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## Original Article

# Japanese encephalitis in Uttar Pradesh, India: A situational analysis

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### ABSTRACT

**Introduction:** Japanese encephalitis (JE) is a vector-borne, viral illness caused by the Japanese Encephalitis Virus. Permanent neurologic or psychiatric sequelae can occur in 30%–50% of those with encephalitis; hence, JE is a cause of major public health concern. For the ease of diagnosis and facilitation of surveillance, National Vector Borne Disease Control Programme uses the term Acute Encephalitis Syndrome (AES). In this study, an attempt has been made to ascertain the status and trends of AES and JE in Uttar Pradesh, India. **Methodology:** This is a record-based retrospective study. The data were obtained from the Directorate of Medical and Health Services of Uttar Pradesh and analyzed using software SPSS version 24.0. **Results:** In Uttar Pradesh, there were 47,509 reported cases of AES from 2005 to 2018. With yearly fluctuations, the average Case Fatality Rate of AES was 17.49% with highest in 2005 (24.76%) and lowest in 2018 (8%). Among the patients with AES, 9.98% were found positive for JE. The most commonly affected age group is 1-5 years for both AES and JE, closely followed by the age group of 5-10 years. Peak occurrence of both AES and JE was recorded in month of September. Among the AES-affected patients 53.8% were males and 46.2% were females. **Conclusion:** The most commonly affected age group was 1-5 years with peak occurrence in the month of September. Though there was a downward trend in CFR, awareness activities like “Dastak” campaign and intersectoral preventive activities, needs to be strengthened.

**Keywords:** Acute Encephalitis Syndrome, case fatality rate, Japanese encephalitis

### Introduction

Japanese encephalitis (JE) is a vector-borne, viral illness. It is caused by the Japanese Encephalitis Virus (JEV) of Group B Arbovirus (flavivirus) related to Dengue, Yellow fever and West Nile virus and is transmitted to humans by the culicine (*Culex* species) mosquito.<sup>[1]</sup> JE presents clinically with the onset of acute

febrile illness and alteration in mental status (e.g., confusion, disorientation, inability to talk, and coma) with or without new onset of seizures.<sup>[2]</sup> There is increased muscle tone, neck rigidity and superficial abdominal reflexes. Permanent neurologic or psychiatric sequelae can occur in 30%–50% of those with encephalitis; hence, JE is a cause of major public health concern.<sup>[1]</sup>

Since the clinical presentation of JE comprises a very nonspecific prodrome and in children, frequent seizures in many cases, which might as well be the symptom of some other disease entities which may be viral, bacterial, protozoal, fungal or even non-infectious in etiology; therefore, for the ease of diagnosis and facilitation of surveillance, National Vector Borne

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Disease Control Programme (NVBDPC) uses the term Acute Encephalitis Syndrome (AES). AES is a multifactorial clinical condition which is defined as the acute onset of fever and alteration in mental status (which includes signs and symptoms of confusion, disorientation, delirium or coma) and/or new onset of seizures (excluding simple febrile seizures) in a person of any age at any time of the year.<sup>[3]</sup> Although the definition of AES is broad and includes illnesses caused by many infectious and non-infectious causes, viral encephalitis remains a major contributor to the disease burden. JE has been considered to be the leading cause of AES in Asia.<sup>[1]</sup>

## Aim and objective

To ascertain the status and trends of AES and JE cases in Uttar Pradesh through the data obtained from health authorities and draw out seasonal variations in the occurrence of cases, regional variations, age predilection, mortality and case fatality rate associated with the disease condition. Knowledge of epidemiological trends is of vital importance for clinicians as an aid to early diagnosis and treatment, which in turn affects the mortality and morbidity associated with the disease.

## Methodology

This is a record-based retrospective study conducted in the state of Uttar Pradesh, which is the most populous state of the country with a population of more than **199 million**.<sup>[4]</sup> It consists of 75 districts that have been clustered into 18 administrative divisions.<sup>[4]</sup>

The health facilities in the high JE-AES caseload districts of the state admit all paediatric age group patients (up to 15 years) presenting with high-grade fever out of which patients suspected of progressing to AES are subsequently confirmed for five conditions: JE, Malaria, Dengue, Chikungunya and Scrub Typhus. IgM ELISA test is used for JE. Each case admitted with AES is reported to district health authorities by the concerned health facility authority. Thereafter, district health authorities report cases to the Integrated Disease Surveillance Project (IDSP) unit of Directorate of Medical and Health Services of the state.

