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FULL PAPER

An outbreak of Japanese encephalitis in Southeast Asia: A meta-analysis

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Japanese encephalitis (JE) remains a major vector-borne neurological disease across Asia and the Western Pacific, with substantial morbidity and mortality, despite the availability of effective vaccines. This meta-analysis synthesized seroprevalence data from Southeast Asia to provide an updated regional estimate and identify key demographic and environmental risk factors. Following PRISMA guidelines, eight eligible studies published between 2001 and 2024 were analyzed. The pooled seroprevalence of Japanese encephalitis virus (JEV) was 37.11%, with wide geographical variability across countries. Diagnostic methods included ELISA (IgM/IgG), neutralization assays, and hemagglutination inhibition tests. Risk factor assessment showed no significant differences between young and adult or adult vs. elderly populations. In contrast, gender- and location-based variations were observed: males showed a modestly higher risk in some models, and rural populations exhibited a 35% higher likelihood of seropositivity than urban communities. These findings highlight persistent JE transmission in high-risk areas and support the need for strengthened vaccination coverage, enhanced vector management, and improved diagnostic capacity, particularly in rural settings. Continued surveillance and targeted public health strategies are essential to reduce the burden of JE and to guide future vaccine implementation efforts in Southeast Asia.

KEYWORDS

Demographic risk factors; Japanese encephalitis; Japanese encephalitis seroprevalence; meta-analysis; Southeast Asia; vector-borne disease.

Introduction

The Japanese encephalitis virus (JEV) causes Japanese encephalitis (JE), a significant health condition affecting a large number of individuals in Asia and the Western Pacific region. JEV is responsible for encephalitis epidemics in the tropical regions of Asia, extending from Japan to India, parts of Southeast Asia, India, and more recently, Australia [1–4]. According to the World Health Organization (WHO), approximately 3 billion individuals residing in around 27 countries in the Asia-Pacific region are at risk of contracting JE. There are five different viral genotypes in various regions. Genotype I is present in Thailand, Cambodia, and Korea; genotype II is located in Southern Thailand, Indonesia, Malaysia, and Australia; genotype III is distributed across temperate Asian regions, including Japan, Korea, China, Taiwan, the Philippines, India, and Sri Lanka; genotype IV is present in Indonesia; and genotype V is found in Malaysia [5–8]. Japanese encephalitis is transmitted through a cycle involving mosquitoes and pigs, with migratory birds traveling from Indonesia to New Guinea contributing to the spread of the virus in Torres Strait [9–11].

The molecular pathogenesis of JEV infection remains unclear, although it is known to induce two distinct types of neuronal cell death: indirect neuronal cell death, which results from viral replication within neuronal cells, and direct neuronal death [12]. Due to its wide spectrum of symptoms and the necessity to distinguish it from other causes of encephalitis, diagnose JE is difficult. A reliable diagnosis requires a combination of laboratory tests, travel history, and clinical presentation. A history of travel to a JE-endemic region, especially during the mosquito season, is suggestive. The initial symptoms include diarrhea, headaches, and rigors, followed by seizures and altered consciousness. Complications may lead to deafness, flaccid paralysis, and movement disorders, such as hemiballismus, dystonia, and Parkinsonism [13,14]. Symptomatic treatment, neurological support, immunomodulatory medication, antiviral therapy, and preventative measures are the mainstays of clinical care [15–20]. This meta-analysis highlights the diverse seroprevalence of JE and associated risk factors across Southeast Asia, emphasizing the importance of targeted control measures, such as mass immunization campaigns and improved vector management in rural areas.

