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Japanese Encephalitis Virus Emergence in Australia: Public Health Importance and Implications for Future Surveillance

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Abstract

Japanese encephalitis virus (JEV) continues to cause significant numbers of human infections and fatalities despite the availability of efficacious vaccines. It is regarded as an emerging mosquito-borne pathogen with the potential of introduction into many countries. In 2022, JEV was detected in Australia on a hitherto unprecedented scale, with local transmission by indigenous mosquitoes to amplifying swine hosts and to humans. In this study, we review this recent disease activity, propose possible routes of virus movement, ecological drivers of activity, and consider possible future transmission scenarios. Measures to enhance current surveillance systems and potential strategies for health authorities to minimize future risks are discussed.

Keywords: Japanese encephalitis, virus ecology, clinical importance, surveillance, outbreak, Australia

Introduction

E NCEPHALITIC DISEASE CAUSED by infection with mosquito-borne flaviviruses has been an enduring public health problem in Australia. Murray Valley encephalitis virus (MVEV) and West Nile virus (Kunjin strain [WNV_{KUN}]) are enzootic in northern Australia where they are responsible for sporadic human cases (Mackenzie et al, 1994). Epidemic transmission of these viruses can occasionally occur in southern regions with widespread activity occurring as recently as 2011 (Frost et al, 2012; Selvey et al, 2014). Outbreaks in these southern latitudes are usually associated with heavy rainfall and flooding resulting from *La niña* dominated weather patterns (Whelan and Frederiksen, 2017). Other than MVEV and WNV_{KUN}, there have been no other mosquito-borne encephalitides with known enzootic transmission on the Australian mainland, until 2021.

Outbreaks of human viral encephalitis and reproductive disease in farmed pigs in the summer and autumn of 2021–2022 in southeastern Australia revealed unexpected wide-

spread transmission of Japanese encephalitis virus (JEV) in the region (van den Hurk et al, 2022). In this study, we review this recent disease activity, propose possible routes of virus movement, ecological drivers of activity, and consider possible future transmission scenarios. We also suggest measures to enhance current surveillance systems and broadly discuss strategies of health authorities to minimize future risk.

JEV Classification, Virus Ecology, and Clinical Importance

A member of the *Flavivirus* genus, JEV is a positive strand RNA virus genetically and antigenically related to other mosquito-borne encephalitides, such as WNV, MVEV, and St Louis encephalitis virus. First isolated from the brain of a fatal case in 1935 (Mitamura et al, 1936), JEV infection in humans occurs in eastern, southeastern, and south Asia, eastern Siberia, the Indian subcontinent, and the Western Pacific (including Papua New Guinea). Formerly common in Japan and China, rates of infection are declining in those

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countries predominately due to specific vaccination programs and changes in agricultural practices (Kuwata et al, 2020). Estimates suggest that there are 68,000 cases of clinical disease with an estimated 15,000 deaths attributed to JEV infection annually in the world (Campbell et al, 2011).

Clinical disease leading to Japanese encephalitis (JE) occurs in ~ 1 in 25 to 1 in 300 JEV infections. In patients developing a clinically evident infection, disease can manifest as a self-limiting febrile illness through to severe and potentially fatal acute encephalitis syndrome (Turtle and Solomon, 2018). Case mortality estimates vary from 5% to 50%, whereas just >40% of survivors will have ongoing neurological sequelae. There are no specific antiviral treatments for JEV and vaccination with any of a number of effective vaccines is considered the best way to limit human disease (World Health Organization, 2015).

JEV is a zoonotic virus principally circulating in waterbirds and pigs through mosquito-borne transmission, with occasional spillover to humans, who are dead-end hosts (Walsh et al, 2022). The main vector species implicated in transmission belong to the *Culex* subgenus within the *Culex* genus, and are variously members of the Sitiens, Vishnui, and Gelidus subgroups. The virus has, however, been isolated from numerous species of mosquito in different genera, including *Aedes* spp., *Armigeres* spp., *Anopheles* spp., and *Mansonia* spp.

