
REVIEWS

Expert Opinion on Vaccination of Travelers Against Japanese Encephalitis

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Existing recommendations for Japanese encephalitis (JE) vaccination of travelers were framed to avoid unnecessary exposure to the highly reactogenic mouse brain-derived vaccine and limited the vaccine's use to extremely high-risk circumstances. However, serious and fatal JE cases in travelers not covered under current recommendations have suggested a justification for broader vaccine coverage. The discontinued availability of the mouse brain-derived vaccine and licensure of a novel, well-tolerated, inactivated cell culture-derived vaccine has led to a reexamination of JE risk in travelers and a reconsideration of recommendations to prevent the unnecessary occurrence of these frequently devastating, vaccine-preventable, cases. In the context of these new circumstances, an expert committee on travel vaccines proposed these revised recommendations:

Recommendations of an *ad hoc* Travel Vaccines Expert Group, Helsinki May 21, 2008.

The above-mentioned individuals attended an advisory board meeting convened on May 21, 2008, in Helsinki, Finland by Novartis Vaccines and Intercell AG, in which Japanese encephalitis and other travel vaccines were discussed. This publication summarizes the group discussion and recommendations for Japanese encephalitis vaccine.

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Advise

Advise all travelers to areas of Asia where JE virus is transmitted in an enzootic cycle (including Japan) about the risks and consequences of JE and characteristics of available vaccines.

Recommend JE vaccination before departure, to ensure an adequate level of protection, to avoid potential delays in arranging immunizations on arrival, and to ensure vaccination with a well-characterized vaccine to:

- All expatriates.
- Repeat travelers who return frequently to the region or who, cumulatively, have a prolonged duration of exposure.
- Any individual with a prolonged duration of stay, independent of itinerary.
- Any individual with a travel itinerary including rural areas.
- Travelers wishing maximum protection.

Consider Vaccination

- All other travelers visiting regions with enzootic transmission during a transmission period, particularly,
 - Those with greater outdoor exposure.
 - Individuals ≥ 50 years of age.
 - Children < 10 years of age.
 - Individuals with chronic conditions, such as
 - History of solid organ transplant,
 - History of cochlear implants, ventriculoperitoneal shunts, and other devices impinging the central nervous system (CNS) or history of or medical

- conditions associated with cerebrospinal fluid (CSF) leakage.
- Hypertension
- Diabetes mellitus
- Chronic renal disease
- Anti-TNF therapy
- Individuals known from previous history to be homozygous for CCR5Delta32
- Pregnant women (balancing unknown risks associated with vaccination)

Japanese encephalitis, a mosquito-borne flaviviral infection in Asia, is the most important cause of viral encephalitis in that region and, sporadically, has been a cause of serious, sometimes fatal illness in travelers. Recommendations for vaccinating travelers to the region that were promulgated by the Advisory Committee on Immunization Practices (ACIP) in 1993 appeared to be successful in reducing the number of cases reported in US travelers, while limiting the potential occurrence of serious adverse reactions associated with the available mouse brain-derived vaccine. However, in recent years, an increasing number of cases have been reported in travelers who did not meet the criteria for vaccination set out in the ACIP recommendations.¹⁻⁸ With the recognition of these cases, and as production of the currently licensed inactivated mouse brain-derived vaccine has been discontinued and a novel inactivated cell culture-derived vaccine (IXIARO) has been licensed recently in the United States and is close to licensure in Europe, it is appropriate to revisit risks for acquiring JE during travel and how a vaccine with a different adverse reactions profile might be used.⁹⁻¹²

Background

Although 30,000 to 50,000 JE cases in the region are reported annually, epidemiological surveillance probably underestimates the true burden of disease. The majority of infections are asymptomatic, resulting in a case-infection ratio of at least 1 in 250.¹³ However, approximately 30% of symptomatic cases are fatal and in up to 50% of surviving patients, significant neurological impairment complicates recovery.¹⁴⁻¹⁷ There is no specific treatment for JE; however, effective vaccines are available.

JE is transmitted in an endemic pattern throughout Asia and episodically has spread to islands in the Torres Strait of Australia or in the Pacific (Figure 1).¹⁸⁻²¹ JE virus is transmitted in a cycle between mosquitoes (principally *Culex tritaeniorhynchus*) and vertebrates, with pigs and aquatic birds playing important roles as amplifying hosts (Figure 2).^{14,22-25} Hence, incidence rates are highest in rural areas, where pigs, aquatic birds, and paddy-breeding vector mosquitoes are prevalent. Personal protective measures, such as avoidance of outdoor exposure and application of repellents during crepuscular (twilight) periods, when vector mosquitoes are most active, can reduce the risk of infection, but vaccination remains the most effective means of prevention. Vaccines against JE have been available since the 1930s, and public health programs of vaccination in China, Japan, Korea, Nepal, Taiwan and Thailand have been highly effective in reducing the burden of disease.^{14,26-31}

Travel to Asia

Expatriates and travelers visiting areas of Asia where JE virus is transmitted are at risk of acquiring the disease.