Methodology

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1). Medline/PubMed, Science Direct/Scopus, Google Scholar, and Web of Science were searched using the following keywords: Japanese encephalitis, JE, vector-borne, flavivirus, CNS invasion, neuroinflammation flavivirus, seroprevalence, seroepidemiology, and others related to incidence and risk factors in Southeast Asia (a detailed search strategy is provided in the supplementary file). Search queries included MeSH terms and Boolean operators "OR" and "AND," to find studies with relevant keywords in the title, abstract, and full text for the systematic review and meta-analysis. The study included observational research on JEV infection in Southeast Asia targeting at both the general population, sex, and specific age groups. Original research publications in English and those published between 2001 and November 2023 using the most recent data were included. The qualifying studies' JEV seroprevalence reports included those based on laboratory tests, employing techniques such as Enzyme-Linked Immunosorbent Assay (ELISA) IgG, ELISA IgM, and neutralization assays, in case-control, cross-sectional, and cohort studies. Screening was conducted by reviewing titles and abstracts to extract information on the sample size and outcome data. The full texts were reviewed, and duplicates or incomplete articles were excluded. Case reports and reviews were utilized for reference purposes only and were not incorporated into the main analysis, disregarding test specificity and sensitivity. Data extraction was performed between June 15, 2024, and August 15, 2024. There were no disputes in the first pass of the title and abstract review (Z. Z. Khan & S. S. A. Majeed). **Q2** Seroprevalence was observed in each article, and information from the full articles was entered into an Excel spreadsheet. The inverse variance approach and binomial equation were used to obtain the individual research weight, standard error, and 95% CI [21,22]. In addition, the logit transformation of proportionate prevalence, as well as the variance and standard error, were calculated.

The qualitative data were summarized in tabular form. Quantitative data were analyzed using R Studio via the Meta package. A random or fixed effects model was used based on the presence or absence of significant heterogeneity. I^2 statistics were used to measure the extent of heterogeneity as follows: no heterogeneity (0%), low (≤25%), moderate (25%-50%), substantial (50%-75%), and high (≥75%). Seroprevalence data reports were summarized by reference and study area, which included the study design, sample size, and type of test used [21]. Descriptive statistics were employed, and the results are displayed in figures and tables [23]. The risk of bias assessment for the study was conducted using the Newcastle-Ottawa Scale, and the quality assessment details are provided in the supplementary file.

Results of systematic review

The PRISMA flowchart of the overall procedures for selecting the final included articles is shown in Figure 1. The initial search identified 166 articles that were published between 2001 and 2024. First, no duplicate records were found. After further screening, 109 articles were excluded based on the evaluation of the abstracts and titles of the research papers. For secondary screening, 57 full-text articles were assessed, of which 19 were found to be eligible. Of the 57 studies, 38 were excluded for reasons such as non-human studies, assay methods, vaccine follow-up studies, systematic reviews, non-English language, and one protocol. Subsequently, 19 articles were assessed for eligibility criteria, and ultimately, 8 studies were included in the qualitative and quantitative meta-analysis. The selected papers reported the findings of studies conducted in Southeast Asia, including India, Nepal, Thailand, South Korea, Japan, and Taiwan. Three types of assays were used for the diagnosis across the studies for seroprevalence: ELISA IgM/IgG, neutralization assays, and hemagglutination inhibition (HAI) tests.

