JAPANESE ENCEPHALITIS DISEASE: A REVIEW

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Summary

Japanese Encephalitis (JE) is a mosquito borne zoonotic viral disease caused by arbovirus (flavivirus), involving the Central Nervous System. In nature, the virus is maintained in ardied birds (e.g. cattle egrets, pond herons etc.) and other animals particularly pigs. Although infection in human is incidental, the virus can cause serious neurological disease in human. Presence of one clinical case in the community suggests that 300 to 1000 people have been infected. The disease occurs with sudden onset and the common symptoms are headache, high fever, stiff neck, abnormal movements (coarse tremor, convulsions in children), impaired consciousness and coma. Case fatality rate is high ranging from 20-40%. JE occurs in a large number of countries/area of Asia. It is a disease of public health importance because of its epidemic potential and high case fatality rate. In patients who survive complications may lead to life long sequelae. Although there is no treatment to stop the progression of the diseases, there are treatments available to help control the symptoms. The present review deals with the occurrence of the diseases in various regions of India as well world. The review also deals with etiology, pathophysiology and current drug treatment options and future therapeutic intervention for JE.

Key words: Japanese encephalitis, epidemic, zoonotic.

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Introduction

Japanese Encephalitis (JE) is commonly known as Brain fever. The word Encephalitis means inflammation of brain. The first cases of this disease in the world were recorded way back in 1870s in Japan and hence its name – the Japanese Encephalitis. JE is a communicable disease of public health importance because it often occurs in epidemic form resulting in deaths or permanent brain damage among the affected individuals. JE is a viral disease occurring mainly in rural & peri urban areas. The virus belong to the family Flaviviridae (formerly known as the group B arbovirus) named as Flavivirus mosquitoes, particularly Culex tiritaeniorhynchus breeding in rice fields are major vectors involved in the transmission of disease. The natural cycle involves water birds, including herons and egrets. The culex mosquitoes feed at dusk and prefer pigs and cattle among mammals, biting human beings only as an alternative. Pigs develop prolonged viremias and function as important amplifying hosts. There is no man – to – man transmission. Man is only an accidental and dead end host. [1, 2] Children below the age 15 are often victims of the disease. The disease manifests with high grade fever, convulsions leading to coma etc. sometimes leading to death. Case fatality is around 20 to 40 percent. The problem of JE is amenable for mitigation through effective implementation of integrated prevention and control measures.[3]

JE virus: History of discovery [1]

1870's:	"Summer encephalitis" epidemic in Japan
1924	Great epidemic in Japan 6,125 human cases; 3,797 deaths
1924	Agent from human brain tissue isolated in rabbits
1933	The virus was isolated for the first time from a post-mortem human brain in Japan
1934	Isolate of this virus produced experimental encephalitis in monkeys
1935	First isolated-from a fatal human encephalitis case
1938	Isolated from Culex tritaeniorhynchus
1940-1978	Disease spread with epidemics in China, Korea and India
1930s	First mouse brain-derived vaccines developed
1954	"Refined" mouse brain vaccine developed
1954	Japanese Encephalitis vaccine was licensed.
1954	Identified virus could also infect pigs, bovines, dogs and sheep.

