Japanese Encephalitis Vaccine for Travelers: Exploring the Limits of Risk

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The prevention of Japanese encephalitis in travelers presents the juxtaposition of 4 factors: a disease that is widespread throughout Asia, a disease with a low incidence in travelers, a vaccine about which there are safety concerns, and a clinical course that can result in death or permanent disability in two-thirds of symptomatic cases. Travel medicine practitioners often seem to be polarized into 2 groups: a group that gives more weight to the severity of the disease (and therefore often recommend vaccination) and another group that is more persuaded by the low occurrence of cases in travelers (and therefore rarely recommend vaccination). This review assesses the known risks of contracting Japanese encephalitis and the risks associated with the vaccine and tries to develop an appropriate way to recommend this vaccine to travelers who may be at significant risk.

The popular movie “Chicken Run” is about chickens trying to escape from a prisoner-of-war camp–like enclosure to avoid being turned into chicken pot pies. After a series of unsuccessful escape attempts, one of the fearful chickens says to the heroine, Ginger, “The chances of us getting out of here are a million to one.” To which Ginger replies, “Then there’s still a chance.”

The chance of a traveler contracting symptomatic Japanese encephalitis (JE), a viral disease carried by mosquitoes exclusively in Asia, is also ~1,000,000 to 1 [1]. Although many travel medicine practitioners may be reassured by this figure that the risk of JE to travelers is minimal, others may believe, as Ginger did, that there is still a chance that a traveler will contract the disease. JE is a disease that pushes the limits of understanding risk and risk avoidance among travelers. The risk of falling ill with JE while traveling in Asia is 10 times less than the risk of contracting meningococcal meningitis in the general population of Americans, who do not opt for immunization to prevent that disease [2].

However, many medical practitioners correctly point out that JE is a potentially severe disease for which there is no available treatment. The associated mortality rate is 30%–40%, and 50% of those who survive have permanent neuropsychiatric problems [3]. Thus, the prevention of JE presents a dichotomy: an extremely low risk of contracting disease versus a very serious and untreatable illness.

JE is endemic throughout Asia. Yet despite this widespread potential risk, the actual risk to most travelers remains low. Although the disease is preventable by a vaccine that has been available for >50 years, the vaccine has been associated with rare adverse effects that have made some travel medicine practitioners cautious about when to recommend its use. In 1993, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) published recommendations regarding vaccination against JE, which were widely circulated. However their implementation has been controversial; some practitioners believe that the vaccine is being overused, and others believe that it should be used more widely [4]. The purpose of this review is to assess the known risks to a traveler or expatriate of contracting JE, along with the risks that have been associated with the vaccine, and to try to develop an appropriate way to recommend this vaccine to travelers who may be at significant risk.
CLINICAL FEATURES OF JE

Those who have actually seen and treated JE are much more inclined to recommend immunization than are those for whom it remains only a theoretical risk for their traveling patients. After 5–15 days of incubation and a few days of a seemingly innocuous febrile illness, which may include symptoms of headache, coryza, cough, vomiting, and diarrhea, patients develop features of neurological disease. These may include meningoencephalitis, confusion, paralysis, parkinsonian movement disorders, abnormal posturing, convulsions, and coma [5]. A proportion of patients with JE have an acute flaccid paralysis that is easily mistaken for poliomyelitis [6], but the majority present with a reduced level of consciousness, often heralded by generalized convulsions. If not controlled, these convulsions rapidly lead to status epilepticus. Signs of brain stem damage caused either directly by viral invasion or indirectly by increased intracranial pressure and brain stem herniation are also common. Approximately one-third of patients with JE die, and approximately half of the survivors have severe neurological sequelae.

Epidemiology

JE virus is a flavivirus antigenically related to West Nile virus, St. Louis encephalitis virus, and Murray Valley encephalitis virus. Dengue and yellow fever are also caused by flaviviruses [7]. JE virus is spread mainly by Culex mosquitoes, of which Culex tritaeniorhyncus is the principal vector in most of Asia. This is an ornithophilic (bird-biting) mosquito that also feeds on other animals and humans. It feeds at night, seeks blood meals mainly outdoors, feeds repeatedly during a brief life span, and disperses widely after a blood meal [8]. It breeds in rural areas (e.g., rice paddies and ditches) where birds are found but is also found on the edges of cities.

