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TROPICAL, TRAVEL AND EMERGING INFECTIONS (LH CHEN AND F NORMAN, SECTION EDITORS)

Japanese Encephalitis: Emergence in Australia

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Abstract

Purpose of Review Recent changes in Japanese encephalitis (JE) distribution, including its emergence in mainland Australia, call for a review of the epidemiology, diagnosis, treatment and prevention of this important disease.

Recent Findings Climate change, urbanisation and changes in vector ecology have driven changes in JE epidemiology including expansion to new areas. Residents of and travellers to endemic areas face potential exposure risks. Surveillance gaps and diagnostic challenges lead to under-appreciation of the true disease burden. Treatment is supportive, but modern vaccines are safe and efficacious.

Summary The recent emergence of JE in south-eastern Australia highlights its changing epidemiology and the threat this disease poses to other areas with largely naive human populations and with competent mosquito vectors and vertebrate hosts. Awareness of disease features and diagnostic approaches is critical to case detection in travellers and endemic populations, and preventive measures including vaccination should be advised for those with exposure risk.

Keywords Japanese encephalitis virus · Vaccination · Australia · Outbreak · Surveillance · Travellers

Introduction

Japanese encephalitis virus (JEV) is endemic throughout most of Asia and parts of the western Pacific and is the leading cause of viral encephalitis in Asia, causing an estimated 100,000 cases and 25,000 deaths per year [1•]. JEV is a zoonotic flavivirus transmitted primarily by *Culex* mosquitoes in an enzootic cycle involving water birds and pigs; humans are considered dead-end (incidental) hosts (Fig. 1) [2].

Prior to 2022, only sporadic reports of locally acquired human JEV infections had been reported in Australia, all in residents of Australia's tropical far north [4–6•]. In 2022, an unprecedented outbreak of Japanese encephalitis (JE) occurred in Australia including the first known locally acquired human cases in temperate areas [7]. Ongoing seasonal transmission in south-eastern Australia is likely given the reporting of JE cases in two consecutive summers and ongoing La Niña weather patterns attracting waterbirds and providing conditions for increased mosquito breeding [2, 7].

This article reviews the history and epidemiology of JE in Australia and globally, the virus and vectors, the clinical features of infection, diagnostic tests and their limitations and the available options for prevention and treatment. We also discuss the implications of the changing epidemiology of

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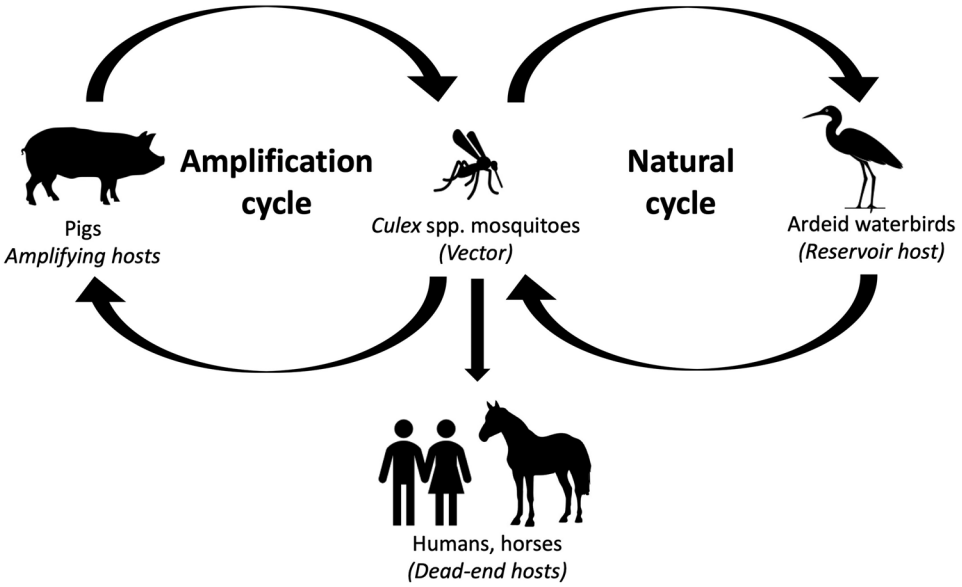

Fig. 1 Japanese encephalitis virus enzootic transmission cycle. The virus is maintained in a natural transmission cycle between mosquitoes and reservoir hosts (primarily Ardeid waterbirds). Pigs act as amplifying hosts. Humans and other vertebrates such as horses are dead-end (incidental) hosts because they do not develop sufficient concentrations of JEV in their bloodstreams to infect feeding mosquitoes. Figure adapted from [3]

this disease for clinical care and public health in Australia, including for those providing care to travellers.