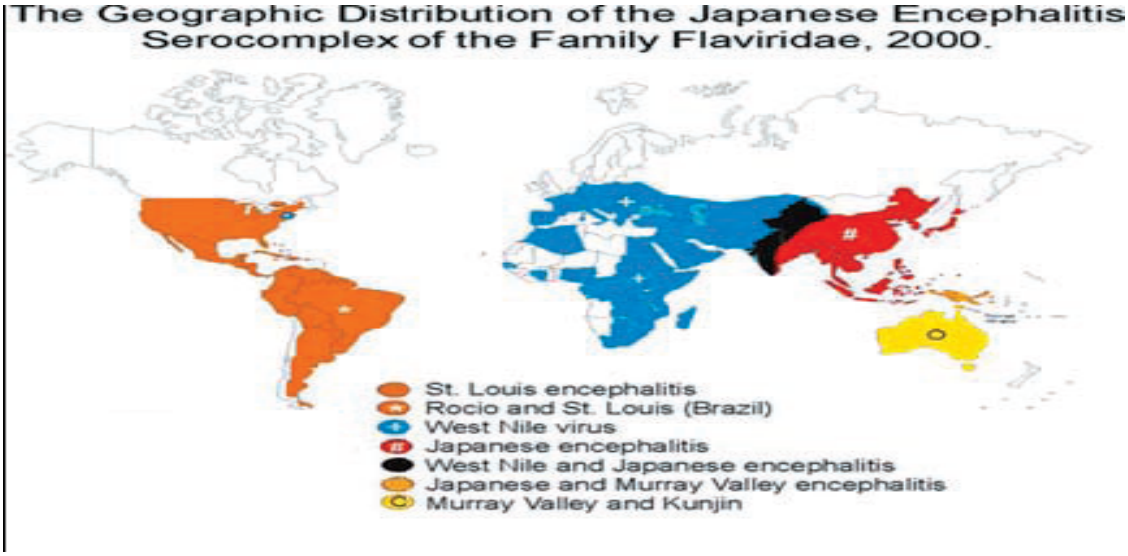
Occurrence

Habitats supporting the transmission cycle of JE virus are principally in rural, agricultural locations. In many areas of Asia, however, the appropriate ecologic conditions for virus transmission occur near or occasionally within urban centers. Transmission is seasonal and occurs in the summer and autumn in the temperate regions of China, Japan, Korea, and eastern areas of Russia. Elsewhere seasonal patterns of disease are more extended or vary with the rainy season and irrigation practices. Risk of JE varies by season and geographic area.[4]

DISEASE SCENARIO

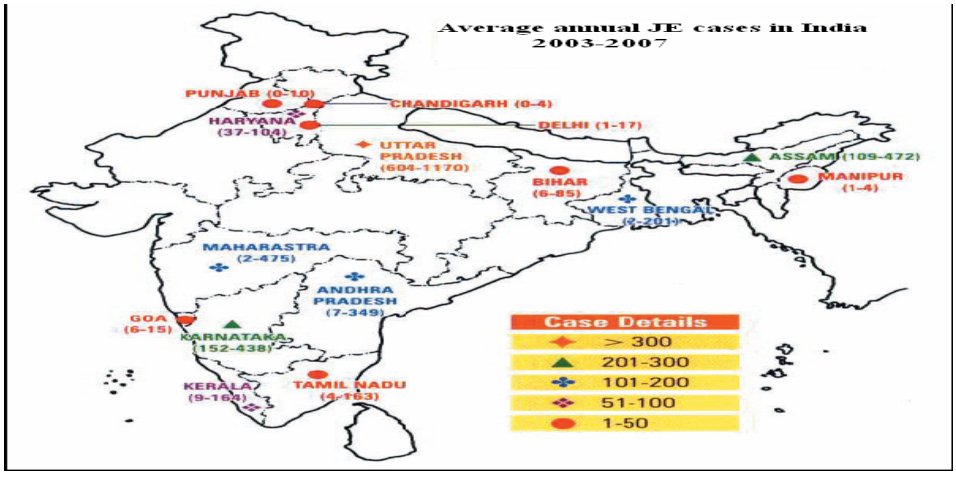
Global Scenario

Recently, a growing number of JE cases are seen in China, India, Nepal, Philippines, Sri Lanka, Northern Thailand, Vietnam, Myanmar, Korea, Malaysia, Taiwan and other parts of the world. JEV is the most common documented cause of viral encephalitis in Cambodia. JEV infections were occasionally found in Indonesia and Northern Australia. In recent years, JE is rare in Japan due to JE-virus vaccination, use of agricultural pesticides and controlled pig [5, 6]



Indian Scenario.