The relative importance of different species of mosquitoes as vectors varies in different geographic locations (Endy and Nisalak, 2002). In Asia, *Culex tritaeniorhynchus, Cx. vishnui. Cx. pseudovishnui, Cx. gelidus,* and *Cx. fuscocephala* have been specifically implicated. In the Western Pacific, *Culex annulirostris* is considered the primary vector of JEV. Infected vectors may play a key role in survival of the virus through winter conditions through hibernating infected mosquitoes, transovarial, and sexual transmission.

JEV in Australia

In Australia, JEV infection in humans has been infrequently reported, with some infections being acquired during travel to endemic countries (*e.g.*, Pyke et al, 2020). In 1995, the first outbreak of JEV in Australia occurred, and comprised three cases (two of which were fatal) in the Torres Strait, between the Australian mainland and Papua New Guinea (Hanna et al, 1996). A second outbreak occurred in the Torres Strait in 1998, and included a human case on the nearby Cape York Peninsula on the far northern part of the Australian mainland (Hanna et al, 1999).

A JEV vaccination program was implemented after the initial outbreak (Hanna et al, 1996) and vaccination is recommended for residents and seasonal visitors of the outer Torres Strait islands (ATAGI, 2018). Implementation of sustained mosquito control was prohibitive due to the vast wetlands that serve as larval habitats for *Cx. annulirostris* and accessibility to the remote region in northern Australia where activity was occurring. Local maintenance and drainage work to eliminate larval habitats and relocation of domestic pigs likely helped to reduce the virus transmission risk proximal to community areas but did not eliminate risk entirely (van den Hurk et al, 2008).

This intermittent virus activity prompted fears of JEV establishment in northern Australia, similar to what eventually occurred after the introduction of WNV in North America (Kramer et al, 2019). Thus, arbovirus surveillance in the Torres Strait and northern mainland Australia was instigated, and included establishment of a sentinel pig program on four Torres Strait islands and on Cape York, enhanced mosquito sampling for virus detection during recognized incursions and deployment of remote mosquito trapping systems (Ritchie et al, 2007; Shield et al, 1996).

Surveillance of mosquitoes and pigs continued in various forms and with variable intensity until it was gradually phased out by 2011. A replacement mosquito-based virus surveillance system in the northern end of Cape York was implemented by the Northern Australian Quarantine Service and Queensland Health, and while detecting MVEV and WNV_{KUN}, it has not detected JEV to date (van den Hurk et al, 2019). Therefore, despite recognized incursions in 1998 and 2004 (Hanna et al, 1999; van den Hurk et al, 2006), and ongoing speculation about potential introduction to mainland Australia (Russell and Kay, 2004), lack of definitive evidence suggests that establishment of JEV on the mainland never eventuated (van den Hurk et al, 2009).

The 2021–2022 JEV Outbreak: Widespread Emergence

JEV did not appear again until early 2021, when a fatal human case was reported from the Tiwi Islands of the Northern Territory (World Health Organization, 2022). In late February 2022, JEV was confirmed as the cause of fetal and neonatal pig deaths in commercial pig farms in southeastern Australia (World Organisation for Animal Health, 2022). As of May 10, 2022, a total of 73 piggeries across four states have been affected and the virus has been detected in wild pigs in the Northern Territory (World Health Organization, 2022). In March 2022, the first human JE cases were reported, and by August 17th 2022, there have been a cumulative 40 cases (confirmed and probable), from four states and one territory (Queensland 5 cases, New South Wales 13, South Australia 9, Victoria 12, and Northern Territory 1 case), with five deaths (Australian Government, 2022). We contend that such geographically disseminated activity in an area hitherto free of JEV represents a regional emergence of the pathogen in Australia.

