Japanese Encephalitis

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Medical Summary

What's New

The Ixiaro (Japanese encephalitis vaccine; Valneva) primary dosing schedule has been revised by ACIP; Shoreland now recommends 2 doses, 1 each on 0 and 7-28 days (previously 0 and 28 days) in adults aged 18-65 years. A booster dose (third dose) should be given ≥ 1 year after completion of the primary series only if ongoing exposure or re-exposure to Japanese encephalitis virus is expected. Pediatric dosing remains unchanged.

Introduction

Japanese encephalitis (JE), caused by a flavivirus, is a potentially severe arboviral disease occurring throughout south-central, southeastern, and eastern Asia and parts of the Western Pacific and is transmitted via the bite of infected mosquitoes (primarily *Culex* species). JE is the leading cause of mosquito-borne encephalitis in these areas.

Epidemiology

JE virus (JEV) is the most common vaccine-preventable cause of encephalitis in Asia, extending in a wide belt from Japan and northern coastal China throughout southeastern Asia and across India to Pakistan and is present through the Western Pacific islands from Indonesia to Papua New Guinea and as far north as the Philippines. Cases occur primarily in rural agricultural areas, often associated with rice cultivation and flood irrigation. However, in some areas, these ecological conditions may occur near (or occasionally within) urban centers. Among local populations, the incidence of JE is 5 to 50/100,000 per year, mostly in children aged < 15 years (most adults have acquired natural immunity after childhood infection).

In temperate areas of Asia, transmission is seasonal (occurring toward the end of the summer rains) and peaks in the summer and fall. In the subtropics and tropics (including Indonesia, the Philippines, southern Thailand, and southern Vietnam), transmission varies seasonally with monsoon rains and irrigation practices, but it may be prolonged or even occur throughout the year. However, altitude and local variations in rainfall and temperature affect mosquito breeding and seasonality of transmission.

Fewer than 100 cases of JE have been reported in travelers going to endemic areas of Asia since the 1970s; most cases were acquired in Thailand and Bali, Indonesia (followed by China and the Philippines). The overall incidence of JE among travelers going to Asia is estimated to be less than 1 case per 1 million travelers. Among travelers from the U.S., all age groups are equally susceptible to JEV infection due to lack of prior exposure. No travel-related cases have been reported among exclusively urban travelers.

Mode of Transmission

JEV is transmitted to humans through the bite of infected mosquitoes (primarily *Culex* species). *Culex tritaeniorhynchus* are early evening-biting and night-biting mosquitoes that breed in rice fields. The virus is maintained in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily wading birds and pigs.

Humans are incidental or dead-end hosts because they usually do not develop a level or duration of viremia sufficient to infect mosquitoes. Therefore, infected travelers pose little risk for introducing the virus into the U.S. or other nonendemic areas.

Risk Factors

Current risk in travelers is estimated to be low (< 1/100,000 travelers per month of travel) to very low (< 1/1,000,000 travelers per month of travel).

Overall risk is very low for short-stay travelers and for those who confine their travel to urbanized areas or brief daytime rural exposures during typical tourist excursions. However, cases may be sporadic and have occurred in short-stay visitors traveling out of the JE transmission season whose only rural travel had been to beach resorts. Travelers with extensive unprotected outdoor, evening/nighttime exposure in rural areas, who participate in activities such as biking, hiking, camping, fishing, hunting, and certain occupational activities, may be at high risk even if their trip is brief.

Expatriates and long-stay travelers (> 1 month) in rural areas are likely at a risk similar to the susceptible resident population (5-50 cases/100,000 children per year) where JE is endemic or epidemic.

Clinical Presentation

The incubation period is 5 to 15 days. Onset is abrupt, with high fever, nausea, vomiting, headache, and altered mental status (including symptoms such as confusion, disorientation, coma, or inability to talk). Convulsions, muscular paralysis, and respiratory difficulties may follow. Seizures are common, especially in children, and gastrointestinal pain and vomiting may be the dominant symptoms.

The case-fatality ratio is as high as 30%, with young children (aged < 10 years) having a greater risk of severe disease and a higher case-fatality rate. Among survivors, 30% to 50% have serious neurological, cognitive, or psychiatric sequelae.

