

An Update on JE Vaccine Development and Use

Pankaj Sharma*, **Veena Mittal***, **Mala Chhabra***, **Priyanka Singh****, **Lakhvir Singh Chauhan*,****, **Arvind Rai****

Abstract

Japanese encephalitis (JE) is an emerging and re-emerging arboviral infection of global significance. Its causative agent Japanese encephalitis virus (JEV) is the leading cause of viral encephalitis in Asia, Southeast Asia and Pacific. Nearly 3 billion people living in JE endemic areas account for 10000- 15000 deaths annually. The disease has high fatality rate (~30%) and nearly 50% survivors develop permanent neuropsychiatric sequelae. There is no specific treatment for JE. Vaccination is the only effective strategy available for prevention and control of JE. The wider availability and inclusion of JE vaccination in the national immunization programme in many of the affected countries have resulted in better prospects for control of JE. This review is an update on vaccines currently available, their development, recommended immunization schedule for them as well as the upcoming challenges related with cross-protectivity against heterologous genotypes.

Keywords: Japanese encephalitis, vaccination, immunization, cross-protectivity.

Introduction

Japanese encephalitis is a zoonotic, arboviral infection and the leading cause of encephalitis. It is one of the most important vaccine preventable cause of flaviviral encephalitis in Asia, Southeast Asia and Pacific.¹ Nearly 3 billion people live in JE endemic countries, which accounts for 10000- 15000 deaths reported each year.^{1, 2} The estimated annual incidence of JE is found to be in the range of 50000 to 175000 cases, depending upon the age group, geographical area, and immunization status.^{3, 4} The principle vectors for Japanese encephalitis virus (JEV) transmission are mosquitoes of *Culex vishnui* group.⁵ In Eastern, Southern and South-eastern Asia *C. tritaeniorynchus* is the principle vector. However in Indian studies, role of secondary vectors such as *Anopheles subpictus*, *An. pedtaeniatus* and *Mansonia uniformis* has also been found to be important.⁶ Japanese encephalitis mostly affects children between the age group of 3- 15 years. Nearly 20%– 30% of the cases are fatal, while 50% cases develop

permanent neuropsychiatric sequelae.⁷ At present, there is no specific treatment for Japanese encephalitis and vaccine administration is the only means for effective sustainable prevention. Currently there are three cell culture- derived vaccines available, which are safe and effective but requirement of multiple doses, effective transportation of vaccine to rural areas, and cross-protectivity against heterologous genotypes are some of the major considerations for control and prevention of JE.

Virus

JE virus belongs to JE serocomplex of *flavivirus* (Family: *flaviviridae*) which includes several other etiological agents of encephalitis such as West Nile virus, Murray Valley encephalitis virus and St. Louis encephalitis virus. It is an enveloped virus of nearly 50 nm diameter containing plus sense RNA of nearly 11 kb in length flanked by short non-coding region at 5' and 3' ends. The RNA encodes for three structural (C, prM and E) and seven non-

*Division of Zoonosis, National Centre for Disease Control, Delhi, India

**Division of Biotechnology, National Centre for Disease Control, Delhi, India

Correspondence to: Dr. Veena Mittal, Additional Director & Head, Division of Zoonosis, National Centre for Disease Control, 22-Sham Nath Marg, Delhi-110054. **E-mail:** veena_m12@yahoo.com

structural (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) proteins which are formed after translation of genome in cap- dependent manner into polyprotein precursor which are further cleaved by host and viral protease into functional proteins.⁸ While structural genes are important for virus nucleocapsid and envelope formation, the non structural genes are associated with virus assembly, RNA replication, host immune response, and neuroinvasiveness.^{9, 10, 11, 12, 13}

The virus originated around the 16th century in Indonesia– Malaysia region and evolved into 5 genotypes. The GIV and GV are considered to be older genotypes while genotype G1, GII and GIII are recently evolved.^{14, 15} Different genotypes are found in different geographical area. All 5 genotypes have been isolated from Indonesia-Malaysia region, while in Japan-Korea- China region GI, GIII and in India- Sri Lanka- Nepal region only GIII have been found to be the circulating genotypes. In recent time, emergence of genotype V in China and South Korea and replacement of GIII by GI in some countries including India has been observed.^{16, 17, 18}

Vaccines

Prevention of JE consists of personal protection from mosquitoes, vector control, and vaccination. Human immunization through vaccination is the most effective way for long term sustainable protection against JE virus. The 4 different types of vaccine developed for JE are (1) Mouse brain derived killed inactivated (2) Cell culture derived live attenuated (3) Cell culture derived killed inactivated (4) Genetically engineered live-attenuated chimeric vaccine.