Sequence analysis indicates that both the Tiwi Islands and southeastern Australian viruses belong to JEV Genotype 4 (CSIRO, 2022a), which contrasts with the dominance of Genotypes 1 and 2 associated with virus activity between 1995 and 2005. Subsequent enhanced surveillance of mosquito collections and detections of the virus in archived samples from early in the 2021-2022 summer, together with widespread human cases and piggery detections, have led the Australian government to declare the JEV situation a Communicable Disease Incident of National Significance (Australian Government, 2022). Initial responses to the emergence of JEV in southeastern Australia have included enhanced surveillance to delimit the geographical and temporal distribution of the virus, vaccination of at-risk groups, targeted mosquito control, and the development of industryspecific vector management guidelines.

Origins of the Current JEV Outbreak

The presence of a single genotype associated with the 2021– 2022 activity is indicative of a common geographical source, such as the southeastern Indonesian archipelago or the New Guinea landmass. However, the mode of introduction and subsequent dissemination into southeastern Australia has yet to be determined with certainty. One plausible explanation for the introduction and dissemination of JEV in Australia is that the above average rainfall associated with La niña weather patterns in central and eastern Australia that commenced in 2020 increased migratory bird movement between PNG (where JEV is enzootic) and northern Australia.

Thirty-seven species of migratory shorebirds fly from numerous countries to and within Australia along several flyways stretching from Asia to New Zealand in the South and to Alaska in the North (Birdlife Australia, 2014). Alternatively, atmospheric transport of infected mosquitoes could have introduced the virus, as was suggested previously for incursions in 1995 and 1998 (Ritchie and Rochester, 2001). Given the recent detection of the predominant Asian JEV vector Cx. tritaeniorhynchus in Darwin in 2020, and its genetic similarity of that to nearby forms in Timor-Leste, one explanation may be an introduction through infected mosquitoes. Together with the circulation of JEV in Timor Leste and Indonesia, this remains a plausible entry pathway for further scrutiny.

Once introduced, widespread rainfall also facilitated rapid dissemination of JEV within and between waterbird communities, potentially with the involvement of wild pigs, whose populations in Australia number in the millions. Local epizootic transmission was enabled by an abundance of floodwater mosquitoes, particularly Cx. annulirostris (New South Wales Government, 2022).

Alternatively, JEV may have been circulating undetected in cryptic enzootic foci in Australia. Although this concept cannot be discounted entirely, this is a less likely scenario than the recent introduction of the virus. Given the regular detection of other encephalitic flaviviruses (MVEV and WNV_{KUN}) in sentinel chicken flocks, livestock, and mosquitoes (Frost et al, 2012; Selvey et al, 2014), and enzootic activity of these viruses (including human cases) in northern Australia, it is more likely that JEV would have revealed itself before now if present. Furthermore, viruses that originated from incursions between 1995 and 2005 are not the source of enzootic foci for the current outbreaks because they constitute different JEV genotypes to those that circulated in 2021–2022.

Possible Scenarios for Future JEV Activity in Australia

The widespread distribution of virus activity in 2022 and evidence of the virus in mosquito populations and wild pig populations suggest that the virus has already become established in natural transmission cycles in Australia. Future activity of JEV will be highly dependent on the climatic conditions associated with flood and drought cycles that influence abundance of mosquito and reservoir host populations, as has been speculated for other endemic arboviruses (Russell, 2009). Given some of the ecological similarity in transmission cycles, including utilizing the same mosquito vectors and waterbirds as vertebrate hosts, it is plausible that JEV could follow a similar zoonotic pattern as MVEV and WNV_{KUN} but with the expectation that feral pig populations may play a relatively greater role in persistence of enzootic cycles.

expected with occasional epizootic activity in eastern and southern Australia in (or following) years of above average rainfall. In this scenario, notification of human cases, detections in piggeries, and in mosquito collections in eastern and southern Australia would be expected to decline should this region experience less rainfall, as is typical in neutral or El Niño southern oscillation (ENSO) weather conditions (Australian Bureau of Meteorology, 2022). There remains much speculation regarding the role of a changing climate and resulting influences over ENSO and the implications for rainfall conditions in Australia (Delage and Power, 2020). With this uncertainty, it is unlikely that future JEV risk can be confidently forecast based on climate models alone.

