

Epidemiology of Japanese encephalitis: past, present, and future prospects

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Abstract: Japanese encephalitis (JE) is one of severe viral encephalitis that affects individuals in Asia, western Pacific countries, and northern Australia. Although 67,900 JE cases have been estimated among 24 JE epidemic countries annually, only 10,426 have been reported in 2011. With the establishment of JE surveillance and vaccine use in some countries, the JE incidence rate has decreased; however, serious outbreaks still occur. Understanding JE epidemics and identifying the circulating JE virus genotypes will improve JE prevention and control. This review summarizes the current epidemiology data in these countries.

Keywords: Japanese encephalitis, Japanese encephalitis virus, acute encephalitis syndrome

Introduction

Japanese encephalitis (JE) is one of serious vector-borne viral encephalitis disease found worldwide, especially in Asian, the Western Pacific countries, and in northern Australia.¹ Over 3 billion individuals live in JE epidemic and/or endemic countries. It is estimated that approximately 67,900 JE cases have occurred annually in 24 countries, with only 10,426 cases reported in 2011.^{2,3} The fatality rate in JE cases ranges from 20%–30%, with neurologic or psychiatric sequelae observed in 30%–50% of survivors.³

JE is induced by infection with Japanese encephalitis virus (JEV), which belongs to the JEV serogroup in the genus *Flavivirus*, family *Flaviviridae*.⁴ JEV has a single-stranded, positive-sense RNA genome of ~11 kb in length. The JEV virion contains seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) and three structural proteins: nucleocapsid or core protein (C), non-glycosylated membrane protein (M), and glycosylated envelope protein (E).⁵ The main JEV transmission vector is the *Cx. mosquito* especially *Cx. tritaeniorhynchus*, and the main vertebrate amplifying hosts are pigs and wading birds.⁶

Epidemiology of JE

Epidemiological patterns

Two epidemiological patterns of JE are recognized: epidemic and endemic (Figure 1).^{6,7} Epidemic patterns observed mainly in northern areas (Bangladesh, Bhutan, People's Republic of China, Taiwan, Japan, South Korea, North Korea, Nepal, northern Vietnam, northern India, northern Thailand, Pakistan, and Russia) demonstrate typical seasonal characteristics with occasional outbreaks. Endemic patterns found in southern areas (Australia, Burma, Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Papua New Guinea (PNG), Philippines, Singapore, southern Vietnam, southern Thailand, southern India, Sri Lanka, and Timor-Leste) occur sporadically throughout the year.

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Figure 1 Global distribution of Japanese encephalitis (JE) infection countries and risk areas.

Notes: ■ Japanese encephalitis risk countries that the epidemiological pattern of JE is epidemic; ■ Japanese encephalitis risk countries that the epidemiological pattern of JE is endemic.

Geographic distribution of JE

The characteristics of JE epidemics among the 27 countries and regions have changed with adjustments in JE prevention and control measures. The characteristics of epidemic and endemic JE, the sort of vaccine, as well as the JEV genotypes in these areas are summarized below and in Table 1.

Australia

JE was first recognized in 1995 in an outbreak of three cases in the Torres Strait, Australia; two JEV isolates were obtained from the serum of two patients.^{8,9} Mosquito surveillance indicated that *Cx. annulirostris* was the major vector, which was carried by the wind from New Guinea.^{9–13} Two additional JE cases were reported, including the first cases on mainland Australia. A serological survey in domestic pigs showed widespread JEV activity in north Queensland in 1998.^{14,15} Follow-up surveillance on pigs and mosquitoes indicated that the JE risk was not eliminated.^{16,17} The inactivated mouse brain-derived (MBD) JE vaccine was used exclusively on the residents of the Torres Strait Islands, as well as the people who lived or worked over 30 days on the Torres Strait islands during the rainy season.²

Bangladesh

First reported in 1977, a JE outbreak involving 22 cases with seven deaths was confirmed by serological testing. More than two-thirds of the patients were under 15 years old. However, serological surveillance revealed a low JE positive antibody rate after two years.¹⁸ In 2003–2005, a hospital-based surveillance of 492 patients at four sites revealed 20 JE cases (4%) with two deaths; all JE cases were from rural areas. The age distribution ranged from 1.5 months to 55 years, and 90% of the JE cases occurred during May–October, with nearly half in October.¹⁹ It is estimated that the JE incidence rate was 0.6–2.7 per 100,000 in Chittagong and Rajshahi.²⁰

Bhutan and Brunei Darussalam

Little is known about JE epidemiology in this region.

