Japanese encephalitis among adults: A review

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Key words: Japanese encephalitis, adult, immunization, vaccine, disease

Word counts: Abstract: 180 words; Text: 2,007 words

Number of tables: 1

Running head: Review of Japanese encephalitis among adults

Abstract

Japanese encephalitis (JE) is becoming an increasingly important issue among adults. The reasons for this are multifactorial. During the past decades, new areas of JE virus (JEV) transmission have occurred in several locations, most notably in a markedly expanded area of Australia during 2021–2022. When JEV enters new areas, cases in adults frequently occur. This is unlike the typical pattern in endemic areas where the burden of disease is in children because most adults are protected through natural immunity following earlier exposure to the virus. Even in endemic areas, JEV has become relatively more important in adults because improved JE control through childhood immunization programs has resulted in a substantial decrease in pediatric JE cases and thus more prominence of adult JE cases. Finally, increases in tourism to JE risk areas have resulted in more exposure of adult travelers, who are usually non-immune, to infection in JE risk areas. In this review we describe the increasing importance of JE in adults in some areas and then consider the comparative clinical presentation and severity of illness among children and adults.

Introduction

Japanese encephalitis virus (JEV) is transmitted throughout much of Asia and parts of the western Pacific.[1] Recently, the recognized transmission area has grown with detection of the virus in a markedly expanded area of Australia.[2] JEV is transmitted in an enzootic cycle between mosquitoes, mainly *Culex* species, and vertebrate hosts, primarily pigs and wading birds.[3, 4] Accordingly, Japanese encephalitis (JE) is primarily a disease of rural areas where *Culex* breeding sites and vertebrate hosts are found in close proximity to humans. JE is often a severe disease, with a case-fatality rate of up to 30% among persons with neurologic infection and sequelae in 30–50% of survivors.[5] To reduce the burden of JE, the World Health Organization has recommended JE vaccination be integrated into national immunization schedules in all areas where JE is a recognized public health priority.[6]

During the past decades, the geographic range of JEV has expanded with new areas of transmission identified in several locations in Asia and the Western Pacific region, including in recent decades in Tibet, parts of India, and higher altitude areas in Nepal.[7-11] In Australia, only five JE cases had been reported prior to 2021, all in 1998 or earlier in Far North Queensland; these included four cases on Badu Island, an outer Torres Strait island, and one case on the mainland following a short-lived incursion of the virus.[12] However, in 2021 through the first half of 2022 more than 40 JE cases were identified on the Australian mainland, in areas up to 1,500 miles further south and substantially further west than previously reported.[2, 13] After no detectable JEV activity during the 2022 Australian winter, infections were again identified in persons in three Australian states in November 2022 strongly suggesting the virus is now permanently established on the Australian mainland.[13, 14] Further expansion in the area of JEV transmission overall could result from the ongoing increases in Asia of rice cultivation and pig farming, evolving environmental conditions related to climate change, or even long distance spread from viremic migratory birds or windblown mosquitoes.[15-19] As JEV enters new areas, cases in adults are often observed, unlike in most endemic areas with long-term JEV transmission where the burden of disease is in children.[18, 20]

In addition to JEV expansion into new areas, in endemic areas JEV has become relatively more important in adults as pediatric cases decrease because of the substantial progress in introduction and strengthening of childhood JE immunization programs; indeed, a predominance of adult cases in Assam, India, resulted in the Indian government initiating an adult vaccination program there in 2011.[21, 22] Furthermore, travelers from non-endemic countries are usually non-immune and JE cases can occur among persons of any age. A growth in tourism to JE risk areas has resulted in an increase in reported adult JE cases.[23] These many factors mean JE among adults is an increasingly important issue. In the following sections we describe in more detail the shifts in age distribution of JE and then consider the comparative clinical presentation and severity of illness among children and adults.

Changes in prominence of JE among adults

JE is typically considered a childhood disease because most adults living in endemic areas have immunity following previous JEV exposure and subclinical infections, protecting them from subsequent disease as adults. However, when the virus enters a new area, all age groups are susceptible to infection, and cases in adults and children are observed. For example, with JEV transmission in new areas in Australia, many of the cases have been in adults.[24] A similar pattern was seen when virus transmission occurred in Saipan in the Northern Mariana Islands in 1990, with cases in persons aged ≥ 15 years representing 90% (9 of 10) of cases among local residents.[18] In Nepal, JE was recognized as a public health problem starting in the late 1970s, when cases were reported from the southern part of the country.[25] Annual outbreaks with cases predominantly among children were reported from this area for many years.[25] However, beginning in the mid-1990s, JEV began to spread further north, initially to the Kathmandu Valley and subsequently to other hill and mountain districts.[8, 26] In these new areas, the proportion of adult cases was as high as 45%.[8, 27]

