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Japanese encephalitis

Prevention in travellers

This article is the fourth in a series providing a summary of prevention strategies and vaccination for infections that may be acquired by travellers. The series aims to provide practical strategies to assist general practitioners in giving travel advice, as a synthesis of multiple information sources which must otherwise be consulted.
Japanese encephalitis (JE) is a potentially fatal arboviral infection prevalent in large parts of Asia, as well as Papua New Guinea and the outer Torres Strait Islands. It is the commonest cause of encephalitis worldwide. Although it seldom affects travellers, its serious consequences and at times unpredictable epidemiology make its prevention an important part of the pre-travel consultation. The phasing out of the previously used mouse brain derived inactivated JE vaccine, and the availability of new, safer vaccines now and in the near future, have prompted a reassessment of vaccination recommendations internationally to include a greater number of travellers.

Keywords: travel; preventive medicine; immunisation; communicable/infectious diseases; tropical medicine

Japanese encephalitis (JE) is a serious arboviral disease caused by a flavivirus closely related to other flaviviruses such as West Nile, Murray Valley encephalitis and Kunjin (the latter two occur in Australia). Other well known flaviviral infections include yellow fever and dengue fever.[1] Japanese encephalitis is thought to be the most common form of encephalitis in the world today.[2]

Japanese encephalitis is a zoonosis that is transmitted in an enzootic cycle between Culex mosquitoes and amplifying vertebrate hosts, mainly pigs and wading birds (especially egrets). Infection and illness in humans and some domestic animals such as horses is incidental. There is no person-to-person transmission.[1,2] The Culex mosquito feeds outdoors from dusk to dawn and breeds in flooded rice paddies and marshy environments.

About 1 in 250–1000 infections in susceptible human hosts is symptomatic,[2–5] however in nonindigenous individuals such as travellers, this figure may be up to 1 in 25.[5]

Epidemiology

Japanese encephalitis occurs in rural areas, city peripheries and urban areas of most Asian countries;[4,6] in Papua New Guinea; and in the outer Torres Strait Islands of Australia *(Table 1)*. It was first detected in the outer Torres Strait following three cases on Badu Island, two of which were fatal. One known case in western Cape York was acquired on the Australian mainland, and evidence of JE has been found in sentinel pigs in northern Cape York. To date, five known cases have been acquired in Australia.[5]

The incidence of JE is declining in certain parts of Asia including Japan, Taiwan, South Korea, and a number of Chinese provinces; it has been eradicated from Singapore. Immunisation programs, changes in pig and rice farming patterns, improved socioeconomic circumstances and mosquito control are thought to contribute to this decline.[2,5] However, the virus is geographically mobile due to bird migration and windblown mosquitoes, with factors such as deforestation, land use for agriculture, population growth, and possibly global climate change contributing to its spread and increase in incidence in other areas.[2] This, along with local differences in geography, weather patterns (such as timing and intensity of monsoons), land use, farming patterns and many other factors, lead to variations in risk within specific locations and from year-to-year, affecting the precision of available data.[6]

There are two main patterns of transmission:

- seasonal in the temperate or subtropical regions of Asia; in May to September in the northern temperate regions of China, Korea, Siberia and Japan; and during a longer warm season (March to October) further south
- in India and southeast Asia it is endemic. Transmission depends on local monsoon and bird migration patterns and may have two annual peaks, or be year round (eg. Bali).[1,3,5,7]

Clinical features

The illness manifests as widespread encephalomyelitis of white matter, thalamus, brainstem and spinal cord. More than 75% of

children have seizures. Adults usually present with headache, meningism, fever and confusion/altered consciousness.[2] However, JE may sometimes present as a simple febrile syndrome, acute flaccid paralysis or aseptic meningitis, depending on geographical region.[5,6] This range of presenting symptoms, along with poor surveillance in less developed countries, leads to significant underreporting of disease incidence.[3,6] The case fatality rate is up to 30%,[2] and 60% of survivors, especially children, have permanent and often debilitating neurological sequelae, including motor paresis, spasticity, movement disorders, chronic seizures and developmental delay.[2,5,6]

Who is most at risk?

Behavioural risk factors include dawn, dusk or night visits to rice growing areas, and living in villages near rice paddies and farm animals during transmission season. Individuals especially at risk of contracting JE include soldiers, aid workers, missionaries, students, researchers in endemic areas in wet season; cyclists, backpackers and adventure travellers with uncertain itineraries travelling to these areas; and expatriates.

