Journal of Communicable Diseases
XIV Annual Conference of Indian Society for Malaria & Other Communicable Diseases (ISMOCD)
Pg. No. 90-94

Research Article

Role of Scrub Typhus in Acute Encephalitis Syndrome (AES) in Gorakhpur and its Effective Management

Rajni Kant

Indian Council of Medical Research (ICMR), Ansari Nagar, New Delhi, India.
DOI: https://doi.org/10.24321/0019.5138.202342

I N F O

E-mail Id:
rajnikant.srivastava@gmail.com
Orcid Id:
https://orcid.org/0000-0001-8127-8140
How to cite this article:
Kant R. Role of Scrub Typhus in Acute Encephalitis Syndrome (AES) in Gorakhpur and its Effective Management. XIV Annual Conference of Indian Society for Malaria & Other Communicable Diseases (ISMOCD). 2023;90-94.

Date of Submission: 2023-08-15
Date of Acceptance: 2023-09-28

A B S T R A C T

Gorakhpur region in eastern Uttar Pradesh has been known for acute encephalitis syndrome (AES) with severe morbidity and mortality along with an outbreak having more than 5000 cases in 2005. BRD Medical College was the only tertiary care hospital and it was overflooded during the peak season. With the introduction of live attenuated JE vaccine (SA-14-14-2) in the area, the cases of JE came down but AES remained unaffected majorly. Further investigation revealed Scrub Typhus as the major aetiology contributing to around 50% of the AES cases. Early diagnosis of the acute febrile illness and early treatment with azithromycin and doxycycline along with improvement of health care services at PHCs, CHCs and district Hospital level and inter-departmental coordination helped in reducing the incidence of AES as well as mortality by more than 90%. The challenge remains to sustain the achievements gained as well as to identify the remaining 20-30% unknown aetiology to win the final war against this scourge.

Keywords: Acute Encephalitis Syndrome (AES), Japanese Encephalitis (JE), JE Vaccine, Scrub Typhus, Effective Management, Gorakhpur

Introduction

Gorakhpur and its adjoining districts in eastern Uttar Pradesh (UP) have been known for the high incidence of Acute Encephalitis (AES) with high morbidity and mortality.[1-5] Gorakhpur is geographically situated on the river Rapti, which is a tributary of the Ganges and originates in Nepal, the district is also surrounded by rivers Rohill and Ami, which makes the entire area flood-prone with a bowl-shaped terrain that results in complexity of water logging. Intensive irrigation, agricultural practices particularly rice farming, water storage for live stocks, and ponds for fish farming create a conducive environment for the *Culex vishnui* group of mosquitoes, the vectors of Japanese Encephalitis (JE). Pigs act as a reservoir of the intermediate host of JEV are largely farmed and support transmission of JE. The region also shares a porous international border with Nepal and Bihar which are known as JE endemic areas. This kind of existing ecosystem makes this region vulnerable to JE/ AES.

Seasonal outbreaks of AES with high fatality have been reported from Gorakhpur division since 1978 (3500 cases, 1100 deaths). From 1978-2000 – JE remained consistent and the leading cause of AES outbreaks. In 2005 second largest outbreak with 5737 cases and 1344 deaths happened and the major aetiology was found to be JE. Annually about 2000 AES patients were admitted to BRD Medical College (BRDMC) – the only tertiary care hospital. Case

fatality ratio (CFR) was ranging between 20–30%. Japanese Encephalitis virus (JEV) accounted for half of the AES cases admitted during 2005.[6-8] In 2006, Mass vaccination with JE vaccine was started in the area. However, JE cases declined substantially, after the introduction of the JE vaccine but AES remain the riddle.[9-11]

Understanding Aetiology of AES: Focus on Non-JE Aetiology

JE vaccination with live attenuated JE vaccine (SA-14-14-2) was started in 2006. It resulted in the decline of JE, but it did not have much effect on the AES numbers. Between 2008 and 2012, JE accounted for < 10% of AES cases admitted at BRD, Medical College. AES patients were investigated for other viral and non-viral agents including herpes simplex, entero-viruses, Chandipura virus, measles, mumps, dengue, varicella, Parvovirus, West Nile, malaria, and typhoid, but the aetiology remained largely unknown. Studies focusing on AES patients in the Gorakhpur Division documented unknown aetiology for 40-60% of cases between 2007-2014. Studies showed the possibility of enteroviruses due to contamination of groundwater. Activities were shifted to safe drinking water and having standard hand pumps with a specified depth. But it also did not have much effect on non-JES cases. Herpes simplex virus (HSV) & Varicella Zoster Virus (VZV) were also tested +ve in a few of the AES cases, in some cases, *Rickettsia prowazekii* was also reported. But still, in the majority of AES cases, aetiology remained unclear (Figure 1).

