A review of Japanese encephalitis in Uttar Pradesh, India

Roop Kumari\textsuperscript{a}, Pyare L Joshi\textsuperscript{b}

**Background:** Japanese encephalitis (JE) is a major public health problem in India. When the first case was reported in 1955, the disease was restricted to south India. The disease spread to north India in 1978 from where extensive and recurrent outbreaks of JE have been reported ever since. An attempt has been made to review the epidemiology of JE over the past 30 years and suggestions made for its prevention and control.

**Methods:** An epidemiological profile of JE (1978–2009) has been compiled and analysed to understand the trend and status of the disease.

**Results:** In India, while 24 states are endemic for JE, Uttar Pradesh contributed more than 75\% of cases during the recent past. Over the years, the seasonal trend has changed and the epidemic peak of the disease has advanced by one month.

**Conclusion:** JE is closely associated with the pattern of precipitation, flooding and rice production systems. Analysis of trends and influencing factors will help in designing suitable strategies for the prevention and control of JE in the country. Continuous monitoring of vector populations and JE virus infection rates in vector mosquitoes will help in predicting an outbreak and in taking effective intervention measures.

**Key words:** Japanese encephalitis, epidemiology, Uttar Pradesh, India, vector, high-risk districts

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**Introduction**

Japanese encephalitis (JE), a vector-borne viral disease, is endemic to large parts of Asia and the Pacific regions.\textsuperscript{1} An estimated 3 billion people are at risk, and the disease has recently spread to new territories globally.\textsuperscript{2} JE is a major public health challenge due to its high epidemic potential, high case–fatality and neuropsychiatric sequelae among survivors. JE was first recognized in Japan in 1924. Since the late 1960s, the size of epidemics in Japan and the People’s Republic of China has steadily declined. In contrast, new epidemic foci of JE were reported in the parts of tropical southeastern Asia as late as 1969.\textsuperscript{3}

In India, the first human case was reported from North Arcot district of Tamil Nadu in 1955.\textsuperscript{4} Until 1973, the disease was confined to southern parts of India, with low prevalence; subsequently the disease spread to various other parts of India. The first outbreak of

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JE was recorded in 1973 from Burdwan and Bankura districts of West Bengal. In 1978, suspected outbreaks of JE were reported from 18 states and 24 states and Union Territories have reported suspected JE cases till recent past.

The State of Uttar Pradesh (UP) is highly endemic; since the first report of a JE epidemic in 1978, extensive and recurrent outbreaks have been reported from the eastern parts of the State. An attempt has been made in this article to review the epidemiology of JE since 1978, particularly in UP, and to make recommendations for its prevention and control.

Study area
Uttar Pradesh, 241,000 km², is the most populous State in India with over 199 million people as of 2011. The majority of the population is engaged in agriculture, which contributes to 41% of the State’s economy. Since its division in 2000 into two states, UP has 71 districts, 106 thousand villages, 3640 primary health centres and 18565 sub-centres.

Climatically, while the State experiences tropical monsoons, weather conditions change significantly as per the location and onset of the season. UP has three broad seasons – winter from October to February (minimum temperatures of 3–4 °C), summer from March to mid-June (temperatures up to 45 °C), and the rainy season from June to September (85% of average annual rainfall of 99 cm and temperatures of 30–45 °C). The entire region is prone to annual flooding due to its topography. Five districts in Eastern UP (Gorakhpur, Kushinagar, Maharajganj, Sant Kabir Nagar and Siddarth Nagar), a region surrounded by embankments and drainage structures, are the most affected by floods as they are traversed by major rivers originating in the Nepali hills. Regular flooding is devastating for the crops, life and property of the farming community, and to a large extent determines their socioeconomic and political lives.

Domestic animals
The common domestic animals include cows, buffaloes, goats, pigs, dogs and horses. The pig is known to be the amplifier host of the JE virus (JEV). Despite this knowledge, unorganized piggeries are common in most districts in the region.

Methodology
Surveillance and case definitions
Clinical diagnosis is made by the respective medical officers of the health centres/hospitals who attend the JE cases in outpatient or inpatient departments, using standard case definitions as per national guidelines. Serum and cerebrospinal fluid samples of suspected cases are tested by IgM enzyme-linked immunosorbent assay (ELISA) for confirmation of JE. Previously, laboratory and treatment facilities were only available at Baba Raghav Das (BRD) Medical College, Gorakhpur; King George Medical College, Lucknow (now Shahuji Maharaj Medical University) and Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow. Since 2005, district hospitals are being strengthened for diagnosis of JE cases. Eastern districts of UP are highly endemic, and most JE patients from these areas have been treated at BRD Medical College, along with JE patients from border districts of Bihar and even neighbouring Nepal.