Current predictions indicate a possible continuation of La niña ENSO conditions into the summer of 2022-2023, which typically brings above average rainfall to eastern Australia (Australian Bureau of Meteorology, 2022). Irrespective of rainfall over the remainder of 2022, given the extensive flooding of many regions in eastern Australia, conditions may remain conducive for mosquitoes and waterbirds during spring. Alternatively, low natural immunity in vertebrate populations and an abundant source of farmed and wild pigs may allow JEV activity to persist in southern regions if the virus can utilize a mechanism of overwintering (van den Hurk et al, 2009).

The presence and abundance of feral pigs in all Australian states, especially in wetlands and in river systems (Australian Government Department of Sustainability, Environment, Water, Population and Communities) may make eradication of JEV especially difficult. It is estimated that there are several million feral pigs in Australia with densities ranging from 1 to 20 per square km in wetland areas (Australian Government Department of Sustainability, Environment, Water, Population and Communities, 2011; Hone, 2020).

Effective control of feral pigs (that may range over an area of 43 square km and have a reproductive rate that can increase a population by 86% per annum) is notoriously difficult. Gaps remain in our understanding of blood feeding preferences of mosquitoes on feral pigs in southern regions of Australia. Studies in northern Australia suggest other native animals, such as macropods, may dilute the importance of feral pigs in arbovirus transmission cycles (van den Hurk et al, 2003), but there is still much to learn before reliable risk assessments can be made.

A potentially significant concern is the effect that JEV may have on indigenous species of vertebrates in Australia. As seen with WNV after its introduction into North America, it is hard to predict the consequences when a virus is introduced into a new area where all species are naive, and some species may be highly susceptible. In the United States, WNV has been detected in many avian species (https://www.cdc.gov/westnile/ dead-birds) and a relatively limited study concluded that 23 of 49 species studied had been negatively impacted by WNV, with perhaps 37 million of one species, the red-eyed vireo (Vireo olivaceus) having been killed by WNV (George et al, 2015). A strategy to protect vulnerable especially endangered species may need to be considered, perhaps with vaccination as tested for California condors (Gymnogyps californianus) in the United States (Chang et al, 2007). Unfortunately, the time needed for the development of such an approach, may be running out, if the spread of JEV cannot be controlled.

There is much that authorities in Australia can learn from JEV transmission risk from the experiences within regions of historical JE activity as well as the research and management initiatives in northern regions of the country since the 1990s. However, there remain many significant gaps in our understanding of JEV transmission cycles in temperate regions, specifically regarding not only vector species and their biology but also their interactions with local waterbirds and feral pigs and other determinants of transmission risk.

Although a focus remains on the role of *Cx. annulirostris* as the primary vector of JEV, consideration also needs to be given to other mosquito species and their contribution to enzootic and epidemic transmission within specific regions. Mosquitoes such as *Cx. gelidus* and *Cx. tritaeniorhynchus* are present in Australia (Lessard et al, 2021; Muller et al, 2001; Williams et al, 2005) and within their known geographic range will need to be considered in vector surveillance and management programs.

However, consideration also must be given to other mosquitoes whose vector competence has not yet been investigated or determined (van den Hurk et al, 2022). There is a suite of mosquito species known to be effective vectors of other endemic flaviviruses or known to feed on waterbirds and, or at least potentially, pigs (Gyawali et al, 2019; Jansen et al, 2009; Ong et al, 2021; Russell, 1998; Stephenson et al, 2019). The role of these other mosquitoes in transmission cycles will be important to consider where targeted surveillance programs are implemented or where high-risk locations require consideration of vector management programs (*e.g.*, piggeries).

