

3.10 JAPANESE ENCEPHALITIS

Virology

Japanese encephalitis (JE) is caused by a mosquito-borne flavivirus.

Clinical features

The disease is typically an acute neurological illness characterised by headache, fever, convulsions, focal neurological signs and depressed level of consciousness. It has a high case-fatality rate and there is a high prevalence of neurological sequelae (up to 50%) in those who survive the acute illness.¹ Less commonly, the disease may present as an acute flaccid paralysis.¹ Milder forms include febrile illness with headache, and aseptic meningitis. It is recognised, however, that most infections are asymptomatic; published estimates of the symptomatic to asymptomatic infection ratio vary in different populations from 1:25 to 1:1000.¹

Epidemiology

JE is a significant public health problem in many parts of Asia including the Indian subcontinent, southeast Asia and China.¹ In recent years, however, the disease has extended beyond its traditionally recognised boundaries with, for example, outbreaks occurring in the Torres Strait and north Queensland in 1995 and 1998.^{2,3}

The JE virus is essentially a zoonosis of pigs and wading birds, and is transmitted between these animals by Culicine mosquitoes.¹ The virus replicates, leading to a transient high-level viraemia, within these so-called 'amplifying' hosts but not within other large vertebrates such as horses and humans.

Indeed, humans are an incidental host infected when living in close proximity to the enzootic cycle; this usually occurs in rural areas where there is prolific breeding of the vectors in flooded rice fields.¹

There are two recognised epidemiological patterns of JE.¹ In the temperate or subtropical regions of Asia (northern Thailand, northern Vietnam, Korea, Japan, Taiwan, China, Nepal and northern India), the disease occurs in epidemics during the summer or wet season months (April to May until September to October). In the tropical regions (most of southeast Asia, Sri Lanka, southern India), the disease is endemic, occurring throughout the year, but particularly during the wet season.¹

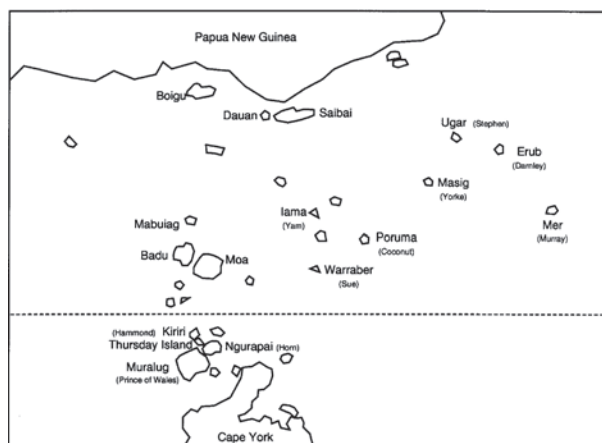
In some countries (Japan, Taiwan, South Korea, and some provinces of China), the incidence of JE has declined considerably in recent decades, and it has been eradicated from Singapore. Immunisation, changes in pig husbandry, a reduction in land utilised for rice farming, and improved socioeconomic circumstances have all contributed to these changes.¹

In early 1995, 3 cases of JE, 2 of them fatal, occurred on Badu island in the Torres Strait.² Subsequent serological surveys showed that JE virus activity was widespread in many other remote 'outer' islands of the Torres Strait (see Figure 3.10.1) at or about that time.² Although the 1995 outbreak was the first known incursion of JE virus into Australia, surveillance using sentinel pigs has shown incursions into the Torres Strait in virtually every wet season (December to May) since then.

In early 1998, a further case of JE occurred in an unvaccinated Badu resident and the first ever mainland case of JE occurred in a person working on the west coast of Cape York.³ However, serological surveys revealed no evidence of JE virus infection in people in several nearby communities.³ To date, there have been 5 cases of JE acquired in Australia.

An investigation subsequent to the 1995 outbreak of JE in the Torres Strait documented the presence of the JE virus in the Western Province of Papua New Guinea.⁴ A severe case of JE acquired near Port Moresby occurred in early 2004,⁵ indicating that the JE virus is now probably widespread in Papua New Guinea.

Figure 3.10.1: Map of the Torres Strait. The outer islands are north of the dotted line



Vaccine

- **JE-VAX** – Sanofi Pasteur Pty Ltd (Japanese encephalitis virus vaccine inactivated). Each 1.0 mL reconstituted monodose vial contains formaldehyde inactivated Japanese encephalitis virus; 0.007% thiomersal; 470 µg gelatin; <100 µg formaldehyde; 5 mg monosodium glutamate; <50 ng mouse brain serum protein.

The JE vaccine available in Australia is an inactivated mouse brain-derived vaccine manufactured in Japan. However, the manufacturer has recently discontinued its production and, although the Australian distributor has access to a stockpile, shortages of the vaccine could occur over the next few years. New generation JE vaccines are expected in the mid to longer term.

The vaccine is prepared by inoculating mice intracerebrally with Nakayama-NIH strain JE virus. Infected brains are harvested, homogenised, then centrifuged. The supernatant is inactivated with formaldehyde and purified by ultracentrifugation; the suspension is then lyophilised. No myelin basic protein can be detected at the threshold of the assay (<2 ng/mL).

A randomised clinical trial in Thailand in the early 1980s determined that 2 doses of the inactivated mouse brain-derived vaccine, administered to children 7 days apart, had a protective efficacy of 91%.⁶ However, immunogenicity studies have demonstrated that 3 doses of the vaccine are required to ensure adequate immunity in vaccinees from JE non-endemic areas.⁷

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.⁸ Store at +2°C to +8°C. Do not freeze. Reconstituted vaccine should be used immediately, but it can be stored at +2°C to +8°C and used within 8 hours.

