

# Japanese Encephalitis: An Emerging and Spreading Arbovirosis

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## 1. Introduction

Japanese encephalitis virus (JEV) is a mosquito-borne flavivirus which causes significant epidemics of encephalitis worldwide with 50,000 cases of encephalitis mostly affecting the children below 10 years of age causing 10,000 deaths annually (Saxena 2008, Diagana et al., 2007). It is well distributed all over Asia and posing threat to many other nations (Yamanaka et al., 2010) JEV strong presence can be felt in the south, southeast, and the east regions of Asia (Shimajima et al., 2011). It is transmitted in an enzootic cycle involving water birds, domestic pigs and rice paddy-breeding mosquito's humans and other non-avian vertebrates. Pigs plays role of major amplifying host (Yamanaka et al., 2010). Humans are accidental/dead end hosts of JEV (Schuh et al., 2009) as their immune system cannot sustain high viral titres. Factors underlying the molecular clinical manifestations and pathogenesis of JEV infection are not completely elucidated. JEV consists of five genotypes: GI, GII, GIII, GIV and GV which are distributed worldwide and phylogenetic studies have revealed that GIII is predominant genotype of JEV with 15 strains in Japan and Korea (Schuh et al., 2009). JEV is expanding to the newer horizons as it is evident from the cases reported from the western parts of the globe. In the present scenario there is no specific treatment against JEV strains, few vaccines are available but they cannot treat all the strains of JEV further studies are require for the proper evaluation and their use in treating JEV infections.

## 2. History

Encephalitis outbreaks have been recorded since early 19<sup>th</sup> century in countries like Southeast Asia including Japan, Viet Nam, Cambodia, Myanmar, India, Nepal, Malaysia, China, Korea, Taiwan, Thailand and reached to the West including Pakistan and the northeast and southwest of India, also the East (New Guinea), the South (Northern

Australia Archipelago) and it is estimated theoretically to spread further West (Afghanistan). Between 1978 and 1992, 24 imported cases were reported in above regions due to high transmission.

<b>Transmission:</b>	Spread to humans by <i>Culex</i> mosquitoes, which pick up the virus from infected pigs.
<b>Symptoms:</b>	One in 200/800 infected people develop clinical signs like high fever and nausea. A quarter of patients with symptoms die; a third of survivors suffer brain damage.
<b>Treatment:</b>	Effective anti-viral drugs have yet to be found. Medicines are given mainly to relieve symptoms.
<b>Prevention:</b>	Vaccination for people at risk, eliminate mosquito breeding grounds, improve drainage, maintain clean piggeries, use insect repellent and mosquito nets

Table 1. Japanese Encephalitis: *at a glance*

Since the 1990s, the transmission of JE virus in humans has extended beyond its original geographical limits as it is evident from the case reports like in 1996, a woman in France suffered from JE after she had visited Thailand, in 1938. JE epidemic reported for first time in restricted seacoast areas of the 'USSR' and it reappeared in 1939. JE was isolated from human in the 'USSR' representing the first genetically characterized strain of JEV from this region, in 1946 major outbreaks of JE were recorded in Korea, in the civilian population in 1949 and among American military personnel in 1950 (Schuh et al., 2009).

Sequencing of JEV strains suggests that JEV is divided into five genotypes (GI-V) (Shimojima et al., 2011), which arose from its ancestor virus in the Indonesia-Malaysia region and evolved into five genotypes: GI, GII, GIII, GIV and GV, out of which GIV and GV are the most divergent which remained confined to the Indonesia-Malaysia region. GI, GII and GIII are the most recent genotypes spread across Asia (Diagana et al., 2007). Phylogenetic characterization in 1930s showed that GIII is predominant genotype of JEV in Japan and Korea since 1935 with 15 strains and GII is present from more than 19 years (Schuh et al., 2009).

GI was first isolated in Cambodia in 1967 and then in China in 1979 while genotype III strains were isolated before the 1970s (Fan et al., 2010). In Vietnam and Japan GIII strains were isolated between 1986 and 1990 and then GI was seen in 1995 and 2002 (Nga et al., 2004) proving that all the strains clustered into two distinct genotypes (III and I) and strains isolated before 1991 belonged to genotype III, whereas those strains isolated after 1994 belonged to genotype I (Ma et al., 2003).

### 3. New geographical regions covered

JEV Sequencing analysis results exhibiting alarming signal to the new regions as the growing evidences suggests the spreading of different JEV groups to the endemic regions Papua New Guinea and Australia GI includes strains isolated from Northern Thailand,

Cambodia, Korea, China, Japan, Vietnam, Taiwan and Australia between 1967 and the present. GII includes strains isolated from Southern Thailand, Malaysia, Indonesia, Papua New Guinea and Northern Australia between 1970 and 1999, GIII includes strains isolated in temperate regions of Asia from 1935 to the present. GIV includes strains isolated in Indonesia between 1980 and 1981 only, and GV includes a single strain isolated in Singapore in 1952. Sequence analyses of viral genes are further showing that a “genotype shift” from III to I has occurred in Japan since early 1990s, reasons for which remains unclear (Shimajima et al., 2011). Japanese encephalitis (JE) is spreading in the newer areas of northern states of India (Saxena et al., 2006, 2009).

