A review of the epidemiology and surveillance of viral zoonotic encephalitis and the impact on human health in Australia

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Abstract: Human encephalitis in Australia causes substantial mortality and morbidity, with frequent severe neurological sequelae and long-term cognitive impairment. This review discusses a number of highly pathogenic zoonotic viruses which have recently emerged in Australia, including Hendra virus and Australian bat lyssavirus which present with an encephalitic syndrome in humans. Encephalitis surveillance currently focuses on animals at sentinel sites and animal disease or definitive diagnosis of notifiable conditions that may present with encephalitis. This is inadequate for detecting newly emerged viral encephalatides. Hospital-based sentinel surveillance may aid in identifying increases in known pathogens or emergence of new pathogens that require a prompt public health response.

Human encephalitis causes substantial morbidity and mortality in Australia, frequently resulting in severe neurological sequelae and long-term cognitive impairment. While herpes simplex virus is the most commonly identified causative pathogen, the majority of adult encephalitis hospitalisations (70%, range 62–79%) have no specific pathogen identified and an increasing proportion of encephalitis deaths are due to 'unknown' causes – from 47% between 1979 and 1992 to 57% between 1993 and 2006. Recently emerged or resurging pathogens

in Australia, including Murray Valley encephalitis virus, West Nile virus (Kunjin clade), Japanese encephalitis virus, Hendra virus and Australian bat lyssavirus, cause a human encephalitis syndrome; consequently, encephalitis surveillance may be useful for signalling the emergence of novel infectious diseases, particularly viral zoonoses that may impact on human health.

Emerging infectious diseases pose a substantial threat in Australia and globally due to increased urbanisation, climate change, new farming practices, virus re-assortment and changes in human behaviours.^{3–5} The close interaction between animals and humans has provided opportunities for viruses to jump between species with 60% of known human infectious diseases and 75% of emerging infectious diseases being of animal origin.^{5,6} A One Health approach, which recognises the interdependence of human and animal health and the environment, is required to improve the surveillance of and response to Australian emerging infectious diseases.

Surveillance for viral zoonotic encephalitis

Surveillance for human viral zoonotic encephalitis in Australia depends on four different systems: notifications of specific infections to state and Commonwealth governments under public health legislation; serological surveillance of sentinel animals for flaviviruses; confirmatory testing of bats submitted after human contact for Australian bat lyssavirus; and mosquito surveillance for flaviviruses.

Although the encephalitis syndrome per se is not notifiable in Australia, specific diagnosis of a number of viral zoonotic encephalitides (Murray Valley encephalitis virus, West Nile virus (Kunjin clade), Japanese encephalitis virus, other flavivirus encephalitides and Australian bat lyssavirus) are notifiable by all states and territories, using common case definitions, to the Australian Government Department of Health and Ageing National Notifiable Diseases Surveillance System.⁷ Human Hendra virus infection is only notifiable in Queensland, although equine infections have occurred in both Queensland and northern New South Wales (NSW).8 Unfortunately, mandatory notification does not guarantee comprehensive reporting as it is based on detection of a causative organism. Therefore encephalitis due to rare or emerging pathogens may go unrecognised, which has led to proposals for systematic surveillance of the encephalitis syndrome.^{2,9}

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Zoonotic encephalitis viruses

Zoonotic encephalitis viruses fall into two groups, each with their own particular wildlife hosts, transmission mechanisms and ecologies. The first are the vectorborne and transmitted flaviviruses: Japanese encephalitis virus, Murray Valley encephalitis virus and West Nile virus (Kunjin clade). The second are the batborne viruses where bats act as the reservoir host: Hendra virus and Australian bat lyssavirus.

Vectorborne flaviviruses

The three flaviviruses Japanese encephalitis virus, Murray Valley encephalitis virus and West Nile virus (Kunjin clade) are closely related members of the Japanese encephalitis serological complex. Their maintenance hosts are ardeid waterbirds and their vectors are Culex spp. mosquitoes.

Japanese encephalitis virus (JEV)

JEV is the major cause of childhood viral encephalitis and associated disability in Asia. ^{10,11} Only 1:25–1:300 infections result in clinical disease ^{12,13} but 25% of clinical cases are fatal and 50% of affected humans experience neurological sequelae. Transmission cycles involve *Culex* spp. mosquitoes (especially Cx. tritaeniorhynchus), ardeid birds, such as black-crowned night herons (Nycticorax nycticorax), and pigs as vertebrate amplifying hosts.¹⁴ Humans become infected by a bite from an infected mosquito but they are incidental, dead-end hosts. It is worth noting that JEV also causes encephalitis in horses, and they too are incidental, dead-end hosts.