Myanmar (Burma)

A serological survey proved the existence of JE in Burma in 1968. A JE outbreak was first reported in 1974 in Shan State in which five cases and four deaths were reported; 42 cases and 32 deaths were reported in the following year.

Table 1 The information of JE and JEV in the epidemic and/or endemic countries or area

No	Country and regions	Existed of JE	Surveillance	JE age characteristics	Epidemic season	JE outbreak	Estimated JE incidence	Virus isolation year	Vector	JEV genotype	Sort of vaccine	Reference
1	Australia*	1995	National	Teenage and adult	April	2 in 1995/2 in 1998	<3 cases	1995	Mosq./H-S	G1, 2	MBDV	8-17
2	Bangladesh	1977	Hospital-based (4 sites/2 years)	2/3 patients <15 years old	May to Dec/pick in Oct	22 patients with 7 died in 1977	0.6-2.7/100,000	-	-	-	-	18-20
3	Bhutan	-	-	-	-	-	-	-	-	-	-	-
4	Brunei	-	-	-	-	-	-	-	-	-	-	-
5	Darussalam	-	-	-	-	-	-	-	-	-	-	-
5	Burma (Myanmar)	1968	National	83.3% <20 years old	July to Oct	5 cases (4 deaths) in 1947 and 43 cases (32 deaths) in 1948	-	-	-	-	-	21,22
6	Cambodia	1965	Hospital-based (6 sites/2 years)	92% <12 years old	Year-round; no prominent seasonal peak	-	11.1/100,000 in under 15 years old	1965	Mosq.	-	LAV-SA 14-14-2	23-28
7	People's Republic of China	1940s	National	Mainly children; adults in some outbreak	May to Oct/pick in July and Aug	Mainly in 1960-1970 the morbidity higher than 10/100,000	0.1-0.9/100,000	1949	Mosq., midge, pig, bat and H-S, H-CSF, H-B	G1, 3, 5	VCDV-P3, LAV-SA 14-14-2	29-37
8	Taiwan	1938	All area	20-70 years old	May to Oct/pick in July and Aug	Mainly in 1960-1970 the morbidity nearly 12.4/100,000	0.03/100,000	1962	Mosq.	G1, 3	MBDV	38-47
9	Guam	1947	-	-	-	46 reported JE cases	-	-	-	-	-	48-50
10	India	1950s	Hospital-based	Mainly children	July to Oct in north/year-round in south	5,700 cases and 1,315 deaths in 2005	15/100,000 in 5-9 years	1973	Mosq., horse, H-CSF	G1, 3	LAV-SA 14-14-2	51-73
11	Indonesia	1974	Hospital-based (15 sites/2 years)	95% <15 years old	Year-round	No	8.2/100,000 in under 10 years old	1972	Mosq.	G1, 2, 4	-	74-78
12	Japan	1933	National	>40 years old	July to Oct	Mainly before 1960	<10 cases	1935	Mosq., H-CSF	G1, 3	VCDV- Beijing-1	79-94
13	Laos	1989	Hospital-based (1 site/8 years)	More than 50% <15 years old	-	-	-	2009	CSF	G1	-	95-99
14	Malaysia	1952	National	Mainly children	Year-round	154 cases and 42 deaths in 1999	4.3/100,000	1952	Mosq., H-B	G2, 4	MBDV	6,100-104
15	Nepal	1978	Hospital-based	Mainly children	July to Oct	2,040 cases and 205 deaths in 2005	<12 years old 1.3/100,000	1978	Mosq.	G1, 3	LAV-SA 14-14-2	105-114

(Continued)

Table 1 (Continued)