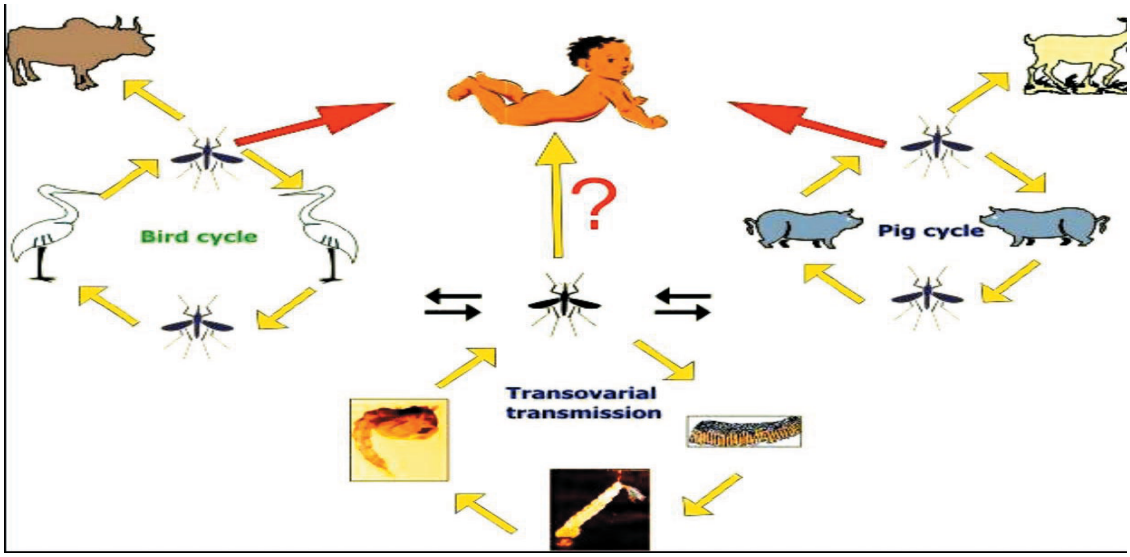
During the last 3 decades JEV is responsible for the major outbreaks of the disease in India. In India JE was first recognized in 1955 from cases of encephalitis admitted to the Christian Medical College and Hospital, Vellore (Tamilnadu). In 1958, this virus was isolated from wild-caught mosquitoes in the same area and isolated from brain tissue of human cases. The first major outbreak of JE involving more than 700 cases and 300 deaths occurred in Burdwan and Bankura districts of West Bengal in 1973 and followed by second outbreak in 1976. Since the number of outbreaks has been reported from the states of Bihar, Uttar Pradesh, Assam, Manipur, Andhra Pradesh, Karnataka, Madhya Pradesh, Maharashtra, Tamilnadu, Haryana, Kerala, West Bengal, Orissa and Union territories of Goa and Pondicherry. Nearly 1145 cases of Japanese encephalitis have been reported from 14 districts of Uttar Pradesh state India from 29th July to 30th August 2005. About one fourth of these (n=296) cases died. Entomological surveys in the affected villages have revealed high density of Culex tritaeniorhynchus and Culex vishnui group – the vectors of JE [7, 8]



JE cases in India (Source: CRME) State wise JE cases and deaths from 2001 – 2007 are reported in table 1.

LIFE CYCLE OF JAPANESE ENCEPHALITIS

Japanese encephalitis maintains a complex life cycle that involves pigs as amplifying hosts, ardied birds as reservoirs, and mosquitoes as vectors. Mosquitoes transmit the virus to many species of birds and to swine. The Culex vishnui subgroups of mosquitoes are major vectors and are playing important role for JE epidemiological outbreaks in India. The Culex vishnui sub-group includes Culex tritaeniorhynchus Giles, C. vishnui Theobald, and *C. pseudovishnui Colless*. These species are extremely common, widespread and breed mainly in paddy fields. These mosquitoes are predominantly cattle blood feeders and humans are the dead end host [9]



Transmission season

Transmission is usually more frequent in rural areas especially during rainy season. Even in endemic areas, only 1% to 3% of mosquitoes are infected with this virus. Epidemics usually occur towards the end of the rainy season. In temperate zones of China, Japan, Korea and Northern areas of South East Asia, Japanese encephalitis is transmitted during summer and early autumn- May to September of a year. In Northern parts of India and Nepal transmission occurs from June to November and in India and Srilanka epidemics are found from September to January. The total number of cases is estimated at more than 50,000 annually in these places where China contributes more than 50% and India about 20% of the disease. According to recent reports JE transmission relates to socioeconomic status. In central China more JE cases were observed among poor children living in unhygienic condition of houses and whose parents had lower income [10]