In 2006, the National Vector Borne Disease Control Programme (NVBDCP) modified the case definition of JE. Since then, epidemiological surveillance for acute encephalitis syndrome (AES) was initiated...
and suspected JE cases are now reported as follows: “Clinically, a case of AES is defined as a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) AND/OR new onset of seizures (excluding simple febrile seizures). Other early clinical findings may include an increase in irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness”. JE surveillance therefore aims to identify patients with AES and thereafter confirm JEV infection using IgM ELISA test.

Methods
Epidemiological data for JE over the past 32 years (1978–2009) as reported by State Health Authorities and from published and unpublished documents were collected and analysed for the purpose of this study. The burden of JE morbidity, annual incidence rate (number of cases per 100,000 risk area populations) and case–fatality rate (proportion of deaths against the total number of cases reported per year) were estimated.

Results
As compared with the total number of JE cases reported in the country, UP contributed a fifth of the disease burden (20.4% of cases and 18.7% of deaths) during 1978–1987 (Figures 1A and 1B). Its contribution increased between 1988 and 1997 to 24.3% cases and 20.9% deaths, and represented well over half of the total cases and deaths reported in the country between 1998 and 2009. While the proportion of JE cases reported from Uttar Pradesh in 1997 was only 14%, it started increasing dramatically from 1998 and in 2005, a major outbreak in UP contributed over 90% of all suspected JE cases (6061) – and over 89% deaths (1501) – in the country. During the four following years, 2006–2009, 80.8%, 73.6%, 78.5% and 77.0% of cases, respectively, were contributed by the State of Uttar Pradesh (Figure 1C).

Figure 1A: Proportion of Japanese encephalitis cases contributed by Uttar Pradesh in national figures by decade, 1978–2007

![Figure 1A](image-url)
Figure 1B: Proportion of Japanese encephalitis deaths contributed by Uttar Pradesh in national figures by decade, 1978–2007

Figure 1C: Contribution of Japanese encephalitis cases by Uttar Pradesh in national figures by year, 1997–2009
Trend of JE cases and deaths in Uttar Pradesh

Figure 2 shows that, despite year-to-year fluctuation, there was no definite trend of JE cases and deaths in the State since 1978. In the first decade (1978–1987), a total 9299 reported JE cases, and 3103 deaths attributed to suspected JE cases, were reported from 46 districts. The first outbreak of suspected JE was recorded in UP in 1978, during which 3550 cases and 1117 deaths were reported from 40 districts. While in 1979 only 150 cases were reported, this number again increased in 1980 to 1604 cases reported from 15 districts. Thereafter, the incidence of JE declined until 1985. In the second decade (1988–1997), the total number of reported cases and deaths were 10 064 and 3194, respectively, from 25 districts. During 1998–2009, the burden of JE was much higher than the previous decades, at 18 760 cases and 4189 deaths, reported from 40 districts in the State.

Case–fatality rate

The annual case–fatality rate (CFR) of reported suspected cases shown in Figure 2 was higher in the beginning (1978–1987), ranging from 31.2% to 48.0%, before declining in 1988–1997 (range 21.0–39.9%) and 1998–2007 (18.6–24.9%). In the 2005 JE outbreak, the overall CFR was 24.9% as compared with earlier outbreaks in 1978 (31.5%), 1985 (34.5%) and 1988 (31.5%). This indicates an improvement in the management of JE cases over time.

Seasonal variation

Monthly reported JE cases from 1998 to 2007 indicate that sporadic cases occurred in the month of June and reached a peak in September before declining thereafter.
Seasonal peaks of JE cases have occurred during the months of August to October in the State; data also indicate that maximum cases were concentrated in the period from July to October, coinciding with rainy and post-rainy seasons. With the onset of winter, JE incidence declined substantially.

Average AES/JE cases in recent years compared with data of 1988 (Figure 3) show some variation in seasonal trends and cyclic patterns of the disease. For example, cases have started to increase from early July, peaking in October as opposed to September (cases also peaked in October in the 1970s and 1980s). During the outbreak in UP in 2005, weekly data indicated that cases started occurring in July with a sharp peak in end August/early September. In contrast, the 1988 outbreak in Gorakhpur and Deoria districts witnessed JE cases starting in September and reaching a peak in the second week of October, before subsiding in November. The entire course of the disease during the 1985 outbreak was of 8 to 9 weeks’ duration from mid September to mid November. However, the 1978 outbreak reported cases reported from mid October until November. Thus, over three decades, the peak of the epidemic has advanced by one month approximately.