#### 4. Morphology and properties

Flavivirus species, which like the Pestivirus and Hepacivirus, is related to the Flaviviridae family. The Flavivirus species not only includes the JE virus but also dengue, yellow fever and tick-borne encephalitis viruses. JE virus is an enveloped RNA virus with ssRNA as genome. It is spheroidal in shape having cubical symmetry, with size of 40-50 nm. Several non-structural and structural genes are present, where the three structural genes are vitally involved in the capsid formation process and are named as core(C), premembrane (prM) and envelope (E). E is expressed on surface and hence plays an important role in antigenicity.

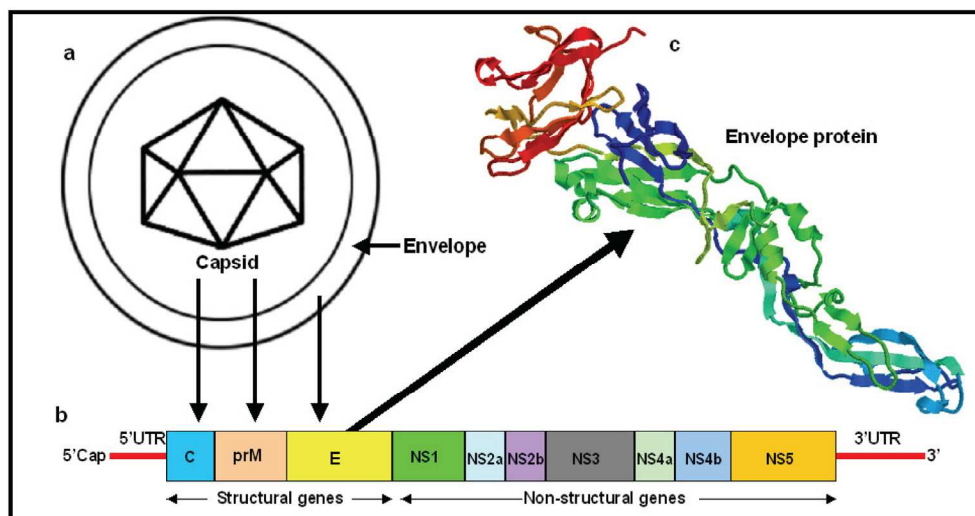


Fig. 1. Japanese encephalitis virus. Japanese encephalitis virus (JEV) structure (A), genomic organization (B), and assimilated structure of the JEV envelope protein (C). JEV genome contains a single open-reading frame (ORF) flanked by 5' and 3' UTRs. ORF consists of three structural genes (C, prM and E) and seven nonstructural (NS1 to NS5) genes

#### 5. Genome

JEV isolate from a pool of *Culex tritaeniorhynchus* collected in southern China had genome consisting of 10,965 nucleotides and included a single open reading frame that encodes a

3,432-amino-acid polyprotein (Zhang et al., 2009). The RNA genome is about 11kb in length having positive polar 5'cap but no 3' poly tail. Its genome can be divided into two parts: structural genes (codes for capsid, C; premembrane, prM; and envelope, E) and nonstructural genes (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5 are involved in viral replication). NS3 codes for Serine protease and NS5 codes for RNA dependent RNA polymerase, which is cause of mutation, JEV. The functions of other genes are still not understood. Replication of virus happens in cytoplasm and maturation on intracellular membranes (Saxena, 2008).

## 6. Transmission cycle

JEV was isolated from the brain of an encephalitis patient in Tokyo in 1934, and also from *C. tritaeniorhynchus* mosquitoes in 1938. Studies in Japan, showed pattern of JEV transmission cycle between pigs, mosquitoes, and humans. JE virus is transmitted through a zoonotic cycle between mosquitoes, pigs and water birds. Transmission cycle of JEV was elucidated, where pigs and wild birds played role as amplifying hosts and *Cx. tritaeniorhynchus* as the primary vector species. Pigs are important for pre-epizootic amplification of virus, although sometimes epidemics may rise even in their absence. Humans and horses also are only incidentally infected and are dead-end hosts of the virus due to low level and transient viremia (Misra and Kalita, 2010).

Numerous studies show similar cycles of JEV transmission, although in some cases virus may be detected in mosquitoes prior to amplification in the pigs. Differences in porcine infection rates within countries can also influence human infection, as was evidenced in Sri Lanka, where porcine synchronous seroconversions led to significant transmission to humans (van den et al., 2009) confirmed by enzyme-linked immunosorbent assay (Rajendran et al., 2003).

