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Epidemiology of Japanese Encephalitis: A Mosquito-Borne Disease *Vis A Vis* Human Health and Life in Gorakhpur District, Uttar Pradesh, India

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Abstract

Japanese Encephalitis (JE) is the leading cause of viral encephalitis in various parts of world. It is a deadly vector-borne viral infection of human brain that leads inflammation of the brain parenchyma and cerebral edema through the bite of infected mosquitoes of *Culex* species. JE virus is the widespread pathogen of encephalitis in India. The disease is predominantly found in rural and peri-urban areas. JE falls under a spectrum of diseases known as Acute Encephalitis Syndrome (AES). The largest AES load with repeated outbreaks is found in Uttar Pradesh after the first time detection of the virus in 1978. JE is referred as 'Mastishk Jwar' or 'Dimaghi Bhukhar' in endemic districts of Uttar Pradesh. Encephalitis can develop shortly after an initial viral infection. Every year sporadic JE cases are reported from the various districts of Uttar Pradesh. As per the report of the Directorate of National Vector Borne Diseases Control Programme (NVBDCP) 26,686 cases of encephalitis were reported in Uttar Pradesh during 2010 to August 2017. This review reveals the present scenario to review the epidemiology of JE among acute encephalitis syndrome (AES) cases in Uttar Pradesh, India including different species of the mosquitoes reported by the Malaria workers in different parts of rural and urban areas of the district Gorakhpur. Monitoring and cutting edge steps will assist to minimize outbreak leading to understand the trend and status of the disease for better prevention and control of JE in the prone district.

Keywords: *Japanese encephalitis/Acute encephalitis syndrome; Vector; Culex; Gorakhapur;*

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Introduction

Outbreaks of acute encephalitis syndrome (AES) have been occurring in Uttar Pradesh for several years. Encephalitis denotes inflammation of the brain parenchyma that clinically manifests with the syndrome of fever, headache, altered cognition, seizures and focal neurological dysfunction leading to significant mortality and permanent neurological sequelae worldwide (Bale JF, 2015). JE is a disease of public health importance because of its epidemic potential and high fatality rate. In endemic areas, the highest age-specific attack rates occur in children of 3 to 6 years of age (Hoke., *et al*. 1992).

The virus is carried by the bloodstream to the nerve cells of the brain where they multiply and scatter all the way through the brain. The mosquito-borne Japanese encephalitis virus (JEV) is an enveloped, positive-sense single-stranded RNA virus and member of the genus *Flavivirus* under the family Flaviviridae related to dengue, yellow fever and West Nile viruses (Lindenbach & Rice, 2001). JEV is the sole etiologic agent of Japanese Encephalitis as a neurotropic killer disease being one of the major causes of viral encephalitis in human since the isolation of this virus in Japan in 1935 (Tanaka., *et al*. 1991). In India, the first human case was reported from North Arcot district of Tamil Nadu in 1955 (Webb & Pereira, 1956). However, unlike many other mosquito-borne diseases, an amplifying host is important in the epidemiology of human JE. In Asia, pigs are considered to be the most important amplifying host providing a link to humans through their proximity to housing (Kabilan., *et al.* 2004).

The first clinical case of JE was recorded in 1871 in Japan. Half a century later, also in Japan, a large JE outbreak involving more than 6,000 cases was documented. Subsequent outbreaks occurred in 1927, 1934, and 1935. Genetic studies suggest that JEV originated from an ancestral virus in the area of the Malay Archipelago (Solomon., *et al*. 2003). Almost half of the human population is gradually being adversely affected with this endemic disease. It is estimated that 67 900 clinical cases of JE occur annually with approximately 13 600 to 20 400 deaths, and an overall incidence rate of 1.8/100 000 in the 24 countries with JE risk (Halstead and Jacobson, 2008). As per WHO reports major outbreaks of JE occur every 2-15 years. JE transmission intensifies during the rainy season which favors to increase the populations of the vectors. JEV is the main cause of viral encephalitis in many countries of Asia with an estimated 68,000 clinical cases every year. Japanese encephalitis has increased risks in the countries including Australia, Bangladesh, Bhutan, Brunei, Myanmar, Cambodia, China, India, Indonesia, Japan, North Korea, South Korea, Laos, Malaysia, Nepal, Pakistan, Papua New Guinea, Philippines, Russia, Singapore, Sri Lanka, Taiwan, Thailand, Timor-Leste, Vietnam and Western Pacific Islands (CDC, 2011).