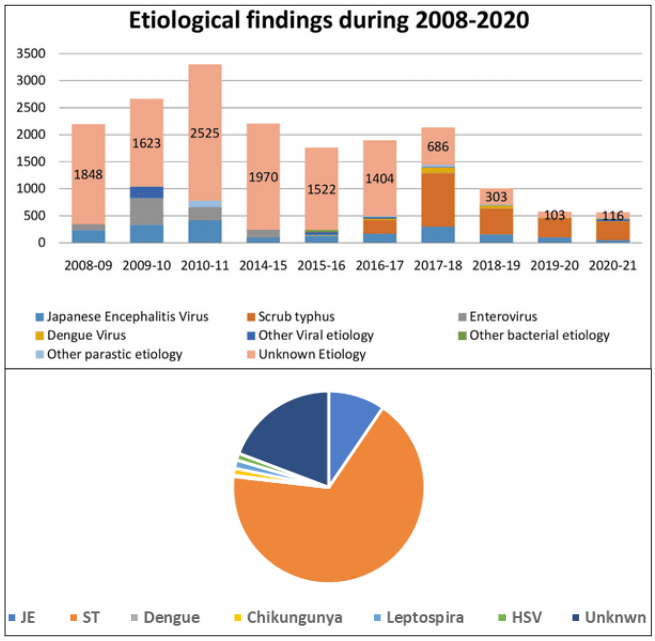


Figure 1.Major Aetiologies of AES

Multi-pronged Studies by the ICMR: Role of Scrub Typhus

Looking into the gravity of the situation, ICMR initiated a multi-institutional JE/ AES intervention project with a focus on vector control, understanding the unknown aetiology of AES, studying risk factor analysis, vaccine safety and efficacy studies as well as a social determinant of health, involving institutes like Vector Control Research Centre (VCRC), Puducherry, National Institute of Malaria Research (NIMR), Delhi, National Institute of Epidemiology (NIE), Chennai, National AIDS Research Institute (NARI), Pune and others. Investigations conducted by ICMR in 2014 and 2015 indicated the possibility of scrub typhus (ST) infection in AES patients. Scrub typhus is an infectious disease caused by *Orientia tsutsugamushi*. The infection is transmitted through the bite of the larval mites or 'chiggers' belonging to the family Trombiculidae. The infection is fully treatable with antibiotics doxycycline and azithromycin. These drugs are effective when given during the initial stages of illness. *Suncus murinus* (shrew) was found to be the commonest animal reservoir. More than 80 per cent of the trapped shrew/ rodents were found infested with the trombiculid mites (*Leptotrombidium delicense)* the predominant species. The overall chigger index, defined as the proportion of shrews/ rodents having trombiculid mite infestation, was highest for *S. murinus* (21.3%).

Risk factor analysis showed the presence of high water table with water-logged areas, dense vegetation, intensive rice cultivation, vegetation-infested water bodies, poor socio-economic conditions, poor health infrastructure, lack of awareness, belief in traditional healers, illiteracy, open defecation, inadequate sanitation, vicinity of human beings with domestic animals including rodents, storage of fire-woods, favourable climate, demography without any monitoring mechanism as the major reason for a high incidence of the disease as they create conducive conditions for the proliferation of disease vectors both mosquitoes and mites and rodent and pig population act as a reservoir of pathogens. Delay in early treatment due to belief in traditional practitioners and the unavailability of adequate health facilities makes the problem more complex. Hence a multi-pronged approach was needed to tackle the persistent problem of JE/ AES in the area.

Inter-departmental Coordination

Based on the risk factor analysis, it was found that the Health Department alone cannot solve the complex problem of JE/ AES in the region. Hence inter-departmental coordination was solicited with departments like the Ministry of Drinking Water and Sanitation to improve the supply of drinking water and its quality, the Ministry of Housing and Urban Poverty Alleviation to estimate slum households and slum population require adequate facilities for safe drinking water and sanitation, Ministry of Human Resource Development, Department of School Education to provide special facilities for children disabled from JE/ AES

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202342

by setting special schools and training centres, Ministry of Women and Child Development to improve the nutritional status of the children in affected areas, Ministry of Social Justice and Empowerment to provide rehabilitation services to target population and the Ministry of Health and Family Welfare remained the nodal agency to monitor the progress on the implementation of programmes recommended by Group of Ministers.[12] ICMR played an important role in doing research in understanding the aetiology, support in diagnostics and developing treatment algorithms (Figure 2).

