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Japanese Encephalitis: A vector-borne viral disease of public health significance

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Abstract

Japanese encephalitisis a vector-borne viral zoonotic disease caused by Group B Arbovirus of genus flavivirus.It is a leading cause of viral encephalitis in the Asia-Pacific region. It's transmitted to humans by the bite of infected mosquitoes. The Japanese encephalitis virus naturally maintains in the enzootic cycle between mosquitoes and migratory birds. The virus has recently tended to extend to other geographic regions. The disease is responsible for significant morbidity and mortality per year, especially in children below 15 years of age. Case fatality may reach up to 30%, and almost 50%of survivors are left with permanent neuropsychiatric sequelae. Although many vaccines are available for humans, currently, there is no specific cure for Japanese encephalitis except symptomatic treatment. Since flavi virus infection induces cross-reactive antibodies, there is growing concern regarding the diagnostic accuracy of serological tests. Therefore, diagnostic tests for field utility are still evolving. This review aims to provide an overview of Japanese Encephalitis and its epidemiology to increase awareness of the disease as a serious public health problem.

Keywords: Epidemiology**,** Japanese encephalitis, Pathogenesis, Public health, Vector-borne, Zoonosis

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1.INTRODUCTION

Japanese encephalitis(JE) is an emerging and re-emerging vector-borne viral illness that threatens humans and their environment, especially in healthcare settings. Among the well-known pathogens causing acute encephalitis syndrome, it is one of the leading viral agents in the Asia-Pacific region [1,2].Most parts of China, Southeast Asian countries, northern Australia, and the Indian subcontinent are endemic to this virus. In India, the Integrated Disease Surveillance Programme (IDSP) has also identified the prevalence of JE distributed all over India except Jammu, Kashmir, and Punjab [3].Japanese encephalitis virus (JEV) is transmitted to humans through the bite of infected *Culex*species mosquitoes. Disease causes substantial morbidity and mortality. A worldwide influence from JE in 2002 was estimated at 709,000 disability-adjusted life years annually [4].Approximately, 68,000 clinical cases and 15,000 deaths annually occur due to JE[5,6].About one-third of patients die, and almost half of the survivors suffer from cognitive dysfunction and severe neuropsychiatric sequelae imposing lifelong support in terms of socio-economic burden[7].

The emergence and re-emergence of JE are influenced by a variety of factors, such as humans, the environment, disease-carrying vectors, and pathogen-related factors. The disease is spreading at an alarming rate, and the recent identification of JE cases from the new epidemiological area outside the endemic zone has raised public health concerns[8, 9]. This communication is an attempt to delineate the public health implications of Japanese encephalitis.

2.EPIDEMIOLOGY

2.1.Geographic distribution

Although the first case of JE was documented in 1871 in Japan, the disease spread widely in the 20th century[6].The geographic overlapping of JEV is throughout eastern and southern Asia and the Pacific rim [10].According to the World Health Organization [6], twenty-four countries in South-East Asia and Western Pacific regions have endemic JEV. Almost half of the human population lives in these countries susceptible to JE outbreaks, subject inga giant proportion [more than 3 billion]of people to risks of infection [11].The annual incidence of disease ranges from <1 to >10 per 100 000 people. A resemblance in topography, climatic conditions [rainfall, monsoon, and post-monsoon season], and agricultural practices [paddy cultivation with flood irrigation method] play a role in providing a favorable environment for mosquito development and virus transmission [12].

In general, two epidemiological patterns of disease transmission have been addressed: endemic and epidemic. The endemic pattern is observed sporadically year-around in tropical southern areas [Australia, Burma, Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Papua New Guinea, Philippines, Singapore, southern Vietnam, southern Thailand, southern India, Sri Lanka, and East Timor][13].In an endemic region, JE viral circulation is observed throughout the year, with a seasonal peak after the start of the rainy season and possibly due to irrigation practices in farmlands. However, the epidemic pattern is more prevalent in temperate regions with typical seasonal characteristics. The northern areas, including Bangladesh, Bhutan, the People's Republic of China, Taiwan, Japan, South Korea, North Korea, Nepal, northern Vietnam, northern India, northern Thailand, Pakistan, and Russia, observe huge epidemics during the late summer/early autumn [2, 13].

Japanese encephalitis virus has expanded its geographical zone. In recent years JEV has been emerging in previously unaffected areas like Africa [8,14] and Europe [11,15]. The geographical extension of JEV is the outcome of biotic and abiotic factors and their dynamic interaction. Any changes in these variables, such as huge vector and host population, distribution, and travel and commerce, can influence the local transmission cycles to the susceptible area.

