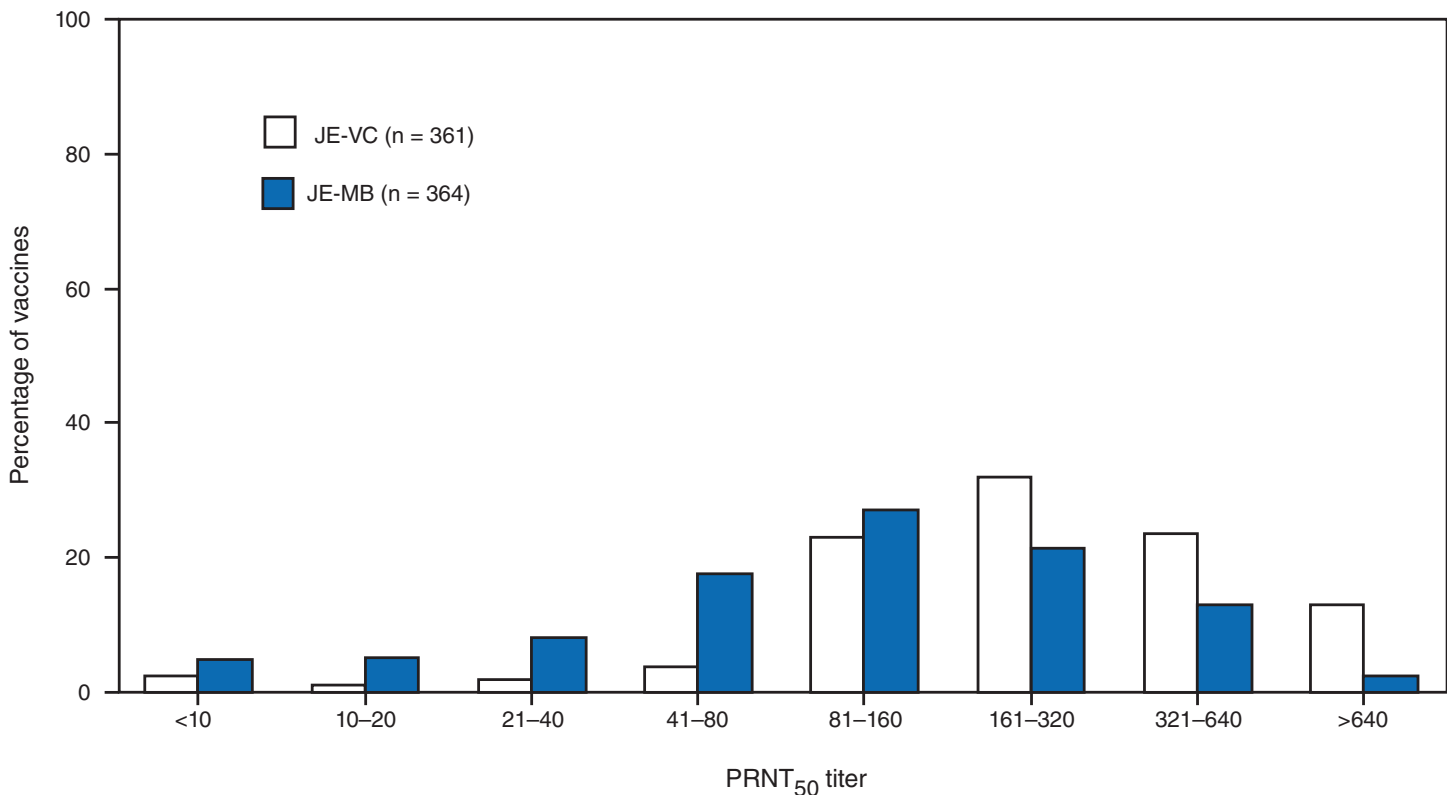
¶ Confidence interval.

** Proportion of vaccinees with 50% PRNT₅₀ titer ≥10 at 56 days after the first dose.

†† PRNT₅₀ assay used SA₁₄₋₁₄₋₂ JEV strain as the challenge virus.

§§ Noninferiority of JE-VC compared with JE-MB was demonstrated based on the lower bound of the two-sided CI for the seroconversion rate difference (JE-VC minus JE-MB) being > -10% at day 56.

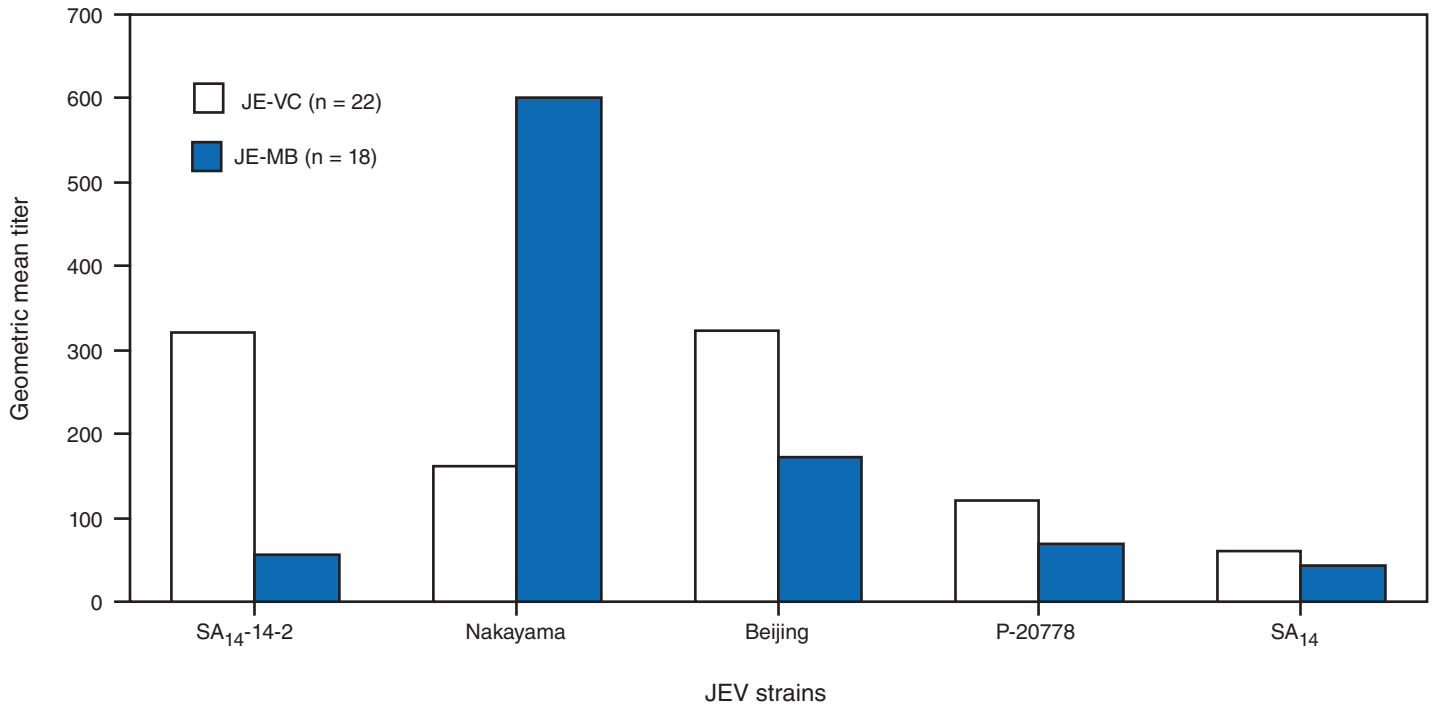
¶¶ Noninferiority of JE-VC compared with JE-MB was demonstrated based on the lower bound of the two-sided CI for the GMT ratio (JE-VC/JE-MB) being >1/1.5 at day 56.