**Districts with repeated occurrence of JE cases**

Figure 4 shows the districts where JE cases occurred repeatedly from 1978 to 2007. Of the total 72 districts in the State, 17 districts have reported only sporadic cases of suspected JE (not laboratory confirmed) at one time in 30 years. Of these districts, 7 (Bijnor, Bulandshahr, Etah, Kaushambi, Deharadun, Pauri and Mainpuri) reported only 1 or 2 cases of suspected JE, 6 districts (Agra, Etawah, Hamirpur, Badaun, Ormoi
and Lalitpur) reported 3–10 cases and the remaining 4 districts (Farrukhabad, Mirzapur, Rampur and Varanasi) reported 11–26 cases. However, 15 districts were reported once only in 1978 and JEV infection in these districts was not confirmed serologically.

Among the remaining affected districts, nine reported suspected JE cases for only 2–4 years since 1978, the number of cases ranging from 4–51. Three districts reported suspected JE cases only twice in a period of 30 years. Figure 4 also reveals that 15 districts reported JE 5–9 times during last three decades. JE occurred almost every year in four districts (Azamgarh, Basti, Deoria and Gorakhpur). Since 1978, repeated occurrence of JE cases in each year was recorded in Deoria and Gorakhpur districts in eastern UP, while Basti district JE was reported 26 times during the 30-year period in question.

During the second decade under review (1987–1997), JE emerged for the first time as a problem in Siddharth Nagar district in 1989, in Maharajganj in 1990 and in Kushinagar in 1997. Since then, these districts have regularly reported JE cases every year. An in-depth review of the origins of these districts indicates that Siddharth Nagar was created in 1988 out of Basti district; Maharajganj was carved out from Gorakhpur district in 1989, and Kushinagar emerged in 1994 from Deoria district. Thus, the high incidence of JE reported in the newly created districts was due to their geographic affinity with their highly JE endemic parent districts since 1978. However, in 1995 and 1996, no case was reported by the state, therefore, there was less number of districts affected.

The three new districts that emerged in the decade 1998–2007 – Balrampur, Sant Kabir Nagar and Shravasti – have also reported JE
cases since their creation. Sant Kabir Nagar emerged in September 1997 from Basti district, while Balrampur was created from Gonda district in 1997. Shravasti became a new district in 2000 carved out from the districts of Bahraich and Gonda. All these parent districts were highly endemic for JE. Figure 5 shows the increasing number of districts affected by JE in Uttar Pradesh.

Disease burden by district

Figures 6A–C indicate the distribution of cases in different districts from 1978 to 2007. The incidence rates appear to be higher in eastern districts of UP. The district-wise estimation of JE cases per 100 000 population (annual incidence rate) from 1978 to 1987 ranged from 0.01 to 9.87. Deoria district had the maximum average annual incidence rate (9.87) followed by Gorakhpur (9.40), Pilibhit (3.14), Azamgarh (2.01), Ballia (1.66) and Kheri (1.19). The remaining districts (Lakhimpur, Bahraich, Gonda, Gazipur, Lucknow, Bareilly and Sultanpur) showed a sporadic distribution of cases from 0.5 to 1.0 per 100 000 population.

From 1988 to 1997, like the earlier decade, the highest incidence rate was reported from Deoria (11.90 cases per 100 000 population) followed by Gorakhpur (11.59). It is important to highlight that during this decade, a serious JE problem emerged for the first time in the two newly created districts of Maharajganj (847 cases and an attack rate of 3.84 per 100 000 population) and Siddartha Nagar (274 cases with an attack rate of 1.38 per 100 000). Since then, these districts have reported JE cases every year.

First time JE incidence was reported from Kushinagar district immediately after its creation, which has since emerged as the most problematic district in the State with the highest average annual incidence rate (29.90 per 100 000 population), followed by
Figure 6: Distribution of reported Japanese encephalitis cases in Uttar Pradesh


Maharajganj (21.80), Gorakhpur (10.01), Siddharth Nagar (7.60), Deoria (6.59) and Bahraich (3.62).

During the period from 1998 to 2007, Kushinagar, Maharajganj, Gorakhpur, Siddharth Nagar, Deoria and Bahraich were the most JE problematic districts in the State. Data indicate that Azamgarh, Ballia, Kheri and Pilibhit districts had been highly endemic from 1978 to 1988, after which time the disease burden declined.