The JE endemic districts in eastern Uttar Pradesh are a predominantly rural as north east tip of the state. Major population of low land 'Terai' region generally cultivate paddy in densely populated area due to high levels of poverty, unemployment, illiteracy and malnutrition (Khushinagar, data, 2014). Outbreaks of acute encephalitis syndrome (AES) with high case-fatality rates have been occurring in Gorakhpur Division of Uttar Pradesh, India, since 1978 (Watt & Parola, 2003). According to CDC, among patients who develop encephalitis, 20%-30% die. The World Health Organization (WHO) estimates that children are the worst-affected form the Japanese Encephalitis as most adults have immunity against the disease. The incubation period of JEV is on average 5-15 days. Seasonal outbreaks of AES with high case fatality and disability are frequently reported from Gorakhpur division of Uttar Pradesh (Kakkar., *et al.* 2012). The disease is being explored by favorable climatic conditions leading to arrest more human beings.

Since several decades the virus is adversely affecting the large number of individuals in the district due to lack of awareness specially people living below poverty line. Due to repeated outbreaks approx 6,000 children have died in Gorakhpur region since 1978 during the major outbreaks recorded between July and November 2005 in Gorakhpur. The outbreak turned out to be one of the biggest epidemics in three decades. Japanese Encephalitis and Acute encephalitis show similar behavior in Gorakhpur district because of major population generally cultivate paddy in densely populated area due to high levels of poverty, unemployment, illiteracy. The conditions favor the differentiation and proliferation of many opportunistic pathogens like bacteria, fungi and viruses of different strains which are difficult to identify individually. WHO coined the term AES in 2006 to denote a group of diseases which seem similar to one another but are difficult to differentiate in the frenzied environment.

Epidemiological acuity of JE with Gorakhpur district

AES is reported mainly from Assam, Bihar, Karnataka, Uttar Pradesh and Tamil Nadu which contributes approximately 80% of cases. The case fatality and morbidity is very high. Japanese encephalitis (JE) is considered as a main viral an etiology of patients with AES. In the year 2006, West Nile (WN) virus emerged as another cause of acute encephalitis syndrome in India. Leptospirosis and toxoplasmosis is a zoonotic disease and its severe form can cause AES. The causative agent of the AES varies with season and geographical location.

Massive JE outbreaks occurred in 2005, mainly in Bihar and Eastern Uttar Pradesh (UP). Around 6000 AES/JE cases/1500 deaths were reported from UP and around 6500 AES/JE cases/1600 deaths from ten other states of India were reported.

The JE vaccination coverage is relatively low and not consistent over the years. Sentinel site-based surveillance was started in 2005. Over the years from 2008-2013, the reported AES cases increased significantly, but only 15% of AES are due to JE. In the state of Assam in 2013, approximately 80% JE confirmed cases were among adults. (JE Report Bangkok, 2014). The outbreak of AES and JE usually coincides with the monsoon and post monsoon period when the density of mosquitoes increases. Encephalitis due to entero-viruses occurs throughout the year as it is water borne disease. The most common causes of acute viral encephalitis are Japanese encephalitis virus, West Nile virus (WNV), Eastern equine encephalitis virus (EEEV), Western equine encephalitis virus (WEEV), Venezuelan equine encephalitis virus (VEEV), Hendra virus (HeV), entero viruses (ENV), Chandipura virus (CHPV), Nipah (NiV), Kyasanur forest disease (KFD), St. Louis encephalitis virus, Herpes simplex, poliovirus and measles virus (Cordia Wan., *et al*. 2017).