FIGURE 3. Distribution of 50% plaque reduction neutralization test (PRNT₅₀) titers against the Japanese encephalitis virus (JEV) SA₁₄₋₁₄₋₂ strain at 56 days after the first dose of inactivated Vero cell culture-derived JE vaccine (JE-VC) or inactivated mouse brain-derived JE vaccine (JE-MB)*

SOURCE: Tauber E, Kollaritsch H, Korinek M, et al. Safety and immunogenicity of a Vero cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. *Lancet* 2007;370:1847–53.

* PRNT₅₀ ≥10 is considered a surrogate of immunity.

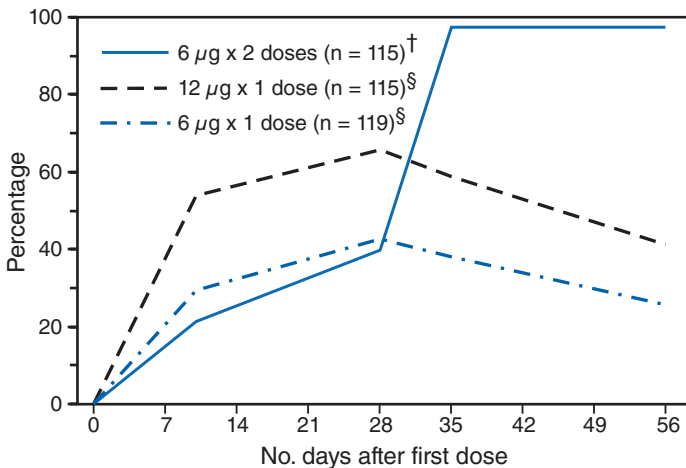
FIGURE 4. Comparison of 50% plaque reduction neutralization test (PRNT₅₀) geometric mean titers (GMT) with selected Japanese encephalitis virus (JEV) strains at 56 days after the first dose of inactivated Vero cell culture-derived JE vaccine (JE-VC) or inactivated mouse brain–derived JE vaccine (JE-MB) vaccines*



SOURCE: Intercell Biomedicals, unpublished data, 2007.

* PRNT₅₀ ≥ 10 is considered a surrogate of immunity.

FIGURE 5. Percentage of inactivated Vero cell culture-derived JE vaccine (JE-VC) recipients with 50% plaque reduction neutralization test (PRNT₅₀) titers ≥ 10, by dosing regimen*



SOURCE: Schuller E, Klade CS, Wolf G, Kaltenbock A, Dewasthaly S, Tauber E. Comparison of a single, high-dose vaccination regimen to the standard regimen for the investigational Japanese encephalitis vaccine, IC51: a randomized, observer-blind, controlled Phase 3 study. *Vaccine* 2009;27:2188–93.

* PRNT₅₀ ≥ 10 is considered a surrogate of immunity.

[†] Two doses administered at days 0 and 28.

[§] One dose administered at day 0.

and 91% (310/339), respectively. JEV PRNT₅₀ GMTs were also similar between the groups after 2 doses of JE-VC (207 and 187, respectively).

Duration of Neutralizing Antibodies

In a study performed in central Europe to evaluate the duration of neutralizing antibodies, 95% (172/181) of the subjects who received 2 doses of JE-VC maintained protective neutralizing antibodies (PRNT₅₀ ≥ 10) at 6 months after receiving the first dose, and 83% (151/181) still had protective antibodies at 12 months after the first dose (164). However, another study that used similar methods but was performed in western and northern Europe concluded that only 83% (96/116) of adults receiving 2 doses of JE-VC had protective antibodies at 6 months after their first vaccination, and the seroprotection rate had dropped to 58% (67/116) and 48% (56/116) at 12 and 24 months, respectively (165). Among 44 subjects who no longer had protective antibodies (17 subjects at 6 months after their first dose and 27 subjects at 12 months after their first dose), all developed PRNT₅₀ ≥ 10 after receiving a booster dose.

TABLE 3. Number and percentage of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) recipients with 50% plaque reduction neutralization test (PRNT₅₀) titers ≥ 10 , by tickborne encephalitis virus (TBEV) antibody status

Time after vaccination	TBEV antibody positive* (N = 81)		TBEV antibody negative* (N = 339)		p-value
	No.	(%)	No.	(%)	
After 1 dose (day 28) [†]	62	(77)	166	(49)	<0.01
After 2 doses (day 56) [†]	78	(96)	310	(91)	0.17

SOURCE: Schuller E, Klade CS, Heinz FX, et al. Effect of pre-existing anti-tick-borne encephalitis virus immunity on neutralising antibody response to the Vero cell-derived, inactivated Japanese encephalitis virus vaccine candidate IC51. *Vaccine* 2008;26:6151–6.

* Based on TBEV IgG enzyme-linked immunosorbent assay.

[†] Two doses of JE-VC were administered at days 0 and 28.

Concomitant Administration of Hepatitis A Vaccine

A clinical trial in which the first dose of JE-VC was administered concomitantly with hepatitis A vaccine (HAVRIX) indicated no interference with the immune response to JE-VC or hepatitis A vaccine (166). Among the 58 subjects who received both JE-VC and hepatitis A vaccine in the per-protocol analysis, all had protective neutralizing antibodies against the SA₁₄₋₁₄₋₂ JEV strain compared with 98% (57/58) of subjects who received JE-VC alone (Table 4). PRNT₅₀ GMTs also were similar at 203 and 192, respectively. Subjects receiving JE-VC and hepatitis A vaccine also had similar seroconversion rates for anti-hepatitis A virus (anti-HAV) antibody (100%; 58/58) compared with subjects receiving hepatitis A vaccine alone (96%; 50/52). However, some differences were noted between men and women in the levels of anti-HAV antibody achieved, and both seroconversion rates and antibody titers varied depending on which anti-HAV assay was used. Whether these observations have any clinical significance is not known.

