Review

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Japanese encephlu emergence in Australia: the potential population at risk

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Abstract

Japanese encephalitis virus (JEV), an RNA virus transmitted by Culex mosquitoes, primarily cycles between aquatic birds and mosquitoes with pigs as amplifying hosts, posing a significant global encephalitis threat. The emergence and spread of the JEV in new epidemiological regions, such as recent cases in Australia and nonendemic areas like Pune, India, raise significant concerns. With an estimated 68 000 clinical cases and 13 600 to 20 400 deaths annually, JEV poses a substantial global health threat. The virus primarily affects children, with a case-fatality ratio of 20–30% and long-term neurological sequelae in survivors. The changing epidemiology, influenced by factors like bird migration, climate change, and increased urbanization, contributes to the geographic expansion of JEV. The recent outbreaks underscore the potential for the virus to establish itself in nonendemic regions, posing a threat to populations previously considered at low-risk. With limited treatment options and high rates of neurological complications, continued surveillance, traveler vaccination, and research into treatments are crucial to mitigate the impact of JEV on human health. The evolving scenario necessitates proactive measures to prevent and control the spread of the virus in both endemic and newly affected areas.

Keywords: epidemiology, flavivirus, global impact, Japanese encephalitis virus (JEV), reservoir hosts, transmission cycle, vector mosquito

Introduction

The Japanese encephalitis virus (JEV) is an increasingly important global cause of virus-induced encephalitis. JEV is an RNA virus belonging to the genus *flavivirus*, which includes dengue virus, yellow fever virus, Murray Valley encephalitis, West Nile virus, Zika virus, and St. Louis encephalitis virus[1]. Like its other family members, JEV is transmitted by mosquito bites, principally the Culex species mosquitoes. *Culex tritaeniorhynchus* is the primary vector in most endemic areas. Other potential vector mosquito species include the *Aedes*, *Anopheles*, and *Armigeres* species, which have important implications for spreading the virus beyond the endemic regions due to the geographic distribution of their habitats[2].

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The transmission cycle of the JEV involves both vertebrates and arthropods. The main hosts of the virus are aquatic birds (such as herons, egrets, and ducks), which act as the primary reservoirs of the virus due to the development of high-grade viremia. The female *Culex* mosquito then plays the vector role in transmitting the virus from the primary hosts to other animals through mosquito bites. Pigs act as amplifying hosts for the virus, and due to the production of low-grade viremia, humans are the accidental, dead-end hosts in the transmission cycle. Thus, it is essential to note that mosquitos cannot transmit the virus from person to person. Cattle and horses can also become accidental, dead-end virus hosts.[3] Figure 1 shows the disease spread pathway of Japanese encephalitis (JE)[4].

According to the 2019 WHO report, nearly 68 000 clinical cases of JE arise globally each year, with ~13 600 to 20 400 deaths. JEV infections are most commonly asymptomatic in humans. It is estimated that <1% of people infected develop clinical disease[1]. Of those developing symptoms, disease manifestations can range from nonspecific febrile illness to acute meningitis or encephalitis, with acute encephalitis being the most common clinical manifestation[5]. Children aged 0–15 years are the most affected group and likely to have more neurological complications than adults[1]. The case-fatality ratio is 20–30%. Among survivors, 30–50% have significant neurologic, cognitive, or psychiatric sequelae[6]. Moreover, recent studies have reported the emergence of JEV in nonepidemic areas; the distribution of the disease has changed from being concentrated in Asia and the Western Pacific to now involving Europe, Australia, and Africa[1]. Up until 2021, JEV activity was limited to the far Northeastern region of Queensland, Australia. Eventually, the rare genotype IV (out of genotypes I–V), was identified in the Tiwi

Islands in the Northern territory, marking its appearance outside Indonesia[7].

With treatment options being limited and a high rate of neurological sequelae, the threat posed by JEV to public health is significant; its spread to newer geographical regions implies that an increasing proportion of the global population is at risk. Thus, the purpose of this review is to highlight the changing epidemiology of JE, its global impact, factors contributing to it, and possible proactive measures that can be taken to limit its spread.

