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SHORT PAPER

Japanese Encephalitis can be devastating

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Parole chiave: Encefalite giapponese; arbovirus; cambiamenti climatici; zanzare; vaccinazione

Abstract

Japanese encephalitis, caused by the JE virus transmitted by mosquitoes, is the most common type of epidemic encephalitis in Asia. It is endemic in most of South and Southeast Asia, but the number of cases can vary greatly between areas. While many infections do not lead to disease, the symptomatic cases can be very severe and life-threatening. It mainly affects children, whereas adults are generally immune to the disease due to either being infected in childhood or receiving vaccination. However, individuals who are not immune, such as travelers from non-endemic countries, are susceptible to the disease when exposed to the virus for the first time, regardless of age. Without antiviral treatment options, vaccination is the only strategy to establish effective protection against Japanese encephalitis.

Introduction

Japanese encephalitis (JE) is an infectious disease of the central nervous system caused by JE virus (JEV), a zoonotic mosquito-borne flavivirus. It is prevalent in much of Asia and the western Pacific, with billion people living at risk of infection. Despite the low frequency of clinical forms compared to other infections, the disease has a significant impact due to the severe and life-threatening nature of most symptomatic cases (1, 2).

Virology

JEV is a member of the JE serogroup of the genus Flavivirus, family Flaviviridae, and is transmitted between vertebrate hosts by mosquitoes, principally *Culex tritaeniorhynchus* (3), which has nocturnal behavior. The JEV was isolated in Japan in 1935, but the disease hd been described as early as 1870. JEV evolved from its ancestral form to its current form in the Indonesia-Malaysia region. From there, it spread north to Asia and it was then isolated in northern

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Table 1 - Clinical stages of JE – adapted from (7, 11, 13), and CDC Yellow Book 2024[1]

Transmission Stage	Prodromal Stage	Acute stage	Late stage	Sequelae Stage
- Incubation: 5–15 days - Most infections in humans asymptomatic	- Fever - Chills - Headache - Fatigue - Nausea - Vomiting	- Acute encephalopathy - Change in mental status - Mild confusion to agitation or coma - Parkinsonian syndrome - Upper & lower paralysis - Seizures	- Gradual recovery - Possible persistence of some CNS signs and symptoms	- Cognitive & memory impairments - Psychiatric & behavioral disturbances - Neuromuscular dysfunction - Impairment of daily activities - Seizures

[1] https://wwwnc.cdc.gov/travel/diseases/japanese-encephalitis

Australia (11). Although JE virus corresponds to a single serotype, at least five antigenic groups have been differentiated based on nucleotide sequence of the viral genome (1). The five JE virus genotypes (GI-GV) show specific geographic patterns in their distribution: while in some areas all are similarly diffused, in other areas only one maybe prevalent. Concerns have arisen regarding the potential differences in antigenicity between JEV strains, which could affect the vaccine's effectiveness, as minor antigenic variations could partially influence differences in immune response (1, 4). However, current vaccines offer significant protection against the disease (5). Due to its zoonotic diffusion, JEV cannot be eradicated, even though some strategies (such as vector control, focusing on bite avoidance, immunizing humans and pigs) have reduced the number of cases (1).

Being an arthropod-borne virus (arbovirus), JEV is transmitted in an enzootic cycle among mosquitos and vertebrate hosts, particularly pigs and birds: humans become infected when bitten by an infected mosquito. Although many vertebrate animals can be infected with this virus, domestic pigs play a crucial role in the transmission to humans, not only because they develop high titers and long-lasting viremia after natural infection but also because they live on farms in close proximity to human habitat. Humans, horses, and other non-avian vertebrates are considered incidental dead-end hosts because they do not produce a level of viremia sufficient to infect new mosquitoes (6). In addition to horizontal transmission through mosquito bites, JEV can also be transmitted from infected female mosquitoes to their offspring, through eggs. Vertical transmission contributes to the virus's persistence and maintenance in mosquito populations, making it more challenging to control and eliminate the disease (6).

Clinics

JE is a potentially fatal disease for which there are no specific, but only symptomatic treatments. Inability of host to produce antibodies against virus is associated with increased likelihood of disease becoming lethal. Crossing the blood-brain barrier is an important factor in increasing pathogenesis and clinical outcome of neurotropic viral infection (11).

Although symptomatic JE is rare, for those affected the consequences can be devastating (2, 7) (Table 1). In a population of 144 patients infected with JEV (7) 12% died, and 50% suffered from moderate to severe disabilities, while 19% suffered of minor sequelae, and only 19% recovered completely. Patients who experience complications may be unable to work or live independently, which can have an impact on them, their families, and society (8). Neurological complications, such as seizures, cognitive complications, like speech disorders, and physical complications can occur. A research has addresses the underreporting of JE cases and deaths, suggesting that the disease burden is higher than previously estimated (9).