Immunogenicity in Children

A phase 2 trial investigated the safety and immunogenicity of JE-VC in healthy children aged 1 and 2 years in India, using a standard (6- μ g) or half (3- μ g) dose (167). Children in both groups received 2 doses of JE-VC administered 28 days apart. A third group of children received 3 doses of an inactivated mouse brain-derived JE vaccine (JenceVac) on days 0, 7, and 28. JenceVac is produced by the Korean Green Cross Vaccine Corporation and is not licensed in the United States. At 28 days after the vaccination series was complete, seroconversion rates in the 6- μ g (n = 21) and 3- μ g (n = 23) JE-VC recipient groups and the inactivated mouse brain-derived group (n = 11) were 95%, 96%, and 91%, and PRNT₅₀ GMTs were 218 (95% confidence interval [CI] = 121–395), 201 (CI = 106–380),

TABLE 4. Immunogenicity of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) and hepatitis A vaccine (HAVRIX), coadministered and alone

Serologic response	JE-VC plus hepatitis A vaccine*	JE-VC alone [†]	Hepatitis A vaccine alone
	(N = 58)	(N = 58)	(N = 52) [§]
JEV [¶] PRNT ₅₀ ** ≥ 10 ^{††}	100%	98%	— ^{§§}
JEV PRNT ₅₀ GMT ^{¶¶}	203	192	—
HAV ^{***} seroconversion ^{†††}	100%	—	96%
HAV antibody GMT ^{†††}	150	—	124

SOURCE: Kaltenbock A, Dubischar-Kastner K, Eder G, et al. Safety and immunogenicity of concomitant vaccination with the cell-culture based Japanese encephalitis vaccine IC51 and the hepatitis vaccine HAVRIX1440 in healthy subjects—a single-blind, randomized, controlled phase 3 study. *Vaccine* 2009;27:4483–9.

* Two doses of JE-VC administered at days 0 and 28 and 1 dose of hepatitis A vaccine administered at day 0.

[†] Two doses of JE-VC administered at days 0 and 28 and 1 dose of placebo at day 0.

[§] One dose of hepatitis A vaccine at day 0 and 2 doses of placebo at days 0 and 28.

[¶] JE virus.

** Plaque reduction neutralization test with a cutoff value of 50%.

^{††} Measured at 56 days after the first dose.

^{§§} Not reported.

^{¶¶} Geometric mean titer.

^{***} Hepatitis A virus.

^{†††} Measured at 28 days after the dose of hepatitis A vaccine.

and 230 (CI = 68–784), respectively. None of the differences in seroconversion rates or GMTs was statistically significant. Further pediatric clinical trials are planned.

Adverse Events with JE-VC

Local and systemic adverse events caused by JE-VC are similar to those reported for JE-MB or placebo adjuvant alone. No serious hypersensitivity reactions or neurologic adverse events were identified among JE-VC recipients enrolled in the clinical trials. However, because JE-VC was studied in <5,000 adults, the possibility of rare serious adverse events cannot be excluded. Additional postlicensure studies and monitoring of surveillance data are planned to evaluate the safety of JE-VC in a larger population.

Local and Systemic Adverse Events Of JE-VC Compared with Placebo Adjuvant

The pivotal safety study comparing 1,993 subjects who received 2 doses of JE-VC with 657 subjects who received 2 doses of placebo adjuvant (phosphate buffered saline with 0.1% aluminum hydroxide) indicated similar reactogenicity and adverse events (Tables 5 and 6) (168). The most common local reactions after JE-VC administration were pain and tenderness. Two cases of urticaria were noted during the study: one case of urticaria localized to both inner thighs that occurred 6 days after the second vaccination in the placebo group, and one case of generalized urticaria (affecting the face, chest,

arms, and abdomen) that occurred 8 days after the second vaccination in the JE-VC group. The case of urticaria in the JE-VC group was described as being of “moderate intensity”; it was treated with cetirizine hydrochloride and resolved after 3 days. Angioedema was not observed. The event was considered by the investigator to be unlikely to be related to study vaccine, and the subject completed the study. A total of 17 subjects, 12 (0.6%) in the JE-VC group and five (0.8%) in the placebo group, terminated the study prematurely because of adverse events. Two of the events (gastroenteritis and rash) in the JE-VC group were severe, and eight of them (headache [two events], influenza-like illness, allergic dermatitis, injection site pain, nausea, fatigue, and rash [one event each]) were considered to be at least possibly related to study treatment. No serious neurologic events were identified.

Local and Systemic Adverse Events of JE-VC Compared with JE-MB

In the noninferiority immunogenicity trial, the frequency of adverse events reported following JE-VC vaccination (428

subjects) was similar to that reported by persons receiving JE-MB (435 subjects) (161). Severe redness, swelling, tenderness, and pain at the injection site were each reported by ≤1% of JE-VC recipients (Table 7). Reported systemic adverse events following JE-VC vaccination generally were mild; the most commonly reported adverse events in the 7 days after each dose were headache (26%), myalgia (21%), influenza-like illness (13%), and fatigue (13%). One serious adverse event was reported in the JE-VC group; a male aged 50 years had a nonfatal myocardial infarction 3 weeks after the second vaccination. The event was considered by the investigator to be unlikely to be related to study vaccine.

Pooled Safety Data

In a pooled analysis of 6-month safety data from seven studies, severe injection-site reactions were reported by 3% of the 3,558 JE-VC subjects, which was comparable to the 3% among 657 placebo adjuvant recipients but lower than the 14% among 435 JE-MB recipients (169). Systemic symptoms were reported with similar frequency among subjects who received JE-VC (40%), JE-MB (36%), or placebo (40%). Serious adverse events were reported by 1% of the subjects in the JE-VC group. Serious allergic reactions were not observed in any study group, including JE-VC, JE-MB, or placebo recipients.

Vaccination of Women During Pregnancy and Breastfeeding

FDA classifies JE-VC as a “Pregnancy Category B” medication (14). No controlled studies have assessed the safety, immunogenicity, or efficacy of JE-VC in pregnant women. Preclinical studies of JE-VC in pregnant rats did not show evidence of harm to the mother or fetus. No data exist on the safety or efficacy of JE-VC in breastfeeding women.

TABLE 5. Number and percentage of adverse events occurring within 56 days after the first dose of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) or placebo adjuvant (phosphate buffered saline plus 0.1% aluminum hydroxide)*

Event	JE-VC (N = 1,993)		Placebo adjuvant (N = 657)	
	No.	(%)	No.	(%)
Any	1,173	(59)	372	(57)
Medically attended	254	(13)	80	(12)
Serious	10	(0.5)	6	(0.9)
Terminated study	12	(0.6)	5	(0.8)

SOURCE: Tauber E, Kollaritsch H, von Sonnenburg F, et al. Randomized, double-blind, placebo-controlled phase 3 trial of the safety and tolerability of ic51, an inactivated Japanese encephalitis vaccine. *J Infect Dis* 2008;198:493–9.