For the study, the data were obtained from the IDSP division of the Directorate of Medical and Health Services of Uttar Pradesh. After taking prior permission for the same, the data thus obtained was entered into MS Office Excel Spreadsheet.

At first, the data were arranged year wise to reflect the yearly incidence of AES and JE cases and the number of deaths among the affected patients in the state from 2005 to 2018. These data were analyzed to draw out trends of disease occurrence as compared with the number of deaths and case fatality rates (proportion of deaths against the total number of cases reported per year) of both AES and JE. The data were further segregated into the number of cases reported from each division through various months of the year; therefore, harnessing a regional and seasonal variation in the occurrence of the disease.

Information on the number of cases of both AES and JE was analyzed to surface out the peak seasons of occurrence and whether both conditions have similar trends round the year. The first major outbreak of the disease in Uttar Pradesh was reported in 2005. Hence, it was taken as the starting point for observing trends in incidence, the number of deaths and CFR of the disease.

To study other epidemiological determinants of disease, line list of patients comprising information about age, sex, religion, date of onset of symptoms, date of admission, date of sample collection and date of outcome was used for the past 6 years as from 2013 to 2018. The data set was analyzed for completeness and patients with incomplete entry in any of the above-mentioned variables were excluded from the study. Analysis of the data was done to figure out age predilection of the infection as well as gender predilection, if any. Symptoms were categorized into three types: fever, alteration in mental status and seizures. The date on which any one of the three symptoms first appeared was considered as the date of onset of symptoms. Days lapsed between the date of onset of symptoms and dates of admission to hospital are of critical importance and were analyzed for effects on outcome of disease. The outcome was divided into two types: death and other outcomes that include discharged without disability or discharged with disability. The number of days of hospital stay, calculated from the date of admission to the date of outcome, was also analyzed for effects on disease outcome. Association of time interval between admission and sample collection, for confirmation of JE or any other specific aetiology, also holds the key to prompt and accurate treatment, and thus disease outcome was also analysed. Ethical clearance for this study was obtained from Ethical Clearance Committee of Uttar Pradesh University of Medical Sciences.

## Results

Analysis of data revealed that, from 2005 to 2018, there were 47,509 AES cases reported in Uttar Pradesh among which 8373 patients died. During this period, the average CFR was 17.49%. There was year to year fluctuation in the number of cases; with a maximum of 6061 cases reported in 2005 followed with a sharp decline in 2006 with a total number of cases being 2075. This decline in 2006 was followed by a gradual increase in reported cases with maximum of 4041 cases in 2017. In 2005, there were 1501 deaths followed by a sharp fall in 2006 with 476 deaths among the patients with AES. With small annual differences, the number of deaths remained on an average between 476 and 647 during 2006-2017 with minimum in 2006 (476 deaths) and maximum in 2014 (647 deaths). There was a steep fall in the number of patients dying due to AES in 2018 with 252 mortalities. The CFR decreased continuously between 2005 and 2010 followed by two spikes in 2011 and 2013 after which a continuous downward trend was observed, CFR in 2018 being lowest at 8.1% [Figure 1].

For JE, total 4677 cases with 881 deaths were reported during 2005-2018 in Uttar Pradesh with an average CFR of 18.6%. In

2005, there were 1042 cases with 304 deaths of JE cases. There was a sharp fall in number of cases (170) and deaths (49) in 2006. During 2006-2018, the number of cases and deaths among the patients with JE showed significant annual fluctuations with the lowest number of cases and death in 2012 and the highest number of cases and deaths in 2017. Since year 2014, there was an overall downward trend of CFR among the patients with JE, with an exception of year 2016, minimum in 2018 (9.12%) [Figure 2].