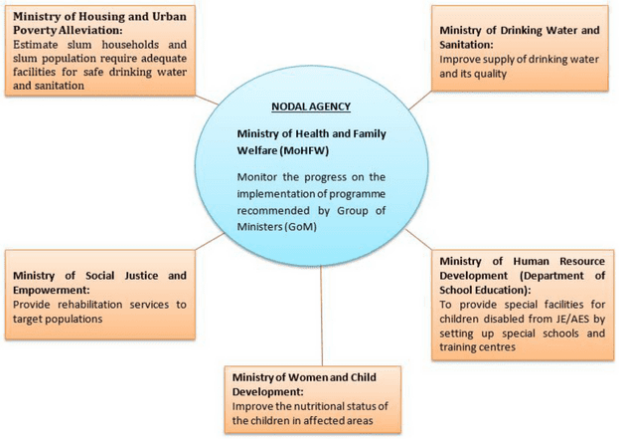


Figure 2.Inter-departmental Coordination[12]

Research Studies Conducted by ICMR

Entomological Investigations: Considering the continued AES activity in the region, ICMR initiated multi-institutional studies to understand and demonstrate the effect of intervention in selected regions. Five blocks in Gorakhpur district Bhathat, Khorabar, Chargawan, Belghat, and Campiarganj were selected for various interventions. Mazhgaon in Deoria was identified as the control block. Vector Control Research Center (VCRC), Puducherry carried out studies on mosquito bionomics including seasonal prevalence, species variation, distribution, and association with JE transmission. In JE-AES-affected region intervention measures such as the use of long-lasting insecticide-treated nets (LLIN) and indoor residual spray (IRS) were also attempted. National Institute of Malaria Research (NIMR) New Delhi helped in the biological control of mosquitoes using larvivorous fishes like guppy (*Poecilia reticulata)* and Gambusia (*G. affinis*). Mosquito bionomics studies showed the predominance of the *Culex vishnui* group of mosquitoes, particularly the *Cx. tritaeniorhynchus*, followed by *Cx. vishnui* and Cx. *Pseudovishnui.*

Out of 679 rodents screened, a total of 5526 mites were retrieved belonging to 14 species. The primary vector was found to be *Leptotrombidium deliense (76%).* Chigger (all mite species) index was 8.2 per rodent/ shrew, *Leptotrombidium deliense* index was 5.3 per rodent/ shrew. The vector index was well above the critical level of 0.69 per animal. Rodent's ear pinna was found infested with trombiculid mites.

National Institute of Virology, Gorakhpur unit helped in studying the Anti-JEV neutralising antibody in pigs as a marker of JE epidemiology as well as seasonal variation in anti-JEV neutralising antibodies and correlation with JE cases, while, the National Institute of Epidemiology, Chennai extended support in estimation of single dose JE vaccine coverage in susceptible population and the Enterovirus Research Center, Mumbai carried out the studies on the circulation of entero-viruses (EV) in normal pediatric (control) population in the AES endemic region, while National AIDS Research Institute, Pune did the sociological studies and community engagement in awareness for JE / AES prevention and control in the AES endemic region.

Genetic Characterisation of *Orientia tsutsugamushi* Gene (56 kDa) from Scrub Typhus Cases

Orientia tsutsugamushi DNA was detected by PCR from 37.4% (607/1620) AES cases during 2016 and 2017. The DNA samples were detected and further characterised using 56 kDa outer membrane protein of *Orientia tsutsugamushi.* Gilliam (93%) is the major genotype of *Orientia* followed by Karp (7%) detected in these AES cases (Figure 3).