No	Country and regions	Existed of JE	Surveillance	JE age characteristics	Epidemic season	JE outbreak	Estimated JE incidence	Virus isolation year	Vector	JEV genotype	Sort of vaccine	Reference
16	North Korea	-	-	-	-	-	-	-	-	-	-	-
17	Pakistan	Early of 1980s	None	-	-	-	-	-	-	-	-	2,115,116
18	Papua New Guinea	1995	Sentinel	-	-	-	-	1997	Mosq.	G2	-	15,117,118
19	Philippines	Early of 1950s	Hospital-based (1 site/3 years)	72.9% < 17 years old	Year-round	No	-	1977	Mosq.	G3	-	119-121
20	Russia†	-	-	-	-	-	-	-	Bird/human	-	-	122,123
21	Saipan	1990	-	-	-	10 cases (3 lab confirmed, 7 suspected) in 1990	-	No	-	-	-	124,125
22	Singapore	1952	National	Mainly children	-	-	<5 cases	1952	Human	G3	-	1,126-129
23	South Korea	1946	National	40-49 years old	Aug	Mainly before 1960	0.013-0.055/100,000 < 10 cases annually	1946	Mosq.	G1, 3, 5	MBDV	6,130-137
24	Sri Lanka	1968	National	All age	Nov to Dec	3 times	< 100 cases	1974	Human	G3	-	6,138-140
25	Thailand	1961	National	<15 years old	May to July in north/Year-round in south	In north	About 300 cases annually reported	1964	Mosq., pig, H-CSF	G1, 3	MBDV	141-144
26	Timor-Leste	-	-	-	-	-	-	-	-	-	-	-
27	Vietnam	1960	National	<15 years old	May to July in north/Year-round in south	In north	1-8/100,000	1951	Mosq.	G1, 3	MBDV	145-147

Note: †The JE epidemic in limited area focus on the Torres Strait Islands. †The JE epidemic in limited area focus on the Siberia.

Abbreviations: JE, Japanese encephalitis; JEV, Japanese encephalitis virus; mosq., mosquitoes; H-S, human serum; H-CSF, human cerebrospinal fluid; H-B, human brain tissue; lab, laboratory; MBDV, inactivated mouse brain-derived JE vaccine; VCDV-P3, inactivated Vero cell culture-derived P3 JE vaccine; VCDV-Beijing-1, inactivated Vero cell culture-derived Beijing-1 JE vaccine; LAV-SA 14-14-2, live attenuated SA 14-14-2 JE vaccine.

All cases occurred in July–October, and 83.3% of the patients were under 20 years old.²¹ The subsequent investigation showed that *Cx. tritaeniorhynchus* was likely to have been the main vector, and the JE antibody positive rates were 81.5% and 42% in domestic animal and human populations, respectively.²¹ Another serological survey confirmed the prevalence of JEV infections in northwest Burma in a location distant from the JE outbreak in 1978.²²

Cambodia

JEV was first isolated from mosquitoes in 1965. Existing JE data were from several sentinel hospitals, with no national JE epidemiological data available. Among 50 pediatric clinical encephalitis cases diagnosed in the National Pediatric Hospital in Phnom Penh from July 1996 to September 1998, JE was confirmed in nine (18%) patients, all of whom were under 10 years of age.²³ In another surveillance performed by Takeo Provincial Hospital from October 1999 to September 2000, 31% of the JE patients were under 15 years.²⁴ Subsequently, two years of sentinel surveillance performed in six hospitals revealed that 95% of JE patients were under 12 years of age, and cases occurred throughout the year with no prominent seasonal peak. The estimated incidence of JE was 11.1 per 100,000 in children under 15 years of age.²⁵ The extent of disability after JE resulted in 11% with severe sequelae.²⁶ A study assessing JEV infection in pigs in eight provinces showed that pigs older than 6 months had high rates of JEV infection, suggesting that human JE disease also had the potential for high prevalence.²⁷ After a cost and effectiveness analysis for the JE vaccine, the live attenuated SA 14-14-2 JE vaccine (LAV-SA 14-14-2) was used in the routine immunization strategy in Cambodia.^{2,28}

People's Republic of China

JE was first reported in the 1940s, and became the main cause of viral encephalitis in the People's Republic of China. The JE case reporting system has been mandated by law since 1951.^{29,30} The morbidity due to JE was 10–15 per 100,000 in 1960–1979, which reached the highest level (20.92 per 100,000) in 1971. The seasonal distribution of JE in the People's Republic of China is from June to October, with a peak in July and August. Children under 15 years of age constitute the majority of JE cases.²⁹ Use of the MBD JE vaccine (P3 strain) began in the late 1970s, and the LAV-SA 14-14-2 was introduced in 1989. The reported cases of JE decreased dramatically from 10,308 in 1996 to 2541 in 2010.^{29,30} However, adult JE cases and outbreaks have been reported.³¹ Since 2008, JE immunization has been included in the national immunization program using the