The Virus and Vectors

JEV was first recovered in 1935 from an infected human in Tokyo, Japan. [8••] It is a neurotropic zoonotic flavivirus belonging to the Japanese encephalitis serogroup of viruses, which includes two other viruses endemic to Australia, namely, West Nile virus Kunjin subtype (WNV/KUNV) and Murray Valley Encephalitis Virus (MVEV) [9–11]. JEV includes five genotypes (GI-GV) that differ in their geographic distribution and disease [12•]. Genotypes I, II and III are the most prevalent, accounting for 98% of JEV strains isolated from 1935 to 2009, and are distributed throughout Asia [13]. Until recently, genotype IV was believed to be restricted to the Indonesia archipelago but is now documented to be circulating in Australia [6•, 14••]. Genotype V is older and more divergent than other genotypes and is rarely detected, although there have been reports regarding recent circulation in some parts of Asia [15, 16].

JEV is maintained in a natural transmission cycle between mosquitoes (primarily *Culex* spp.) and ardeid water birds, such as herons and egrets (reservoir hosts; Fig. 1). Feral and domestic pigs are important amplifying hosts of JEV as they have a high natural infection rate and develop high levels of viraemia [14••, 17]. Humans and horses are considered dead-end hosts as viraemia is not believed to reach levels that are infectious to mosquitoes [2]. JEV is transmitted to humans through mosquito bites. To date, there have only been rare case reports of human-to-human transmission via blood transfusion [18•] and liver transplantation. [19•] Screening of blood and organ donors is not routinely recommended [20, 21].

JEV has been isolated from over 30 mosquito species from the genera *Aedes, Anopheles, Armigeres, Culex* and *Mansonia*, although how many of these are competent vectors is unclear [22]. *Culex tritaeniorhynchus*, typically associated with rice production, is the primary mosquito vector in most endemic areas; its distribution is widespread across southeast Asia and extends into the Middle East, Africa, Europe and Australia [23, 24]. Many areas including the Pacific Islands, southern Europe, the United States and Africa remain receptive to JEV due to the presence of both competent mosquito vectors and vertebrate hosts [8••, 22, 25]. A case of apparent autochthonous JEV transmission has been reported in a febrile patient from Angola in Africa [26]. *Culex annulirostris* is considered the primary vector of JEV in Australia; however, at least six species from the subgenus *Culex* that are capable of vectoring JEV have been locally documented [15, 23]. All of these species are nocturnal in behaviour [27, 28].

Changing Epidemiology of JE, Including Emergence in Australia

Global Epidemiology

Epidemics of JEV (originally designated Japanese B encephalitis virus) were first described in Japan in the 1870s, with subsequent spread throughout large parts of Asia and part of the western Pacific [25, 29, 30]. Four

billion people currently live in countries with endemic JEV transmission, with approximately 1.5 billion estimated to live in areas most suitable for transmission [31•]. Two distinct epidemiologic patterns of JEV are recognised: epidemic and endemic [32]. In temperate areas, such as in China, Japan, Nepal and northern India, cases typically follow a seasonal pattern with periodic large outbreaks every 2–15 years [25, 32, 33]. In tropical areas, such as southern Thailand, Indonesia and the Philippines, cases are more sporadic, but transmission is year-round, with peaks typically observed during the rainy season [25, 32]. Although JEV has historically been considered a rural disease, population growth and economic development have led to extending into new geographic areas and increased peri-urban transmission in many countries, including South Korea, China, Singapore, Taiwan and India [13, 30, 34].

