Effectiveness of introduction of JEV vaccination into routine immunization program in a tribal district of Odisha

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ABSTRACT

Background: A severe outbreak of Japanese encephalitis (JE) and acute encephalitis syndrome (AES) with high case fatality among tribal children was reported from Malkangiri district of Odisha, during September to November 2016 affecting 336 children with 103 deaths. Following the outbreak, a mass vaccination campaign was introduced in Malkangiri district in 2017. In 2018, the JE vaccine was introduced into the routine immunization program as per National Immunization Schedule. Our study surveys the JE vaccination coverage among children of Malkangiri and the incidence of JE cases for a period of three years. Methodology: The current study was conducted by establishing prospective and retrospective AES surveillance system and household vaccine coverage surveys in Malkangiri district. In the target population, the vaccination coverage survey was undertaken and also additional immunization coverage data from sub-centers was collected. Results: After 2016 JE outbreak, a mass vaccination campaign was carried out in children up to 15 years of age, where 96% of children were covered in the district in 2017 and only four AES cases were detected. Under routine immunization program, the vaccine coverage for the year 2018 was 68% for JE-1 dose and 37% for JE-2 dose. There were 8 AES cases detected in 2018 out of which four children died. Vaccination coverage for 2019 was 97% for JE-1 dose and 84% for JE-2 dose. The AES cases detected in 2019 was nil. Conclusion: Vaccination against JEV and AES surveillance systems has an important role in prevention and control of AES outbreaks.

Keywords: Acute encephalitis syndrome, immunization, Japanese encephalitis disease, Japanese encephalitis virus, surveillance, vaccination

Introduction

Japanese encephalitis (JE), the primary form of viral encephalitis of Asia, western Pacific countries, and northern Australia is a zoonotic disease. The JE is caused by the Japanese encephalitis virus (JEV), which belongs to Flavivirus, a single-stranded, positive-sense RNA genome of 11 kb in length, spread by the bite of infected Culex tritaeniorhynchus and Culex vishnui mosquitoes.[1,2] The major vertebrate amplifying hosts of Japanese encephalitis are pigs and wading birds. Common signs of infection include headache, vomiting, fever, confusion, and seizures. In more severe cases, the infection can cause brain swelling. As JE surveillance is not well established in many countries, and laboratory confirmation is challenging, the exact level and prevalence of the infection is not well understood. About 20–30% of clinical cases of JE are fatal among children aged 0–14 years and up to 30–50% of survivors have significant sequelae.

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complications in the central nervous system. Researchers have estimated that 67,900 clinical cases are reported annually, and 13,600 to 20,400 cases are found dead.

**Japanese encephalitis** is epidemic and sporadic encephalitis in India and has been reported from around 171 districts of 19 states. In 1955, the JE was reported for the first time at Vellore, Tamil Nadu, India via a serological survey and the first outbreak occurred in 1973 at Burdwan district of West Bengal. One outbreak of JE was accounted in 1989 from the Rourkela, Sundergarh district of Odisha. In 2005, 5,737 clinical cases and 1344 deaths were reported from Uttar Pradesh. Cx. tritaeniorhynchus & Cx. seudovishnui are the main mosquito vectors and Anopheles subpictus is a secondary vector in India. The World Health Organization (WHO) recommends the implementation of JE vaccine in combination with cleanliness and good agricultural practices to control the outbreak of Japanese encephalitis and for prevention in rural areas known to be high risk for JE virus (JEV).

In Odisha AES cases due to JEV has been confirmed in outbreaks from tribal-dominated districts like Malkangiri, Keonjhar, Mayurbhanj and other districts like Jaipur and Puri causing high mortality in children. JE has also been reported in sporadic form in 10 out of 30 districts of the state covering both coastal and tribal areas. This reflects a higher population at risk of JEV infection and related mortality. Recently in 2016 (Sept – Nov) large no. of AES cases with high mortality in Malkangiri raised public health concern. Meanwhile, mass vaccination campaign has been introduced in children between 1-15 yrs in Malkangiri in January 2017 to reduce the annual disease incidence of JE. As per National Immunization Schedule, in 2018 the JEV vaccine was introduced in the routine immunization program as a two-dose strategy with the first dose (JE-1) given 9–12 months aged children and the second dose (JE-2) at the age of 16–24 months. The current study intends to undertake surveillance for AES cases in the context of JEV vaccination and provide support to this emerging health problem. Through retrospective and prospective surveillance, AES cases were enumerated, and viral etiology was investigated. We will evaluate the JE vaccination coverage through immunization record review and sample survey and investigate on the number of JE cases in the district before and after the introduction of the immunization program.