1.1 **Etiological agent**

Japanese encephalitis is caused by Group B Arbovirus belonging to the genus *Flavivirus* and

family *Flaviviridae* [16]. Hematophagous or blood-sucking arthropods [such as mosquitoes and ticks] carry and transmit the virus to humans during the bite. Thus, flaviviruses are also often referred to as arboviruses. More than half of the viruses in the genus flavivirus are serious human pathogens, for example, yellow fever, West Nile, Zika virus, St Louis encephalitis, tick-borne encephalitis virus, and Japanese encephalitis virus. They share a close genetic and antigenic relationship [2].

It is an enveloped single-stranded positive-sense RNA virus. Structurally, it has ~ 50 nm icosahedral-shaped lipoprotein capsid (envelop) enclosing eleven kb viral genome embedded with core protein [17, 18]. Phylogenetically, JEV has been divided into five genotypes (GI, GII, GIII, GIV, and GV)based on the sequence of the E (envelope) gene [19,20]; GI and GIII being the most common [21].Japanese encephalitis virus is one of the most important causes of viral encephalitis in Asia. It is a mosquito-borne virus transmitted to humans by the culicine (Culex species)mosquito[12].

1.2 Vectors

In general, vectors are arthropods [mainly blood-sucking mosquitoes and ticks] that, without getting infected, subsequently transmit the virus to vertebrate hosts. In vertebrate hosts, pathogen establishes infections and completes their growth cycle.

Japanese encephalitis virus is transmitted by several culicines, Aedes, anopheles, and armiger's mosquito species [22,23,24].Mosquitoes belonging to the genus *Culex*are the primary vector and reservoir of JEV. The *Culex tritaeniorrhynchus* predominantly transmit the disease in endemic regions[18].Extensive virus isolation and vector competence tests implicated the role of other Culex species in JEV transmission, such as *Cx. vishnui, Cx. pseudovishnui, Cx. gelidus, Cx. sitiens and Cx. fuscocephela*. In Australia, *Cx. annulirostris* has been established as the most probable prime vector[25] along with other Culex spp. These species, including *Cx. tritaeniorynchus*, are nocturnal [24].However, each species has life-cycle preferences; for example, *Cu. tritaeniorrhynchus* prefers to breed in irrigated paddy fields and bite throughout the night, especially in twilight [24, 26].The virus can co-opt many vectors whose ranges extend beyond Asia, indicating the potential for the virus to spread.

1.3 Host

Japanese encephalitisis an anthropozoonotic disease "transmitted from animals to humans."Horses are the primary and most susceptible host of JEV [27]. Man is the incidental host and gets only transient viremia. Both humans and horses are considered to be dead-end hosts. Although they can be infected by JEV, they do not achieve high concentrations of the virus in their blood, therefore unlikely to infect biting mosquitoes for further transmission [2,18].Other vertebrate hosts include cattle [28,29], sheep, goats, dogs, rabbits, etc.[27,30] also show detectable viremia but not enough to enable transmission to mosquitoes.

While birds play an essential role in the maintenance of the virus in its sylvatic cycle, pigs act as amplifier hosts in epidemic areas and maintenance hosts in endemic areas[31].Aquatic wading birds of the family Ardeidae, such as herons[black-crowned night heron], egrets, and bitterns, are the reservoir host of JEV, which often spills the virus over the wild and domestic animals present nearby[18,30].The virus has been isolated from bats [32,33];thus, capable of cross-species transmission between bats and other animals. Similarly, experimental studies have shown viremia in domestic birds [chickens, ducks, pigeons, etc.] similar to pigs [34,35]. Therefore, domestic birds can play the role of alternative amplifying vectors.

1.4 Predisposing Risk factors

Several factors are associated with JE occurrence and its spread. These can be classified as host, environment and pathogen associated factors.