## 7. Molecular epidemiology

JEV is classified into 5 genotypes: GI, GII, GIII, GIV, GV. Genotype III (GIII) is widely distributed in Asian countries, including Japan, South Korea, Republic of China, Taiwan, Vietnam, the Philippines, India, Nepal, and Srilanka. By, past decade, JEV GI has been introduced into South Korea, Thailand, and China and has replaced the GIII strains that had been circulating in Japan and Vietnam during the mid-1990s (5). The strains JEV isolated from India till 2007 belonged to GIII (Saxena et al., 2008). JEV emerged in Japan in 1870's, four genotypes of it are recognized presently genotypes I to III are fully sequenced. Complete nucleotide and amino acid sequence of a genotype IV representative, (Indonesian isolate (JKT6468) and its comparison with other fully sequenced genomes has been done. In experimental studies, almost 290 JEV isolates are sequenced showing that all genotypes of JEV circulating in Indonesia- Malaysia region including divergent genotypes GIV and GV which represent the oldest lineages, whereas genotypes GI, GII and GIII circulating in the epidemic and endemic regions are very recent once. Phylogenetic comparisons with other flaviviruses show that it evolved from an African ancestral virus (Solomon et al., 2003). Nucleotide sequencing of C/PrM and E genes, have helped to identify four genotypes of virus. GI includes isolates from northern Thailand, Cambodia, and Korea, GII includes isolates from southern Thailand, Malaysia, Indonesia, and Northern Australia, GIII includes

Japan, China, Taiwan, the Philippines and Asia, and GIV includes isolates from Indonesia. One strain of JEV (Muar strain) is isolated from Singapore in 1952 from a patient, which may represent a fifth genotype. But in some cases this paradigm is violated as in Vietnam epidemic disease occurs in the north and endemic disease occurs in the south.



Fig. 2. Sequence phylogeny of JEV isolates. Sequence phylogeny of Japanese encephalitis virus isolates from the Gorakhpur (India) 2005 epidemic, with reference to other Southeast Asian isolates and flaviviruses based on partial E gene sequence. The tree was generated by neighbor-joining method. Bootstrap values are indicated at the branch points. DEN, WNV, KUN, SLEV and MVE denotes Dengue virus, West Nile virus, Kunjin virus, Saint Louis encephalitis virus and Murray Valley encephalitis virus respectively. (Source: Saxena et al. 2009)

Sequencing and phylogenetic analysis show that JEV strain JKT6468 virus genome is 10,978 nucleotides long and on comparison with 17 sequenced JEV genomes, it was seen that JKT6468 has least similarity, with high nucleotide divergence as compared to GI, GII and GIII strains. Analysis has shown that PrM gene has the greatest divergence.

Phylogeny distribution of the JEV strains was based on the E- gene which represents genotypes of the group/groups present in that country. In few instances different genotypes are present within the same country. So the countries are grouped into geographical areas based on geographical proximity, temperature, rainfall, etc which shows dispersed distribution of genotypes (Solomon et al., 2003).

Phylogenetic tree analysis for all JEV strains encircling E, C/PrM, or NS5/3 genes analysis, and GIV, GV comparison with GI, GII, and GIII confirm that the distribution of genotypes

have true differences. Other group analysis also shows a significant difference in the geographical distribution of genotypes. All genotypes are present in the Indonesia-Malaysia region, but only the most recently evolved genotypes (I, II, and III) are present in the other geographical regions. C protein and E protein structural analysis shows that JEV isolate from GIV (JKT7003) is found to retain identical sequence to JKT6468. GIII is the most widely distributed genotype and found in India, and it is predicted to eventually reach Australia, and GII might be found in China or Japan (Solomon et al., 2003).

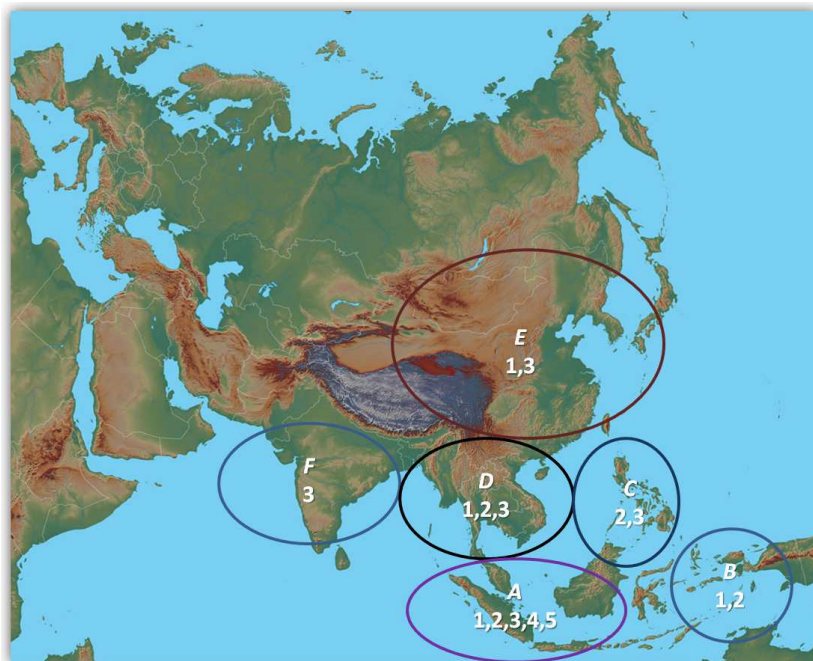


Fig. 3. The geographical distribution and spread of JEV genotypes. Countries are grouped into geographical regions: A, Indonesia (excluding New Guinea) and Malaysia; B, Australia and New Guinea; C, Taiwan and the Philippines; D, Thailand, Cambodia, and Vietnam; E, Japan, Korea, and China; F, India, Sri Lanka, and Nepal. Region A contains all genotypes of JEV, including the oldest. The newer genotypes (I, II, and III) have subsequently spread to other geographical areas. (Source: Solomon et al., 2003)