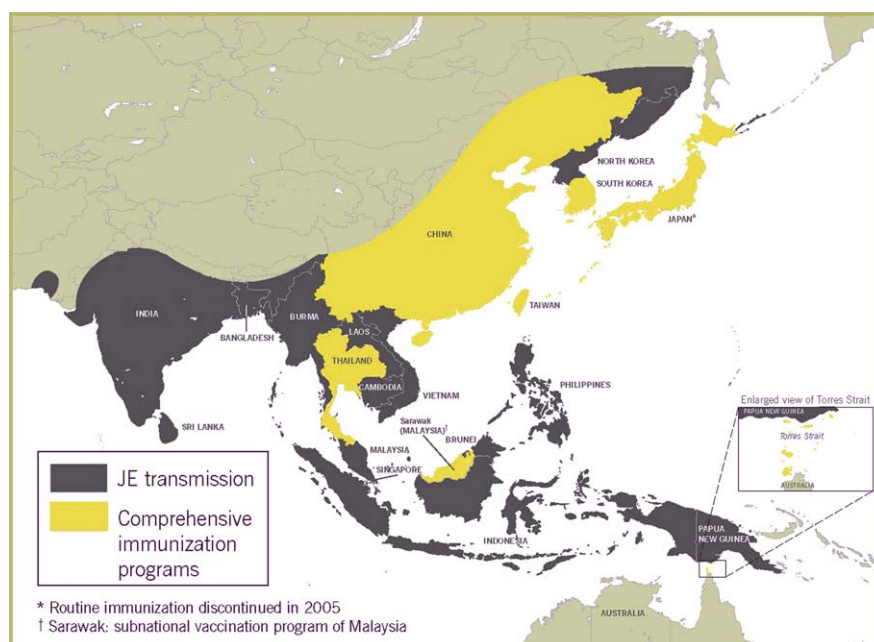


Figure 1 Japanese encephalitis distribution in Asia and the Pacific. Adapted from reference.¹⁴

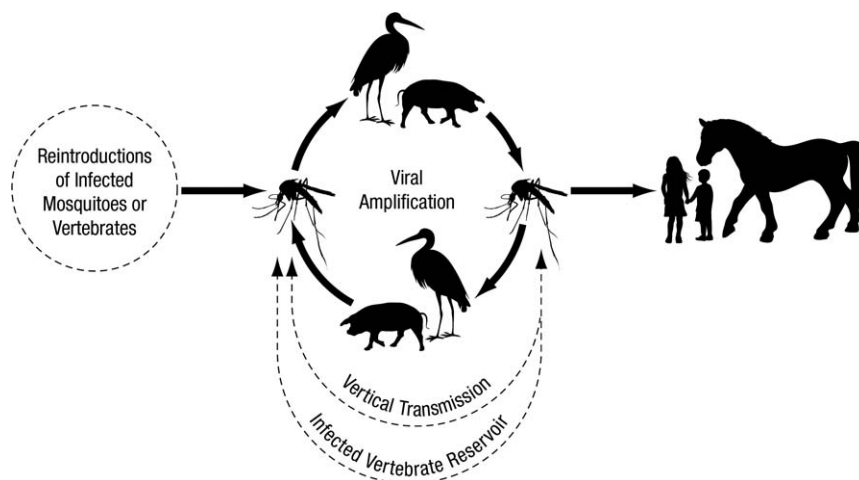


Figure 2 Japanese encephalitis transmission cycle. Solid lines denote well-characterized components of the transmission cycle; dashed lines denote speculative aspects. Adapted from reference.¹⁴

Asia now is the second most popular travel destination globally, as evidenced by the increase of international air arrivals from 56 million in 1990 to 184 million in 2007. Travel to East Asia, Southeast Asia, and South Asia is predicted to grow faster than to other regions of the world.^{32,33} Tourism is the main reason for traveling to Asia, accounting for nearly half of arrivals, but business travelers and émigrés returning to their country of origin to visit friends and relatives (VFRs) are also important groups, accounting for 15 and 21% of travelers, respectively.³⁴ Although their numbers are smaller, VFRs exhibit behaviors that may place them at greater risk for acquiring the disease.³⁵ Numerous US military personnel and their families have been a consistent presence in Asia for more than 50 years but a growing number of civilian expatriates now are relocating to Asia, often with their families. Depending on the length of assignment, their cumulative risk of infection could emulate that of local residents. Other visitors with an increased risk of acquiring the disease because of their extended duration of stay include students and aid workers. Hence, there is an increasing need to inform travelers of the risk of JE, the consequences of infection, and preventive measures.

Risk of Acquiring Japanese Encephalitis in Travelers to Asia

As the majority of JE infections are asymptomatic, risk for acquiring the disease depends not only on exposure and behavioral factors associated with infection but also on, as importantly, host factors linked to an increased risk for developing clinical disease and sequelae following infection. These various risk factors can be described in epidemiological terms by time, place, and person.

Time

In general, opportunities for infection increase with a longer duration of exposure in the region, and expatriates and persons with a longer duration of stay have an increased potential for exposure and infection than short-

term travelers. A review of outbreaks among American soldiers and other circumstances where immunologically naïve populations were exposed to the virus (as would be the case for most unimmunized travelers) for a delimited period of exposure disclosed attack rates in the range of 1 to 5 per 10,000 (Table 1). However, these rates must be interpreted in view of their particular circumstances, including the activities and exposures of the groups involved, and in the case of outbreaks in the Pacific, the involvement of mosquito vectors not typically involved in viral transmission in Asia. Although these rates overlap annual attack rates for children in the region, some fraction of the children under observation would have been immune from natural infections and the observed rates underestimate the risk for an entirely naïve population. Assuming a 6-month transmission season, an interpolation of the observed attack rates in these outbreaks provides an estimate of monthly risk in the range of 1/10,000.^{19,20,36-42}

JE is transmitted seasonally in large areas of Asia but, in some locations, may be transmitted year round.^{14,22,25,43-45} In areas with a temperate climate, eg, Japan, Korea, northern China, a typical spring–summer–fall seasonality prevails, although the peak month of risk and the duration of the transmission season vary with latitude (Figure 3).⁴⁶ However, like influenza, the severity of annual outbreaks and their months of onset and of completion can vary widely from year to year. Moreover, secular changes in previously observed patterns of transmission, such as an earlier initial and peak month of reported cases that has been seen in Taiwan, could be underway elsewhere in the region, if the trends can be attributed to global warming as suggested.

