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 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,\(^3\)\(^-\)\(^5\) however in nonindigenous individuals such as travellers, this figure may be up to 1 in 25.\(^5\)

**Clinical features**

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

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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.\(^2\)\(^,\)\(^3\) 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).\(^1\)\(^,\)\(^3\)\(^,\)\(^5\)\(^,\)\(^7\)

**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.\(^5\)

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

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, monitors, 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 (e.g. 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.

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

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

<table>
<thead>
<tr>
<th>Area</th>
<th>Country</th>
<th>Transmission season</th>
<th>Disease presentation</th>
<th>Vaccine status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Queensland mainland</td>
<td>Australia</td>
<td>December to May; all human cases reported from northern Queensland mainland</td>
<td>Little data, probably widespread</td>
<td>No data</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>Bangladesh</td>
<td>Unknown; most human cases reported from May to October</td>
<td>Unknown; most human cases reported from May to October</td>
<td>Unknown; most human cases reported from May to October</td>
</tr>
<tr>
<td>Bhutan</td>
<td>Bhutan</td>
<td>Unknown; presumed year round transmission</td>
<td>Unknown; presumed year round transmission</td>
<td>Unknown; presumed year round transmission</td>
</tr>
<tr>
<td>Burma (Myanmar)</td>
<td>Burma (Myanmar)</td>
<td>Unknown; most human cases reported from May to October</td>
<td>Unknown; most human cases reported from May to October</td>
<td>Unknown; most human cases reported from May to October</td>
</tr>
<tr>
<td>Cambodia</td>
<td>Cambodia</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>China</td>
<td>China</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Indonesia</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
</tr>
<tr>
<td>Korea North</td>
<td>Korea North</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Japan*</td>
<td>Japan*</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Malaysia</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
</tr>
<tr>
<td>Philippines</td>
<td>Philippines</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
</tr>
<tr>
<td>Russia</td>
<td>Russia</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
</tr>
<tr>
<td>Singapore</td>
<td>Singapore</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>Sri Lanka</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
</tr>
<tr>
<td>Thailand</td>
<td>Thailand</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
</tr>
<tr>
<td>Vietnam</td>
<td>Vietnam</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
<td>Presumed to be endemic countrywide</td>
</tr>
</tbody>
</table>

**Note:** 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.
<table>
<thead>
<tr>
<th>Country</th>
<th>Area/Transmission Season</th>
<th>Country</th>
<th>Area/Transmission Season</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Outer islands of Torres Strait; one human case reported from northern December to May; all human cases reported from February to April</td>
<td>Bangladesh</td>
<td>Little data; probably widespread Unknown; most human cases reported from May to October</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bhutan</td>
<td>No data No data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brunei</td>
<td>No data; presumed to be endemic countrywide Unknown; presumed year round transmission</td>
</tr>
<tr>
<td>Burma (Myanmar)</td>
<td>Limited data; presumed to be endemic countrywide Unknown; most human cases reported from May to October</td>
<td>Cambodia</td>
<td>Presumed to be endemic countrywide Probably year round with peaks reported from May to October</td>
</tr>
<tr>
<td></td>
<td></td>
<td>China</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Korea, South**</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laos</td>
<td>No data; presumed to be endemic countrywide Presumed to be May to October</td>
</tr>
<tr>
<td>Malaysia</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nepal</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pakistan</td>
<td>Limited data; human cases reported from around Karachi Most human cases reported from May to October</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philippines</td>
<td>Limited data; presumed to be endemic on all islands Outbreaks reported in Nueva Ecija, Luzon, and Manila Unknown; probably year round</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russia</td>
<td>Rare human cases reported from the far eastern maritime areas south of Khabarous Most human cases reported from July to September</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singapore</td>
<td>Rare sporadic human cases reported Vaccine not routinely recommended Year round transmission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan**</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timor-Leste</td>
<td>Limited data; anecdotal reports of sporadic human cases No data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vietnam</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Pacific Islands</td>
<td>Outbreaks of human disease reported in Guam in 1947–1948 and Saipan in 1990 Unknown; most human cases reported from October to March</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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 vaccinees3 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 [Sanofi Pasteur]) is a lyophilised 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

<table>
<thead>
<tr>
<th>Contents</th>
<th>Purified, inactivated JE virus, hydrated aluminium hydroxide 0.1%, phosphate buffered saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications</td>
<td>Active immunisation against JE virus for persons aged 18 years or over</td>
</tr>
</tbody>
</table>
| 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 safe3,10  
• 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 |
| 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 available13 |
| Children | • Not to be used in children aged <18 years  
• Immunogenicity and safety trials in children are currently in progress13 |
| Duration of protection/booster timing | As yet uncertain3 |
| Approximate cost | $150.00 per dose |
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
- Centers for Disease Control: www.cdc.gov/travel/default.aspx (with link to outbreak news and yellow book 2010)
- International Society of Travel Medicine: www.ism.org/WebForms/NonIstmLinks/Outbreak_News.aspx

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Conflict of interest: none declared.

**Acknowledgment**

Thanks to Dr Stanley Khoo and Ros Fairless (Rn) from Travel Medicine Centre Perth for their help with information about the Korean Green Cross vaccine.

**References**


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**Table 3. Dosage and administration of the Green Cross inactivated, mouse brain derived JE vaccine**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and children &gt;3 years of age</td>
<td>1 mL</td>
<td>Day 0</td>
</tr>
<tr>
<td>Children 1–3 years of age</td>
<td>0.5 mL</td>
<td>Day 0</td>
</tr>
<tr>
<td>Vaccination schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First dose</td>
<td>1 mL</td>
<td>Day 7</td>
</tr>
<tr>
<td>Second dose</td>
<td>0.5 mL</td>
<td>Day 7</td>
</tr>
<tr>
<td>Third dose</td>
<td></td>
<td>Day 28</td>
</tr>
</tbody>
</table>

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

**Current NHMRC vaccine recommendations in Australia**

- 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

**Likely future recommendations (based on the newer safer vaccines)**

- 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)

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**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 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

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