## 8. Epidemiology

JEV, transmitted by *Culex spp* mosquitoes, perhaps causes more cases of acute encephalitis than the other arthropod-borne viruses (Richard and John, 2002). JEV is a member of the JEV serological complex, which causes significant morbidity and mortality. The complex consists of eight species and two strains/subtypes including Japanese encephalitis. JEV is the most important member of the JEV group, with an estimated worldwide annual incidence of 45,000 human cases and 10,000 deaths. However, because of insufficient medical facilities and inadequate data collection, JE cases are underreported. Thus, the true annual incidence

of encephalitis cases is estimated to be closer to 175,000 (van den et al., 2009). JEV is distributed in temperate and tropical areas of eastern and southern Asia. Its geographic range extends from eastern Asia (China, Japan, Korea, maritime Siberia, Taiwan, the Philippines, and Vietnam), to Southeast Asia and northern Australasia (Cambodia, Indonesia, Laos, Malaysia, Papua New Guinea, Thailand, and the Torres Strait islands of northern Australia), and to southern Asia (Bangladesh, Bhutan, India, Myanmar, Nepal, and Sri Lanka). A single report has also suggested that JEV may occur in Pakistan (Solomon and Winter, 2004). JE is largely a disease of rural areas, especially associated with irrigated rice agriculture. In general, two epidemiological patterns of JEV have been recognized: endemic activity in tropical regions, such as southern Thailand, and epidemic activity in temperate and subtropical regions. In endemic areas, no seasonal pattern exists and sporadic cases of encephalitis occur throughout the year, most often in infants and young children, although cases may peak after the onset of the rainy season. Serological tests have shown that by the time children reach adulthood all have been exposed to JEV and possess neutralizing antibodies. Epidemic activity in temperate and subtropical areas occurs most commonly in summer or early autumn after the rainy season, which may extend from spring to late autumn (van den et al., 2009). Because of its prevalence and mortality JE is a major public health problem in endemic-epidemic regions as due to severe susceptibility of the Children and young adults (Diagana et al., 2007). There is a peak in vector density and virus activity during the north-east monsoon period, October-December (Mani et al., 1991 in endemic zones the percentage of JE antibodies increases with age whereas during an epidemic outbreak both adults and children are equally susceptible (Diagana et al., 2007).

REGION	AREA	SEASON	HOST/VECTOR
<b>Endemic region</b>	Southern India, Southern Vietnam, Southern Thailand, Philippines, Malaysia and Indonesia.	Rainy	Mosquitoes, birds, pigs and human cases are rare.
<b>Intermediary subtropical region</b>	Includes Northern India, Nepal, North and Central Burma, Northern Thailand, Northern Vietnam, Southern China and Bangladesh.	Rainy	Epidemics in contrast, and severe and concentrated among children.
<b>Temperate epidemic region</b>	Northern China, Korea, Taiwan and Southern extremities of Russia. Also Pakistan, Afghanistan, Nile valley, Madagascar and Oriental Africa.	Summer and Autumn	Postulated explanations are migration of birds, certain irrigation projects, animal smuggling and global warming.

Table 2. JE is primarily found in South East Asian countries. Three epidemiological regions can be distinguished (Diagana et al., 2007)

From past 75 years the focus was on China and Southeast Asia, but now Japanese encephalitis has expanded westward to India and Pakistan, northward to eastern Russia, eastward to the Philippines, and southward to Australia. In the northern region, epidemics

occur during the warm summer months, In China, 20 000 symptomatic cases are reported annually. The ratio of symptomatic to symptomless infections is around 1:25 to 1:1000. In areas where Japanese encephalitis is common, it is primarily a paediatric disease; however, more cases are seen in adults in new place of exposure (Richard and John, 2002). Occurrence of JE is more closely related to temperature than to humidity in the atmosphere (Misra and Kalita, 2010). JEV has caused major epidemics as it invaded new areas, often enabled by rice culture and amplification in domesticated swine (Weaver and Reisen, 2010).

