8: Emerging viral infections in Australia

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New viruses have appeared, while previously known ones are increasing in incidence and range

Abstract

- Hendra virus infection should be suspected in someone with close association with horses or bats who presents acutely with pneumonia or encephalitis (potentially after a prolonged incubation period).
- Australian bat lyssavirus infection should be suspected in a patient with a progressive neurological illness and a history of exposure to a bat.
- Rabies vaccine and immunoglobulin should be strongly considered after a bite, scratch or mucous membrane exposure to a bat.
- Japanese encephalitis vaccine should be considered for people intending to reside in or visit endemic areas of southern or eastern Asia for more than 30 days.

MJA 2002; 177: 45–49

WHILE MANY VIRUSES THAT infect humans in Australia are found worldwide, some are unique to our country or region. Some of these are classed as "emerging", including:

- Hendra and Menagle viruses, which were identified for the first time in Australia, in 1994 and 1997, respectively,[1,2] and have not been found elsewhere. Another new agent, Nipah virus, has been found in nearby Malaysia and Singapore, but has not yet appeared in Australia.
- Australian bat lyssavirus, which is also newly described and unique to Australia, but is closely related to lyssaviruses found elsewhere.
- Murray Valley encephalitis and Kunjin viruses, which have been found predominantly in Australia for many years but are now causing an increasing incidence of infection.
- Japanese encephalitis virus, which is widespread in many of our South-East Asian neighbours and was recently encountered in Australia for the first time.

The clinical and epidemiological features of these viruses are summarised in Box 1. Infection with these viruses has no specific treatment; management comprises supportive measures.

Hendra, Menangle and Nipah viruses

Hendra virus

Hendra virus infection has been identified in three people. In Brisbane, in 1994, a 49-year-old horse trainer died after a fulminating septic pneumonic illness, while a 40-year-old worker at his stable survived an influenza-like illness. Eighteen horses in the same stable developed a pneumonic illness, and fourteen died. Serological evidence of infection was demonstrated in three other horses which were asymptomatic.[1,3] A year later, a 36-year-old farmer died as a result of Hendra virus encephalitis in Mackay, Queensland.[4] Two of his horses were subsequently shown to have died of Hendra virus infection 13 months earlier.

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Subsequent seroepidemiological testing for Hendra virus in a large number of human contacts of these three people was completely negative.[5] Seroepidemiological studies of more than 2000 horses and more than 5000 samples from 46 other animal species in Queensland also failed to identify a single Hendra virus infection.[6] However, antibody to Hendra virus was found in 20 of 224 serum samples from four species of fruit bats from as far north as Madang, Papua New Guinea, and as far south as Melbourne.[7] Fruit bats (Box 2) now seem a likely source of Hendra virus, although they appear to be asymptomatically infected.

Diagnosis: Although no further cases have occurred, Hendra virus infection should be suspected in patients presenting with an acute flu-like illness with pneumonia or encephalitis and a history of exposure to fruit bats or sick horses (Box 1). Serum antibody testing may be diagnostic.

Menangle virus

Menangle virus was isolated from stillborn piglets in New South Wales in 1997, and serological evidence of infection was found in pigs, humans and fruit bats closely associated with the piggery. Two piggery workers developed an influenza-like illness with a spotty, red, non-pruritic rash.[2] No further cases have been identified. The wider prevalence of Menangle virus remains to be determined.

Diagnosis: Infection with this virus should be considered in patients presenting with a flu-like illness and rash and a history of exposure to piglets or fruit bats in NSW (Box 1).