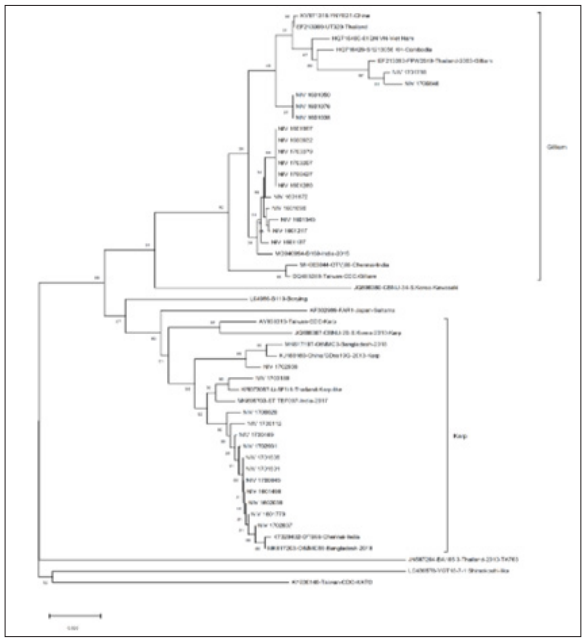


Figure 3.Genetic Characterisation of Orientia tsutsugamushi

Setting Up An AES Cell in BRD Medical College

For early diagnosis and prompt treatment, an AES cell was established in the BRD, Medical College, Gorakhpur. This served as a centralised facility for the collection and storage of clinical specimens from AES cases. All the laboratory

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202342

investigations for biochemical, and pathological parameters were done at the BRD, Medical College, Gorakhpur, while diagnostic tests for suspected etiologic agents were carried out at ICMR-NIV, Unit, Gorakhpur (Now RMRC, Gorakhpur). Data Center was set up for electronic storage of clinical, demographic, epidemiologic and laboratory data. This helped in early diagnosis and prompt treatment. A total of 3679 AES cases were enrolled during 2017-2020, 1619 patients tested positive for OT IgM (including samples from either CSF/ Serum), and 498 were positive for IgM JE. Results for scrub typhus PCR: 999/1736 (57.54%), where the subtypes seen were Gillium (90%) and Karp (10%). The rickettsia-specific generic PCR amplified in 11.3% of cases. Scrub typhus remained the major etiological agent (44%). JE is still an important aetiology (13.76%). In a large group of patients (32.31%) with a significant mortality the etiology still remained unidentified.

Key Reforms

It was decided to set up an ELISA testing facility for dengue, JE and Scrub typhus at PHCs, CHCs and District Hospitals as well as to ensure the availability of doxycycline and azithromycin at all PHCs, CHCs and District Hospitals. Training of clinicians, as well as all health care providers for identification of signs and symptoms of scrub typhus infection and treatment, was done on a time-to-time basis. Sensitisation of the community for risk factor reduction for scrub typhus infection was done. Even the UP Govt with support from UNICEF started the DASTAK programme for community awareness and behaviour change communication. Encephalitis Treatment Centres (ETC) were set up at the District level to avoid the burden on tertiary care hospitals. Vaccination with Japanese encephalitis vaccine was continued ensuring high coverage with both doses of the vaccine. The AES diagnostics algorithm was developed by an expert group constituted by ICMR and shared with the state Govt for early diagnosis and prompt treatment (Figures 4A and 4B).

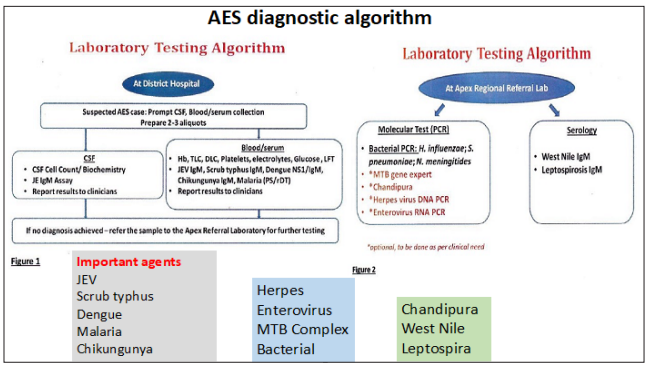


Figure 4A.Treatment Algorithm for AES

The State Government also made an effort to provide safe drinking water to the population as well as better sanitation and improved nutrition. *Swachch Bharat Mission* was started in 2014. It has helped in increasing the percentage of toilets from 27% in 2015 to more than 90% in 2022 and in reducing the problem of open defection, which helped in reducing the incidence of exposure to vector bites, particularly mites. The *Ujjawala Yojna* which helped in the supply of cooking gas resulted in the reduction of storage of firewood that used to provide shelter to rodents.