## 9. Geographical distribution

JEV, the most frequent arboviral cause of encephalitis worldwide, has spread throughout most of Asia and as far south as Australia from its putative origin in Indonesia and Malaysia. Here is a brief outlook:

### 9.1 Japan

Until 1990s, only GIII JE virus was identified in Japan, and then the genotype seemingly shifted to GI. On the basis of molecular epidemiological study in Vietnam, China, and Japan, it was found 8 subgroups of GI JEVs are circulating in East Asia and introduced to Japan through China due to the bird migration and/or infected mosquitoes (Morita, 2009.) JEV infects numerous animal species including humans, horses, pigs, raccoons, wild boars and raccoon dogs recently a study found that it was present in *C. tritaeniorhynchus* feed on small Asian mongooses on Okinawa Island indicating that they are sensitive to JEV (Saito and Nakata et al., 2009). (Ohno et al., 2009). Distribution of JEV has dispersed to new areas due to migratory birds like wild ducks (*Anas poecilorhyncha*) which highlight that there may be circulation of JEV in these captured birds. A sero-epizootiological showed several race horses showing high antibody titer (Sugiura and Shimada, 1999). Serum samples of cattle raised in Saitama and Kagoshima Prefectures also showed antibody titers against JEV (Horimoto et al., 1989).

*C. tritaeniorhynchus* is major mosquito vector in Japan, but recent surveys show that *C. pipiens* and *Aedes albopictus* as potent competitors too (Konishi, 2005). GI JEV was also collected from mosquitoes and from swine serum samples collected in Okinawa Island. GI is distributed from northern Thailand to Cambodia and recently expanded to Australia, Vietnam, the Republic of Korea, and Japan (Saito and Taira et al., 2007). Wild boars in the Northern area of the main Okinawa Island in Okinawa Prefecture are infected with JEV which is amplified on pig farms tested for JEV antibody by hemagglutination inhibition assay and IgG enzyme-linked immunosorbent assay (Nidaira et al., 2007).

### 9.2 Bali/Java

Pigs are effective amplifying hosts for JEV, as antibodies to JEV is present majorly in pigs of bali and java (Yamanaka et al., 2010).

### 9.3 Thailand

Here the estimated occurrence is more than 40/1000 in hospitalized patients (Diagana et al., 2007) who serve as evidence of acute flavivirus infection. 10% of patients in Bangkok



hospitals and 28% patients in southern Thailand were found to have JEV infection (Sonja et al., 2010). JEV genotypes studies in pigs and mosquitoes collected near houses of confirmed human GI JEV cases (Nitapattana et al., 2008). This surveillance study shows an increase of JEV cases during the rainy-seasons.

#### 9.4 India

Epidemiological investigations incorporating identification of blood meals of vector mosquitoes proved their involvement in the transmission of JEV from the Kuttanadu area, Kerala. *C. tritaeniorhynchus* is highly zoophagic and human feeding and also *Mansonia indiana* and *Ma. uniformis* feed on humans showing significant role played by these mosquitoes in the transmission of JEV (Philip Samuel et al., 2008). JEV activity in endemic areas of Tamil Nadu (southern India) is studied, using ELISA (Tewari et al., 2008). JEV was detected using antigen capture ELISA in dry specimens of the mosquito *C. tritaeniorhynchus* in Karnal (Haryana) (Das et al., 2005). *A. subpictus* serves as a secondary vector in JEV transmission in Cuddalore, Tamil Nadu showing natural transovarial transmission of the virus through *A. subpictus* (Thenmozhi et al., 2006). JE is found endemic in Cuddalore district, TamilNadu (Kabilan et al., 2004). In a serological survey of birds in Kolar District (Karnataka) by hemagglutination-inhibition test it was showed that bird species such as Pond Herons, Little Egrets Grey Partridges and Quails are infected with JEV and play role in the JEV infections (Jamgaonkar et al., 2003) (Rajendran et al., 2003). Three cases of JE were reported for the first time from two villages in Krishnagiri Health Unit district of Tamil Nadu. Sixteen serum samples from patients were sent to the Department of Virology, Calcutta, which is first documentation of concomitant JEV and HIV infection in the eastern India (Neogi et al., 1998).

#### 9.5 Malaysia

JEV is an important encephalitis virus in Malaysia, which was thoroughly studied in Sarawak, Malaysia. JEV is endemic in Sarawak, with cases occurring throughout the year (Wong et al., 2008) a few cases have been reported in tropical Asian countries (Kari et al., 2006). JEV is an important causative agent of viral encephalitis among pediatric admissions in Penang, Malaysia was proved by an IgM capture ELISA (Cardosa et al., 1995). Studies also show encephalitis in Perak, Malaysia with data showing titers of neutralizing antibodies against JEV (Cardosa et al., 1991). JE epidemic occurs sporadically throughout the year and is generally asymptomatic (Sinniah, 1989).

#### 9.6 Philippines

A long-term study in Philippines confirmed acute cases of Japanese encephalitis via IgM-capture ELISA, which detects anti-JEV immunoglobulin M (IgM) in cerebrospinal fluid (CSF) samples (Natividad et al., 2006) (Kari et al., 2006). Mosquitoes were collected from Tagudin, Ilocos Sur Province, Philippines, and found positive for the presence of JEV by the help of microneutralization test (Trospier et al., 1980).

#### 9.7 Korea

Serological survey of JEV infection in goats in Korea provide incidence of positive cases indicating that JEV infection is frequent in goat farms in Korea (Yang et al., 2007).