JE is prevalent in Asia. Most populations in this region develop natural immunity due to the high prevalence of the disease. As a result, symptomatic cases of JE tend to occur mainly in children, but also in the the elderly. In childhood, 0.1–0.3% of infections result in disease, but in people exposed in old age, the symptomatic disease rate may also be higher, up to 4% of infections (2). Importantly, because JEV is kept in nature in an animal-mosquito cycle, non-immune travelers or expatriates remain at risk of infection (12).

Epidemiology

The annual incidence of clinical disease varies both across and within endemic countries, ranging from <1 to >10 per 100 000 population, or higher during outbreaks. Nearly 68,000 clinical cases globally are estimated each year, with approximately 13,600 to 20,400 death[2].

A recent study (9), although published before the Australian epidemics – see below -, has combined spatial analysis and force of infection estimates to assess the current burden and vaccination impact against JE in Asia, highlighting significant underreporting and the potential for reducing disease burden through increased vaccination coverage. An estimated 1.54 billion people live in areas at risk for JEV transmission. Spatial analysis identified critical factors sustaining viral transmission, including proximity to wetlands, rice cultivation, and presence of key mosquito vectors. Force of infection analysis revealed significant variations within countries in JEV transmission intensity (9).

JE is considered the most common cause of viral encephalitis in Asia (9), going from the China-Russia border region in the north to Australia in the south, and from the Western Pacific islands in the east to the India-Pakistan border region in the west. Over the past few decades, the incidence has decreased considerably in some countries, but has increased in others. Two distinct epidemiological models of JE have been described in Asia: in temperate areas large epidemics occurring in the summer months, while in tropical areas cases occur more sporadically and peaks are usually observed during the rainy season (14). In the late 1990s, JEV began to emerge in the Torres Strait islands and spread onto the Cape York Peninsula (North Australia) posing a serious risk to public health and raising a significant concern that the virus could continue to spread. The concern was right. Later the virus has spread also in continental Australia, in addition to 25 Asian and Western Pacific countries (15).

In fact, in 2022, unprecedented rainfall in Australia led to a shocking outbreak of JEV. Extensive flooding is thought to have played a main role in the virus's spread. It created conditions that allowed mosquitoes to thrive, providing a suitable habitat for aquatic birds, which are main carriers of the virus. The outbreak affected both humans and pigs: it brought attention to the intricate relationship between weather, wildlife, and disease, and raised concerns regarding its possible connection to climate change (16, 17). A total of 45 cases with seven deaths were reported during the outbreak[3]. A serological survey conducted in New South Wales showed that the JEV was prevalent in that area and may have infected a large number of people (18).

Vaccination and other preventive measures

Since there is no cure for JE, human vaccination is the only effective long-term control measure. WHO recommends that at-risk populations be vaccinated. In fact, several Asian and Western Pacific countries have established vaccination programs (15). It has been estimated that vaccination prevented 314,793 cases and 114,946 deaths from 2010-2019, and had a significant impact in China (9). However, there is still a need for more targeted vaccination strategies in countries with a high JE burden and those with limited vaccination coverage.

Overall risk of JE for travelers to Asia may be considered low, however, cases have occurred in travelers not fitting the usual "at risk" profile. In fact, contrary to popular belief, JE does not only affect long-term travelers and those staying in rural areas, as over one in three reported cases occurs in people traveling for less than four weeks, as shown in two series of clinical cases published in 2009 and 2015 (19, 20). In fact, a single mosquito bite can be enough to contract the disease: *"Mosquitoes do not acknowledge the rule not to bite travelers within their first 28 days of staying"* (20). In addition, in the past, it used to be true that staying away from rural areas could avoid the risk. Currently, due to climate changes, Culex mosquitoes can be found not only in rural areas but even in sub-urban and also urban areas, in addition to tourist locations (21, 22). Among 16 cases of JE in travelers reported in literature following trips to at-risk areas, published between 1992 and 2019, most recent publications reported cases from short stays in non-rural areas (23, 24). Another review, showed that among 37 travel-associated JE cases, 24 (65%) spent

[2] https://www.who.int/news-room/fact-sheets/detail/japanese-encephalitis

[3] https://health.gov.au/news/statement-on-the-end-of-japanese-encephalitis-virus-emergency-response#:~:text=Since%201%20January%202021%2C%2045,in%20Australia%20since%20December%202022.