* Two doses administered at days 0 and 28.

TABLE 6. Percentage of local reactions within 7 days after each dose of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) or placebo adjuvant (PBS + 0.1% aluminum hydroxide)*

Reaction	Post dose 1		Post dose 2		Post dose 1 or 2	
	JE-VC (N = 1,963)	Placebo adjuvant (N = 645)	JE-VC (N = 1,951)	Placebo adjuvant (N = 638)	JE-VC (N = 1,963)	Placebo adjuvant (N = 645)
Pain	28	28	18	18	33	36
Tenderness	29	27	23	18	36	33
Erythema	7	5	5	4	10	7
Induration	5	5	4	3	8	7
Edema	2	3	2	2	4	5
Pruritis	3	3	2	2	4	5

SOURCES: Food and Drug Administration. Product approval information [package insert]. Ixiaro (Japanese encephalitis virus vaccine inactivated). Intercell Biomedical, Livingston, United Kingdom. Washington, DC: Food and Drug Administration; 2009. Available at <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm179132.htm>. Tauber E, Kollaritsch H, von Sonnenburg F, et al. Randomized, double-blind, placebo-controlled phase 3 trial of the safety and tolerability of IC51, an inactivated Japanese encephalitis vaccine. *J Infect Dis* 2008;198:493–9.

* Two doses administered at days 0 and 28.

TABLE 7. Number and percentage of local and systemic adverse events occurring within 7 days after administration at days 0 and 28 of inactivated Vero cell culture-derived Japanese encephalitis vaccine (JE-VC) or inactivated mouse brain-derived JE vaccine (JE-MB)*

Severe local adverse events	JE-VC [†]		JE-MB [§]	
	No.	(%)	No.	(%)
	(n = 421)		(n = 427)	
Redness	4	(1)	46	(11)
Swelling	3	(1)	23	(5)
Hardness	4	(1)	25	(5)
Any [¶]	9	(2)	59	(14)
	(n = 428)		(n = 435)	
Systemic adverse events				
Headache	113	(26)	125	(29)
Myalgia	88	(21)	69	(16)
Influenza-like illness	54	(13)	55	(13)
Fatigue	54	(13)	48	(11)

SOURCE: Tauber E, Kollaritsch H, Korinek M, et al. Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. *Lancet* 2007;370:1847–53.

* Analysis includes all participants who entered into the study and received ≥ 1 dose of vaccine

[†] Two doses administered at days 0 and 28 with one dose placebo at 7 days.

[§] Three doses administered at days 0, 7, and 28.

[¶] Difference between two vaccines $p < 0.01$ (Fisher's exact test).

Inactivated Mouse Brain-Derived JE Vaccine (JE-VAX [JE-MB])

Vaccine Composition, Storage, and Handling

JE-MB is an inactivated vaccine prepared by inoculating mice intracerebrally with the JEV Nakayama-NIH strain (Table 1) (146). Thimerosal is added as a preservative to a final concentration of 0.007%. Each 1.0-mL dose also contains approximately 500 μg of gelatin, <100 μg of formaldehyde, <0.0007% v/v Polysorbate 80, and <50 ng of mouse serum protein. No myelin basic protein can be detected at the detection threshold of the assay (<2 ng/mL).

The lyophilized vaccine should be stored at 35°–46°F (2°–8°C); it should not be frozen. The vaccine should be reconstituted according to the package insert only with the supplied diluent. After reconstitution the vaccine should be stored at 35°–46°F (2°–8°C) and used within 8 hours. Reconstituted vaccine should not be frozen.

Efficacy of Inactivated Mouse Brain-Derived JE Vaccine

An inactivated mouse brain-derived JE vaccine was first licensed in Japan in 1954 and then modified in the 1960s and

1980s. Similar vaccines are produced in several Asian countries using the Nakayama or Beijing-1 JEV strains. Inactivated mouse brain-derived vaccines have been used effectively to control disease in several JE-endemic countries, including Japan, South Korea, Taiwan, and Thailand. They also have been used for several decades to prevent infection in tourists and military personnel from nonendemic countries traveling to JE-endemic regions.

Efficacy of inactivated mouse brain-derived JE vaccine has been demonstrated in two large controlled trials. A precursor of the current mouse brain-derived JE vaccine was studied in Taiwan in 1965 (170). Approximately 265,000 children were enrolled and received 1 dose of JE vaccine (22,194 children), 2 doses of JE vaccine (111,749 children), or tetanus toxoid (131,865 children). Another 140,514 unvaccinated children also were observed. After 1 year of follow-up, JE incidence among children who received 2 doses of JE vaccine was 3.6 per 100,000 population compared with 18.2 per 100,000 in recipients of tetanus toxoid, for a vaccine efficacy of approximately 80%. A single dose of JE vaccine was not efficacious.

Efficacy of JE-MB was demonstrated in a placebo-controlled, randomized trial conducted among 65,000 children aged 1–14 years in Thailand (68). Study participants were randomized to receive 2 doses of monovalent vaccine prepared with the Nakayama-NIH JEV strain administered 7 days apart (21,628 children), 2 doses of a bivalent JE vaccine that contained both the Nakayama-NIH and Beijing-1 JEV strains (22,080 children), or tetanus toxoid (21,516 children). After 2 years, one JE case was identified in each of the two study vaccine groups (five cases per 100,000) compared with 11 JE cases (51 cases per 100,000) in the children who received tetanus toxoid. The efficacy in both JE vaccine groups combined was 91% (CI = 70%–97%) with no difference observed between the monovalent and bivalent vaccines.

Immunogenicity of Inactivated Mouse Brain-Derived JE Vaccine

Immunogenicity of 2 Versus 3 Doses for Travelers

For travelers from nonendemic countries, the recommended primary vaccination series for JE-MB is 3 doses administered on days 0, 7, and 30. Children in JE-endemic countries usually receive 2 doses of inactivated mouse brain-derived JE vaccine separated by 1–4 weeks and followed by a booster dose 1 year later (147). However, immunogenicity studies performed in adults from nonendemic countries indicated that $\leq 80\%$ of participants seroconverted following 2 doses of vaccine and only about 30% still had measurable neutralizing titers after 6–12

months. By contrast, between 87% and 100% of adults from nonendemic settings developed neutralizing antibodies after receiving 3 doses of vaccine (Table 8) (13,138,171–173). The vaccine's efficacy and immunogenicity after 2 doses in Asian subjects might be a result of prior immunity or subsequent exposures to flaviviruses present in Asia including JEV, West Nile virus, and dengue virus (174). Although exposure to flaviviruses is almost universal at an early age in most countries in Asia, flaviviral infections are much less common in North America and Europe.

