

# Japanese Encephalitis Vaccine

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## ABSTRACT

Travelers to 24 endemic countries in Asia may be at risk for Japanese encephalitis. The ACIP has recently expanded guidelines on the use of Ixiaro, the inactivated Japanese encephalitis vaccine. This article reviews the disease burden of Japanese encephalitis and the role of a travel clinic in guiding travelers to Asia regarding decision-making about the use of this highly protective vaccine.

**KEYWORDS:** Japanese encephalitis, Asia travel, Japanese encephalitis vaccine, flavivirus, pig farming

## INTRODUCTION

Travelers may be at risk for Japanese encephalitis (JE) in 24 endemic countries in Asia. Japanese encephalitis is caused by a Flavivirus closely related to West Nile virus and is transmitted predominantly by *Culex* mosquitoes that feed from dusk to dawn.<sup>1</sup> The JE virus is maintained in nature by mosquitoes and animal hosts, mainly pigs and water birds. Infection risk is therefore highest in rural farming areas but is also present in urban and periurban areas in Asia.

JE is endemic in most of Asia and parts of the western Pacific region and is one of the most common causes of encephalitis in Asia. Transmission is seasonal in some areas – May to September in northern Asia and monsoon season-related in India and Southeast Asia – but can occur year-round in other geographic regions such as in Bali, where rice paddies, pig farms, birds and *Culex* mosquitoes are abundant.<sup>1</sup> JE has also been reported in the Torres Strait Islands in northern Queensland, Australia. Interestingly, the great demand for pork in Asia has led to relocation and establishment of pig farms closer to urban centers for ease of distribution.<sup>2</sup> This may allow for increasing evolution of movement of risk for JE virus. Travel clinic consultation can help individuals navigate the country-specific information taking into account transmission months that can be found in the CDC Yellow Book.<sup>1</sup> JE infection is uncommon in tourists, with an estimated risk of one in 200,000 per week of exposure, and <1% of infections result in symptomatic illness. However, symptomatic cases are associated with significant morbidity related to acute encephalitis and present with a wide range

of neurological symptoms. Case fatality rate of symptomatic cases is up to 30%. Of those who survive, 30% to 50% report long-term neurological, psychological, and cognitive impairment including polio-like weakness and life-long seizure disorders.<sup>1,2</sup> severe cases are very severe. Travelers to JE-endemic areas should be advised to take precautions against mosquito bites, particularly from dusk to dawn. Vaccination should also be considered, and recommendations must take into account the risk of infection (country, urban vs. rural, farming areas, seasons, outdoor activities, trip duration, and repeated travel). The high risk of death and serious long-term sequelae from symptomatic infections and the cost of vaccines are other important considerations.

The Advisory Committee on Immunization Practices (ACIP) has modified their guidelines.<sup>3</sup> As a general rule, it recommends vaccination for travelers who plan to spend a total of one month in endemic areas during the transmission season. Given that some US cases occurred in short-term travelers – some with less than one week of unexpected exposure – duration may not be the best factor in decision-making about vaccination against JE for an individual traveler to Asia. This disease is rare but has significant consequences. We offer JE vaccine for persons traveling outside of major urban areas. Those who plan to return to Asia will benefit from vaccination against the cumulative risk. Those traveling for <1 month should consider choosing vaccination if spending time in rural areas; taking part in high-risk activities (e.g., farming, outdoor sporting activities); staying in accommodations without screens, bed nets, or air conditioning; or traveling to outbreak areas.<sup>1</sup> Vaccination is strongly recommended for expatriates planning to live in Asia for more than 6–12 months, even in urban areas, because they often travel extensively throughout the region for work and vacations.<sup>3</sup> The only JE vaccine available in the USA is an inactivated Vero cell culture vaccine, Ixiaro (Valneva). In 2009 it was licensed for use in those aged 17 years, and in May 2013 the license was extended to children aged 2 months. Primary immunization consists of two IM doses given on days 0 and 28, completed at least a week before departure. Each dose is 0.25 mL for children aged <3 years and 0.5 mL for those aged 3 years. For adults with ongoing exposure to JE a booster dose is recommended 1–2 years after the primary course. There is currently limited evidence about the need for boosters for those aged <18 years.

An accelerated schedule on day 0 and day 7 with a booster in 1 year has been shown to provide excellent protection and is approved for last minute travelers to risk regions who are ages 18 to 65, weighing seasonal risk and planned outdoor activity.<sup>4</sup>

### Adverse reactions

Local reactions such as pain and swelling are reported in 1% of vaccine recipients. Systemic reactions include headache, myalgia, fatigue, and fever.

### Contraindications

Ixiaro is contraindicated in persons who have had serious adverse reactions from any JE vaccines or any of the vaccine components (including protamine sulfate or formaldehyde). No preservatives, stabilizers, or antibiotics are added to the formulation. For the manufacturing process Ixiaro also contains bovine serum albumin (not more than 100 ng/mL), Vero host cell DNA (not more than 200 pg/mL), sodium metabisulfite (not more than 200 ppm), and host cell protein (not more than 100 ng/mL). Safety data in pregnant women are currently lacking. The risk of vaccination to mother and fetus really cannot be defined, so this is an undefined situation in terms of making a decision based on risk. Ixiaro use should generally be avoided during pregnancy or breastfeeding unless the high-risk travel cannot be avoided. Some pregnant women opt to have the vaccine after consideration of their travel needs and discussion of disease risk.

### OTHER CONSIDERATIONS

- For travelers who have been vaccinated with the previously available mouse brain-derived JE vaccine (JE-Vax, Biken), there is currently insufficient evidence regarding the effectiveness and duration of protection from a single booster dose of Ixiaro. Until further data are available, these travelers should be given a primary two-dose course of Ixiaro.
- For adult travelers who do not have time to complete the two-dose primary course before departure, an accelerated course of two doses on days 0 and 7 may be considered.<sup>4</sup>
- In immunocompromised hosts the immune response to Ixiaro is not well documented.
- Vaccination is recommended for residents of the Torres Strait Islands in Australia, as well as those traveling to the area for a cumulative total of 30 days during the wet season (December to May). Very few international tourists travel to the Torres Strait Islands, which are situated between the northern tip of Queensland and Papua New Guinea.

There are some JE vaccines available outside the USA in case travelers find themselves with last-minute plans while abroad, although use is generally discouraged without consultation. A live attenuated recombinant Vero cell vaccine (Imojev, Sanofi Aventis) is available in Australia and some

countries in Asia, including Thailand, Malaysia, Hong Kong, Singapore, and the Philippines.<sup>5</sup> The vaccine is licensed for use in those aged 9 months. A single dose of 0.5 mL subcutaneously provides long-term protection in adults, but a booster is recommended for those aged 9 months to 18 years. Imojev is a live attenuated vaccine and therefore contraindicated in pregnant women, breast-feeding mothers, and immunosuppressed hosts. In Australia and New Zealand, Ixiaro is marketed as JEspect. In some countries a mouse brain-derived vaccine, with a poorly understood and worrisome safety profile, and other live attenuated vaccines, are also in use.<sup>5</sup> Given high risk of allergic responses with this product – including late onset of anaphylaxis – travelers are urged to seek travel advice in the US a few months prior to embarking on a trip to Asia to consider the safe and effective Ixiaro product. Hopefully, a coronavirus vaccine will also soon be available to facilitate all world travel once again!

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