Inactivated
Japanese Encephalitis Virus
Vaccine

Recommendations of the
Advisory Committee on
Immunization Practices (ACIP)

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This report was prepared by:

Theodore F. Tsai, M.D., M.P.H.
Chief
Arbovirus Diseases Branch
Division of Vector-Borne Infectious Diseases
National Center for Infectious Diseases*

*Dr. Tsai's current address is: Clinical Microbiology Services, National Institutes of Health, Building 10 2C385, Bethesda, MD 20892.

Contents

Inactivated Japanese Encephalitis Virus Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

Japanese encephalitis (JE) vaccine was available in the United States from 1983 through 1987 on an investigational basis, through travel clinics in collaboration with CDC (1). JE vaccine manufactured by Biken and distributed by Connaught Laboratories, Inc. (Japanese encephalitis virus vaccine, inactivated, JE-VAX), was licensed on December 10, 1992, to meet the needs of increasing numbers of U.S. residents traveling to Asia and to accommodate the needs of the U.S. military.

INTRODUCTION

Japanese encephalitis (JE), a mosquito-borne arboviral infection, is the leading cause of viral encephalitis in Asia (*2–4*). Approximately 50,000 sporadic and epidemic cases of JE are reported annually from the People's Republic of China (PRC), Korea, Japan, Southeast Asia, the Indian subcontinent, and parts of Oceania. Viral transmission occurs across a much broader area of the region than is recognized by epidemiologic surveillance (Figure 1).

JE virus is related antigenically to the flaviviruses of St. Louis encephalitis and Murray Valley encephalitis, and to West Nile virus (*5*). Infection leads to overt encephalitis in only 1 of 20 to 1,000 cases. Encephalitis usually is severe, resulting in a fatal outcome in 25% of cases and residual neuropsychiatric sequelae in 30% of cases (*2,6*). Limited data indicate that JE acquired during the first or second trimesters of pregnancy causes intrauterine infection and miscarriage (*7,8*). Infections that occur during the third trimester of pregnancy have not been associated with adverse outcomes in newborns.

The virus is transmitted in an enzootic cycle among mosquitoes and vertebrate-amplifying hosts, chiefly domestic pigs and Ardeid (wading) birds (*2*). Culex mosquitoes, primarily *Cx. tritaeniorhynchus*, are the principal vectors. Viral infection rates in the mosquitoes range from <1% to 3%. These species are prolific in rural areas where their larvae breed in ground pools and especially in flooded rice fields. All elements of the transmission cycle are prevalent in rural areas of Asia, and human infections occur principally in this setting. Because vertebrate-amplifying hosts and agricultural activities may be situated within and at the periphery of cities, JE cases occasionally are reported from urban locations.

JE virus is transmitted seasonally in most areas of Asia (Table 1). In temperate regions, JE virus is transmitted during the summer and early fall, approximately from May to September (*2–6*). In subtropical and tropical areas, seasonal patterns of viral transmission are correlated with the abundance of vector mosquitoes and of vertebrate-amplifying hosts. These, in turn, fluctuate with rainfall, with the rainy season, and with migratory patterns of avian-amplifying hosts. In some tropical locations, however, irrigation associated with agricultural practices is a more important factor

affecting vector abundance, and transmission may occur year-round (*9–12*). Patterns of JE viral transmission vary regionally, within individual countries, and from year to year.

   In areas where JE is endemic, annual incidence ranges from 1 to 10 per 10,000 (*13*). Children <15 years of age are principally affected. Seroprevalence studies indicate nearly universal exposure by adulthood (calculating from a ratio of asymptomatic to symptomatic infections of 200 to 1, approximately 10% of the susceptible population is infected per year). In developed countries of Asia and in areas where children are

