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Review of Japanese Encephalitis Vaccines in India

Kripasindhu Chatterjee[1]*, Atanu Bhadra[2], Swapan Kumar Ray[3], Subhasis Mukherjee[4], Sukanta Sen[5]

Abstract

Japanese encephalitis virus belongs to the genus Flavivirus. Case fatality averages 30% and almost 50% of the survivors are left with permanent neuropsychiatric sequelae. Japanese encephalitis occurs in nearly all Asian countries including India. Patterns of JE transmission vary within individual countries and from year to year. In endemic areas, sporadic cases occur throughout the year. Japanese encephalitis or AES has been reported from 231 districts of 23 states. The best way to control JE in humans is through vaccination. Currently available vaccines in India are live attenuated, cell culture-derived SA 14-14-2, inactivated SA 14-14-2 vaccine (IC51; IXIARO® by Intercell and JEEV® by Biological Evans India Ltd.) and inactivated Vero cell culture-derived Kolar strain, 821564XY, JE vaccine (JENVAC® by Bharat Biotech). As 2006 position paper of WHO stated that mouse brain derived vaccines should be withdrawn and replaced by newer vaccines due to safety profile and as it is not available in our country now, this vaccine will not be discussed henceforth.

Keywords: Japanese Encephalitis, Vaccine, India

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Epidemiological Considerations

Japanese encephalitis virus (JEV) belongs to the genus Flavivirus that also includes three other important pathogens, West Nile virus, St. Louis encephalitis virus, and Murray Valley encephalitis virus. JEV also bears a close genetic relationship to other clinically significant flaviviruses, for example, yellow fever virus (YFV), dengue virus, and tick-borne encephalitis (TBE) virus.[1] JEV (family *Flaviviridae*, genus *Flavivirus*) represents one of the most significant etiologies of childhood viral neurological infection and disability in Asia. Despite the existence of effective vaccines to control this disease, JEV is responsible for an estimated 68,000 human cases and a reported 10,000–15,000 deaths annually.[2]

The JEV has shown a tendency to extend to other geographic regions. Case fatality averages 30% and almost 50% of the survivors are left with permanent neuropsychiatric sequelae.[3] Japanese encephalitis (JE) occurs in nearly all Asian countries, whether temperate, subtropical, or tropical, and has intruded into new areas through importation of infected vectors. At present, an estimated 3 billion people live in the 24 countries, mainly in the World Health Organization (WHO) South-East Asia and Western Pacific Regions, considered at risk of JE.[4]

The Pathogen

JEV, approximately 50 nm spherical particles, consists of a lipoproteinous envelope surrounding the nucleocapsid and core. The genome is single-stranded positive-sense RNA packaged in the capsid, consists of three structural proteins (C: Capsid; prM: Pre-membrane; and E: Envelope) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). Structural proteins form an icosahedral cage encasing the genome and being enveloped by host cell membrane. The outer membrane of JEV comprises an envelope protein (E) that facilitates the virus entry into host cell. E protein is also recognized as a protective antigen.[5,6]

Genotypes

The JEV exists as five distinct genotypes: G-I, G-II, G-III, G-IV, and G-V, based on nucleotide homology in the E protein gene. Three subtypes (a, b, and c) are present within G-I. However, all JEV strains belong to a single serotype.[7] GIb is associated with the displacement of GIII as the dominant JEV genotype throughout Asia in the 1990s [Figure 1]. Phylogeographic analysis indicated that GI-a diverged in Thailand or Cambodia and has remained confined to tropical Asia, whereas GI-b diverged in Vietnam and then dispersed to China, from where it subsequently dispersed to Japan, Korea, and Taiwan. An increased multiplicative ability of GI-b viruses early in mosquito infection may have resulted in shortened extrinsic incubation period that led to increased number of GI enzootic transmission cycles and the subsequent displacement of GIII.[8]

Vector

JEV has been isolated from 17 mosquito species in our country. Maximum isolations have been recorded from *Culex vishnui* group consisting of *Culex tritaeniorhynchus, C. vishnui,* and *Culex pseudovishnui*. Preference for breeding places during rainy season

[1]Department of Pediatrics, Santiniketan Medical College, Bolpur, West Bengal, India

[2]Department of Pediatrics, ESI Hospital, Asansol, West Bengal, India

[3]Department of Pediatrics, Mata Gujri Memorial Medical College and Lions Seva Kendra Hospital, Kishanganj, West Bengal, India

[4]Department of Physiology, Santiniketan Medical College, Bolpur, West Bengal, India

[5]Department of Pharmacology, ICARE Institute of Medical Sciences and Research, Haldia, West Bengal India

Corresponding Author: Dr. Kripasindhu Chatterjee, Department of Pediatrics, Santiniketan Medical College, Bolpur - 731204, West Bengal, India. E-mail: kschatterjee@gmail.com

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and irrigation channels bordering the paddy fields supports breeding during non-monsoon season.[9]

Seasonality

Patterns of JE transmission vary within individual countries and from year to year. In endemic areas, sporadic cases occur throughout the year. In North temperate area (Japan, Taiwan, Nepal, and North India), large epidemics occur from May to October. In Southern tropical areas (South India, Indonesia, and Sri Lanka), the disease is endemic but peak starts after rains, that is, from July to December.[10]

Age Distribution

Annual incidences vary by age group and have been estimated to be in the range of 5.4/100,000 in the 0–14 years' age group and 0.6/100,000 in the ≥15 years' age group. With decrease in cases in children due to vaccination programs, there is frequently a demographic shift of cases to older age. However, in some areas without vaccination programs like Bangladesh, over 50% of cases are in the adult age groups.[11] The Indian Council of Medical Research (ICMR) National Institute of Virology (NIV), Pune, investigated adult acute encephalitis syndrome (AES) epidemic in West Bengal and Assam in 2014. The study comprised about 398 AES cases, mostly (70.8%, 282/398) adults. JEV infection was detected in 134 (49.4%) among 271 AES cases tested. Case fatality rate was 28.9% (115/398).[12]