The expansion of public health vaccination programs in endemic areas has led to dramatic reductions in the economic burden of human JE disease [25], with an estimated 45,000 JE cases averted in 2015 [1•]. As of 2020, 15 countries had national or subnational public health vaccination programs in JE-endemic areas, including Australia (outer Torres Strait Islands only), Malaysia (Sarawak only), Japan, Republic of Korea, Thailand, Cambodia, Lao PDR, Myanmar, Indonesia (Bali only), Philippines (three high-incidence regions), China, India (about 40–50% of districts), Nepal, Sri Lanka and Vietnam [35••]. Although JE incidence in many endemic countries is stable or declining, epidemic activity in some areas (such as India and Nepal) appears to be escalating, and the risk remains for unvaccinated individuals visiting or living in these areas due to ongoing enzootic JEV circulation [1•, 8••, 12•]. Due to diagnostic limitations and the low rate of clinical disease amongst those infected, human case surveillance data have limited ability to provide early signals of transmission; mosquito and animal surveillance are therefore important in monitoring JEV activity and informing control strategies to limit transmission [7]. Surveillance and diagnostic testing capacity vary across endemic areas, and under-reporting is likely to be substantial [36].

Japanese encephalitis (JE) has long been considered a disease of children in JE-endemic settings as immunity to JEV by natural infection is widespread by adulthood and likely lifelong in the context of natural boosting [9, 35••]. However, a shift in the epidemiology of clinical cases from children to adults, likely contributed to by childhood vaccination programs and potentially less intense transmission, has been documented in several countries, raising questions about the need for adult vaccination [35••, 37, 38]. The introduction of JEV into immunologically naive populations typically results in cases being reported across all age groups [9, 34, 39].

Epidemiology in Australia

Local transmission of JEV in Australia was first documented in April–May 1995, with a small outbreak of 3 human cases in the Torres Strait Islands in Australia's tropical north [5]. Between 1995 and 2021, only two further locally acquired cases in the Torres Strait Islands and Cape York peninsula were recorded. In 2021, a fatal locally acquired case of JEV infection was documented in a patient from the Tiwi Islands, Northern Territory, now considered a sentinel case to the current outbreak on the basis of viral genomic data [6•]. Prior to 2022, JE vaccine recommendations in Australia were limited to laboratory workers, those living or working on the outer islands of the Torres Strait and travellers intending to spend a month or more in JE-endemic areas, leaving the population largely susceptible [40].

In early 2022, an outbreak of JEV was declared in south-eastern Australia, following the detection of JEV in stillborn and weak piglets at piggeries with subsequent detection of human cases, in keeping with a pattern documented in previous outbreaks in new geographic areas [2, 41, 42]. As of February 2023, 46 human JE cases have been reported, with 7 deaths, and the majority of cases have occurred in older adults [7]. This is the first major outbreak of JEV in mainland Australia, with cases widely distributed across five jurisdictions (Victoria, New South Wales, South Australia, Queensland and the Northern Territory) [14••, 43]. Most human cases have been acquired within the Murray-Darling Basin (a system of interconnected rivers and lakes including the Murray and Darling Rivers), which spans four affected jurisdictions in south-east Australia [7, 44]. Two recent voluntary serosurveys of NSW and Victorian residents living in the Murray-Darling Basin found evidence of exposure to JEV in 1 in 11 (80/917; 8.7%) and 1 in 30 (27/820; 3.3%) people, respectively [45, 46]. Detection of JEV in piggeries, mosquitoes and sentinel chickens, along with human JEV cases across two consecutive summer seasons in the Murray-Darling Basin may reflect the establishment of enzootic transmission [2, 7]. This outbreak has probably been driven in part by increased rainfall and flooding due to three consecutive La Niña weather events, which have attracted waterbirds and provided conditions for increased mosquito breeding [2]. Affected areas, recently mapped in another paper [7], closely mirror those of previous outbreaks of other neurotropic flaviviruses endemic to Australia associated with La Niña rainfall events (MVEV and WNV/KUNV) [14••]. Modelling studies indicate that competent vectors are widely distributed along the northern and eastern coastlines of the continent, inland regions within the Murray-Darling Basin and some areas of the southwestern coastline [44].