Childhood JE immunization programs have had an impact on the observed age distribution of JE cases in some countries. In locations with long-term programs with high coverage and high immunity levels in younger persons, the age distribution has shifted toward adults, including in Japan, South Korea, Taiwan, Sri Lanka, and in some locations in Malaysia (Sarawak)(Table 1).[28-41] Additionally in some countries, such as India and China, the majority of cases still occurs among children aged < 15 years, but in certain areas within the country the proportion of adult cases among all JE cases is increasing and outbreaks among adults have occurred.[21, 22, 42-48] In a study conducted in Assam, India, during 2011–2012, following implementation of mass vaccination in many districts for children aged 1–15 years from 2006, 41 (21%) of 194 JE cases were aged < 15 years and 153 (79%) were adults.[22] In China, in a nationwide study that investigated etiologies of acute meningitis or encephalitis from 2009–2018, there

was a comparatively low number of cases among persons aged ≥60 years, but JEV was the most common viral etiology identified in this age group (44% of all viral diagnoses); comparatively, it was the least common etiology among children aged ≤17 years.[49]

Beyond the shift in relative cases among adults versus children, there might actually be a true increase in cases among adults, especially the elderly.[28, 31, 32, 40, 45] Immunosenescence, reduced opportunities for JEV exposure and natural boosting because of urbanization, and waning vaccine-induced immunity (among those previously vaccinated) might be contributing factors. In one study in South Korea, JEV neutralizing antibody levels were assessed among younger persons who would have had access to a vaccination program and persons aged ≥45 years who were born prior to the JE vaccine being readily available.[50] Rates of neutralizing antibody positivity showed a progressive decrease as age group increased. Rates were 95–100% in those aged 15–29 years, 84–89% in those aged 30–44 years, 75–81% in those aged 45–69 years, and 60% in the oldest age group of persons aged ≥70 years.

Disease among adults

The great majority of JEV infections are inapparent. Studies, primarily among children, have demonstrated that only one in approximately 200–300 infected individuals develops encephalitis; lower ratios of 1 in 25 and 1 in 63 for U.S. adult males were demonstrated in American military studies in Asia.[51-57] Neither of the military studies included children, so whether the different ratios were related to age or other factors cannot be confirmed. There are very limited additional data on the likelihood that encephalitis will develop among older compared with younger persons. One study in Thailand estimated that the ratio of apparent to inapparent infections was 1 to 312 in persons aged < 40 years overall, but ratios decreased as age increased; in persons aged 1–9 years, 10–19 years, and 20–30 years, the ratios were 1 in 350, 1 in 277, and 1 in 250, respectively.[53] It would be unsurprising if older adults were more likely to develop encephalitis following JEV infection, as studies for the related flavivirus, West Nile virus

(WNV), have shown that increasing age substantially increases the risk for developing neuroinvasive WNV disease.[58]

The most commonly recognized clinical presentation of JEV infection is acute encephalitis, but milder forms of disease such as aseptic meningitis or nonspecific febrile illness with headache also occur.[5, 59-62] Initial symptoms of JE are usually nonspecific and can include fever, diarrhea, and rigors followed by headache, vomiting, and generalized weakness. Subsequently, mental status changes, focal neurologic deficits and/or movement disorders can develop.[5] A very distinctive clinical presentation is a Parkinsonian syndrome resulting from extrapyramidal involvement; findings include dull, flat, mask-like facies with unblinking eyes, tremor, and cogwheel rigidity.[5] Patients occasionally present with a poliomyelitis-like acute flaccid paralysis due to anterior horn cell damage, without any alteration in consciousness.[63, 64] JE cannot be clinically differentiated from acute neurologic infection due to other causes, so laboratory testing is important to confirm the diagnosis.

A small number of studies has specifically investigated symptoms and signs, laboratory or imaging findings, and/or outcomes of JE in cohorts that include both children and adults.[21, 22, 65-69] Results have been variable and many of the studies have had methodologic limitations, such as incomplete laboratory confirmation of JEV infection or conduct at a tertiary care hospital where the referral patterns for adults and children might be different. Generally, the clinical presentation of JE among adults and children has been shown to be very similar. However, seizures have been reported at a significantly higher rate in children in almost all studies.[21, 22, 66, 67, 69-71] Other differences between children and adults have also been reported, but not consistently; these include a higher rate of neck stiffness, abnormal behavior, and electroencephalogram abnormalities and a lower level of consciousness among children, and higher mean or median cerebrospinal fluid white cell counts and protein levels among adults.[21, 22, 65-67, 69, 71] While results in studies of outcome following JE have again been variable, many studies suggest the case fatality rate might be higher among adults than children; however among

survivors, sequelae might be more frequent among children.[21, 22, 65, 67, 69, 72-75] This suggests that children with severe disease are more likely to survive but end up with severe neurologic and other sequelae. Immunologic, structural, and functional differences between the brains of adults and the developing brains of children could contribute to differences in the clinical course of disease in these different age groups.