Gorakhpur is considered as the initial spot of Japanese encephalitis since 1978 in Uttar Pradesh. Actually Gorakhpur is a bowl shaped city with high groundwater tables. The gradient of the city is low to flat which leads to problem of water logging and flooding. This creates abundant tenancy for JE vectors to thrive in urban areas. This district is located in mid-Gangetic planes between the river Rapti and Rohin basins. One of the most important causative factors for JE is cultivation and management of paddy under the agricultural land. JE vectors thrive easily in irrigated paddy fields. At Gorakhpur out of the total population about 63% of the total workforce practice agricultural works with supplement income by cattle rearing.

Primary carriers of the JE virus are pig and pond heron. The neighboring districts of Gorakhpur like Siddharthnagar, Kushinagar, and Maharajganj make JE more vulnerable. The prevalence rate of JE is higher in these districts compared to the rest of the state. The temperatures in Gorakhpur range from 8.9^0C and 38.0^0C which favors JE. The district receives rainfall between June and August with an average of 52.2 days in a year. The most appropriate condition for increase in mosquito density is favored at 28^0C temperature with 50-55% relative humidity (Murty., *et al.* 2010). The breeding of mosquitoes are flattered at Gorakhpur due to hot and humid weather. Presently the emerging research suggests that JE virus may not necessarily be constrained to rural environments in contrast to urban areas.

Population (Urban and Rural) census 2011

According to the census 2011 report the total population of the district is 4.4 million with a population density of 1,337 persons sq/km which depict higher than average of 829 persons sq/ km density. 18.83 percent of present population resides in urban region of Gorakhpur district of total population including figures about 439,051 males and 397,078 females out of total population 836,129 and sex ratio reveals about 904. The child population under the six years age in urban population was 91,259 having 48,238 males 43,021 females respectively with 10.99 percent of the total population respectively. Literacy rate in 2011 of urban region of the district is about 82.39 percent in connection to 87.76 percent males and 76.46 percent females accordingly.

Out of the total population of Gorakhpur districts more than 81.17 percent people reside in rural areas in figures 3,604,766 revealing 1,838,726 males and 1,766,040 females according to the census report of the year 2011 respectively and sex ratio in the area is 960 females per 1000 males while in case of child it is 912 girls per 1000 boys of the age group 0-6 years revealing the total no in figures 537,183 followed by 281,014 males and 256,169 females contributing 15.28 percent of the total population. As for the literacy prospects it is 68.02 percent. In respect to the gender based literacy the rate prolong 80.30 percent males and 55.35 percent females respectively. Among the total population of 2,086, 628, the number of literate individuals were 1,250, 910 male and 835,718 females respectively. As per the census 2011 about 81% of the population is rural while 18% is urban respectively in Gorakhpur district.

Discussion

Gorakhpur is situated on the plane plateau and has poor drainage systems which lead the accumulation of water in puddles generating natural breeding grounds to the mosquitoes. In winter and summer the populations of mosquitoes are found in large swarms (Sanjay., et al. 2014). According to WHO more than 68,000 clinical cases are found every year in different parts of Asia in which children are the worst affected. The most common mosquito species found throughout the year in the Gorakhpur are primary and secondary vector such as *Culex tritaeniorhynchus, Culex vishnui, Culex pseudovishnui, Culex bitaeniorhynchus, Culex. Gelidus, Culex. Whitmorei, Culex. Fuscocephalia, Culex. Quinquefasciatus, Culex. Epidesmus, Mansonia uniformis, and Anopheles subpictus.* The advanced genomic techniques certainly have great potential in improving the diagnosis and management of patients with a range of viral infections (Mbisa., et al. 2016). Four Indian states are JE endemic viz. Uttar Pradesh, Assam, West Bengal, and Bihar. Annually due to outbreak of AES/JE about 20 to 25 % mortality rate has been reported at the district Gorakhpur.

