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Review Article

Japanese Encephalitis/Acute Encephalitis Syndrome: Prevention and Control Strategies in India

Ranganath BG
Professor & Head, Dept of Community Medicine, Sri Devaraj Urs Medical College, Kolar, Karnataka, India

Abstract

Outbreaks of acute encephalitis syndrome (AES) occur seasonally in the country and lead to substantial mortality and disability. Japanese encephalitis (JE) virus traditionally is known to be causing AES with significant mortality and disability. However, enteroviruses and other causes are being increasingly incriminated in AES outbreaks in different regions of the country. Hence newer strategies have been developed under national vector borne disease control programme (NVBDCP) to prevent and control JE/AES. Many ministries have converged with the lead of health ministry to successfully operationalize the JE/AES prevention and control strategies in the country.

Acute Encephalitis Syndrome

Acute encephalitis syndrome (AES) is a general description of the clinical presentation of a disease characterized by high fever with altered consciousness and other mental signs and symptoms mostly in children below 15 years of age. Simple febrile seizures are excluded under AES.[1] AES is believed to have a complex aetiology and Japanese encephalitis (JE) virus is now considered as one among the many causative agents of encephalitis. It has been found that many of the occurrences of AES being reported in India are caused by enteroviruses spread through unsafe drinking water. One hundred and seventy one districts in 19 states have been identified as JE/AES endemic in the country. Epidemiological analyses of the data from the states reporting JE/AES show the age group of 1-5 years to be more vulnerable to the disease and cases occur mainly in September and October. Cases attain a peak in the month of July in Assam and due to circulation of enteroviruses in eastern Uttar Pradesh AES cases are reported round the year. The number of AES cases reported to NVBDCP from 2010 to 2015 ranges from 5174 to 10867 and the average of mortality rate for the same period is 14.6%. During 2015 around 9086 AES cases were reported with a mortality rate of 13.3 % (1208). Out of these 1698 were JE cases with a mortality rate of 17.0%.[2]

To tackle the burden of JE/AES in the country the Government of India has initiated strategy to cover many of the known determinants of the disease and its outcomes. Efforts are being made under the programme to prevent AES, improve case management to reduce morbidity and mortality, and rehabilitation of those surviving with disability following AES.

Japanese encephalitis

Japanese encephalitis is one of the leading causes of viral encephalitis and neurological infections in Asia. It is estimated that 67 900 severe clinical cases of JE occur annually, with approximately 13 600 to 20 400 deaths in Asia.[3] The disease was first recognized in India in 1955, when cases of encephalitis from north Arcot district of Tamil Nadu and neighboring districts of Andhra Pradesh, admitted to Christian medical college hospital, Vellore, were serologically diagnosed as JE encephalitis.[4] Since 1972, JE spread to newer areas and epidemics were reported from West Bengal, Uttar Pradesh, Assam, Bihar, Karnataka and Maharastra. Subclinical infections are relatively high and the ratio to clinical infections being around 250:1. The clinical disease in the late stage is marked by complete recovery or persistent neurological sequel in 30-50% of the survivors. Children are at greatest risk, but JE can occur in all ages. The infection is maintained in the enzootic cycle among the pigs, ardeid birds and mosquitoes. Because infected pigs act as amplifying hosts, domestic pig rearing is an important risk factor in the transmission of JE to humans.[5] 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.[6]

***Corresponding Author**

Dr. Ranganath BG
Professor & Head, Dept of Community Medicine.
Sri Devaraj Urs Medical College, Kolar-563101, India
E-Mail: ranganath477@gmail.com
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Man is the dead end host in the natural cycle and plays no role in transmission of the virus. Although the virus has been isolated from many species of mosquitoes belonging to genus culex, aedes and anopheles the species culex tritaeniorhynchus and culex vishnui are considered as the main vectors which mainly proliferate in paddy fields and pools of stagnant water. Transovarian transmission in these mosquitoes is considered as an important mechanism for maintenance of the virus in nature. Due to its complex eco-epidemiology JE continues to be a significant public health problem in India over the years and has contributed to around 13.7% of the AES cases annually in the last six years.[2,7]

