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Japanese encephalitis prevalence and outbreaks in Nepal and mitigation strategies: an update on this mosquito-borne zoonotic disease posing public health concerns

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Dear Editor,

Japanese encephalitis virus (JEV), a single-stranded, enveloped RNA virus, is a mosquito-borne flavivirus causing encephalitis, and one of the principal causes of 'Acute encephalitis syndrome' worldwide, especially in Asian countries[1–3]. This vector-borne disease is of high public health concern because of its propensity to cause epidemics and high mortality rate. The first Japanese encephalitis (JE) outbreak was reported in Japan in the year 1871[1]. Since then, the epidemiological trend in Asia, and particularly South East Asia, has been upward. The WHO estimates that around 68 000 JE cases occur worldwide annually, with 75% of the cases in the pediatric age group especially children aged less than 14 years, and ~10 000–20 000 people die annually. JE is of major public health concern in Nepal. The present correspondence article focuses on the JE prevalence and outbreaks in Nepal presents an overview on risk factors associated with JEV transmission and spread, advances in diagnosis and developing vaccines, and salient prevention and control strategies to counter this important disease.

Twenty-four countries in Asia and the Western Pacific are at risk for the virus[4]. However, cases and deaths are pointedly underreported and the true burden of the disease is not well understood in most endemic countries. Countries with known JEV epidemics are Pakistan, Burma, Laos, Philippines, Indonesia, China, Nepal, Sri Lanka, Korea, Vietnam, Malaysia Singapore, India, and Japan. Epidemic activity in Northern and Central India and Nepal has escalated since 1970[1]. In Cambodia, JEV was found to be causing acute meningoencephalitis (AME) in 35% of patients ($n = 1160$). Prevalence data from Vietnam indicate that JEV was responsible for 52% of AME cases ($n = 421$) between 1998 and 2007, and from 2007 to 2010, it was responsible for 23% of AME cases[1].

Outside Asia, JEV outbreaks have been reported from Australia and Papua New Guinea in the mid-1990s. Recently in 2021, the first case of JEV was detected in the Tiwi Islands in Northern Australia[5]. In a statistical estimation, based on the baseline number of people at risk of infection, there were an estimated 56 847 JE cases and 20 642 deaths in the year 2019. In the same year, India had the largest estimated JE burden, followed by Bangladesh and China[6]. Very recently, in March 2022, JE was declared a 'Communicable Disease Incident of National Significance' in Australia, a human case was recorded in Southern Queensland, and by May 2022, 41 human JE cases were notified in four states of Australia[7].

JE was an alarming menace in Nepal and is presently also a major health risk for its people. Cases showed a remarkable decline after an effective immunization program was established in 2009. JE is spread primarily by mosquitoes breeding in flood-irrigated rice fields. The first recorded JE epidemic in Nepal was in 1978, in the south of the Himalayan foothills. Thereafter, JEV spread to districts in the bordering hills and to the north, including the capital city – Kathmandu. From 2007 to 2015, 1823 JE cases were reported in 63 of 75 districts (84%) of Nepal with a cumulative mean incidence of 0.735/100 000 population and a 6.6% case fatality rate. A strong seasonal pattern peaked in the monsoon season, South-western and South-eastern Terai regions are endemic for JE, and high-altitude zones of hills and mountains also harbors JEV[8].

Nepal's Ministry of Health (MOH) recognized this peril and implemented a national-level surveillance network to better understand the disease epidemiology. Utilizing technical assistance from the WHO, Nepal expanded JEV laboratory testing to

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64 hospitals throughout the country in 2004, such enhanced surveillance provided a better estimate of the JE burden. So, in 2006, Nepal applied for a loan from the World Bank and purchased JE vaccine to add it to the routine immunization program for children in high-risk districts. This immunization program was expanded to more districts beginning in 2016 after the vaccine received WHO prequalification[9].