During 2011-2018, four districts of Gorakhpur division (Gorakhpur, Maharajganj, Deoria and Kushinagar) and three districts of Basti division (Basti, Sant Kabir Nagar and Sidharth Nagar) contributed to 86% of total AES cases of Uttar Pradesh. This is followed by Lucknow division (Hardoi, Lakhimpur Kheri, Lucknow, Raebareli, Sitapur and Unnao) which contributed to 6% of AES burden of the state. Devipatan division (Baharaich, Balrampur, Sharawasti and Gonda) accounts for 4% of cases, while Faizabad division and Azamgarh division having 2% and 1% of AES cases, respectively. Small number of cases (<1%) were reported from division of Varanasi, Moradabad, Bareilly and Jhansi. Disease was mainly confined to eastern districts of the state with around 93% of disease burden followed by central region with 6% of disease burden. Bundelkhand and western region of state are reporting sporadic cases and contributes to less than 1% of total disease burden of the state [Figure 3].

Sporadic cases of AES were being reported throughout the year starting from January (1.3% cases) with gradual increase up to late June (June: 2.9% cases) and early July. Then there was a sharp rise in the number of cases starting from early July, which peaks in September (24.70% cases) in which maximum number of cases has been reported. This peak is followed by gradual decrease that continues till December (4.1% cases). Like AES, there is a sharp rise in number of cases of JE in July, which peaks in September (35% cases), followed by a gradual decrease up to December (4.5% cases) [Figure 4].

Both AES and JE were more common in children than adults with an average age of the patients with AES and JE being 10.29 and 13.26 years, respectively; the most commonly affected age group was 1-5 years with 39.6% cases of AES and 31.3% cases of JE, closely followed by the age group of 5-10 years with 27.9% cases of AES and 30.2% cases of JE. The least affected age group in both the patients with AES and JE was 0-1 year, in which 4.7% and 4% cases of AES and JE have been reported, respectively [Figure 5].

From 2013 to 2018, total 20,385 cases of AES have been reported in the state. Out of this data, 6926 were found to be incomplete in one or the other variable, during screening, and were therefore excluded from the statistical analysis. Among the AES-affected patients, 88.2% were Hindu and 11.2% were Muslim, 53.8% were males and 46.2% were females. Out of total AES cases, 9.98% were found to be JE positive. Hindu constituted 84.8%, while Muslim constituted 15.2% of JE-affected cases, of which 52.9% were males and 47.1% were females. There was no statistically

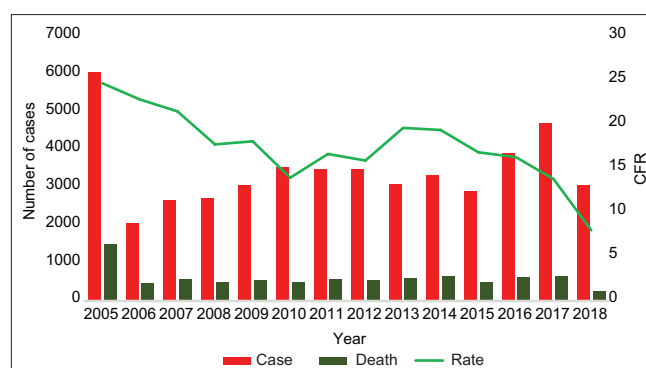


Figure 1: Trend of AES in Uttar Pradesh

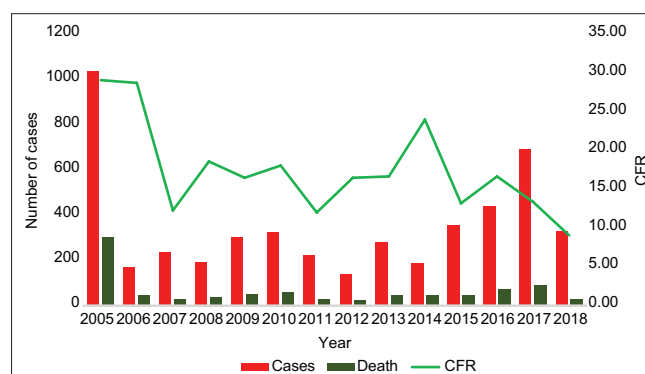


Figure 2: Trend of JE in Uttar Pradesh

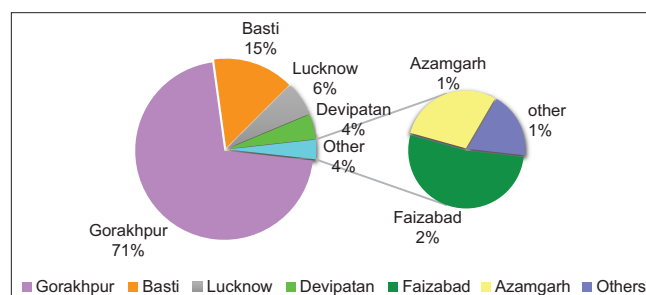


Figure 3: Division-wise distribution of AES cases in Uttar Pradesh (Years 2011-2018)

significant relationship between gender and JE positivity. CSF for anti JEV IgM in males and females were found positive in 2.15% and 2.41%, respectively, while serum anti-JE IgM was positive in 4.07% in males and 4.28% in females [Table 1].