Dosage and administration

JE vaccine is administered by the subcutaneous route. The volume injected is 0.5 mL in 1–3-year-old children and 1.0 mL for all individuals >3 years of age. In those from non-endemic regions, including Australia, a 3-dose regimen (ie. days 0, 7 and 28) over a month is required. An accelerated schedule of 0, 7 and 14 days can be used, but this is likely to result in lower antibody levels than the standard schedule.⁷ If the accelerated schedule is used, a further dose should, if possible, be administered 1 to 3 months later.

NB. The volume of the reconstituted vaccine is greater than 1.0 mL. Because the dose of JE vaccine is 1.0 mL (0.5 mL in 1–3-year-old children) this means a small portion of the total reconstituted vaccine should be discarded.

Recommendations

(i) Travellers

Although the risk of travellers in Asia acquiring JE is extremely low, there have been instances of even short-term travellers developing the disease.⁹ Therefore, all travellers to Asia (and other tropical regions) must be fully aware of the need to take appropriate measures to avoid mosquito bites.

The risk of JE to travellers to Asia is determined by the season of travel, the regions visited, the duration of travel, the extent of outdoors activity and the extent to which mosquito-avoidance measures are taken.¹ Clearly the risk is

greater during prolonged travel to rural areas of Asia during the wet season; it is probably negligible during short business trips to urban areas.

NB. A recent study has shown that the JE virus is hyperendemic in Bali, that it causes substantial human illness, and that it circulates year round.¹⁰

Therefore JE vaccination is recommended for:

- travellers spending 1 month or more in rural areas of Asia. However, as JE has occurred in travellers after shorter periods of travel, JE vaccination should be considered for shorter-term travellers, particularly if the travel is during the wet season, and/or there is considerable outdoor activity, and/or the accommodation is not mosquito-proof,⁹
- for all other travellers spending a year or more in Asia (except Singapore), even if much of the stay is in urban areas, and
- travellers intending to spend a month or more in Papua New Guinea, particularly if the travel is during the wet season.

(ii) Residents of Far North Queensland

JE vaccination is recommended for:

- all residents (>1 year of age) of the outer islands in the Torres Strait, and
- all non-residents who will be living or working on the outer islands of the Torres Strait for a cumulative total of 30 days or more during the wet season (December to May).

NB. The period of greatest risk is from February to March and the vaccination course should be completed before February. Those arriving in the outer islands late in the wet season (ie. in May) have arrived after the risk period and do not require vaccination. Those visiting the outer islands in the dry season (June to November) do not require vaccination. Those visiting only the inner islands, including Thursday Island, do not require vaccination.

(iii) Laboratory personnel

JE vaccination is recommended for all research laboratory personnel who potentially might be exposed to the virus.

(iv) Booster doses

Single booster doses are recommended at 3-yearly intervals.

Contraindications

- Anaphylaxis following a previous dose of JE vaccine or a significant allergic reaction, such as generalised urticaria, to a previous dose.
- Anaphylaxis following any component of the vaccine. A past history of allergic disorders (including urticaria, angioedema, anaphylaxis) following bee-stings, medications, foods etc. must be considered as possible contraindications to vaccination.
- The inactivated mouse brain-derived JE vaccine is contraindicated in those <1 year of age.

Precautions

There are few data on the safety and efficacy of JE vaccine in people with impaired immunity. A small study undertaken in Thailand has documented that HIV-infected infants respond less well to 2 doses of JE vaccine than do non-infected infants;¹¹ the response to further doses was not studied.

Adverse events

- Local reactions and minor systemic reactions are common to very common following vaccination against JE.¹ About 20% experience tenderness, redness and/or swelling at the injection site, and 10% experience systemic reactions such as fever, headache, being 'off-colour', chills, dizziness, aching muscles, nausea and/or vomiting.
- Although the manufacturing process purifies the infected mouse brain suspension so that no myelin basic protein can be detected in the vaccine, serious neurological events following immunisation have been reported. In 1994, 4 cases of severe neurological illness, 2 of which were fatal, were reported from South Korea, and surveillance in Japan indicates the rate of severe neurological adverse events following JE vaccination is 1.8 cases per 1 million doses of vaccine.⁷
- Hypersensitivity (allergic) reactions are uncommon and occur in about 0.5% (ie. 1 in 200) vaccinees. These reactions include urticaria that is often widely distributed over the body, angioedema of the limbs, face and throat, and generalised pruritus (sometimes without a rash). In the early 1990s, apparently severe allergic reactions to the inactivated mouse brain-derived JE vaccine were reported from several industrialised countries, including Australia.⁷ In a few cases, upper airway swelling with respiratory distress and hypotension occurred; some had to be hospitalised.

An important feature of the hypersensitivity reactions to JE vaccine is that they may be delayed for several days, in some cases up to 10 days, after the actual time of vaccine administration. The risk of these delayed reactions seems to be increased after the first and second doses, and they appear to be more likely to occur in those with a history of allergic reactions, especially urticaria.⁷ Although

the pathogenesis of the more severe hypersensitivity reactions remains uncertain, there is some evidence that gelatin, added to stabilise the vaccine, may be the provoking agent.⁷ As a precaution, vaccinees should ideally remain within access to medical care for 10 days after vaccination.

Use in pregnancy

Although JE vaccine might pose a theoretical risk to the developing fetus, no adverse outcomes of pregnancy have ever been attributed to vaccination against JE. Because JE virus infection during the first and second trimester is also associated with miscarriage, pregnant women at risk of acquiring JE should be offered JE vaccine.

Variations from product information

The product information states that 'definitive recommendations cannot be given on the timing of booster doses at this time' and that 'a booster dose may be given after 2 years'. The NHMRC recommends that single booster doses be given at 3-yearly intervals.

References

Full reference list available on the electronic *Handbook* or website <http://immunise.health.gov.au>.