LAV-SA 14-14-2 in 28 Chinese provinces, excluding Qinghai, Xinjiang, and Tibet.³² Tibet is a traditionally non-epidemic area in the People's Republic of China; however, JEV was isolated from *Cx. tritaeniorhynchus* in Linzhi, Tibet in 2009. In the same region, the JEV antibody was also tested in pig and human serum.^{33–35} A laboratory for JE surveillance of hospital-reported encephalitis cases was later set up in that area. In history, JE cases were mainly clinically reported. A survey based on the laboratory testing of the hospital-reported JE cases in Guizhou in 2006 showed nearly 87.6% of the reported clinical JE cases were laboratory confirmed and the high number of JE cases was mainly reported in county hospitals.³⁶ Acute meningitis and encephalitis syndrome (AMES) surveillance in four prefectures in the People's Republic of China during 2006–2008 indicated that the adjusted estimate of JE incidence was three to ten times higher than that reported previously.³⁷ The JE lab-net were set up in 2011 and with the improved JE surveillance system in the People's Republic of China, more than 90% of reported JE cases have been diagnosed by laboratory testing.

Republic of China (Taiwan)

“Summer encephalitis” was first documented in 1931; however, JEV isolation and serological evidence for the disease was not obtained until 1938.^{38–40} A JE vaccination campaign in infants and new school children was launched in 1968, and the complete JE immunization strategy was adjusted to include a total of four doses of MBD JE vaccine.^{40–42} At the same time, a live attenuated JE vaccine (M strain) was also used to protect swine against stillbirths in Taiwan.⁴³ The incidence rate of confirmed JE cases decreased significantly from 2.05 per 100,000 in 1967 to 0.03 per 100,000 in 1997.⁴⁰ The number of annual confirmed JE cases decreased dramatically from 35 cases in 2000 to only 20 in 2007.⁴⁴ The epidemic season appeared from May to October, with a sharp peak in July and August.^{38–40,44} The age distribution shifted from mainly children to adults, with nearly 90% of laboratory-confirmed JE cases older than 20 years (range, 20–70 years).^{40,44} Currently, JE is a disease found predominantly in adults living in eastern, central, and southern Taiwan, ie, in regions with more livestock breeding and agricultural industry.⁴⁴ Mosquito surveillance showed that *Cx. tritaeniorhynchus* and *Cx. annulus* were the most important JEV vectors to human and domestic animals. *Cx. fuscocephala* showed an overwhelming preference for the water buffalo, documented to be involved in JEV transmission in Taiwan.^{45–47}

Guam

Although there is no evidence for any encephalitis in Guam, a JE outbreak in the Pacific islands occurred with a

total of 46 clinical JE cases reported from October 1947 to April 1948.^{48,49} The mosquito survey showed that the *Cx. annulirostris marianae* was a suspected vector during this outbreak.⁵⁰

India

JE was first recognized via a serological survey in the 1950s.^{51–53} The first JE outbreak was reported in West Bengal in 1973, followed by reports in southern, eastern, and western states.^{54–58} JE was first reported in Uttar Pradesh, the main JE epidemic area in the northern state of India in 1978.⁵⁹ After that, a severe outbreak of JE occurred with 5,700 cases and 1,315 deaths in Uttar Pradesh state in 2005.^{60,61} The clinical features of the cases were severe, and the in-hospital mortality was 34% in one hospital.⁶² Hospital-based acute encephalitis syndrome (AES) surveillance in north and northeast India showed that ~25% of cases were positive for JE, which were prevalent mainly in children.^{63–65} The estimated JE incidence rate was 15 per 100,000 in 5–9-year-olds in Tamil Nadu, a state in southern India.⁶⁶ The JEV infection rate reached as high as 70.7% of the cases.⁶⁷ Laboratory tests confirmed that the JE cases occurred throughout the year, with more cases in the rainy season.^{68,69} A routine program was implemented in this JE epidemic area starting from 2006 using the LAV-SA 14-14-2. The *Cx. vishnui* subgroup, and the *Cx. tritaeniorhynchus*, *Cx. pseudovishnui* and *Anopheles subpictus*, were the main mosquito vectors and secondary vectors in India.^{70–72} The minimum infection rate of JEV in mosquito remained as low as 0.8 annually from 1996 to 2004.⁷³