With the isolation of JE virus, efforts were made to develop vaccines for prevention of JE infection. The first vaccine was prepared by utilization of mice and became available in 1950s. With the progress in cell culture techniques, the vaccine production was undertaken in controlled and predictable environment. In recent years, recombinant technology based chimeric vaccines and protein subunit vaccines have also been developed. Chimeric vaccines are based on yellow fever virus 17D and have shown promising future towards vaccine development.

Mouse brain derived killed-inactivated vaccine

The first vaccine was derived from formalin inactivated, infected mouse brain homogenate based on Nakayama strain of JEV which was the first isolate, recovered from JE patients in 1935.¹⁹ The vaccine was developed from intracerebral inoculation of suckling mice with the virus. It was the first generation vaccine and was first used in Japan in 1954.²⁰ In 1989, the strain used for vaccine production was changed to Beijing-1 considering it to be more efficacious against a wider range of JEV strains.²¹ However, a large scale clinical trial in Thailand showed equivalent protection offered by either monovalent (Nakayama strain) or bivalent (Beijing and Nakayama strains) vaccines with a combined efficacy of 91%.^{20, 22} The Nakayama strain based vaccine was marketed as JE-VAX and used in several countries including Korea, Vietnam and India.²³ It was available in lyophilized form that is stabilized with gelatin, sodium glutamate and preserved with thimerosal.²⁴ Although the vaccine was highly immunogenic and effective but there were some limitations such as high production cost, need of 2- 3 primary doses before booster dose, neurological side effects and allergic response. In some cases, acute disseminated encephalomyelitis was also observed.^{25, 26} In spite of all the drawbacks, this vaccine was used successfully to control JE in many countries like Thailand, Korea, Taiwan, Vietnam, India, and Sri Lanka.²⁷ Primary immunization schedule consisted of first dose at the age of 1- 3 years and second dose 1- 4 weeks later. Thereafter, one booster dose given a year after the primary vaccination followed by repeated booster doses at every 1- 3 years up to the age of 10- 15 years.²⁸ With the development of cell culture derived vaccine, the production of JE-VAX was discontinued in 2006.²² In India, Central Research Institute, Kasauli stopped its production in 2008.

Cell culture derived live- attenuated vaccine

The first cell culture derived live attenuated vaccine was developed and licensed in China in 1988. The vaccine was based on attenuated form of JEV SA14 strain named as SA14-14-2 and produced on primary hamster kidney (PHK) cell line.²⁹ This second generation

vaccine proved to be highly immunogenic as high protection efficacy was observed after one dose (85%- 99%) and complete protection efficacy was observed after 2 doses (98%).^{27, 30, 31} The presence of neutralizing antibodies after 4 years of single dose was observed in nearly 90% cases.³² The vaccine has been licensed in many Asian countries including India, Nepal, Thailand, Sri Lanka, South Korea, Cambodia, and Myanmar.³³ Recently, the SA14-14-2 has been incorporated into the national extended program for immunizations in Nepal and China.²⁷ The vaccine is available in a 5- dose vial as a lyophilized milky- white crispy cake and used after reconstitution with supplied diluents. The immunization schedule consists of 2 doses one year apart in children (9- 12 months) and a booster dose at school entry age.³⁴ In 2013, WHO added SA14-14-2 developed by Chengdu Institute of Biological Products into the lot of prequalified vaccines.³⁵ Despite the fact that SA14-14-2 provided significant contribution towards JE prevention, use of this vaccine has been restricted to Asia because of the possible risk of attenuated SA1414-2 virus reverting to virulent form.

Government of India introduced SA14-14-2 under a pilot project in 2006 for immunization of children in hyper- endemic district viz, 7 districts in Uttar Pradesh, 2 in Assam and 1 each in West Bengal and Karnataka. The vaccination was carried out in a campaign mode targeted towards children aged 1- 15 yrs as a single subcutaneous dose.³⁶ Based on the experience, vaccine has been introduced under the programme for routine immunization in JE endemic areas. The dose (0.5ml) is given subcutaneously with 2 doses schedule, first dose given at 9 months with measles immunization and second dose with DPT booster at 16- 24 months of age.^{37, 38} No serious adverse events have been reported with this vaccine.