FIGURE 1. Reported Japanese encephalitis cases by endemic countries and regions of Southeast Asia where viral transmission is proven or suspected, 1986–1990
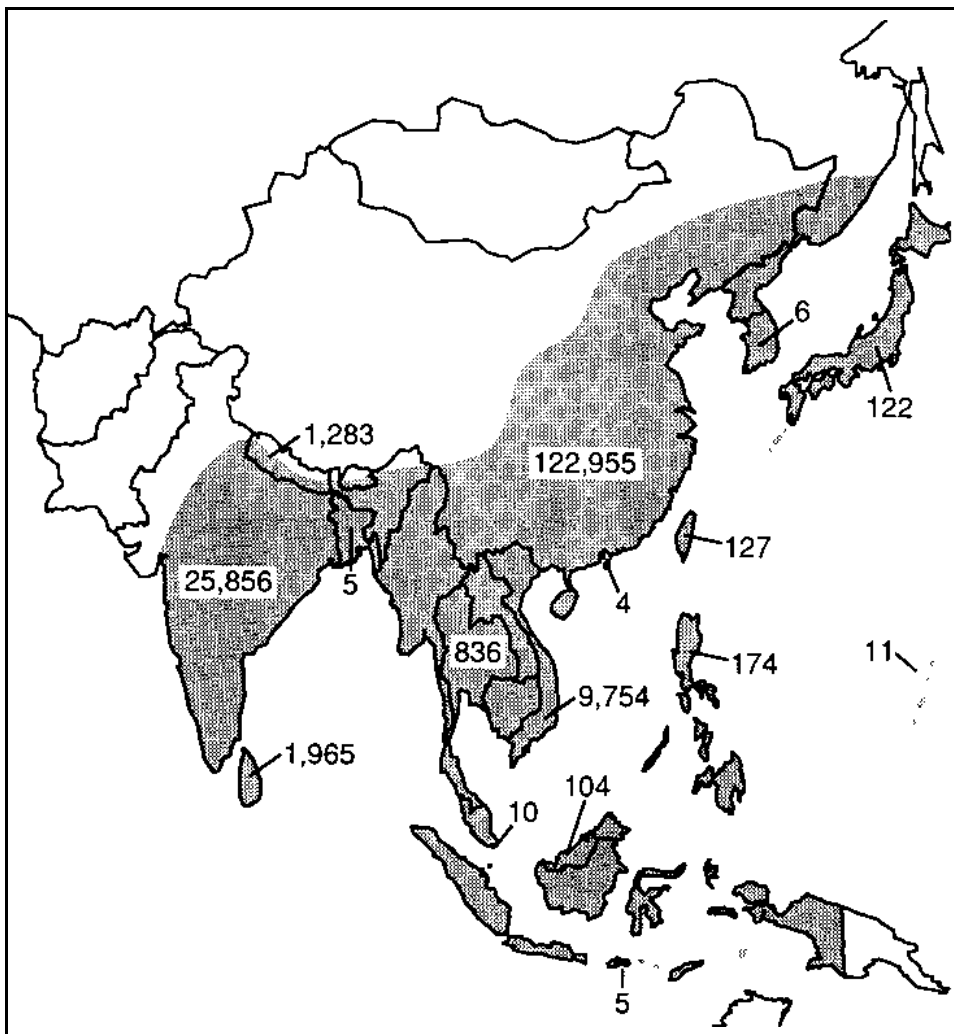
Source: Tsai TF. Japanese encephalitis vaccines. In: Plotkin SA, Mortimer E, eds. Vaccines, second edition. Philadelphia, PA: WB Saunders (in press).

TABLE 1. Risk of Japanese encephalitis by country, region, and season

Country	Affected areas/ jurisdictions	Transmission season	Comments
Bangladesh	Few data, probably widespread	Possibly July–December as in northern India	Outbreak reported from Tangail district
Bhutan	No data	No data	Not applicable
Brunei	Presumed to be sporadic — endemic as in Malaysia	Presumed year-round transmission	
Burma	Presumed to be endemic — hyperendemic countrywide	Presumed to be May–October	Repeated outbreaks in Shan State in Chiang Mai Valley
Cambodia	Presumed to be endemic — hyperendemic countrywide	Presumed to be May–October	Refugee camp cases reported from Thai border
Hong Kong	Rare cases in new territories	April–October	Vaccine not routinely recommended
India	Reported cases from all states except Arunachal, Dadra, Daman, Diu, Gujarat, Himachal, Jammu, Kashmir,Kerala, Lakshadweep, Meghalaya, Nagar Haveli, Orissa, Punjab, Rajasthan and Sikkim	South India: May–October in Goa October–January in Tamil Nadu August–December in Karnataka; second peak (April–June in Mandya district) Andrha Pradesh: September–December North India: July–December	Outbreaks in West Bengal, Bihar, Karnataka, Tamil Nadu, Andrha Pradesh, Assam, Uttar Pradesh, Manipure and Goa Urban cases reported, e.g., Lucknow
Indonesia	Kalimantan, Java, Bali, Lombok, Nusa Tenggara, Sulawesi, Mollucas, and Irian Java	Probably year-round risk; varies by island; peak risks associated with rainfall, rice cultivation and presence of pigs; November–March peak period of risk; June–July in some years	Human cases recognized on Bali and Java only
Japan*	Rare-sporadic cases on all islands, except Hokkaido	June–September except Ryukyu islands (Okinawa) April–October	Vaccine not routinely recommended for travel to Tokyo and other major cities. Enzootic transmission without human cases observed on Hokkaido
Korea	No data from North Korea; South Korea sporadic — endemic with occasional outbreaks	July–October	Last major outbreaks in 1982–1983
Laos	Presumed to be endemic– hyperendemic country wide	Presumed to be May–October	No data available
Malaysia	Sporadic–endemic in all states of Peninsula, Sarawak, and probably Sabah	No seasonal pattern; year-round transmission	Most cases from Penang, Perak, Selangor, Johore, and Sarawak