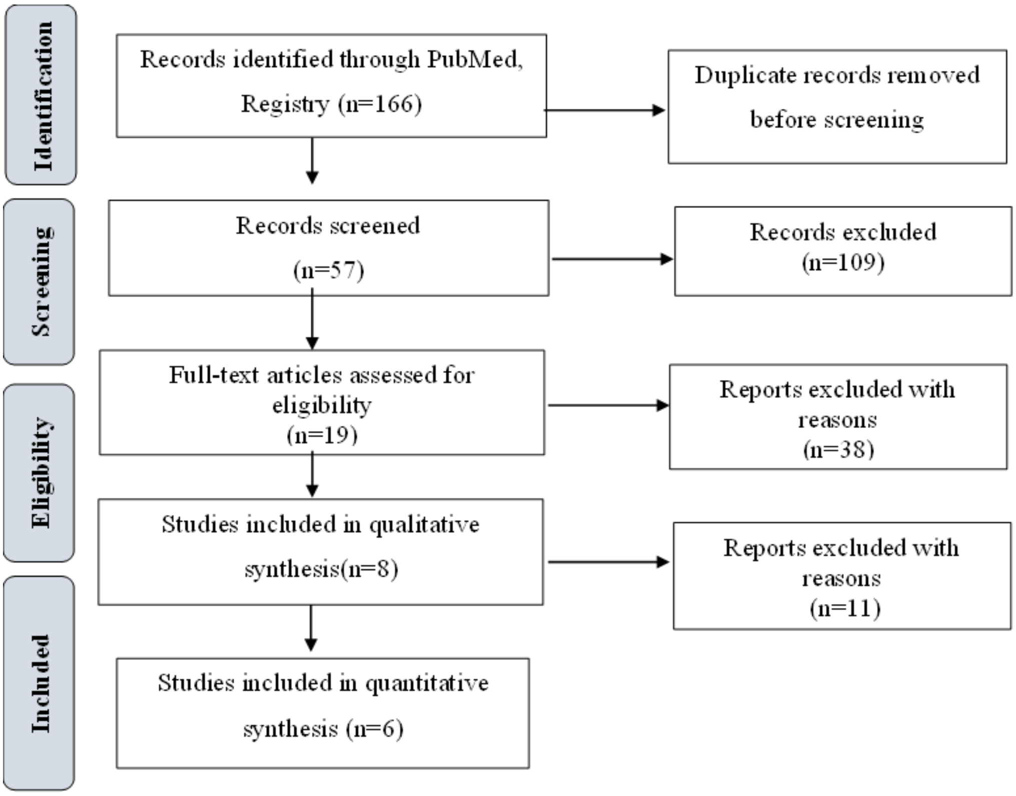

FIGURE 1 The search strategy and article selection process for the current review, as published between 2001 and 2024, using the PRISMA 2020 flowchart

Risk factors associated with JE seroprevalence

This meta-analysis provides key insights into the prevalence and risk factors of JE in Southeast Asia (Figure 2). A meta-analysis of the selected studies with a total sample size of 3,659 seropositive participants yielded a pooled seroprevalence estimate for JEV of 37.11%. These studies covered several Southeast Asian countries, including India, Nepal, Thailand, South Korea, Japan, and Taiwan, providing a comprehensive regional overview of JE prevalence. Several diagnostic methods have been used, including ELISA, neutralization assays, and hemagglutination inhibition tests, which, while potentially introducing variability, contribute to a more comprehensive understanding of JE detection. The seroprevalence data showed significant variations across countries and studies, with rates varying from 8.9% in Japan to 98% in South Korea (Table 1).

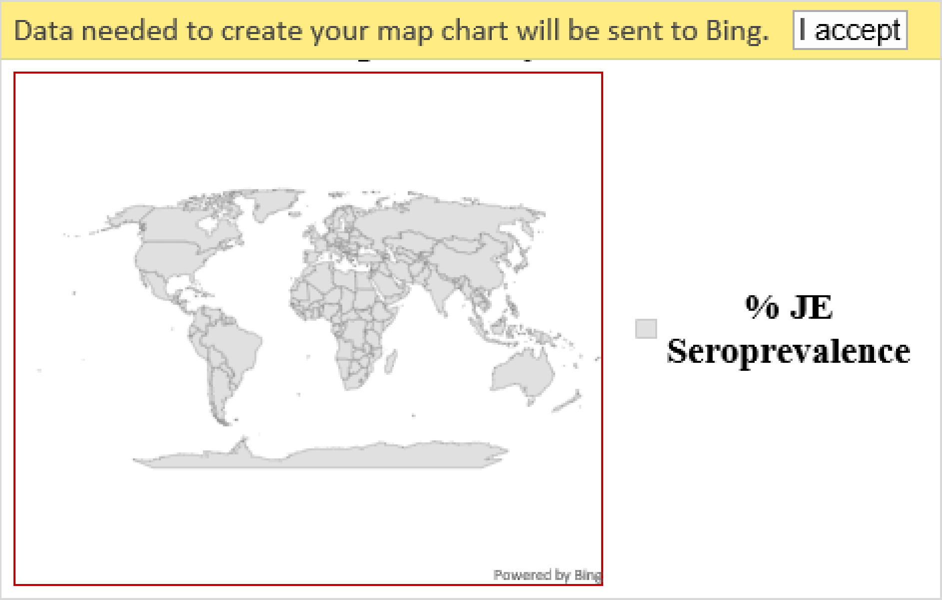

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FIGURE 2 The map depicts JE disease in selected Southeast Asia with % of seroprevalence in publications from 2001 to 2024, using MS Excel 2021. Data visualized using Microsoft Excel 2021. Darker shades indicate higher seroprevalence. Country values: India (15%), Vietnam (22%), Cambodia (18%), Japan (98%), Thailand (14%), and Philippines (12%). Grey indicates no data