In a study of 55 cases of travelers with JE, 10 died (case-fatality rate = 18%). Of the survivors, 24 (44%) had sequelae, 12 recovered completely, and 9 had an uncertain outcome. Sequelae were severe (neuropsychological or physical, including total incapacitation) in 10 cases (42%) and nonsevere (mild tremor, poor concentration, or memory problems) in 7 cases.

Among local residents, more than 99% of infections are asymptomatic; asymptomatic rates among travelers are not known.

Need for Medical Assistance

Medical assistance should be sought in the event of onset of acute fever within 15 days of leaving an endemic zone, especially if neurological symptoms are present. JE should be considered a possible cause of fever in travelers recently returned from Asia.

Prevention

Nonvaccine

Personal protective measures are the main prevention strategy. Mosquitoes that transmit JEV (*Culex*spp.) are generally night biters but have peak biting activity at dusk and again at dawn. Regardless of vaccination status, travelers should be especially vigilant in applying repellent during peak biting activity times. Treat outer clothing, boots, tents, and sleeping bag liners with permethrin (or other pyrethroid) when traveling in a very high-risk area for JE. See *Insect Precautions*.

Vaccine

Cell-culture vaccines are available in the U.S. and elsewhere (see Vaccines). These vaccines induce protective antibody levels in nearly 100% of recipients within 7 days of administration of the second dose of a 2-dose (days 0, 28) primary series (a single dose is not protective). At 12 months after a 2-dose primary series, 58% to 83% of vaccinees were seroprotected. In adults, 6 years after receiving a booster dose at 12 to 24 months, 96% of vaccinees were seroprotected, and modeling predicted that 75% of vaccinees would be protected for ≥ 10 years. In children, 2 years after administration of the booster dose, 100% of vaccinees were seroprotected; despite gradual waning over time, seroprotective titers were significantly greater than that in children who did not receive a booster dose.

A single study indicates a 99% seroconversion rate 7 days after the second dose of a 2-dose accelerated regimen (days 0, 7), with 94% still seroprotected after 1 year.

Indications for Vaccination

Note: Shoreland's vaccine recommendations, which focus primarily on the risk to the individual traveler, reflect a synthesis and reconciliation of available advice from CDC, ACIP, AAP, and WHO, as well as ongoing global surveillance and the published literature. These recommendations may differ from those of individual countries' public health authorities.

Routine

Vaccination is recommended for laboratory workers with a potential for exposure to infectious JEV.

Travel

Refer to Travax Destinations for country-specific recommendations that take into account destination, duration of stay, frequency of travel to risk areas, activities, level of risk of JE in the country, and transmission season.

Vaccination is recommended for:

- Travelers who plan to spend ≥ 1 month in endemic areas during the JEV transmission season.
- Travel to an area with a current known epidemic or outbreak.
- Shorter rural travel (< 1 month) to endemic areas during transmission season by persons with extensive outdoor exposure (e.g., travelers spending substantial time outdoors in rural or agricultural areas, especially during the evening or night; those participating in outdoor activities, such as camping, hiking, trekking, biking, fishing, hunting, or farming).
- Long-stay urban expatriates, due to the likelihood of occasional rural travel or repeated short visits to endemic areas of the country during a high-risk period of JEV transmission.
- Travelers going to endemic areas who are uncertain of specific destinations, activities, or duration of travel.
- Risk-averse travelers desiring maximum pretravel protection and traveling for short stays in risk areas (because sporadic cases have occurred in this situation, albeit rarely).

Vaccination is not recommended for short-stay (< 1 month) travelers whose travel will be limited to urban areas, day trips to usual tourist sites in rural areas, or during times outside a well-defined JEV transmission season.

Vaccines

See also: Administration for Japanese Encephalitis Vaccine

Vaccines: U.S.

Inactivated Vero Cell Vaccine, SA14-14-2

Ixiaro (JE-VC; Valneva/VaxServe)

- Approved for use in persons aged ≥ 2 months
- Available in single-dose, prefilled syringes (6 µg/0.5 mL dose)
- Contains formaldehyde, bovine serum albumin, sodium metabisulphite, aluminum hydroxide, and protamine sulfate
- Preservative- and thimerosal-free
- Latex-free

Vaccines: Available Outside the U.S.