Importantly, in some tropical locations, the timing of seasonal epidemics corresponds to the appearance of annual monsoons or rainy seasons, which can be highly specific to those locations.^{14,22,25,44,47} In southern India, eg, monsoons visit the eastern and western coasts in different months, so that even at the same latitude, intervals with

Table 1 Incidence of laboratory confirmed Japanese encephalitis in immunologically naïve populations (in bold) or in children residing in areas with endemic transmission

Year(s), study site	Cases/population	Annual rate/10,000	Comment
2001–2003, Bali, Indonesia ³⁶	89/502,200	0.7 (0.4–1.0)	Hospital-based surveillance
1995, Torres Strait, Australia ²⁰	3/8,000	3.8 (1.3–11.0)	<i>Culex annulirostris</i> -borne outbreak
1991, Okinawa, Japan ³⁷	3/20,000	1.5 (0.5–4.4)	Heterogenous population at risk; island highly urbanized
1990, Saipan, Northern Mariana Islands ¹⁹	10/40,000	2.5 (1.4–4.6)	<i>C. annulirostris</i> -borne outbreak
1984–1985, Kamphangphet, Thailand ³⁸	11/21,516	2.5 (1.4–4.6)	Placebo recipients in vaccine trial, 1- to 14-y-old
1972, Nham Phong, Thailand ³⁹	9/2,101	42.8 (22.6–81.2)	US soldiers
1970, Chiangmai valley, Thailand ⁴⁰	100/680,000	1.5 (1.2–1.8)	Transmission extended over 8 mo
1968–1971, Taiwan (except Taipei) ⁴¹	120/>12 × 10 ⁶	0.1 (0.08–0.13)	Consecutive years after mass vaccination initiated in 1967
	240/>12 × 10 ⁶	0.2 (0.18–0.23)	Consecutive years after mass vaccination initiated in 1967
1965, Taiwan (except Taipei) ⁴²	35/140,514	2.5 (1.8–3.5)	Unvaccinated
	24/131,865	1.8 (1.2–2.7)	Placebo recipients in vaccine trial, 3- to 7-y-old

heavy rainfall and vector mosquito abundance differ, and with those differences, risk of JE virus transmission.¹ As the timing and intensity of rainy seasons can be highly specific to location and also can vary from year to year, advising travelers on distinct periods when JE poses a risk (or not) can be difficult and may lead to assessments that overestimate the precision of available data.

Many areas with tropical climates hold a potential for year round transmission; however, as these conditions also allow multiple crops of rice to be planted, the monthly abundance of paddy-breeding mosquitoes, among them *C tritaeniorhynchus*—the principal JE virus vector, depends on when paddies are flooded by irrigation.^{14,22–25} Consequently, the intervals when adult mosquitoes are most prevalent depend on agricultural practices and schedules as well as by natural phenomena, and the peak periods of risk could vary in a given area depending on when the first and second crops—or even a third crop, are planted.

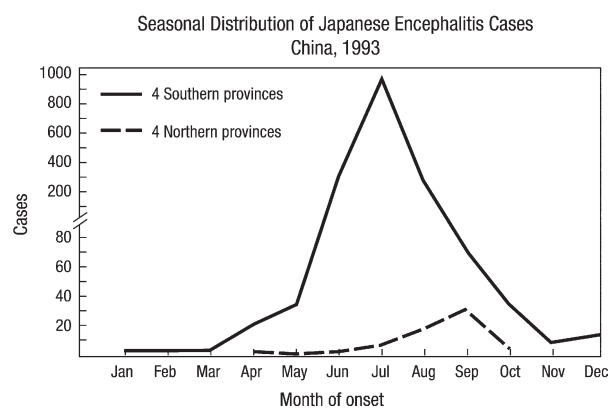
A traveler's risk also will depend on the time of day of outdoor activity. Unlike dengue, which is transmitted during daylight hours by *Aedes aegypti*, a diurnal vector,

the principal JE vectors are crepuscular—most active during twilight hours, especially at dusk. Consequently, outdoor activity exclusively during the day, even in a location with active viral transmission, could be associated with a lower probability of exposure and infection. Conversely, with some exceptions (see below), outdoor activities at twilight and early evening pose a greater risk.