### 9.8 Nepal

Regional survey conducted in Nepal for antibody to JEV in pigs, ducks and horses showed positive result for the presence of antibodies against JEV (Pant et al., 2006). Intense transmission of JEV in the area of the British Military Cantonment at Dharan was confirmed by serological studies from the healthy Nepalese from Dharan and animals from the Cantonment farm which indicates rapid transmission of JEV occurring within the Cantonment area. (Henderson, 1983). The first proven outbreak of JE in Kathmandu Valley of Nepal was in 1995 (Zimmerman et al., 1997). Viral studies of serum and cerebro-spinal fluid (CSF) confirm JEV as the causative agent (McCallum, 1991).

### 9.9 Indonesia

Geographical range of endemic JE is much vast than estimated (Kari et al., 2006), It is no longer rare to tropical Asia, a study was conducted to measure the prevalence with hemagglutination-inhibition (HI) and neutralizing antibodies against JEV in horses of Java, Indonesia indicating a high risk of JEV infection (Widjaja et al., 1995).

### 9.10 Singapore

Detection of neutralizing antibodies to JEV in a population of wild boars, as well as two human cases of JE in Singapore indicates that JEV may still be actively transmitted in the peripheral part of the Singapore Island (Ting et al., 2004). A study was conducted to determine the presence of prevalence with hemagglutination inhibition (HI) and neutralization antibodies against JEV in wild pigs of an island in Singapore showing positive results for antibodies against JEV (See et al., 2002).

### 9.11 Cambodia

JEV is an important causative agent of acute encephalitis in Cambodia, this issue still remains unclear, but some survey shows that infection with JEV is the principal cause for it (Srey et al., 2002).

### 9.12 Taiwan

Sero epidemiological survey of JEV in Taiwan indicated that the JEV vaccination, in conjunction with JEV natural infection, maintains high JEV Neutralizing (NT) antibody level among rural children of Taiwan (Hsu et al., 1997) showing confirmed Japanese encephalitis (JE) cases (Ku et al., 1994).

### 9.13 Bangkok

Study of JE was conducted in suburban Bangkok and the primary vector species are found to be *C. gelidus* and *C. tritaeniorhynchus*. Human cases occurred from May-July (Gingrich et al., 1987). In a 5 year study, 121 encephalitis patients were admitted to Bangkok Children's Hospital out of which 79 were proved to be JE (Thisyakorn and Nimmannitya, 1985).

### 9.14 Spain

JEV antigenic complex of *flaviviruses* are recognized as emerging and re-emerging pathogens. Their circulation is recently detected in different mosquito and vertebrate species

in several European countries. Serosurvey using a competitive enzyme-linked immunosorbent assay showed seropositivity in Common Coot (*Fulica sp.*), Montagu's Harrier (*Circus sp.*), Black Kite (*Milvus sp.*), Black Vulture, (*Coragyps sp.*), Bonelli's Eagle (*Aquila fasciata*), Spanish Imperial Eagle (*Aquila adalberti*), Egyptian Vulture (*Neophron percnopterus*), and Eurasian Spoonbill (*Platalea leucorodia*) in autumn season. Real-time reverse transcription-polymerase chain reaction indicated that JEV antigenic group circulates in migratory and resident wild bird species (García-Bocanegra et al., 2001).

### 9.15 Vietnam

JE is an important public health problem in Vietnam (Yen et al., 2010). Many patients are suspected with CNS Infections and children infected with JE virus (JEV), suffered from hemiparesis, meningism including limb paralysis and some of them subsequently became encephalopathic (Solomon T et al., 2008).

### 9.16 Hawaii Island

JEV is emerging arboviruses which is undergoing intercontinental expansion; it is transmitted between mosquito vectors and vertebrate reservoir hosts, including birds. A potential route of JEV introduction from Asia to western North America is via the Hawaiian archipelago also frequent air traffic from both Asia and North America to Hawaii increases the chances of flaviviral infection (Nemeth et al., 2010).

### 9.17 Central China

Studies with four strains of JEV isolated from CSF of aborted fetuses collected in central China through RT-PCR and sequencing, suggested that GIII is the major subtype of JEV, circulating in central China, Fujian, and Heilongjiang (Fan et al., 2010). However, Shanghai isolates belong to GI (Li et al., 2009). GI strain is distributed well in Southeast Asian countries, whereas, genotype III strains in Northern Asia (Fan et al., 2010). Viral encephalitis emerged in Yuncheng city, Shanxi Province was proved to be Japanese encephalitis B (Zhang et al., 2008). Recent JEV isolates from China are divided into two genotypes, genotype 1 and genotype 3; recent JEV isolates from China are grouped into the same clusters within GI and GIII but GIII strains are ancient than GI (Wang et al., 2007).