The directorate of NVBDCP reported 1698 JE cases in 2015 from 16 states and union territories, with a mortality rate of 17%. Three states namely Assam, West Bengal and Uttar Pradesh (UP) contributed to 77% of the JE cases in 2015.[2] Following the major outbreak of JE in the eastern parts of UP particularly Gorakhpur, Mahrajganj, Kushinagar and Deoria districts in the year 2005, the government of India took initiatives to introduce a vaccine to contain the disease in the endemic areas of the country. The national vector borne disease control programme (NVBDCP) since then is involved in aspects related to disease surveillance, case management, and prevention and control of JE/AES. Since then considerable research has implicated many types of entero-viral and other non-JE infections to be significantly responsible for the AES outbreaks in UP.[8,11]

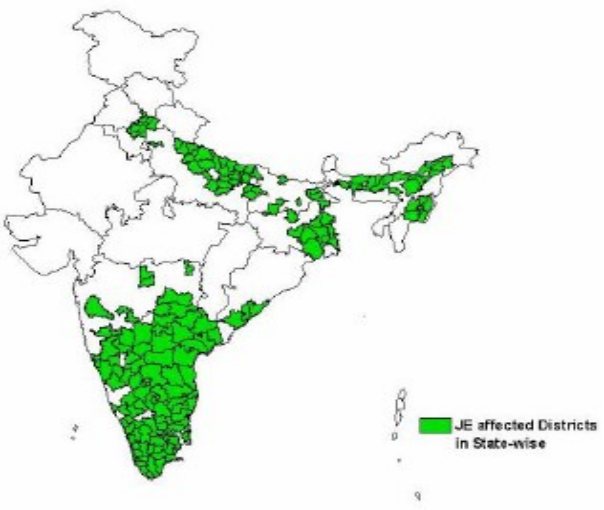


Fig 2. JE endemic districts in the country [12]

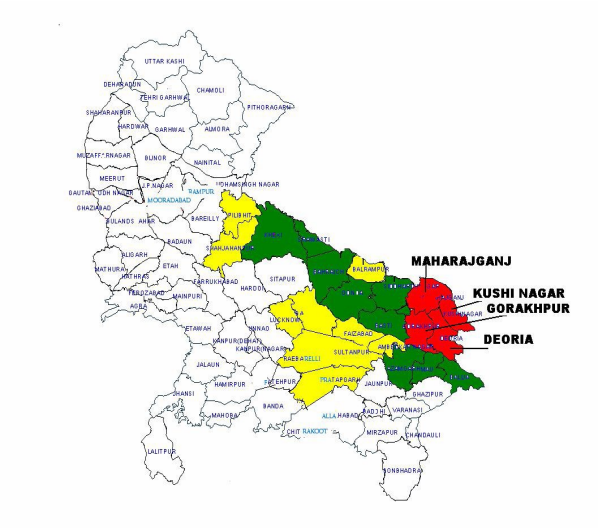


Fig 3. Endemic areas of JE/AES in UP state [13] (hyper endemic-red; endemic-yellow; low endemic-green)

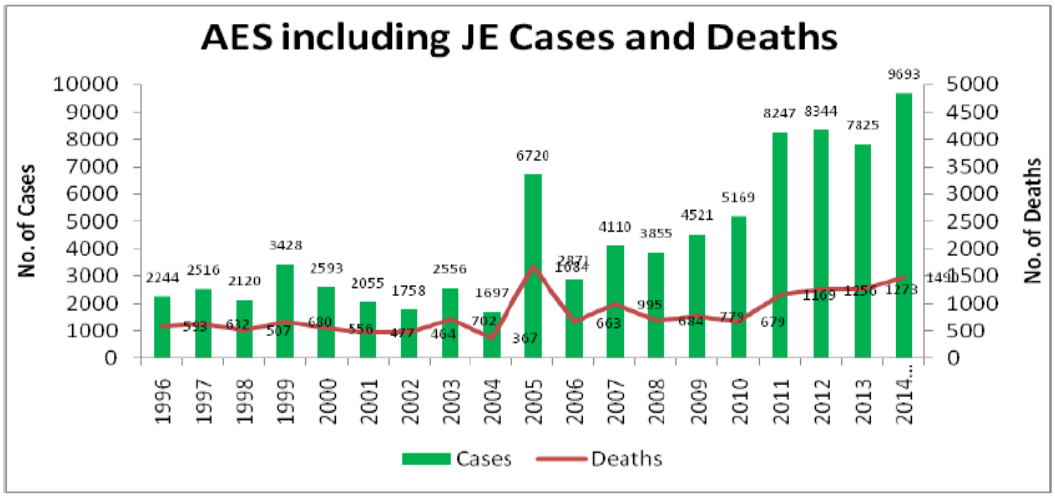


Fig 1. AES and mortality reported in India[12]