TABLE 1. Risk of Japanese encephalitis by country, region, and season — Continued

Country	Affected areas/ jurisdictions	Transmission season	Comments
Nepal	Hyperendemic in southern lowlands (Terai)	July–December	Vaccine recommended only for travelers visiting southern lowlands
People's Republic of China	Cases in all provinces except Xizang (Tibet), Xinjiang, Qinghai. Hyperendemic in southern China; endemic — periodically epidemic in temperate areas	Northern China: May–September Southern China: April–October (Guangshi, Yunnan, Gwangdong, and Southern Fujian, Szechuan, Guizhou, Hunan, Jiangsi provinces)	Vaccine not routinely recommended for travelers to urban areas only
Pakistan	May be transmitted in central deltas	Presumed to be June–January	Cases reported near Karachi, endemic areas overlap those for West Nile virus
Philippines	Presumed to be endemic on all islands	Uncertain, speculations based on locations and agroecosystems: West Luzon, Mindoro, Negro Palowan: April–November; Elsewhere: year-round — greatest risk April–January	Outbreaks described in Nueva Ecija, Luzon, and in Manila
Russia	Far eastern maritime areas south of Khabarousk	Peak period July–September	First human cases in 30 years recently reported
Singapore	Rare cases	Year-round transmission — April peak	Vaccine not routinely recommended
Sri Lanka	Endemic in all but mountainous areas; periodically epidemic in northern and central provinces	October–January; secondary peak of enzootic transmission May–June.	Recent outbreaks in central (Anuradhapura) and northwestern provinces
Taiwan*	Endemic, sporadic cases; island-wide	April–October, June peak	Cases reported in and around Taipei
Thailand	Hyperendemic in north; sporadic — endemic in south	May–October	Annual outbreaks in Chiang Mai Valley; sporadic cases in Bangkok suburbs
Vietnam	Endemic, hyperendemic in all provinces	May–October	Highest rates in and near Hanoi
Western Pacific	Two epidemics reported on Guam, Saipan (Northern Mariana Islands) since 1947.	Uncertain, possibly September–January	Enzootic cycle may not be sustainable; epidemics may follow introductions of virus

*Local JE incidence rates may not accurately reflect risks to nonimmune visitors because of high immunization rates in local populations. Humans are incidental to the transmission cycle. High levels of viral transmission may occur in the absence of human disease.

Note: Assessments are based on publications, surveillance reports, and personal correspondence. Extrapolations have been made from available data. Transmission patterns may change.

protected by immunization, a secondary increase in JE incidence has been observed in the elderly (*14*). These observations suggest a biological basis for increased JE risk with age because of waning immunity or other factors.

RISK FOR ACQUIRING JAPANESE ENCEPHALITIS AMONG TRAVELERS

Risk for acquiring JE among most travelers to Asia is extremely low; however, the risk for an individual traveler is highly variable and depends on factors such as the season, locations and duration of travel, and activities of the person. Travel during the transmission season and exposure in rural areas, especially for extended periods of time, are the principal factors contributing to risk. The extent and nature of outdoor activity, use of protective clothing, bed nets and repellents, and lodging in air-conditioned or well-screened rooms are additional factors that affect exposure. Residents of developed countries usually have no natural immunity to JE virus and travelers of all ages are equally susceptible to infection with JE virus; however, the elderly may be more susceptible to developing neuroinvasive disease.

Although the probability of exposure to JE viral infection and illness increases with the duration of stay in rural endemic areas, one case occurred in a traveler who made only a few excursions into rural areas while on a 2-week vacation (*15*).