Epidemiology

The first clinical case of JE was reported in 1871 in Japan. In 1935, the prototype strain called the Nakayama strain, was isolated for the first time from the brain of a patient who succumbed to the disease. The history of the spread of the virus can be summarized as follows: The first outbreak of JE occurred in Japan in 1924, accounting for about 3000 deaths in 6 weeks[8]. The first Korean case of JE was recorded in 1933, followed by China in 1940 and the Philippines in the 1950s. By 1983, the JE epidemic had reached Pakistan, and by the late 1990s, cases were reported in Papua New Guinea and northern Australia (Torres Straight)[9]. Consequently, in 2005, large outbreaks occurred in northern India and Nepal, with 5000 cases and 1300 deaths[8]. Currently, the significant burden of the disease lies in the Southeast-Asian and Western Pacific regions, including countries like India, Nepal, Burma, Bangladesh, China, Korea, Vietnam, Taiwan, Thailand, Philippines, Malaysia, and Indonesia, with an estimated 3 billion people at risk in the endemic regions[1]. Figure 2 shows the current geographical areas at risk of spread of the virus[10].

Due to the enzootic circulation of JEV, the virus has historically been considered a rural disease. However, population growth and economic development have led to its extension into new geographic areas, including peri-urban areas in many countries. JE has been declared a 'Communicable Disease Incident of National Significance' in Australia as of March 2022[11]. Between January 2021 and February 2023, there have been 45 cases of JE in Australia, with seven deaths attributed to the infection[3]. Additionally, in November 2022, a case of JE was reported in Pune, India, a nonendemic region for the virus[12]. This has raised concerns over a potential outbreak in a previously nonendemic region. The incidence of JE in newer geographical locations prompts the discussion of factors contributing to its spread. Several studies have suggested that seasonal bird migration across the globe could be responsible for the geographical expansion of JEV[13]. Other studies indicate that an increasing number of natural events, like cyclones due to climate change, can lead to wind-blown mosquitoes reaching newer areas, such as the ones responsible for the movement of JEV from the Torres Straits into Northern Mainland Australia[5]. Furthermore, the movement and transportation of infected hosts, namely pigs, has also been a significant contributor. Increasing populations have led to increased pig farming, especially in peri-urban areas, resulting in a massive increase in amplifying hosts[2]. Additionally, increasing urbanization means that a more significant number of people are turning to urban agriculture as an extra source of food and income, which brings amplifying hosts near humans, the impact of which is significant according to a study by Lindahl *et al.*[14]. Thus, the changing epidemiology can be contributed to various factors that have important implications for the further spread of the virus, if not managed appropriately.

Changing epidemiology of JE

South and Southeast tropic regions are endemic for JEV, and it is the most prevalent cause of vaccine-preventable encephalitis

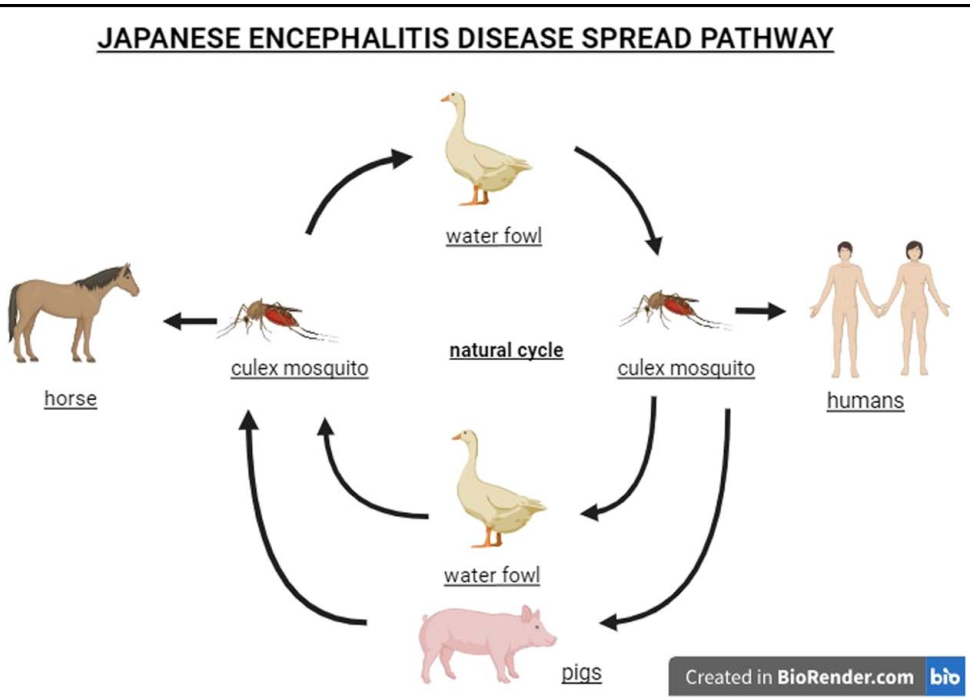

Figure 1. Japanese encephalitis virus (JEV) spread pathway.