Place

The geographical range of JE in Asia is poorly defined and is dynamic. Epidemiological surveillance and reports of human cases undoubtedly underestimate the distribution of the virus, which is described by the area in which the virus is transmitted in an enzootic cycle, and which is a better indication of the area of risk to travelers. While fewer than 10 JE cases now are reported annually in Japan and no more than 10 cases have ever been reported from Papua New Guinea, the occurrences of a JE case in a traveler who fell ill within a month of arriving, and a case in an American expatriate in Papua New Guinea, illustrate the potential fallibility of relying on reported disease incidence as an indicator of risk (E. Jong, personal communication).⁴⁸

Reports of human cases may fairly represent the true occurrence of cases in some countries with good surveillance systems and laboratory diagnostic capacities. But even in Japan and other developed Asian countries, cases with atypical clinical presentations could be missed, contributing to an underestimation of disease incidence and risk. For example, studies of febrile patients in northern Thailand and in Malaysia underscore that the spectrum of clinical JE encompasses a simple febrile syndrome with headache, but without signs of acute encephalitis, reminiscent of mild cases of St Louis encephalitis (StLE), and West Nile viral infection.^{49,50} In addition, recent case reports of JE presenting as acute flaccid paralysis and aseptic meningitis without an encephalitis syndrome illustrate the potential insensitivity of passive surveillance that is likely to detect mainly acute encephalitis cases.^{51,52} Moreover, adult JE cases may be missed as clinicians and

**Figure 3** Seasonal distribution of Japanese encephalitis cases in China, 1993. Adapted from reference.⁴⁶

epidemiological surveillance principally focuses on children, the age group in which incidence rates generally are highest.

In less developed countries, patients in rural areas may die at home or in outlying hospitals with a reduced chance of coming to the attention of public health authorities.⁵³ These realities contribute to underascertainment even where surveillance relies on syndromic reporting, ie, reporting based on a clinical diagnosis of encephalitis without a requirement for laboratory confirmation. On the other hand, syndromic reporting may lead to an overestimation of cases, as sporadic cases and outbreaks of encephalitis due to other causes in the region could be mistaken for JE, eg, infections due to other flaviviruses (eg, West Nile virus, dengue), bunyaviruses (Snowshoe hare virus and Chandipura virus), reoviruses (Banna virus), as well as nonarthropod borne agents (mumps virus, enteroviruses, various herpes viruses, measles and Nipah viruses, and tuberculosis), Reye syndrome, and toxins.

Relatively few reports are available on the distribution and incidence of JE in countries such as Bangladesh, Bhutan, Cambodia, Indonesia, Laos, Myanmar, Pakistan, Papua New Guinea, and the Philippines, yet aspects of their geography and ecology suggest that JE could be transmitted more broadly in these countries than has been reported. Instructive examples come from Cambodia, where construction of a pediatric hospital in Phnom Penh led to the recognition of hundreds of encephalitis cases in children that previously would have gone unrecognized, and the Philippines, where few cases of JE ever have been reported, and a laboratory-based study between 2002 and 2004 disclosed JE-specific immunoglobulin M in 11.7% of 614 CSF samples, a proportion not dissimilar from ratios in other countries where JE is recognized to be endemic.^{54,55}

While there may be more examples of locations where the virus circulates silently because human surveillance fails to detect it or where people infrequently intrude on a sylvatic cycle, there is, equally, an underappreciation that JE virus continues to circulate in countries like Japan, Taiwan, and Korea, where resident populations are protected by immunization. A review of reported cases in Japan between 1992 and 2004 disclosed 361 JE cases, for which outcomes were reported for 320: 58 (18%) died, 160 (50%) recovered with neuropsychiatric sequelae, and 102 (32%) completely recovered.⁵⁶ Cases principally were in unvaccinated individuals and 78% were 40 years old or over with a peak age group of 60 to 69 years old. Moreover, animal serosurveys in Japan and Korea have disclosed continued high rates of viral transmission in enzootic cycles. Most compelling, annual abattoir surveys in Japan over the past decade have shown that nearly 100% of pigs coming to slaughter during summer months are seropositive.⁵⁷ In addition, serosurveys of horses in two Japanese prefectures found a point seroprevalence in horses of ~50% and of wild boars on the main island of Okinawa, evidence of infection in 65% of 99 animals studied.⁵⁸⁻⁶¹ In Korea, an investigation of 804 goats on

144 farms found 21.1% were seropositive.⁶² Mosquito collections also confirm the continued circulation of JE virus-infected vector mosquitoes where surveillance has been conducted.⁶³

Obtaining similar evidence of human infection has been confounded by routine childhood vaccination, which has made conventional serological assays useless in differentiating vaccine acquired from naturally acquired immunity in humans.^{64,65} A serosurvey that measured antibodies against NS1, ie, a nonstructural protein purified of the inactivated mouse brain vaccine used in Japan, and that presumably reflect naturally acquired infection, found a point prevalence of 4.4%, indicating ongoing exposures to the virus in people across the broad area of the country that was sampled. Using this assay, annual infection rates in Japan were estimated to range from 5% in urban residents to 10% in rural residents.

Cumulatively, these environmental and human surveys indicate that despite the small numbers of reported clinical cases, JE virus continues to be transmitted in highly developed Asian countries and that travelers to those destinations should not overlook the possibility of acquiring the infection and illness. The occurrence of two travel-associated cases acquired in Japan (see above) proves the possibility.