2.5.1.Host-associated factors

It may include growing urbanization, deforestation, population bloom, traveling in an endemic area, etc. Behavioral characteristics and age specificity also have a significant role [36].For instance, the incidence rate is lower among young and adolescent children of <3 years old to 15 years due to more outdoor activity after dusk[37].It is primarily a disease in children and young adults. Similarly,

occupational exposure makes males more vulnerable[27].Recently a change in epidemiological characteristics of JE has been documented in China with an increased incidence of adult cases (>40 years old)[36].Although most cases occur in rural areas, JEV is also found on the periphery of cities. Common agricultural practices such as artificial flooding during irrigation, rice cultivation with pig rearing in rural areas, canal systems, and harvest cycles may greatly influence local mosquito density due to the availability of an optimal habitat for larval development [2,18]. Besides, the expansion of the Asian meat market due to increased demand and supply chains across Asia has also raised concerns regarding disease distribution [38].

2.5.2. Environment/ climate-associated factors

Geographical suitability is a significant contributor to endemic city and epidemics of the JE. Temperature, humidity, Rainfall pattern, monsoon and post-monsoon season, and abundance of the potential vector, are strongly correlated with the high prevalence of JEV in mosquitoes and seasonal outbreaks[31].Extensive study of the ecology between *Cx. tritaeniorhynchus* and paddy fields advocate that rice fields provide a better habitat for breeding for *Cx. tritaeniorhynchus* than natural breeding sites[22,24].Other climatic events such as floods, strong winds, and bird migration have been linked to outbreaks of JE and long-distance dispersal of disease-carrying vectors.

Global warming and climate change, including changes in precipitation and wind patterns, can significantly affect the dispersal of the vectors, reservoirs, and amplifying hosts of JEV[38].The expansion of JEV into Tibet [39] and Nepal [40,41], topographically elevated (up to 3100 m) and previously thought to be JEV-free, has raised queries regarding the role of climate change [42].Increased vector competence, i.e., the intrinsic ability of a mosquito to acquire the pathogen, and subsequently transmit the pathogen to a new host, is another factor that may be associated with climate change [16].

2.5.3 Virus-related factors

Flavi viruses have evolved to modulate the immune system to its favor and utilize many immune evasion strategies that limit host immune responses and viral replication [43].Japanese encephalitis virus genotype shift from Genotype III to Genotype I is an example of a virus-associated factor. From 1935 till the last decade of the 20th century, GIII was the dominant genotype prevailing in most Asian countries [1,10,44]and got replaced by GI isolates over the previous two decades. Recently, the number of GI isolates has increased and re-emerged as the dominant genotype instead of GIII in the same geography [45].Accumulated evidence implies that JEV down regulates the protective immune response [43] and promotes an immunosuppressive microenvironment [46] to persist in the host.

2.6 Transmission cycle

Japanese encephalitis virus is maintained in a sylvatic cycle by naturally transmitting the virus between wild and domestic birds, pigs, and *Culex* mosquitoes breeding in paddy fields [47].The enzootic or Sylvatic cycle is a natural maintenance or transmission cycle of a pathogen occurring uninterruptedly among non-human animals in a particular region or locality [37].

Although JEV can infect many animals, including horses and humans, only those with high viremia to infect mosquitoes contribute to disease transmission[27].For maintaining and amplifying JEV in distant places, birds have a significant role Ardeid birds are resident throughout the tropical regions but migrate to warmer climates during winter, thus introducing disease-causing viruses to a new geographical area[4].These wading birds brood near paddy fields and transmit the virus via mosquitoes to the pig population. Pigs are the primary source of infection for susceptible humans because they are often in close proximity, have sustained and high viraemias, and are prolific breeders to provide a constant pool of uninfected new hosts, i.e., newborn piglets. Pigs and avian hosts develop immunity shortly after initial infection; thus, newborn piglets as new susceptible hosts are required for the continuous transmission cycle.

Pig-to-pig disease transmission occurs via vectors. Boars are reported to transmit the virus in

semen [37]. Ricklin and co-investigators[48]recently demonstrate da direct transmission between pigs via oronasal discharges. Until now, there have been no reports of human-to-human transmission [49]; therefore, the probability of international disease spread due to human contact is low. Infected mosquitoes vertically transmit JEV [50], thus enhancing the magnitude of viral load in the endemic area.

Like other viruses, JEV does not persist well outside living beings. It is still ambiguous how the virus manages to last in cold climates; however, various potential secondary reservoirs, such as reptiles, amphibians, and bats, have been suggested to maintain viremia throughout hibernation [4,37], which may reestablish the virus in migrating birds.

1.5 Incubation period

The usual incubation period may range from 5-15 days in JEpatients [51].Experimentally infected horses may show clinical signs within 4-14 days, while pigs can develop signs after three days. However, some animals may develop febrile conditions within a day after being bitten by the infected mosquito[27].