Epidemiology in Travellers

Previous JE risk estimates in travellers have ranged from 1 case per 400,000 trips to < 1 case per million trips to an endemic area [25]. Although these estimates suggest the risk of travel-related acquisition is low overall, it is important to note that these figures are based on clinical infections and are likely to substantially underestimate risk due to under-reporting and the frequency of mild or sub-clinical infections [25, 30]. Individual traveller risk is highly variable (depending on the traveller's activities, season, location and duration of travel), and severe outcomes in travellers have been reported [25, 47]. A 1973–2008 case series of 55 published cases in travellers from non-endemic areas identified cases in travellers of all ages (range 1–91 years) and included cases resulting in death or severe sequelae [48]. While, historically, many travel-related cases occurred in military personnel [29], increased tourism to South-East Asia in past decades has led to more cases being identified amongst tourist travellers, with the most common countries of acquisition being Thailand and Indonesia [48, 49].

Published cases of travellers from non-endemic areas since 2008 are summarised in Table 1. Of these 21 cases, almost half (10/21; 48%) were in short-term (< 1 month) travellers, 5 (24%) were fatal, and 10 (48%) resulted in long-term sequelae, confirming the devastating consequences of JE from previous reports. Thailand (8/21; 38%) and Indonesia (4/21; 19%) remained the most common countries of acquisition for travellers.

Clinical Manifestations and Consequences

Most JEV infections are asymptomatic, with less than 1% of infections overall progressing to encephalitis [65–68]. However, the risk of clinical disease varies with age at first exposure, and for adults from non-endemic countries, it can be as high as 1 in 25 [25]. Reported outcomes vary widely, but recent reviews estimate the case fatality rate of reported JE cases to be 14–21%, with almost 50% of survivors having persistent neurological deficits at 1-year post hospital discharge [69••, 70].

Symptoms typically occur after an incubation period of 5–15 days (average 7 days) [71]. Neurologic symptoms typically follow a short, non-specific febrile prodrome [9]. Amongst symptomatic cases, the most commonly identified clinical syndrome is acute encephalitis, characterised by decreased or altered level of consciousness, headache, vomiting and often seizures (particularly amongst children) [70]. Focal neurological signs are variable and reflect anatomical sites of involvement. Parkinsonian features, including mask-like facies, tremors and cogwheel rigidity reflect basal ganglia involvement and typically appear 1–4 weeks after illness onset [70–73]. Poliomyelitis-like flaccid paralysis reflects spinal cord involvement [63]. Cranial nerve signs include facial palsies, ptosis and abnormal eye movements. Ocular manifestations are rare, but chorioretinitis has been reported [62]. JEV has occasionally been associated with Guillain–Barre syndrome, as has been reported with other flaviviruses such as the Zika virus [74]. Although JEV is not usually considered to cause congenital infection, this may be because of high seropositivity rates among women of childbearing age in endemic countries [75]. Limited case reports suggesting potential for transplacental infection and adverse pregnancy outcomes, indicating that the risks of JEV infection in immune-naïve pregnant women, need better elucidation [75, 76].

During acute illness, abnormalities of routine peripheral blood tests are non-specific, with common findings including neutrophilia and sometimes hyponatremia [70]. Analysis of cerebrospinal fluid (CSF) typically shows a mild to moderate pleocytosis with a lymphocytic predominance, slightly elevated protein and a normal ratio of CSF-to-plasma glucose.

Diagnostic Challenges

Preliminary diagnosis relies on the individual's clinical presentation and thorough exposure history, including recent travel and outdoor activities [77]. Clinical features may overlap with those of other neurotropic flaviviruses, including those that are endemic to Australia (see Table 2) [70, 72].