TABLE 1 Seroprevalence of JE infections in Southeast Asia from selected publications from 2001 to 2024

Author	**Year**	**Region**	**Diagnostic Test**	**Total population**	**Seroprevalence of JE**	**% of Seroprevalence**	**Ref.**
A. Balakrishnan , *et al.*	2017	Kerala, India	Neutralization assay	1,125	179	15.9	[24]
A. Rayamajhi et al.	2007	Nepal	IgM ELISA	84	48	57.1	[25]
D. Lakhotia *et al.*	2023	Thailand	Neutralization assay	241	107	44.3	[26]
E. J. Lee *et al.*	2016	South Korea	Neutralization assay	945	927	98	[27]

Konishi, E *et al.*	2010	Japan	IgG ELISA, Neutralization assay, Hemagglutination inhibition (HAI) test	345	31	8.9	[28]
L. C. Hsu *et al.*	2014	Taiwan	IgM/IgG ELISA, Hemagglutination inhibition (HAI) test	2948	297	10	[22]
L. S. Singh *et al.*	2019	Manipur India	IgM ELISA	1770	251	14.1	[29]
T. Akiba *et al.*	2001	Nepal	IgM ELISA	2,403	1,819	75.7	[30]

This meta-analysis investigated age-related risk factors, comparing young (0-14 years) vs. adult (15 – 40 years) and adult vs. old (>40 years). The analysis showed no statistically significant difference in the risk between the young and adult groups (risk ratio, 1.01; 95% CI: 0.80-1.29, p=0.9145). A comparison of adults and the elderly also revealed no significant overall effect (p=0.2307), with a slight non-significant trend favoring an increased risk among the elderly. Gender-based analyses have produced intriguing findings. While one study (A. Balakrishnan *et al.*) **Q2** noted a highly significant rate among females, the overall common effect model suggested a modest but significant effect among males (RR = 1.13, CI excluding 1) [24]. However, the random-effects model revealed a larger but non-significant effect among males. Study design variations or local factors may significantly impact on gender-based risk, as indicated by the extremely high heterogeneity (I^2 = 98%) across the studies. The comparison between the rural and urban environments produced a borderline statistically significant result (p = 0.0506), indicating a potentially higher risk in rural areas. Both authors reported a high prevalence of JE in rural areas with 160 and 228 seropositive cases, respectively, while 19 and 23 seropositive cases were reported in urban areas, respectively [24,29]. A risk ratio of 1.35 indicates that JE events are 35% more likely in rural groups. The analysis showed that there was no statistically significant difference in risk between the young and adult groups (p = 0.9145). The overall risk ratio of 1.01 (95% CI: 0.80-1.29) indicates a small and non-significant risk increase for the young group (Figure 3). Additionally, with I^2 = 0% and τ^2 = 0, there is no evidence of heterogeneity among the studies, implying consistent results across all three.

A comparison of adults and the elderly (p = 0.2307) indicated no significant overall effect, as most studies and effect estimates had CIs that crossed 1 (Figure 4). Lakhotia *et al.* found a significant effect favoring the older age group (risk ratio < 1, CI does not cross 1), while Lee et al. had the highest weight in both models because of their large sample size. The overall effect, with an RR slightly below one, suggests a small, non-significant trend favoring the elderly. Moderate heterogeneity (I^2 = 41%, τ^2 = 0.0059) indicates some inconsistency between studies, which might require further investigation.

A significant difference between genders is shown in Figure 5 (p < 0.0001), favoring females (RR = 7.74, CI excluding 1), according to Balakrishnan et al. In contrast, the other three studies reported smaller effects with CIs that included 1, implying no significant difference between the sexes. The common effects model suggests a modest but significant effect favoring males (risk ratio = 1.13, CI excluding 1), whereas the random effects model shows a larger but non-significant effect

(RR = 1.83, with a wide CI including 1). The extremely high heterogeneity (I^2 = 98%, τ^2 = 0.9240) indicated a significant inconsistency across studies.

