

THE PHARMA INNOVATION

Japanese Encephalitis Epidemic In India

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Japanese encephalitis (JE) is a serious infection caused by a virus. It occurs mainly in rural parts of Asia. JE virus spreads through the bite of infected mosquitoes. It cannot spread directly from person to person. The risk of JE is very low for most travelers, but it is higher for people living or traveling for long periods in areas where the disease is common. Most people infected with JE virus don't have any symptoms at all. For others, JE virus infection can cause illness ranging from fever and headache to severe encephalitis (brain infection). Symptoms of encephalitis are fever, neck stiffness, seizures, changes in consciousness, or coma. About 1 person in 4 with encephalitis dies. Of those who don't die, up to half may suffer permanent brain damage. There is some evidence that an infection in a pregnant woman can harm her unborn baby. JE is an inflammation of the brain tissue and is caused due to the infection by a mosquito bite which carries the virus. At present, there is no anti-viral therapy and the vaccination is considered the most effective way to control the disease. India's first Japanese encephalitis vaccine launched. JE is highly prevalent in south-east Asia and the Far East and nearly 67,900 cases are recorded annually with 1169 deaths reported from India alone. An epidemic outbreak of Japanese Encephalitis in Uttar Pradesh, India, and Nepal killed more than 1,200 children in 2005. During the last few years, over 10 million children have been affected worldwide by JE and 4 million have died or become permanently disabled, Pharma firm Biological E Limited (BEL) today launched the country's first indigenous vaccine to tackle Japanese encephalitis (JE), a deadly viral disease.

Keyword: Japanese Encephalitis, Infected Mosquitoes Encephalitis Vaccine, Neuroinvasive Disease.

INTRODUCTION: Japanese encephalitis is a viral disease spread by mosquitoes, which transfer the virus from infected animals - usually pigs and wading birds - to humans. Areas such as rice fields, where mosquitoes thrive and there is a lot of pig farming, are especially risky.

It was first recognized in Japan in the late 1800s (hence the name) and has since been found throughout most countries of east and South East Asia where it is the leading cause of viral encephalitis. Approximately 30,000 to 50,000 cases are reported every year, and there are about 10,000 deaths, mostly in children. In fact it's now thought that many more people have the infection (research shows that by the age of 15 most people in South East Asia have had it) but symptoms are usually minimal so it doesn't get reported. Most

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human JEV infections are asymptomatic or cause a non-specific febrile illness. Less than 1 percent of JEV infections results in symptomatic neuroinvasive disease. However, when neurological disease does occur, it is usually very severe with a high case fatality rate; among survivors, neurological sequelae are common. All travelers to JEV-endemic countries should be given advice on measures to prevent JE, and JE should be considered among the differential diagnoses for patients with suspected neurological infection who have returned from recent travel in a JEV-endemic country in Asia or the Western Pacific region. Japanese encephalitis virus (JEV), a mosquito-borne flavivirus, is the most important cause of viral encephalitis in Asia based on its frequency and severity. With the near eradication of poliomyelitis, JEV is now the leading cause of childhood viral neurological infection and disability in Asia. JEV is closely related to West Nile, St. Louis encephalitis, and Murray Valley encephalitis viruses. Japanese Encephalitis is a mosquito-borne arboviral disease that can affect the central nervous system and cause severe complications and death. It is a disease of rural, semi-urban and agricultural areas. Transmitted by female mosquitoes of genera *Culex*, *Anopheles*, *Aedes*, *mansonia* and *Armegeres* mosquitoes. Vector mosquitoes proliferate in close association with pigs, wading birds and ducks, the principal amplifying hosts. JE virus. Sporadic cases (Occasional cases, widely distributed in time and place): are observed in China, Japan, Taiwan, Korea, Philippines, Indonesia, Malaysia, Singapore, Myanmar, Bagladesh and Eastern areas of Russia. Regional, seasonal outbreaks (large number of cases occurring simultaneously at the same time and place): Occurs in Thailand, parts of India and Srilanka. JE was clinically diagnosed for the first time in India in 1955 at Vellore, erstwhile North Arcot district of Tamil Nadu. Subsequently, the outbreaks have occurred in 25 States / Union Territories of India. JE virus infection is widespread and is particularly very high in Southern States of India viz., Andhra Pradesh (AP) Tamil Nadu and some parts of Karnataka. As many as 765 people died this year due to