Other causes of AES

After introducing JE vaccination in the endemic districts of the country JE is no longer being considered as the major cause of AES. The proportion of JE laboratory-confirmed positive cases is around 15.5%. The state of UP accounts to over half of the cases and deaths followed by the states of Assam and West Bengal. There is variation in the causation of AES in the country according to place. Various enteroviruses such as EV-76, EV-89 and Coxsackie virus B5 have been found to be associated with AES in UP and have been attributed to consumption of contaminated drinking water. Chandipura virus is being increasingly attributed to AES in Gujarat and West Nile virus in Kerala. Temporal variations in AES distributions are being documented. In North India AES earlier was mainly reported in September and October whereas recently are being reported in June and July.[14,16]

The epidemiology of recent outbreaks of AES has been unusual. None of the cases tested positive for JE in the AES outbreaks in 2012 and 2014 at Muzaffarpur in Bihar which had a mortality of around 35%. The affected have been predominantly the poor and malnourished children who have incidentally eaten unripe litchi fruit, hypothesized to have caused hypoglycaemic syndrome due to a toxin present in it. Some investigators have also attributed heat stroke as the cause of AES in children in Muzaffarpur. Better clinical case management strategies to assess and correct hypoglycaemia in these situations are attributed to have reduced the mortality rates following AES in Bihar. Hence the Indian government took a major initiative by introducing a national programme for prevention and control of JE/AES.[17,19]

National programme for prevention and control of JE/AES[30]

Under this unique programme there is a convergence of the ministries of drinking water and sanitation, women and child development, social justice and empowerment, housing and urban poverty alleviation (HUPA) and human resource development. In the districts reporting AES, efforts are being made for provision of safe water supply, providing high quality nutrition to the vulnerable children, empowerment of the district disability rehabilitation centres and supply of safe water to slums and towns. It is believed that the implementation of these programme components may significantly reduce the mortality and morbidity due to JE/AES in the country.

The ministry of health and family welfare (MoHFW) has been designated as the nodal agency for overseeing the progress made by the national programme for prevention and control of JE/AES.[20] The various activities to prevent and control JE/AES includes JE vaccination, case management, ULV fogging, establishing PICU, monitoring, surveillance and IEC/BCC.

Strengthening and expanding JE vaccination

The 2005 seasonal epidemic of JE accounted for 6,584 cases in India, including 1,765 deaths reported from 11 states. Majority of the cases were reported from the state of Uttar Pradesh alone with a case fatality rate of 23.3%.[21-23] Following this outbreak the government of India (GoI) with support from partner agencies namely PATH, WHO and UNICEF who campaigned intensively against the disease decided to use the live-attenuated SA 14-14-2 JE vaccine, which was being produced and widely used in China since 1988.[22] A single dose of the vaccine had a protective effect of 98.5% (95% CI 90% - 99.2%) 12 to 15 months after vaccination.[24] A large randomized trial had established the short-term safety of the vaccine among the Chinese children.[25]

Subsequent to the introduction of the vaccine in 2006 the vaccine was introduced in all the JE endemic districts of the country. In the short term longitudinal studies conducted on children of 6 to 15 years following immunization with the vaccine, serious adverse events have not been reported.[26,27] Under universal immunization programme (UIP) two doses of the JE vaccine, SA-14-14-2 is to be given one along with measles at the age of nine months and the second with DPT booster at the age of 16-24 months in the 181 JE endemic districts of the country.[28]

Following mass vaccination campaigns with JE vaccine among children, adult JE cases have increased in many states. The government of Assam has conducted special JE vaccination campaigns for adults. NVBDCP has identified districts with a high burden of JE in the three states of Assam, UP and West Bengal for adult JE vaccination.[29]

Behavior Change Communication (BCC) / Information Education and Communication (IEC)

Behavior change communication (BCC) is a process of any intervention with individuals and communities to develop communication strategies to promote positive behaviors which are appropriate to their settings. This in turn provides a supportive environment which will enable people to initiate

and sustain positive and desirable behavior outcomes. Since BCC is target specific it varies among various society groups. It includes preparation of community education, printing material and street plays at PHC.