Inactivated Vero Cell Vaccines, SA14-14-2 Strain

Ixiaro (Valneva): Canada, Europe, Hong Kong, Iceland, Israel, Liechtenstein, Norway, Singapore, and U.K.

- Same as the U.S. vaccine
- Approved for use in persons aged ≥ 2 months

JEspect (bioCSL/Seqirus): Australia, New Zealand, Pacific Islands, and Papua New Guinea (same as Ixiaro)

- Approved for use in persons aged ≥ 18 years (use in children aged 2 months through 17 years only if an alternative vaccine is unavailable)
- Available in single-dose, prefilled syringes (0.5 mL)
- Contains aluminum hydroxide but no preservatives or antibiotics

JEEV (Biological E. Ltd/Valneva): Bangladesh, Bhutan, India, Nepal, Pakistan

- Approved for use in persons aged 1-49 years (0.25 mL/dose for ages 1-3 years and 0.5 mL/dose for ages > 3 years)
- Available in single-dose vials (0.5 mL)

Inactivated Vero Cell Vaccines, Beijing-1 Strain

JEBIK V (Biken): Japan

- Approved for use in persons aged ≥ 6 months
- Contains no adjuvant
- 99% and 100% seroconversion rates following second and third doses, respectively

ENCEVAC (Kaketsuken; Boryung): Japan, Korea

- Approved for use in persons aged ≥ 6 months
- Contains no adjuvant

Inactivated Vero Cell Vaccine, 821564-XY Strain

JENVAC (Bharat Biotech): India

- Approved for use in persons aged ≥ 1 year
- Available in liquid formulation in single- and multidose vials
- Contains aluminum and thimerosal (0.025 mg)

Live Attenuated Hamster Cell Vaccine, SA14-14-2 Strain

CDJEVAX (Chengdu Institute of Biological Products/Biogenentech): Cambodia, China, India, Laos, Myanmar, Nepal, North Korea, South Korea, Sri Lanka, Thailand

- The most widely used JE vaccine in Asia
- Approved for use in persons aged ≥ 9 months
- Available in single- and 5-dose vials (0.5 mL/dose)
- Single-dose vaccine given subcutaneously (SC) followed by a booster dose given later

Live Attenuated Chimeric Recombinant Vaccine, SA14-14-2 Strain

JE-CV (Sanofi Pasteur/GPO-MBP): Malaysia; branded as Imojev MD in the Philippines, Imojev in Australia, and Thaijev in Thailand

- Approved for use in in persons aged ≥ 9 months in Australia and in persons aged ≥ 12 months in the Philippines
- Single-dose vaccine (0.5 mL) given SC followed by a booster dose given later for persons aged < 18 years
    - Seroprotection is reached 14 days after vaccination in 93% of vaccinees.

- 99% and 95% seroconversion rates after 1 dose in adults and children, respectively
- In Australia, preliminary data demonstrated considerable protective antibody levels for 60 months following a single dose.
- Available as freeze-dried powder in single- and 4-dose vials for reconstitution with diluent in separate vials
- Contains lactose, histidine, mannitol, and human serum albumin but no adjuvants or antimicrobial preservatives
- Information on latex content is not available

Killed Inactivated Mouse-Brain Vaccines

Mouse-brain vaccines are potentially toxic and no longer recommended by WHO.

Japanese Encephalitis Vaccine (Green Cross): Korea, Malaysia

- Primary series: 3 doses (given at 0, 7, 28 days) given SC
- Approved for use in some Southeast Asian countries; available in Europe by special release

Jevax (Vabiotech): Vietnam

- Approved for use in persons aged ≥ 1 year
- Primary series: 3 doses (given at 0, 14 days, and at 1 year) given SC
- Approved for use in Vietnam

Side Effects

The most common side effects to Ixiaro in persons aged > 12 years include injection-site reactions, with headache and myalgia occurring in adults. In children aged < 12 years, fever is the most common side effect, with irritability and diarrhea also occurring in infants.

The most recent available data indicate that the rates of adverse events (AEs) following vaccination with Ixiaro are 15.2 per 100,000 doses distributed for all AEs; for life-threatening/serious AEs, the rate was 1.8 per 100,000 doses distributed. Hypersensitivity reactions (both immediate and delayed) were the most common AEs reported.