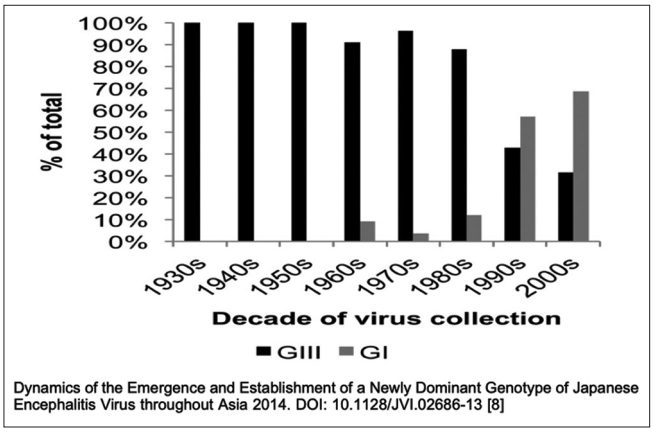

Figure 1: Relative proportion of GIII and GI in decades

Global Burden

JE is one of the most important causes of viral encephalitis in Asia. High case fatality rates, significant long-term neurological sequelae among survivors, make this otherwise geographically defined focal disease a public health problem. The WHO recommends integration of JE vaccination into national immunization schedules in all areas where the disease is public health priority. According to the WHO, nearly 50,000 cases of JE occur worldwide per year with 15,000 deaths.[13] The first case of JE was documented in 1871 in Japan. In endemic areas, the annual incidence of disease ranges from 10 to 100/100,000 population. Japan, South Korea, North Korea, Taiwan, Vietnam, Thailand, and the People's Republic of China practice routine childhood immunization against JE. Countries have not been able to generate adequate JE surveillance data because of the difficulty in making a clinical recognition of the disease, reporting issues, and insufficient laboratory support. Strengthened JE surveillance, continued commitment, and adequate resources for JE vaccination should help maintain progress toward prevention and control of JE.[14]

The majority (75%) of JE cases occur in children aged <15 years. Twenty-four countries in the WHO South-East Asia and Western Pacific regions have endemic JEV transmission, exposing more than 3 billion people to risks of infection [Figure 2]. There is no cure for the disease. Treatment is supportive only. Safe and effective vaccines are available to prevent JE. The WHO recommends that JE vaccination be integrated into national immunization schedules in all areas where JE disease is recognized as a public health issue.[15]

Indian Burden

JE or AES has been reported from 231 districts of 23 states. Thirty-seven more districts have been added in 2018 taking the total to 268. The JEV has a tendency to extend to other geographic regions. The ratio of overt diseases to inapparent infection varies from 1:250 to 1:1000. Thus cases of JE represent only the tip of the iceberg compared to the large number of inapparent infections.

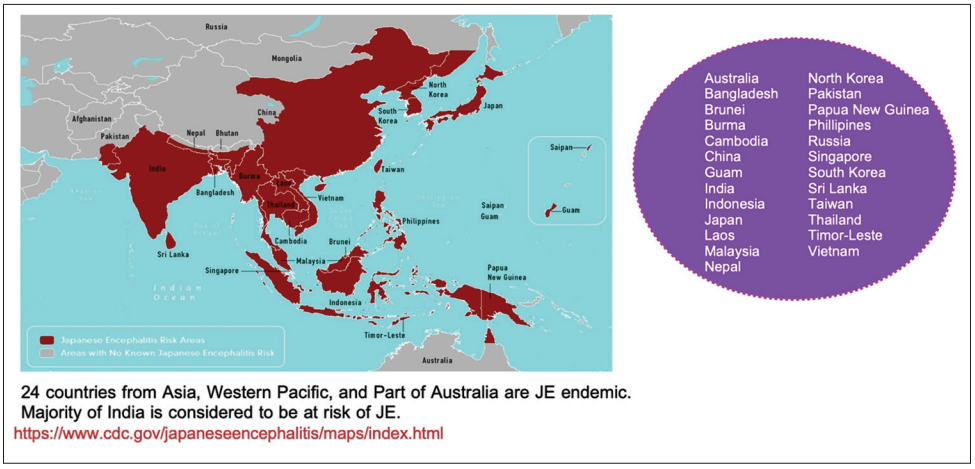

Figure 2: Global map of Japanese encephalitis

Outbreaks of JE in India

In India, JE was first diagnosed in Vellore in 1955 and the first major outbreak took place in West Bengal in 1973. Since then, the virus was found active almost in every part of India and outbreaks have been reported regularly. The most affected states comprise Andhra Pradesh, Assam, Bihar, Haryana, Karnataka, Kerala, Maharashtra, Manipur, Tamil Nadu, Orissa, Uttar Pradesh, and West Bengal [Figure 3].[16]

In 2005, Uttar Pradesh faced a devastating epidemic of JE mostly confined to Gorakhpur district affecting 6061 cases with 1500 deaths followed by another outbreak in 2006 with 2320 cases and 528 deaths. Similarly, JE cases in Uttar Pradesh were confined predominantly in Gorakhpur during 2007 reporting 3024 cases and 645 deaths.[17,18]

The regions of East UP (Gorakhpur and Basti divisions) are conducive for the spread of the virus due to the abundance of paddy fields, a bowl-shaped terrain and are also prone to annual flooding. An outbreak of encephalitis in Lakhimpur Kheri district was investigated for the identification and characterization of the etiologic agent that showed homology with JEV.[19-21]

Recently, India witnessed another large outbreak in Malkangiri during 2012 and Manipur in July 2016.[22,23] An unexplained acute neurologic illness affecting children with high case-fatality rates was reported from Muzaffarpur district of Bihar since 1995. The disease was linked with the cultivation of litchi fruits by some. However, the disease was ascribed to the presence of hypoglycin A or methylenecyclopropylglycine, presents in litchi that can cause hypoglycemia and metabolic derangement.[24,25]

Prevention of JE

There are three strategies for prevention and control of JE

1. Surveillance for cases of encephalitis
2. Vector control
3. Vaccination.

Control of mosquitoes through chemical or biological means is an option, but such strategies could potentially lead to ecological imbalance since they could affect all the mosquitoes. Another way is to specifically target the reduction of *Culex* mosquitoes by genetic engineering, but this has not been tested widely in the field. On the other hand, it is near impossible to control JE in pigs due to the unorganized nature of pig keeping, prolific reproduction rates, and the wallowing habit of pigs in mosquito breeding habitats. Following the onset of rains, a high proportion of pigs get infected with JEV and produce high level of viremia, and are essentially the first indicators of circulating JEV in an area before outbreaks in humans. Given these constraints, the best way to control JE in humans is through vaccination.[7]