JEV emerged unexpectedly in the Torres Strait in 1995 (probably following importation from Papua New Guinea), causing three human cases of encephalitis in Badu, two of whom died. A further case occurred in Badu in 1998, as well as the first human JEV case on mainland Australia near the mouth of the Mitchell River, Cape York. 15 Virus activity has been detected in the Torres Strait in almost all years since 1995, and in Cape York on the Australian mainland in 1998 and 2004.

Sentinel pig herds were kept on various Torres Strait islands and locations in northern Cape York for serological surveillance but, as these sites were usually close to human habitation and pigs are major virus amplifiers, the sentinel pig program was discontinued except for a single site on Cape York. Sporadic opportunistic mosquito collections are made by Queensland Health for virus isolation. Future JEV activity surveillance may be incorporated in the National Arbovirus Monitoring Program of Animal Health Australia, as cattle are safe animals for surveillance. ¹⁶

A safe and effective inactivated, cell culture propagated JEV vaccine is available for those living or travelling in endemic areas, 17 and several newer vaccines with

potentially greater efficacy and safety are undergoing clinical trial.

Murray Valley encephalitis virus (MVEV)

Encephalitis outbreaks due to MVEV were first detected on Australia's east coast in the early 20th century, and then re-emerged as epidemics in the Murray-Darling River basin in 1951 and 1974. MVEV is now considered enzootic in the Kimberley and possibly the adjacent areas of the Northern Territory. The virus is maintained in a cycle primarily involving Cx. annulirostris and ardeid waterbirds, and variable activity occurs every year in these areas. 18 Virus activity outside these enzootic areas generally follows heavy rainfall and flooding within normally arid areas of northern and central Australia, as infected waterbirds migrate across the flooded areas. 19,20 This may explain the reappearance of MVEV encephalitis in central Australia and western NSW in 2000–2001.²¹ It now appears that low level MVEV activity may occur occasionally in NSW, and may have resulted in a locally acquired human infection in 2008.²² MVEV throughout Australia is predominantly genetically homogeneous, consistent with a single major enzootic source. 23,24

Clinical MVEV encephalitis cases are uncommon in Australia with an average of 2–3 cases each year since the late 1970s. The incubation period ranges from 1 day to 4 weeks, and most infections are either asymptomatic or the patient only develops a self-limiting febrile illness with or without headache. Encephalitis occurs in only 1:500–1:1000 infected individuals with a mortality rate of 20%; about half of all survivors have significant residual neurological deficits, with worse outcomes in the very young and elderly.

Infection risk depends on the degree of mosquito exposure during a period of MVEV activity. Generally, all residents and travellers are susceptible, with cases in all ages, except amongst Indigenous communities where there is regular virus activity, with infection more likely in young Indigenous children due to protective immunity in older children and adults. 25,26

Currently, there is neither a vaccine nor any specific antiviral therapy for MVEV. Sero-surveillance is carried out using sentinel chicken flocks in Western Australia, the Northern Territory, NSW and Victoria, 27 and by opportunistic mosquito sampling for virus isolation.

West Nile virus (Kunjin clade) (WNV-KUN)

WNV-KUN was first detected in northern Queensland in 1960 and is widely dispersed across tropical northern Queensland, the Northern Territory and Western Australia, being maintained in enzootic cycles similar to MVEV between Culex spp. mosquitoes and ardeid waterbirds. WNV-KUN activity is regularly detected in south-eastern Australia, but usually without recognised human cases.

WNV-KUN is believed to have caused 11% of encephalitis cases in the 1974 Murray Valley outbreak.²⁸ During the following three decades, three encephalitis cases caused by WNV-KUN were reported (all non-fatal), while 68 MVEV encephalitis cases were confirmed. The incubation period appears similar to MVEV infection but the encephalitic illness is more benign with complete or near complete recovery.²⁹

Currently, there is neither a vaccine nor any specific antiviral therapy for WNV-KUN infection. MVEV sentinel chicken flocks are also tested for WNV-KUN infection.

Batborne viruses Hendra virus (HeV)

HeV was first described in 1994 during an outbreak of severe respiratory disease amongst racehorses and humans in Brisbane. 30,31 A second outbreak occurred at the same time but was unrecognised for a further 13 months. A Mackay farmer, infected while assisting with an equine autopsy, suffered mild meningitis and recovered, but 13 months later relapsed with fatal encephalitis. 32 There have been 12 further outbreaks; 33,34 11 in Queensland and one near Murwillumbah in NSW. There have been seven confirmed human HeV infections, with four deaths. Flying foxes of the genus *Pteropus* are the reservoir host,³⁵ but all human infections to date have been epidemiologically linked to horses, the major spill-over host. Horses are believed to become infected after grazing on pastures contaminated with bat urine, birthing fluids or spats (fibrous plant material remaining after mastication by bats). Humans become infected by the virus entering through cuts or grazes after exposure to equine bodily fluids, but humans are dead-end hosts and there is no evidence of human-to-human infection.