2. DISEASE

A human is an accidental host who becomes infected with JEV coincidentally when living or traveling close to the endemic area. The disease pattern may vary from a minor flu-like sickness to deadly meningoencephalomyelitis. Japanese encephalitis is responsible for up to 30% of the case-fatality rate among patients with encephalitis. Up to 30%–50% of encephalitic patients may suffer from permanent neurologic or psychiatric sequelae [12].Early human studies have observed cross-reactivity among the different flavi virus of the Flaviviridaefamily [52,53].

2.1 Pathogenesis

Pathogenesis depends on various factors such as route of entry, virus titer, and neurovirulence of the virus inoculated during the bite, etc. Besides, age, genetic makeup, general health, and pre-existing immunity of the host also play a crucial role in setting up the pathogenesis course. After entering the body viathe bite of an infected mosquito, the JEVamplifies peripherally in dermal tissue and then lymph nodes causing a transit viremia [11].The virus generates antiviral responses leading to several pathological foci inside the host. Being a neurotrophic virus, it starts neuronal invasion and causes encephalitis syndrome or acute susceptibility to the central nervous system [54].However, there is still ambiguity regarding the mechanism by which JEV crosses the blood-brain barrier[4].However, experimental evidence suggests a passive transfer of JEV across the endothelial cells [54,55,56].

2.2 Signs and symptoms

Japanese encephalitis is commonly asymptomatic[37].However, patients suffering from JEmay present onset of acute febrile illness with a runny nose, diarrhea, headache, nausea, and decreased consciousness [27].Another important symptom is altered mental status consisting of confusion, disorientation, Aphasia (inability to talk), Changes in respiratory pattern, coma, and seizures or convulsions[11].Convulsions are more common in children than adults [57, 58].In some instances, unusual behavior is the only presenting feature, especially in adolescents and adults, which may mislead the initial diagnosis. In most children, generalized tonic-clonic seizures occur more commonly than focal motor seizures. Subtle motor seizures causing twitching of a digit, eye, or mouth, nystagmus, eye disorientation, or hypersalivation are seen. The patient exhibitsa classic description of JE- a dull, flat mask-like face, wide and unblinking eyes, tremors, generalized hypertonia, cogwheel rigidity, and other loco motor complications [59, 60].An acute flaccid paralysis similar to poliomyelitis-like has also been reported in a subgroup of JEV-infected children [61].

Rapid spontaneous recoveries are observed in most patients(abortive encephalitis)[62].While most cases will improve in 6 to 12 months, 30%-50% of the survivors continue to have significant neurologic, cognitive, or psychiatric symptoms [51].

3. DIAGNOSIS

Patients with JE exhibit an array of ambiguous signs of an acute encephalitic syndrome

like any other encephalopathy; thus, laboratory confirmation is critical for an accurate diagnosis [54].Like other viruses, flavi viruses can be diagnosed in laboratories using virological, molecular, and serological techniques. Molecular technique, such as reverse transcription polymerase chain reaction (RT-PCR), is one of the most extensively used laboratory methods for detecting viral RNA during the acute phase of the infection[63].However, this method requires an RNA extraction step to isolate the virus nucleic acid from the host before detection. Since JE has a short viremic period with a low titer, attempts to isolate the virus from clinical specimens are usually unsuccessful. Moreover, patients mostly show clinical symptoms after passing the viremic phase.

Isolates may sometimes be obtained from CSF or brain tissue.JEV RNA has been detected in the human throat [64] and CSF [54,65]samples using the reverse transcriptase polymerase chain reaction. Immuno histo chemistry of CSF cells or necropsy tissue with anti-JE virus polyclonal antibodies has been used to detect and confirm the viral antigens in the CNS.

Serological tests are the most practical way of diagnosing Japanese encephalitis. The plaque-reduction neutralization test (PRNT), micro-neutralization test (MNT), Virus-neutralization test(VNT), immunofluorescence assay (IFA), ELISA, and microsphere immunoassay, etc., are various serological tests that can be used for the detection of flaviviruses [66].PRNT quantifies neutralizing antibodies against flavi virus. It is the most specific test and is nowadays considered the standard gold test for detecting and quantifying JEV [67].MNT and VNT are other alternatives to PRNT.