Besides increased disease burdens in some districts, new epidemic foci ofJE have also been emerging in Uttar Pradesh. During the second decade of study from 1988 to 1997 (Figure 6B) first-time JE problems emerged in the new districts of Maharajganj (1990), Siddharth Nagar (1989), and Kushinagar (1997). Since these districts were part of the old endemic districts, they also reported JE cases every year since their creation.

Kushinagar district has become the most high-risk district in the State with an average annual incidence rate over 10 years of 29.90 per 100 000 population, followed by Maharajganj (21.80). The incidence rate was comparatively less in Gorakhpur (10.01) and Deoria (6.59) districts, where a high proportion of JE had been reported repeatedly since 1978.

**Age distribution of JE cases**

Analysis of age distribution of JE cases from Gorakhpur division in outbreaks in 1985, 1988, 2005 and 2009 (Figure 7) show that children were more susceptible than adults. The average age of affected children in eastern UP was 6.8 years between 2004 and 2006. The highest number of cases occurred in children aged between 0 and 10 years: 47% in 1985, 60% in 1988, 88% in 2004, and 94% in 2006 outbreaks, respectively.
**Figure 7**: Distribution of Japanese encephalitis cases by age and sex, Gorakhpur division, Uttar Pradesh

*7A: Distribution of JE cases by age/sex, Gorakhpur, 2009*

- **7B: Distribution of JE cases by age/sex, Gorakhpur, 2005**
**7C: Distribution of JE cases by age/sex, Gorakhpur, 1988**

![Bar chart showing distribution of Japanese encephalitis cases by age/sex in Gorakhpur, 1988.](chart1)

**7D: Distribution of JE cases by age/sex, Gorakhpur, 1985**

![Bar chart showing distribution of Japanese encephalitis cases by age/sex in Gorakhpur, 1985.](chart2)
Analysis of 3887 JE cases reported in 2005 from Gorakhpur and Basti divisions indicated that the maximum cases (58%) were reported in the age group of 4 to 6 years, while 18% of cases were reported in the age group 15 years and above. Age distribution of JE seropositive cases reported by BRD Medical College during 2009 shows that 75.1% of confirmed JE cases were reported in the age group below 15 years. In earlier outbreaks in 1985 and 1988, the proportion of adults was higher – 25% and 22%, respectively – which then declined by 3% in 2004. After JE vaccination in children up to 15 years, the proportion of cases in adults slightly increased in 2009 (24.87%) in 2006.

**Sex distribution of JE cases**

The 2005 JE outbreak in UP reported a case breakdown of 61% males and 39% females (deaths attributed to disease were 59% in males and 41% in females). However, in Gorakhpur division, a line listing of 1087 cases showed a ratio of 56.0% males to 43.8% females. A year later in 2006, a line listing of 249 cases revealed 155 (62.3%) males against 94 (37.7%) females. From 2007 to 2009, line listings showed steady average of male to female cases of JE (68 (57.1%) males and 51 (42.9%) females, and 122 (59.5%) males and 83 (40.5% females, respectively).

**JE vaccination**

In 2006, the Government of India launched a JE vaccination campaign for children from 1 to 15 years of age. This was followed by immunization of new cohorts as an integral component of the Universal Immunization Programme with single dose of live attenuated JE vaccine (SA–14-14-2) in 11 highly endemic districts of four states (Assam, Karnataka, Uttar Pradesh and West Bengal). Of the 11 districts, 7 (Deoria, Gorakhpur, Kheri, Kushinagar, Maharajganj, Sant Kabir Nagar and Siddharth Nagar) reported coverage of above 95% of the estimated target. This success led to the JE vaccination programme being extended in a phased manner to the other endemic districts. During 2007, an additional seven endemic districts (Bahraich, Balrampur, Basti, Gonda, Rae bareli, Saharanpur and Shravasti) were covered. A further 16 districts were included in 2008 and 2009. Sustained high coverage of JE vaccination is clearly required to bring down the disease burden. The percentage coverage of JE vaccination in Uttar Pradesh from 2006 to 2009 is given in Table 1.

Although the reported coverage was very high, an independent evaluation by UNICEF in 2008 showed that only 51% of eligible children received JE vaccination during the campaign. However, it may be said that the proportion of JE sero positive cases in Gorakhpur did not cease to occur but there was decline, from 38.8% in 2005 to 14.2% in 2006, 12% in 2007, 8% in 2008 and 10.8% in 2009 after introduction of JE vaccination in 2006 in high endemic districts (Report of the National Institute of Virology Field Unit, Gorakhpur).