Areas where rice paddies are prevalent pose the greatest risk for human infection because flooded paddies are highly productive of *C tritaeniorhynchus* vector mosquitoes, and vertebrate amplifying hosts—pigs and aquatic birds, are collocated in these settings.²²⁻²⁵ While these elements of the viral amplification cycle are most likely to be combined in rural areas, rice paddies and other flooded pools, as well as amplifying hosts, not infrequently are encountered at the edges of cities or even within some urban environments, providing opportunities for enzootic transmission in metropolitan areas. Examples can be seen in many major Asian cities on the drive from the city center to outlying airports. Epitomizing this juxtaposition, rice paddies comprise the designated greenbelt areas of Denpasar, Bali, providing abundant mosquito-breeding sites in the heart of populated areas, where because of cultural practices, pigs are kept by a large proportion of the population. The intensity of viral transmission in this setting has been speculated to contribute to the earlier age of infection in children in Bali compared to Thailand and other areas of Southeast Asia.⁴³ In Central Sarawak, Malaysia, more than 15% of hospitalized JE cases were reported to have come from urban areas.¹⁷ Sporadic cases and small outbreaks occurring in suburban Bangkok are additional evidence of the ongoing risk for human infection in a major Asian city.^{66,67}

Moreover, unrecognized secondary vectors and transmission cycles could contribute to viral transmission in urbanized settings. For example, JE virus has been isolated from *Culex quinquefasciatus*, a species adapted to urban locations and that is a principal vector of StLE and West Nile virus in US cities. Investigations are needed to ascertain if this ornithophilic species transmits JE virus among birds in urban locations. Although domestic pigs in

developed Asian countries increasingly have been moved to distant centralized facilities for industrial scale rearing, wild boars can invade suburban areas where they have been speculated to contribute to viral amplification.^{59,68} Furthermore, *C tritaeniorhynchus* can fly approximately 5 km and, on wind currents, infected mosquitoes could be carried even further into metropolitan areas.⁶⁹⁻⁷²

Culex tritaeniorhynchus principally feeds outdoors, ie exophagic, and outdoor activities, especially in the late afternoon and at dusk (see above), pose a greater risk for infection than time spent indoors. The same species in different locations may exhibit variable behaviors, however, and in Karnataka state, India, *C tritaeniorhynchus* were abundant in indoor locations during some periods of the year.⁷³ In contrast, dengue can infect travelers in hotels and other indoor locations because *A aegypti*, the principal dengue virus vector, is active near dwellings, including the interior of houses where it deposits eggs in small collections of water and rests in protected locations.

Anecdotal observations suggest a role for regional and local cultural and religious practices in defining locations with enzootic viral transmission. Areas with a principally Muslim population, such as the Brunei Sultanate and most of Indonesia, report no or relatively few cases of JE, possibly because of a reduced number or absence of pigs. The exception of Bali, an Indonesian island that has been the site of acquisition of a disproportionate number of JE cases in travelers and where surveillance of the resident population indicates a high incidence of disease, appears to prove the rule.⁴³ Bali has a predominantly Hindu population that ritually sacrifices pigs on frequent celebratory occasions and, consequently, that maintains an unusually large and dispersed number of pigs, even among suburban and urban households.

These observations suggest that the majority of travelers to Asia who will only visit urbanized areas still may incur some risk for encountering JE virus and acquiring the illness. Anecdotal cases in travelers who had brief, limited excursions to rural areas, as reported in the accompanying review, support this analysis.

Person

Individual behaviors contributing to increased risk of exposure and infection have been mentioned above, eg, outdoor activity in rural areas at dusk, but biological host factors contributing to risk of developing clinical illness following infection also are important to recognize, the most important of which is advanced age (Figure 4).⁷⁴ Virtually, all flaviviruses that cause neurological infections (StLE, Murray Valley encephalitis, West Nile encephalitis, tick-borne encephalitis, Rocio encephalitis, and JE) have exhibited a relatively low case: infection ratio of ~1:300, with an increased age-specific risk for clinical illness with advanced age, especially after the sixth decade. Thus, the proportion of infections resulting in neurological illness is 5- to 10-fold higher in persons older than 50 years compared to the fraction in older children and young adults. While endemic JE cases occur predominantly in children because accumulated asymp-

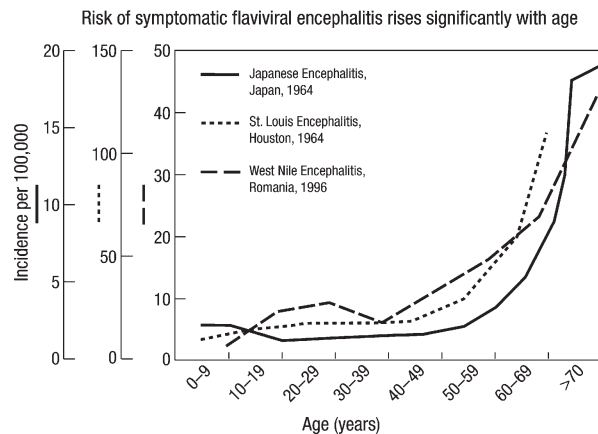


Figure 4 Risk of symptomatic flaviviral encephalitis rises significantly with age. Adapted from reference.⁷⁴

tomatic infections in the majority of the population protect them against reinfection and illness later in life, increasing numbers of cases in adults and especially in older adults are being recognized. Nearly all cases reported from Japan and Taiwan, where vaccination coverage is high, now are in older adults, following the pattern of StLE and West Nile encephalitis in the United States.^{56,75} In China, a similar age shift has been observed in Shanghai and, tellingly, in a 2006 outbreak in Shanxi province, 78% of 45 cases were in persons older than 40 years.⁷⁶⁻⁷⁸ With systematic surveillance, even in developing countries without uniformly high vaccination rates, a moderate proportion of JE cases still may be recognized in adults, as was shown recently in Vietnam.

Although all travelers from nonendemic areas should be presumed to be immunologically naïve and at risk for infection and illness, older travelers, especially those older than 50 years and who are immunosenescent, are, unequivocally, at even greater risk.