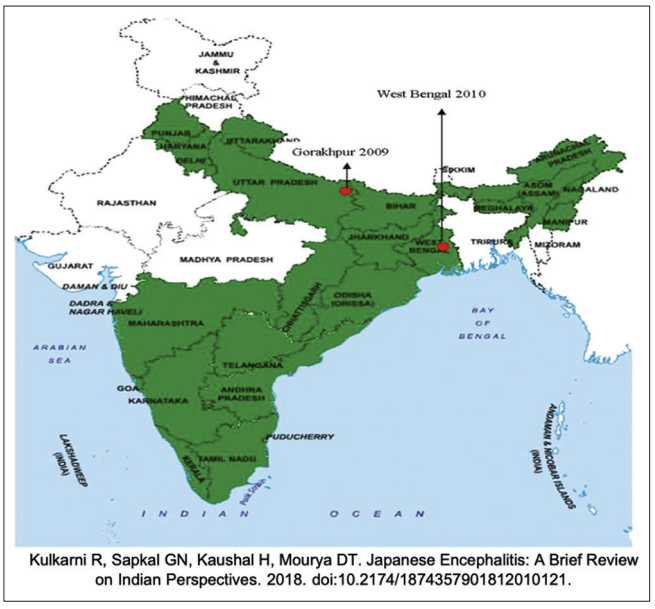

Figure 3: Japanese encephalitis Indian map

Vaccines

Currently available vaccines in India are as follows [Table 1]:

- Live-attenuated, cell culture-derived SA 14-14-2
- Inactivated SA 14-14-2 vaccine (IC51; IXIARO® by Intercell and JEEV® by Biological Evans India Ltd.).
- Inactivated Vero cell culture-derived Kolar strain, 821564XY, JE vaccine (JENVAC® by Bharat Biotech).

As 2006 position paper of the WHO stated that mouse brain-derived vaccines should be withdrawn and replaced by newer vaccines due to safety profile and as it is not available in our country now, this vaccine will not be discussed henceforth.

Three Topics Identified as Critical for the Policy Decision on Caccination[11]

- Protection against disease
- Vaccine safety, and
- Duration of protection.

Vaccine protection assessment is done with three measures, namely, vaccine efficacy, vaccine effectiveness, and immunogenicity. There have only been two efficacy trials of a JE vaccine in the past[26,27] both of which enrolled over 65,000 children. Clinical trials of JE vaccines currently use immunological endpoints as a surrogate of protection, because the occurrence of disease is such that efficacy trials would be too large to be feasible. The generally accepted immunological surrogate of protection is a serum neutralizing antibody titer of at least 1:10 as determined in a 50% plaque reduction neutralization assay (PRNT50). Seroconversion (SCR) is defined as PRNT50 titer <10 at baseline and ≥10 post-vaccination at the time of serum sampling, or a 4-fold rise from a baseline titer of ≥10. There are no current concerns about a deficiency for cross-protection across the five genotypes, and there is no evidence of clustering of vaccine failures even though there is increasing replacement of genotype 3 by genotype 1 strains.

Another important issue is the relevance of natural boosting (i.e., boosting the vaccine-induced immune response by exposure

Table 1: Japanese encephalitis vaccines available in India

Vaccine type	*Manufacturer (Country)*	*Commercial name*
JE vaccine (inactivated)	Biological E. Limited (India)	JEEV
JE vaccine (inactivated)	Bharat Biotech (India)	JENVAC
JE vaccine (live attenuated)	Chengdu Institute of Biological Products (People's Republic of China)	Live-attenuated SA 14-14-2

JE: Japanese encephalitis

to wild circulating virus) and need for booster doses. Data from endemic areas were the primary source for recommendations for newer vaccines with limited follow-up. It is unclear how long vaccine-induced protective level of antibodies may last and whether natural boosting contributes to maintaining protective antibody level. Studies in which vaccinated children who are followed longitudinally found some vaccines were seronegative at one visit and seroprotected at a subsequent visit.[28] This observation suggests that natural boosting occurs but whether these children were protected before the boost cannot be determined.[11]

Individual Vaccines

Live-Attenuated Cell Culture-Derived SA 14-14-2 Vaccine

This vaccine contains genetically stable, live-attenuated SA 14-14-2 strain of the JEV. Reversion to neurovirulence is highly unlikely. The WHO technical specifications have been established for the vaccine production.[29] Chengdu Institute of Biological Products is the only manufacturer authorized to export this vaccine from China. Extensive use of this and other vaccines has significantly contributed to reducing the burden of JE in China from 2.5/100,000 in 1990 to <0.5/100,000 in 2004. This vaccine is also licensed for use in Nepal (1999), South Korea (2001), India (2006), Thailand (2007), and Sri Lanka.[30]

Dosage and Administration

In China, the vaccine is licensed for 0.5 mL dose to be administered subcutaneously to children at 8 months of age and second dose at 2 years.[30] It can be offered to all susceptible children up to 15 years as catch-up vaccination. The vaccine is stable at 37°C for 7–10 days, at room temperature for 4 months, or at 2–8°C for at least 1.5 years.[30]

Immunogenicity and Correlate of Protection

After a single dose, antibody responses are produced in 85–100% of non-immune 1–12 years old children. A PRNT50 titer of more than 1:10 is generally accepted as evidence of protection and SCR.[30]

Efficacy and Effectiveness

Efficacy in China

A study in 1993 in Sichuan Province China in children <15 years reported effectiveness of SA 14-14-2 vaccine at 80% [confidence interval (CI) 44–93%] for a single dose and 97.5% (CI 86–99.6%) for two doses given at a 1 year interval.[31] Five major efficacy trials of SA 14-14-2 vaccine, completed in China from 1988 to 1999 in 1–10 years old, consistently yielded high protection rates, above 98%.[30]

Efficacy in Nepal

In a field trial in Nepal (1999), 160000 doses of JE vaccine were given to children aged 1-15 years. The efficacy of a single dose of JE vaccine was 99.3% (CI 94.9-100%). A single dose of JE vaccine is highly efficacious in preventing Japanese encephalitis when administered only days or weeks before exposure to infection.[32,33] At 5 years, the protective efficacy was 96.2%. The study provides evidence that SA 14-14-2 will be useful to combat epidemics.[34]

Indian experience

In India, single dose of SA 14-14-2 from China is used since 2006 in children between 1 and 15 years of age.[35] Following the campaigns in the high-risk districts, the vaccine is integrated into the UIP of endemic districts.[36] A small case–control study from Lucknow, India found an efficacy of 94.5% (95% CI, 81.5–98.9) after a single dose within 6 months of vaccination.[37] However, data from post-marketing surveillance (PMS) in India showed that protective efficacy of the vaccine in India is not as high as that seen in Nepal. PMS study showed that virus neutralizing antibodies were seen in 45.7% of children before vaccination. SCR against Indian strains 28 days after vaccination was 73.9% and 67.2% in all individuals and in those who were immunologically naive before vaccination, respectively. The protective efficacy of the vaccine at 1 year was 43.1% overall and 35% for those who were non-immune before vaccination, respectively. Preliminary results of a recent case–control study carried out by ICMR on impact of JE vaccine shows an unadjusted protective effect of 62.5% in those with any report of vaccination and vaccine efficacy of around 60% in Uttar Pradesh and around 70% in Assam. Following this report, the ICMR has recommended a study on the impact of two doses versus single dose of SA 14-14-2 vaccine in Assam.[38]

Boosters

National Technical Advisory Group on Immunization (NTAGI) in their meeting on May 18, 2012, decided that for routine immunization in UIP with SA 14-14-2, two doses should be used. Government of India has also recommended two doses of the vaccine to be used in UIP since 2013.