Figure 8 shows that JE cases usually appear in the third month after onset of the monsoon. For example, in 2005 JE cases were reported from August following the monsoon in May, while in 2006 and 2007, the monsoon started in April and cases started being reported in July. Vector mosquitoes proliferate profusely subsequent to a monsoon, stimulating an increase of virus activity in mosquitoes and human–mosquito contacts and thus transmission, followed by JE cases. This preparatory phase of 2–3 months should be used to prepare for the prevention of an outbreak. The reason for the 2005 outbreak may have been caused by prolonged rainfall: as seen in Figure 8, the pattern of rainfall was different in that year, which had two peaks of rainfall – one in July and another in October – with a prolonged rainy season from May to
Table 1: Coverage of Japanese encephalitis vaccine (SA 14-14-A) in Uttar Pradesh

<table>
<thead>
<tr>
<th>Sl No.</th>
<th>Year</th>
<th>District</th>
<th>Target (1–15 year olds)</th>
<th>Total vaccinated children</th>
<th>Total coverage (%)</th>
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<td>1</td>
<td>2006</td>
<td>Gorakhpur</td>
<td>1 390 307</td>
<td>1 349 047</td>
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<tr>
<td>2</td>
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<td>Deoria</td>
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<td>1 085 055</td>
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<td>806 996</td>
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<td>1 183 481</td>
<td>1 218 364</td>
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<tr>
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<td>792 944</td>
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<td></td>
<td></td>
<td><strong>Total</strong></td>
<td><strong>6 838 380</strong></td>
<td><strong>6 836 506</strong></td>
<td><strong>99.97</strong></td>
</tr>
<tr>
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<td>2007</td>
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<td>741 354</td>
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<td>1 063 815</td>
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<td>1 049 252</td>
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<td><strong>10 708 393</strong></td>
<td><strong>98.82</strong></td>
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<td>1 673 687</td>
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<td><strong>Total</strong></td>
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<td><strong>84.58</strong></td>
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Source: NVBDCP
November. Other years had only one peak of rainfall.

**Discussion**

In India, 24 States/UTs were affected with JE but the State of UP contributed more than 75 per cent of JE cases to the country (Figure 1). In Uttar Pradesh, out of total of 71 districts, 7 eastern districts were highly affected due to JE and contributed about 78.27% of the total cases of the State during the recent decade. Gorakhpur, Deoria and Basti have been found to be high risk districts for JE since 1978, and other four districts which were carved out from these three districts namely Maharajganj, Kushinagar, Siddhath Nagar and Sant Kabir Nagar also remained high JE endemic since their inception. The eastern districts are the most prone to JE than western districts. Eastern district’s proneness to floods is attributed, among other things, to heavy rainfall, low and flat topography and the silting of river beds which make river levels rise and have impact on temperature and humidity. Flood problems of eastern UP were due to reduction in the absorptive capacity of the soil. This ‘reduction’ has been magnified with the development of intensive canal irrigation during the past five decades. Due to construction of unlined canal networks and embankment; ground water table increased in this area resulting more flood and more water stagnations after the monsoon rains. As in Eastern UP, Bihar’s flood-prone area too tripled from 2.5 m ha in 1954 to 6.8 m ha in 1994. Flood proneness and water logging hit the lives and livelihoods of people in several ways including the growth of the vector mosquito population. Between 1951 and 1981, the area cultivated in kharif which fell from 214 000 ha to 68 000 ha due to annual flooding and
surface water logging; as a result, in these areas, farmers clung to traditional mixed-crop farming technologies. The tradition of animal husbandry too has been undergoing change due to waterlogging; as grazing lands remain submerged in water for long periods, large bovines have declined in population. Marginal farmers and landless have increasingly taken to pigtery. All these factors contributes to increase of JE incidence in the eastern districts during the past decades.

Studies from peninsular and eastern parts of India indicate that pigs are the main vertebrate host of JEV and the major reservoir of the infection. Because infected pigs act as amplifying hosts, domestic pig rearing is an important risk factor in the transmission of JE to humans. In different parts of the country, 12–44% of the pig population have been found to be positive for JE antibodies, particularly in endemic areas. Pigs play an important role in the natural cycle and serve as an amplifier host since they allow manifold virus multiplication without suffering from disease and maintain prolonged viraemia. Thus, mosquitoes biting pigs can be dangerous for humans. In India, the population of pigs is reported to be more than 135 million, 31.7% (42.84 million) of which are in Uttar Pradesh. As per the last 17th livestock census, UP has the largest pig population in the country. Unorganized piggeries are plenty: the rural population who rear pigs virtually co-exist with these animals. Hence, the chance of human infection is high. The probability of vector mosquito species getting infected with JEV is higher when infected mosquito populations dramatically increase and the human biting rate increases. During the transmission season, when vector density is abundant, infected mosquitoes transmit infection to human beings as incidental, dead-end hosts in the transmission cycle due to low and short-lived viraemia.