Second to the elderly, young children also have an elevated risk for neurological illness after infection with neurotropic flaviviruses, resulting in a J-shaped age-specific incidence curve.⁷⁹ But of potentially greater clinical significance is the high frequency of neurological disability in children surviving the illness.¹⁵⁻¹⁷ More than 50% of surviving children ~<10 years old are left with neurodevelopmental deficits including motor paresis, spasticity, movement disorders, chronic seizures, and developmental delay. In one follow-up study, at a median interval of 4.5 years after hospital discharge, neuropsychological deficits were improved in 36% of cases but in 17% of cases, further deterioration had occurred.¹⁷ JE virus is a teratogen that appears to target the CNS, causing neurological malformations in fetal pigs and, in experimental studies, suppressing proliferation of neural progenitor cells.^{22,23,25,80} Thus, the risk of JE in childhood travelers extends beyond the morbidity of the acute illness to potentially chronic or persistent neuropsychological deficits.

Other host factors that increase the risk for developing flaviviral encephalitis, and that can be extrapolated

to JE, include a history of certain chronic diseases, such as solid organ transplantation, hypertension, diabetes mellitus, cardiovascular, and renal disease. All have been independently associated with risk for developing neurological infections with West Nile virus or of dying from StLE virus.^{81–86} The mechanisms by which these chronic conditions increase risk for neurological infection are unknown; however, immune responses to influenza vaccination in patients with chronic congestive heart failure have been shown to be reduced compared to age-matched healthy adults, suggesting that immune mechanisms should not be excluded.⁸⁷ On the other hand, prior dengue virus infection has been associated with improved prognosis in JE and StLE, indicating a modulating effect of cross-reactive flaviviral immunity in these infections.^{88–90} West Nile encephalitis also has been reported in a patient on infliximab therapy, suggesting that medically induced immunosuppression also may increase risk for developing neurological illness.⁹¹

Next in importance as a host factor may be the presence of physical or physiological disruptions of the meninges or blood-brain barrier. A number of epidemiological, clinical, and experimental observations suggest that such physical disruptions may enhance JE viral neuroinvasion from the blood, which has been hypothesized to occur as the virus crosses brain capillary endothelia during the viremic phase of infection. A compelling observation supporting such an association is the increased prevalence of neurocysticercosis in JE patients compared to patients with other conditions,^{92–97} and the matched laterality and intensity of inflammation in cases of dual infection associated with the location of cysts and surrounding areas of edema. An unusual combined mumps–JE outbreak and experimental animal studies also suggest that dual neurological infections also may enhance viral neuroinvasion.^{18,21,98} Finally, experimental disruption of the blood-brain barrier by electromagnetic radiation that enhanced neurological infection in mice indicates that physiological disturbances in the absence of purely physical disruptions also could increase viral access to the brain.⁹⁹ The biological plausibility of a mechanism by which disruption of meningeal or blood-brain barrier integrity leads to an increased risk of neurological infection is supported by observations of repeated pneumococcal and other bacterial meningitis in persons with cochlear implants and congenital or acquired anomalies associated with CSF leaks and vaccine-associated poliomyelitis in children with CSF shunts.^{100–102} The lowered threshold for bacterial invasion and infection of the CNS in the presence of cochlear implants has led to recommendations to vaccinate all such recipients routinely with pneumococcal conjugate vaccine.

Pregnancy also confers an additional risk associated with JE. JE virus is well known to be a teratogen in pigs, causing neurological anomalies, miscarriage, and fetal death to an extent and frequency that pigs in most Asian countries are routinely vaccinated to prevent economic losses associated with abortions. In areas where the disease is endemic, most women of child-bearing age have ac-

quired immunity from repeated exposures to the virus and asymptomatic infections during childhood or vaccination, so, adverse consequences of infection during pregnancy have not been recognized. But when the virus was introduced to an immunologically naive Indian population, four of nine cases in pregnant women led to spontaneous abortions, and the virus isolated was from products of conception in three, indicating vertically transmitted infection.^{103,104} Vertical transmission of West Nile virus in humans, resulting in congenital infection, also has been reported in the United States, but the risk of this event after infection in pregnancy is uncertain.^{105–110} As several hundred instances of asymptomatic JE virus infection occur for each reported illness in a young adult, and scores of clinical cases have been reported in travelers, it is likely that tens of thousands of travelers to Asia have been infected without illness. Whether such asymptomatic JE infections during pregnancy poses a risk to the fetus is unknown.

Finally, for some time, host genetic factors have been suspected to underlie the low case-infection ratio associated with neurotropic flaviviruses. Recent investigations of West Nile viral infections in the United States disclosed that homozygosity for CCR5Delta32, a nonfunctional variant of chemokine receptor 5, increased the risk for symptomatic West Nile infection, with an odds ratio of 4.2 (95% confidence interval, 2.1–8.3), compared to asymptotically infected, seropositive individuals.^{111–113} Similarly, the allele appears to be significantly more common among patients developing tick-borne encephalitis (another flaviviral infection) than in comparison groups.¹¹⁴ A severe case of tick-borne encephalitis in a patient previously infected with West Nile virus also supports a role for a host, possible genetic, determinant in susceptibility to CNS infection by flaviviruses. Mechanisms underlying these associations have not been elucidated and whether antiretroviral therapy, statins, or other agents that also might modify CCR5 expression have an impact on risk of flaviviral encephalitis is unknown. Specific investigations among JE-infected persons have not been conducted; however, related or other polymorphisms increasing risk for JE neurological infection yet could be uncovered.¹¹⁵ Despite the lack of direct evidence for defined genetic markers increasing risk for JE, it seems prudent for persons who previously have been determined to carry this deletion or who were known to have had a previous West Nile viral infection to take special precautions against acquiring JE, including vaccination.