### 9.18 Australia

Domestic pigs, act as the amplifying host of JEV (van den Hurk et al., 2008). It appears annually in the Torres Strait in far northern Queensland, Australia, and is proving a threat for invasion in Australian mainland. Sentinel pigs have a tendency to develop detectable viremias to JEV. Since pigs are amplifying hosts for JEV, they are health risk to the public (Ritchie et al., 2007) (van den Hurk et al., 2008). *Culex* mosquitoes in Cape Town (van den Hurk et al., 2006) and Saibai Islands may be responsible for JEV activity (Johansen et al., 2004). Still there are no evidences found to prove JE responsible for enzootic transmission cycles on western Cape York (Johansen et al., 2003). In Western Province of Papua New Guinea, pigs and marsupials were studied indicating marsupials as poor JE virus host (van den Hurk et al., 2003), but they may play a vital role (Mackenzie et al., 2003). Collections from Badu Island community yielded *C. annulirostris* (van den Hurk et al., 2001) and from Croydon, Normanton and Karumba yielded *C. annulirostris skuse* and *C. palpalis* mosquitoes

(van den Hurk et al., 2002); (van den Hurk et al., 2003). Mosquitoes from Cape York Peninsula (van den Hurk et al., 2001) and north Queensland appear to have limited transmission on the mainland, nucleotide sequencing indicate that cyclonic winds carried infected mosquitoes from Papua New Guinea to these places (Hanna et al., 1991) and JEV is demonstrating an emergence in the southern part of New Guinea Island (Spicer et al., 1999).

## 10. Symptoms

Symptomatic JEV infection shows febrile illness, aseptic meningitis or encephalitis which manifests sensorium, seizures and focal neurological deficit and acute flaccid paralysis. A wide variety of movement disorders like Parkinsonian features and dystonia are also seen (Solomon et al., 2004). JE mainly affects thalamus, corpus striatum, brainstem and spinal cord. In some incidences co-infection of JE and cysticercosis occurs because of the involvement of pigs (Misra and Kalita, 2010). JEV is also associated with reproductive failure in swine (Lim et al., 2007) and also causes fever, headache aseptic meningitis, change of consciousness convulsions, vomiting and encephalitis (Yang et al., 2007). Surveys suggest shift clinical manifestation from encephalitis to meningitis (Konishi, 2005). Death is presumed to result from infection, dysfunction and destruction of neurons. Patients for seizures and clinical signs of brainstem herniation are also reported. Findings suggest that seizures and raised ICP may be important causes of death in case of JE (Solomon et al., 2002). The neurologic signs like meningeal signs, hyperreflexia, Babinski's sign, hemiplegia, papilledema and other cranial nerve palsies are also seen. Most children have blood leukocytosis with predominant neutrophils (Poneprasert, 1989; Srivastava et al., 1999).

## 11. JEV human infections

Infections of humans with JEV produce vast clinical manifestations, ranging from asymptomatic infection like mild febrile illness, acute and lethal meningomyeloencephalitis. Most infections are asymptomatic and cause a nonspecific influenza-like illness. The ratio of symptomatic to asymptomatic cases has occasionally been higher. Sequelae are more frequent in patients having severe and prolonged acute diseases along with coma and focal neurological deficits.

## 12. Laboratory diagnosis

Laboratory diagnosis of JE is by IgM capture ELISA, which has high sensitivity and specificity. In the absence of specific antiviral therapy, JE is managed by symptomatic and supportive therapies and preventive measures. Encephalitis is an unusual manifestation of human viral infection, whereas many individuals develop systemic viral infections, only a few develop symptomatic infection of the central nervous system (Whitley and Gnann, 2002).

## 13. Risk

JEV may become epizootic and epidemic if it is introduced unintentionally for commercial use or intentionally for nefarious purposes. Even global warming may also facilitate the

distributions of arboviruses, expanding northward into southern Europe, increasing transmission season and capacity of vectors. Greatest health risk of arboviral emergence is due to extensive tropical urbanization and the colonization by highly anthropophilic mosquitoes. Sustained endemic arbovirus transmission, adequate human viremia and vector competence is the minimal requirement to become major human pathogens (Weaver and Reisen, 2010). Recent global warming trends affect vector population dynamics and disease transmission which is measured by hemagglutination-inhibition (HI) antibodies titre tests (Yang et al., 2008). Studies show incidence of dengue virus (DEN) infections in a cohort of Dutch short-term travellers who travelled to endemic areas in Asia, post-travel serological studies were done by DEN immunoglobulin M (IgM) showing that DEN infections are frequent in travellers to endemic areas in Asia (Cobelens et al., 2002).

#### **14. Host immune response**

The factors which govern the clinical presentations and outcome of flavivirus infections are not very well understood, but studies are going on at viral virulence determinants and the host immune response. Distribution of the four genotypes across Asia may relate to the different clinical epidemiology. However nucleotide sequence studies of oldest lineages virus, and phylogenetic analyses of all JEV strains, suggest that the origin is best in the Indonesia-Malaysia region (where all genotypes have been found), and there is spread of the more recent genotypes to new geographical areas. Innate immunity, as evidenced by interferon alpha levels, plays an important role in JEV and other flaviviruses. Cellular immunity is less characterized, but CD8+ and CD4+ T cells may play important role (Solomon and Winter, 2004; Tandon et al. 2002). A failure of the humoral immune response may be associated with death from encephalitis caused by JEV.