Although the burden of disease in Uttar Pradesh has increased, CFRs of JE cases have declined over the years from 31.5% in 1978 to 18.0% in 2009. This is as a result of early detection, better case management and early referral of patients to treatment centres. In contrast in Nepal, overall mortality from JE was 9.8% in the year 2000 and 20.9% in 2003. A similar trend in CFR (7–30%) was reported in Philippines from 1972 to 1985.

An in-depth review of various outbreaks reported from Uttar Pradesh shows that in the 1985 outbreak of JE, the attack rate was 0.08 and 0.16 per thousand population in Gorakhpur and Deoria districts, respectively. The average number of cases per village was 1.1 in Gorakhpur and 1.2 in Deoria. Three years later in the 1988 outbreak, these averages rose to 1.6 cases per affected village in Deoria, and 2.4 in Gorakhpur. This difference may be attributed to variance in the population size and demographic profile of the villages.

Eight UP districts were affected by the 1988 outbreak: Gorakhpur, Deoria, Azamgarh, Basti, Gonda, Bahraich, Ballia and Faizabad. Nearly half of the cases and deaths were recorded from Gorakhpur alone, which was the worst affected district in the entire country. This outbreak became the largest epidemic recorded in any state in India to date, with 4544 cases and 1413 deaths. The next major JE outbreak to affect eastern was in 2005 and was the longest and most severe epidemic in three decades: 6061 persons were affected, 1501 of whom died. The etiologic agent was confirmed to be Japanese Encephalitis virus in 2005 outbreak of viral encephalitis in UP. Analysis of epidemic peaks of JE outbreaks shows that the duration of outbreaks is getting longer. Uttar Pradesh experienced its first outbreak in 1978 from mid October to November, i.e. a duration of 6–7 weeks.
In 1985, an outbreak\textsuperscript{16} started in the second and third week of September with an explosive rise in incidence in the subsequent 4 weeks followed by a decline over the next 2–3 weeks. The entire course of the epidemic was of 8 to 9 weeks duration. Thus, while the duration of epidemics in the 1970s and 1980s was 6–9 weeks,\textsuperscript{16} the 2005 JE epidemic lasted for about 17 weeks. Note that the first JE outbreak in Karnal, Haryana in 1990 continued for about 10 weeks.\textsuperscript{20}

In all outbreaks until 1988, seasonality of the disease was recorded from September to November, the post-monsoon season, which coincides with paddy cultivation and the period of peak mosquito density.\textsuperscript{11,23} The maximum number of cases was generally reported in October.\textsuperscript{22} However, monthly JE cases for the decade 1997 to 2007 indicate that sporadic JE incidence was reported in the month of June, gradually increasing from July and peaking in September before declining (Figure 3). Maximum cases were concentrated in the period August to October, coinciding with the rainy and post-rainy season. With onset of winter, JE incidence subsided. It was also reported that JE cases reached a peak during August/September in the Nepalese districts bordering UP in 2004.\textsuperscript{14} The results reveal that between 1978 and 2009 in UP, the peak of the epidemic season moved forward by approximately one month from October to September, and since 1997, seasonality of the disease has started in July instead of September.

About 90% of the rainfall occurs during the south-west monsoon, lasting from about June to September. Flooding usually occurs from July to August during the rainy season and is a recurrent problem that creates an excellent breeding ground for JE vectors. Comparison of rainfall data with JE incidence indicates vector density, and subsequently JE cases increase one month after the peak rainy months. Relative to the 2005 outbreak, the duration of rainfall was longer compared with other years, starting in May, then peaking in July and August before its decline (Figure 8). However, a second peak of rain occurred in October, which explains the longest duration of JE outbreak (August to November) in that year: incidence increased rapidly in August and reached a peak in the first week of September, but the epidemic peak was not until November due to the prolonged rainy season.