Specific risk factors for developing JE include:

- age greater than 50 years
- infection in childhood
- dual neurological infection, such as with neurocysticercosis or mumps
- those with factors compromising the blood-brain barrier (eg. cochlear implants or cerebrospinal fluid shunts)
- pregnancy (risk of intrauterine infection and miscarriage if JE is acquired in the first or second trimester)
- those with genetic susceptibility, such as homozygosity for CCR5Delta32 (a nonfunctioning variant of chemokine receptor 5), and
- those with chronic conditions such as solid organ transplantation, hypertension, cardiovascular disease, diabetes mellitus and renal disease.[6]

Until recently, the risk of infection with JE was thought to be less than 1 per million.[7] This low risk of contracting JE and the side effect profile of the previously used inactivated mouse brain derived vaccine[1,4,5] had to be balanced with the severity of

Table 1. Risk of Japanese encephalitis, by country[1]*

Country	Area	Transmission season
Australia	Outer islands of Torres Strait; one human case reported from northern Queensland mainland	December to May; all human cases reported from February to April
Bangladesh	Little data; probably widespread	Unknown; most human cases reported from May to October
Bhutan	No data	No data
Brunei	No data; presumed to be endemic countrywide	Unknown; presumed year round transmission
Burma (Myanmar)	Limited data; presumed to be endemic countrywide	Unknown; most human cases reported from May to October
Cambodia	Presumed to be endemic countrywide	Probably year round with peaks reported from May to October
China	Human cases reported from all provinces except Xizang (Tibet), Xinjiang, and Qinghai Highest rates reported from the southwest and south central provinces Hong Kong and Macau: not considered endemic Rare cases reported from the New Territories Vaccine not routinely recommended for travel limited to Beijing or other major cities	Most human cases reported from April to October
India	Human cases reported from all states except Dadra, Daman, Diu, Gujarat, Himachal, Jammu, Kashmir, Lakshadweep, Meghalaya, Nagar Haveli, Punjab, Rajasthan, and Sikkim Highest rates of human disease reported from the states of Andhra Pradesh, Assam, Bihar, Goa, Haryana, Karnataka, Kerala, Tamil Nadu, Uttar Pradesh, and West Bengal	Most human cases reported from May to October especially in northern India. The season may be extended or year round in some areas especially in southern India
Indonesia	Presumed to be endemic countrywide Sentinel surveillance has identified human cases in Bali, Kalimantan, Java, Nusa Tenggara, Papua, and Sumatra	Human cases reported year round; peak season varies by island
Japan*	Rare, sporadic cases on all islands except Hokkaido. Enzootic activity ongoing Vaccine not routinely recommended for travel limited to Tokyo or other major cities	Most human cases reported from May to October
Korea, North	No data	No data

Korea, South**	Rare sporadic cases countrywide. Enzootic activity ongoing Vaccine not routinely recommended for travel limited to Seoul or other major cities	Most human cases reported from May to October
Laos	No data; presumed to be endemic countrywide	Presumed to be May to October
Malaysia	Endemic in Sarawak; sporadic cases or outbreaks reported from all states of peninsula, and probably Sabah Most human cases from reported from Penang and Sarawak Vaccine not routinely recommended for travel limited to Kuala Lumpur or other major cities	Year round transmission
Nepal	Endemic in southern lowlands (Terai). Sporadic cases or outbreaks reported from the Kathmandu valley Highest rates of human disease reported from western Terai districts Vaccine not routinely recommended for travel limited to high altitude areas	Most human cases reported from May to November
Pakistan	Limited data; human cases reported from around Karachi	Most human cases reported from May to October
Papua New Guinea	Limited data; sporadic human cases reported from Western, Gulf, and Southern Highland provinces A case of JE was reported from near Port Moresby in 2004. Human cases documented in Papua Indonesia	Unknown
Philippines	Limited data; presumed to be endemic on all islands Outbreaks reported in Nueva Ecija, Luzon, and Manila	Unknown; probably year round
Russia	Rare human cases reported from the far eastern maritime areas south of Khabarousk	Most human cases reported from July to September
Singapore	Rare sporadic human cases reported Vaccine not routinely recommended	Year round transmission
Sri Lanka	Endemic countrywide except in mountainous areas Highest rates of human disease reported from Anuradhapura, Gampaha, Kurunegala, Polonnaruwa, and Puttalam districts	Year round with variable peaks based on monsoon rains
Taiwan**	Rare sporadic human cases island wide Vaccine not routinely recommended for travel limited to Taipei or other major cities	Most human cases reported from May to October
Thailand	Endemic countrywide; seasonal epidemics in the northern provinces Highest rates of human disease reported from the Chiang Mai Valley. Sporadic human cases reported from Bangkok suburbs	Year round with seasonal peaks from May to October, especially in the north
Timor-Leste	Limited data; anecdotal reports of sporadic human cases	No data
Vietnam	Endemic countrywide; seasonal epidemics in the northern provinces Highest rates of disease in the northern provinces around Hanoi and northwestern provinces bordering China	Year round with seasonal peaks from May to October, especially in the north
Western Pacific Islands	Outbreaks of human disease reported in Guam in 1947–1948 and Saipan in 1990	Unknown; most human cases reported from October to March