In addition to assessing medical conditions that place individuals at increased risk for acquiring JE or for developing serious outcomes after infection or illness, travel counselors also should contemplate the difference between fear and risk and acknowledge that individuals differ in their fears and in their perceptions of risks. Personal views differ in the willingness to take on or to ensure against rare but dreadful or disastrous events. Past experiences or other emotions or convictions can override external assessments. For example, the same danger affecting a child can evoke more concern than the same risk in an

adult. And persons with a family member or acquaintance who experienced a similar grave event or whose personal circumstances would lead to particularly severe consequences in the event of a further catastrophe may have a lower threshold for choosing an intervention than others.

A Sounding Board opinion on meningococcal vaccination was highly instructive in pointing out that public health-based recommendations may be inappropriate and, more to the point, may do individuals a disservice, when they focus on population-based risk assessments.¹¹⁶ Humans play no role in the JE virus transmission cycle and preventing cases in individual travelers has no public health dimension, unlike communicable diseases such as polio. In the context of travel vaccines that are self-paid and not reimbursed by public or insurance funds, the decision to take a vaccine is a decision to make a discretionary purchase and should be a matter of individual choice and not one based on societal considerations. Accordingly, counselors should provide information and support to allow the traveler to make an informed choice.

Japanese Encephalitis Vaccines in Non-Asian Countries

JE-VAX, a mouse brain-derived, inactivated vaccine produced in Japan, has been the principal JE vaccine available to travelers from Europe and the Western hemisphere. The vaccine was registered in the United States in 1992 by a US-based distributor that licensed the vaccine from a Japanese manufacturer.¹ In Europe, JE-VAX and a similar mouse brain-derived vaccine produced in Korea have been available only on a named patient basis. Coincident with the licensure of JE-VAX in the United States, reports of potentially life-threatening facial and upper airway angioedema and related hypersensitivity reactions emerged, occurring at an estimated rate of between 1 and 17 per 10,000 vaccinees.^{1,117–120} The pathogenesis of the adverse events was suspected to be related to gelatin used as a stabilizer in the vaccine; however, the etiology was never confirmed and similar hypersensitivity reactions continue to be reported.^{121–124} Additionally, severe and sometimes fatal acute disseminated encephalomyelitis (ADEM) cases, temporally associated with the administration of the mouse brain-derived vaccine, later were reported, both among travelers and among Asian children receiving the vaccine.^{28,125–127} In response to these cases, JE vaccine was removed from the routine schedule of pediatric vaccination in Japan in 2005.⁹ The manufacturer of JE-VAX discontinued production of the vaccine in 2004 and consequently, the vaccine will no longer be available in the United States, although stockpiles are not expected to be depleted until 2009.¹²⁸

Current Recommendations and Practice

In 1993, the ACIP of the US Centers for Disease Control and Prevention estimated that the risk of JE among all travelers to Asia was <1 in a million annually, but for

travelers to rural areas, the risk could be in the range of 1 per 5,000 per month during the transmission season. The perceived rarity of JE in travelers and the negative adverse event profile associated with the mouse brain-derived vaccine led the ACIP to develop cautious recommendations for vaccination against JE in travelers. Pointedly, the committee underscored that the vaccine should not be regarded as a routine vaccination for all travelers to Asia but was recommended only for those with an increased risk for acquiring infection. Specifically, the committee recommended vaccination for expatriates and travelers visiting endemic areas for 1 month or longer during the transmission season and for short-term visitors to rural areas who had increased risks for exposure. Moreover, because the reported hypersensitivity events often had a delayed onset of up to a week after immunization, the committee advised that travelers should delay their departures until 1 week after receiving a dose. In focusing recommendations so narrowly on a small group of travelers, the committee was being attentive to averting potentially life-threatening and poorly understood vaccine-associated events among a largely healthy traveling population who overall had a low risk for acquiring the disease. In the years that followed the vaccine's licensure and use under this guidance, fewer JE cases in US travelers were recognized than in a similar interval prior to the vaccine's licensure, suggesting that the recommendations, although narrowly prescriptive, were effective.¹²⁹ Similar recommendations currently are in place in many European countries.^{130–132} In practice, the great majority of all doses distributed in the United States is consumed by the military (given principally to personnel stationed on Okinawa) and very little JE vaccine (<10,000 doses per year) is used in travel clinics.

However, in recent years, numerous anecdotal cases have been reported in travelers whose exposures in the endemic region (estimated from their incubation periods) occurred within days of arrival and who did not engage in other activities that are presumed to increase risk.² These travelers would not have been recommended for the vaccine under current recommendations, leading to objections to their narrow scope.

IXIARO (Icks-e-Ə-row), a New Vaccine Against Japanese Encephalitis

A new JE vaccine was approved in the United States in January 2009 and is awaiting a regulatory decision in the EU. IXIARO is a Vero cell-derived, inactivated, alum adjuvanted vaccine based on the attenuated SA14-14-2 attenuated JE viral strain that itself has been used in highly effective vaccination programs in China and South Asia. The parent SA-14 virus was isolated from a *Culex pipiens* mosquito in China. Because JE virus exists as a single serotype, the circulation of different viral genotypes in various geographic regions has not been relevant to the effectiveness of SA14-14-2, Nakayama, or Beijing-based (genotype 3 strain) vaccines when used in regions where other genotypes predominate.