**Methodology**

**Study area**  
Malkangiri is one of the districts of Odisha covering an area of 5,791 sq. km, it lies between 17 degree 45” N to 18 degree 40”N latitudes and 81 degree 10”E to 82-degree E longitude. Malkangiri district has a population of 612,727. The district has a population density of 106 inhabitants per square kilometer (270/sq mi). Malkangiri district is a very remote part of Odisha, in context to distance (around 700 km) from the state headquarter. Moreover, 57.43% of the inhabitants belong to the indigenous tribal population.

**Prospective surveillance for AES cases in the district**  
A systematic framework of identifying any case of AES admitted to CHCs or district hospital of Malkangiri district was established. Sample referral mechanism and laboratory confirmation at district lab or VRDL, RMRC was ensured for timely confirmation and feedback to the health system. Cases identified in the hospitals were traced back to the community setting, looking for sub clinical and clinical cases through a fever survey and contact investigation.

**Laboratory investigation**  
JEV infection was investigated from blood and CSF samples.

**Sample collection, transport and laboratory investigation**  
From each AES case patient around 5 ml of blood was collected in clot activated vactainer and the serum was used for detection of IgM antibody against JE virus. Trained pediatricians attempted collection of CSF (~2 ml) from all admitted patients keeping in view the safety of patients. In case CSF is not available serum IgM with clinical evidence of AES diagnostics were considered of JE infection detection. The samples were also subjected to diagnosis of Dengue (IgM, NS1 Antigen), Chandaipura (RT PCR), Entero Viruses (IgM and RT PCR), Measles (IgM and RT PCR), VZV (IgM and PCR), Chik (IgM and RTPCR) infections by standardized protocol.

**Training**  
Training of the health staff and project staff was undertaken before initiating the surveillance and subsequently every year to maintain uniformity and quality in the process. Protocol of training for investigation and project staff and case identification to ASHA, Anganwadi workers were provided. District lab technicians were trained regarding sample collection, transportation and different laboratory tests and adherence to Standard Operating Protocols SOPs.

**Retrospective surveillance for AES and JEV infection in the district**  
All the reported AES cases in the district since 2016 were enumerated. Using verbal autopsy tool and structured questionnaire for deaths and survivors in the recent outbreak in Malkangiri, information was collected on the mode of death, cause of death, laboratory confirmation on etiology and any other causal risks or association, especially disease sequela from the survivors. Around 100 deaths and 200 survivors were evaluated in detail by assessing the hospitals records and individual information obtained through questionnaire.

**Assessment of JE vaccination coverage**  
**Study design**  
The survey, which is cross sectional, was conducted in all the blocks of the district Malkangiri. The data used for analysis in
this study were obtained from Integrated Disease Surveillance Programme (IDSP), Malkangiri.

**Study population**
In 2017 the target population constitute of children 1-15 years of the district for the mass vaccination campaign, and 2018 onwards after the JE vaccination was introduced in the routine immunization program where the children of 9-12 months and 16-24 months were taken as target population to determine the immunization coverage survey of JE-1 and JE-2 dose from the record of the district health department.

**Sampling framework**
Community survey following Probability Proportional to size (PPS) sampling approach was used. From total villages \( n = 2263 \), 41 villages were selected using PPS sampling method. From each village 15 households were selected by systematic sampling method and if any house had more than one child in age group between 1 and 15, then only one child was selected by using KISH selection method.

**Sample size**
Taking expected coverage rate of 70% and confidence interval of 95%, a sample size of 323 was considered. To overcome the design effect, a total of 650 \( (323 \times 2) \) was taken as the sample size for the study.

**Data collection**
A structured questionnaire was used to collect the history of immunization from the household level by door to door visit and verification of immunization register maintained by the health staff.

**Data entry and analysis**
A data sheet was prepared using Microsoft Excel for surveillance and immunization coverage data analysis. From surveillance data, age wise annual incidence of AES cases, proportion of cases with JEV infection and other viral etiologies and case fatality rate was calculated during the study period. JE vaccine coverage rate was calculated and JEV incidence was compared with pre and post vaccination periods.

**Results**

**Vaccination coverage**
Following the 2016 outbreak, the Government of Odisha introduced the JEV vaccine (live attenuated JE vaccine SA-14-14-2) in the Malkangiri district, as a mass vaccination campaign targeting around 192,000 children aged between 1 to 15 yrs. The coverage of the 2017 mass campaign was around 96% (185,000 children) which was reported from Integrated Disease Surveillance Programme of IDSP, Malkangiri. The coverage of vaccination among the blocks of Malkangiri district were 96% for Kalimela, 94% for Kudumuluguma, 96% for Malkangiri, 100% for Mathili and 94% for Podia [Figure 1]. JEV vaccine was introduced in the routine immunization program as a two-dose strategy in 2018. The total vaccination coverage that year of JE-1 was 68% and of JE-2 was 37% which was significantly low for JE-2 dose [Figure 2]. In this period the block wise vaccination coverage of both JE-1 and JE-2 were Kalimela (71%, 28%), Khairaput (72%, 29%), Korkunda (66%, 36%), Kudumuluguma (65%, 44%), Malkangiri (65%, 28%), Mathili (65%, 47%) and Podia (79%, 49%).