Figure 2. Current geographical areas at risk of spread of the virus.

in the Asian Pacific region of the world[15]. It is also the most important cause of epidemic encephalitis worldwide[16]. It is been declared endemic in tropical regions, primarily infecting children, whereas subtropical and temperate regions are epidemic for this virus, primarily affecting adults[17,18]. Even though the drastic change in JE cases was observed by vaccination introduced by Japan, having been established in almost all 25 endemic countries, aggressive pesticide usage, and improved quality of surveillance, a substantial significant change has been shown by its major expansion in Asia. Almost half of the world's population has now become endemic to JE[19,20]. Although there is variation, globally, 100 000 cases are reported, creating 709 000 disability-adjusted life years owing to its debilitating complications[21].

Diverse factors inevitable for urbanization have been implicated in the contribution of JE transmission. One of them is agricultural changes. Favored options for agriculture in urban countries include pigs and poultry, and multiple studies have reported a significant rise in Aedes species of mosquitoes in the cities where many animal and pig-keeping areas are present[22]. Since pig and pork production has almost doubled in endemic countries, this has likely added to the cases of JE[20]. Besides, flourishing urban husbandry of birds has possibly played a part in its propagation as birds have been documented as expanding and reservoir hosts of JE[20]. Various studies have shown concern for the area spread of JE to new regions, including North America, through birds[23,24,25]. Furthermore, the rising number of cases of JE in travelers has drawn attention as indicated by these reviews, and assumptions that only adventure and leisure travelers are at high-risk of JE have been called to doubt by recent expanding cases in business travelers[26,27,28]. In the current study of travelers to Asia, business has been listed as the purpose of travel by more than 60% of the population, indicating the apparent association of the rise in JE cases with the globalization of the world and the increase in business travelers[28]. Similarly, in coastal urbanized regions of the world, fluctuation in the degree

of temperature leads to a rise in sea levels; considering the salinity tolerant nature of a variety of mosquitoes, including vectors of JE, an exorbitant hike in the cases of JE is seen when temperature increases significantly in temperature climates[25,29]. While it was previously assumed to be a rural disease, numerous urban and peri-urban countries, including South Korea, China, Singapore, and Taiwan, have been recorded as high-risk due to changing epidemiology[22,23]. A study conducted in South Korea demonstrated considerable transmuting of JE cases from rural to urban areas, questioning the assumption that JE is limited to rural areas[6]. A recent outbreak in Australia has further shared in the reckoning of its cases[30].

Emergence of JE in Australia

The emergence of JE in Australia marks a concerning shift in the country's epidemiological landscape. Historically, JE cases were localized and sporadic, with occasional infections reported mainly in the northern regions[31,32]. However, a significant shift occurred in 2022 and 2023 with an unprecedented outbreak in South-Eastern Australia[33,34]. Initially, the JEV was identified as the cause of stillborn and mummified piglets on pig farms in south-eastern Australia, which later led to human infections and affected pig farms[35]. The emergence of JE in Australia became evident with the unfortunate case of a 45-year-old female on the Tiwi Islands in February 2021. The patient, with comorbidities including end-stage renal disease and diabetes, presented with fever and increasing confusion, ultimately succumbing to the illness. The analysis of cerebrospinal fluid (CSF) and MRI findings aligned was carried out that aligned with JEV. Notably, the obtained JEV sequence belonged to genotype IV (GIV), previously believed to be restricted to the Indonesian archipelago. The Tiwi Islands case marked Australia's first locally acquired JEV[33]. With cases reported in the Tiwi Islands and a subsequent outbreak in eastern Australia, it is believed to have originated from enzootic areas in the Indonesian archipelago, Timor Leste, or possibly Papua New Guinea (PNG)[36,37]. This outbreak raises concerns about the potential establishment of JEV GIV strains in northern Australia, driven by population growth, deforestation, irrigated crop areas, and intensive pig farming[22]. Long-distance dispersal by wind currents, air or sea transport, and occasional Asian vagrant birds further facilitates the virus's geographic spread. The situation in eastern Australia suggests year-round transmission cycles may develop involving water birds, bats, and pigs, with Culex annulirostris as a significant vector[13,38]. While the virus's persistence in south-eastern Australia remains uncertain, other related flaviviruses co-circulate in Australia, and climatic factors like heavy rainfall and flooding play a crucial role in virus spread, as seen in the La Niña weather pattern's influence[39]. A comprehensive understanding of these dynamics is essential for assessing and mitigating future outbreaks.