Notwithstanding the direct risk to wildlife health, the role of waterbirds in the local transmission cycles of JEV requires investigation. There is a paucity of information available on specific waterbird species and their relative importance in JEV transmission. In addition to information on abundance and distribution related to prevailing climatic and environmental conditions, their response to JEV infection and resulting viremia will need to be considered in risk assessments. Concomitant with this knowledge gap is a need to understand the role of feral pigs in these enzootic cycles and risks of spillover to human populations.

Depending on what arbovirus surveillance reveals about JEV in Australia, attention will need to turn to the implementation of long-term disease management strategies. Thankfully, vaccines and mosquito control are two immediately available technologies. Lessons can also be learnt from successful JEV control efforts in other countries where JE incidence has declined sharply since 2008, such as in China (Chen et al, 2021) and Japan (Arai et al, 2008).

Arbovirus Surveillance in Australia: An Opportunity for Revision

Our future scenarios of JEV activity are merely conjecture, and only a consistently applied sensitive surveillance system with a unified and linked data and reporting structure can provide the intelligence that can guide decision-making with regard to limiting disease incidence. Currently, surveillance of medically important arboviruses in Australia is primarily organized and funded by state health departments, which understandably have variable budgets and priorities as determined by climate, environmental characteristics, mosquito diversity, and endemic arbovirus activity. These programs mainly target endemic viruses, including MVEV and WNV_{KUN}, as well as Ross River and Barmah Forest viruses through monitoring human disease incidence, virus detection in mosquitoes or sentinel chickens (in the case of the encephalitogenic flaviviruses) or a combination of these strategies (van den Hurk et al, 2012).

There is also the National Arbovirus Monitoring Program supported by Animal Health Australia focusing on livestock diseases, particularly bluetongue, Akabane and bovine ephemeral fever viruses (Animal Health Australia, 2021), and the Commonwealth Scientific and Industrial Research Organisation (CSIRO) and state primary industries support this work with diagnostic services. The CSIRO's Australian Centre for Disease Preparedness has a broad remit for detecting disease in livestock and wildlife (CSIRO, 2022b).

Despite these programs, the geographically widespread JEV activity in early 2022 was not detected until almost simultaneous discoveries in piggeries and the subsequent diagnosis of human cases. There was no early detection, and human health and veterinary authorities at both the national and state level could only respond to the outbreak that was already well underway. The failure of these surveillance programs to provide an early warning of arbovirus activity may be due to a number of reasons.

Notwithstanding the lack of geographic coverage of mosquito and animal surveillance, the trend toward highly focused molecular testing of arboviruses may have left sufficient gaps for exotic viruses to escape detection. As such, the response had limited impact in terms of disease prevention in the short term. Clearly, the existing state- and nationalbased surveillance systems, characterized by different objectives and target viruses, variable methodologies, diverse funding arrangements, and no central reporting mechanism and data linkage, have not proven sufficient for detecting an unprecedented event such as the emergence of JEV.

To ensure Australia is better placed to manage further JEV activity in the coming 2022–2023 summer, and to detect future outbreaks, a significant revision of surveillance programs and data systems is required. Such a revised system should aspire to consistency of surveillance methods, a central repository of data, well-described data sharing and reporting methodology, and a unification of human and animal health reporting and decision-making. Indeed, a One Health approach, whereby animal and human disease surveillance systems, reporting and decision-making is interconnected, is vital.

An opportunity now exists to review existing arbovirus detection technology that has proven effective but is not yet widely deployed (Park et al, 2020; Ramirez et al, 2018), and to consider novel approaches that can be deployed at scale. In considering the nature of a new national surveillance system, attention should be given to deploying surveillance systems at locations that are going to provide epidemiologically relevant data that may be in remote locations, expanding existing wildlife and livestock disease surveillance programs to include JEV, and leveraging existing surveillance of blood-borne pathogens through transfusion services. A unified surveillance system needs to be underpinned by information derived from genotypic and phenotypic

characterization of the virus and its interaction with vectors and amplifying hosts. Thorough knowledge of the geographical and temporal transmission dynamics will inform targeted control strategies to reduce the risk of human and animal disease.

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