Cell culture derived killed- inactivated vaccine

A PHK cell derived Beijing-3(P3) strain based inactivated vaccine was first developed in China and gradually it became the country's principle vaccine for control of JE. Since its development from 1968 to 2005, nearly 70 million doses were administered in China.^{27, 39} However absence of purification step in

manufacturing process and non- approval of PHK cells by WHO for human vaccination were the major reasons, due to which the use of this vaccine was limited to China.²⁴ Efforts were made to switch over from PHK cell derived vaccine to African green monkey kidney (Vero) cell derived vaccine as this cell line is considered to be safe for human vaccine production.⁴⁰ In 1998, Beijing-3 strain based Vero cell derived inactivated vaccine was licensed in China. Similar vaccine based on Beijing-1 strain was licensed in Japan and is available under the two trade names: JEBIK V, approved in 2009, and ENCEVAC (also known as KD-287 or JEIMMUGEN INJ.) approved in 2011.²¹ A new inactivated JE vaccine IC51 was also developed which was based on attenuated SA14-14-2 strain and was produced on Vero cell line. IC51 is licensed and marketed since 2009 under one of the three trade names (IXIARO, JEEV, and JESPECT) in many countries, including Australia, Canada, Europe, Hong Kong, Switzerland, US and India. JEEV, the Indian variant of IC51 was approved by Drug Controller General of India (DCGI) and was licensed in 2011 to prevent JE infection in children and adult population.^{38, 41} IC51 provided new options and benefits to endemic countries because of its improved safety profile and lower dosage requirements. The vaccine was proved to be highly effective when 2 doses given 28 days apart as primary immunization. Single booster dose after 1- 2 year of primary immunization can be sufficient for complete seroconversion. In US and Europe, initially the vaccine was approved only for use in adults (≥ 17 y). However, in early 2013, paediatric use of IC51 has also been approved for children (2 mo to < 17 or 18 y).⁴² In studies, IC51 has been proved to be highly immunogenic and more favourable as compared to mouse brain derived killed inactivated vaccine, JE-VAX.^{43, 44} A study carried out to explore the cross reactive potential of the inactivated vaccines against non vaccine genotypes in European travellers showed protective level of cross reactive neutralizing antibodies to genotypes I-IV after a primary series with inactivated SA14-14-2 based and Nakayama based vaccines, implying good cross reactive capacity for both the preparations against all major genotypes currently circulating.⁴⁵ In subjects vaccinated with JE-VAX, a single dose of IC51 was found to boost immunity suggesting that Nakayama and SA14-14-2 strains of JEV are

immunologically similar to induce significant level of cross reactive immune response indicating the possibility of interchangeability of JE vaccines.⁴⁶ India has launched an indigenous vaccine against JE virus in 2013. The Vero cell derived, inactivated vaccine JENVAC is based on 821564-XY strain of JE virus isolated in Kolar, Karnataka. The vaccine is stated to provide more than 95% seroconversion only after 28 days of administration.⁴⁷

Genetically engineered live- attenuated chimeric vaccine

A Chimeric YF-JE virus was produced by replacing prM and E genes of YFV 17D with the corresponding genes of live- attenuated SA 14-14-2 strain of JEV.⁴⁸ YFV 17D attenuated vaccine strain is a suitable vector for chimeric vaccine development because of its safety and efficacy and approval by the international authorities for human vaccination.⁴⁹ The Vero cells derived live attenuated recombinant vaccine (designated as ChimeriVax-JE) is marketed as one of the three trade names IMOJEV, JE-CV, and THAIJEV. It is commercially available in Australia and Thailand.^{50, 51} For immunization, only single dose is recommended over the age of 12 months, although timing and duration of booster dose is to be assessed.⁴² In studies, single dose of vaccine has shown to provide near complete (~99%) seroconversion in adults (≥ 18 y), similar to that induced by 3 doses of JE-Vax (~95 %) as early as within 14 days.⁵² A randomized, double blind, 5 years phase II study showed that 87% vaccine recipients who were seroprotected at 6th month were still protected at the end of 5 years. This rate increased to 96% among those who received booster immunization at the 6th month.⁵³ The vaccine has not found to be associated with any serious side effects. Furthermore the ChimeriVax-JE virus has found to be restricted in its ability to multiply in different mosquito species (*Culex. annulirostris*, *C. gelidus*, *C. tritaeniorhynchus*, *Aedes albopictus*, *A. aegypti* and *A. vigilax*) and so it is less likely to be transmitted from a vaccinated person to others by mosquito.^{54, 55}