Mortality observed in female patients were higher than male patients, which was reported to be 21.82% and 20.32%, respectively ( $P = 0.03$ ). In the number of cases, the highest mortality was found in the age group of 1-5 years, which was 23.17% followed by 21.14% in the age group of 0-1 year. The association of different age groups with treatment outcome was statistically significant ( $P < 0.001$ ) [Table 2].

Mean duration  $\pm$  SD between the onset of symptoms and admission was  $2.88 \pm 3.34$  days, between admission and sample collection being  $1.95 \pm 1.6$  days. The mean duration of hospital

Table 1: Relationship of JE IgM ELISA results with JE positivity (n=13459)

Variables		JE IgM results						JE positivity**	
		CSF	P*	Serum	P*	CSF + Serum	P*		
Religion	Hindu (n=11,877)	256 (2.16%)		478 (4.02%)		405 (3.41%)		1139 (9.59%)	
	Muslim (n=1582)	49 (3.1%)	<b>0.001</b>	83 (5.25%)	<b>0.001</b>	72 (4.55%)	<b>0.029</b>	204 (12.90%)	<b>&lt;0.001</b>
Sex	Male (n=7245)	156 (2.15%)		295 (4.07%)		259 (3.57%)		710 (9.80%)	
	Female (n=6214)	150 (2.41%)	0.635	266 (4.28%)	0.784	217 (3.49%)	0.793	633 (10.19%)	0.459
Age group	0 to 1 year (n=634)	11 (1.73%)		43 (6.78%)		19 (2.99%)		54 (8.52%)	
	1 to 5 years (n=5342)	90 (1.68%)		191 (3.58%)		139 (2.60%)		420 (7.86%)	
	5 to 10 years (n=3752)	89 (2.37%)	<b>&lt;0.001</b>	167 (4.45%)	<b>&lt;0.001</b>	150 (3.99%)	<b>&lt;0.001</b>	406 (10.82%)	<b>&lt;0.001</b>
	10 to 15 years (n=1868)	34 (1.82%)		92 (4.92%)		60 (3.21%)		186 (9.96%)	
	>15 years (n=1863)	82 (4.40%)		87 (4.67%)		108 (5.80%)		277 (14.87%)	

\*Chi-square test. \*\* Either CSF, serum or both positive

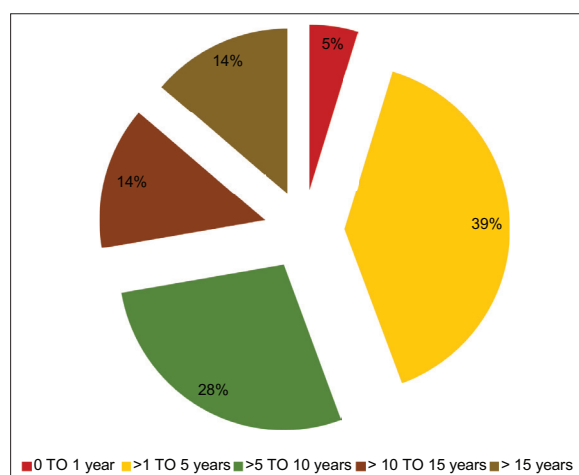


Figure 4: Age-wise distribution of AES cases in Uttar Pradesh (Years 2005-2018)

stay ( $\pm$ SD) was found to be 8.92 ( $\pm$ 9.97 days). The mean number of days between symptoms and admission ( $\pm$ SD) was 2.92 ( $\pm$ 3.4 days) for males and 2.85 ( $\pm$ 3.3 days) for females along with 1.97 ( $\pm$ 1.6 days) between admission and sample collection for males with 1.94 ( $\pm$ 1.6 days for females). The mean duration of hospital stay was 9.1 ( $\pm$ 9.9 days) for males and 8.7 ( $\pm$ 9.9 days) for females and was found to be statistically significant ( $P = 0.018$ ) [Table 3].