Safety

An estimated 300 million children have been immunized with this vaccine without apparent complication.[30] The WHO's Global Advisory Committee on Vaccine Safety acknowledged the vaccine's "excellent" safety profile. Transient fever may occur in 5–10%, local reactions, rash, or irritability in 1–3%. Neither acute encephalitis nor hypersensitivity reactions have been associated with the use of this vaccine.[39]

Inactivated Vero Cell Culture-Derived SA 14-14-2 JE Vaccine (JE-VC), IXIARO® by Intercell and JEEV® by Biological E Ltd. and IXIARO® by Intercell AG

This is an inactivated vaccine (JE-VC) derived from the attenuated SA 14-14-2 JEV strain propagated in Vero cells recommended by ACIP[40] for persons moving to a JE endemic country to take up residence, longer term (e.g., ≥1 month) travelers to JE endemic areas, and frequent travelers to JE endemic areas. JE vaccine also should be considered for shorter term (e.g., <1 month) travelers with an increased risk for JE on the basis of planned travel duration, season, location, activities, and accommodations and for travelers to JE endemic areas who are uncertain about their specific travel duration, destinations, or activities. In March 2009,

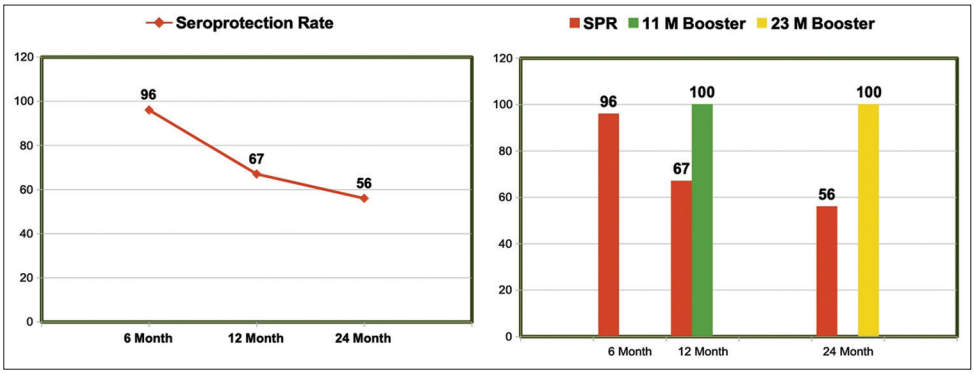

Figure 4: Long-term immune response to a booster dose of IXIARO, IC51. Vaccine in non-endemic area[43]

FDA approved JE-VC for use in persons aged ≥17 years and in May 2013, included children aged ≥2 months. The booster dose was approved for persons aged ≥17 years in October 2010 and for children in April 2018. Each 0.5 mL dose contains 6 antigen units of purified, inactivated JE virus, and approximately 250 μg aluminum hydroxide as an adjuvant. It is alum adjuvanted and contains phosphate-buffered saline as excipient and protamine sulfate in residual amounts (in contrast to gelatin and murine proteins in inactivated mouse brain-derived vaccines). The most widely marketed is the IC51 developed by Valneva Scotland Limited (formerly Intercell Biomedical) called IXIARO in the US and Europe (JESPECT in Australia and New Zealand).

Dose and Schedule, by Age Group

Primary Schedule

Two doses 4 weeks apart will be for all age groups like 2 months to up to more than 65 years. For age group, 18–65 years age group accelerated schedule of day 0 and day 7–28 is approved.

Booster Schedule

Booster schedule recommended if there is ongoing exposure or expected re-exposure. One dose should be given more than 1 year after the second dose and no data are available on the response to a booster dose administered >2 years after the primary series. No ACIP recommendations exist on the need for subsequent booster doses.

Dose

Dose will be in 2–35 months 0.25 ml (3 antigen units) and in ≥3 years 0.5 ml (6 antigen units). For all age groups, two doses have to be completed at least 1 week before potential exposure. Clinical trial data show high rates of seroprotection for at least 6 years after a booster dose. No longer term study data are available. The licensed vaccine schedule was derived in part from a study that compared two 6 μg doses of vaccine administered 28 days apart to a single dose of either 6 μg or 12 μg. Twenty-eight days after receiving 1 dose of the standard 6 μg regimen, only 95 (41%) of 230 JE-VC recipients had seroconverted with a PRNT50 titer ≥10. Fifty-six days after receiving their first dose of vaccine, 110 (97%) of 113 participants who had received two doses had a PRNT50 titer ≥10, compared with 30 (26%) of 117 and 47 (41%) of 114 of those who received a single 6 μg or 12 μg dose, respectively;

	JENVAC (n=22)	SA 14-14-2 (n=09)
GMT (LCL- UCL)	40.90 (41.10 - 64.41)	29.44 (14.49 - 47.52)
Sero - Protection % (≥1:10) after 12 M	81.82	44.44

Figure 5: One year results for dropout subjects after single dose[53]

geometric mean titers (GMTs) in the three groups were 218, 8, and 11, respectively.[41]

Studies in Non-endemic Areas

A multicentric immunogenicity study was conducted in Austria, Germany, and Romania with 181 adults subjects following two doses of IC51. SPR dropped from 99% (95% CI: 96.1–99.7) at 1 month following the primary series to 82% 2 years later and 84.9% (95% CI: 78.3–89.7) 3 years later, however, these results were obtained from a study population among which some had previously been exposed or vaccinated against TBE. GMT values for antibody response also showed values of 84 at 6 months and 41 at 15 months and thereafter up to 60 months remained at the same level around 41–44. Most people immunized with IC51 will have protective neutralizing antibody levels for at least a year.[42]

A multicenter, open-label, Phase 3 follow-up study at two centers in North Ireland and Germany was conducted to assess the long-term immunogenicity of primary IXIARO® vaccination and the immune response to an IXIARO® booster dose in subjects without previous history of TBE vaccination. Study found seroprotection rates showed a gradual decline over time from 96% at 6 months to 67% at 12 months and 56% at 24 months after IXIARO® 2 × 6 mcg primary immunization. One month following booster dose at 12 or 23 months seroprotection increased to 100% in each and GMT values jumped to 676 in 12 months booster and 2496 in 24 months booster [Figure 4].