In BCC for an effective strategy the risk factors of the target group, the obstacles in the way to desired change in behavior, the ideal message and media to communicate with the target group, the resources available and assessment of existing knowledge of the target groups on the issue to be dealt with are all to be considered. The objectives of BCC will be to promote the interventions of the project by creating demand and acceptance among target groups; to bring about desirable behavioral changes in the household child care and feeding practices; to mobilize community participation and support for project activities; to empower the communities to plan and implement sustainable interventions to reduce malnutrition among children and improve health and nutrition status of the community. In order to achieve above objectives there should be collaboration of the programme with health education experts to develop IEC materials.

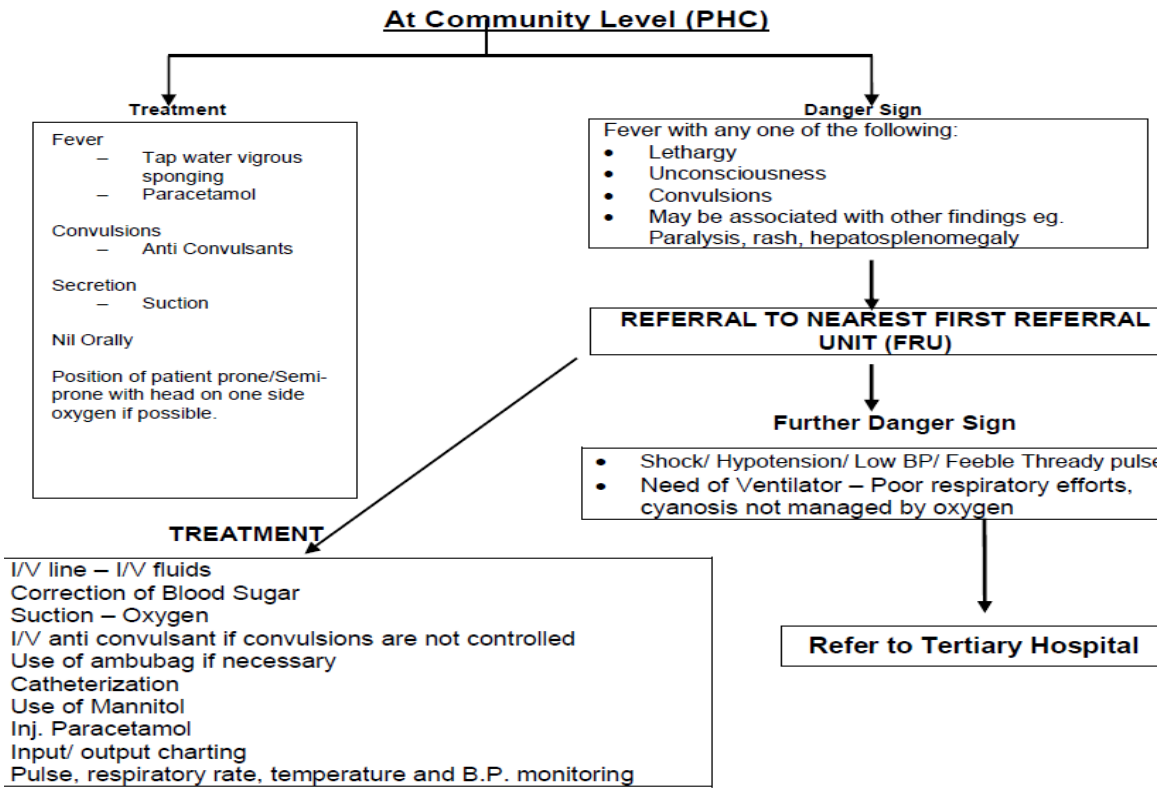
Case management of AES/JE

Cases of AES/JE usually are admitted in health institutions in a serious condition. Hence guidelines for symptomatic case management of JE and other causes of encephalitis are provided by NVBDCP. To reduce severe morbidity and mortality, identification of early warning signs and referral of patients to health facility and education of health workers about the first line of management at the grassroots level is being undertaken.