Since 1981, 11 U.S. residents have been infected with JE virus; eight were military personnel or their dependents (Table 2) (*15–17; Tsai TF, Hoke CH, unpublished observations*). Thirteen additional JE cases have been recognized among other western expatriates and travelers. Although figures for travelers at risk are imprecise, a crude

TABLE 2. Japanese encephalitis cases among expatriates and travelers, 1978–1992

Year	Location	Occupation	Citizenship	Age	Sex	Outcome
1978	Beijing	Diplomat	Italy	NA	M	Fatal
1981	Beijing	Student	U.S.	21	M	Fatal
1981	NA	NA	Australia	NA	NA	NA
1982	Beijing	College Professor	U.S.	62	M	Fatal
1982	NA	Soldier	U.S.	32	M	NA
1982	Manchuria	NA	Canada	36	F	NA
1983	Thailand	Nurse	Holland	30	F	Disabled
1983	NA	Child	U.S.	1	M	NA
1983	Hong Kong	Unknown	U.K.	35	F	Fatal
1985	Thailand	Oil Field Worker	Germany	30	M	Fatal
1985	N. Vietnam	Child	E. Europe	9	M	Fatal
1986	Philippines	Soldier	U.S.	55	M	Disabled
1986	Philippines	Soldier	U.S.	NA	M	Recovered
1988	NA	NA	U.S.	64	M	NA
1988	Indonesia	Child	Australia	10	F	Disabled
1989	Thailand	Student	Israel	22	F	Recovered
1991	Thailand	NA	Austria	NA	NA	NA
NA	Thailand	NA	Germany	NA	NA	NA
NA	Thailand	NA	Denmark	NA	NA	NA
NA	NA	NA	Australia	NA	NA	NA
1991	Okinawa (Japan)	Soldier	U.S.	20	M	Disabled
1991	Okinawa (Japan)	Soldier	U.S.	35	M	Disabled
1991	Okinawa (Japan)	Soldier	U.S.	28	M	Recovered
1992	Singapore	Child	U.S.	19	M	Recovered

NA – Not available

estimate, based on the number of outbound airline passengers to Asia (2 to 3 million U.S. citizens annually during the past 5 years [*U.S. Department of Transportation, unpublished data*]), suggests that the risk of acquiring JE among U.S. travelers is <1 per million annually. This estimate may be low because short-term travelers to developed and urban areas probably constitute the majority of visitors to Asia and not all travelers with JE will have been recognized. Moreover, between 1984 and 1987 JE vaccine was available on a limited basis in the United States and some travelers at high risk were protected by vaccination (*1,17*).

For travelers to rural areas where JE is endemic, risk per month of exposure can be extrapolated from incidence rates in the resident population. Assuming an annual incidence rate of 10 per 10,000, and recognizing that nearly all cases occur within a 5-month period, the estimated risk for JE during a 1-month period (the transmission season) is 1 per 5,000 or 1 per 20,000 per week. Similar rates (<0.1–2.1 per 10,000 per week) have been observed in non-immunized Western military personnel in Asia (data from 1945 through 1991) (*18–23*).

The risk for developing JE after a mosquito bite can be factored into a series of probabilities. Only bites of vector mosquitoes pose a risk and fewer than 3% of vector mosquitoes are likely to be infected. Only one of approximately 200 infections leads to neuroinvasive disease. The use of bed nets, insect repellents and protective clothing, and avoidance of outdoor activity, especially during twilight periods and in the evening, will reduce risk even further.

INACTIVATED JAPANESE ENCEPHALITIS VIRUS VACCINE

An inactivated JE vaccine derived from infected mouse brain has been licensed in Japan since 1954 (*24*). JE vaccine licensed in the United States is produced by the Research Institute of Osaka University (Biken) and is distributed by Connaught Laboratories Inc. The Biken vaccine is the most widely used JE vaccine of its type.

Similar mouse brain derived JE vaccines are produced by other manufacturers in India, Japan, Korea, Taiwan, Thailand, and Vietnam (*25,26*). In the PRC, inactivated and attenuated JE vaccines are produced in primary hamster kidney cells (*27,28*).

The Biken vaccine is prepared with the Nakayama-NIH strain of JE virus, originally isolated in 1935 from an infected human. The vaccine is produced from infected mouse brains by a sequence of protamine sulfate treatment, formalin inactivation, ultra-filtration, and ammonium sulfate precipitation. The vaccine is purified further by ultracentrifugation through a sucrose cushion. Gelatin is added as a stabilizer during several steps of the process. No myelin basic protein (MBP) can be detected in the vaccine at a level of 2 ng/mL, the detection threshold of the MBP assay. Thimerosal is added as a preservative. Vaccine potency is determined in comparison with a reference vaccine of known clinical efficacy.