1: Clinical and epidemiological features of emerging viral infections in Australia

Virus	Epidemiological clues	Clinical features	Key investigations	Prevention
Hendra	Contact with fruit bats or horses in eastern Australia or Papua New Guinea	Flu-like illness, pneumonia, encephalitis	Hendra virus antibodies in serum	Avoid contact with fruit bats or sick horses in endemic areas
Menangle	Contact with stillborn piglets and bats in New South Wales	Flu-like illness, rash	Menangle virus antibodies in serum	Avoid contact with piglets or fruit bats in endemic areas
Nipah	Contact with pigs in Malaysia or Singapore	Flu-like illness, pneumonia, encephalitis	Nipah virus antibodies in serum	Avoid contact with pigs in endemic areas
Australian bat lyssavirus (ABL)	Contact with bats in Australia	Similar to rabies: acute, progressive neurological disorder	Polymerase chain reaction tests of cerebrospinal fluid ± lyssavirus antibodies in serum Examination of bat brain tissue	Avoid contact with bats; immunoprophylaxis (Box 3)
Murray Valley encephalitis (MVE)	Residence in northern Australia or Papua New Guinea, especially during wet season (February to July)	Acute febrile illness, encephalitis	MVE antibodies in serum	Mosquito avoidance measures
Kunjin	Residence in Australia (particularly northern Australia), especially during wet season (February to July)	Acute febrile illness, polyarthralgia, and (rarely) encephalitis	Kunjin antibodies in serum	Mosquito avoidance measures
Japanese encephalitis (JE)	Residence in South-East or East Asia, Indian subcontinent or Torres Strait; exposure to domestic birds and animals, especially pigs	Flu-like illness, encephalitis	JE antibodies in serum or cerebrospinal fluid	Mosquito avoidance measures; JE vaccine if intend to travel to endemic areas for longer than 30 days

2: Australian fruit bats (*Pteropus* sp.)

A serum test for antibodies to Menangle virus may be diagnostic.

Nipah virus

An outbreak of encephalitis involving more than 250 pig farmers occurred in northern Malaysia in 1999, with a 40% case-fatality rate.[8] At about the same time, an outbreak occurred in Singapore involving 11 abattoir workers who had fever with pneumonia or encephalitis; one died.[9] Both outbreaks were shown to be caused by Nipah virus (named after the town of first recognition in Malaysia). Ribavirin therapy was used in many patients without obvious therapeutic benefit.[8] More research is required to define the epidemiology of this virus, although pigs seem to be involved asymptomatically as intermediate hosts. Nipah virus infection has not yet been reported in Australia.

Diagnosis: Nipah virus infection should be suspected in patients presenting with a flu-like illness, pneumonia or encephalitis and a history of contact with pigs in Malaysia or Singapore (Box 1). A serum test for Nipah virus antibodies may be diagnostic.

Australian bat lyssavirus

Infection with Australian bat lyssavirus (ABL) has been identified in two people. In 1996, a 39-year-old woman presented with weakness of the arm and subsequent progressive neurological deterioration with bulbar palsy.[10] She had been exposed to a number of animals, including bats. Her condition deteriorated, and she died on Day 21 of the

3: Post-exposure treatment for rabies and Australian bat lyssavirus in non-immune people*

Immediate local treatment (Day 0)

Wound cleansing with soap and water or antiseptic solution is vital; debridement if indicated.

Rabies vaccine

Immediate (Day 0) administration of 1.0 mL intramuscularly, followed by 1.0 mL on Days 3, 7, 14 and 28.

Rabies immunoglobulin

20 IU/kg of immunoglobulin (150 IU/mL) should be given no later than seven days after the first dose of rabies vaccine; as much as possible should be infiltrated around the wound site, with the remainder given intramuscularly.

*In people who have received pre-exposure prophylaxis, a modified post-exposure rabies vaccine regimen is recommended (ie, doses at Days 0 and 3). Rabies immunoglobulin is not recommended.

illness.[10] In 1998, a 37-year-old woman died of a rabies-like illness, 27 months after being bitten by an Australian flying fox (fruit bat).[11]

Four species of Australian flying foxes and one species of insectivorous bat have been shown to be infected with ABL.[12] Infected bats were distributed from Darwin to Melbourne. The proportion of bats in the wild that are infected is not known.

ABL is closely related genetically to rabies virus. Both the clinical manifestations and pathological changes of ABL infection in the human cases were very similar to those of rabies, with meningoencephalomyelitis and neuronal intracytoplasmic inclusions. Rabies vaccine and immunoglobulin offer significant protection against ABL.