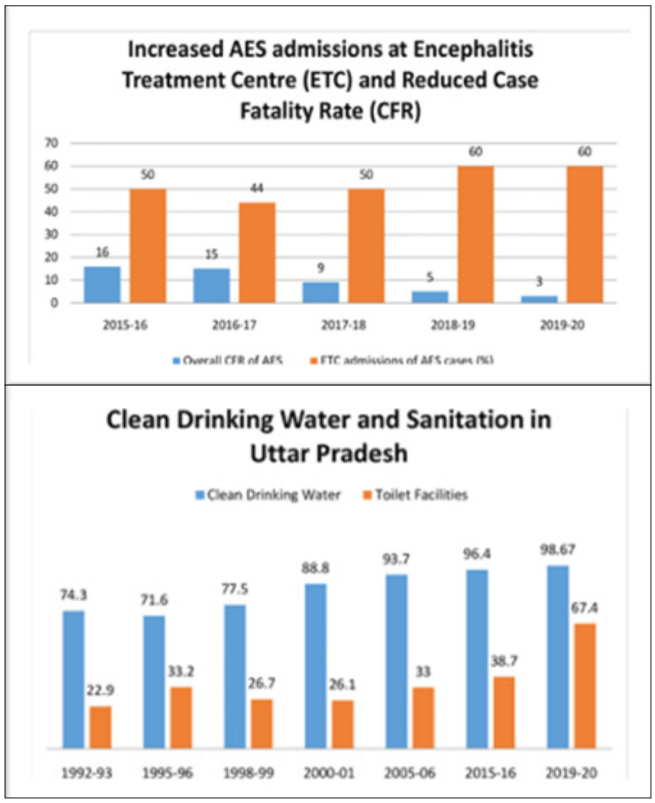
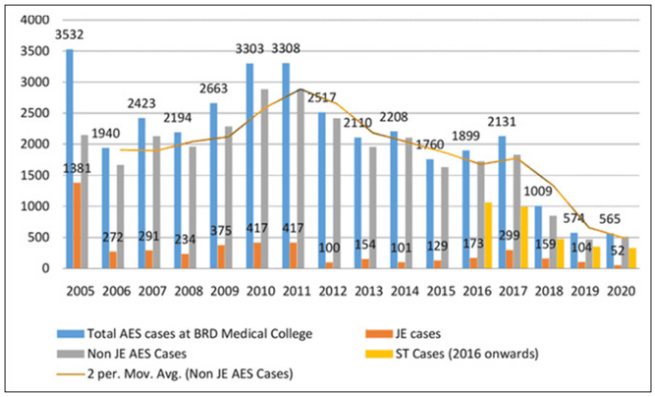


Figure 4B.Encephalitis Treatment Centres and Improvement in Toilet Facilities and Clean Drinking Water[12]

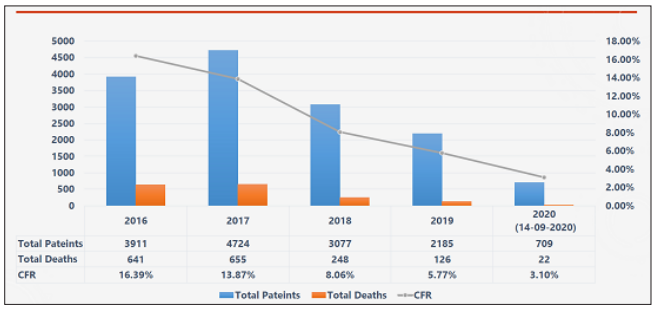
The Impact

Japanese Encephalitis (JE) and Acute Encephalitis Syndrome (AES) have been the major health concerns in eastern UP and were causing huge morbidity and mortality in Gorakhpur and adjoining districts. Intensive studies carried out by ICMR for understanding the aetiology of AES have helped in identifying the role of scrub typhus, as almost 50% of the AES cases were happening because of Scrub typhus only. Though with the introduction of the JE vaccine in 2006, the JE cases came down to less than 10%, AES remained a challenge. Once the role of scrub typhus was delineated efforts were made to strengthen the health infrastructure, particularly at PHC, CHC, and district hospital levels and to ensure the availability of diagnostic services and medicines. Government initiatives also helped in clean drinking water supply and reduction in open defection. This all helped in an almost 90% reduction in AES cases as well as in the mortality because of the AES (Figure 5).