Case definition of suspected case of AES/JE

AES/JE is suspected in a case with acute onset of fever of not more than 5-7 days duration; change in mental status with/without new onset of seizures and other early clinical findings which may include irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness. Certain observations are well established which are helpful to identify AES/JE. In an epidemic situation fever with altered sensorium persisting for more than two hours with a focal seizure or paralysis of any part of body, is encephalitis. Presence of rash on body excludes Japanese Encephalitis and AES with symmetrical signs and fever is likely to be cerebral malaria.

Guidelines for management of AES/JE



Case classification

Laboratory-confirmed case: A suspected case with any one of the following markers namely presence of lgM antibody in serum and/ or CSF to a specific virus including JE/entero virus or others; a fourfold difference in lgG antibody titre in paired sera; virus isolation from brain tissue; antigen detection by immunofluroscence and; nucleic acid detection by PCR. In the sentinel surveillance network, AES/JE is diagnosed by lgM Capture ELISA, and virus isolation is done at national reference laboratory.

Probable cases: A suspected case in close geographic and temporal relationship to a laboratory-confirmed case of AES/JE in an outbreak

AES due to other agents: A suspected case in which diagnostic testing is performed and an etiological agent other than AES/JE is identified.

AES due to unknown agent: A suspected case in which no diagnostic testing is performed / no etiological agent is identified / test results are indeterminate.

The treatment of the patients either in primary and community health centres, and referral centres may require management of airways, breathing and circulation, control of convulsions, management of raised intracranial pressure, control of temperature, management of fluid, electrolytes and nutrition imbalances, general management, specific treatment for any of the treatable causes, sample collection and transportation, case reporting and rehabilitation.

Paediatric intensive care units

Encephalitis most of the times results in neuro muscular sequel which may be temporary or permanent and such patients require more supportive treatment for a longer period. Paediatric intensive care units (PICU) are being established in district hospitals of the JE endemic districts to reduce mortality, morbidity and disability in patients with AES/JE.

Physical medicine rehabilitation (PMR)

One of the reasons for considering JE/AES as a significant public health problem is due to the residual neurological sequelae in 30-40% of children who survive the disease and is mainly attributed to lack of specific treatment. Hence there is an increased need for rehabilitation specialists to assess and manage the disabilities. The programme has agenda to promote setting up of department of physical medicine and rehabilitation departments in medical colleges in high endemic states in the country. To counsel the care takers of the patients with disability following AES/JE, it is planned to set up counseling centres at district hospitals.

JE/AES surveillance

JE and AES Surveillance implies a continuous monitoring of all factors influencing transmission and effective control of JE/AES, building up capacity for early recognition of impending outbreaks or epidemics. The surveillance system collects information on epidemiologic, clinical, laboratory, veterinary and entomological parameters from the identified sites on a regular basis. Such information is compiled at the state programme officer level to predict district wise outbreak and to take preventive measures.

Sentinel surveillance

All health institutions including public and private in endemic areas notify suspected encephalitis cases based on standard case definitions in a standardized reporting format to the higher authorities. These identified sentinel surveillance sites may have laboratory facilities or may be without these facilities. At the district level the surveillance officer will study the received reports and reconcile data with IDSP to identify outbreaks.

Case Investigation

Notified JE/AES cases are verified and investigated by surveillance medical officer or district level epidemiologist within 48 hours of notification. The history is obtained, physical examination is made and collection and transport of laboratory specimens to the identified laboratory is coordinated.

Laboratory based surveillance

In situations where it may be difficult to differentiate JE from other causes of AES laboratory confirmation is considered essential. Such situations require the support of a well equipped laboratory to test blood and CSF. For JE sero-surveillance network of laboratories have been established with capacities ranging from confirmation of JE cases by IgM capture ELISA to virus isolation from brain tissue, antigen detection by immunofluoroscence and nuclic acid detection by PCR.