Epidemics of JE were described in Japan in the 1870s, and the virus was first isolated in 1935. In the first half of the 20th century, the disease was noted to occur mainly in mainland China, Korea, Taiwan, eastern Russia, and Japan. In the second half of the century, the disease was recognized in an expanding pattern throughout all of Asia and as far south as the northern tip of Australia [9].

Broadly speaking, 2 epidemiological patterns of JE are recognized. In northern temperate areas (Japan, Taiwan, China, Korea, northern Vietnam, northern Thailand, Nepal, and northern India), large epidemics occur during the summer months (roughly, May to October). Tables showing more specific data on risk by month for each country are available from several sources [1, 10, 11]. In southern tropical areas (southern Vietnam, southern Thailand, Indonesia, Malaysia, Philippines, Sri Lanka, and southern India), JE tends to be endemic; here, cases occur sporadically throughout the year, with a peak after the start of the rainy season [12].

Serological studies have shown that in parts of rural Asia where JE is endemic, almost all of the human population has been infected with JE virus by early adulthood [13]. Only a small proportion (estimated at between 1 per 250 and 1 per 1000 infected persons) develop symptomatic disease. In areas of endemcity, one-half of all cases occur in children <4 years old, and nearly all cases occur in children <10 years old. When immunologically naive adults are exposed to JE virus, they are as susceptible as children are. Thus, when JE virus caused new epidemics in parts of Sri Lanka, India, and Nepal, adults developed the disease [13]. The susceptibility of immunologically naive adults was also demonstrated by the incidence of JE among American troops during conflicts in Japan, Korea, and Vietnam [14-18]. Among American service personnel in Korea, 1 in 25 infections caused symptoms [19].

The death rate among children in countries in which JE is endemic is high enough to warrant programs of mass immunization in the countries that can afford it. However, because animals, rather than humans, are the natural hosts, mass immunization cannot cut the risk of disease to those who are not immunized. Thus, the risk to tourists is no different in countries with routine JE immunization for children.

Epidemiology Among Travelers

The CDC reviewed cases of JE among expatriates and travelers that occurred during 1978–1992 [1]. They described 24 cases: outcome information was available for 15 patients, of whom 6 died, 5 were listed as disabled, and 4 recovered. Only 1 or 2 of these 24 patients were tourists; the other patients were doing research or medical relief work or were soldiers on maneuvers. Comparisons of disease risk among travelers is hampered because rates of immunization are unknown. However, only 8 cases of yellow fever were reported in travelers between 1979 and 1996, of which 5 were fatal [20].

The CDC concluded that the overall risk of JE for travelers to areas where JE is endemic was <1 case per 1,000,000 travelers. However, they noted that “short-term travelers to developed and urban areas” may have accounted for most of the denominator. When they tried to estimate the risk of JE for travelers actually spending time in rural destinations during the season of risk, they came up with a very rough range of 1 case per 5000 to 1 case per 20,000 travelers per week [1].

Studies have helped to define why the risk is low for short-term travelers to areas of endemicity. JE is transmitted only by specific vector mosquitoes. Even where the disease is hyperendemic, the infection rate among mosquitoes does not exceed 3%. Even when a bite by an infected mosquito results in human infection, symptomatic neuroinvasive illness occurs in <1/250 cases of infection, although its frequency may be higher among foreigners than among local people [21]. If Culex mosquitoes
accounted for 10% of mosquitoes in a given area of hyperendemicity, the chance that a single mosquito bite would transmit the virus and result in symptomatic JE would be \( \sim 1 \) in 10,000. These factors may help account for the apparent low risk for short-term tourists.