Future Vaccines

Efforts are being made to develop vaccine based on Pox virus, plasmid DNA and recombinant protein. These vaccines are still in the experimental stage. Pox virus strains used for JE vaccines are NYVAC, ALVAC, and MVA (attenuated vaccinia strain, attenuated canarypox strain and modified vaccinia Ankara strain).^{56, 57, 58} For the development of plasmid DNA based vaccine prM, envelope and NS1 protein of JE virus has been found to be suitable candidates. In animal subjects, the plasmid DNA expressing these proteins has been found to be eliciting immune response.^{59, 60, 61} Efforts are also being made to develop recombinant protein based vaccines, which include expression of E protein antigenic portion in *E. coli*, fusion of 27 amino acid peptide of E protein to Johnson grass mosaic virus coat protein and fusion of E protein as alone or in fusion with prM or NS1 protein with other virus in baculovirus-insect cell system.^{62, 63, 64}

In some recent efforts, the application of reverse genetics has also been employed towards vaccine development. In reverse genetics, manipulation of genomic RNA is done to produce recombinant virus from cDNA. Full length infectious cDNA clones of CNU/LP2 strain and SA 14-14-2 strain have been produced by utilization of bacterial artificial chromosome (BAC).^{65, 66} This approach will not only be useful for development of genetically modified JEV vaccine but will also be helpful in identifying the role of various genetic elements of JEV involved in neurovirulence and pathogenesis.⁶⁶

Genetic and antigenic variations in JE virus and vaccination

Since the emergence of JE virus, genotype III (GIII) has been the most widely distributed genotype in JE endemic areas, but in the last 2 decades, replacement of GIII by GI has been observed.^{15, 67} It can be a major challenge for vaccination as currently licensed vaccines are based on GIII JEV strains (Nakayama, Beijing-1, Beijing-3, and SA14-14-2). A recent study in humans showed the reduced neutralizing potency against GI by the antibodies elicited by JE-VAX (genotype III).⁶⁸ In a similar study, comparatively lower immune response was

observed against the strains of GI and GIV, when the subjects were vaccinated with GIII based vaccines.⁴⁵ In another study, JEV strain of GI was isolated from the CSF of a patient who was vaccinated with SA14-14-2 (GIII).⁶⁹ The problem gets further complicated, as in some studies reduced capacity of neutralizing antibody against different GIII JEV strains has also been observed when the subjects were immunized with JE-VAX, SA14-14-2 and IC51.^{46, 70, 71, 72} The genotypic variations and strain specific immune response can be major challenges for vaccine development.

Conclusion

Japanese encephalitis is emerging as a major public health problem. Since its emergence in Japan, the disease was limited only to Asian countries for many years, but the first JE outbreak in 1995 in Australia confirmed the possibility of spread of disease to other parts of the world too. Maintenance of virus in natural reservoirs (pigs and wild birds) and widespread occurrence of its vector (*Culex sp.*) are the

main factors, which pose the challenges for eradication of this disease. At present, vaccination is the single most effective strategy for prevention and control of JE. Use of the first developed inactivated mouse brain derived vaccine, which played an important role in control of JE in many Asian countries has been stopped since 2006. In the current generation of vaccines, SA14-14-2, IC51, and ChimeriVax-JE hold a promising future. The vaccination schedule for JE has been included in the immunization schedule in many countries (table 1). However, as the current vaccines are based on GIII JEV strains, the efficacy of the vaccines to protect against other genotypes (GI, GII, GIV, and GV) of JEV needs to be evaluated. With the changing disease dynamics, monitoring of genetic and antigenic variations among JEV strains is essential to determine the efforts required for the development of a new generation of vaccine, which can not only provide protection from the different genotypes but also from the various strains of single genotype.

Country	Immunization programme	Strategy	Scheduled age for commencement of routine immunization	Vaccine
Cambodia	Subnational	Routine	10 months	LAV
China	National	Routine	8 months	LAV, VC
	All areas	Routine	15 months	MB
Taiwan	All areas	Routine	15 months	MB
India	Risk areas	Routine	16-24 months ¹	LAV
Japan	National	Routine	36 months	VC
Korea	National	Routine	12-24 months	MB
Malaysia	Subnational	Routine and outbreak response	9 months	MB
Nepal	Subnational	Routine	12 months	LAV
Sri Lanka	National	Routine	9 months	LAV
Thailand	National	Routine	18 months	MB
Vietnam	Subnational	Annual campaign	12 months	MB

1 = Since April 2013 first dose is given at the age of 9 months with measles vaccine.³⁷

MB = Mouse brain derived killed-inactivated vaccine

LAV = Live-attenuated SA14-14-2 JE vaccine

VC = Vero cell derived killed-inactivated vaccine

Table 1. JE immunization programme in countries with JE virus transmission risk, 2012⁷³

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Journal of Communicable Diseases
Official Publication of Indian Society for Malaria and
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