Diagnosis: ABL infection should be suspected in patients who present with a progressive neurological condition and history of exposure to bats (Box 1). The diagnosis is made by polymerase chain reaction tests for ABL in cerebrospinal fluid or serum antibody tests. Examination of bat brain tissue can also be helpful but is rarely possible.

Management and prevention: Once the disease develops, there is no specific treatment. Post-exposure prophylaxis should be given after a bite, scratch or significant salivary exposure from a bat in Australia (Boxes 2 and 4). Prophylaxis is not indicated after exposure to bat urine or faeces. As long incubation periods (over a year) have been anecdotally described for lyssavirus infection, there is no cut-off period of infectivity after exposure. However, it is suggested that rabies immunoglobulin can be omitted if exposure occurred more than a year earlier.[13]

Pre-exposure prophylaxis with three doses of rabies vaccine, at Days 0, 7 and 28, is recommended for expatriates and travellers spending more than one month in rural parts of endemic areas (advice on high-risk countries is found on the World Health Organization website <www.who.int/>, and on rabies-free countries in the *Australian immunisation handbook*[13]). In Australia, pre-exposure prophylaxis is recommended for people at risk of bites or scratches from bats (eg, bat handlers, veterinarians, wildlife officers and others who are liable to come into direct contact with bats).[13]

Murray Valley encephalitis and Kunjin viruses

Murray Valley encephalitis (MVE) virus and the closely related Kunjin virus are flaviviruses that cause encephalitis, although Kunjin virus more commonly produces a non-encephalitic illness with polyarthralgia. MVE virus is endemic in avian species and is found in humans in northern Western Australia, the Northern Territory and Queensland.[14] The last MVE epidemic occurred in 1974, with the Murray Valley region as epicentre.[15] Kunjin virus occurs over a much wider area, including most of tropical Australia.

There is some evidence that infection with these viruses is increasing in incidence. Nine cases of encephalitis caused by MVE or Kunjin virus and five non-encephalitic cases were identified in Western Australia between March and July, 2000.[16] Recently, seroconversion in sentinel chicken flocks was documented in western NSW for the first time since serological testing began over 20 years ago (Dr Dominic Dwyer, Institute of Clinical Pathology and Medical Research, Westmead Hospital, NSW, personal communication). In northern Australia, cases occur predominantly between February and July, corresponding to the end of the monsoon season, when the mosquito vector (*Culex annulirostris*) proliferates in flooded environments.

Clinical features: Although seroprevalence in enzootic areas ranges from 39% to 46%,[17] clinical illness is rare. The clinical and epidemiological features of MVE in the Northern Territory, where the virus is endemic, were described for 16 of 18 identified cases between 1987 to 1996. Most cases were in children. Fever was universal, and some cases had a variable prodrome, which included diarrhoea, rash and cough. Seizures were common in children, while adults more commonly presented with headache, dysphasia, memory impairment, confusion and tremor. Several distinct clinical patterns were noted, including relentless progression

4: Case history — prophylaxis against Australian bat lyssavirus

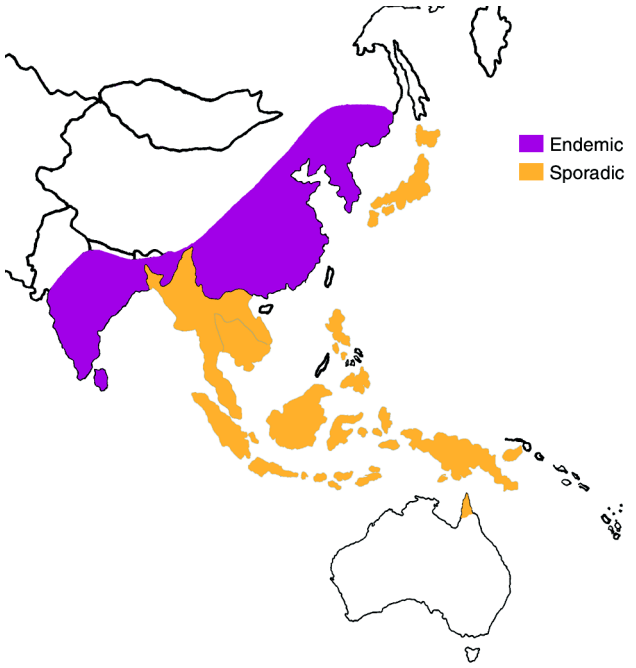
Presentation: A 35-year-old woman was bitten and scratched on her arm by a bat that she accidentally disturbed while walking near her home outside Cairns. She presented to the emergency department of her local hospital.