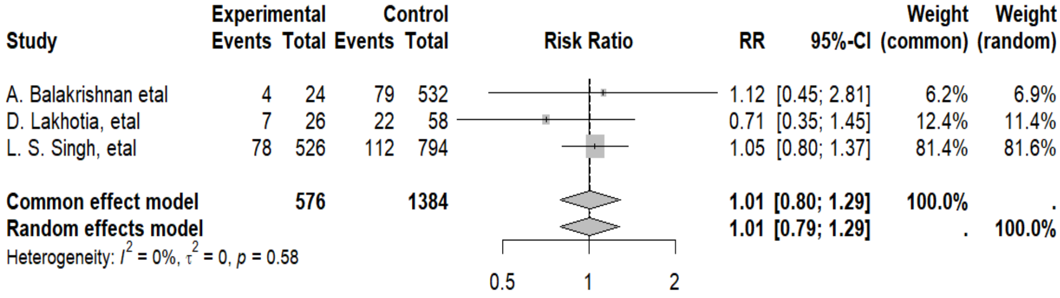

FIGURE 3 Meta-analysis of risk ratios (RRs) comparing JE seroprevalence in young versus adult populations. Effect size estimates are shown under both common and random effects models. No significant heterogeneity was observed (I^2 = 0%, p = 0.58)

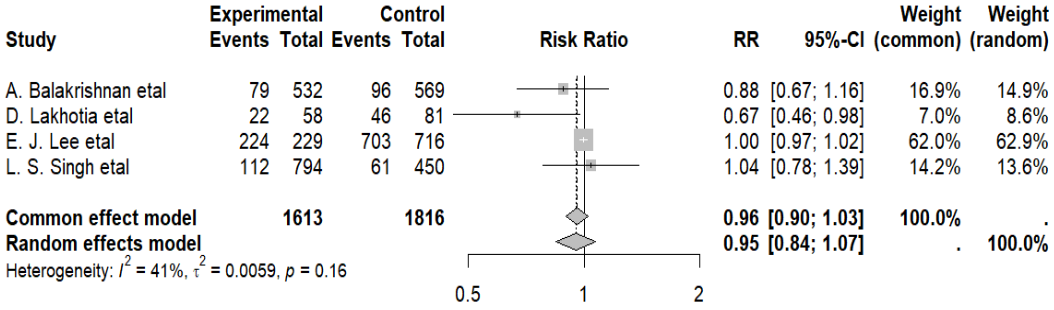

FIGURE 4 Meta-analysis of risk ratios (RRs) comparing JE seroprevalence in adults versus older adults. Pooled effect sizes are shown under both common and random effects models. Moderate heterogeneity was observed (I^2 = 41%, p = 0.16)

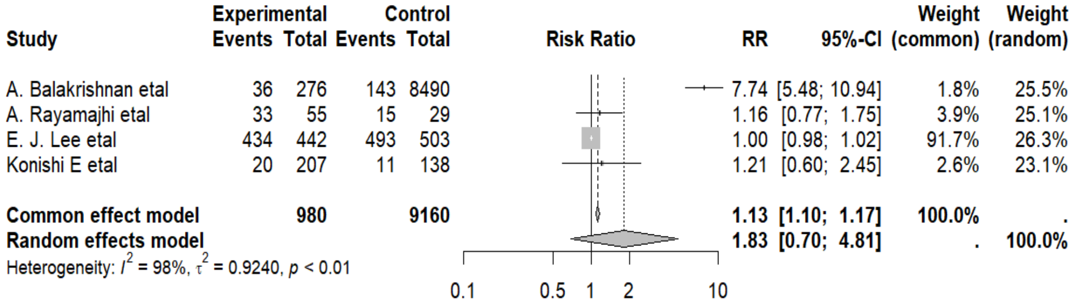

FIGURE 5 Meta-analysis of risk ratios (RRs) comparing JE seroprevalence in males versus females. Pooled estimates are based on a random effects model

A comparison between rural and urban environments suggests that the rural group may be at a higher risk than the urban group, with a risk ratio of 1.35, indicating that the event is 35% more likely to occur in the rural group. The 95% CI (1.00 to 1.82) approached 1.0, indicating a borderline statistically significant result (p = 0.0506) (Figure 6). The effect ranged from no difference to a significant increase in risk. Both studies had a risk ratio of 1.35, and heterogeneity statistics (I^2 = 0%, τ^2 = 0.0, p = 0.99) indicated no significant difference among them. The common and random effects models yielded the same results, suggesting the absence of heterogeneity.