However, the rare cases of JE that have occurred in tourists have shown the limitations in our understanding of the risk factors. Two foreigners staying in hotels in Bali, Indonesia, developed JE in 1994–1995: a nonfatal case occurred in March 1994 in a Swedish woman [22], and a fatal case occurred in January 1995 in a Danish man [23]. The annual number of non-Asian tourists visiting Bali during this time was \( \sim 450,000 \) [24]. The only other reported case from Bali occurred in an Australian tourist in 1989 [25]. There have been no reported cases among tourists in Bali since 1995.

The epidemiology of JE in Nepal highlights some of the difficulties in making sound recommendations to travelers. The disease was first recognized in Nepal in 1978 [26]. Since then, it has been shown to be hyperendemic in the Terai region, with seasonal outbreaks annually affecting thousands of people. Foreign expatriates who reside in the Terai, mainly to do aid work or research, have been immunized against JE since the early 1980s. Tourists to Nepal who visit Kathmandu and go trekking were not thought to be at risk, nor were short-term visitors to the Terai. However, in 1995, 2 cases of indigenous JE among Nepalese in the Kathmandu Valley were documented at 1 hospital [27], and in 1996–1998, 12 more cases were confirmed [28]. In addition, a serosurvey of pigs in the Kathmandu Valley showed that 23 of 44 pigs were positive for antibodies to JE virus [27]. Amid all of this JE activity, not a single foreigner in Nepal has had the disease diagnosed. Because of the recently documented risk of JE in Kathmandu Valley, long-term expatriates are now opting for JE immunization, but no national public health body has yet recommended immunization for tourists visiting Kathmandu.

The difference between 0 and 1 as the numerator of risk is highlighted by the case of an Israeli traveler who developed JE while traveling in Thailand in 1989. She survived a stormy clinical course, but her single case led the Israeli public health authorities to recommend JE vaccine for all Israeli travelers to Thailand.

**JE VACCINES**

Three JE vaccines are currently available worldwide, of which only the inactivated mouse brain–derived vaccine (manufactured by Biken) is in use commercially for travelers. The inactivated mouse brain–derived vaccine was developed in Russia and Japan in the 1930s but became a priority for the US military during World War II. After the war, further vaccine development took place in Japan. The People’s Republic of China uses an inactivated hamster kidney cell–derived vaccine as its main vaccine against JE for children, and >70 million doses are distributed annually. China also has developed a live attenuated JE vaccine, which is safe and effective and has been widely used [24, 29].

Only 1 case-control study has measured the efficacy of the Biken vaccine. Hoke et al. [30] immunized 43,708 Thai children with JE vaccine and administered tetanus toxoid vaccine to another 21,516 children, who served as a control group. Protective efficacy in the JE vaccine group was 91%, and the group receiving JE vaccine also showed a trend toward fewer and less severe cases of dengue fever [30].

**DOSAGE AND ADMINISTRATION OF JE VACCINE**

The recommended schedule for administration of the Biken JE vaccine is 1 dose on each of days 0, 7, and 30 [1]. This schedule achieves a seroconversion rate of virtually 100%. An accelerated schedule, given on days 0, 7, and 14, can be used when time is short. The accelerated schedule achieves seroconversion rates of nearly 100%, but the overall titer of antibody that is reached is lower. Two doses of JE vaccine produce only an 80% chance of seroconversion [31–33].

The question of when to administer a booster vaccination after the initial series has not been satisfactorily resolved. A study of US Army soldiers found that antibody titers at 12 months after vaccination did not differ from those determined at 3 months. Three years after the primary series, 16 (94%) of 17 soldiers retained an adequate neutralizing antibody titer. It is commonly recommended that a booster be administered 2 or 3 years after the initial immunization for persons who remain at risk for JE virus infection. Beyond the first booster vaccination, no studies are available to guide recommendations. At that point, the travel medicine practitioner has the choice of recommending another booster after 3 years or measuring serum antibodies to guide further decisions about when to administer a booster. A neutralizing antibody titer of \( >1:10 \) is generally accepted as evidence of protection [21].