Management: Her wounds were cleaned and debrided. Rabies immunoglobulin was administered (600 IU [4 mL] instilled into the wounds, and another 600 IU [4mL] intramuscularly). She was also given the first dose of a course of human diploid cell rabies vaccine (1 mL of vaccine given intramuscularly) the same night. The following day, she had headache and local pain. Further vaccine doses were given on Days 3, 7, 14 and 28.

Outcome: The patient's wounds healed with minimal scarring. At follow-up after 18 months, she remained well.

- *Rabies vaccine and immunoglobulin offer protection against Australian bat lyssavirus.*
- *A bat scratch or bite in Australia is a strong indication for immediate wound cleaning and medical attention for possible debridement, along with rabies vaccine and immunoglobulin.*
- *The general public should avoid all contact with bats, especially bats that appear unwell.*

5: Distribution of Japanese encephalitis, 1970–1998



South-East Asia and Australia, showing areas where Japanese encephalitis is endemic and sporadic.
(Adapted from Centers for Disease Control website <www.cdc.gov/ncidod/dvbid/jencephalitis/map.htm> and <www.cdc.gov/travel/jenceph.htm>)

6: Case history — Japanese encephalitis

Presentation: A 65-year-old man presented with a three-day history of fever, rigors, headache and progressive confusion. He had recently returned on holiday from north Vietnam, where he had lived for several years.

Examination: He was disoriented, could not remember where he lived, had difficulty recognising his children and was incontinent of urine on several occasions. On examination, he had myoclonus of his upper limbs, with hypertonicity and hyperreflexia of all limbs, and extensor plantar responses. The rest of his physical examination gave normal results. Over the following 24 hours, he developed tonic–clonic seizures and choreoathetotic and lip-smacking movements.

Investigations: Computed tomography and magnetic resonance imaging of the head showed no abnormalities. Cerebrospinal fluid (CSF) was clear, with raised concentrations of mononuclear cells (100 x 10^6/L; reference range [RR], < 5 x 10^6/L), and protein (1.2 g/L; RR, 0.15–0.45 g/L). Japanese encephalitis was diagnosed on the basis of enzyme immunoassay IgM and IgG capture assays of serum and CSF.

Management and course: The patient was treated with intravenous fluids, anticonvulsants and empirical aciclovir. Over the following week, he had progressive neurological deterioration culminating in loss of consciousness and death. No autopsy was performed.

The possibility of Japanese encephalitis was suggested by:

- *a prodromal febrile illness;*
- *rapidly progressive encephalitis;*
- *residence in, or travel to, an endemic area; and*
- *extrapyramidal features.*

to death, a poliomyelitis-like illness, cranial nerve or brainstem involvement with tremor, and a non-specific encephalitic illness. Mortality has been estimated at about 20%, with residual neurological impairment in about half the survivors.[18]

Kunjin virus infection presents with an acute febrile illness and polyarthralgia. The major differential diagnosis is infection with Ross River or Barmah Forest virus. Encephalitis occurs rarely.

Diagnosis: In both MVE and encephalitic forms of Kunjin virus infection, the cerebrospinal fluid shows a modest rise in white blood cell concentration, with a variable proportion of mononuclear cells. Results of computed tomography and magnetic resonance imaging are largely unremarkable, while electroencephalography shows abnormalities in most cases, with generalised rather than focal features. Diagnosis is based on serum antibody testing to MVE or Kunjin virus.