Veterinary based surveillance

JE is a disease of animals where pigs and

birds, mainly cattle egrets and pond herons are the natural hosts. The virus is usually maintained in the enzootic form and may appear as a focal outbreak under specific ecological conditions. Man gets infection as a result of a spill-over from the zoonotic cycle. Migratory birds may be involved in the transfer of virus from one region to another. Cattle's develop antibodies to JE virus and hence the large population of cattle in India as compared to pigs may inhibit the spread of JE infection. Pigs are 'amplifier hosts' as they allow multiplication of the virus in their blood, do not manifest with any overt symptoms and are capable of infecting a large number of mosquitoes. Animal husbandry department helps in the surveillance by collecting random samples of sera from the animals which are natural hosts for JE. Samples are subjected to serology tests to ascertain transmission of JE virus and in localities where HI antibody carrier pigs are high and IgM antibody is detected, such areas are to be considered at risk of JE virus infection. Generally a process of 30 samples of pig sera are collected on regular basis for generating data for early warning signals. The laboratory analysis of the host animal sera samples are done in association with veterinary department.

Vector surveillance

JE virus has been isolated from 17 mosquito species in the country and mainly from Culex vishnui group consisting of Cx. tritaeniorhynchus, Cx. vishnui and Cx. pseudovishnui. For planning vector control measures in JE endemic areas entomological surveillance is undertaken to identify the mosquitoes, to monitor vector abundance, to detect JE virus in vector mosquitoes and to suggest appropriate vector control measures. The entomologist and insect collectors in the districts will be responsible for entomological surveillance in JE endemic areas. They will identify index villages in the district for entomological surveillance which are at least three villages in which JE has occurred in the past five years. Also, two unaffected villages will be monitored in the affected region/block. Sampling is carried out fortnightly. Larval survey, adult survey and susceptibility of the vector to insecticide is undertaken.

Larval surveys

All potential breeding sites will be surveyed and will be reported on the standard proforma. All permanent breeding sites of JE vectors would be mapped and provided to District officers for implementation of control measures. Larvae collected in the field would be reared in laboratory for emergence of adult mosquitoes for identification of vector species.

Adult surveys

In the index villages indoor/ outdoor resting collection and the dusk collection of mosquitoes will be carried out from fixed as well as random sites in indoor sites such as human dwelling/cattle sheds/mixed dwelling and outdoor situations such as bushes, plantations, standing crops, etc. by hand catch method using suction tubes. Per man hour density (PMHD) will be monitored and reported in standard prescribed format. Vector incrimination and isolation of JE virus from suspected JE vector mosquitoes would be done in collaboration with NIV Pune, CRME Madurai and NICD, Delhi.

Vector control

By nature the vectors of JE rest outdoor (exophillic), feed indoor (endophagic) and prefer cattle or pigs blood (zoophilic). As they rest outdoors and mainly are active in the twilight, indoor residual spray is not recommended for JE control. Even the various antilarval measures available are not recommended as these vectors breed in various places like ponds, paddy fields and other water bodies. It is observed that the risk of transmission increases when the human dwellings and the piggeries are situated very close to each other. Hence construction of animal sheds far away from human dwellings is recommended to reduce the transmission risk in areas prone for JE outbreaks.

ULV fogging

Currently ultra low volume (ULV) fogging is recommended for control of JE vectors and is also applicable during JE epidemics. Thermal fogging with portable mist blowers/foggers is undertaken outside human habitation, where JE cases are reported. Fogging is carried out in downwind to upwind direction and directed towards adult mosquito resting sites like bushes, tree-shaded areas and other outdoor resting in peri domestic habitats. ULV fogging is carried out only under right conditions like in the late evening hours and under cool conditions when the vector mosquitoes are more likely to be active. In situations of outbreak fogging applications are carried out at 7-10 days interval till a significant reduction in vector densities is achieved. Under the programme Malathion and Pyrethrum formulations are used for fogging applications. For thermal fogging 5 % Malathion in kerosene/diesel is used (1 litre of technical Malathion in 19 litres of diluents). Generally around <0.5 litres per hectare is applied to a maximum of 1 to 1.5 km radius from the epicenter of outbreak.