Single-dose IXIARO® primary immunization of 1 × 12 mcg and 1 × 6 mcg resulted in only marginal SPRs of 6.0% (7/116) and 4.3% (5/117), respectively, at month 24. Single dose of inactivated JE vaccine was not found to be protective in non-endemic countries and two doses lead to satisfactory SCR but antibody decays fast and response to booster is excellent.[43]

In another very recent 5-year follow-up study[44] in adults from non-endemic regions of Austria, Germany, and Romania, 4 weeks after the primary series, 99% of subjects seroconverted, then slightly decrease to 82% in 24 months and then stabilize to 82–84%

till the end of 60 months follow-up period. The GMT also remains stable between 46 and 43 during the whole period. Data were also stratified to compare the persistence of protective neutralizing antibodies against JE in people with or without TBE vaccination. By months 24, 36, 48, and 60, the percentages were still 90.7%, 91.7%, 90.1%, and 85.9%, respectively, in those who had TBE vaccine compared to 67.9%, 71.9%, 69.1%, and 63.8% in those who had not. No long-term safety concerns were identified. These data indicate that vaccination with IXIARO is able to induce protective titers that persist up to 60 months after the primary immunization. About 82% of the subjects retained the protective antibody titers till the 60 months of follow-up. Throughout the follow-up period, >80% of subjects retained the protective titers, proving the long-term protection of two doses protection rate slightly reduced in the 1st year, then stabilized. The GMTs were >4 times the minimum protective titers needed throughout the follow-up period.

Studies in Endemic Areas

The vaccine has been evaluated in several clinical trials conducted in India and abroad in both adults and children. There are limited data for IXIARO in children and in endemic settings. Clinical studies from seven RCTs in approximately 2890 IXIARO vaccines provided short-term immunogenicity data. Across multiple studies in adults, high rates of seroprotection have been found 1 month following completion of the two-dose primary series.[11]

In one Philippines study,[45] follow-up was continued for 36 months after the primary series (Dubischar-Kastner *et al.*, 2014, and unpublished, quoted with permission from Valneva). One hundred and fifty participants received a booster at month 12, and 150 participants did not. Among those that did not receive a booster, the seroprotection rate at 3 years was 90%. The GMT decreased between 2 months and month 7, but then was relatively stable through the 3 years of follow-up (49–52). Data by age are similar, although the sample size in some age groups was very small (e.g., 16 participants). When children were given a booster, the response was rapid and strong.

Another recent open-label, randomized, controlled, Phase 3 clinical study[46] of immunogenicity to JE vaccine IXIARO was conducted in 496 children from a JEV endemic region (Philippines, metropolitan Manila area) (IC51-323, NCT 01041573) to assess the safety and immunogenicity profile of IXIARO in a pediatric population ≥2 months to <18 years of age and to establish the appropriate IXIARO dose, 0.25 mL or 0.5 mL. SCR rate and JE neutralizing antibody titer and GMT assessed 56 days and 7 months after the first vaccination. At day 56, SCR rates in the 2–<6 months, 6–<12 months, 1–<3 years, 3–<12 years, and 12–<18 years age groups were 100%, 95%, 97%, 94%, and 77%, respectively, and GMT values were 687, 378, 259, 214, and 176, respectively. At 7 months, corresponding values of SCR were 100%, 100%, 86%, 91%, and 97%, respectively, and GMT values were 159, 64, 39, 44, and 87, respectively.

Another important component of the study was that 100 children ≥3–<12 years of age received IXIARO 0.25 mL and 101 received IXIARO 0.5 mL. SCR at day 56 did not differ significantly between the 0.25 mL (95.9%) and 0.5 mL dose groups (100.0%; P = 0.058). GMT at day 56 was statistically significantly higher in the 0.5 mL dose group compared with the 0.25 mL dose group (mean 214 vs. 111, P < 0.001). Immunogenicity and safety during the dose-finding run-in phase in 201 subjects ≥3–<12 years of age showed that the 0.5 mL dose induced a numerically higher SCR and significantly higher GMT than the 0.25 mL dose, with a comparable safety profile. The 0.5 mL dose was thus confirmed for this age group.

The study showed that with two intramuscular injections, 28 days apart IXIARO at a dose of 0.25 mL for children 2 months–3 years of age and 0.5 mL for children 3 years of age and above elicits protective neutralizing antibody levels in over 99% of subjects. Protective immunity lasts for at least 7 months in more than 85% of vaccinated children. In one very recent randomized, controlled open-label study in the Philippines,[47] 300 children who received IXIARO two doses previously between 2 months and 17 years were randomized 1:1 to receive either no booster or a booster 12 months after initiation of the primary series. Neutralizing antibody titers were assessed before and after the booster and up to 3 years after primary series. Safety endpoints included the rate of subjects with solicited adverse events (AEs), unsolicited AEs, and serious AEs within 1 month after the booster. The study was conducted in accordance with the Declaration of Helsinki (2008) (NCT number: NCT00595270). Four weeks after second doses primary series of IXIARO (day 56), all subjects (100%) were seroprotected, with a GMT of 207. Booster and non-booster groups were comparable with regard to antibody persistence before booster administration at 12 months with 93.9% seroprotection and GMT of 53 in the booster group and 89.9% seroprotection and GMT of 46 in the non-booster group. In the non-booster group, follow-up continued without booster up to month 36 (i.e., 3 years after primary immunization), seroprotection remained stable at approximately 90%. GMT declined by 1 year after the primary series, but titers remained above the established protective threshold in 85–100% of children depending on age group. After the booster, seroprotection was observed in 100% of subjects and was maintained until study end (month 36). The GMTs rose substantially after the booster dose in both dose groups from 67 pre-booster to 2911 in the 0.25 mL IXIARO dose group and from 40 pre-booster to 1366 in the 0.5 mL IXIARO dose group. GMTs decreased in the 12 and 24 months after the booster in both dose groups, but titers remained higher compared with those seen after the primary series as from 2911 post-booster to 572 and 427 at months 24 and 36 in the 0.25 mL IXIARO dose group, and from 1366 post-booster to 302 and 280 at months 24 and 36 in the 0.5 mL IXIARO dose group. The booster led to a pronounced increase in GMT and 100% seroprotection rate in all age groups. The booster was well tolerated, with adverse effects lower compared with the primary series. Most adverse effects were mild. A booster dose of IXIARO administered 12 months after the primary immunization was well tolerated and highly immunogenic.