Management and implications for JE prevention

There are no specific antiviral therapies for JE.[76] Treatment consists of supportive care with emphasis on control of intracranial pressure, maintenance of adequate cerebral perfusion pressure, seizure control, and prevention of secondary complications such as infections. Fluid management can be especially challenging, because of the desire to maintain adequate hydration without contributing to cerebral edema. Particular attention should be paid to seizures in children, which are usually generalized tonic-clonic but can present as subtle motor seizures with the only manifestation being twitching of a digit, eye, or mouth, eye deviation, nystagmus, or irregular respiration.[5]

Childhood vaccination programs are the mainstay of JE prevention in endemic areas. As of 2022, 64% of 25 countries with JEV transmission risk have national or subnational JE immunization programs (and one additional country had determined a program is not required).[77] Vaccination in childhood generally provides lifelong protection for individuals living in endemic areas where episodic re-exposure to JEV likely supports ongoing immunity. If adult vaccination programs are under consideration, the factors that should be considered include disease incidence, cost-effectiveness, feasibility, and vaccine effectiveness in older persons. Routine JE surveillance programs that include adults are important to provide essential data to guide decision-making. Travelers from non-endemic areas visiting at-risk countries should be advised to take precautions to avoid mosquito bites, and vaccination may be recommended for those with factors that increase their risk of JEV exposure such as longer duration of

165 travel, spending time in rural areas, participating in extensive outdoor activities, and staying in
166 accommodations without air conditioning, screens, or bed nets.[78]
167
168 **Conclusion**
169 JE among adults is an emerging and increasingly important issue given the expansion of the JEV
170 transmission area into locations with non-immune populations, greater prominence of adult JE cases
171 following improved JE control among children, and ongoing increases in tourism exposing travelers to
172 JEV infection. While studies in Asia have suggested some minor differences in clinical presentation and
173 outcome, a lower frequency of seizures among adults is the only clear difference and overall it is
174 apparent that JE can be a very severe disease in both adults and children with substantial sequelae even
175 with current management practices.[79] Childhood vaccination programs in endemic areas should be
176 strengthened and maintained to reduce the burden of disease during childhood and into adulthood.
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178 **Disclaimer**: The views expressed in this article are those of the authors and do not necessarily represent
179 the official position of the US Centers for Disease Control and Prevention.
180
181 **Disclosures:** The authors declare they have no conflicts of interest. TS is supported by the National
182 Institute for Health Research (NIHR) Health Protection Research Unit in Emerging and Zoonotic
183 Infections (Grant Nos. IS-HPU-1112-10117 and NIHR200907), NIHR Programme Grant for Applied
184 Research (No. RP-PG-0108-10,048), NIHR Global Health Research Group on Brain Infections (No.
185 17/63/110), and The Pandemic Institute, Liverpool.
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Table 1. Examples of locations with changes in age distribution of JE cases following implementation of JE vaccination programs

Country	Vaccination program information	Early period	Disease burden and age distribution in early period	Later period	Disease burden and age distribution in later period	References
Japan	Widespread childhood vaccination from 1967	1956–1964	Median of 1,979 cases annually (range 1,205–4,538); ~ 30%–60% cases each year in children aged < 15 years	1982–2004	Median of 7 cases annually (range: 2–54) 78% cases aged ≥ 40 years; highest number of cases in 60-69 year age group	[29-31]
South Korea	Vaccination began in late 1960s but program substantially expanded after 1983	1955–1966	Mean annual IR 7.3/100,000; 92% (20,286 of 22,111 cases) aged ≤ 14 years	2010–2014	Mean annual IR of 0.03/100,000; 89% aged ≥ 40 years	[29, 32]

Taiwan	Mass vaccination of children began in 1968, followed by routine childhood immunization	1966–1970	Aged < 30 years: mean annual IR 2.8 per 100,000 Aged ≥ 30 years: mean annual IR 0.04 per 100,000 > 90% cases in persons aged 0–29 years (mostly 0-14 years)	2002–2012	Aged < 30 year: Mean annual IR 0.05 per 100,000 Aged ≥ 30 years: Mean annual IR 0.2 per 100,000 83% cases aged ≥ 30 years (including 35% ≥ 50 years)	[28, 29]
Sri Lanka	Childhood immunization program began in 1988 with phased implementation of campaigns for children aged 1–10 years in higher risk districts. In 2011, national routine	1985–1987	Mean annual IR 3.3 cases per 100,000 High risk age group: Children < 15 years	2011–2015	Mean annual IR 0.2 cases per 100,000 73% of cases among persons aged ≥20 years	[33, 41]

	immunization program for children aged 9 months established					
Malaysia (Sarawak state)	Routine childhood vaccination began in 2001	1996–2001	Mean annual IR 1.4 per 100,000 Mean age 7.5 years (sd. 5.8 years)	2010–2015	Mean annual IR 0.5/100,000 Mean age 16.9 years (sd. 10.1 years)	[40]

Abbreviations: IR: Incidence rate; sd: standard deviation