

## JE vaccine: Hope on the anvil

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*Over 400 people, mostly children, in North India succumbed to acute encephalitis syndrome in 2011 alone. Repeated immunization efforts have not yielded expected results, and as Indian companies make a foray into production of the Japanese encephalitis vaccine, there is hope for improvement in the situation*

Each year the monsoon rains bring with them a sense of despair and helplessness among the people in Northern India because of the advent of Japanese encephalitis (JE). This incapacitating disease mainly targets children below the age of 15, with 70 percent of the cases resulting in either death or crippling long term neurological disorders. It is said to be endemic in countries such as China, Burma, Thailand and Sri Lanka and in parts of India. It has been estimated that over the past 60 years, JE has infected approximately 10 million children globally, killing three million and causing long term disability in four million children.

Viral encephalitis which causes inflammation of the brain, can be broadly classified into Enteroviral encephalitis, caused by consuming contaminated water and Japanese encephalitis, propagated by mosquitoes. The debilitating disease of Japanese encephalitis is caused by the JEV virus belonging to the Flaviridae genus. Transmitted via mosquitoes, with pigs and water birds acting as amplifying hosts for the virus, Japanese encephalitis is the leading cause of viral encephalitis in Asia with 30,000-to-50,000 clinical cases reported annually.

The data surrounding Japanese encephalitis in India is shocking, to say the least. Since the first case was reported in 1952, several outbreaks have been reported in the states of Uttar Pradesh, West Bengal, Assam, Andhra Pradesh, Karnataka, Bihar, Tamil Nadu, and Haryana. According to the National Vector Borne Disease Control Programme, since 2003, over 27,000 cases of JE have been reported, causing over 5,800 deaths in India alone. The fact that the disease mainly affects the poorer sections of society has been cited as the reason behind the government's apparent lack of proactive stance in combating this disease. Things changed in 2005 when an epidemic like situation arose in North India where, close to 6,000

cases were reported in Uttar Pradesh alone, causing the death of 1,300 children. This led to a mass immunization program by the Government of India which saw over nine million children being vaccinated in 2006 and the introduction of a plan for a mass vaccination program in 104 endemic districts in 11 states of India in a phased manner for five years.

### **The progress so far**

Taking stock of the impending need for a JE vaccine, Central Research Institute (CRI), Kasauli, Himachal Pradesh, was the first organization to manufacture a Japanese encephalitis vaccine in India. The CRI developed an inactivated vaccine using a mouse brain source. The use of mouse brain cells as a culture system, however, posed many challenges, which included, the evident complications in maintaining consistency in all samples along with the difficulty in large-scale production. The production of the vaccine was stopped in 2007, when the Central Drugs Licensing Approving Authority suspended its production, following failure to abide by the good manufacturing practices guidelines that have been specified by the World Health Organization. Following the subsequent closure of CRI and two other public sector units producing vaccines on the same grounds, there was no JE vaccine manufacturing facility in the country.

The vaccine that is currently being sourced by the government is the SA-14-4-2, which is licensed and produced by Chinese company - Chengdu Institute of Biological Products. The live attenuated Chinese vaccine is being produced since 1988 and is licensed in India and other countries such as Nepal, Sri Lanka, Thailand and South Korea. Since its introduction, over 300 million doses have been administered to children in the various endemic regions around the globe.

Even though the efficacy of Chinese vaccines over other inactivated mouse brain cell-based vaccines has been proven in many studies, the method of dosage is a topic of contention. It is being given in the form of a two-dose vaccine in one or three month schedule in some countries. However, in India, it is a single-dose vaccine. Vaccination with two doses has been shown to give 100 percent sero-conversion rates or 100 percent effectivity in producing JE specific antibodies. A single dose of the vaccine was shown to have 85 to 100 percent seroconversion with 85 percent effectivity in preventing the disease, as opposed to 98 percent effectiveness that is observed in the two-dose regimen. Moreover, even after five years of use, no organized study has yet been carried out in India to test the efficacy of this vaccine.

### **The promising future**

The growth of the Indian vaccine industry during the last few years has encouraged many to try and produce safe and efficacious Japanese encephalitis vaccines indigenously. Prime examples of industry-academia relations are the collaborations of National Institute of Virology (NIV) with Bharat Biotech and the National Institute of Immunology (NII) with Panacea Biotech.

Speaking about the collaboration with NIV, Mr Sai Prasad, vice president, business development, Bharat Biotech says, "Dr Milind Gore who heads the satellite center of NIV at Gorakhpur, Uttar Pradesh, isolated and characterized the Indian strains of JEV and then transferred them to Bharat Biotech to further develop them. We are very thankful to Dr A C Mishra, director, NIV, who helped us immensely in this collaboration and also helped us design the quality control assays for the vaccine." The vaccine is currently in phase III trials and is expected to be launched in the next one-to-two years.

Dr Sudhanshu Vrat, director, NII, who is involved in the research, elaborating on the challenges in doing research on the JEV, says, "One of the major challenges in reducing the cost remains the fact that the JEV is classified as a biosafety level-3 (BSL-3) biological entity by the Center for Disease Control (CDC), and India in the absence of any similar regulatory body has adopted the same classification even though the virus is endemic in most regions of India. This leads to an increase in the production costs and eventually the price of the vaccine." The NII has a collaboration with Panacea Biotech for the further development of the vaccine.

However, Biological E, Hyderabad, has emerged as the leader, being the first to introduce the vaccine. Having completed phase III trials for the JEV vaccine, it has received manufacturing licenses for the same. In collaboration with Intercell, who had carried out the initial development for its use as a traveler's vaccine, Biological E further conducted the clinical development and designed the production for endemic use. Ms Mahima Datla, senior vice president, says, "We expect to have a product launch of our Japanese encephalitis vaccine by January 2012 in the affected areas and all over India by the end of this year. We are looking to initially launch it in the private market and hope to be able to supply it to the government."

All the vaccines that are being developed by the collaboration of NIV-Bharat Biotech, NII-Panacea Biotech and Biological E are inactivated ones based on the Vero cell line, which makes these generally more efficacious and easier to produce on a large scale.

In addition to India, other countries that have reported cases of Japanese encephalitis such as Nepal, Thailand, Burma, Bangladesh also provide distribution markets for the vaccine. European countries, which do not have a presence of this virus,

already have traveler's vaccines available, manufactured by Sanofi.

It is hypothesized that a larger number of players in this segment would definitely help in reducing the eventual price of the vaccine, thus ensuring the wider distribution of the vaccine. The inclusion of the Japanese encephalitis vaccine in the universal immunization programme, especially in the endemic areas, could further ensure that every child is immunized against the virus. A case in point is that of Sri Lanka which, in 2009, decided to include the Japanese encephalitis vaccine in its immunization program in order to ensure that every child in the country was immunized. Reports of the number of infections decreasing are indicators of the positive results of a wide scale immunization program.

An integrated vaccination strategy along with improvement in the sanitation conditions, are urgently needed to help prevent the tragedy of JE that strikes every year.

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