In patients presenting with a suspected flavivirus encephalitis, the diagnostic work-up should include cerebrospinal fluid (CSF) sampling and neuroimaging [77]. Where available, magnetic resonance imaging (MRI) is the preferred imaging modality as it provides better soft tissue contrast than computed tomography (CT); T2 and T2-FLAIR MRI sequences are considered most useful [83••, 84]. Thalamic lesions are the most common focal MRI finding in JE, occurring in around 74% of those presenting with encephalitis; however, such lesions are also described in encephalitis due to other flaviviruses (including dengue, MVEV and WNV/KUNV) and herpesviruses (e.g. Herpes Simplex Virus-1) and are, therefore, not pathognomonic [10, 78, 83••, 85, 86]. Basal ganglia and hippocampus lesions are reported much more frequently in JE than in dengue encephalitis and may be a more useful diagnostic clue in settings where these infections co-exist [83••].

Detection of JEV RNA in whole blood, CSF, urine or brain tissue by nucleic acid amplification testing (NAAT) confirms the diagnosis; prolonged JEV RNA detection out to 26 days in urine and 28 days in whole blood has been reported [59]. However, due to the typically low level and short duration of viraemia that occur in human JEV infection

Table 1 Japanese encephalitis cases in travellers from non-endemic countries reported in the literature since 2008

Case	Year	Age/sex	Travel type	Travel duration	Country of residence	Probable country of acquisition	Outcome	Laboratory confirmed	JE vaccine	Reference
1	2010	11 F	VFR	< 1 month	USA	Philippines	Died	Yes	No	[50]
2	2010	6 M	Refugee	≥ 12 months	USA	Thailand	Survived	Yes	U[k]	[50]
3	2010	33 M	Tourist	< 1 month	USA	China	Survived	Yes	No	[51]
4	2010	26 F	Tourist	1 month	Canada	Thailand	Survived with sequelae[a]	Yes	No	[52]
5	2010	61 M	Tourist	< 1 month	Denmark	Cambodia	Died	Yes	No	[53]
6	2010	76 M	Tourist	3 months	Germany	Thailand	Survived	Yes	No	[54]
7	2011	54 F	Tourist	< 1 month	Germany	Indonesia	Survived with sequelae[b]	Yes	No	[54]
8	2011	61 M	Work-related	4 months	USA	Taiwan	Survived	Yes	No	[51]
9	2012	42 M	Expatriate	≥ 12 months	USA	South Korea	Died	Yes	No	[51]
10	2012	22 M	Volunteer	5 months	France	Nepal	Survived with sequelae[c]	Yes	NR	[55]
11	2013	20 M	Work-related	< 1 month	Spain	Thailand	Survived with sequelae[d]	Yes	No	[56]
12	2014	21 F	Tourist	1 month	UK	Thailand	Survived	Yes	No	[57]
13	2015	31 F	Work-related	NR	UK	China	Survived with sequelae[e]	Yes	No	[57]
14	2015	24 M	Tourist	2 months	UK	Vietnam, Cambodia or Thailand	Survived with sequelae[f]	Yes	No	[57]
15	2017	50 M	Tourist	< 1 month	Germany	Thailand	NR	Yes	NR	[58]
16	2017	69 M	Tourist	< 1 month	Australia	Thailand	Died	Yes	No	[59]
17	2019	14 F	Tourist	< 1 month	Belgium	Thailand	Survived with sequelae[g]	Yes	NR	[60]
18	2019	59 M	Tourist	NR	Australia	Indonesia	Died	Yes	No	[61]
19	2020	45 M	Tourist	< 1 month	Australia	Indonesia	Survived with sequelae[h]	Yes	No	[62]
20	2020	29 F	Expatriate	≥ 12 months	Germany	Indonesia	Survived with sequelae[i]	Yes	No	[63]
21	2022	37 F	Tourist	< 1 month	Abu Dhabi	Vietnam	Survived with sequelae[j]	Yes	No	[64]

NS nil significant, *NR* not reported, *U* unknown

[a]Left upper limb paresis, fatigue and emotional lability 5 months post discharge

[b]Residual fatigue, dizziness, slowing of speech and thought, difficulty in concentrating 2 months post discharge (unable to work in the former profession)

[c]Persistent mild impulsivity, moderate attention disorder and memory recall deficiency 1 year post symptom onset

[d]Ataxic gait, mild memory impairment and emotional lability 3 months post onset