Recently, in September 2022, an outbreak of JE was declared in the Chitwan district of Nepal. Cases of JEV have been confirmed in Bharatpur metropolis, Madi Municipality, Rapti, Ratnanagar, and Kalika municipalities. The first case was detected in the first week of August and a total of nine cases were confirmed in the district, so far. Of the total nine cases, five were females and the rest were males, the age group was from 29 to 75. No mortality has been reported so far. A rapid response team comprising representatives from a local hospital, medical colleges, and the Nepal Red Cross Society was kept on standby for outbreak preparedness[3]. In 2018, 2020, and 2021, the district reported one case each year and no case were detected in the year 2019. In the country, vaccination against JE is a part of the national immunization schedule since 2009. The vaccine is given at the age of 12 months[10].

Over the past few years, we have seen a shift in the geographical and temporal distribution patterns of JE. Climate change, land use patterns (particularly cultivation of land and urbanization), social and economic shifts (the promotion of pig breeding as a food source), and a greater variety of vectors are all contributing to the disease's rapid expansion[11,12]. The virus is transmitted to humans through the bite of infected *Culex tritaeniorhynchus* or *Culex vishnui* mosquitoes, which lay eggs in irrigated rice fields and other stagnant water bodies. More JEV cases are seen in the rainy season and the preharvest period in rice-cultivating regions as vector population increases[10]. Wild birds are the natural reservoir of JEV, while pigs are mainly amplifying hosts which are frequently linked with outbreaks in the human population. Nonetheless, outbreaks do happen in absence of pigs which, in certain instances, indicates that birds may also serve as amplifying hosts. The risk for JEV infection is highest in agricultural areas, as all the components of the enzootic transmission cycle are close to humans[10]. The excess population growth, changing agricultural practices such as excess irrigation, intensified rice farming, and pig-raising affects vector propagation and longevity[5].

Most human infections with JEV are asymptomatic, less than 1% of people become symptomatic and acute encephalitis is the most frequent clinical manifestation. Other less common manifestations are aseptic meningitis or undifferentiated febrile illness. The JE patients can have varied symptoms like sudden onset of fever, headache, disorientation, focal neurological deficits, vomiting, generalized weakness, and abnormal movement disorders. Acute flaccid paralysis, very similar to that in poliomyelitis, has also been documented. The case fatality rate is ~20–30%. Among those who survive, 30–50% show permanent neurological, cognitive, or psychiatric sequelae. WHO estimates that 20–30% of people who outlive their infection suffer permanent intellectual, behavioral, or neurological sequelae such as paralysis, recurrent seizures, etc.[13,14].

Cerebrospinal fluid (CSF) cytochemistry shows a classical increase in lymphocytes, slightly elevated protein, and a normal ratio of CSF to plasma glucose. MRI scan is better than computed tomography for detecting JEV-associated abnormalities such as thalamic changes, and changes in basal ganglia, midbrain, pons, and medulla. JEV infections are confirmed most frequently by the detection of virus-specific IgM antibodies in CSF or serum, usually detectable 3–8 days after the onset of symptoms. Antibodies, which can be produced during preexisting illness or by vaccination, however, can last for up to 3 months[8]. The conventional diagnostics include PRNT (Plaque Reduction Neutralization Test), enzyme-linked immunosorbent assay, reverse transcription-PCR, and virus isolation, while advancements for developing immunosensors, nanotechnology, and CRISPR-based diagnostics, and metagenomic next-generation sequencing are being explored. Seroneutralization is considered the gold standard for diagnosing JE, but is a laborious methodology, poses chances of cross-reactivity with other flaviviruses, require biosafety level 3 facilities, and trained laboratory professionals, and is costly. Anti-JEV IgM antibodies detection by MAC-ELISA is the standard method endorsed by WHO and most commonly utilized method. CSF sample testing provides considerably more reliable confirmation than serum testing[9]. PCR assays for JEV RNA detection has high analytical sensitivity and specificity. As humans have low levels of viremia, that too for a brief period of time, virus isolation/culture and nucleic acid amplification tests are insensitive and are not used for ruling out a diagnosis of JE[13–15].