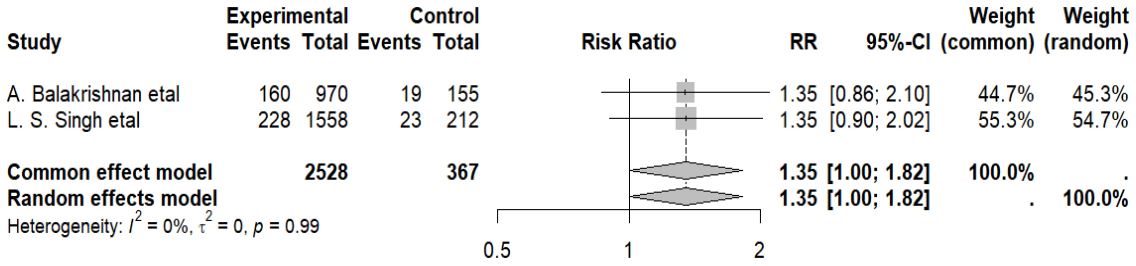

FIGURE 6 Common effect meta-analysis of risk ratios comparing JE seroprevalence in rural versus urban populations

Although there is some indication of increased risk, it is important to consider the magnitude and uncertainty of this estimate when assessing its clinical significance.

Discussion

This meta-analysis showed a higher risk among inhabitants of rural areas. This finding is consistent with the general understanding that rural areas, which frequently have more extensive mosquito breeding grounds and are closer to animal reservoirs, may pose a higher risk of vector-borne diseases such as JE. The prevalence of JE in Southeast Asia is significantly higher than that reported in Southern Europe, Northern Middle Eastern, and Northern Russian countries [31,32]. This disparity prompted an investigation into potential contributing factors. Geographic variations, including climate and ecosystems, may affect the abundance and behavior of Aedes mosquitoes, the primary vectors for JE transmission [31]. Additionally, differences in sanitation and hygiene practices as well as the effectiveness of vector control measures could influence JE prevalence [21]. Diagnostic capacity also plays a role; variations in the accuracy and sensitivity of detection methods may lead to discrepancies in the reported prevalence. This meta-analysis offers an assessment of JE epidemiology in Southeast Asia, revealing notable differences in seroprevalence and identifying the key risk factors. These findings show the need for tailored disease control strategies that consider local conditions, particularly comprehensive vaccination campaigns for all age groups. The heightened risk in rural areas calls for enhanced vector control measures and improved access to healthcare. Despite some limitations, this study's insights are vital for guiding future public health interventions and research efforts aimed at understanding and reducing JE transmission in the region. Future research should prioritize targeted interventions in rural areas and explore the influence of socioeconomic, environmental, and behavioral factors on JE transmission.

Future research on JE vaccines aims to enhance their effectiveness, availability, and safety, focusing on various key aspects. Next-generation vaccine platforms, including virus-like particles (VLPs), recombinant viral vectors, and nucleic acid-based vaccines (DNA or mRNA), provide benefits over traditional vaccines [33]. VLPs are safe and highly immunogenic, mimicking viral structures without the need for genetic material. Recombinant viral vectors such as adenoviruses can effectively deliver antigens and stimulate strong immune responses [34]. Nucleic acid vaccines enable rapid development, and encode multiple antigens to induce comprehensive immunity. Optimizing vaccine formulations and adjuvants is crucial for improving the immune response [35]. Adjuvants, such as Toll-like receptor agonists boost vaccine efficacy, while novel delivery systems like nanoparticles and microneedle patches enhance vaccine uptake and immunogenicity [36]. Developing vaccines that protect against multiple JE virus types and related viruses, such as West Nile and dengue, could expand coverage and lower the risk of new strains. Universal vaccines targeting shared epitopes among flaviviruses may provide broad protection, reducing the need for strain-specific vaccines [37]. Identifying immunological correlates of protection helps guide vaccine development by studying the mechanisms of protective immunity, such as neutralizing antibodies, T-cell responses, and memory immune cells [37]. Enhancing surveillance and integrating vaccination with control measures is crucial for the early detection and containment of JE outbreaks.