Epidemiology among travelers

Traveling for extended periods in regions at high-risk for JE is associated with an increased likelihood of contracting the disease[40]. These high-risk areas encompass Western Pacific countries such as Australia, Cambodia, Japan, Fiji, and various parts of Southeast Asia. While it was once believed that residing in rural areas posed a higher risk for JE, Nealson *et al.*[41] reported the serological presence of JEV in pediatrics of Peri-urban and urban areas in Asian countries like Indonesia, Malaysia, Philippines, and Vietnam. JE is linked to close contact with reservoir hosts like pigs and wading birds, where the virus amplifies, and proximity to flooded rice fields where mosquitoes, the disease vectors, breed[42]. Travelers visiting endemic regions, especially those engaging in outdoor activities, are at greater risk, particularly during the evening or nighttime. Factors that increase exposure to mosquito bites, such as the absence of air conditioning, mosquito repellents, or bed nets, can also heighten the risk. The peak season for JE transmission varies by region, with temperate areas experiencing seasonal peaks in summer and fall. In contrast, tropical and subtropical regions have year-round transmission with peaks during the rainy season[43]. JE can affect individuals of all ages, but it is more prevalent in children under 15 in endemic areas[44]. The disease is more common in regions with childhood vaccination programs in adults. While the overall risk of JE among travelers is relatively low, it becomes comparable to the risk of the resident population in high-risk areas in long-term travelers. This risk depends on the traveling destination, duration, transmission season, activities, and accommodation[40].

In 1992, after her 9-week travels in Malaysia and Thailand, a woman returned to England with complaints of nausea and vomiting, which later developed into fever, confusion, photophobia, and drowsiness. She displayed regular physical exams with evident neurological symptoms like an altered level of consciousness, mild photophobia, constricted pupils, etc. Her EEG and CSF findings were consistent with meningoencephalitis, whereas the serology confirmed the presence of JE IgG and IgM antibodies[45]. In 2019, a 59-year-old unvaccinated male, returning from his 3-month visit to Bali, experienced fatigue, fever, headache, and confusion, which later progressed to flaccid paralysis and neurological dysfunction. He recalled numerous mosquito bites during his trip. His MRI and EEG revealed encephalopathy, and CSF confirmed JEV antibodies and RNA[46]. These cases necessitate using vaccines against JEV when traveling to JE endemic areas. The CDC recommends vaccination based on a person's travel itinerary, future travel to endemic areas, the vaccine's effectiveness, and associated adverse reactions. Regarding pregnancy, delaying travel or administering the vaccine is recommended when the benefits outweigh the risks. The Advisory Committee on Immunization Practices (ACIP) recommends long-term travel vaccinations in JE-endemic regions. For short-term travel (< 1 month), with increased JE risk due to factors like duration, season, and activities, vaccination should be considered[47].

For every million travelers, <1 contract JE; thus, it is a relatively low-risk disease, particularly in urban areas. However, certain activities increase the likelihood of contracting the disease, like visiting rural areas, staying in high-risk areas for at least a month, engaging in outdoor activities like cycling, camping, fishing, trekking, etc., extensive nighttime exposure, visiting during the rainy season, visiting areas close to or accommodations near pig farms, rice fields, and marshlands. Short-term travel, less than 1 month, restricted to urban areas is associated with minimal chances of JE contraction[47]. Due to the growing popularity of international travel for business, pleasure, or multinational corporations (MNC) expansion in JE endemic areas such as Southeast Asian

countries, a rise in travel-associated JE cases can be expected[20]. Of the 21 cases of JE reported among tourists in Southeast Asian countries from 1992 to 2008, half were on short-term travels in popular tourist spots, most notably Thailand, Indonesia, the Philippines, and China[27].

Clinical manifestations and consequences

Fewer than 1% of those infected with JE develop clinical manifestations, but the mortality rate is high among those who do, ranging from 20 to 30%. Symptoms at onset include fever, headache, and vomiting, which may progress to mental changes, limb weakness, and neurological symptoms, including seizure, particularly in pediatrics. Among acute complications, pulmonary failure and respiratory infection are the highest, requiring intensive care support. Out of those who survive, 30–50% continue to experience neurological, cognitive, or psychiatric issues[48,49]. Hyporeflexia, seizures, and abnormal muscle tone, including flaccidity and rigidity, are associated with poor patient outcomes[50]. Neurological symptoms like jet vomiting, irritability, drowsiness, convulsions, and twitching are more common among the pediatric population[51].