## Discussion

The current study investigates the trend of AES and JE in Uttar Pradesh along with epidemiological determinants of the disease. There was a consistent decline in CFR of AES between 2005 (24.76%) and 2010 (14.03%) but due to spikes between 2011 and 2013, it again escalated to 19.67%. Since 2013, again there was a consistent downfall in CFR of AES with the lowest value of 8% in 2018. This downward trend of CFR may be attributed

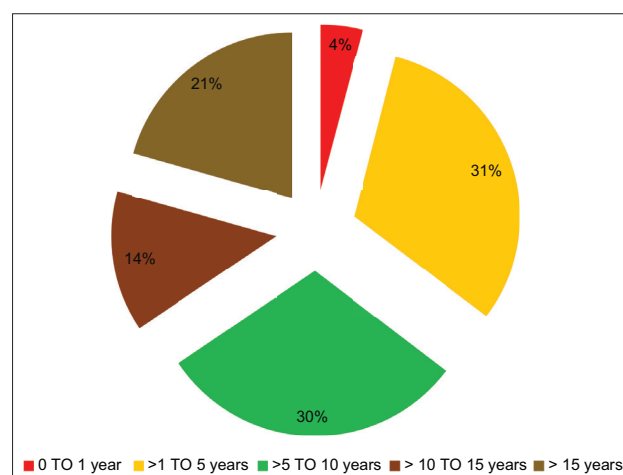


Figure 5: Age-wise distribution of JE cases in Uttar Pradesh (Years 2005-2018)

to early diagnosis and preliminary treatment, at the primary level where “Encephalitis Treatment Centres” (ETC) were being established at block level in AES affected areas, after introduction of term AES in 2007.<sup>[5]</sup> For JE cases in the state, there was no definite trend in either the burden of cases or deaths and CFR between 2005 and 2013. However, despite a consistent rise in the number of cases of JE being observed between 2014 (191) and 2017 (693), CFR decreased from 24.08% in 2014 to 9.12% in 2018 due to constant efforts by functionaries of health department and administration in the form of effective measures for its control. This rise in the number of cases of JE between 2014 and 2017 may be due to improved surveillance activities resulting in reporting of JE positive cases from some districts of Lucknow and Devipatan division of the state in whom incidence was nil in previous years. These findings are consistent with other studies by different researchers.<sup>[6-8]</sup> However, a study conducted by Kumar *P et al.* in Bihar reported an average CFR from AES to



be 30%, which was significantly higher than that observed in our study.<sup>[9]</sup> In 2018, there was a steep fall in the number of cases and deaths for both AES and JE due to massive interdepartmental preventive activities in form of “Sanchari Rog Niyantaran Campaign (Communicable Disease Control Campaign)” and awareness drive “Dastak (A knock at the door)” conducted by the state government in that year. In all, 96% cases of AES were reported from the eastern and central regions of the state. This may be due to geographical similarities of terrain, agricultural practices (paddy cultivation and flood irrigation practices), rainfall and flood in monsoon season. Sample positivity rate for anti-JEV IgM was 9.98%. Similar results have been reported in many studies: Vasanthapuram R *et al.* reported 16% positivity for JEV among the patients with AES, but Kaliban L *et al.* and Gogoi A *et al.* reported significantly higher proportion of JE positive patients among the AES cases.<sup>[10-12]</sup> The affected age group for both AES and JE in majority was 1-5 years, followed by 5-10 years, while the least affected age group was 0-1 year. Similar results were seen in the study conducted by Kumari R *et al.* in Uttar Pradesh, in which 58% of AES cases were from

the age group 4-6 years for AES, and 75.1% cases of JE were in the age group of 15 years or less.<sup>[13]</sup> Dey AK *et al.* reported similar age group predilection from a study conducted in Assam in 2016.<sup>[14]</sup> On the other hand, a study conducted by Ghosh *et al.* in Agartala reported that the maximum JE patients were from the age group of 5-10 years.<sup>[15]</sup>