In year 2016, death cases by JE were recorded as 25.5%. Up to 60% of viral encephalitis cases are supposed to remain unexplained due to the failure of conventional diagnostic techniques used to detect the pathogen. Initially as a Centre of outbreak in Gorakhpur 5,737 persons were affected by the disease in seven districts of eastern UP with death of 1,344 persons. Highest numbers of larvae for JE vectors were collected when rice fields were plowed with water (Keisar., *et al*. 2005). The areas adversely affected by JE/AEs have been shown in the Figure 1. The data for AES cases and deaths has been collected from the Directorate of National Vector Borne Disease Control Programme, Delhi presenting the year wise number of AES cases and Deaths from 2010-2017 respectively. The conclusions are made on the basis of annual comparatives cases. The year wise comparative description of AES cases and deaths in UP has been depicted in the Figure 2.

Figure 1: *JE/AES affected area.*

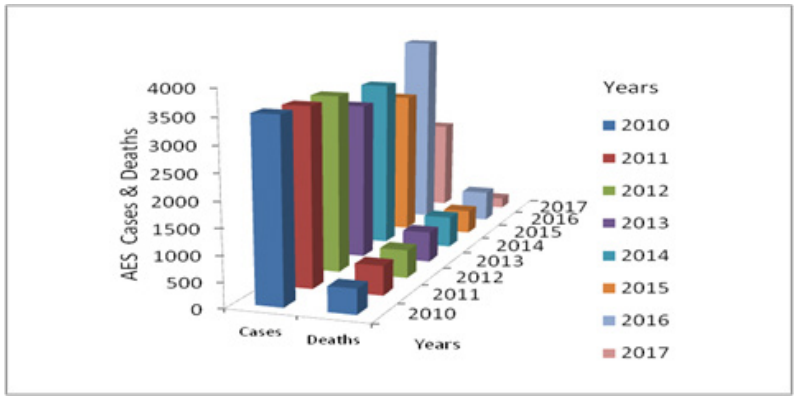

Figure 2: *Acute Encephalitis Syndrome (AES) cases and deaths occurred in Uttar Pradesh by year, 2010–2017.*

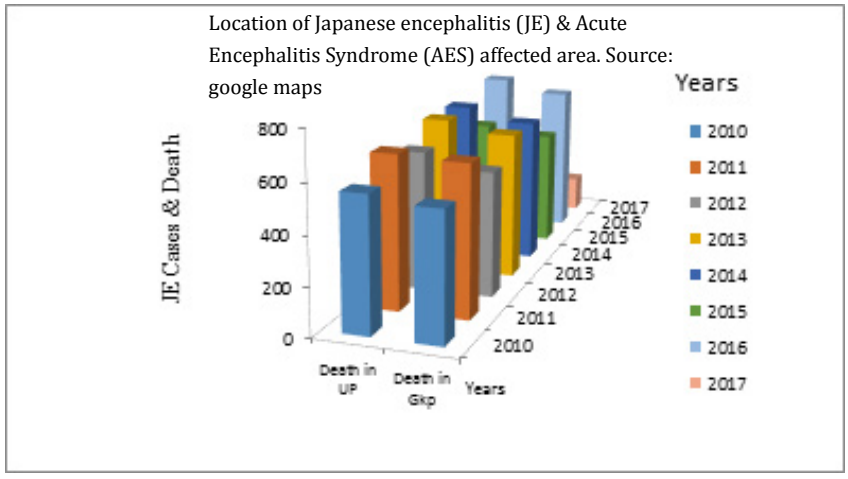

Figure 3: *Japanese encephalitis cases and deaths occurred in Gorakhpur district by year, 2010–August 2017.*