Following the study of the effects of JEV on brain organoids, Zhang *et al*. concluded that the virus triggered the interferon signaling pathway more strongly in older organoids than younger ones. This difference in response might explain the increased severity of the virus in younger individuals[52]. A recent study found that increased IL-1β and IL-10 expression contribute to increased severity and worse outcomes in JE infection[53]. The adult population has a range of moderate to severe complications, while children develop mild to sensible complications. Adult JEV infection is more prone to develop complications like bronchopneumonia, pulmonary atelectasis, gastrointestinal bleeding, septicemia, and urinary tract infection[51].

Clinical manifestations of other flavor viruses like West Nile virus include flu-like symptoms, for example, fever, chills, cough, malaise, arthralgia, myalgia, retro-orbital pain, and rashes in 50% of patients. St. Louis virus also has flu-like symptoms with neurological signs. Dengue infection ranges from a nonspecific febrile illness to a fever-arthralgia-rash syndrome. The disease may progress to dengue hemorrhagic fever, which is characterized by bleeding manifestations and dengue shock syndrome[54] (Table 1).

Treatment and management

Potential JEV drug targets

A range of proteins essential for viral processes could serve as potential targets for drug development. Opting to target host-related proteins may offer advantages over viral proteins by enabling the simultaneous targeting of multiple viruses, thereby reducing the risk of drug resistance. However, this approach might also result in cytotoxicity and adverse effects. Unique drug targets could include structural and nonstructural proteins such as capsid, envelope, NS3, and NS5[55].

C Protein

The 11 kDa C protein within the JEV engages with the viral genomic RNA, forming the nucleocapsid. This interaction predominantly occurs at the α4-4' site situated on the dimeric interface, which is identified by its coiled-coil-like structure near the C-terminal region of the protein[56]. Blocking the C protein's dimerization or the RNA-protein interaction at this particular site can pave the way for creating anti-JEV medications to enhance the stability of viral RNA[57].

M and E proteins

The prM and E proteins in the immature virion prevent the premature budding of virus particles. The dimeric E protein, a crucial element on the surface of the immature virion, undergoes structural modifications as it matures, leading to the creation of the mature virion. Within Domain 1 (D1) of the E protein, a site

Table 1

Clinical manifestations and consequences of Japanese encephalitis (JE) and other flavivirus infections.

Clinical manifestations	Japanese encephalitis (JE)	Other flaviviruses
Incidence rate	Fewer than 1% of infected individuals develop clinical manifestations	Variable incidence rates depending on the specific flavivirus
Mortality rate	High mortality rate among those with clinical manifestations, ranging from 20 to 30%	Variable mortality rates for different flaviviruses
Initial symptoms	- Fever - Headache - Vomiting	Fever - Chills - Cough - Malaise - Arthralgia - Myalgia - Retro-orbital pain - Rashes (in some cases)
Progressive symptoms	- Mental changes - Limb weakness - Neurological symptoms (including seizures, particularly in pediatrics)	Neurological signs and symptoms (specifics vary by flavivirus)
Acute complications	- Pulmonary failure - Respiratory infections (requiring intensive care support)	Neurological complications (specifics vary by flavivirus)
Long-term consequences	- 30–50% continue to experience neurological, cognitive, or psychiatric issues	Variable long-term consequences, depending on the specific flavivirus and severity of infection
Poor outcome indicators	- Hyporeflexia - Seizures - Abnormal muscle tone (flaccidity and rigidity)	Variable indicators, depending on the specific flavivirus and its impact on the nervous system
Pediatric vs. adult cases	- Pediatric cases often exhibit neurological symptoms like jet vomiting, irritability, drowsiness, convulsions, and twitching	Adult JEV infection can lead to complications like bronchopneumonia, pulmonary atelectasis, gastrointestinal bleeding, septicemia, and urinary tract infection
Age-related response	- Younger individuals may have a less robust interferon signaling response, potentially explaining the increased severity of the virus in this age group	Response to infection may vary with age and specific flavivirus
Increased severity factors	- Increased expression of IL-1β and IL-10 contributes to increased severity and worse outcomes in JE infection	Specific factors may influence the severity of infection with different flaviviruses

linked with N-glycans is associated with virion infectivity and its interaction with cellular receptors. This indicates that the glycan at N154 is the binding site for receptors. Through structural analysis, several potential sites for targeting within the E protein have been identified, including the β-OG ligand binding pocket in the fusion loop of EDII, the E-protein rafts in mature virus, and the E homotrimers in the postfusion state[58].

NS2B-NS3 protease

A vital function is carried out by a heterodimeric complex composed of NS2B and NS3, which cleaves sites sensitive to protease activity. These sites include NS2A-NS2B, NS2B-NS3, NS3-NS4A, and NS4B-NS5. NS3 possesses a serine protease domain at its N-terminus that is inactive when isolated but becomes active in conjunction with NS2B. This crucial proteolytic step is essential for creating the viral replicase complex and offers a promising target for potential treatments[59].