To prevent human cases, high JE vaccine coverage must be maintained due to the persistent presence of JEV in birds and mosquitoes. As JEV spreads to new areas, vaccination targets may change and expand. Monitoring JE spread is crucial because of the potential changes in mosquito distribution from migration, land use, and climate change. Additionally, vaccine hesitancy is increasing, even in the JE-affected regions [32]. In 2019, the World Health Organization (WHO) identified vaccine hesitancy as a major global health threat, highlighting the importance of maintaining trust in vaccination programs for high JE vaccine coverage. To ensure a stable supply of the widely used CD-JEV vaccine, a contingency plan is required. This plan should include off-site bulk storage and finding alternative manufacturing materials to mitigate risks from events, such as natural disasters, disease outbreaks, or issues with the source of vaccine cells [38]. Manufacturers need time to produce vaccines, which makes it difficult for countries to respond quickly to outbreaks. Ordering of vaccines in advance is necessary because of production timelines and limited stockpiles. For instance, CD-JEV takes up to nine months to produce and has a shorter shelf life than other WHO-prequalified vaccines [39]. The WHO suggests a one-time dose of CD-JEV without a booster, but India and China use it as a two-dose series, which affects vaccine availability. CD-JEV is preferred in many low-income countries because of its price and effectiveness, although other options are less favorable [40]. However, a variety of JE vaccines are still required globally. Insufficient surveillance and vaccination data pose significant challenges to understanding the impact of JE and supporting vaccine programs. Without immunization records, it is difficult to track vaccination status long-term, which is crucial for studying vaccine effectiveness and knowing when booster shots might be necessary [39,41]. Lab surveillance faces issues such as poor coordination between lab and epidemiology teams in some places, along with common challenges such as sample quality upon arrival, and international transport issues for testing at reference laboratories. The shortage of JE IgM kits poses a significant risk to routine diagnostics, especially if the sole producer stops production [42]. Reduced support from regional labs could jeopardize progress in diagnosis quality and capacity. Safety concerns regarding vaccines, particularly severe adverse events such as encephalitis, can fuel vaccine hesitancy, as evidenced by a 2014 incident in India where suspected encephalitis cases arose post-JE vaccination campaign and were later found unrelated, stressing the need for thorough investigations to avoid unwarranted fears. Ensure the safety of live-attenuated vaccines by thoroughly testing for potential risks such as reverting to virulence and adverse reactions [39]. Enhance vaccine safety monitoring and adverse event reporting to uphold public trust in vaccination efforts. Develop methods to manage vaccine storage, transport, and distribution in low-resource areas by creating stable formulations and delivery systems that are not reliant on cold chains. Monitor new viral strains that might affect vaccine effectiveness, and adjust vaccines based on continuous monitoring and research [43]. Ensure adherence to global safety, efficacy, and quality standards in navigating vaccine approval processes and also securing policy backing and funding for JEV vaccine initiatives [43].

Conclusion

In conclusion, JE remains a significant public health concern in Asia and the Western Pacific, affecting both children and travelers. The development and availability of effective vaccines, such as IXIARO® by Valneva, represent a critical advancement in combating this life-threatening disease. Despite the lack of existing antiviral therapies, vaccination has proven to be a pivotal tool for preventing JE, with immunogenicity rates for IXIARO® exceeding 90%. In 2006, PATH and CDIBP collaborated to offer affordable SA 14 14 2 vaccines to India, Nepal, and Sri Lanka until 2026, protecting millions of children from JE. The WHO recommends using IgM-capture ELISA to detect JEV-specific IgM in CSF or serum and suggests gold-standard molecular diagnostics, such as IFA, neutralization assays, HI assays, RT-PCR, and RT-LAMP. Universal vaccines targeting common flavivirus epitopes could offer broad protection, lessening the need for strain-specific vaccines by focusing on immune mechanisms, such as neutralizing antibodies, T cell responses, and memory immune cells. Future JE vaccine research seeks to improve its efficacy, accessibility, and safety by utilizing advanced platforms, such as virus-like particles (VLPs), recombinant viral vectors, and nucleic acid-based vaccines (DNA or mRNA). Valneva's dedication to innovation and global health, exemplified by the development of the IXIARO® vaccine, is crucial for reducing the burden of JE and for improving health outcomes worldwide. This meta-analysis highlights the varying JE seroprevalence and risk factors in Southeast Asia, emphasizing the importance of localized control strategies such as widespread vaccination and increased vector control in rural areas.

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