#### **15. Future risk**

There is potential risk of introduction and establishment of JEV in newer areas of the world. JEV is endemic to Asia and when transmitted to humans (accidental host), may lead to JE, mostly in children with a fatality rate up to 30%. The geographical expansion of JEV in Asia shows the ability of arboviruses to rapidly extend their distributions. As for example, studies have shown that California is at risk for JEV introduction because it functions as a hub for international travel and commerce with Asia, indirectly allowing the introduction of mosquitoes infected with JEV. Introduction of JEV in California, might pose challenge to the health sector due to establishment of susceptible mosquito vectors and vertebrate will lead to the flaws in the surveillance of JEV, and cross reactivity of serological test between JEV and other flaviviruses, and may be JE may not be considered as a possible diagnosis, these all will lead to delay and this delay in detection of JEV may pose challenge in eradicating the virus from California so there is need of considerations for future control efforts if JEV emerges in the United States (Nett et al., 2009).

In the last decade had introduction of huge number of encephalitic viruses and the emergence or spread in the Southeast Asian and Western Pacific regions. JEV has spread its wings through the Indonesian archipelago to Papua New Guinea and to the islands of the Torres Strait of northern Australia, and also to Pakistan and new areas in the Indian

subcontinent (Mackenzie, 2005). The incidence of JE in recent times is showing an increasing trend. It appears that JE may become one of the major public health problems in India considering the proportion of JEV infections among the encephalitic children (Kabilan et al., 2004).

## 16. Prevention/vaccination

Vaccination proves to be the best to protect the individual against any disease. In the case of JE, it is essential to immunize the pigs also to interrupt the transmission cycle (Kabilan et al., 2004). Japanese racehorses are vaccinated with inactivated JE vaccine every year which lessens up the JE cases (Konishi et al., 2004). Screening of goats and cattle are also suggested for JE infection risk to the human population (Rajendran et al., 2003). JEV and JEV-induced macrophage-derived factor (MDF) can modulate nitric oxide synthase (NOS) activity in brain and tumor necrosis factor-alpha (TNF-alpha) (Khanna et al., 1991 and Mathur et al 1992; Saxena et al., 2001) NOS activity gets enhanced in JEV or JEV-induced MDF-treated mice (Saxena et al., 2001). The enhanced level of TNF-alpha correlates well with enhanced inducible nitric oxide synthetase (iNOS) activity, thus provide evidence for protective role of iNOS during JEV infection and hence indicate that iNOS may be a key mediator in host innate immune response (Saxena et al., 2000, 2001, 2003). Administration of inactivated mouse-brain derived JEV were reported in Japan and the United States which had some problem (Takahashi et al., 2000). There is continuous need for constant surveillance and monitoring so as to prevent future large outbreaks (Victor et al., 2000). In fact, three doses of mouse-brain vaccine are enough to protect children against the local Taiwan JEV and choice of selection for best strain for a JE vaccine depends on level of Nt Ab [neutralisation antibody] it induces, the molecular epidemiology and antigenic variation. The future vaccine must produce better B- and T-cell memory in the vaccinated populations (Ku et al., 1994) Vaccinia virus (NYVAC) was engineered to express the JEV prM, E, and NS1 genes, the recombinant viruses were tested as vaccine candidates in pigs showing that after immunization, JEV levels detected in the were reduced demonstrating the ability of NYVAC-vectored recombinants to protect pigs from JEV viremia (Konishi et al., 1992). Extracellular HeLa cells produce extracellular subviral particles which were infected with a recombinant vaccinia virus encoding the prM and E gene and were purified. Mice when received a single inoculation of the purified extracellular particles were fully protected against LD50 of JEV (Konishi and Pincus et al., 1992). Although vaccinia recombinants expressing NS1 can provide some protection from lethal JEV infection, recombinants expressing prM and E have higher levels of protective immunity (Konishi et al., 1991). Antipyretics, anticonvulsants, anticerebral edema agents, adequate respiration and nutrition and physical and occupational therapies are needed by patients (Poneprasert, 1989).

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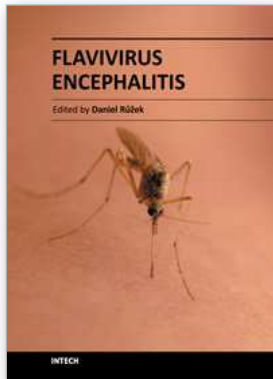
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Encephalitis is an inflammation of the brain tissue associated with clinical evidence of brain dysfunction. The disease is of high public health importance worldwide due to its high morbidity and mortality. Flaviviruses, such as tick-borne encephalitis virus, Japanese encephalitis virus, Murray Valley encephalitis virus, or St. Louis encephalitis virus, represent important causative agents of encephalitis in humans in various parts of the world. The book *Flavivirus Encephalitis* provides the most recent information about selected aspects associated with encephalitic flaviviruses. The book contains chapters that cover a wide spectrum of subjects including flavivirus biology, virus-host interactions, role of vectors in disease epidemiology, neurological dengue, and West Nile encephalitis. Special attention is paid to tick-borne encephalitis and Japanese encephalitis viruses. The book uniquely combines up-to-date reviews with cutting-edge original research data, and provides a condensed source of information for clinicians, virologists, pathologists, immunologists, as well as for students of medicine or life sciences.

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