Immunogenicity of Two 3-Dose Regimens

The immunogenicity of two different, 3-dose vaccination regimens was evaluated in 528 U.S. military personnel in 1990 (173). Vaccine was given on days 0, 7, and either 14 or 30. All vaccine recipients demonstrated neutralizing antibodies at 2 months and 6 months after initiation of vaccination. The longer schedule of days 0, 7, and 30 produced higher antibody titers than the days 0, 7, and 14 schedule. When 273 of the original study participants were tested at 12 months after vaccination, a statistically significant difference in GMTs did not exist between the two groups (146).

Neutralizing Antibodies Following a Booster Dose

Marked anamnestic responses with ≥ 10 -fold increases in neutralizing antibody titers have been demonstrated after a booster dose of JE-MB (147,175,176). In a study in Japan, among 152 subjects who had received either a 1- or 2-dose primary vaccination schedule, a booster dose at 1 year increased neutralizing antibody GMTs from ≤ 20 immediately prior to the booster to $\geq 1,360$ at 4 weeks (175).

Duration of Neutralizing Antibodies

Only a few studies have measured the duration of protection after primary or booster vaccinations in populations from non-endemic or low-endemicity areas. Studies conducted in most parts of Asia are complicated by the boosting effect of naturally acquired flaviviral infections. In U.S. military personnel who received a 3-dose primary vaccination course, 100% (21/21) and 94% (16/17) still had protective neutralizing antibody titers at 2 years and 3 years, respectively (177). In a study in a nonendemic area of Japan, 38 (92%) of 41 recipients maintained protective antibody titers 2 years after a booster dose (175). Another study in an area of low JE endemicity in Japan applied a random coefficient model to data from 17 children and estimated that 82% would have protective antibodies at 5 years after a booster dose (4th dose) of vaccine and that 53% would still be protected 10 years following the booster dose (178). In contrast to these studies, which indicated persistence

TABLE 8. Seroconversion with inactivated mouse brain–derived Japanese encephalitis vaccine in previously unvaccinated persons from countries where disease is not endemic

Study	2 doses		3 doses	
	No. seroconverted/ No. vaccinated	(%)	No. seroconverted/ No. vaccinated	(%)
A*	5 / 14	(36)	41 / 47	(87)
B†	91 / 118	(77)	71 / 72	(99)
C‡	16 / 20	(80)	25 / 25	(100)
D¶	—**	—	470 / 470	(100)

* **SOURCE:** Henderson A. Immunisation against Japanese encephalitis in Nepal: experience of 1152 subjects. *J R Army Med Corps* 1984;130:188–91. Two doses administered at 0 and 10 days, or three doses at 0, 10, and 20 days. Serum collected at 10 days after last dose. Study includes British army soldiers stationed in Nepal, Nepalese soldiers, and civilian employees.

† **SOURCE:** Poland JD, Cropp CB, Craven RB, Monath TP. Evaluation of the potency and safety of inactivated Japanese encephalitis vaccine in US inhabitants. *J Infect Dis* 1990;161:878–82. Two doses administered at 0 and 1–2 weeks, or three doses at 0, 1–2, and 4 weeks. Serum collected 1 month after last dose.

‡ **SOURCE:** Sanchez JL, Hoke CH, McCown J, et al. Further experience with Japanese encephalitis vaccine. *Lancet* 1990;335:972–3. Two doses administered at 0 and 1 week, or three doses at 0, 1, and 26 weeks. Serum collected at 8 weeks or 30 weeks.

¶ **SOURCE:** Defraites RF, Gambel JM, Hoke CH, Jr., et al. Japanese encephalitis vaccine (inactivated, BIKEN) in U.S. soldiers: immunogenicity and safety of vaccine administered in two dosing regimens. *Am J Trop Med Hyg* 1999;61:288–93. Three doses administered at 0, 7, and either 14 or 30 days. Serum collected at 2 months.

** Not reported.

of immunity for several years, a study conducted on Badu Island in the Torres Strait, Australia, indicated that only 70 (32%) of 219 persons had protective antibodies 30–36 months after either primary vaccination or receipt of a booster dose (179). The reason for the unusually low level of immunity in this study was not clear, although high prevalence of chronic medical conditions among the population studied was proposed as a contributing factor.

Immunogenicity in Persons with Preexisting Flavivirus Antibodies

Immunogenicity studies with another flaviviral vaccine (inactivated tick-borne encephalitis [TBE] vaccine) have indicated that previous yellow fever vaccination augmented the antibody response to TBE vaccine (180). This effect has not been observed among JE-MB recipients (135,173).

Adverse Events with Inactivated Mouse Brain–Derived JE Vaccine

Local and Systemic Adverse Events

Inactivated mouse brain–derived JE vaccine has been associated with localized erythema, tenderness, and swelling at the injection site in about 20% of recipients. Mild systemic side effects (e.g., fever, chills, headache, rash, myalgia, and gastroin-

testinal symptoms) have been reported in approximately 10% of vaccinees (138,146,173).

Allergic Hypersensitivity Reactions

JE-MB has been associated with serious, but rare, allergic and neurologic adverse events. Allergic hypersensitivity reactions, including generalized urticaria and angioedema of the extremities, face, and oropharynx, have been reported primarily among adult travelers and military personnel (13,66,147,181–188). Accompanying bronchospasm, respiratory distress, and hypotension were observed in some patients. Although most of these reactions occurred within 24–48 hours after the first dose, when they occurred following a subsequent dose, symptom onset often was delayed (median: 3 days; range: 1–14 days) (185). Most of these reactions were treated with antihistamines or corticosteroids on an outpatient basis; however, up to 10% of vaccinees with these reactions have been hospitalized. Several deaths attributed to anaphylactic shock have been associated temporally with receipt of this vaccine, but none of these patients had evidence of urticaria or angioedema, and two had received other vaccines simultaneously (43,185,189). Estimates of the frequency of severe hypersensitivity reactions range from 10 to 260 cases per 100,000 vaccinees, and vary by country, year, case definition, surveillance method, and vaccine lot (Table 9) (13,181–188). Persons with a history of anaphylaxis, urticaria, or other allergies are 2–11 times more likely to develop a hypersensitivity reaction following receipt of JE vaccine (185,190). Gelatin, which is used as a vaccine stabilizer, might be responsible for some of these allergic reactions (191–193). In one study from Japan, among 10 children who developed an immediate hypersensitivity reaction within 1 hour after receiving inactivated mouse brain–derived JE vaccine, all had measurable IgE antibodies against gelatin (193). By contrast, only one (4%) of 28 children who developed a delayed hypersensitivity reaction at 1–48 hours following administration of inactivated mouse brain–derived JE vaccine, and none of 15 controls had evidence of anti-gelatin IgE antibodies.