Indonesia

The first serologically confirmed JE cases were reported in 1996.⁷⁴ Subsequently, hospital-based surveillance in Bali from 2001–2003 showed a total of 86 laboratory confirmed (with 4 probable) JE cases in 239 pediatric patients. The estimated JE incidence rate was 8.2 per 100,000 in children under 10 years of age. The JE cases occurred throughout the year, but mainly in the rainy season.⁷⁵ A sentinel surveillance involving 15 hospitals in six provinces from 2005–2006 further confirmed the presence of JE cases in all provinces throughout the year, with 95% of cases occurring in children under 10 years of age.⁷⁶ A survey of JEV antibodies in pigs showed that the antibody positive rate in Bali was higher than that in East Java, indicating that exposure to JEV infection and JEV transmission in nature were more active in Bali than in East Java.^{77,78} JEV was first isolated from *Cx. tritaeniorhynchus* in 1972.⁷⁶

Japan

After experiencing a serious summer encephalitis, Japan implemented the National Epidemiological Surveillance of Vaccine Preventable Diseases in 1965. The comprehensive surveillance included laboratory confirmation of reported JE cases, serological survey on JEV antibodies in the population, and a sentinel survey of JEV seroconversion rates in pig.⁷⁹ The inactivated MBD JE vaccine using the Nakayama strain was distributed widely in 1967.⁸⁰ Subsequently, the annual number of JE cases decreased from more than 1,000 to 90 in 1991, and less than ten cases after that. All cases were reported from July to November. The age distribution changed from children to adults, with 78% of cases over 40 years old; 51% had records showing the lack of JE vaccinations.⁷⁹ Although the numbers of JE cases were low, unexpected outbreaks still occurred.^{81,82} Inactivated Vero cell-derived JE vaccine produced with the Beijing-1 strain was used after 2005.⁸³ The JEV NS1 antibody-based testing method was used as a marker to test the JEV natural infection rate, as the NS1 protein was not expressed after inoculation with the inactive vaccine. A survey on natural infection of JEV in humans and horses indicated that JE remains prevalent in Japan.^{80,84–89} *Cx. tritaeniorhynchus* is the main vector in Japan.⁹⁰ Serological surveillance on JEV was performed in various animals including raccoons, raccoon dogs, wild boars, and horses. The results suggested that JEV was prevalent in wild animals and they may be potential sentinels to estimate JEV infection risk.^{91–94}

Laos

The first reported cases of JE were described in 1990. A seroepidemiological study of JE in the Vientiane and Khammouane provinces showed that the JE antibody positive rate increased with age, reaching over 50% by 31–40 years of age.⁹⁵ A separate serological investigation in Khammouane province further proved the JE epidemic, with 1.3% positivity to JEV.⁹⁶ A large-scale serosurvey for flavivirus including the dengue virus (DENV) and JEV was conducted in Vientiane, the capital of Laos, which contains 5% of the national population. This study indicated that urbanization affected the risk of virus infection.⁹⁷ A hospital investigation from 2001 to 2008 showed a 10.1% JE positive rate in AES and meningitis cases, with more than half of the JE cases under 15 years of age.⁹⁸ The first JEV was isolated from human blood in 2009, which belonged to genotype 1.⁹⁹

Malaysia

Although information is scarce regarding the national JE epidemic in Malaysia, three JE outbreaks were recorded in

1974, 1988, and 1999, with 154 reported JE cases (42 laboratory confirmed cases) and 56 deaths in the 1999 outbreak. Most of the patients were adult males who worked on pig farms.^{100,101} The MBD JE vaccine was introduced to children under 15 years of age in July 2001. According to a hospital-based surveillance study focused on cases in Sarawak, the estimated JE incidence rate decreased from 9.8 to 4.3 cases per 100,000 children under 12 years of age.^{101–103} JEV isolation from mosquitoes indicated that the main vectors were *Cx. tritaeniorhynchus* and *Cx. gelidus*, which breed primarily in rice fields.⁶ However, infection experiments suggested that *Cx. sitiens* also had the capacity to transmit JEV in Peninsular Malaysia.¹⁰⁴

Nepal

JE cases were first reported in 1978 in the Terai districts near India.¹⁰⁵ JE was a seasonal disease epidemic from July to October and the incidence rate decreased with altitude, showing higher rates in the south and lower rates in the northern mountains; however, the JE is still epidemic in the mountainous altitude.¹⁰⁶ Four western Terai districts had significantly higher JE incidence rates than the other areas in Nepal.^{107,108} The laboratory-based surveillance of JE spanned from mid-2004 to 2010 and covered 126 hospitals in the country. A total of 2,040 JE cases including 205 deaths were reported from 2005 to 2010 after mass immunization in 2006.¹⁰⁹ The JE incidence rate decreased to 1.3 per 100,000 after the JE immunization campaign.¹¹⁰ A routine program was implemented in this JE epidemic area starting from 2006 using the LAV-SA 14-14-2, followed by mass vaccination campaigns conducted in 23 districts with high JE epidemic area.¹¹⁰ Pigs in Terai, the lower border district, were vaccinated with live attenuated virus in 2001. JEV Serological data in pig indicated a serious risk for farmers, residents, and travelers.^{111–114}

North Korea

Little is known about JE epidemiology in North Korea.