Indian Trial

JEEV® – the Indian Variant of IC51, IXIARO by Biological E Ltd. Intercell established a partnership with Biological E for production and distribution of the vaccine in India. Under the trade name JEEV® in India JEEV® was launched in 2012 by Biological E. Ltd., after licensed by DCGI in September 2011 and WHO Prequalified JE Vaccine (July 2013). Biological E Ltd. has been manufacturing and marketing the above vaccine in India, Bhutan, Nepal and Bangladesh. Composition and dosing of the vaccine are same as its Western counterpart.[48]

This open-label randomized Phase II study[49] of immunogenicity and safety was performed in M.S. Ramaiah Medical College and Teaching Hospital, Bengaluru, India. Two different doses of IXIARO®

(3 μg and 6 μg) manufactured by Intercell Biomedical, Livingston, were compared to the licensed dose for children below 3 years of JenceVacTM, JE-MB vaccine, produced by the Korean Green Cross Vaccine Corporation, Korea, using the Nakayama JE strain and are licensed and distributed in India by Shantha Biotechnics Ltd., the standard JE vaccine in the region. The primary endpoint of this study was the SCR at day 56. Sixty children were randomized into one of the three study groups (3 μg and 6 μg of IXIARO® or 0.5 ml JenceVacTM) as 24, 24, and 12, respectively. A half-dose given to young children (1–3 years of age) has the excellent immunogenicity and the safety profile comparable to that of adult dosage. At 28 days after first vaccination series, SCR in the 6 μg (n = 21) and 3 μg (n = 23) JE-VC recipient groups and the JE-MB vaccine group (n = 11) was 72%, 65%, and 64%, and plaque reduction neutralization test (PRNT50) and GMTs were 21, 24, and 20, respectively. At 56 days after first dose after the vaccination series was complete, corresponding values in the 6 μg and 3 μg JE-VC recipient groups and the JE-MB vaccine group were 95%, 96%, and 91%, and GMT values were 218, 201, and 230, respectively. None of the differences in SCR or GMTs was statistically significant. IXIARO® was safe and well-tolerated in this study. Local and systemic adverse effects were consistent with the known safety profile. IXIARO® induced an immune response comparable to JenceVacTM and also 3 μg and 6 μg induce comparable immunogenicity validating 3 μg as dose for < 3 years age group.

In 2011, the Biological E Ltd., India, conducted a multicentric open-label randomized controlled Phase II/III study to evaluate safety and immunogenicity of JEEV® vaccine in ~450 children (≥1–<3 years old) and compared to control Korean Green Cross Mouse Brain Inactivated (KGCC) vaccine. This study demonstrated SCR of 56.28% on day 28 and 92.42% on day 56 in JEEV® vaccinated group. Non-inferiority of JEEV® established against control in terms of proportion of subjects seroconverted. GMTs in JEEV® group were significantly higher than GMTs achieved in KGCC-JE vaccine group (218 vs. 126). There was no significant difference between the groups in proportion of subjects' seroprotected and in proportion of subjects reporting AEs between groups. JEEV® has been licensed by Drug Controller General of India for use in prevention of JEV infection in children and adult population on the basis of its ability to induce JEV neutralizing antibodies as a surrogate for protection.[50]

Safety Studies

Two pooled data on adult vaccination were analyzed for safety. In the first analysis, safety data for IXIARO from seven clinical trials were reviewed in comparison to the trial comparators [placebo (PBS+alum) or mouse brain-derived JE vaccine (JE-VAX)]. Solicited local AEs up to 6 days after the first vaccination were comparable with any AE around 64% and severe AE between 4.5% and 6.5%. Severe local reactions of hardening, swelling, and redness occurred more in JE-VAX (13.8%) than IXIARO (3.2%) or placebo (3.2%) mostly on the second and third doses. Solicited systemic AEs occurred within a week after first dose in similar proportions in the three groups [33% IXIARO, 29% JE-VAX, and 31% placebo]. Systemic reactions were higher after first dose than after second or third doses. Hypersensitivity reactions occurred as 3.5%, 5.5%, and 3.7% in IXIARO, JE-VAX, and placebo, respectively. In summary, in adults, there was comparable tolerability and reactogenicity with placebo (adjuvant alone) and mouse brain-derived JE vaccine except for local reactions.[51]

A recent analysis has included a summary of safety data across 10 clinical trials in 4043 adult vaccines up to the first 12 months of post-licensure passive reporting which showed the incidence of any AEs 66% of which (39% considered vaccine related). The most common vaccine-related AEs were headache (19%), myalgia (13%), fatigue (10%), flu-like illness (9%), and nausea (5%). According to the WHO pre-qualification assessment, these data can be considered to support the safety of JEEV.[52] It can be concluded that Inactivated Vero cell vaccine (specifically IXIARO) has an acceptable safety profile based on currently available data.

These studies indicate that Inactivated Vero cell vaccines [based on two doses of IXIARO given in the indicated age range, at a 4 weeks interval] have evidence of good seroprotective neutralizing antibody titers at 1 month after primary immunization. The seroprotection rates and GMTs gradually decline over 12 months post-immunization but are much above protective level and are maintained for up to 5-year period in some studies. Studies also show that single dose of inactivated JE vaccine is not protective both in non-endemic and endemic countries and two doses lead to satisfactory SCR but antibody decays fast but response to booster is excellent. Studies also show persistence of antibodies longer and better in previous TBE vaccinated subjects than not. A booster dose is indicated >12 months after the primary series in non-endemic settings for longer protection.

There are limited data for IXIARO in children and in endemic settings. Based on preliminary data from one study of 150 children in the Philippines,[45] adequate seroprotective titers may persist for at least 3 years after the primary immunization. Studies in India and the Philippines[46,53] show that 0.25 ml (3 μg) is optimal and safe dose in <3 years age group and single dose is not immunogenic. Another recent study from the Philippines[47] showed that booster dose of IXIARO administered 12 months after the primary immunization was well tolerated and highly immunogenic. Further studies across a variety of transmission settings and a more detailed assessment will provide further evidence on the booster needs of IXIARO when used in children living in endemic settings.

Inactivated Vero Cell Culture-Derived Kolar Strain, 821564XY, JE Vaccine (JENVAC®)

JENVAC® is a Vero cell culture derived, inactivated, Kolar strain, 821564XY, adjuvanted, and thiomersal containing vaccine developed by Bharat Biotech International Ltd. (BBIL). The original virus strain used in the vaccine was isolated from a patient in the endemic zone in Kolar, Karnataka, India, by NIV, Pune, and later transferred to BBIL for vaccine development. A Phase II/III, randomized single-blinded, active controlled study[54] to evaluate the immunogenicity and safety of the vaccine was conducted (CTRI/2011/07/001855). Out of 644 subjects, 212 were between the age of ≤50 years and >18 years, 201 subjects were between the age of ≤18 years and >6 years and 231 subjects were between the age of ≤6 years and >1 years.