Neurologic Adverse Events

JE-MB contains no myelin basic protein at the detection threshold of the assay. However, the use of mouse brains as the substrate for virus growth has raised concerns about the possibility of neurologic side effects associated with the JE vaccine. Moderate to severe neurologic symptoms, including encephalitis, seizures, gait disturbances, and parkinsonism, have been reported at a rate of 0.1–2 cases per 100,000 vaccinees with variation by country, case definition, and surveillance method (Table 9) (13,186,188,194). In addition, cases of severe or fatal acute disseminated encephalomyelitis (ADEM) temporally

TABLE 9. Incidence of allergic hypersensitivity reactions and neurologic events temporally associated with receipt of inactivated mouse brain–derived Japanese encephalitis vaccines

Event	Cases	Denominator	Incidence*
Allergic hypersensitivity reactions			
Japan (NARRS†)	71	9,400,000 doses	1
United States (VAERS§)	51	813,822 doses	6
Sweden	1	15,000 vaccinees	10
United Kingdom	1	1,950 vaccinees	50
Denmark	21	41,500 vaccinees	50
Australia	7	4,000 vaccinees	200
United States	38	14,249 vaccinees	266
Neurologic events			
Japan (1965–1973)	NR¶	Vaccinees	0.1
Japan (1996–1998)	17	9,400,000 doses	0.2
United States (1993–1998)	2	813,822 doses	0.2
Denmark (1983–1996)	10	384,000 doses	2.6

SOURCES: Berg SW, Mitchell BS, Hanson RK, et al. Systemic reactions in U.S. Marine Corps personnel who received Japanese encephalitis vaccine. *Clin Infect Dis* 1997;24:265–6. Takahashi H, Pool V, Tsai TF, Chen RT. Adverse events after Japanese encephalitis vaccination: review of post-marketing surveillance data from Japan and the United States. The VAERS Working Group. *Vaccine* 2000;18:2963–9. Plesner AM. Allergic reactions to Japanese encephalitis vaccine. *Immunol Allergy Clin North Am* 2003;23:665–97. Plesner AM, Arlien-Soborg P, Herning M. Neurological complications to vaccination against Japanese encephalitis. *Eur J Neurol* 1998;5:479–85.

* Per 100,000 population.

† National Adverse Reaction Reporting System.

§ Vaccine Adverse Event Reporting System.

¶ Not reported.

associated with JE vaccination of children in Japan and Korea have been reported (43,186,195–199). In 2005, in response to these cases, Japan suspended routine vaccination with mouse brain–derived JE vaccines (5,200). In reviewing this decision, the WHO Global Advisory Committee on Vaccine Safety determined that no evidence existed of an increased risk for ADEM associated with mouse brain–derived JE vaccine and that a causal link had not been demonstrated. The committee recommended that, although current use and policies should not be changed, the inactivated mouse brain–derived vaccine should be replaced gradually by new-generation JE vaccines (5,200).

Vaccination of Women During Pregnancy and Breastfeeding

FDA classifies JE-MB as a “Pregnancy Category C” medication (146). No specific information is available on the safety of JE-MB in pregnant women, and animal reproductive studies have not been conducted with JE-MB. In addition, no data exist on the safety or efficacy of JE-MB in breastfeeding women.

Cost Effectiveness of JE Vaccines

Several studies have demonstrated that using JE vaccine to immunize children in JE-endemic countries is cost saving (201–203). 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 (less than one case per 1 million travelers), and the high cost of JE vaccine (\$390 per 2-dose primary series for JE-VC in 2009) (204), providing JE vaccine to all travelers to Asia would not be cost-effective. In addition, for some travelers, even a low risk for serious adverse events attributable to JE vaccine 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. Travel vaccines typically are not covered by insurance plans, and the travelers themselves usually must pay for vaccine administration. Therefore, travelers should be counseled about their individual risk on the basis of their planned itinerary and activities.

Summary of Rationale for JE Vaccine Recommendations

When making recommendations regarding the use of JE vaccine for travelers, health-care providers should weigh the overall low risk for travel-associated JEV disease, the high morbidity and mortality when JE does occur, the low probability of serious adverse events following vaccination, and the cost of the vaccine. Evaluation of an individual traveler's risk should take into account their planned itinerary including travel location, duration, season, and activities (Box 1).

The risk for JE for most travelers to Asia is very low but varies based on destination, duration, season, and activities (3,8–10,13,118). Since 1992, when a vaccine was first licensed for use in the United States, only four cases of JE have been reported among travelers from the United States; none of the patients had received JE vaccine. 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. However, the risk for JE among expatriates and travelers who stay for prolonged periods in rural areas with active JEV transmission is likely similar to the risk among the susceptible resident population (6,9). 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 (119–121). Short-term (<1 month) travelers whose visits are restricted to major urban areas are at minimal risk for JE.

BOX 1. Factors to consider when evaluating a traveler's risk for Japanese encephalitis virus (JEV) exposure

Destination

- JE occurs in areas throughout most of Asia and parts of the western Pacific.
- The highest risk of JEV exposure occurs in rural agricultural areas, often associated with rice production and flooding irrigation.
- JE can occur in large, focal outbreaks indicating extensive active JEV transmission in that area.

Duration of travel

- Most reported travel-associated JE cases have occurred among expatriates or long-term travelers (i.e., ≥ 1 month).
- Although no specific duration of travel puts a traveler at risk for JE, a longer itinerary increases the likelihood that a traveler might be exposed to a JEV-infected mosquito.

Season

- In most temperate areas of Asia, JEV transmission is seasonal, and human disease usually peaks in summer and fall.
- In the subtropics and tropics, JEV transmission patterns vary, and human disease can be sporadic or occur year-round.

Activities

- The mosquitoes that transmit JEV feed on humans most often in the outdoors, with peak feeding times after sunset and again after midnight.
- Extensive outdoor activities (e.g., camping, hiking, trekking, biking, fishing, hunting, or farming), especially during the evening or night, increase the risk of being exposed to a JEV-infected mosquito.
- Accommodations with no air conditioning, screens, or bed nets increase the risk of exposure to mosquitoes that transmit JEV and other vector-borne diseases (e.g., dengue and malaria).

Additional information

- Information on expected JEV transmission by country is available from CDC at <http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/japanese-encephalitis.aspx>.

The highest risk for JEV exposure occurs in rural agricultural areas, often those associated with rice production and flooding irrigation. In most temperate areas of Asia, JEV transmission is seasonal, and human disease usually peaks in summer and fall. In the subtropics and tropics, transmission patterns vary, and human disease can be sporadic or occur year-round.

Although no minimum duration of travel eliminates a traveler's risk for JE, a longer itinerary increases the likelihood that a traveler will spend time in an area with active JEV transmission. The mosquitoes that transmit JEV feed most often in the outdoors with peaks after sunset and again after midnight. Outdoor activities, especially during the evening or night, increase the risk for being exposed to a JEV-infected mosquito.