Pakistan

JE was confirmed by a seroepidemiological survey in the early 1980s in Pakistan.¹¹⁵ An acute encephalitis case was further confirmed during the JE epidemic in 1992 by molecular diagnosis using reverse transcription-polymerase chain reaction (RT-PCR) for JEV from cerebrospinal fluid (CSF).¹¹⁶ No national JE epidemiology information is available due to the lack of a surveillance program.²

Papua New Guinea (PNG)

A JE outbreak had been a concern in the island between Papua New Guinea and Australia. JEVs were isolated from mosquitoes, and clinical cases were reported in the west province. In 2004, serological testing confirmed JE in a 66-year-old male from Port Moresby.^{15,117,118}

Philippines

JE was first recorded in the early 1950s, and JEV was first isolated from mosquitoes in 1977.¹¹⁹ A serological study on clinical viral encephalitis cases revealed that 85.2% of JE cases were under 15 years old, and occurred mainly in February–September.¹²⁰ In 2002–2005, a total of 614 CSF specimens were tested by IgM-capture enzyme-linked immunosorbent assay (ELISA), of which 11.7% were positive. Laboratory-confirmed JE cases were reported each year in individuals ranging from 2 to 77 years, however, 72.9% were under 17 years of age. JE cases occurred year-round, and mainly in the rainy season.¹²¹

Russia

The JE epidemic area was limited to the eastern coastal area of Siberia. JEV isolates were obtained from blood in migratory birds¹²² and human brain,¹²³ however, the genotype was not clear due to lack of viral sequences.

Saipan

An outbreak of JE occurred in Saipan in October 1990. Ten cases (three laboratory-confirmed and seven probable) were identified in a human population of approximately 40,000. A community serosurvey showed that the neutralizing antibody of JEV was positive in lifelong Saipan residents in 1991, but negative in 1984. An animal serosurvey showed positive JEV antibody in 96% swine, an important amplifying host of JEV when epidemics occur in ducks, dogs, and goats.¹²⁴ No virus was isolated from mosquitoes. *Cx. tritaeniorhynchus*, an abundant and widely distributed species, is the first recorded in Saipan.¹²⁵

Singapore

JE cases were first reported in 1952.¹ Approximately 100 JE cases were reported in the 1970s and early 1980s, and a dozen were reported during 1985–1992.^{126,127} The incidence of JE decreased dramatically in Singapore after pig farming was completely eliminated in 1992, with six reported JE cases from 1991–2005.¹²⁸ However, seroepidemiological data on wild pigs and other local animals indicate that JEV is still circulating in nature, and the risk of JEV infection persists.^{126,127} JEV isolates were obtained from mosquitoes and human blood.¹²⁹

South Korea

A human JE case was first confirmed in 1946,¹³⁰ which was included in the national surveillance system in 1949.¹³¹ Before 1983, hundreds to thousands of JE cases were reported.⁶ The MBD JE vaccine was first administered to children in 1971, and the mass vaccination program started during a large outbreak in 1983.¹³¹ The JE incidence rate decreased to 0.013–0.055 per 100,000 (about ten cases reported annually), with affected individuals in the age range of 40–49 years. The largest epidemic appeared in August.¹³¹ Mosquito surveillance showed that the *Cx. tritaeniorhynchus* first appeared in June, were trapped in large numbers from mid-August to early September, then significantly decreased in early October.^{132,133} With the decline in JE cases, the serological surveillance on JEV in potential animals has been strengthened. The incidence of JEV was 51.3% in domestic cattle,¹³⁴ 12.1% in goat,¹³⁵ 49.7% in horses,¹³⁶ and 86.7% in wild bird.¹³⁷ At present, the most important public health problem is how to issue JE protection in adults who live in an urban or suburban environment with a strong immunization program in children.