The most common side effects to CDJEVAX and JE-CV (Imojev, Thaijev) include injection-site reactions, headache, fever, myalgia, malaise, and abnormal crying (in children).

Suspected allergic reactions or adverse effects or medical care required after any vaccination should be reported through the Vaccine Adverse Event Reporting System (VAERS). See also Table: Reportable Events following Vaccination and the VAERS form.

Precautions and Contraindications

Precautions

Consider postponing vaccination in persons with moderate or severe illness (with or without a fever) until recovery, to minimize potential adverse effects.

Contraindications

Anaphylactic reaction to a previous dose of a vaccine or a vaccine constituent contraindicates further vaccination with that vaccine or constituent.

Conditions commonly misperceived as contraindications or precautions

Conditions incorrectly perceived as contraindications or precautions to vaccination (i.e., vaccines may be given under these conditions)

- Mild acute illness, with or without fever
- Mild to moderate local reaction (e.g., swelling, redness, soreness); low-grade or moderate fever after previous dose
- Lack of previous physical examination in a well-appearing person
- Current antimicrobial therapy
- Convalescent phase of illness
- Preterm birth
- Recent exposure to an infectious disease
- History of penicillin allergy, other nonvaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy
- History of Guillain-Barré syndrome

Bleeding Disorders

Ixiaro is an intramuscular injection and may pose a risk for persons with bleeding disorders or those receiving anticoagulation drugs. Consider scheduling vaccination just prior to the next dose of anticoagulant drugs. Morning anticoagulant doses can be deferred until after an early morning vaccine dose, or the vaccine dose can be given late in the afternoon in the case of evening anticoagulant doses. Use a fine-gauge needle (23-gauge or smaller) and apply firm, direct pressure to the site for at least 2 minutes following the injection. Do not rub or massage the injection site. A bruising rate of less than 4% results using this approach. See *Bleeding Disorders and Vaccination*.

Compromised Immunity and HIV

Immunocompromised individuals may have a diminished response to Ixiaro. Live attenuated vaccines CDJEVAX and JE-CV (Imojev, Thaijev) are contraindicated in immunocompromised persons. See *Immunocompromised Travelers* and *HIV-Infected Travelers*.

Household and other close contacts of immunocompromised persons should receive all age- and exposure-appropriate vaccines, with the exception of smallpox vaccine.

Pregnancy and Breastfeeding

Safety and efficacy data for Ixiaro (the only JE vaccine licensed in the U.S.) in pregnant women or breastfeeding mothers are not available. Use in pregnancy only if clearly needed (e.g., the theoretical risk of immunization is outweighed by the risk of infection).

Whether Ixiaro is excreted in human breast milk is unknown. Breastfeeding is not a contraindication; however, exercise caution when administering Ixiaro to a breastfeeding woman.

Although both inactivated and live attenuated vaccines are available outside the U.S., inactivated vaccines should be used in pregnant women and breastfeeding mothers, if indicated.

CDJEVAX and JE-CV (Imojev, Thaijev), live attenuated vaccines, are contraindicated in pregnant women and breastfeeding mothers. Pregnancy should be avoided for 28 days following vaccination with JE-CV and for 3 months following vaccination with CDJEVAX.

See *Pregnant Travelers* for additional information.

Compatibility

Ixiaro (JE-VC) vaccine can be administered simultaneously with (or at any time before or after) other vaccines.

No evidence of interference with the immune response to Ixiaro or Havrix was noted when these vaccines were administered concomitantly. No data exist on the effect of concurrent administration of JE vaccines with other vaccines.

Ixiaro can be administered simultaneously with (or at any time before or after) any antibody-containing preparation (e.g., immune globulin, hyperimmune globulin, and intravenous immune globulin) but should be given at a different anatomic location if administered simultaneously.

Separate vaccines should not be combined into the same syringe to be administered together unless indicated for the patient's age and explicitly specified on the FDA-approved product label inserts. The safety, immunogenicity, and effectiveness of unlicensed combinations are unknown.

Travax content represents decision-relevant, expert synthesis of real-time data reconciled with new and existing available advice from authoritative national and international bodies. National body recommendations such as ACIP/CDC may differ from the manufacturers' recommendations as found in vaccine package inserts. Travax recommendations may differ from those of individual countries' public health authorities.