Recommendations for the Prevention of JE Among Travelers

Travelers to JE-endemic countries should be advised of the risks of JEV disease and the importance of personal protective measures to reduce the risk for mosquito bites. For some travelers who will be in a high-risk setting based on season, location, duration, and activities, JE vaccine can further reduce the risk for infection.

Personal Protective Measures

All travelers should take precautions to avoid mosquito bites to reduce the risk for JE and other vector-borne infectious diseases (Box 2). These precautions include using insect repellent, permethrin-impregnated clothing, and bed nets, and staying in accommodations with screened or air-conditioned rooms. Additional information on protection against mosquitoes and other arthropods is available at <http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/protection-against-mosquitoes-ticks-insects-arthropods.aspx>.

Recommendations for the Use of JE Vaccine

JE vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JEV transmission season (Box 3). 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 JEV transmission.

JE vaccine should be considered for the following persons:

- Short-term (<1 month) travelers to endemic areas during the JEV transmission season if they plan to travel out-

BOX 2. Personal protective measures to reduce the risk for Japanese encephalitis and other vectorborne infectious diseases

- All travelers should take precautions to avoid mosquito bites to reduce the risk of Japanese encephalitis and other vectorborne infectious diseases
 - Use insect repellent
 - Wear permethrin-impregnated clothing
 - Sleep under permethrin-impregnated bed nets
 - Stay in accommodations with air conditioning or screens
- Additional information on protection against mosquitoes and other arthropods can be found at <http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/protection-against-mosquitoes-ticks-insects-arthropods.aspx>.

side of an urban area and have an increased risk for JEV exposure. Examples of higher-risk activities or itineraries include 1) spending substantial time outdoors in rural or agricultural areas, especially during the evening or night; 2) participating in extensive outdoor activities (e.g., camping, hiking, trekking, biking, fishing, hunting, or farming); and 3) staying in accommodations without air conditioning, screens, or bed nets.

- Travelers to an area with an ongoing JE outbreak.
- Travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel.

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

Information on expected JEV transmission by country can be obtained from CDC at <http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/japanese-encephalitis.aspx>. These data should be interpreted cautiously because JEV transmission activity varies within countries and from year to year.

Recommendations for the Use of JE Vaccines in Laboratory Workers

At least 22 laboratory-acquired JEV infections have been reported in the literature (205). Although work with JEV is restricted to Biosafety Level 3 (BSL-3) facilities and practices, JEV might be transmitted in a laboratory setting through needlesticks, and theoretically, through mucosal or inhalational accidental exposures. Vaccine-induced immunity presumably protects against exposure through a percutaneous route. Exposure to aerosolized JEV, and particularly to high concen-

BOX 3. Recommendations for the use of Japanese encephalitis (JE) vaccine**Recommended**

- Laboratory workers with a potential for exposure to infectious JE virus (JEV)
- Travelers who plan to spend a month or longer in endemic areas during the JEV transmission season

Consider

- Short-term travelers (<1 month) to endemic areas during the JEV transmission season if they plan to travel outside of an urban area and have an itinerary or activities that will increase their risk of JEV exposure
- Travelers to an area with an ongoing JE outbreak
- Travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel

Not recommended

- Short-term travelers whose visit will be restricted to urban areas or times outside of a well-defined JEV transmission season.

trations of virus, that might occur during viral purification, potentially could lead to infection through mucous membranes and possibly directly into the central nervous system through the olfactory epithelium. Whether vaccination provides protection following such exposures is unknown, but vaccination is recommended for all laboratory workers with a potential for exposure to infectious JEV (Box 3).

Administration of JE Vaccines

Dosage and Administration

JE-VC

The primary vaccination series for JE-VC is 2 doses administered 28 days apart (Table 1). Each 0.5-mL dose is given by the intramuscular route; this route is different from that of JE-MB, which is administered subcutaneously. JE-VC is supplied in 0.5-mL single-dose syringes. The 2-dose series should be completed at least 1 week before potential exposure to JEV. The dose is the same for all persons aged ≥ 17 years. The vaccine is not licensed for use in persons aged <17 years.

JE-MB

For travelers, the recommended primary vaccination series for JE-MB is 3 doses administered subcutaneously on days 0, 7, and 30 (Table 1). An abbreviated schedule (days 0, 7, and 14) can be used when the longer schedule is impractical. Both regimens produce similar rates of seroconversion among recipients, but neutralizing antibody titers at 2 and 6 months are lower following the abbreviated schedule. Among 80% of vaccinees, 2 doses, administered 1 week apart, will confer short-term immunity. However, this schedule should be used only under unusual circumstances and is not recommended routinely. The last dose should be administered at least 10 days before travel begins to ensure an adequate immune response and access to medical care in the event of a delayed adverse reaction. The dose is 1.0 mL for persons aged ≥ 3 years. For children aged 1–2 years, the dose is 0.5 mL. The vaccine is not licensed for infants aged <1 year.

Recipients should be observed for a minimum of 30 minutes after vaccination and warned about the possibility of delayed allergic reactions, in particular angioedema of the extremities, face or oropharynx, or generalized urticaria. Vaccinees should be advised to remain in areas with access to medical care for 10 days after receiving each dose of JE-MB because of the possibility of delayed hypersensitivity. The full course of vaccination should be completed at least 10 days before travel.

Booster Doses

JE-VC

The need for and timing of booster doses following a 2-dose primary series with JE-VC has not been determined, and further study is needed. The full duration of protection following primary vaccination with JE-VC is unknown. One immunogenicity study indicated that 95% (172/181) of subjects maintained protective neutralizing antibodies 6 months after receiving the first dose and 83% (151/181) still had protective antibodies 12 months after primary vaccination (164). However, a subsequent study determined that only 83% (96/116), 58% (67/116), and 48% (56/116) of subjects had protective antibodies at 6, 12, and 24 months after their first vaccination, respectively (165).

JE-MB

The full duration of protection following primary vaccination with JE-MB also is unknown. However, immunogenicity studies indicate that neutralizing antibodies likely persist for at least 2 years (175,177–179). A booster dose of 1.0 mL (0.5 mL for children aged <3 years) of JE-MB may be administered 2

years after the primary series when indicated for planned travel or possible laboratory exposure (see Recommendations for the Prevention of JE Among Travelers and Recommendations for the Use of JE Vaccines in Laboratory Workers). The duration of immunity after serial booster doses has not been well established.

No data exist on the use of JE-VC as a booster dose after a primary series with JE-MB. Because of limited supply, remaining doses of JE-MB are being reserved for use in children aged 1–16 years. If a booster dose of JE-MB is not available, adults aged ≥ 17 years who have received JE-MB previously and require further vaccination against JEV should receive a 2-dose primary series of JE-VC.

Interchangeability of JE Vaccines

No data exist on the interchangeability of JE-VC and JE-MB for use in the primary series or as a booster dose.