[e]Ventilator dependent (via tracheostomy), residual upper limb and partial lower limb paralysis (unable to stand or transfer but can operate a bike)

[f]Ventilator dependent (via tracheostomy), fed via gastrostomy, quadriplegic with slight movement in hands and head

[g]Persistent extra-pyramidal symptoms (dysphagia, mask-like facies), tracheostomy due to persistent weakness with absent cough reflexes at 1 month post infection

[h]Ongoing impairment in memory and concentration more than 1 month after symptom onset

[i]Residual upper limb paralysis one year after symptom onset

[j]Able to follow simple commands but unable to communicate verbally 3 months post symptom onset

[k]Case in a child from a refugee camp in Thailand who had reportedly received routine childhood vaccines (which in Thailand include the JE vaccine), but no records confirming his receipt of the JE vaccine were available

Table 2 Epidemiological and clinical features of neurotropic flaviviruses present in Australia [8••, 9, 10, 78–82]

	JEV	MVEV	WNV/KUN
Geographic area	South Asia, Southeast Asia, New Guinea, Australia	Australia, New Guinea	Northern Australia, periodically in south-eastern Australia
Main vectors	*Culex triaeniorhyncus, C. vishnui, C. gelidus, C. pipiens*	*C. annulirostris, C. quinquefasciatus, Aedes normanensis*	*C. annulirostris,* other *Culex* spp
Incubation period (days)	5 to 15 days (average 7 days)	1–4 weeks (average 2 weeks)	Unknown, but likely similar to WNV (median 3 days, range 2—14 days)
Prodrome	Yes, 2–3 days	Yes, 2–5 days	Unknown
Ratio of symptomatic to asymptomatic infections	1 in 25 (nonimmune adults) to 1 in 250–1000 (children)	1 in 150 to 1 in 1000	Unknown, although symptomatic cases are rarely reported
Case fatality rate[a] (%)	20–30%	15–30%	No reported deaths attributable to WNV/KUN encephalitis
Neuropsychiatric sequelae at hospital discharge (%)	50–60%	30–50%	Rare, most make full recovery or have mild neurological sequelae
Main vertebrate hosts	Waterbirds (herons, egrets), pigs	Waterbirds (herons, egrets), possibly feral pigs	Waterbirds (particularly *Nycticoras calendonicus*, the rufous night heron)
Clinical features[b]			
Fever	+ + +	+ + +	+ + +
Headache	+ +	+ + +	+ + +
Confusion	+ + +	+ + +	+ +
Rash (macular)	+	+	+ +
Arthralgia	−	−	+ +
Seizures	+ + + in children; + in adults	+ + + in children; + in adults	−
Flaccid paralysis	+ to + +	+ to + +	−
Parkinsonian features	+ to + +	+	−
Cranial nerve signs	+ to + +	+ to + +	−
Cerebellar ataxia	+ to + +	+	−

JEV Japanese encephalitis virus, *MVEV* Murray Valley encephalitis virus, *WNV/KUN* West Nile Virus/Kunjin subtype infections

[a]Among reported cases

[b]+ + + indicates commonly associated features (> 50%); + + often associated (10–50% of cases); + sometimes associated (< 10% of cases); − rare/not reported

and the neurotropism of the virus, detection of JEV from clinical specimens is often unsuccessful [87••, 88]. Recent laboratory data from one Australian jurisdiction exemplify the low sensitivity of NAAT and the critical role of serology [43]. Viral culture is also diagnostic and may be attempted from CSF, whole blood, urine or brain tissue, but is time and resource intensive and requires a biosafety level 3 laboratory. [87••]. Metagenomic next-generation sequencing is a promising tool for cases of unexplained encephalitis where targeted investigations fail to yield a diagnosis and has assisted in recognising at least one unsuspected JEV infection in the current Australian outbreak, but largely remains a research tool in well-resourced settings [43, 87••].