Since flavi virus infection induces cross-reactive antibodies [68], there is growing concern regarding the diagnostic accuracy of serological tests like enzyme-linked immunosorbent assays [ELISAs] and hemagglutination inhibition[54]. However, IgM and IgG capture ELISAs are accepted standards for diagnosing JE. IgM capture ELISA is the most popular and extensively used diagnostic method [51,69].Recently, a nitrocellulose membrane-based IgM capture dot enzyme immunoassay has been developed, which can be read via the naked eye through a color change reaction [61].It is quick, easy to use, and requires no specialized equipment. It can be a tool applicable in field conditions for diagnosing the disease.

4. TREATMENT

There is no cure for JE except symptomatic treatment to alleviate the symptoms and stabilize the patient's condition to fight off the infection [6].Fortunately, vaccines are available to prevent disease. Depending upon the condition, symptomatic treatment may include fluids therapy, over-the-counter pain medications, sedatives, and respiratory support to relieve some symptoms [27].A comparative review of the different drugs used to treat JE has demonstrated that minocycline, a semisynthetic tetracycline, reduces the severity of the disease and shows the most promising results [70].It efficiently penetrates CSF and demonstrates neuro protective and antiviral properties.

5. VACCINATION

JE is a vaccine-preventable disease, and diverse types of vaccines are available for humans. As per WHO[71], four main types of JE vaccines are currently in use:

1. Inactivated mouse brain-derived vaccines (purified vaccine)
2. Inactivated Vero cell-derived vaccines
3. Live attenuated vaccines
4. Live recombinant [chimeric] vaccines

In 1930, the first inactivated JE Vaccine derived from mouse brain tissue was used all over Southeast Asia [72].Although it is proven to be of high efficacy, there was frequent reporting of severe side effects [2].Thus, live-attenuated vaccines were developed, which are more immunogenic and induce long-term immunity.SA14-14-2 live attenuated vaccine manufactured in China was prequalified by WHO in October 2013 and is one of the most well-established vaccines in endemic countries [71,73,74].It is safe, effective, inexpensive, and requires one or two doses in childhood [74,75,76].

A Vero cell-derived JE vaccine [JE-VC] was certified by the United States FDA in 2009.Currently, it can be used for adults 18- 65 years of age and in children two months to sixteen years of age [63,77].Various other vaccines, such as DNA vaccines, recombinant virus-based or chimeric vaccines, are still in different stages of development and testing [78].

6. PREVENTION AND CONTROL

All the effective measures targeted to control JEare those which interfere with the enzootic cycle and those which prevent disease spread in humans. Hence, prevention and controlare primarily based on three interventions; immunization system, mosquito control, and awareness campaigns.

Human vaccination is the most effective alternative for disease prevention. In pigs also, inactivated and live attenuated vaccines have been used widely to protect against the virus in an endemic area to break the enzootic cycle [2]. However, it is not a feasible approach in most settings. Residents and travelers to endemic areas should take personal protection to reduce the number of Culex bites. As per CDC recommendation, people who travel to JE endemic areas and engage in outdoor activities, are on short-term trips lasting less than a month, visiting affected areas during or after a recent outbreak should get vaccinated.

To avoid exposure to JEV-infected mosquitoes, travelers and outdoorsy people should use an EPA-registered insect repellent having at least 30% DEET (N, N-diethyl-3 methlybenzamide), wear long-sleeved shirts and long pants, and sleeping under bed nets. Avoid stepping out at dusk and dawn as culex activity peaks at these hours [6].While these measures may be possible for short-term visitors, most are not practical for residents of endemic areas.

Environmental sanitation measures are another critical target to control JE transmission. To stop or reduce the breeding of Culex mosquitoes, for instance, applying larvicides to paddy fields and insecticide spraying could be beneficial.

7. CONCLUSIONS AND RECOMMENDATIONS

Japanese encephalitis is a serious public health threat in many Asian countries. Due to the complex enzootic cycle, adaptation in mosquito species, sizeable human population, and proximity to pigs, it is nearly impossible to eradicate the disease. Although competent vaccines are available in the market, vaccination rates remain poor in most affected countries due to a lack of awareness and resources. Moreover, with ongoing challenges such as climate change, and global warming, there is no guarantee that disease will not affect the geographical area previously unaffected. There is a risk of emergence and re-emergence of JE into new regions due to ineffective vector control programs and changes in the migration pattern of birds due to climate change. Therefore, increased surveillance, immunotherapy, and the development of effective and practical diagnostic tools should be the focus area of research.

CONFLICT OF INTEREST

The authors declare that they do not have a conflict of interest.

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