Thus, seasonality of the disease and a shift in epidemic peak may be attributed to the pattern of monsoons, floods and change of weather in the State.\textsuperscript{24} It is also observed that JE cases usually appear in the third month after onset of the monsoon; thus the pattern of rainfall influences vector breeding and occurrence of JE cases. As per studies carried out from 1990 to 1996 in Gorakhpur, vector density increased after onset of the monsoon and reached its peak in September.\textsuperscript{25} However, the peak of JE cases was reported in October when the vector population, particularly \textit{Culex tritaeniorhynchus}, was on the decline.\textsuperscript{25} Such a relationship between the epidemic and declining vector population has also been observed in Japan, where this type of pattern was attributed to the differences in total and infected populations of vector species.\textsuperscript{26}

The present analysis shows that, though both sexes were affected, males usually outnumbered females. The female to male ratio in 2007 was 1:1.3. The 2005 outbreak showed female to male ratios of 1:1.28 and 1:1.58 while it was 1:1.7 in 1988\textsuperscript{27} and 1:1.5 in 1985.\textsuperscript{16} Male predominance was also seen in the first JE outbreak in 1978. Previous reports and recent analyses clearly indicate that in general men are more prone to JE infection than women, which could be attributed to more outdoor activity by the male population during the peak biting time of exophilic vectors and more exposed body parts, especially the
lower extremities, to mosquito bites, while women tend to be fully covered by dresses.

Data also reveal that, in the first JE epidemic in 1978 in UP, while no age group was spared more cases (42.5%) occurred in children below 10 years of age. A high number of cases in children was also reported in the 1988 outbreak (adults 22%, children >10 years, 60% of total cases). In contrast, the number of adult cases was higher in the 1985 and 1987 outbreaks. Similar observations were made in the Indian states of Assam, Bihar and West Bengal. An analysis of age distribution from 1990–1996 revealed that the maximum number of cases occurred in children aged between 1 and 15 years, with the highest occurrence in the age group 6–10 years in Gorakhpur region. In 2004, of the total 115 cases analysed from Gorakhpur, 105 (91.3%) were among children below 15 years of age. In 1988, 22% cases occurred in adult age groups: This figure declined to 16% in 2005, largely because most adults in the area were immune to JEV, and the majority of cases were seen in children below 15 years of age. Since introduction of JE SA14-14-2 vaccine in 2006, JE cases reported in upper age groups, including from Uttar Pradesh, have increased from 3% in 2006 to 25% in 2009. Similarly in Japan, JE has become a disease of older age groups since 1967, the CFR being higher in the elderly. A gradual decrease of herd immunity in older persons has been taking place, creating a potential for future disease outbreaks.

Over the years, children in UP have become a more susceptible group to JE. However, those with debilitating chronic illness or immunosuppression are at greater risk of disease, with symptoms ranging from malaise to meningoencephalitis with seizures and death. The attack rate decreases with age in endemic populations due to the presence of neutralizing antibodies as a result of natural exposure and subclinical infections in such individuals. The estimated population at risk in endemic areas is 45.1%. However; in relatively non-endemic areas where the virus is introduced for the first time, individuals of all age groups are susceptible.

After vaccination in 2006, the proportion of JE laboratory-confirmed positive cases declined in the Uttar Pradesh (NVBDCP Report). However, the virus remains a major and consistent cause of outbreaks in the eastern region of the State, accounting for approximately 10%–15% of total AES cases annually.

Culexvishnui subgroup mosquitoes, comprising Cx. tritaeniorhynchus, Cx. vishnui and Cx. pseudovishnui, have been implicated as major vectors of JE in India as well as in many countries of south-east Asia. These mosquitoes are usually found in rural rice-growing and pig-farming regions of Asia, but can also be found at the outskirts of cities in close proximity to human populations. They prefer to breed in rice fields, and outbreaks of JE are commonly associated with intensive rice cultivation. In Uttar Pradesh, based on the elevated density and infection with JEV, Cx. tritaeniorhynchus is considered responsible for causing epidemics in the area. Cx. pseudovishnui, Cx. whitmorei, Cx. gelidus, Cx. epidesmus, Anopheles subpictus, An. Peditaeniatus and Mansonia uniformis are suspected to play some role in the epidemiology of JE in the region.

In Gorakhpur area, JEV infection was detected in female Cx. tritaeniorhynchus and Cx. epidesmus tested by ELISA. But JEV could be isolated only from Cx. tritaeniorhynchus by the Toxorhynchites splendens inoculation-indirect immunofluorescence (Toxo-IFA) insect bioassay. Isolation of JEV from Cx. epidesmus has been reported in Bankura, West Bengal. During the 1991 outbreak in...
Gorakhpur, JEV was isolated from wild caught *Cx. tritaeniorhynchus*. However, JEV has since been detected by ELISA at the National Centre for Disease Control from adult *Cx. gelidus, Cx. pseudovishnui, Cx. bitaeniorhynchus*, in addition to *Cx. tritaeniorhynchus* reared from wild caught immature mosquitoes from Gorakhpur region (2009). JEV was detected in adult mosquitoes raised from wild caught immatures and males of the following vector species: *Cx. tritaeniorhynchus, Cx. vishnui, Cx. infula, Cx. gelidus, Cx. fuscocephala* and *Ma. indiana*. Vertical transmission of JEV occurred in both hot and cool seasons, and is thus regularly maintained in nature during the non-transmission season as well. The presence of a wide variety of vector species, their different bionomics and vectorial capacity, therefore needs to be studied. The monitoring of virus infection in vector mosquitoes should form an essential component of a surveillance system to assess monthly infection rates of vectors to predict disease outbreaks and to develop an early warning system in order to take remedial measures in the State of Uttar Pradesh.