Sri Lanka

The presence of JE was recorded in 1968, and the first JE outbreak was reported in 1971.¹³⁸ Subsequently, three major outbreaks were reported in 1985–1987,⁶ with hundreds of JE cases occurred during the fall. Comparing epidemic (1987) and non-epidemic (1988) years, the difference can be explained by the abundance of major mosquitoes (*Cx. tritaeniorhynchus* and *Cx. gelidus*) and virus infection rate.¹³⁹ Immunization was launched in Sri Lanka in 1988 using two kinds of JE vaccines: the MBD JE vaccine and the live attenuated SA14-14-2 JE vaccine (LAJEV); however, the country's immunization program selected only the inactivated vaccine.^{138,140} JEV was first isolated in 1974.¹³⁹

Thailand

Serological testing identified the JEV antibody in 1961. Records for all types of encephalitis were included in the routine disease surveillance system in Thailand. JE was epidemic with high incidence and significant seasonal characteristics that occurred from May to September, with a peak in June or July, in the northern and northeast region. Endemic and sporadic cases were reported in the central and southern area. A total of 1500–2500 encephalitis cases were reported annually from the 1970s–1980s, which decreased to 297–418 per year from 2002–2008.^{141–143} A hospital-based survey found that 74% and 15% laboratory-confirmed

JE cases were under 15 years of age in 1987 and 2003, respectively.^{142,143} The MBD JE vaccine was introduced into the Thai National Immunization Program (NIP) in 1990.¹⁴⁴ *Cx. tritaeniorhynchus*, *Cx. gelidus* and *Cx. fuscocephala* were the main vectors of JE in Thailand.¹⁴²

Timor-Leste

Little is known about JE epidemiology in this country.

Vietnam

Viral encephalitis (including JE) has been reported in the national surveillance system in Vietnam. The highest estimated JE incidence rate was 22 per 100,000 in the 1960s, which decreased to 1–8 per 100,000 individuals. The highest incidence rates were reported in the provinces near the Red River delta region in the north and the Mekong River delta region in the south. MBD JE vaccine was introduced in 12 high-risk districts in the northern region in 1- to 5-year-old children in 1997, and expanded to 65% of districts in Vietnam.¹⁴⁵ JE displayed an obvious age distribution and seasonal pattern in the northern region. Over 65% of AES cases under 18 years old were laboratory-confirmed JE cases, mainly from May–July. On the other hand, sporadic JE cases were reported throughout the year.^{146,147} JEV was first isolated in 1951.¹⁴⁵

JEV genotype distribution

The prototype Nakayama JEV strain was isolated from a post-mortem human brain in Tokyo, Japan, in 1935.¹⁴⁸ Subsequently, more JEV isolates were obtained from mosquitoes, pigs, humans, bats, midges, and wild birds worldwide. Phylogenetic analysis of JEV strains revealed that JEVs can be divided into four genotypes using the *prM* gene^{149,150} and five genotypes according to the E gene and full length genome.^{151,152} The most recent common ancestor (TMRCA) analysis according to the complete genomic sequences of JEV isolated from human, various mosquitoes, midges, pigs, and bats, indicates that the JEV genome appeared 1695 years ago. Genotype 1 JEV expanded in epidemic areas over the last 30 years, and an alternative genotype 3 became a domestic pathogen.^{153,154}

Three JEV genotypes (G1, 3, and 5) from mosquitoes, bats, midge, and humans were isolated in Mainland China,^{31,34,155–158} and two JEV genotypes (G1 and 3) were isolated in Taiwan. The JEV isolates from mosquitoes, pigs, bird, and human belonged to G3 before 2008, after which G1 was the only isolate from mosquitoes.^{159–161} Two JEV genotypes (G1 and 3) had been isolated in Japan. The JEV

isolates from mosquitoes, pigs, and human belonged to G3 before 1992, co-circulated from 1993–1994, after which G1 dominated. JEV G1 was isolated from mosquitoes and horses, and G1 sequences were found in wild boar and a meningitis patient; however, G3 was also isolated or identified by RT-PCR in JE cases.^{81,85,162–174} Three JEV genotypes (G1, 3 and 5) were isolated or sequenced in South Korea. G3 was dominant before 1993; G1 and G3 co-circulated in 1993–1994, after which G1 was the only genotype isolated from mosquitoes and pig.^{130,175–178}

India, Nepal, Thailand, and Vietnam also had G1 and G3 genotypes, and G1 became the dominant genotype in this area.¹⁷⁹ In India, phylogenetic analysis of the JEVs isolated from human CSF in 2009–2010 showed that G1 and G3 were co-circulating.^{180,181} However, the equine isolates also belonged to the G3, similar to the old strain.^{182,183} In Vietnam, the JEV isolated from mosquitoes, pigs, and human belonged to G3 before 2001, after which G1 was the only genotype isolated from mosquitoes.^{184–187} JEV G1 was isolated from mosquitoes from 2000–2004 in Australia,¹⁶ where the G2 genotype was isolated from mosquito and patients,^{9,10} and also in PNG.¹¹⁷