JEV infection confers lifelong natural immunity, and efficacious vaccines have been available since 1950 when a mouse-brain-grown, formalin-inactivated virus preparation was licensed for use in Japan. By the late 1950s, that first vaccine with proven efficacy was used widely in Japan and Taiwan, causing a decline in JE cases. In the 1960s, JEV vaccines eliminated the disease in Japan, Korea, and Taiwan and there was ten times reduction in the yearly incidence in China. But the killed vaccines required multiple doses, were difficult to be distributed in remote areas and there was a complex manufacturing process involved. It was phased out by 2011. Currently, almost 15 next-generation vaccines are available for JEV[16–18].

The live attenuated SA 14-14-2 vaccine is known to have the efficacy of above 95%, a 2005 study conducted in Nepal found that even with a single dose, the protective efficacy of 99% could be established, waning to 96% after a period of 5 years. The vaccine was prequalified by the WHO in 2013, and it became the first JE vaccine prequalified for use in children. This vaccine is included in the routine immunization schedule in Nepal and vaccination campaigns need be revamped against JE. Inactivated vero cell culture-derived JE vaccine (Ixiaro) is the only JE vaccine that is licensed and available in the USA[16–18]. The JE vaccine is recommended for high-risk travelers visiting endemic areas. Many endemic areas have adopted childhood vaccination to counteract JE[18].

Taking into account the considerable percentage of JEV outbreaks occurring in developing countries, the need for effective, cheap, and easily available drugs is certain, besides amplifying the vaccine coverage to eliminate JEV. There are no antiviral treatments for JE, management depends on supportive care such as control of intracranial pressure, maintenance of adequate cerebral perfusion pressure, prevention of seizures control, and secondary complications[17,18].

Prevention is critical for JE, which is accomplished by routine immunization and avoiding mosquito bites entirely. While mosquito nets and repellents may help avoiding the individual risk, there is no replacement for vaccination. Proper protective clothing that includes long sleeves, long pants, and covered feet should be adopted while going out. Clothing can be treated with repellents containing permethrin or other mosquito repellants to reduce the risk of mosquito bites. There is a need of further expansion of vaccination program at large scale and an effective vector control program.

As a result of successful pig and human immunization efforts, as well as improvements in agricultural practices, JE has been brought under control in many other nations. In contrast, JEV's coverage area in Nepal continues to grow annually, and possible causes of emergence and re-emergence of JE include insufficient human vaccination coverage, no vaccination in pigs, low public awareness, insufficient use of mosquito avoiding practices, climate change with the expansion of vector into new locality, expanding pig husbandry without sanitary and hygienic considerations, and existing irrigated rice farming agriculture system. The Nepal government can combat spread of JEV by adopting the following mitigation strategies[8,15,19]: (1) increasing the number of people who have access to vaccine by providing it free of charge; (2) educating public about JEV and the disease (JE), and enhancing awareness about salient prevention strategies through effective use of media, health sectors, educational institutions, or community intervention; (3) encouraging and supporting adequate use of mosquito avoidance practices, such as mosquito nets and repellants; (4) placing a high priority on improved agricultural practices like irrigation system management and pig husbandry practices; and (5) work in collaboration with India at border region to control cross country transmission of disease; and (6) strengthen diagnostic and surveillance facilities. Repeated outbreaks of JE in endemic areas and its geographical expansion into newer areas have posed huge challenges. Therefore, JEV surveillance and monitoring systems need to be improved for better understanding the drivers of its expansion in Nepal, exploring detailed epidemiology, spatial and temporal distribution of this disease, which would help in formulating and implementing an adequate JE control program along with needful location-specific prevention and control measures. Nepal must address these concerns and develop short-term, intermediate-term, and long-term strategies to better manage incidences and outbreaks of JE and safeguard health of the public.

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The authors declare that they have no financial conflict of interest with regard to the content of this report.

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