The larval habitat of *Cx. tritaeniorhynchus* is primarily low lying flooded areas containing grasses and rice paddies. Eastern Uttar Pradesh is mainly a paddy growing area, with clay soil and a very high water table. The ecosystem comprising rivers, lakes, irrigation canals, ponds, reservoirs and rice fields favour vector breeding. Surface water bodies are perennial breeding sources in UP and provide a wintering and staging ground for a number of migratory waterfowls and a breeding ground for resident birds. They also act as mother foci for vector mosquitoes. After the monsoon, vectors spread to other water stagnation areas and rice fields. Thus breeding control with appropriate larvicides or using larvivorous fish in all permanent water bodies, before the start of monsoon and paddy irrigation, may check proliferation of breeding of *Cx. tritaeniorhynchus* and other JE vectors and even contain the vector population during JE transmission season. In addition, rice fields support waterfowl, especially egrets and herons, which are the reservoirs of JEV. Surveillance should be strengthened during the lean season to map breeding sites of vector mosquitoes in order to plan appropriate control measures.

Rice fields being the most productive breeding sites of *Cx. tritaeniorhynchus*, its population dynamics is closely associated with paddy cultivation. In Gorakhpur, a single paddy crop is grown per year and the majority of JE vectors show one peak a year, i.e. in September. The occurrence of JE in the region has therefore been closely associated with this peak. Interestingly, two peaks of JE vectors were recorded when double paddy crops were cultivated in Tamil Nadu.

The steady spread of JE confirmed cases to new areas in India is a serious public health concern. Eastern districts of Uttar Pradesh have been highly endemic since 1978; in 1990, the disease spread to the west, affecting neighbouring state Haryana for the first time, followed by Saharanpur and Muzaffarpur in western Uttar Pradesh in 2003 and 2005, respectively. Climate change may also influence the migration patterns of birds, which may result in the introduction of JEV to new areas. Since little is known about reservoir bird migration patterns, this is an important issue to investigate. Climate change is also affecting agricultural patterns, and the development of agriculture in the region has resulted in the vast expansion of water bodies and irrigation systems which support mosquito breeding, and in turn JEV.

Most of the JEV strains isolated in India belong to genotype III. However, JEV
genotype I has recently been reported in human patients from Gorakhpur. Due to the evolution of new viral strains and/or re-emergence of older strains, children lack protective immunity. Although health management facilities have improved in UP (CFR reduced), concrete steps should be taken to combat JE, including the development of more efficient surveillance in human, vector and vertebrate hosts and strengthening of JE vaccination programme. In addition, first and secondary referral health facilities need to be reinforced for better management of JE cases.

**Conclusion**

Japanese encephalitis is still a major health problem in eastern Uttar Pradesh, north India. No antiviral drug against JEV is available. Chemical control of vector populations with insecticides plays a marginal role in control of the disease due to their exophilic behaviour. The use of larvicides is limited as vector mosquitoes prefer to breed in large water bodies. In some situations, e.g. during outbreaks of JE, space-spraying may interrupt the transmission cycle for a short time. Wider issues, including current agricultural practices, water management systems, and human behaviour patterns, need to be investigated. The most important long term strategy to fight flood-proneness is of rapid increase in groundwater irrigation which will not only lower water tables but also help reduce the intensity of floods which will further impact on public health and to improve the socioeconomic status of people in JE-affected areas. Awareness needs to be developed on personal protection against mosquito bites and the importance of early referral of cases.

In summary, JE could be controlled with effective surveillance systems, segregation of pigs, an integrated vector control approach, early detection of JE outbreaks, and high coverage of eligible children with JE vaccine. Continuous monitoring of vector populations and virus infection rates in vector mosquitoes would help to predict outbreaks more in advance and to implement proper control measures. To this end, a combination of strategies involving other sectors and the community would be required to instil the sense of urgency needed to accelerate effective control of JE in the country.

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