Simultaneous Administration of Other Vaccines or Drugs

JE-VC

A clinical trial in which the first dose of JE-VC was administered concomitantly with hepatitis A vaccine (HAVRIX[®]) indicated no interference with the immune response to JE-VC or hepatitis A vaccine (166). Subjects who received concomitant vaccination with JE-VC and hepatitis A vaccine were more likely to report pain, redness, and swelling than subjects who received either vaccine alone. No other differences were reported in safety or reactogenicity with concomitant administration of JE-VC and hepatitis A vaccine compared with administration of each vaccine alone.

No data exist on administration of JE-VC with other vaccines or medications. If JE-VC is administered concomitantly with other vaccines, they should be given with separate syringes at different sites.

JE-MB

Limited data suggest that immunogenicity and safety are not compromised when inactivated mouse brain–derived JE vaccines, including JE-MB, are administered simultaneously with measles-mumps-rubella, diphtheria-tetanus-pertussis or oral polio vaccines (206,207). No data exist on the effect of concurrent administration of medications or other biologicals on the safety and immunogenicity of JE-MB.

Contraindication and Precautions for the Use of JE Vaccines

Allergy to Vaccine Components

JE-VC

A severe allergic reaction (e.g., anaphylaxis) after a previous dose of JE-VC is a contraindication to administration of subsequent doses. JE-VC contains protamine sulfate, a compound known to cause hypersensitivity reactions in some persons (14).

JE-MB

A history of an allergic or hypersensitivity reaction (i.e., generalized urticaria and angioedema) to a previous dose of JE-MB is a contraindication to receiving additional doses (146). Hypersensitivity to thimerosal is a contraindication to vaccination, and persons with a proven or suspected hypersensitivity to proteins of rodent or neural origin should not receive JE-MB.

Persons with a history of previous allergic reactions or urticaria attributed to any cause (e.g., medications, other vaccinations, or insect bite) might be at higher risk for allergic complications from JE-MB (185,190). This history should be considered as a precaution when weighing the risks and benefits of the vaccine for an individual patient. When patients with such a history are offered JE vaccine, they should be alerted to their increased risk for reaction and monitored appropriately. No data exist that support the efficacy of prophylactic antihistamines or steroids in preventing JE-MB-related allergic reactions.

Age

JE-VC

The safety and effectiveness of JE-VC among children has not been established; studies are in progress. Until data are available, JE vaccination of children aged 1–16 years should be performed with JE-MB.

JE-MB

JE-MB is licensed for use in persons aged ≥ 1 year. No data are available on the safety and efficacy of JE-MB among infants aged < 1 year. Although other inactivated mouse brain–derived JE vaccines have been administered to infants as young as age 6 months in Japan and Thailand (5,147), vaccination of infants traveling to JE-endemic countries should be deferred until they are aged ≥ 1 year.

Pregnancy

Practitioners should use caution when considering the use of JE vaccine in pregnant women. Vaccination with JE vaccines usually should be deferred because of a theoretic risk to the developing fetus. However, pregnant women who must travel to an area in which risk for JE is high should be vaccinated if the benefits outweigh the risks of vaccination to the mother and developing fetus.

Special Populations

Age

JE-VC

JE-VC is approved for use in persons aged ≥ 17 years. Data are limited on the use of the vaccine in persons aged ≥ 65 years ($n = 24$) but suggest that safety and immunogenicity are similar to that among younger subjects (14). However, further trials are needed to determine whether older adults respond differently than younger subjects. (For information on children aged < 17 years, see the section on age under Contraindications and Precautions for the Use of JE Vaccines).

JE-MB

JE-MB is approved for use in children aged ≥ 1 year. JE-MB remains the only JE vaccine that is approved for use in children in the United States. Although JE-MB still is approved for use in adults, to conserve supply and help meet the JE vaccine needs for children, Sanofi Pasteur has reserved its remaining JE-MB inventory for use in children aged 1–16 years. Health-care providers should contact Sanofi Pasteur to order doses of JE-MB.

Pregnancy

JE-VC

FDA classifies JE-VC as a “Pregnancy Category B” medication. No studies of JE-VC in pregnant women have been conducted (14). See the section on pregnancy under Contraindications and Precautions for the Use of JE Vaccines for more information.

JE-MB

FDA classifies JE-VC as a “Pregnancy Category C” medication. No specific information is available on the safety of JE-MB in pregnancy (146). See the section on pregnancy under Contraindications and Precautions for the Use of JE Vaccines for more information.

Breastfeeding Women

Breastfeeding is not a contraindication to vaccination. However, whether JE-VC or JE-MB is excreted in human milk is not known. Because many drugs are excreted in human milk, practitioners should use caution when considering the use of JE vaccine in breastfeeding women.

Altered Immune States

JE-VC

No data exist on the use of JE-VC in immunocompromised persons or patients receiving immunosuppressive therapies.

JE-MB

In limited studies in children infected with HIV or with underlying medical conditions including neoplastic disease, the safety profile of JE-MB was similar to that in healthy children (208–210). A reduced immune response was seen in HIV-infected children. However, most children with immune recovery after highly active antiretroviral therapy developed a protective antibody response (209,210).

Postlicensure Surveillance for Vaccine Adverse Events

JE-VC is a promising JE vaccine for travelers given its favorable immunogenicity and reactogenicity profile after a 2-dose primary series. In addition, because JE-VC does not contain gelatin or murine proteins, it might be associated with fewer hypersensitivity or neurologic adverse events than the mouse brain–derived vaccine. However, the actual cause of these reactions following mouse brain–derived vaccine is unknown. Because JE-VC has been studied in $< 5,000$ recipients, the possibility of these or other rare adverse events cannot be excluded. Postlicensure studies and surveillance data from the United States, Europe, and Australia will be used to evaluate the safety profile of JE-VC in larger populations.

Reporting of Vaccine Adverse Events

As with any newly licensed vaccine, surveillance for rare adverse events associated with administration of JE vaccine is important for assessing its safety in widespread use. Even if a causal relation to vaccination is not certain, all clinically significant adverse events should be reported to the Vaccine Adverse Events Reporting System (VAERS) at <http://vaers.hhs.gov> or at telephone 800-822-7967.

Future Research on JE-VC

Additional studies of JE-VC will be needed to evaluate safety and effectiveness further, including children and adults aged ≥ 65 years; duration of protection and need for booster doses; the ability of JE-VC to provide an anamnestic immune response in persons previously vaccinated with JE-MB; and concomitant administration with other travel vaccines or medications.

Additional information

Additional information about JE is available from CDC at <http://www.cdc.gov/ncidod/dvbid/jencephalitis/index.htm> and in CDC's recommendations for international travel (3). Additional licensure information for the two JE vaccines approved in the United States is available from FDA at <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm142556.htm> and at <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094048.htm>.

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