VACCINE EFFICACY

Efficacy was demonstrated in a single placebo-controlled trial conducted in Thailand (*13*). The study compared the efficacy of two doses of monovalent JE vaccine prepared with the Nakayama-NIH strain (21,628 children) with two doses of a bivalent vaccine also containing the Beijing strain (22,080 children); 21,516 children were ad-

ministered tetanus toxoid (TT) as a placebo. After 2 years, two JE cases were reported among recipients of either JE vaccine and 11 cases were observed in the placebo cohort, for an overall vaccine efficacy of 91% (95% confidence interval [CI] of 70%–97%). The monovalent and bivalent vaccines did not differ in their efficacy.

A prototype of the currently licensed vaccine, which was a less refined mouse brain-derived product, was field tested in Taiwan in 1965 (29). Two doses of JE vaccine or TT were administered under masked protocol to 111,749 and 131,865 children, respectively; 22,194 children were administered a single dose of JE vaccine and 140,514 unvaccinated children also were observed. Observations during a single year showed rates of 4 per 100,000 in recipients of two JE vaccine doses and 18 per 100,000 in recipients of TT for a vaccine efficacy of 80%. A single vaccine dose had no demonstrable efficacy.

IMMUNOGENICITY

Levels of neutralizing antibody that are considered protective have been defined by animal challenge experiments (24). A neutralizing antibody titer of ≥1:10 in passively immunized mice protected against challenge with 10^5 LD_{50} of JE virus, a viral dose that might be transmitted by an infected mosquito. Thus neutralizing antibody titers ≥ 1:10 (as determined by the technique used at Biken) have been presumed to protect against natural infection.

The dosage regimen shown to be efficacious in the trials cited previously, which is used for primary vaccination in many areas of Asia, consists of two doses administered 1-4 weeks apart. However, immunogenicity studies in the United States and among British subjects indicate that three doses are needed to provide protective levels of neutralizing antibody in a suitable proportion of vaccinees (Table 3) (17,30). Fewer than 80% of vaccinees receiving two doses seroconverted (reciprocal neutralizing antibody titer of ≥8–10). Moreover, after 6–12 months, only 29% of vaccinees still had adequate antibody levels (17). The vaccine's efficacy and immunogenicity after two doses in Asian subjects may reflect the effects of prior immunity or subsequent exposures to JE, West Nile, dengue, and other flaviviruses circulating in Asia (31). Although exposure to flaviviruses is almost universal at an early age in developing

TABLE 3. Immunogenicity of inactivated Japanese encephalitis virus vaccine among western subjects after two or three doses

	Two-dose series			Three-dose series		
	n	seroconversion rate	GMT*	n	serconversion rate	GMT
United States (17)	118	77%	28	72	99%	141
Nepal						
British subjects (30)	27	33%	31-61	94	88%	146-214
United States (34)	20	80%		25	100%[†]	
United States[§]				526	100%	140/692[¶]

*Geometric mean titer (reciprocal).
[†] Third dose at week 26.
[§] DeFraites R, unpublished data.
[¶] Day 60 serum; short and long three-dose schedules (p < .0001).

areas of Asia, flaviviral infections are rare in North America and in most areas of Europe.

Immunogenicity studies with another flaviviral vaccine (inactivated tick-borne encephalitis [TBE] vaccine) showed that previous flaviviral infections or yellow fever immunization augmented and accelerated the antibody response to TBE vaccine (*32*). Preliminary studies do not indicate such an effect among JE vaccine recipients (*De-Fraites R, unpublished data*).

The vaccine was more immunogenic when administered in three doses during a 30-day period (days 0, 7, and 30) than during a shorter period of 2 weeks (days 0, 7, and 14) (Table 3). Although all subjects seroconverted with either regimen, at 6 months geometric mean titers (GMT) were higher with the longer schedule (p<.0001) (*DeFraites R, unpublished data*).

The longevity of neutralizing antibody after primary vaccination is not known. The GMT of vaccinees receiving three doses was unchanged between 6 months and 1 year (1:76) after the primary series. After a booster dose was administered at 1 year, neutralizing antibody titers increased sharply 3 months later to a mean titer of 1:1,117 (*DeFraites R, unpublished data*). Twenty-one subjects who did not receive a booster retained elevated antibody titers for 2 years after primary vaccination (GMT 1:105). Additional data on the persistence of antibody are pending. In one Japanese study, antibody titers above 1:10 persisted for 3 years after a booster dose (*33*).