Japanese encephalitis in the country, with the maximum of 275 in Bihar. The total 765 deaths due to the disease till September one included 214 in Uttar Pradesh, 213 in Assam, 40 in Tamil Nadu and 15 in West Bengal, Health and Family Welfare Minister Ghulam Nabi Azad told Rajya Sabha in a written reply. The Health Ministry has identified 171 Japanese encephalitis-prone districts in the country, 60 of which are in Assam, Bihar, Tamil Nadu, Uttar Pradesh and West Bengal, he said. The disease claimed 1,169 lives last year, 679 in 2010 and 774 in 2009, according to a Health Ministry data.

JAPANESE ENCEPHALITIS EPIDEMIC IN INDIA

Japanese encephalitis (JE) - so called as the deadly disease broke out first in the 1940s in Japan but has been contained since - is again claiming lives in Uttar Pradesh, Bihar and Assam in pockets in northern and eastern India. Grey herons were found to be the avian reservoirs, rice field breeding mosquitoes the vector and pigs the amplifiers. The Japanese produced a vaccine and vaccinated all pigs. The infection ended. It never appeared again in Japan. The first big JE epidemic in India occurred in North Arcot district of Tamil Nadu in 1957-58, in Burdwan and Bankura in West Bengal (1976) and in Tirunelveli in Tamil Nadu (1978). One can expect JE epidemics in India year after year in regions subjected to prolonged drought-like conditions followed by heavy rains. This causes heavy mosquitogenic conditions. In India, there are 'pond herons' (*Ardeola grayii*) and 'cattle egrets' (*Bubulcus ibis*) which share the similar niche. Pigs circulate high concentration of the virus and can infect a large number of mosquitoes. The mosquitoes which pick up the infection are mainly zoophilic (i.e. they prefer to feed on animals including birds). The cattle can circulate virus but do not play any significant role in the transmission. When the mosquito population increases enormously following heavy rains and floods, an odd mosquito- out of thousands- bites man. Unfortunately, an impending JE epidemic is recognized by the authorities only when the first human case is

reported. It is too late. It is now accepted that once JE infection is detected in man, there is no use carrying out any vector control measure. This is because while in the case of malaria or filariasis a mosquito can pick up the infection from one man and transmit to another, this does not happen in JE. The chances are very remote for the vectors of JE to transfer infection from man to man. After getting a blood meal, the JE mosquito must wait till its egg-laying is complete - which takes 7-10 days - before it can bite another man. So the time to launch vector control measures is when the conditions are ripe for vectors to start biting humans, not after detecting the first case. In a country like India, where drought and floods occur periodically or with regular frequency, the occurrence of JE can be forecast. Large water pools ideal for breeding of vectors of JE are conducive for nesting and breeding of Ardeid birds such as egrets and herons. The mosquitoes are there, the avian hosts are there and in the adjacent villages cattle, poultry and pigs are present. JE will strike humans when all these factors co-exist. One can therefore predict with reasonable accuracy an impending epidemic. In fact, research on methods of predicting an epidemic should be a continuous process. Instead the authorities prefer to carry out fire-fighting operations during epidemics. There does not seem to be a long term plan vis-a-vis JE control. The government's efforts to produce an effective vaccine are laudable but the question is: to whom will this vaccine be given. To prevent recurrence of JE epidemics, the first priority is to delimit endemic areas where JE has occurred in the past. The meteorological, animal husbandry, agricultural and revenue departments should coordinate their efforts to share data to predict any unusual changes in ecology and ecosystem. Once it is possible to predict an epidemic, effective use of insecticidal residual sprays will help slow down transmission, provided this is done before the epidemic starts. For successful forecast, the existing district level entomological units under the National Malaria Eradication Programme should be fully equipped to monitor mosquito populations. Strengthening the infrastructure to recognise cases immediately and