NS3 helicase

Through the resolution of DNA duplexes, the initiation of RNA synthesis, and the melting of secondary structures, NS3 helicase is essential for viral replication. To produce energy for strand separation, it possesses ATPase activity (NTPase)[60]. However, due to a lack of knowledge and concerns with cytotoxicity, utilizing NS3 helicase as an antiviral therapeutic target is difficult. Instead of conventional tests, high-throughput screening techniques using DNA substrates are now used to investigate helicase inhibitors[61].

NS5 methyltransferase (MTase)

The NS5 MTase presents a potential drug target because of its involvement in RNA 5'-capping, specifically in methylating the guanine cap at the 5' end and the ribose 2'-OH position. Mutations within the NS5 MTase impede viral replication, underscoring its essential function[62].

NS5 RNA-dependent RNA polymerase (RdRp)

The NS5 C-terminus has RNA-dependent RNA polymerase (RdRp) activity, initiating RNA synthesis without primers. NS5 RdRp is an attractive target because humans lack RNA-dependent RNA polymerase. Extensive research has explored nucleoside and non-nucleoside analogs to target viral polymerase activity. Non-nucleoside compounds impact allosteric sites, whereas nucleoside analogs, once activated, hinder the enzyme at the active site, providing an advantage in preventing drug resistance[63].

Potential JEV antivirals

Considering the disease's potential seriousness and capacity to spread beyond endemic regions, insufficient research into JE treatment options presents a significant issue. Currently, no cure for JE is developed, but supportive treatments benefit patients. Additionally, specific clinical problems that increase the risk of death can be managed[64].

Broad spectrum (Nonspecific) anti-JEV molecules

Numerous compounds exhibit potential as antiviral agents against the JEV. Rosmarinic acid, sourced from Labiatae herbs, diminishes GP78 strain JEV replication in mouse brains[65]. Curcumin disrupts the ubiquitin protease system, displaying antiviral properties against JEV[66]. Minocycline, a tetracycline antibiotic derivative, demonstrates significant antiviral effects by reducing virus levels, preventing neuronal cell death, inhibiting microglial activation, and safeguarding the integrity of the blood-brain barrier[3]. Ribavirin, an inhibitor of guanine nucleotide synthesis targeting inosine monophosphate dehydrogenase, exhibits limited efficacy against JEV, particularly in children[67]. Interferons and interferon inducers like aloe-emodin elicit an adaptive immune response against JEV infection[68]. Furthermore, inhibitors of HSP70, such as apoptozole, have proven effective in inhibiting JEV in laboratory settings[69].

Nucleic acid-based anti-JEV molecules

Advancements in micro-RNA-based technologies have opened doors for nucleic acid-based drug development against JEV. Using miRNA to target the viral genome inhibits virus propagation at the transcription and translation levels[70]. Additionally, shRNA can effectively silence specific portions of the viral genome, with studies demonstrating successful viral inhibition by targeting E, NS4b, and C genes[71]. Other nucleic acid-based drug approaches include morpholino oligomers and peptide nucleic acids (PNAs), which selectively bind to complementary viral genome sequences, allowing for precise inhibition of viral replication at specific sites[72].

Replication cycle-based anti-JEV molecules

Inhibiting viral replication at different stages is a potential strategy for drug development against JEV. Proteoglycans like heparin sulfate and chondroitin sulfate, crucial cellular receptors, are potential targets[73]. With its nuclease domain, MCPIP1 (monocyte chemoattractant protein 1-induced protein 1) displays anti-JEV activity by targeting RNA sites and inhibiting replication[74]. The phytochemical pokeweed protein extracted from Phytolacca americana depurinates viral RNAs, leading to JEV inhibition in mice[75]. Kaempferol, a natural flavanol, neutralizes JEV by binding to a frameshift site on viral RNA, demonstrating inhibitory activity[76] (Table 2).

Preventive strategies and vaccination

Vaccination is the most successful strategy for preventing JE, and the WHO recommends incorporating the JE vaccine into national immunization schedules in regions where JE is a public health threat. Even in areas with a moderate number of confirmed cases, vaccination should be seriously considered due to the potential for JEV transmission[49]. Randomized controlled trials provide conclusive evidence of the effectiveness of JE vaccination, establishing a clear correlation between neutralizing antibodies and protection against the disease[77]. Various JE vaccines, including purified, formalin-inactivated mouse-brain-derived, inactivated cell culture-produced, and live attenuated vaccines derived from cell culture, are available[78].