ADVERSE REACTIONS

JE vaccination is associated with a moderate frequency of local and mild systemic side effects (*13,17,25,26,34,35*) (*DeFraites R, unpublished data*). Tenderness, redness, swelling, and other local effects have been reported in about 20% of vaccinees (<1%-31%). Systemic side effects — fever, headache, malaise, rash, and other reactions such as chills, dizziness, myalgia, nausea, vomiting, and abdominal pain — have been reported in about 10% of vaccinees.

The neural tissue substrate of the vaccine has raised concerns about the possibility of vaccine-related neurologic side effects (*36*). The amount of mouse MBP in the vaccine, if any, is well below levels associated with an encephalitogenic effect in a guinea pig model. Surveillance of JE vaccine-related complications in Japan during the years 1965–1973, disclosed neurologic events (principally, encephalitis, encephalopathy, seizures, and peripheral neuropathy) among 1 to 2.3 per million vaccinees (*37*) (*Biken, foundation for vaccination research, unpublished data*). One case of Guillain Barré syndrome temporally related to JE vaccination has been reported in the United States since 1984; however, this patient also had pharyngitis 3 weeks before the onset of weakness and had a positive monospot test (*DeFraites R, unpublished data*). A causal relation between JE vaccination and temporally related neurologic events has not been established in this or other cases.

Since 1989, an apparently new pattern of adverse reactions has been reported, principally among travelers vaccinated in Australia, Europe, and North America (*35,38–39*)(*Navy Environmental Health Center, unpublished data; Cambridge Self Diagnostic Services, unpublished data*; and *Andersen MM, Rone T, personal communication*) (Table 4). The reactions have been characterized by urticaria, often in a generalized distribution, and/or angioedema of the extremities, face, and oro-

pharynx, especially of the lips. Three vaccine recipients developed respiratory distress. Distress or collapse because of hypotension or other causes led to hospitalization for several persons. Most reactions were treated successfully with antihistamines or oral steroids; however some patients were hospitalized for parenteral steroid therapy. Three patients developed associated erythema multiforme or erythema nodosum, and some patients have had joint swelling. Some vaccinees have complained of generalized itching without objective evidence of a rash. The immunologic mechanism of these adverse events has not been defined. Additional immunologic studies are pending.

An important feature of these reactions has been the interval between vaccination and onset of symptoms. Reactions after a first vaccine dose occurred after a median of 12 hours following vaccination (88% of reactions occurred within 3 days). The interval between administration of a second dose and onset of symptoms generally was longer (median 3 days) and possibly as long as 2 weeks. Reactions have occurred after a second or third dose, when preceding doses were received uneventfully. Although some observers have reported that reactions occur chiefly after a second or third dose, one prospective study found similar reaction rates after first and second doses (*Navy Environmental Health Center, unpublished data*).

A case-control study among U.S. military personnel found an association between reactions to JE vaccine and a past history of urticaria (after hymenoptera envenomation, medications, physical or other provocations or of idiopathic cause [relative risk 9.1, 95% CI 1.8–50.9]) (*Navy Environmental Health Center, unpublished data*).

Surveillance of adverse reactions during a mass immunization campaign of 35,000 active duty U.S. military personnel and their dependents on Okinawa disclosed the sudden death of a 21-year-old man who had received a first dose of JE vaccine 60 hours earlier. He also had received a third dose of plague vaccine on the day of death. The man had a medical history of recurrent hypersensitivity phenomena and an episode of possible anaphylaxis. He reported no antecedent symptoms before he was found dead, and the cause of death was not established at autopsy.

The incidence of these adverse reactions has varied widely depending on the circumstances of vaccine administration and surveillance (Table 4). In two reports from travelers' clinics in Australia and Canada, rates of 50–104 per 10,000 vaccinees were reported. National surveillance estimates in Denmark, Australia, the United Kingdom, and Sweden are about 10-fold lower and range from 0.7 to 12 per 10,000. Studies among U.S. citizens have disclosed rates of 15–62 per 10,000 (Table 4).