Management and prevention: No specific therapy exists. Prevention relies on avoiding mosquito bites, including use of repellents containing *N*,*N*-diethyl-*m*-toluamide (DEET), especially in the two hours after dusk, which is the preferred feeding time for *C. annulirostris*.

Japanese encephalitis virus

Japanese encephalitis (JE) virus is another flavivirus that is considered rare in Australia. However, in 1995, JE was documented in the Torres Strait Islands, with three cases, two of which were fatal.[19] Seroepidemiological studies revealed relatively widespread infection in humans and pigs on at least nine islands. Subsequently, in 1998, a human case was recognised in mainland Australia, in a fisherman from the Mitchell River on Cape York.[20]

The global importance of JE is significant, with about 50 000 cases and 15 000 deaths a year worldwide.[21] It occurs across eastern and southern Asia and the Pacific rim (Box 5). It is transmitted between animals by *Culex* mosquitoes, with an enzootic cycle involving wild and domestic birds and animals, particularly pigs. Humans are infected as accidental hosts, and, as human viraemia is usually brief and of low concentration, rarely transmit the virus. The ratio of symptomatic to asymptomatic infection is estimated to be between 1:25 and 1:1000.[22] Two epidemiological patterns are recognised:[23] epidemics occur during the summer in northern areas (eg, northern Vietnam, northern Thailand, Korea, Japan, Taiwan, China, Nepal and northern India), whereas the disease tends to be endemic throughout the year in southern areas (southern Vietnam, southern Thailand, Indonesia, Malaysia, the Philippines, Sri Lanka and southern India).

Clinical features: JE has a short prodrome which may include coryza, diarrhoea, and rigors.[21] Headache, vomiting, obtundation and seizures may ensue, with some individuals presenting with personality change or abnormal behaviour.

Evidence-based recommendations

- Rabies vaccine and immunoglobulin offer protection against infection with Australian bat lyssavirus and should be given after a bite or scratch from a bat in Australia[13] (E4).
- Vaccine against Japanese encephalitis should be recommended for people who intend to live in an endemic area for over 30 days[13] (E4).

Seizures are common, particularly in children, and extrapyramidal features, such as tremor, hypertonia, cogwheel rigidity, choreoathetosis, opsoclonus, myoclonus and lip smacking, are suggestive of JE.[21] Upper motor neurone facial nerve palsies and opisthotonos or a clinical syndrome of acute flaccid paralysis may occur.[24] Overall mortality is about 30%, with residual neurological damage in about half the survivors.

Diagnosis: Diagnosis is usually serological, with enzyme immunoassay IgM and IgG capture assays useful for testing serum and cerebrospinal fluid (case history, Box 6).

Management and prevention: No specific therapeutic agent has proven beneficial, but there is early suggestion of improvement with interferon-α.

A formalin-inactivated vaccine is available for prevention and is recommended for:

- residents of endemic areas;
- laboratory workers potentially exposed to the virus; and
- travellers spending 30 days or longer in endemic areas, particularly if they intend to spend a lot of time outdoors in rural areas during the wet season.[13]

The vaccine is administered in a series of three doses, at 0, 7 and 30 days, with a booster recommended at one year. Tenderness, redness and swelling occur in up to 20% of recipients, and fever, headache, malaise and chills in about 10%. The combination of itching, urticaria, and occasionally angio-oedema of the face, which can be severe, has been recognised since 1989, with an incidence estimated at 2–10 per 1000 vaccine doses, and higher in those with a history of urticaria.

Conclusion

Infection with these seven viruses may present similarly — an acute febrile illness and encephalitis are common. ABL may present similarly to rabies. The epidemiological pattern is an important clue to diagnosis, and questions about patients' residence, travel and contacts are vital.

The spectrum of disease and geographical distribution of viral infections in Australia continue to evolve, providing an ongoing challenge for clinicians and researchers. The increased ease of travel has reduced the remoteness of Australasia. Recent experience has shown that new infectious diseases can emerge from both within and outside Australia, and further new viral infections can be expected in the future.

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