Japanese encephalitis virus in Australia: an ecological and epidemiological enigma

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Japanese encephalitis virus (JEV), a mosquito-borne flavivirus, is the most important vaccine-preventable viral cause of human encephalitis in Asia.[1] Five distinct genotypes of JEV are recognised (I–V). It is closely related to two Australian flaviviruses, Murray Valley encephalitis virus (MVEV) and the Kunjin strain of West Nile virus (WNV_{KUN}).

One human infection with JEV genotype IV was reported in the Northern Territory in February 2021.[2] A year later, the same genotype caused a widespread outbreak of disease among pigs in more than 80 commercial piggeries in four states in eastern Australia, and was responsible for 44 cases of clinical human disease. The unexpected emergence of JEV genotype IV has raised questions about the origin, ecology, and incidence of JEV in Australia.[1] Prior to the 2021–22 outbreak, the neurovirulence of JEV genotype IV was relatively unknown; infections had only been reported in Indonesia, including an Australian tourist who died in Bali in 2019.[3] In outbreaks caused by genotype I and III viruses, the two most frequent JEV genotypes, only 0.1–1.0% of infections result in encephalitis,[4] depending on virus virulence, vector competence, and the virus load injected by the mosquito, as well as on host factors, such as age, genetic determinants, general health, and previous exposure to related viruses.[5] As 44 confirmed and probable JEV infections in humans were reported in eastern Australia during the 2022 outbreak, 4400 to 44 000 subclinical infections could be predicted in the broader community at risk. Data on the incidence and risks of symptomatic JEV infection in immunologically naïve populations are limited, but the risk of encephalitis is greatest for young children and older people.[6,7]

Two studies reported in this issue of the *MJA*[8,9] investigated important factors that influence the spread and risk of JEV infection in Australia: the number of subclinical infections and the possible risk factors for exposure to the virus. The studies were undertaken in towns and areas of New South Wales and Victoria at particular risk of JEV outbreaks, 4–6 months after the initial recognition of the 2022 outbreak. The authors found serological evidence of past exposure to JEV in a small but significant proportion of people tested, all of whom were IgG-positive and IgM-negative. As JEV IgM typically persists for at least a month after infection, and often longer,[10,11] the total absence of IgM was unexpected, and needs further consideration in future studies. The incidence of JEV IgG-seropositivity in the selected NSW towns was 8.7% (80 of 917 participants, including five of 42 Aboriginal and Torres Strait Islander participants [12%]), whereas in northern Victoria the incidence was 3.3% (27 of 813 participants). Both studies found that seropositivity increased with age. The different seropositivity levels in NSW and Victoria may reflect differences in geography, or possibly differences in testing methods or participant selection. However, despite the two studies surveying a range of factors that could influence exposure to JEV, neither identified any specific risk factors, apart from the suggestion that exposure to feral pigs might have been a factor in Victoria.

Both studies had several limitations, particularly the lack of age-matched controls from urban or lower risk environments, and the opportunistic nature of participant recruitment that resulted in higher numbers of older and female participants.

The Victorian study also estimated the seroprevalence of MVEV and WNV_{KUN} when the residual JEV serosurvey blood sample volume was adequate; the authors report estimates of 3.0% and 3.3% respectively.[9] These values were similar to those of an opportunistic seroprevalence study in 2011 following a large outbreak of MVEV activity in eastern Australia, with widespread seroconversion in sentinel chicken flocks in northern Victoria,[12] a case of Murray Valley encephalitis in NSW,[13] and the detection of MVEV in horses in Victoria.[14] It was therefore unsurprising that some MVEV seroconversions in the study by Marsland and colleagues[9] were in people born after the 1974 outbreak. Further, a large outbreak of equine encephalitis caused by WNV_{KUN} was reported in inland Victoria[14] and NSW[15] in 2011, and a spillover of subclinical human infections could have contributed to antibody seropositivity in Victoria.

Accurate and reliable serological studies in both humans and animals are essential if we are to understand the epidemiology, ecology, and impact of JEV in Australia. Unfortunately, flavivirus serological studies are challenging because of the broad cross-reactivity of both IgG and IgM antibodies against related flaviviruses in most serological tests.[16] This is one of the major barriers to accurate JEV seroprevalence estimates in areas where other flaviviruses are found, including NSW and Victoria, or where any flavivirus vaccine has been used. The studies reported in this issue of the *MJA*[8,9] used epidemiological characteristics and, in the Victorian study, testing for two other major flaviviruses, to reduce this risk, but would not have eliminated it completely. Neutralisation assays are the gold standard for species-specific flavivirus antibody detection, but they are technically difficult, expensive, and slow. Both of the reported studies instead used specific epitope-blocking assays, DEB-ELISAs, which are better suited for use in serosurveys. These assays are developed and employed in the testing laboratory, and studies such as those described here build our confidence in these tests.

To further complicate interpretation, flaviviruses exhibit an immune recall phenomenon (original antigenic sin), whereby people or animals previously infected with or vaccinated against one flavivirus will, when infected with or vaccinated against a different flavivirus, express an early antibody response to the earlier flavivirus. Only later is there a detectable response to the more recent infecting virus. This has been described for a wide range of flavivirus combinations, including with JEV.[17,18]

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For these reasons, there is a clear need to continue to explore and evaluate specific, cost-effective, widely available species-specific flavivirus antibody tests.

Importantly, the findings of the two studies, taken together with the wide geographic spread of human infections and infected piggeries over a relatively short period, have shown that the 2022 JEV outbreak was more extensive than first thought, with important implications for vaccine recommendations and future surveillance activities.

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