JENVAC (5 μg/0.5 mL/dose) was administered intramuscularly on day 0 and day 28 ± 2. SA-14-14-2 was injected subcutaneously as a single dose on day 0, with a placebo administered on day 28 ± 2, since a 2-dose regimen of this vaccine had not been approved in India at the time of initiation of the study. Vaccines were followed up till 24 months. Solicited AEs were recorded during visits on day 0, day 28 ± 2, and day 56 ± 2. Solicited AEs were monitored for 7 days after vaccination, using diary cards, and unsolicited AEs were followed up for the entire study duration.

The results revealed that even a single dose of the test vaccine was sufficient to elicit the immune response. On the 28th day, the subjects who had received a single dose were 98.67% seroprotected and 93.14% seroconverted (4-fold) for ≤50–≥1 years, whereas the corresponding figures for the reference vaccine were 77.56% and 57.69%, respectively ($P < 0.001$) [Table 2]. The SCR (93.14% and 96.90%) and seroprotection (98.67% and 99.78%) percentages on the 28th and 56th day were not significantly different, and similarly, no statistically significant difference in these rates was noted among different age groups. The SCR (93.14% and 96.90%) and seroprotection (98.67% and 99.78%) percentages on the 28th and 56th day were not significantly different, and similarly, no statistically significant difference in these rates was noted amongst different age groups. Higher GMTs were achieved in younger age groups.

Higher GMTs were achieved in younger age groups. After the second dose of the test vaccine, the GMTs increased exponentially from day 28 (145) to day 56 (460.5) in ≤50–≥1 years. However, there was waning of both SCR and GMTs in both the test vaccine and reference vaccine groups at 24 months. A total of 22 subjects in JENVAC group and nine subjects in reference vaccine group dropped out from study after the first dose. Results show that JENVAC offers 81.8% seroprotection, even after 360 days, whereas SA-14-14-2 gives around 44.4% [Figure 5].

All the subjects were followed up for 56 ± 2 days. There was no serious AE or AE of any special interest noted in the study.

Another Phase 4, multicenter, open-label, randomized, control trial[55] was conducted on immunogenicity, safety, and interchangeability of a single-dose, inactivated, Vero cell derived, JENVAC and compared to the live-attenuated SA 14-14-2 vaccine in 360 healthy children. Children were equally randomized to receive study or comparator vaccine on day 0 and a subset from each group was divided and allocated to receive a booster dose of same or comparator vaccine on day 720. Peripheral venous blood samples (2 mL) were obtained on day 0 (before vaccine administration) and on days 28, 56, 90, 180, and 360 (post-vaccination). For the interchangeability study, samples were collected on day 720 (pre-booster) and on day 748 (post-booster/interchange). Children were given a single dose of either JENVAC or SA 14-14-2. At day 360 (post-vaccination), GMTs were 33.7 (95% CI, 27.9–40.77) and 12.2 (95% CI, 10.3–14.4) in the JENVAC and SA 14-14-2 groups, respectively, and 81.7% (95% CI, 74.9–87.3) in the JENVAC group and 47.9% (95% CI, 40.1–55.8) in the SA 14-14-2 group achieved seroprotection. For interchangeability study, 178 children (96 and 82 in the JENVAC and SA 14-14-2 groups, respectively) were assigned (non-randomly) to receive a booster dose or interchanged to receive the other vaccine. Forty-six children received JENVAC + JENVAC, 50 children received JENVAC + SA 14-14-2, 46 children received SA 14-14-2 + JENVAC, and 36 children received SA 14-14-2 + SA 14-14-2. At day 720 (post-receipt of a single dose of either vaccine), 88.5% (95% CI, 80.4–94.1) in the JENVAC group and 68.3% (57.1, 78.1) in the SA 14-14-2 group achieved seroprotection [Figure 6].

On day 748 or 28 days following booster dose, GMTs of JENVAC+ JENVAC, JENVAC+ SA 14-14-2, SA 14-14-2 + JENVAC, and SA 14-14-2 + SA 14-14-2 were 994.9, 507.2, 237.4, and 153.6 respectively, indicating better response when JENVAC is given as first dose [Figure 7]. A total number of children reporting at least 1 AE were 57 and 62 in the JENVAC and SA 14-14-2 groups, respectively. Fever was the most commonly reported solicited AEs with a reporting of 39.1% and 28.6% of events in the JENVAC and SA 14-14-2 groups, respectively. There was no significant difference between the JENVAC and SA 14-14-2 groups in either local or general AEs ($P = 0.31$). In the interchangeability study, 11 general AEs were reported (4, 2, and 5 in the JENVAC + JENVAC, JENVAC + SA 14-14-2, and SA 14-14-2 + JENVAC groups, respectively).

This study reported an SPR of 92.4% (95% CI, 88.4–96.4) and 81.7% (95% CI, 75.8–87.6) at days 28 and 360, respectively, from a single dose of JENVAC. A more appropriate assessment would be to compare immune responses between JENVAC and other inactivated JE vaccines in endemic settings. An IXIARO study in the Philippines (endemic for JE) reported an SPR of 89.6% (95% CI, 80.0–94.8) 1 year after the primary immunization series (two doses administered 4 weeks apart)[47] Thus, a single dose of JENVAC offers

Table 2: JENVAC Phase 2/3 trials: Results

Parameter	*JENVAC (n=452)*	*SA 14-14-2 (n=156)*	*P-value*
Seroconversion, %, (95% CI)			
D 0-28	93.14 (90.81–95.74)	57.69 (49.94–65.45)	<0.001
D 0-56	96.90 (95.3–98.50)	39.74 (32.06–47.42)	<0.001
Seroprotection, %, (95% CI)			
D 0	11.28 (8.37–14.20)	17.95 (11.93–23.97)	0.05
D 28	98.67 (97.62–99.93)	77.56 (71.02–84.11)	<0.001
D 56	99.78 (99.35–100.00)	60.26 (52.58–67.94)	<0.001
GMT (95% CI)			
D 0	6.13 (5.74–6.39)	6.52 (5.91–7.19)	0.51
D 28	145.04 (127.19–165.39)	38.56 (29.41–50.57)	<0.001
D 56	460.53 (404.19–524.73)	25.29 (19.28–33.17)	0.001