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202342



(a) Decline in JE/ AES in Gorakhpur



(b) AES Cases, Mortality and CFR in UP

Figure 5.Impact of Interventions on JE/ AES Decline in (a) Gorakhpur as well as in (b) UP[12]

Conclusion

Though AES in Gorakhpur has been an enigma and has been causing huge morbidity and mortality, particularly in the paediatric population, over the years through consistent research to understand the aetiology, developing diagnostics, treatment algorithm, and support by the State health authorities in strengthening health infrastructure and facilitating diagnostic and treatment facilities at PHC, CHC and district hospital levels with inter-departmental coordination has helped in reducing the incidence by 90% as well as sharp decline in mortality as well. The aetiologies of AES as identified include Japanese encephalitis virus (5–20%), Enterovirus (0.1–33%), Orientia tsutsugamushi (45–60%) and other viral (0.2–4.2%), bacterial (0–5%) and Rickettsial (0.5–2%) causes. The aggressive immunisation programmes against Japanese encephalitis with vaccination coverage of 72.3% in UP helped in the decline of JE cases in the region.

Conflict of Interest: None

References

1. Mathur A, Chaturvedi UC, Tandon HO, Agarwal AK, Mathur GP, Nag D, Prasad A, Mittal VP. Japanese encephalitis epidemic in Uttar Pradesh, India during 1978. Indian J Med Res. 1982;75:161-9. [PubMed] [Google Scholar]
2. Rathi AK, Kushwaha KP, Singh YD, Singh J, Sirohi R, Singh RK, Singh UK. JE virus encephalitis: 1988 epidemic at Gorakhpur. Indian Pediatr. 1993;30(3):325-33. [PubMed] [Google Scholar]
3. Mittal M, Kushwaha KP. AES: Clinical presentation and dilemmas in critical care management. J Commun Dis. 2014;46:50-65.
4. Kakkar M, Rogawski ET, Abbas SS, Chaturvedi S, Dhole TN, Hossain SS, Krishnan SK. Acute encephalitis syndrome surveillance, Kushinagar District, Uttar Pradesh, India, 2011–2012. Emerg Infect Dis. 2013;19(9):1361-7. [PubMed] [Google Scholar]
5. Narain JP, Dhariwal AC, MacIntyre CR. Acute encephalitis in India: an unfolding tragedy. Indian J Med Res. 2017;145(5):584-7. [PubMed] [Google Scholar]
6. Singh AK, Kharya P, Agarwal V, Singh S, Singh NP, Jain PK, Kumar S, Bajpai PK, Dixit AM, Singh RK, Agarwal T. Japanese encephalitis in Uttar Pradesh, India: a situational analysis. J Family Med Prim Care. 2020;9(7):3716-21. [PubMed] [Google Scholar]
7. Kumari R, Joshi PL. A review of Japanese encephalitis in Uttar Pradesh, India. WHO South East Asia J Public Health. 2012;1(4):374-95. [PubMed] [Google Scholar]
8. Murhekar M, Thangaraj JW, Mittal M, Gupta N. Acute encephalitis syndrome in eastern Uttar Pradesh, India: changing etiological understanding. J Med Entomol. 2018;55(3):523-6. [PubMed] [Google Scholar]
9. Murhekar MV, Thangaraj JW, Sadanandane C, Mittal M, Gupta N, Rose W, Sahay S, Kant R, Gupte MD. Investigations of seasonal outbreaks of acute encephalitis syndrome due to *Orientia tsutsugamushi* in Gorakhpur region, India: a one health case study. Indian J Med Res. 2021;153(3):375-81. [PubMed] [Google Scholar]
10. Ranjan P, Gore M, Selvaraju S, Kushwaha KP, Srivastava DK, Murhekar M. Changes in acute encephalitis syndrome incidence after introduction of Japanese encephalitis vaccine in a region of India. J Infect. 2014;69(2):200-2. [PubMed] [Google Scholar]
11. Srivastava N, Deval H, Khan N, Kant R, Das A. Decline of Japanese encephalitis in Eastern Uttar Pradesh, India, 2009-2019. Asian Pac J Trop Med. 2022;15(5):230-1. [Google Scholar]
12. Srivastava N, Deval H, Mittal M, Kant R, Bondre VP. The outbreaks of acute encephalitis syndrome in Uttar Pradesh, India (1978–2020) and its effective management: a remarkable public health success story. Front Public Health. 2022;9:793268. [PubMed] [Google Scholar]

ISSN: 0019-5138
DOI: https://doi.org/10.24321/0019.5138.202342