* Data are based on published reports and personal correspondence. Risk assessments should be performed cautiously as risk can vary within areas and from year-to-year; surveillance data regarding human cases and JE virus transmission are incomplete

** In some endemic areas, human cases among residents are limited because of vaccination or natural immunity. However, because JE virus is maintained in an enzootic cycle between animals and mosquitoes, susceptible visitors to these areas still may be at risk of infection

the disease and the fact that JE has occurred even in short term travellers with low risk itineraries (eg. to resorts in Bali).[6,7] The risk for rural travellers in JE season is considered to be about 1 per 5000 to 1 per 20000 travellers per week,[7–9] or 1 per 5000–10000 per month.[4,6] As new vaccines with an improved safety profile are becoming available, the benefits of vaccine are likely to outweigh the risks in a greater number of travellers.[3,4,6]

Prevention

Prevention includes: mosquito precautions, regardless of vaccination status; avoidance of high risk activities; advice about the disease to those travelling to areas of JE transmission; and advice about the risks and benefits of vaccination.

Vaccines

An older inactivated, mouse brain derived vaccine (JE-Vax) is no longer manufactured and is not available in Australia. Problems with the vaccine included concerns about severe immediate and delayed hypersensitivity reactions in 1–17 per 10 000 vaccinees[3] and the rare possibility of developing severe neurological adverse events.[3,5] It was also relatively expensive, difficult to produce, required multiple doses, and lacked clear information about some aspects of long term protection and booster requirements.[3]

The new inactivated JE vaccine IC-51 (Jespect/Ixiaro [CSL]) was approved by the Therapeutic Goods Administration (TGA) in Australia in January 2009[12] for active immunisation against JE virus for persons aged 18 years and over[11,12] (*Table 2*).

An as yet unavailable chimeric vaccine (Chimerivax-JE [Sanofi Pasteur]), is a lypohilised recombinant, attenuated, single dose, live vaccine which incorporates JE virus genes into a 'backbone' of an attenuated strain of yellow fever virus.[3] Similar vaccines against other flaviviruses are being developed using this method.[15] It promises to be highly immunogenic and low cost, but there are theoretical concerns about possible adverse recombination events and rare, but potentially fatal, side effects as seen with the yellow fever vaccine.[3] The vaccine may be available by the end of 2010; it is likely that it will be registered for use in children.

Vaccines in children

Until the release of a JE vaccine appropriate for use in children, a Korean inactivated mouse brain derived JE vaccine (Green Cross Vaccine Corp) can be accessed under the TGA Special Access Scheme (see *Resources*). It can be used in adults as well as children aged 1 year or over.[16] The risks, adverse effects and contraindications are similar to those of JE-Vax, including the need for a 30 minute observation period after the vaccine and avoidance of travel until 10 days after completion of the course. Boosters need to be given at 12 months following the primary course, then every 3 years unless at particular risk (then boost annually). Accelerating the schedule (days 0, 7 and 14) will lead to lower antibody titres and shorter duration of protection (*Table 3*). Contraindications specific to the Green Cross vaccine include neurological conditions (especially convulsions in the past 12 months), and caution exercised in persons with a past history of urticaria.[17] The vaccine, once ordered, can be available within 10–14 days.

Table 2. Administration recommendations for inactivated JE vaccine IC-51: Jespect/Ixiaro[14]