Because of the possibility of delayed, but potentially serious, hypersensitivity reactions to JE vaccine (discussed in the next section), recipients of JE vaccine should remain where adequate medical care is available for up to 10 days after they receive the last dose [1]. However, given that there have been no fatal anaphylactic reactions to JE vaccine, the risk of JE might lead to a decision to immunize travelers even if they must depart <10 days after they receive the last dose.

**ADVERSE REACTIONS TO JE VACCINE**

The Biken JE vaccine had been used for years, and millions of doses had been administered to Asian populations, before it...
began to be given to travelers to and expatriates in Asia. Severe adverse events were extremely rare; surveillance of JE vaccine recipients over an 8-year period in Japan (1965–1973) detected severe neurological reactions at a rate of 1–2.3 cases per 1,000,000 vaccine recipients. With more widespread use in travelers, however, an apparently new pattern of adverse reactions began to be reported.

The first set of adverse reaction reports were reported from Denmark, Australia, and Canada [34–36]. These reports described urticaria and angioedema that occasionally involved the face and lips. Respiratory distress was reported in 3 vaccine recipients. Of concern to travel medicine practitioners was the observation that the reactions were often delayed by several days to, possibly, 2 weeks, which meant that some reactions could occur in recipients of the vaccine who had already begun their travels. However, it should be noted that anaphylaxis—and the consequent risk of sudden death—has never been reported in relation to the administration of Biken JE vaccine.

Surveillance of JE vaccine reactions in Denmark showed that mucocutaneous reactions occurred in 73 recipients between 1983 and 1995, corresponding to a rate of 1–17 cases per 10,000 vaccine recipients [37]. The investigators noted, however, that the majority of—but not all—cases were clustered in the period 1989–1992, around the time that the first similar reactions were reported in other centers. Three batches of vaccine were implicated as having caused the highest number of reactions, but reactions have not been limited to persons who received vaccine from these batches. Investigation of the batches found no obvious clue as to why they may have been more reactogenic.

The same investigators in Denmark have also produced a report detailing possible severe neurological reactions to JE vaccine [38]. Between 1983 and 1995 in Denmark, 10 persons who were vaccinated with JE vaccine were followed up because they had various neurological syndromes that were temporally related to vaccination (i.e., 0.1–2.3/10,000 vaccine recipients). These reactions included encephalopathy, paresthesias, leg weakness, headache, and ataxia. The wide variety of reactions, the lack of a control group, and the fact that the onset of symptoms occurred 1–27 days after vaccination make it difficult to know whether some of these observations were coincidental. No further cases of severe neurological reaction have been reported from Denmark since the 1995 case, despite continued surveillance.

Among the mucocutaneous reactions, 2 different syndromes were noted in a study from Japan: a syndrome involving urticaria and wheezing, which was associated with measurable IgE antibodies to gelatin in serum samples, and a syndrome consisting of hypotension and cyanosis, which was not associated with antigelatin antibodies [39]. Small amounts of gelatin are used as a stabilizer in the Biken vaccine. Other studies have found that prior history of urticaria or allergy to bee venom were separate risk factors for an increased chance of allergic reaction to JE vaccine [1, 40]. An Australian study noted that excessive alcohol intake after JE immunization was statistically associated with an increased chance of allergic reaction [41].

Only 1 fatality was noted during surveillance of >10,000,000 doses of JE vaccine administered in Japan and the United States. A 3-year-old boy developed fever, cerebral edema, and coma 2 days after JE vaccination and died within 4 days of vaccination [42]. Surveillance of 813,000 doses distributed in the United States between 1993 and 1998 found that the rate of all adverse events was 15 events per 100,000 doses, and the rate of urticaria or angioedema was 6.3 cases per 100,000 doses. No adverse neurological events were noted by use of passive surveillance. Of note is the unexplained observation that the rates of adverse events were 3 times higher in the first year of the study in 1993.