Reservoir of infection

JE virus has its natural cycle in vertebrates and mosquitoes. The animal hosts mainly include pigs whereas other animals such as cattle and horses have no significant role in disease transmission and amongst birds are the water birds e.g. pond herons, cattle egrets, poultry birds and ducks play a significant role in the natural history of JE virus. Pigs are the major vertebrate hosts and are considered as amplifying hosts. Infection in man appears to be correlated with living in close proximity with animal reservoirs especially pigs. Currently available evidences does not indicate major role of cattle and horses. In India, birds particularly those belonging to family Ardeidae and pigs play important role in maintenance of JE virus in nature. Various studies conducted on detection of the presence of JE antibodies in the sera of birds belonging to different species have indicated that *Ardeola grayii* (pond heron) and *Bubulcus ibis* (cattle egret) play a definite role in maintenance of JE virus in nature. In different parts of the country, 12 to 44 per cent pig population has been found to be positive for JE antibodies particularly in JE endemic areas. Besides birds and pigs, bovines and bats have also been found positive for JE antibodies but their role in maintenance of virus in nature is doubtful as the titers found in them are very low [1, 4].

Vectors

Mosquitoes belonging to *Culex vishnui* group are most important vector species in India. *Culex* mosquitoes generally breed in water bodies with luxurious vegetation like irrigated rice fields, shallow ditches and pools. Mosquitoes are zoophilic, feeding primarily on animal and wild birds. Epidemics usually coincide with monsoons and post-monsoon period when the vector density is high. Female mosquitoes get infected after feeding on a viraemic host and can transmit the virus to other hosts after an extrinsic incubation period of 9 to 12 days. The mosquitoes remain infected for life. The average life period of a mosquito is about 21 days. Culex mosquito can fly for long distances (1-3 kms or even more).[7]

Table 1: Risk of Japanese encephalitis by Country, Region and Season [11]

Country	**Affected Areas**	**Transmission Season**	**Comments**
Australia	Islands of Torres Strait.	Probably year-round transmission risk.	Localized outbreak in Torres Strait in 1995 and sporadic cases in 1998 in Torres Strait and on mainland Australia at CapeYork Peninsula.
Bangladesh	Few data, but probably widespread.	Possibly during July to December, as in northern India.	Outbreak reported from Tangail District, Dhaka ivision; sporadic cases in Rajshahi Division.
Brunei	Presumed to be sporadicendemic as in Malaysia.	Presumed year-round transmission.	No comments.
Burma (Myanmar)	Presumed to be endemic-hyperendemic countrywide.	Presumed to be May to October.	Repeated outbreaks in Shan State in Chiang Mai valley.
Cambodia	Presumed to be endemic-hyperendemic countrywide.	Presumed to be May to October.	Cases reported from refugee camps on Thai border.
India	Reported cases from all states except Arunachal, Dadra, Daman, Diu, Gujarat, Himachal, Jammu, Kashmir, Lakshadweep, Meghalaya, Nagar Haveli, Orissa, Punjab, Rajasthan, and Sikkim.	South India: May to October in Goa; October to January in Tamil Nadu; August to December in Karnataka. April to June in Mandya District. Andhra Pradesh: September to December. North India: July to December.	OutbreaksinWest Bengal, Bihar, Karnataka, Tamil Nadu, Andrha Pradesh, Assam, Uttar Pradesh, Manipur, and Goa. Urban cases reported (for example, Lucknow).
Indonesia	Kalimantan, Bali, Nusa, Tenggara, Sulawesi, Mollucas, and Irian Jaya (Papua), and Lombok.	Probably year-round risk; varies by island; peak risks associated with rainfall, rice cultivation, and presence of pigs. Peak periods of risk: November to March.	Human cases recognized on Bali, Java, and possibly in Lombok.