Contents	Purified, inactivated JE virus, hydrated aluminium hydroxide 0.1%, phosphate buffered saline
Indications	Active immunisation against JE virus for persons aged 18 years or over
Contraindications	• Previous serious reaction such as anaphylaxis to this vaccine • Known hypersensitivity to any component • Age <18 years
Precautions	• Acute febrile illness • History of flavivirus infection and/or vaccination (including JE, dengue fever, Murray valley encephalitis) • Immunosuppressive therapy or immunodeficiency may lead to diminished immune response
Administration schedule	Give 0.5 mL IM into the deltoid muscle (SC administration could result in suboptimal vaccine response) on day 0 and day 28. Shake well before administration
Adverse reactions	• Shown to be safe[3,10] • Headache (20%) and myalgia (13%) occur, usually within the first 3 days after vaccination • Usually mild, less prominent after the second vaccine dose • No serious adverse reactions reported
Interactions	• No assessment available regarding administration of other flavivirus vaccines including yellow fever • Jespect and hepatitis A vaccine (Havrix 1440) may be given concomitantly • Previous tick borne encephalitis vaccine did not interfere with immunity against JE • Information not yet available on whether previous JE-Vax should be considered[3]
Pregnancy and breastfeeding	Due to lack of data, IC-51 vaccine should not be given unless clearly needed.[11] The product information classifies it as Category B1, but adequate human data is not available[13]
Children	• Not to be used in children aged <18 years • Immunogenicity and safety trials in children are currently in progress[13]
Duration of protection/booster timing	As yet uncertain[3]
Approximate cost	$150.00 per dose

Table 3. Dosage and administration of the Green Cross inactivated, mouse brain derived JE vaccine[16,17]

	Adults and children >3 years of age	Children 1–3 years of age	Vaccination schedule
First dose	1 mL	0.5 mL	Day 0
Second dose	1 mL	0.5 mL	Day 7
Third dose	1 mL	0.5 mL	Day 28

Table 4. Current NHMRC recommendations and likely future recommendations for JE vaccination

Current NHMRC vaccine recommendations in Australia[5] (based on the use of mouse brain derived vaccine)	Likely future recommendations (based on the newer safer vaccines)
• Travellers spending 1 month or more in rural areas of Asia or western Papua New Guinea, especially during wet season, and/or considerable outdoor activity, and/or staying in suboptimal accommodation; or <1 month in areas experiencing epidemic transmission • All other travellers spending 1 year or more in Asia, including urban areas (except Singapore) • All residents (>1 year of age) of the outer Torres Strait Islands • All nonresidents living or working in the outer Torres Strait Islands for a cumulative total or 30 days or more during wet season (December to May). Late wet season (eg. May arrivals) do not require the vaccine, nor do dry season visitors to the outer islands, or visitors to the inner islands (eg. Thursday Island) • All those who wish to minimise risk/ request vaccine if fully informed of risks and benefits	All current recommendations plus: • Repeat travellers who are at risk through cumulative duration of exposure • Any individual with prolonged duration of stay, regardless of itinerary • Any traveller whose itinerary includes rural areas • Consider vaccinating all travellers visiting regions at risk of JE transmission who: – have greater outdoor exposure – are aged >50 years – are aged <10 years (once an appropriate vaccine for children becomes available) – have chronic conditions such as hypertension, diabetes mellitus, chronic renal disease – have had solid organ transplant, cochlear implant, ventriculoperitoneal shunts – are on anti-TNF therapy – have known homozygosity for CCR5delta32 – are pregnant (exposure risk must be balanced with as yet unknown vaccine risks)

Vaccine recommendations

Vaccine recommendations are under revision as new vaccines with an improved risk profile, and more information about the risks and epidemiology of JE, become available. Current vaccination recommendations are shown in *Table 4*. In view of the relative safety of the new vaccine(s), expert opinion[6] now suggests expanding vaccine recommendations (*Table 4*).

Conclusion

Recently revised recommendations for vaccination against JE, a serious arboviral infection with a poorly predictable risk profile, will become more pertinent to the Australian setting when safer, nonmouse brain derived vaccines become available for travellers aged less than 18 years. These vaccines will take the place of discontinued and currently used vaccines for this age group. In the meantime, specialist advice may be sought where clarification is needed in individual situations. General preventive advice is always important. A new, inactivated JE vaccine (IC-51), registered in Australia in 2009, is available for travellers aged more than 18 years, and another, chimeric vaccine is due for release soon.

Resources

Updates on the JE situation are available from the following sites:

- International Society for Infectious Diseases program for monitoring emerging diseases: (ProMed) www.promedmail.org
- World Health Organization: http://gamapserver.who.int/mapLibrary/Files/Maps/Global_JE_ITHRiskMap.png and www.who.int/ith/updates/en/index.html
- Centers for Disease Control: www.nc.cdc.gov/travel/default.aspx (with link to outbreak news and yellow book 2010)
- International Society of Travel Medicine: www.istm.org/WebForms/NonIstmLinks/Outbreak_News.aspx
- TGA Special Access Scheme: www.tga.gov.au/docs/html/sasinfo.htm or www.tga.gov.au/docs/pdf/unapproved/sas.pdf.

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