For both AES and JE, the number of cases starts increasing from the end of June and early days of July, peaking in September and then gradually declining thereafter. This may be ascribed to monsoon season and flood in areas reporting the maximum number of AES and JE cases. Similar seasonal trend was reported in many studies in the country.<sup>[15,16]</sup> A study, conducted by Kumar P *et al.* in Bihar, reported peaking of AES cases in the month of June.<sup>[9]</sup> While a study conducted in Bellary, Karnataka, Kamble S *et al.* reported, peak occurrence in post monsoon period.<sup>[17]</sup> This variation in peak season can be caused due to Spatio-temporal variation in density of culex mosquitos in these regions.<sup>[18]</sup>

Out of the total JE positive cases, 52.87% were males and 47.13% were females. Bandyopadhyay B conducted a study in Kolkata and found JE positivity to be 59.92% in males and 41.08% in females, whereas Kumari R *et al.* found JE positivity in 61% males and 39% females in Uttar Pradesh.<sup>[13,19]</sup> Among 1343 patients who were positive for anti-JEV IgM, 41.77% were positive for serum, 22.71% for CSF and 35.44% for both serum and CSF. The age group wise maximum percentage of JE positivity in serum, CSF, and serum plus CSF was observed in the age group of 5-10 years and was statistically significant (*P* value <0.001). This study conducted by Jain P *et al.* in Uttar Pradesh.<sup>[20]</sup> Mean duration  $\pm$  SD of hospital stay among those who either died or survived was  $6.46 \pm 8.74$  days and  $9.78 \pm 10.23$  days, respectively, and was found to be statistically significant (*P* value <.001). Similar findings have been reported by other studies.<sup>[21]</sup> Higher duration of hospital stay among survivors may be attributed to prolonged recovery time and neuropsychiatric complications.

**Table 2: Relationship of outcome with age and sex (n=13459)**

Variable		Death	P*
Sex	Male (n=7245)	1472 (20.32%)	<b>0.030</b>
	Female (n=6214)	1356 (21.82%)	
Age group	0 to 1 year (n=634)	134 (21.14%)	<b>&lt;0.001</b>
	>1 to 5 years (n=5342)	1238 (23.17%)	
	>5 to 10 years (n=3752)	759 (20.23%)	
	>10 to 15 years (n=1868)	390 (20.88%)	
	>15 years (n=1863)	306 (16.43%)	

\*Chi-square test

**Table 3: Relationship of religion, sex and outcome with duration between symptoms and hospital admission, between admission and sample collection and admission and outcome. (n=13459)**

Variables		Mean $\pm$ SD duration between symptoms and admission	P*	Mean $\pm$ SD duration between admission and sample collection	P*	Mean $\pm$ SD duration between admission and outcome	P*
Religion	Hindu (n=11,877)	2.84 $\pm$ 3.34		1.95 $\pm$ 1.59		8.9 $\pm$ 9.98	
	Muslim (n=1582)	3.27 $\pm$ 3.24	<b>&lt;0.01</b>	2.0 $\pm$ 1.70	0.88	8.9 $\pm$ 9.88	0.60
Sex	Male (n=7245)	2.92 $\pm$ 3.37		1.97 $\pm$ 1.61		9.1 $\pm$ 9.99	<b>0.01</b>
	Female (n=6214)	2.85 $\pm$ 3.28	0.41	1.94 $\pm$ 1.59	0.51	8.7 $\pm$ 9.94	
Outcome	Death (n=2830)	3 $\pm$ 3.5		1.85 $\pm$ 1.4		6.46 $\pm$ 8.7	<b>&lt;.001</b>
	Others (n=10629)	2.8 $\pm$ 3.3	<b>0.01</b>	1.99 $\pm$ 1.6	<b>0.04</b>	9.78 $\pm$ 10.2	

\*Mann Whitney U Test. The significance level is .05

## Conclusion

Japanese encephalitis virus is the most important cause of viral encephalitis in Asia especially in India. The most commonly affected age group is 1-5 years with peak occurrence in the month of September. Safe and effective JE vaccines are available in all JE endemic states in India to prevent the disease and additionally to reduce the risk for JE and AES; all travellers to JE-endemic areas should take precautions to avoid mosquito bites especially in high peak season. Though the downward trend in CFR has been started and several encephalitis treatment centres have been established at block level in JE-endemic districts of eastern Uttar Pradesh, but still government needs to be strengthened awareness activities like “Dastak” campaign and intersectoral preventive activities.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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