Serology remains the cornerstone of diagnosis for JEV, but testing and interpretation are complex and require knowledge of patient demographics, the timing of potential exposure, and any prior vaccination against or infection with other flaviviruses [87••]. Australian guidelines promote universal pan-flavivirus serology in patients presenting with encephalitis in Australia, but uptake is generally low [89, 90]. The diagnostic criteria used to confirm JEV infection in the Australian setting have recently been revised [91]. Detection of anti-JEV IgM in CSF is generally considered to confirm the diagnosis of JE, with a sensitivity and specificity of > 95% by day 10 of illness, but the capacity for CSF collection may be limited in rural areas where cases often occur [35••, 87••]. Additionally, alternative diagnoses including dengue, tuberculosis and rickettsial infections have been identified through PCR or pathogen isolation in some patients with detectable anti-IgM in CSF in endemic settings [92]. Serum anti-JEV IgM has the greatest sensitivity in early illness (75% of patients have anti-JEV IgM by day

4 after illness onset), but results can be difficult to interpret in areas with other co-circulating flaviviruses due to cross-reactivity [87••, 93]. Additionally, anti-JEV IgM can persist for 30–90 days (or even longer) following acute infection and for one month or more following JEV vaccination, and therefore its detection may occasionally reflect recent infection or vaccination rather than acute infection [35••, 87••]. Anti-JEV IgG is detectable in serum and/or CSF in about 80% of patients by day 7 post illness onset and peaks around day 30 [87••]. The timing of testing in relation to clinical illness is an important consideration, and where possible, serology should be performed at presentation and repeated on day 10 of illness to assess for seroconversion or a four-fold or greater rise in antibody titres [90].

Treatment

Treatment focuses on supportive care, as no specific treatment options are currently available, although in endemic countries, optimising supportive care does improve outcomes [94, 95]. Previous double-blind, placebo-controlled, randomised clinical trials of dexamethasone, interferon alpha 2a, ribavirin, intravenous immunoglobulin (IVIG) and minocycline in patients with JE did not demonstrate detectable benefits on any clinical outcome measure, but the sample size may have been too small [70]. Pre-clinical studies have highlighted a number of compounds that are potentially suitable for treatment, but pragmatic human trials are needed [70, 96]. Given the evidence that JE pathogenesis is driven by both direct viral and immune-mediated effects, future trials should consider a combination of both anti-viral and immune-modulatory treatments [70].

Prevention

JE vaccines have been available for decades, but their introduction and uptake have been limited by high cost and (in some cases) multiple-dose regimens [35••]. Efficacy and safety concerns related to early inactivated mouse brain-derived vaccines have largely led to their replacement with three newer generation vaccine classes: inactivated Vero cell-derived, live attenuated (i.e. CD-JEV) and live recombinant (chimeric) vaccines (i.e. JE-CV), all of which are safe and immunogenic [97, 98••]. All licensed vaccine viruses are genotype III JEV but have been found to elicit protective levels of neutralising antibodies against genotypes I-IV [99]. Neutralising antibody data and differences between genotype V and III viruses suggest that current vaccines may not be as efficacious against genotype V virus [35••]. The World Health Organisation recommends the integration of JE vaccines into national immunisation schedules in all areas where JE is recognised as a public health priority [100]. Most current country-supported JE immunisation programs (including China and India) use CD-JEV; four use JE-CV (Australia, Malaysia, Thailand, Taiwan), three use Vero cell vaccines (Japan, South Korea and Taiwan); and one (Vietnam) continues to use mouse brain-derived vaccines but has plans to scale-up local production of an inactivated Vero cell-derived vaccine for broader use [35••, 101]. JE vaccine availability in non-endemic areas varies; the only vaccine available in Europe and North America is the inactivated Vero cell-derived vaccine IXIARO® (Valneva) [102].