**Vaccination status and JE cases**
During the 2016 outbreak, 336 AES cases were observed in children, out of which 146 (43%) were laboratory confirmed with presence of JE IgM. The cases were spread over 173 villages of Malkangiri, Odisha. It was seen that the majority of 52.7% of patients were in the age group of 1-3 years, followed by 30.48% cases between 3-5 years. For the 336 cases, the mean age was 3.8 years, the median age was 3 years, and the range was between 4 months to 13 years. With 103 deaths among the cases, the case fatality rate was high up to 30% which raised a public health concern. The significant decline of JE cases in 2017 could be attributed to the successful mass vaccination campaign which might have played a major role in control of JE cases [Figure 4]. The vaccination coverage of JE under the Universal Immunization Programme was significantly low in 2018 giving rise to 8 JE cases among children with 50% mortality. All the cases of 2017 and 2018 were laboratory confirmed. There was high vaccination coverage for both JE-1 and JE-2 in 2019, which resulted in nil JE case that year. It can be ascertained that the vaccination of JE in a particular year plays an important role in controlling the rise of its cases.

**Discussion**
Japanese Encephalitis is a viral disease of major public health importance. Areas with rice fields, where mosquitoes...
Vaccine Coverage

Numerous studies have shown that the routine use of JEV vaccines in campaigns and routine immunization, no major improvement have been reported in context to JE epidemiology in India.[23] There are contradictory reports concerning safety and efficacy of this vaccine in India. The single dose efficacy of SA-14-14-2 JEV vaccine was recorded to be as high as 98.5% following 12-15 months of vaccination in Nepal.[23] An unmatched case-control study among children aged 24-54 months found 84% effectiveness of this vaccine despite a low coverage 51% from Gorakhpur division in India.[24]

Since the JE IgM ELISA kits have very low sensitivity, around 20-60%. The rate of false-negatives is so high that if these kits are used for a diagnostic procedure in a population, then 40-83% of JEV infections will not be detected.[25] The cross-reactivity of IgM antibodies to the conserved immunogenic epitopes on the flavivirus envelope protein, specificity of JEV IgM-ELISA can be low, particularly in areas where multiple flaviviruses such as Dengue IgM co-circulate and the population is likely exposed.[26,27] This makes the laboratory diagnostic of JEV very challenging.

For many countries, JE surveillance has been developed or enhanced over the last few years. National surveillance programs have been developed in Brunei, Democratic People’s Republic of Korea and expanded in India and Nepal. Several countries are using laboratory diagnostic testing for suspecting the JE cases by using both serum and CSF specimens. Good surveillance system will be needed in to determine whether morbidity and mortality from JE are reduced through this strategy of a mass vaccination campaign followed by routine immunization or whether further mass vaccination campaigns may be necessary, as is the case in Nepal.[28] The need to develop and improve the standard of JE surveillance is therefore well recognized.[29,30] It is uncertain if the ongoing rise in the occurrence of AES/JE is primarily related to poor vaccination coverage, vaccine ineffectiveness, emergence of a new strain or maybe a combination of those factors. It calls for robust epidemiological investigations of JE outbreaks,[31] in addition to largescale postvaccination sero-surveillance studies to resolve some of these issues.[21]
Conclusion

JE is a vaccine-preventable disease for which there are no effective control or treatment strategies. Very few evidence are there to support a reduction in JE burden through interventions apart from the vaccination of humans. Improving the two-dose JE vaccination coverage can control or eliminate JE disease in many areas. Accurate laboratory diagnosis of JEV infections and differentiation is absolutely necessary for public health decision making. As the virus detection sensitivity is low, therefore a negative result by JE IgM ELISA cannot be used to rule out JE cases. Although the present post vaccination study documents the decrease of cases in the tribal district of Malkangiri, it calls for a continuous surveillance to understand the long-term efficacy of the vaccination in high endemic districts.

Summary

The current article focuses on the importance of inclusion of JE vaccine into routine immunization of children. JE and AES outbreaks can be controlled and prevented through vaccination and establishment of surveillance systems for the disease. Primary healthcare physicians are the first to contact for treatment of any disease among children. Hence their knowledge and involvement to routinely immunize children for JE at primarily level is of at most importance to prevent such outbreaks.

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Ethics approval

The Institutional Human Ethics Committee of the ICMR - Regional Medical Research Centre, Bhubaneswar approved this study, and the Indian Council of Medical Research has reviewed and approved the study design and protocols.

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Key message

Vaccination against JEV and AES surveillance systems has an important role in prevention and control of AES outbreaks. Physicians and community health workers can play an important role in saving the lives of children by maximizing the coverage of vaccination and creating awareness among the community members.

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Conflicts of interest

There are no conflicts of interest.

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