Table 2 - Immunogenicity of SA_{14}-14-2 vaccine (2 × 6 mcg on d 0, 28) in adults from non-endemic countries without co-administration of other vaccines (28), adapted – Full references of the publications incuded in the table are reported in (28)

Study	Subjects (n)	Seroconversion rate (%)	GMT
Analysis 28 days after the second vaccination, except Erra (4–8 weeks after the last vaccination dose)			
Tauber et al., 2007	361	352 (98%)	244 (range 5–19 783)
Lyons et al., 2007	22	21 (95%)	327 (95% CI 253.3/422.8)
Schuller et al., 2009	113	110 (97.3%)	218 (95% CI 179.81/264.41)
Woolpert et al., 2012	57	57 (93%)	79 (95% CI 54/114)
Erra et al., 2012	31	29 (94% Nakayama) 30 (97% SA14-14-2)	120 (Nakayama) 499 SA14-14-2
Kaltenböck et al., 2009	58	57 (98.2%)	192 (95% CI 147.9/249.8)
Jelinek et al., 2015	49	49 (100%)	>300 (data only in figure)

≥1month in JE risk areas, while out of the 13 (35%) travelers who stayed <1 month, three (23%) spent the majority of their time in rural areas, but six (46%) stayed in coastal or non-rural areas taking day trips to rural areas or national parks, and one (8%) stayed in a coastal area and took day trips to unspecified destinations. No exposure-related information was available for three (23%) travelers (12).

Therefore, in planning a trip where there is a risk of contracting JE it is recommended to vaccinate. As mentioned, since the virus is kept alive by a enzootic cycle between mosquitoes and various host animals, non-immune travelers and expats remain at risk of infection (12, 20). One can be protected from bites in different ways, using skin repellents and wearing appropriate clothes, staying indoors or protected, and avoiding the times of greater exposure to the risk of bites (such as the evening hours). Personal protection measures are important, since mosquitoes can transmit various other diseases, even non-vaccine-preventable, but they are not completely effective. Vaccination remains the best means of protection (25). Vaccination against JE should be offered to travelers on the basis of destination, season, adoption of personal protective measures, type of accommodation, uncertainty about the destination, activity and duration of travel.

As JEV is a clinically important emerging and re-emerging human pathogen of global importance, research has led to the development of different types of JE vaccines, such as inactivated mouse brain-derived, inactivated Vero cell-derived, live attenuated vaccines, and a live recombinant (chimeric) vaccine (10, 26). Over the past half-century, the mouse brain-derived inactivated vaccine has been used internationally for active immunization. In recent years, production of this vaccine has been discontinued, but new cell culture-derived vaccines have been developed and are available in various parts of the world. In Europe, an inactivated Vero cell-derived, inactivated vaccine is approved and recommended for both adult and pediatric use (starting from 2 months of age) (strain SA_{14}-14-2).

This vaccine provides significant protection against the most important JEV genotypes circulating in endemic countries (27). Primary vaccination consists in two doses four weeks apart, but a fast schedule (interval one week) is possible for adults 18-65 years. The vaccine can be administered concurrently with other vaccines for travelers, such as those against hepatitis A and rabies. As reported in the Summary of Product Caracteristics[4], seroconversion rates after the primary cycle is ≥99% in children and adolescents, 99% in adults 18-65 years at day 14 (rapid schedule, 2nd dose at day 7, co-administered with rabies vaccine), and 97.3% in adults 18-76 years, at day 35 (conventional schedule, 2nd dose at day 28). A third dose should be administered between 12 and 24 months after primary vaccination, if a potential re-exposure to Japanese encephalitis virus is expected. Long-term data suggest the administration of a second booster 10 years after the first booster dose and before potential re-exposure. Most adverse events following vaccine administration, both the first and subsequent doses, are usually mild and resolve in a few days.

A systematic review published in 2020 (28) which included 32 studies from 16 countries on immunogenicity and safety of vaccination against JE with this vaccine administered to adults, showed that seroconversion rates ranged from 93% to 100% (data from seven studies - Table 2). Rates of serious adverse events were <5% in all age groups, most of which were not causally related to the vaccine.

[4] https://www.ema.europa.eu/en/medicines/human/EPAR/ixiaro

Conclusions and future outlook

JE is a highly dangerous mosquito-borne disease that is often underestimated. Although cases among travelers are rare, they can be extremely severe. Climate change and intensive pig farming are responsible for increasing the risk of disease and extending the affected areas. JE can be prevented by the means of appropriate counselling and improved access to vaccination. Strengthening disease surveillance and control in the endemic areas is paramount, as well as raising awareness in non-endemic countries and recommending vaccination where appropriate.

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Riassunto

L'encefalite giapponese può essere devastante

L'encefalite giapponese, causata dal virus trasmesso dalle zanzare, è il tipo più comune di encefalite epidemica in Asia. È endemica nella maggior parte dell'Asia meridionale e sudorientale, ma il numero di casi può variare notevolmente tra le aree. Mentre molte infezioni non portano alla malattia, i casi sintomatici possono essere molto gravi e causa di decesso. Colpisce principalmente i bambini, mentre gli adulti sono generalmente immuni alla malattia a causa dell'esposizione al virus in età infantile o per la vaccinazione. Tuttavia, gli individui che non sono immuni, come i viaggiatori provenienti da paesi non endemici, sono suscettibili alla malattia se esposti al virus per la prima volta, indipendentemente dall'età. Senza opzioni di trattamento antivirale, la vaccinazione è l'unica strategia per stabilire una protezione efficace contro l'encefalite giapponese.

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