transport them to the nearest hospital is the only way to save lives. JE cases will still occur but the intensity of the epidemic will be low and manageable. At least deaths can be prevented. There is some missing knowledge that requires some research. How and from where does the JE virus get introduced into an area where the epidemic occurs. What happens to the virus during the inter-epidemic period. Even if the grey herons and some Ardeid birds are infected, how is the infection transferred to the fledglings. Are there other animals or birds involved in the natural cycle. In recent years the Indian Council of Medical Research (ICMR) has been downgrading medical entomology as a subject by switching its focus to molecular biology. Even universities in India do not teach zoology or entomology these days, but only life sciences and biotechnology.

CAUSES OF JAPANESE ENCEPHALITIS

- Japanese encephalitis is caused by a Flaviviridae virus (or flavivirus), which is transmitted by the bite of an infected mosquito.
- Transmission of the disease is most likely during the summer months in temperate areas and during the rainy season and early dry season in tropical areas, when the mosquito populations are the highest.
- Japanese encephalitis is rare in travellers and the risk to short-term visitors to the region is very low, especially if they are just visiting urban areas. However, it has a high fatality rate, and can cause chronic complications so it should be taken seriously.

SYMPTOMS

- Most people who are infected show only mild symptoms or no symptoms at all. However, in severe cases the disease may be fatal.
- Japanese encephalitis begins like flu with headache, fever, and weakness. As it progresses to inflammation of the brain

there may be confusion and delirium. Gastrointestinal problems, including vomiting, may also be present. About one third of these patients will die, and 25-30 per cent have neurological damage including paralysis, speech difficulties, Parkinson's-like syndrome or psychological problems. Children are most vulnerable.

SIGNS OF JAPANESE ENCEPHALITIS

- High fever with rigors.
- Headache.
- Sleepiness.
- Lack of normal activity.
- Neck stiffness.
- Difference in movements on both sides of the body.
- Stare (Vacant look).
- wide open eyes.
- Convulsions.
- Hyper ventilation (Rapid breathing or irregular breathing).
- Involuntary movements.
- Marked loss of weight.

CARDINAL SIGNS OF JAPANESE ENCEPHALITIS

- High fever with rigors.
- Altered sensorium.
- Involuntary movements.

PREVENTION

The best way to prevent JE is to avoid mosquito bites by:

- Remaining in well-screened areas,
- Wearing clothes that cover most of your body,
- Using an effective insect repellent, such as those containing DEET,
- Using bed nets when accommodations are not adequately screened or air-conditioned.

EPIDEMIOLOGY

JE is endemic throughout most of Asia and parts of the Western Pacific region. Within the JE-endemic region, there are two typical patterns of transmission:

- In areas with temperate climates (including China, Japan, South Korea, Nepal, northern Vietnam, and northern India), most cases occur over a period of several months when the weather is warmest, usually after the monsoons begin or associated with heavy rainfall. The peak months of transmission and the length of the season vary from place to place. There are sometimes large, explosive outbreaks.
- In areas with tropical climates (including Cambodia, Indonesia, southern Vietnam, and southern Thailand), there is year-round transmission. An increase in cases may be observed during the rainy season.

CLINICAL FEATURES OF JAPANESE ENCEPHALITIS

Depending upon the disease process vis – a – vis involvement of Central Nervous System, the encephalitis can be categorised into 3 stages.