IXIARO is formulated without thimerosal, gelatin, or other stabilizers. In clinical trials, the proportion and severity of adverse reactions among ~4,000 vaccine recipients were similar to those in placebo recipients (given vaccine excipients only) and compared to recipients of the licensed mouse brain–derived vaccine, IXIARO recipients had significantly fewer local reactions.^{10–12} While potentially life-threatening facial angioedema was the hallmark of hypersensitivity reactions to the mouse brain–derived vaccine, occurring at rates as high as 17/10,000 recipients, no hypersensitivity reactions featuring angioedema have been reported among recipients of the cell culture–derived vaccine. Perhaps the best characterized study of angioedema risk among recipients of the mouse brain–derived vaccine, from a prospective study of US Marines on Okinawa, disclosed an incidence of 13/14,249 (9.12/10,000).³⁷ The incidence of angioedema among clinical trial subjects receiving IXIARO database was significantly lower, 0/4210, $p=0.049$, FET, 2-sided. The new, inactivated vaccine was as immunogenic (non-inferior with respect to proportion achieving a protective level of neutralizing antibody) after two doses given 4 weeks apart compared with responses to three doses of the mouse brain–derived vaccine.¹¹ However, postvaccination geometric mean titers in IXIARO recipients were significantly higher. Clinical and animal studies have provided evidence in support of an immunological correlate of immunity, and the new, inactivated vaccine was licensed on the basis of this serological correlate (established by the World Health Organization as a neutralizing antibody titer of $\geq 1:10$) in lieu of a field efficacy trial. Neutralizing antibodies at this protective level have persisted as long as 24 months in 83% of IXIARO–vaccinated subjects; however, the durability of protective immunity and when booster vaccination is needed are still under investigation. IXIARO has been given concomitantly with hepatitis A vaccine without significant interference on the immune response to either vaccine or an impact on the frequency of adverse events.¹³³ Data on concomitant administration with other vaccines frequently used in travelers currently are unavailable. Unlike the currently available mouse brain–derived vaccine that requires three 1.0-mL subcutaneous doses, the new, inactivated vaccine is administered as two 0.5-mL intramuscular doses. The new, inactivated vaccine initially will be licensed in the United States for use in persons 17 years of age and older and in Europe, for adults ≥ 18 years old. Dose finding studies in children disclosed that a 0.25 mL dose is sufficiently immunogenic in children, and Phase III studies in children, including concomitant use with routine pediatric vaccines, are ongoing. Postmarketing safety studies in 20,000 young adults and additional elderly subjects also are underway.

Rationale for Revision of Japanese Encephalitis Vaccine Recommendations

Current recommendations for JE vaccination of travelers were predicated on minimizing exposure to a mouse brain–derived vaccine with a poorly understood

but worrisome safety profile, while the risk of acquiring JE itself during travel was assessed to be relatively low. However, with the discontinuation of this vaccine, and the availability of a new cell culture–derived vaccine with an apparently better safety profile, it is appropriate to reconsider benefit–risk considerations for the vaccination of travelers. The series of cases reported in travelers with brief itineraries that did not include prolonged visits to rural areas, underscores the difficulty of providing prescriptive guidance against a disease that occurs infrequently but, that if acquired, is clinically devastating.² With the availability of a vaccine that, thus far, appears to have no remarkable safety concerns, the focus of travel counseling on JE risks and prevention can now be directed at the risks of acquiring the disease and its consequences, instead of the risks of vaccination.

Recommendations

Advise

Advise all travelers to areas of Asia where JE virus is transmitted in an enzootic cycle (including Japan) about the risks and consequences of JE and characteristics of available vaccines.

Recommend JE vaccination before departure, to ensure an adequate level of protection, to avoid potential delays in arranging immunizations on arrival, and to ensure vaccination with a well-characterized vaccine to:

- All expatriates.
- Repeat travelers (eg, property owners, seasonal workers, visitors of friends and relatives) who return frequently to the region or who, cumulatively, have a prolonged duration of exposure.
- Any individual with a prolonged duration of stay, independent of itinerary.
- Any individual with a travel itinerary including rural areas.
- Travelers wishing maximum protection.

Consider Vaccination

- All other travelers visiting regions with enzootic transmission during a transmission period, particularly
 - Those with greater outdoor exposure.
 - Individuals 50 years of age or older.
 - Children under 10 years of age.
 - Individuals with chronic conditions, such as
 - History of solid organ transplant.
 - History of cochlear implants, ventriculoperitoneal shunts, and other devices impinging the CNS or history of or medical conditions associated with CSF leakage.
 - Hypertension
 - Diabetes mellitus
 - Chronic renal disease
 - Anti-TNF therapy

- Individuals known from previous history to be homozygous for CCR5Delta32.
- Pregnant women (balancing unknown risks associated with vaccination).

Conclusions

In conclusion, vaccination against JE should be recommended to all long-term and repeat travelers and expatriates going to areas of Asia where the disease is recognized or suspected to be endemic. All travelers to such regions should be informed about risk factors for acquiring JE and consequences of the illness and should be advised of the availability of a vaccine for their consideration. Persons with certain risk factors, including persons older than 50 years of age, are recommended for vaccination, depending on the traveler's itinerary.

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Declaration of Interests

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E.C.J. has accepted fees for speaking from Sanofi Pasteur, GlaxoSmithKline, and Novartis and has served on Advisory Boards for GlaxoSmithKline and Novartis.

T.F.T. is a full-time employee of Novartis Vaccines.

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