Inactivated mouse brain-derived JE vaccine

In 1934, Tenji Taniguchi developed JE-VAX, the first JE vaccine, gaining US FDA approval[79]. In 1965, Taiwan trialed a basic JE vaccine, demonstrating 80% effectiveness. Refined vaccines

achieved 80–100% seroprotection in adults in various countries. The Beijing-1 strain (P1) replaced Nakayama in 1988, providing better cross-neutralization and broader protection[80]. In 1967, China developed an inactivated vaccine based on JEV Beijing-3 (P3) in PHK cell culture, with lower adverse effects(78). Japan removed it in 2005 due to potential risks, but the WHO clarified no direct causation[81]. CDC recommended a three-dose schedule for children aged 1–3 years, resulting in 100% improved neutralizing antibodies within 6 months. Some maintained immunity for up to 2 years without a booster, though recommended[78]. Consequently, cell-culture-based vaccines have mostly replaced the JE-MB vaccine[81].

Inactivated cell culture-derived JE vaccine

JE-VC is a vaccine using the inactivated SA 14-14-2 strain of JEV in Vero cell cultures, with 0.1% aluminum hydroxide as an adjuvant[40]. Known as IXIARO (US, many countries), JESPECT (Australia, New Zealand), and JEEV (India), it includes a variant called TC-JEV from the inactivated Beijing-1 strain, licensed as JEBIK-V and ENCEVAC in Japan (2009, 2011) and Korea (2013)[82]. Initially for those aged 17 and older, JE-VC is now approved for use in those aged ≥ 2 months to 16 years[83], showing improved immunogenicity and antibody levels compared to the JE-MB vaccine. Common side effects, like headache, myalgia, flu-like symptoms, and fatigue, were observed in 13–26% of participants during the first week of immunization[40].

Live attenuated JE vaccine

The Live Attenuated SA 14-14-2 JE Vaccine (LAJEV), approved in China in 1988, is widely administered in Asia. It is a live attenuated vaccine created by introducing the SA14 strain of JEV to the PHKC[79]. Administered as a single dose for children aged 8–9 months and older, a booster shot is recommended 3–12 months later. Clinical trials show 85–95% effectiveness whether given as a single or double dose. According to the WHO, around 90% of those vaccinated develop neutralizing antibodies, which protect JE for at least 5 years[80]. Common postvaccination symptoms include local redness, swelling, and discomfort, while systemic reactions like cough, vomiting, runny nose, diarrhea, drowsiness, and fever (>38°C) typically resolve within 1–2 days[84]. Despite its widespread use due to its effectiveness, limited adverse effects, and cost efficiency, a drawback is its PHKC substrate in production, not endorsed by the WHO for human vaccine development[85].

Live recombinant (chimeric) JE vaccine

Sanofi Pasteur developed 'IMOJEV', a chimeric vaccine, using recombinant DNA techniques in Vero cells. This live attenuated viral vaccine replaced genes from the yellow fever 17D virus with those from the SA14-14–2 LAJEV virus[86], resulting in a highly effective single dose vaccine with a seroconversion rate of ~95%[78]. Advised for individuals aged ≥ 9 months to ≤ 18 years, a booster shot is recommended after 1–2 years. Adults (>18 years) in JEV endemic regions are also recommended to receive an initial single dose with an optional booster every 5 years[80]. Common side effects, noted in 17–24% of recipients during clinical trials, include headache, fatigue, myalgia, and malaise[87].

JENVAC

JENVAC, an additional JE vaccine produced using Vero cells, has obtained approval from the Drug Controller General of India through a partnership between Bharat Biotech Ltd. and the Indian Council of Medical Research (ICMR)(86). In clinical trials spanning individuals aged 1–50 years, the vaccine demonstrated excellent results, achieving seroconversion rates exceeding 90–96% and providing seroprotection within 28 days of immunization. Adverse effects were limited to mild symptoms such as fever, headache, vomiting, injection site pain, and body aches[88]. Notably, compared to the live attenuated SA-14-14-2 vaccine, it displayed superior immunogenicity. This vaccine is advised for individuals aged one year and older, including adults and children[89].

The population at risk: vulnerable groups and future considerations

JEV transmission has been limited to Asia and the Western Pacific, leading to limited global awareness. While occasional

Table 2

Potential JEV drug targets and antiviral molecules.