Prodromal Stage

Lasts 2–3 days. (Preceding the signs of CNS involvement). Onset of the disease may be 1. Acute (less than 24 hours), 2. Sub acute (1–3 days), 3. Gradual (More than 3 days). The essential features of this stage are generalised malaise, headache and fever with chills & rigors in 90% of cases. The duration of this stage is between 1 – 6 days. It is observed that with rapid onset of disease, the case fatality will be higher. Hence, shifting the case to an appropriate medical care unit is vital at this stage.

Acute Encephalitis Stage

Lasts 3–4 days (is marked by CNS manifestastions).The predominant features of this stage are continuous fever, neck rigidity, motor deficits, convulsions and altered sensorium progressing in many cases to coma. fever continues from prodromal stage, usually high and varies from 100.0 to 107.0 F. The patient sometimes presents with sudden behavioural changes like confusion, delirium, restlessness, disorientation, irrelevant speech, grasping etc. Speech disturbance like motor aphasia, dysphasia, monotonous speech may be observed. Abnormal spontaneous eye movement with absent corneal reflex and absent pupillary light reflex are also noted.In acute stage, patient can exhibit signs of Raised Intracranial Pressure which can be identified by irregular breathing, headache, vomitting and asymmetric paralysis. Sometimes it may lead to convulsions & Coma.

Convalescent Stage (Recovery Stage)

Lasts 4–7 weeks. Marked by gradual recovery and sequaela.After a period varying from few days to few weeks of acute stage, either steady improvement occurs or neurological deficits get established. This stage begins when active inflammation is subsiding, suggested by temperature and ESR coming to normal and neurological signs becoming stationary or tending to improve. Patients who recover from acute episode may have neurological sequelar with variable frequency. This depends on the age and severity of the illness.

FACTS ABOUT JAPANESE ENCEPHALITIS

The mosquitoes become infected by feeding on domestic pigs and wild birds (infected with the virus). The virus is amplified in the blood systems of domestic pigs and wild birds. Only domestic pigs and wild birds carry the virus, no other animal. Japanese Encephalitis is not transmitted from human-to-human. If you touch an infected person you cannot catch it.

Japanese Encephalitis Symptoms:

- Mild infections (without symptoms)
- Fever - (More severe infection)
- Headache - (More severe infection)
- Stiff Neck - (More severe infection)
- Stupor - (More severe infection)
- Disorientation - (More severe infection)
- Tremors - (More severe infection)
- Occasional Convulsions - (More severe infection)
- Spastic (but rarely flaccid) Paralysis - (More severe infection)

- Incubation Period
5 - 15 days

- Mortality Rate
0.3% - 60%

Japanese encephalitis is a viral disease spread by mosquitoes. It is associated with inflammation of the brain and hence termed encephalitis. This severe and potentially life-threatening disease is rare.

The illness occurs in two forms - a primary form and a secondary form. The primary form of the disease is more serious, while the secondary form is more common. But because of the milder nature of secondary encephalitis, more cases of primary encephalitis are seen.

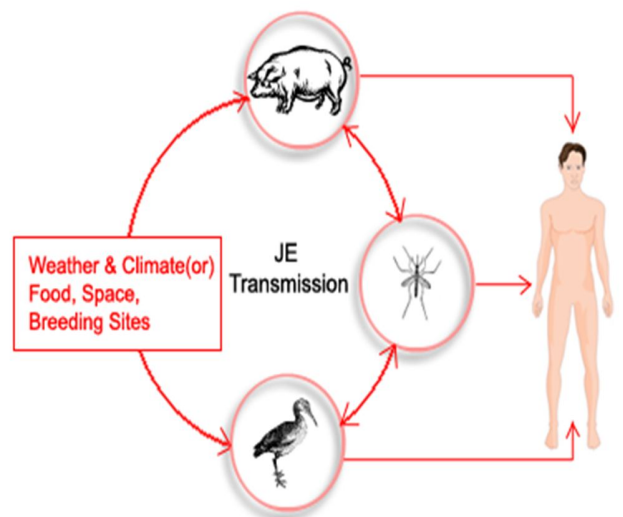


Figure-1 The disease is transferred from infected animals

The disease is transferred from infected animals - usually pigs and wading birds - to humans. Japanese encephalitis is the leading cause of viral encephalitis in Asia with 30-50,000 cases reported annually. The best way to reduce the risk