Japan*	Rare-sporadic cases on all islands except Hokkaido.	June to September, except April to December on Ryuku Islands (Okinawa).	Vaccine not routinely recommended for travel to Tokyo and other major cities. Enzootic transmission without human cases observed on Hokkaido.
Korea	North Korea: No data. South Korea: Sporadicendemic with occasional outbreaks.	July to October.	Last major outbreaks in 1982 and 1983. Sporadic cases reported in 1994 and 1998.
Laos	Presumed to be endemic-hyperendemic countrywide.	Presumed to be May to October.	No comments.
Malaysia	Sporadic-endemic in all states of Peninsula, Sarawak, and probably Sabah.	Year-round transmission.	Most cases from Penang, Perak, Salangor, Johore, and Sarawak.
Nepal	Hyperendemic in southern lowlands (Terai).	July to December.	Vaccine not recommended for travellers visiting only high-altitude areas.
Pakistan	May be transmitted in central deltas.	Presumed to be June to January.	Cases reported near Karachi; endemic areas overlap those for West Nile virus. Lower Indus Valley might be an endemic area.
Papua New Guinea	Normanby Islands and Western Province.	Probably year-round risk.	Localized sporadic cases.
China	Cases in all provinces except Xizang (Tibet), Xinjiang, Qinghai. Hyperendemic in southern China. Endemic–periodically epidemic in temperate areas. Hong Kong: Rare cases in new territories. Taiwan: Endemic, sporadic cases; islandwide.*	Northern China: May to September. Southern China: April to October (Guangxi, Yunnan, Guangdong, Southern Fujian, Sichuan, Guizhou, Hunan, and Jiangxi provinces). Hong Kong: April to October. Taiwan: April to October, with June as peak season.*	Vaccine not routinely recommended for travellers to urban areas only. Taiwan: Cases reported in and around Taipei and the Kaohsiung–Pingtung river basins.*

Philippines	Presumed to be endemic on all islands.	Uncertain;speculations based on locations and agroecosystems. West Luzon, Mindoro, Negros, Palawan: April to November. Elsewhere: year-round, with greatest risk April to January.	Outbreaks described in Nueva Ecija, Luzon, and Manila.
Russia	Far Eastern maritime areas South of Khabarousk.	Peak period July to September.	First human cases in 30 years recently reported.
Singapore	Rare cases.	Year-round transmission, with April peak.	Vaccine not routinely recommended.
Sri Lanka	Endemic in all but mountainous areas. Periodically epidemic in Northern and central provinces.	October to January; secondary peak of enzootic transmission May to June.	Recent outbreaks in central (Anuradhapura) and Northwestern provinces.
Thailand	Hyperendemic in North; sporadic-endemic in South.	May to October.	Annual outbreaks in Chiang Mai Valley; sporadic cases in Bangkok suburbs.
Vietnam	Endemic-hyperendemic in all provinces.	May to October.	Highest rates in and near Hanoi.
Western Pacific	Two epidemics reported in Guam & Saipan since 1947.	Uncertain; possibly September to January.	Enzootic cycle might not be sustainable; epidemics might follow introductions of virus.

Table 2: State wise JE cases and deaths from 2001 – 2007. [3]

State	2001		2002		2003		2004		2005		2006 (P)*		2007 (P)*	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D
Andhra Pradesh	33	4	18	3	329	183	7	3	0	0	4	2	1	0
Assam	343	200	472	150	109	49	235	64	145	52	126	34	119	29
Bihar	48	11	-	-	6	2	85	28	192	64	158	24	117	16
Chandigarh	-	-	4	-	0	0	0	0	0	0	0	0	0	0
Delhi	-	-	1	-	12	5	17	0	2	0	4	1	3	1
Goa	6	2	11	-	0	0	0	0	5	0	0	0	0	0
Haryana	47	22	59	40	104	67	37	27	38	31	24	17	19	10
Karnataka	206	14	152	15	226	10	181	6	108	8	84	5	42	1

Kerala	128	5	-	-	17	2	9	1	-	-	10	2	-	-
Maharashtra	126	1	27	2	475	115	22	0	66	30	47	24	27	18
Manipur	-	-	2	1	1	0	0	0	1	0	0	0	0	0
Punjab	-	-	10	2	0	0	0	0	0	0	0	0	0	0
Tamilnadu	-	-	-	-	163	36	88	9	8	1	5	2	2	0
Uttar Pradesh	1005	199	281	69	1124	237	1030	228	5928	1458	4235	1235	4152	998
West Bengal	119	21	-	-	2	1	3	1	6	1	4	1	5	2
Grand Total	2061	479	1037	292	2568	707	1714	367	6550	1645	4701	1347	4487	1073

C - Cases; D - Deaths Source: NVBDCP data; P* - Provisional, Source: NVBDCP

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