Drug target	Description	Potential drugs/Compounds
C protein	Involved in nucleocapsid formation by binding to viral genomic RNA	Dimerization blockers, RNA-protein interaction inhibitors
M and E proteins	Prevent premature budding of virus particles; E protein interacts with cellular receptors	Various potential sites for targeting within E protein
NS2B-NS3 protease	Essential for cleaving sites sensitive to protease activity	Inhibitors of NS2B-NS3 protease activity
NS3 helicase	Essential for viral replication; possesses ATPase activity	High-throughput screening techniques to investigate helicase inhibitors
NS5 Methyltransferase	Involved in RNA 5′-capping, methylating guanine cap, and ribose 2′-OH position	Targeting NS5 MTase function
NS5 RNA-dependent RdRp	Initiates RNA synthesis without primers; attractive target due to lack of humans	Nucleoside and non-nucleoside analogs to target viral polymerase activity
Broad spectrum antivirals	Nonspecific antiviral compounds with potential against JEV	Rosmarinic acid, Curcumin, Minocycline, Ribavirin, Interferons, and HSP70 inhibitors, among others
Nucleic acid-based antivirals	Target JEV through nucleic acid-based approaches	miRNA, shRNA, Morpholino oligomers, Peptide nucleic acids (PNAs), targeting specific viral genome sequences
Replication cycle-based antivirals	Target specific stages of viral replication	Proteoglycans like heparin sulfate and chondroitin sulfate, MCPIP1, pokeweed protein, and kaempferol, among others

outbreaks garner attention, the disease and its control have received little publicity. Countries like Japan, South Korea, Thailand, China, India, and Nepal have implemented vaccination programs, reducing the disease burden[90]. To prevent JEV, public health, and veterinary authorities must prevent its spread[91], primarily through vaccination, mosquito population control in endemic areas, and effective management of cattle herding and human dwelling sites.

Vector control

JEV primarily spreads through mosquito vectors such as *C. tritaeniorhynchus*, which breed in stagnant water areas like paddy fields. While controlling these vectors can help during short-term outbreaks, it is often costly and has limited efficacy due to mosquito insecticide resistance. Alternative approaches include using natural pesticides like 'neem' in rice fields and introducing larval fish into rice paddies. Insecticide-treated mosquito nets have effectively reduced JEV transmission in pigs and people in Assam, northeast India[86]. Another strategy involves using cattle to divert mosquitoes from pigs and people (zooprophylaxis). Long-term measures include better water management, disrupting mosquito reproduction in rice fields, and personal protective measures like mosquito nets and repellents[85].

Strategies for vertebrate hosts and human protection

Efforts should focus on separating pig populations from areas prone to mosquito breeding and controlling mosquito populations in regions with large-scale pig farming. It is essential to ensure that pig farms are situated away from human settlements and to immunize pigs and cattle in endemic areas. While vaccination is the primary preventive measure for humans against JE, its accessibility is limited in many underdeveloped countries. While strategies like mosquito repellents, protective clothing, window screens, and behavioral changes can help reduce mosquito exposure for short-term visitors or urban residents, they are insufficient in rural endemic areas with prolonged exposure[92]. Collaborative initiatives, often led by organizations like the Program for Appropriate Technology in Health (supported by the Bill and Melinda Gates Foundation), have played a crucial role in JE control[85]. Improved urban development, socioeconomic conditions, and agricultural practices have reduced JE burdens in numerous Asian countries. Effective reduction of JE's impact requires public awareness programs and efficient vaccine distribution, particularly in endemic areas where educating the population about the disease and preventive measures is crucial[85].

Limitations and future consideration

Current knowledge and research on JEV face significant limitations, primarily from diagnostic challenges and the low incidence of clinical disease among those infected. Human case surveillance, often the primary data source, provides limited early signals of transmission due to under-reporting and the asymptomatic nature of most infections. While informative, the reliance on mosquito and animal surveillance may not capture the full extent of JEV circulation. Moreover, regional disparities in surveillance capacity and global variations in resource allocation contribute to incomplete data. Addressing these limitations requires improved diagnostic tools, standardized surveillance practices, and collaborative research efforts[33].

In conclusion, JEV presents a growing global health concern with its changing epidemiology, expanding beyond traditional endemic regions. The emergence of JEV in new areas, such as Australia, underscores the need for proactive measures to contain its spread. Vaccination for travelers to endemic regions, particularly during outdoor activities, is crucial to reducing the risk of infection. While there is no specific treatment for JEV, ongoing research into potential drug targets offers hope for future antiviral therapies. Furthermore, continued surveillance and monitoring of JEV's spread and its impact on local populations and travelers are essential to understand better and manage this evolving public health challenge.

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