of contracting the disease is to reduce exposure to mosquitoes. This can be done by avoiding being outside in the cooler hours between dusk and dawn when mosquitoes are most actively feeding. The use of mosquito repellent, portable bednets, aerosol room insecticides and permethrin, which can be applied to clothing, is also recommended. Japanese encephalitis (JE)-epidemics have been reported in many parts of the country. The incidence has been reported to be high among pediatric group with high mortality. 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 quantum of the vulnerable pediatric population, the proportion of JEV infections among the encephalitic children and wide scattering of JE-prone areas. JE burden can be estimated satisfactorily to some extent by strengthening diagnostic facilities for JE confirmation in hospitals and by maintenance of contact with the nearby referral hospitals to collect the particulars on JE cases. 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 (amplifying host) also to interrupt the transmission of the disease.

PREVENTION MOSQUITO BITES

Immunisation is only one aspect of preventing illness whilst abroad. Immunisation is not 100% effective and you should also try to avoid mosquito bites when in 'at risk' areas.

Mosquito bites can be avoided by the following:

- Sleep in rooms that are properly screened. For example, rooms with close fitting gauze over windows and doors.
- Spray the bedroom with insecticide just before evening. This kills mosquitoes that may have come into the room during the day.
- If you sleep outdoors or in an unscreened room, use mosquito nets impregnated with an insecticide (such as permethrin). The net should be long enough to fall to the floor all round your bed and be tucked

under the mattress. Check the net regularly for holes. Impregnate with fresh insecticide every six months.

- Use an electric mat to vaporise insecticide overnight. Burning a mosquito coil is an alternative.
- Mosquitoes that carry the Japanese encephalitis virus are most active at dusk and in the evening. If possible, avoid going out after sunset. If you do go out after sunset then wear long sleeved clothing, trousers, and socks. Light colours are better as they are less attractive to mosquitoes.
- Apply insect repellent to clothing or exposed skin. Diethyltoluamide (DEET) is safe and effective, but take advice on the best repellent in the area you visit.

TREATMENT

There is no specific treatment for Japanese encephalitis and treatment is supportive; with assistance given for feeding, breathing or seizure control as required. Raised intracranial pressure may be managed with mannitol. There is no transmission from person to person and therefore patients do not need to be isolated. A breakthrough in the field of Japanese encephalitis therapeutics is the identification of macrophage receptor involvement in the disease severity. A recent report of an Indian group demonstrates the involvement of monocyte and macrophage receptor CLEC5A in severe inflammatory response in JEV infection of brain. This transcriptomic study provides a hypothesis of neuroinflammation and a new lead in development of appropriate therapeutic against Japanese encephalitis.

CONCLUSION

Japanese encephalitis is caused by a virus. It is passed to humans by the bite of infected mosquitoes. It cannot be transmitted by other humans. Japanese encephalitis is usually a mild illness. In many cases there are no symptoms. However, in a small number of cases (about 1 in

200 infected people) the illness is much more serious. In these people the infection may start with fever, tiredness, headache, vomiting, and sometimes confusion and agitation. This may progress to encephalitis (inflammation of the brain). This can cause permanent brain damage and is fatal in some cases. Japanese encephalitis occurs throughout South East Asia and the Far East. It is mainly a problem in rural farming areas. It occurs more commonly in the rainy season (roughly May-September) when the mosquitoes are most active. The best way to reduce the risk of contracting the disease is to reduce exposure to mosquitoes. This can be done by avoiding being outside in the cooler hours between dusk and dawn when mosquitoes are most actively feeding. The use of mosquito repellent, portable bednets, aerosol room insecticides and permethrin, which can be applied to clothing, is also recommended.

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