Whether this pattern of adverse reactions is new for JE vaccine is unclear. Data from Denmark and Australia suggest that this may be the case. From 1983 to November 1989, no such adverse reactions were reported to the Danish State Serum Institute among recipients of 161,000 doses. From November, 1989 to June 1991, 19 cases were reported among 62,000 vaccine recipients ($p < 10^{-6}$, Poisson) (*38*). Although JE vaccine had been distributed to 4,000 persons in Australia since 1987, the seven adverse reactions meeting the above description were reported only after June 1990 (*38*). Other patients with similar clinical features were reported from the United Kingdom in 1991, from Canada in 1990, and Sweden in the period from 1989–1990. However, in retrospect, similar adverse events were observed in a JE vaccine trial conducted from 1983 to 1987 in the United States (*17*). One patient had an anaphylactic reaction occurring within 5 minutes of vaccination; the other subject developed generalized

urticaria 7 hours after vaccination. Although the latter case initially was diagnosed as exercise-induced urticaria, a relation of the reaction to JE vaccine cannot be excluded.

The vaccine constituent(s) responsible for these adverse events has (have) not been identified. Twelve of 45 vaccine lots produced from April 1988 to January 1991 have been associated with this pattern of adverse reactions. However, 26 of the remaining 33 lots were distributed exclusively to Asian countries. The absence of similar reports associated with these lots may be related to differences in the sensitivity of surveillance for adverse reactions, variations in susceptibility of vaccinees in Asia, or other lot variations. Therefore, whether the reactogenicity of JE vaccine produced recently is associated only with certain lots, or whether a uniform pattern of reactogenicity has gone undetected, is uncertain.

Post-marketing surveillance for adverse reactions occurring in the United States will be established by the manufacturer.

TABLE 4. Hypersensitivity reactions* following immunization with inactivated Japanese encephalitis virus vaccine (Biken)

Country	Lot #	Cases	Estimated # of vaccinees	Estmated rate per 10,000 vaccinees	95% confidence interval
Denmark	16	13[†]	17,500	7	4–13
	32	2[§]	7,500	3	0.3–9.6
	33	2	10,000	2	0.2–7.2
	12	4	6,500	6	1.7–16
Sweden[¶]	30	1	15,000	0.7	.02–3.7
United Kingdom	13	1	1,950	5	0.13–29
Australia					
Nationwide	(9**),17,42	4[††]	3,400	12[††]	3–30
Fairfield Hospital	17,42	3	601	50	10–140
Canada					
Nationwide	32,54	3	NA	NA	NA
Univ. of Calgary	32	1	96	104	2.6–567
United States					
Travelers (CDC)	NA	2[§§]	1,328	15	1.8–54
Active duty army	29,30,31	1[¶¶]	526	19	0.5–105
Active duty military & dependents (Okinawa)	49,55	220	35,253	62	54–71

*Generalized urticaria or angioedema.
[†]One additional case of erythema multiforme.
[§]One additional case of erythema nodosum.
[¶]Two cases, lots unknown.
**Use unknown.
[††]Lots unknown for four cases; estimated rate is based on total number of vaccinees.
[§§]Puffy eyes reported; not documented to have urticaria.
[¶¶]One case diagnosed as exercise-induced anaphylaxis; one case of generalized anaphylaxis.
NA – Not available

VACCINE USAGE

U.S. Expatriates

JE vaccine is recommended for persons who plan to reside in areas where JE is endemic or epidemic (residence during a transmission season) (*40–44*). Risk for acquiring JE is highly variable within the endemic regions (Table 1, Figure 1). The incidence of JE in the location of intended residence, the conditions of housing, nature of activities, and the possibility of unexpected travel to high-risk areas are factors that should be considered in the decision to seek vaccination.

Travelers

JE vaccine is NOT recommended for all travelers to Asia. In general, vaccine should be offered to persons spending a month or longer in endemic areas during the transmission season, especially if travel will include rural areas. Under specific circumstances, vaccine should be considered for persons spending <30 days in endemic areas, e.g., travelers to areas experiencing epidemic transmission and persons whose activities, such as extensive outdoor activities in rural areas, place them at high risk for exposure. In all instances, travelers should be advised to take personal precautions; e.g., to reduce exposure to mosquito bites.

The decision to use JE vaccine should balance the risks for exposure to the virus (Table 1, Figure 1) and for developing illness, the availability and acceptability of repellents and other alternative protective measures (*44*), and the side effects of vaccination. Risk assessments should be interpreted cautiously (Table 1, Figure 1) since risk can vary within areas and from year to year and available data are incomplete. Estimates suggest that risk of JE in highly endemic areas during the transmission season can reach 1 per 5,000 per month of exposure; risk for most short-term travelers may be ≤1 per million. Although JE vaccine is reactogenic, rates of serious allergic reactions (generalized urticaria or angioedema) are low (1 to 104 per 10,000). Advanced age may be a risk factor for developing symptomatic illness after infection. JE acquired during pregnancy carries the potential for intrauterine infection and fetal death. These special factors should be considered when advising elderly persons and pregnant women who plan visits to areas where JE is endemic.