Personnel protection against mosquito

Personnel protection measures reduce man vector contact and may reduce disease transmission. Hence IEC activity to use measures for personnel protection is part of the programme. Mosquito coils, electric vaporizer mats and liquid vaporizers and pyrethrum space sprays are extensively marketed and are being used for personal protection against mosquitoes. Properly covering the body with clothing will reduce man mosquito contact. Mosquito repellants in the form of chemical creams are also promoted

JE outbreak management

Monitoring outbreaks

Monitoring for the early warning signals to predict a JE outbreak relies on information collected from various sources. It includes prediction of high rainfall by the meteorological department, an unusual increase in the adult vector density, relative increase in pig population and water frequenting birds, detection of virus in animal hosts and mosquitoes, and microanalysis of epidemiological data of the district for the last ten years to predict areas at risk for an outbreak of JE. The monitoring reports are sent by the health authorities to the programme directorate monthly in the inter-epidemic period and weekly during the transmission season and epidemic periods.

Outbreak investigation

Investigation of an outbreak requires a system to receive early warning signals and to confirm the diagnosis. In low JE endemicity areas even a single suspect JE case is to be investigated. Whereas in JE endemic areas there should be an unusual increase in suspected JE cases compared to the normal transmission range. The steps essentially are to define the outbreak; assess of the number of suspected cases in the area to confirm the outbreak; delineation of the area involved in outbreak; investigation of reported cases in the case investigation forms; line listing of cases with their age, gender, date of onset of fever and other symptoms in a chronological order and severity of illness of the cases and deaths; laboratory confirmation of suspected cases; assessment for presence of pigs, cattle, poultry in the near vicinity of suspected cases; vector surveillance; analysis and report on the distribution and risk factors associated with the outbreak; and submission of a detailed report of the outbreak to the directorate of NVBDCP.

Preparation for outbreak management of JE

Anticipatory preparations are made under the programme for availability of drugs, equipments and trained medical, nursing and paramedical personnel. CHCs, district hospitals and medical colleges are identified for case management well before the JE transmission season. Rapid response teams consisting of experts in epidemiology, entomology, microbiology and medicine are constituted for investigation of an outbreak and containment of an outbreak. Peripheral institutions will have provisions for technical malathion, fogging machines, health education materials, preliminary laboratory investigations and transportation of cases to referral centers before the transmission season as part of outbreak management preparation. Peripheral staffs are oriented towards case detection, reporting of cases in prescribed formats, immediate case management and follow up for laboratory confirmation.

Outbreak containment

Once warning signals of an outbreak is received disease control measures and investigation of the suspected outbreak is simultaneously conducted. The rapid response team is mobilized into action. Cases are referred from the periphery to the identified referral centres. Daily monitoring of the outbreak, cases and deaths are to be reported to state health authorities. The PHC doctor and district health officials must be aware of the disease profile in their area. Since the number of AES cases does not exceed more than 2 cases, the local health personnel and the community at large must be alerted about reporting occurrence of any fever case with altered sensorium. Hence involvement of key members of the community is essential for community participation. Vector control measures by ULV fogging using malathion technical is to be carried out immediately in the affected villages. Community education to use bed nets, wear full sleeved clothes, use of mosquito repellants and to keep piggeries away from human habitations is to be intensified.

Monitoring of the programme

Successful implementation of disease control porgrammes largely depends upon a strong supervision and monitoring mechanism. It requires clear basic data forms which are to be filled up appropriately and analysed properly for providing feed back to the health authorities. Consultants under the AES/JE control programme at state level and district level are to work closely with VBDCP for monitoring, supervision and surveillance. They have to make regular field visits to ensure programme implementation and to provide technical support to

the staff. They have to ensure timely data analysis, presentation and interpretation for surveillance. They should provide technical support to programme officers and health officers for preparing district plans for control of JE/AES. They have to seek and ensure involvement of state administration, NGOs, community based organizations (CBOs) and the health and non-health private sectors under various schemes.

Conclusion

The profile of causation of AES has shown newer infectious and toxic causes apart from JE. The complex eco-epidemiological findings of JE/AES have lead to additional strategies in prevention beyond vector control and JE vaccination. Health sector plays a major role in co-ordination with departments of water and sanitation, social welfare, women and child development and HUPA in prevention and control of JE/AES.

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