It has a state prominent mean that acute encephalitis syndrome (AES) with high fatality have been occurring in Gorakhpur division, Uttar Pradesh, India since several years. These outbreaks occur during rainy season predominantly. Several other diseases exist like Chikungunya, Dengue and Malaria but most of the times it may be difficult to differentiate Japanese Encephalitis from those caused by other bacteria and viruses. Sometime clinical signs of JE are indistinguishable from other causes of AES which finally depend on laboratory confirmation for essential for accurate diagnosis. Infection caused by any of these pathogens triggers fever, an altered mental status causing the patient to behave abnormally and seizures.

There have been cases in the area which are clinically different from one another. Baba Raghav Das Medical College Gorakhpur serves as referral hospital for nearby localized people for treatment of Acute Encephalitis Syndrome (AES). Information's revealing the cases over duration of eight years have been used from The Hindu, India's national newspaper in the issue of August 16, 2017 as per official records which is serving the nation since 1878. *Japanese encephalitis* cases and deaths occurred in Gorakhpur district by year, 2010–2017 has been illustrated in figure 3. However specific research is urgent need of time to overcome despite decades of annual outbreaks.

Disease prevention and control

Actually it is the need of the present scenario to elevate close monitoring and evaluation of JE/AES surveillance system. Human vaccination is the most successful control strategy. Globally about fifteen JE vaccines are currently being used. The major types of JE vaccines are Inactivated Vero cell-derived, live attenuated, live recombinant and inactivated mouse brain-derived. A number of strategies exist worldwide to control JE including the early case detection and treatment, reduction of breeding source for larvae, intermittent irrigation of paddy field, using *Gambusia Affinis* as bio control agents of mosquitoes, Individual preventive measures using repellents, long-sleeved clothes, vaporizers, vaccination for travelers staying in JE endemic areas, pig vaccination and improving living conditions may reduce the outbreaks.

Sometimes weak immunity leads to a bounce back of the disease also need to be further investigated. It is very important to ensure the timely availability of JE vaccine to the target populations. There is a need to strengthen potable water treatment to make it safer especially the hand pumps including successful practices associated with solid waste management. The relevant strategies for constantly changing needs of the communities with ameliorated awareness may unleash them to work freely for better tomorrow with environmental sustainability. For resilience improved infrastructure need to develop via wise use of the resources in the localities procuring effective studies by trained persons. Such developments will certainly improve safe vaccination with delivery of more cost effective vaccines complying regulatory norms. Finally the rigorous monitoring will go a long way in controlling JE/AES.

Conclusion

At present Japanese encephalitis is a major public health problem with high case fatality rate of 20-30% in many parts of the world. Safe and efficient vaccines are available against prevention of JE. Precautions such as wearing long-sleeved clothes reducing exposure during dawn and dusk to avoid mosquito bites. Prevention of the disease should be the important intention for controlling the JE spread due unavailability of the specific treatment.

The JE vaccination campaign was launched in Uttar Pradesh during 2006 as under consideration of the most sensitive state. As per WHO recommendations vaccination is conducted in recognized areas under JE infection revealing public health issues. Monitoring the early warning signals for predicting an outbreak of JE is utmost step for investigation as risk reduction. Undue attention on syndromic identification of JE and management approaches of etiological research may turn to be a better preventive measure. Proper performance of a vaccination for children in connection to advance agricultural practices, pig vaccination, vector growth control with improved living standards can significantly reduce the risk of JE.

This review article is consistent with ambiguity of identifying aetiological factors of encephalitis with annual out breaks exploring the way to capture emerging agents for better health and life to maintain the sustainable environment for future prospects. It is the urgent need of the time to facilitate better and cost effective vaccines for throng immunization with awareness of prevention and control measures introducing the fine sensitive strategies at priority for humanity. Still a lot need to be done to eradicate the JE/AES on the basis of epidemiological investigations of havoc outbreaks.

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