HeV is one of two members of the genus Henipavirus, the other being Nipah virus, the cause of fatal encephalitis affecting pigs and humans in Malaysia in 1999.³³ Nipah virus, like HeV, is a virus of Pteropid bats, but with pigs as the spill-over hosts. Very recent studies have indicated that pigs could also potentially act as spill-over hosts for HeV.³⁶ Human-to-human transmission with Nipah virus resulting in cases of clinical disease has been documented, with some of the cases probably being due to ingestion of bat-contaminated palm juice, whereas others may be due to other routes of infection.^{33,37} Human-to-human transmission of HeV has not been reported. Over the past decade, sero-epidemiological studies have shown that HeV and Nipah virus, or closely related viruses, are widely distributed over the range of Pteropid bats. 33,34,38

There is no active surveillance for HeV in Australia, in either humans or animals, and spill-over infections are uncovered when there is clinical evidence of infection in horses. Veterinarians and others likely to be exposed to

infected bats or horses should take appropriate personal protection measures. It is not practical to prevent all interactions between flying foxes and horses, and no vaccines are available, although post-exposure prophylaxis is currently being investigated and shows promise.

Australian bat lyssavirus (ABLV)

ABLV was first isolated in 1996 in NSW from the brain of a black flying fox (Pteropus alecto) which was behaving strangely.³⁹ It is closely related to rabies virus, ⁴⁰ but is distinguishable genetically and thus classified as lyssavirus serotype 1, genotype 7. ^{34,41} ABLV has been found in all four species of Australian flying fox (genus *Pteropus*) throughout their geographic range, and in at least one species of insectivorous microbat, the yellow-bellied sheath-tailed bat (Saccolaimus flaviventris), in Queensland. 34,42 Serological evidence of infection has also been found in a number of other genera, and the ecology and diversity of this virus is yet to be fully understood. Less than 1% of flying foxes in the wild are infected with ABLV, but this increases to as many as 15% of sick or injured flying foxes and about 3% of yellow-bellied sheath-tailed bats. 43 Limited studies to infect terrestrial wildlife have failed, although experimental exposure of domestic cats and dogs can produce mild signs and seroconversion but with no evidence of viral persistence.⁴⁴

ABLV has caused two human deaths in Australia. The first was a bat carer who had been scratched by a yellow-bellied sheath-tailed bat 5 weeks earlier 45,46 and the second, a woman bitten 2 years prior by a flying fox.⁴⁷ In both patients the disease was similar to classical rabies, with non-suppurative encephalitis accompanied by hypersalivation, aggression and agitation. Currently available cellculture derived vaccines appear efficacious in protecting against ABLV infection in exposed humans. 48,49 Bat carers and others at risk of ABLV exposure are offered preexposure vaccination and those exposed are given standard preparations of vaccine and the rabies immune globulin. 17,43 It is important that, wherever possible, the bat responsible for the potential exposure is sent for testing.

Discussion

Globally, many of the recently emerged Australian zoonotic viruses have presented with an encephalitic syndrome in humans, 6,50 including the highly pathogenic HeV and ABLV. 51,52 Other zoonotic viral encephalitides have appeared in new Australian regions, including JEV, MVEV and WNV-KUN.53 Current Australian surveillance, which focuses on seroconversion in sentinel animals in a limited number of sentinel sites (pigs for JEV and chickens for MVEV and WNV-KUN), definitive diagnosis in reservoir hosts (culled bats that have had potential transmission contact with humans for ABLV or horses for HeV), or definitive diagnosis in humans, has the potential to miss encephalitis cases caused by notifiable conditions, and is particularly inadequate for detecting newly emerged viral encephalitides.2 A recent study examining the diagnostic assessment of encephalitis in three Regional Referral Hospitals in NSW determined that only 15% of encephalitis patients were tested for flaviviruses and 0-7% were tested for specific zoonotic encephalitis viruses.⁵⁴

Conclusion

Given that viral encephalitis generally causes relatively serious illness resulting in hospitalisation, 55 the utility of hospital sentinel surveillance of adults or paediatric medicine inpatients deserves prompt investigation, as does the use of a standardised diagnostic and testing algorithm which includes viral zoonotic encephalitides. Improvements in encephalitis surveillance at the animal, human, environment interface would aid in earlier identification of known pathogens and in alerting authorities to the emergence of new pathogens or outbreaks that may require public health investigation and action.

Editor's note

During 2011 there has been a resurgence in MVE across Australian states with 14 confirmed cases notified in the National Notifiable Diseases Surveillance System, including one in NSW, and two deaths. Canadian authorities also confirmed the additional death of a Canadian tourist who was infected in the Northern Territory. 56-59

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