In summary, detailed studies in America, Japan, and Europe have shown that severe adverse events following JE vaccination are extremely rare and that milder events are more common, but both occur at rates considered acceptable for many other vaccines. The persistent impression that JE vaccine is associated with a higher rate of adverse reactions probably stems from the first years of its introduction into travel clinics, when the rate of adverse reactions actually was higher than it is at present.

**JE VACCINATION RECOMMENDATIONS**

The conventional advice on recommending JE immunization for travelers is to focus on those travelers who will spend ≥50 days in an environment in which JE is endemic, or less time if they are visiting areas experiencing epidemic transmission [1]. This duration of travel in a single area also selects for those travelers who will likely venture away from the usual tourist paths.

However, use of an arbitrary duration-of-travel cutoff cannot protect all travelers who will be at risk. Knowledge of the purpose of the trip and the risk for a given area could result in a desire to immunize someone who will be in a village for only a few days. The risk of JE has clearly been associated with nighttime visits to rice-growing areas. Travelers for whom JE immunization should be considered include the following: persons who will be spending time living in a village setting near rice paddies and farm animals during a season of transmission; soldiers who will be on maneuvers in an area of endemicity during the season of risk, which can be year-round in the tropics; aid workers, missionaries, students, and researchers whose work will involve spending time in an area of endemicity during the season of risk; bicyclists, backpackers, and other adventure travelers whose itinerary is uncertain but may include significant time in areas of endemicity; expatriates taking up residence in a country in which JE is endemic, even if they...
will not reside in a high-risk area (frequent travel to rural areas may result in cumulative exposure over time); and travelers who request the vaccine after the risk of JE has been discussed, even if the travel medicine practitioner feels the risk is low. Because a theoretical—and occasionally unpredictable—risk exists in all Asian countries, the travel medicine practitioner should not be dogmatic in refusing to give JE vaccine when it is requested.

Given the low risk of transmission from a single mosquito bite, the use of appropriate clothing, insecticides, bed netting, and insect repellent containing diethyltoluamide (DEET) can dramatically lower the chances of falling ill with JE. Because the vaccine is not 100% protective, travelers to areas of high endemicity will also want to practice these preventive measures, which will decrease the chances of acquiring malaria and dengue fever as well.

CONCLUSIONS

The difficulties in knowing when to recommend JE vaccine will persist. The very low statistical risk suggests that most travelers are not at risk on typical tourist or business itineraries to Asia. A blanket recommendation that all travelers to Asia be immunized against JE would vastly overprotect those who will not truly be at risk and will increase the number of rare adverse reactions to the vaccine.

The unsettling concern is what to do about visitors to areas where a risk to foreigners has very rarely occurred or theoretically could exist. An example of the former includes the island of Bali, where 3 cases of JE in travelers have been documented during a 13-year period, and where the risk of JE may have been underestimated. An example of the latter is the Kathmandu Valley, where indigenous transmission has recently been documented among Nepalese farmers just outside the metropolitan area of Kathmandu.

Because the incidence of JE is on the rise throughout Asia, because epidemics are usually detected only after they have occurred, and because there are regions where endemic disease may go largely unnoticed, travelers may rarely find themselves exposed in an area that is currently thought to carry minimal risk. By fine-tuning travel advice to select the subgroup of travelers at greatest risk, travel medicine practitioners can probably fulfill their goal of protecting travelers from a severe, untreatable disease. Safer vaccines, if they reach market, may further lower the threshold for recommendation of the vaccine more widely [43].

No matter how carefully we evaluate each traveler’s itinerary, the fact remains that a risk of 1,000,000 to 1 means that there is still a chance of getting the disease. When a case of JE does occur, it is likely to seem unexpected and tragic, but lawyers may argue that it was predictable and preventable. Travel medicine has not been successful in finding a common interpretation of acceptable risk. A study determined that the risk of dying while trekking in Nepal was 15 deaths per 100,000 trekkers [44]; one reviewer insisted that the authors of that report must conclude from these numbers that trekking is a high-risk activity, whereas another reviewer insisted that the author must conclude—from the same data—that trekking is relatively safe.

References