Two JE vaccines are currently licensed and available in Australia: the live recombinant vaccine Imojev® (Sanofi Pasteur), licensed from 9 months of age; and the inactivated Vero cell-derived vaccine JEspect® (Valneva; marketed in other countries as Ixiaro®), licensed from 2 months of age [39, 103]. Both are well-tolerated, and their efficacy is comparable, but they differ in cost and the number of doses required [40, 98••]. The recommended primary schedule for JEspect® is two doses, given 28 days apart, whereas for Imojev®, it is a single dose. In Australia, a booster dose is recommended for those at ongoing risk of JE virus exposure if more than 1 year has passed since the primary schedule, regardless of which vaccine was received, except in people who received a dose of Imojev as an adult (≥ 18 years), where a booster dose is not required [104]. As no studies have examined the interchangeability of JEspect® and Imojev®, it is preferable to use the same vaccine for booster doses as was used for the primary course [104]. Provision of a booster dose of a newer generation class vaccine (e.g. JEspect® or Imojev®) to someone previously vaccinated with a mouse brain-derived vaccine has been shown to be effective and safe [105••]. Current data are insufficient to inform recommendations regarding the need for or timing of further booster doses in those at long-term, ongoing risk. Pooled seropositivity rates following a primary schedule plus booster dose (where indicated) are above 95% and appear to remain stable for up to 6 years [105••]. Imojev® is contraindicated in pregnant women and people who are immunocompromised [104]. Pregnant women at risk of acquiring JE are recommended to receive JEspect® [103]. No data on the safety or efficacy of JEspect® in immunocompromised persons are available [106]. As an inactivated vaccine, JEspect® is not expected to cause any safety concerns in immunocompromised persons, but vaccine responses may be diminished in this population [103, 106].

In Australia, constraints to vaccine supply have influenced the public health rollout of JE vaccination, with funded vaccine eligibility generally limited to people with relevant occupational risk and those who live or routinely work in affected areas and are regularly outdoors for long periods [7]. As vaccination campaigns with live recombinant JE vaccine may result in the unintentional vaccination of

people with a contraindication or precaution to vaccination, such as pregnant women, ongoing post-marketing vaccine surveillance remains important. There is growing interest in the use of intradermal (ID) administration of live recombinant JE vaccine as a dose-sparing strategy, but comparative vaccine effectiveness and immunogenicity data are needed [107•, 108, 109]. Further studies are planned, including in Australia (see https://www.ncirs.org.au/clinical-research/japanese-encephalitis-vaccine-study).

JE vaccine guidance for travellers generally recommends vaccination for those spending a month or more in risk areas during the transmission season and suggests consideration of vaccination for those undertaking shorter-term travel with additional risk factors or those undertaking multiple short trips which cumulatively result in the potential for more than 4 weeks at risk [84, 87••, 90]. Currently, the vaccine is underutilised among travellers, with most travellers to endemic areas not receiving a vaccination, even if pre-travel advice is sought [30, 110, 111]. Given the unpredictable epidemiology of JE, its propensity to cause severe disease and death, expansion to new geographic areas, and recent reports of JE in short-term travellers (reported travel duration < 1 month for 10/21 published cases from 2008 to 2022; Table 1), there is a compelling case to consider more widespread vaccination, including in travellers [35••, 47].

Another key preventive strategy for those living in or visiting endemic areas is mosquito bite avoidance. Mosquitoes that transmit JEV are nocturnal in behaviour and the greatest risk period for bites is between dusk and dawn [22, 30]. Strategies to avoid bites include the use of insect repellents, wearing protective clothing (such as long-sleeved shirts and pants), treating clothing and gear with an insecticide such as permethrin, and sleeping in screened or air-conditioned rooms or under an insecticide-impregnated bed net [112-113].

Conclusion

JEV remains an important health threat in Asia and the Western Pacific, with significant morbidity and mortality. Experience from recent decades indicates that outbreaks are unpredictable, as has been exemplified in Australia, and are likely to continue to occur as urban growth, globalisation and climate change continue. Mosquito and animal surveillance is important since human case surveillance data may not provide early signals of transmission. Clinical features may overlap with those of other flaviviruses, and the interpretation of serology may be challenging. Treatment is supportive, as no treatment options with proven efficacy are available, and more highly powered clinical trials combining virus-directed and immune response-directed treatments are needed. Modern vaccines are safe and effective. Clinicians seeing those at risk, including in the pre-travel setting, should maintain best practice approaches around risk communication and give advice on insect bite precautions as well as vaccination based on individualised risk assessment.

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Compliance with Ethical Standards

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- • Of importance
- •• Of major importance

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