All parental strains currently used for JEV vaccines (SA14 and Beijing-1 from the People's Republic of China, and Nakayama from Japan) are derived from JEV G3. Although five genotypes of JEV are found in nature, only one JEV serotype occurs naturally. In theory, the vaccine that is currently in use could protect against the epidemic JEV. The study indicated that the vaccine currently used prevents the G1 and G3 JEV infections prevalent in the People's Republic of China.¹⁸⁸ At present, the licensed JE vaccines used in different countries include inactivated MBD (Nakayama and Beijing-1), inactivated Vero cell-based (Beijing-1, P-3, SA 14-14-2, Kolar strain-JEV 821564XY), live attenuated vaccine (SA14-14-2) from Chengdu Institute of Biological Products, and the chimeric live attenuated SA14-14-2 vaccine. The live attenuated SA14-14-2 vaccine is the first Chinese vaccine to have its safety and quality endorsed by the World Health Organization (WHO) for use with children. The efficiency of the present JE vaccine in eliciting protective neutralizing antibodies against different JEV strains needs to be evaluated.

Summary and future prospects

According to the current epidemic/endemic characteristics of JE, the disease surveillance and vaccination strategies in these countries and regions could be divided into four levels.

Group 1: Japan, South Korea, and Republic of China (Taiwan) have reported JE epidemics; however, these countries

conducted complete surveillance and JE immunization programs, resulting in <30 reported JE cases annually. The characteristics of the JE epidemics were analyzed and JE control measures have continued. The main public health problem, prevention and future control, will focus on adult JE cases following long-term mass JE immunization.

Group 2: Cambodia, People's Republic of China, India, Malaysia, Nepal, Sri Lanka, Thailand, and Vietnam, have reported JE epidemics, endemics and/or outbreaks. National or sentinel (hospital-based) surveillance programs were established, and JE vaccines were used in national or sub-national areas (in high-risk area). The JE cases reported worldwide are mainly from these countries, especially India and the People's Republic of China, which account for 95% of all cases. JE prevention and control are the main issues for global JE control. The following comprehensive measures should be adopted: 1) expansion of the surveillance system to include i) laboratory confirmation of JE and AES cases to understand the actual JE incidence, ii) virus isolation in mosquitoes and JE cases to grasp the molecular characteristics and mutation of the JEVs, iii) seroconversion rates in amplifying vectors (sentinel pigs or wild birds) nationwide, iv) assessment of the prevalence of JE antibodies in the general population. 2) Incorporation of the JE vaccine into routine immunization programs in children. Japan's success has demonstrated the JE vaccine as the most effective measure to reduce JE incidence. 3) Establishment of different pig breeding patterns by moving large-scale pig farms away from rice paddies. This measure will greatly reduce the chance of people becoming infected with JE; however, it is closely related to the economic level of the country. 4) Mosquito vector control, improvement in the living environment, and health education are important, especially during a JE outbreak.

Group 3: Bangladesh, Bhutan, Brunei Darussalam, Burma (Myanmar), Indonesia, Laos, North Korea, Pakistan, PNG, Philippines, and Timor-Leste have no known established sentinel JE surveillance systems, and no JE immunization programs. Future national surveillance programs should focus on JE cases to understand the disease burden, although these countries report fewer than 100 JE cases.

Group 4: Australia (risk area), Guam, Russia (Siberia), Singapore, and Saipan have reported fewer than three JE cases annually. Therefore, maintenance of the existing surveillance systems and developing immunization strategies as a one-time campaign in the target population are suggested.

Though JE is highly distributed, outbreaks still occur in epidemic areas. Other than the present conventional practices

(mosquito control, health education propaganda, etc), emergency vaccination campaigns are currently the most effective measures against outbreaks.

Conclusion

Although JE remains a prominent public health problem in Asia, the reported cases are decreasing due to JE immunization (especially in the People's Republic of China and India), agricultural pattern changes, urbanization, and improved living conditions. As JEV will likely remain in nature and the risk of JE will persist, it is important to implement strategies that strengthen JE surveillance systems in order to understand the disease burden and apply vaccination protocols in national childhood immunization programs.

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Disclosure

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