Primary Immunization Schedule

The recommended primary immunization series is three doses of 1.0 mL each, administered subcutaneously on days 0, 7, and 30. An abbreviated schedule of days 0, 7, and 14 can be used when the longer schedule is impractical or inconvenient because of time constraints. Two doses administered a week apart will confer short-term immunity among 80% of vaccinees (Table 3). However, this schedule should be used only under unusual circumstances and is not routinely recommended. The last dose should be administered at least 10 days before the commencement of travel to ensure an adequate immune response and access to medical care in the event of delayed adverse reactions.

The immunization schedule for children 1-3 years of age is identical except that the manufacturer recommends 0.5 mL administered subcutaneously. No data are available on vaccine safety and efficacy in infants <1 year of age.

Booster Doses

Protective levels of neutralizing antibody persist for at least 2 years in vaccinees who have completed a three-dose primary series. The full duration of protection is unknown, therefore, definitive recommendations cannot be given on the timing of booster doses. Booster doses of 1.0 mL (0.5 mL for children <3 years of age) may be administered after 2 years.

PRECAUTIONS AND CONTRAINDICATIONS

Adverse Reactions and Hypersensitivity

Adverse reactions to JE vaccine manifesting as generalized urticaria and angioedema have occurred within minutes to as long as 2 weeks after vaccination. Epinephrine and other medications and equipment to treat anaphylaxis should be available. Vaccinees should be observed for 30 minutes after vaccination and warned about the possibility of delayed urticaria and angioedema of the head and airway. Vaccinees should be advised to remain in areas with ready access to medical care in the 10 days after receiving a dose of JE vaccine.

Persons with a history of certain allergic disorders (see ADVERSE REACTIONS) appear to have a greater risk for developing adverse reactions to JE vaccine. This history should be considered 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. There are no data supporting the efficacy of prophylactic antihistamines or steroids in preventing JE vaccine-related allergic reactions.

JE vaccine is produced in mouse brains and should not be administered to persons with a proven or suspected hypersensitivity to proteins of rodent or neural origin (other vaccines produced in rodent neural tissue include experimental hantaviral vaccines produced in Korea and the PRC and the previously used French neurotropic strain yellow fever vaccine [discontinued in 1982]). Hypersensitivity to thimerosal is a contraindication to vaccination.

The vaccine should not be administered to persons who have had a previous adverse reaction after receiving JE vaccine. Patients who develop allergic or unusual adverse reactions after vaccination should be reported through the Vaccine Adverse Event Reporting System (1-800-822-7967).

Age

No data are available on the safety and efficacy of JE vaccine among infants <1 year of age. Whenever possible vaccination of infants should be deferred until they are ≥1 year of age.

Pregnancy

No specific information is available on the safety of JE vaccine in pregnancy. Vaccination poses an unknown but theoretical risk to the developing fetus, and the vaccine should not be routinely administered during pregnancy. Pregnant women who must travel to an area where risk of JE is high should be vaccinated when the theoretical

risks of immunization are outweighed by the risk of infection to the mother and developing fetus.

Altered Immune States

The only data on the use of inactivated JE vaccine in patients with altered immune states come from a small study among children. These data did not suggest a changed pattern of adverse reactions or immune response after vaccination (*45*).

Simultaneous Administration of Other Vaccines or Drugs

Limited data suggest that the immunogenicity and safety of JE vaccination is not compromised by simultaneous administration with DTP vaccine (*Nisalak A, unpublished data*). No data exist on the effect of concurrent administration of other vaccines, drugs (e.g., chloroquine, mefloquine), or biologicals on the safety and immunogenicity of JE vaccine.

VACCINATION OF RESEARCH LABORATORY WORKERS

Twenty-two cases of laboratory-acquired JE have been reported (*46*). Although work with JE virus is restricted to facilities with BL-3 capabilities, JE virus may be transmitted in a laboratory setting through needlesticks and other accidental exposures. Vaccine-derived immunity presumably protects against exposure through these percutaneous routes. Exposure to aerosolized JE virus, and particularly to high concentrations of virus, that may 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 vaccine-derived immunity protects against such exposures is unknown, but vaccination is recommended for all laboratory workers with a potential for exposure to infectious JE virus.

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