GMT: Geometric mean titer

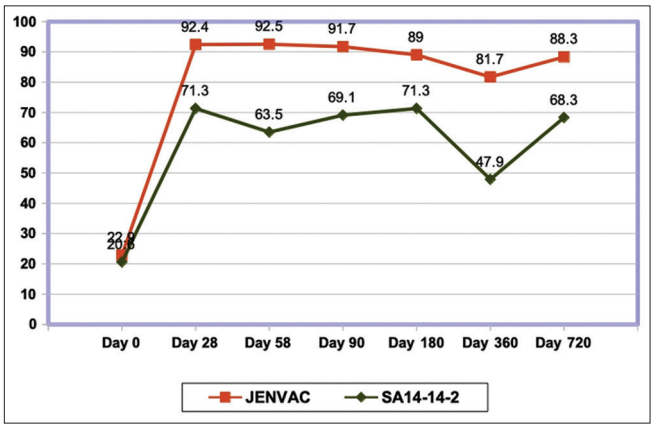

Figure 6: JENVAC: Phase IV clinical trial persistence of seroprotection percentage[54]

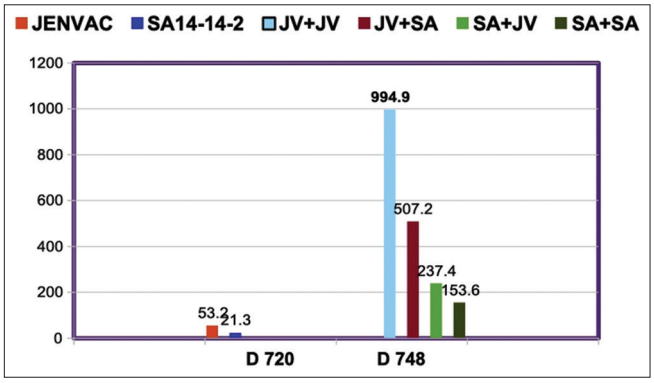

Figure 7: Interchangeability study[54]

similar long-term immune responses to that exhibited by 2 doses of the other inactivated JE vaccines.

Live-Attenuated Recombinant SA 14-14-2 Chimeric Vaccine (JE-CV, IMOJEV® by Sanofi Pasteur)

A promising new genetic approach is adopted in the construction of a chimeric live-attenuated vaccine. IMOJEV® (JE-CV, previously known as ChimeriVax™-JE) and developed initially by Acambis, is a novel recombinant chimeric virus vaccine, developed using the YFV vaccine vector YFV17D, by replacing the cDNA encoding the envelope proteins of YFV with that of an attenuated JEV strain SA14-14-2. IMOJEV® MD contains live-attenuated, recombinant JEV: 4.0–5.8 log plaque-forming unit per dose (0.5 mL) with mannitol, lactose, glutamic acid, potassium hydroxide, histidine, and human serum albumin as excipient and 0.9% sodium chloride acts as diluents. No adjuvant or antimicrobial preservative is added.[56] This novel, live, recombinant vaccine, is a safe, highly immunogenic and capable of inducing long-lasting immunity in both pre-clinical and clinical trials.[57] A single dose was sufficient to induce protective immunity, similar to that induced in adults by three doses of JE-VAX® with a SCR rate of >97%.[2] One randomized, controlled Phase 3 immunogenicity, and safety trial was done in Thailand among children of 12–18 months show SCR of 95% 28 days after vaccination with acceptable safety profile.[58] The clinical development of this vaccine (IMOJEV) is currently on hold in India due to severe delays in authorization of the Phase III study.

Interchangeability of JE Vaccines

The issue of interchangeability between three JE vaccines, that is, live-attenuated JE vaccine (SA-14-14-2, Chengdu, China), Jeev (Biological E), and JenVaC (Bharat Biotech) was considered in the NTAGI meeting on December 17, 2018. It was decided that live-attenuated JE vaccine (SA-14-14-2) can be administered interchangeably with Jeev as well as JenVaC vaccine in interest of the immunization program. However, there is a need to generate data on the interchangeability between Jeev and JenVaC vaccines. It was also expressed that the issue of interchangeability is not only of completion of the primary series of vaccination but also of replacing a vaccine product in an area where another product was being used earlier with different dose recommendations.[59] Another Phase 4, multicenter, open-label, randomized, control trial[55] with interchangeability data showed favorable response with good safety profile.

Number of Doses in Primary Vaccination and Booster

Single dose of live-attenuated SA 14-14-2 is poorly immunogenic.[60] It is currently recommended that both inactivated and live JE vaccines be administered in two doses (4 weeks apart) as a primary immunization series with the exception of IMOJEV, live-attenuated chimeric JE vaccine. A contributing factor to improving JE vaccine coverage would be limiting the number of doses, either in a primary immunization series or the number of booster doses required. JE vaccine coverage surveys conducted in India reported rates of 75% and 42% for the first and second dose, respectively.[61] Studies in non-endemic countries[44] show persistence of antibodies longer and better in previous TBE vaccinated subjects than not. A booster dose is indicated >12 months after the primary series in non-endemic settings for longer protection.[43] A recent study from the Philippines[47] showed that 90% were seroprotected following two dose primary series at 36 months after vaccination. It also showed response to booster dose of IXIARO administered 12 months after the primary immunization was well tolerated and highly immunogenic. GMTs remained high at 428 at 12 months and 350 at 24 months after the booster dose. Data[48] also were used in a mathematical model to estimate the duration of protection after the booster dose and suggested a median duration of 9 years (range: <5–≥30 years). Further studies across a variety of transmission settings and a more detailed assessment will provide further evidence on the booster needs of IXIARO when used in children living in endemic settings. Further boosting at later time points may be beneficial. In a Phase III immunogenicity study from India,[54] single dose dropouts of JENVAC offer 81.8% seroprotection, even after 360 days. Another Phase 4, multicenter, open-label, randomized, control trial[55] showed seroprotection following single dose of JENVAC, on day 360 (post-vaccination) 81.7% (95% CI, 74.9–87.3) and at 720 day 88.5% (95% CI, 80.4–94.1). The Drug Controller of India has approved the licensure of JENVAC as a single dose in 2016.

Going through these studies, now single dose JENVAC is a reality that can save cost of vaccination as well as reduce vaccine dropouts. It is yet to be determined whether we need booster in our endemic country because of facts that in apparent infection is very high in JE but lead to long-lasting immunity and also response to booster in JENVAC is exponential.

Coadministration with Other Vaccines

A clinical trial in which the first dose of inactivated JE vaccine was administered concomitantly with hepatitis A vaccine indicated no interference with the immune response to inactivated JE vaccine or hepatitis A vaccine. Among the 58 persons who received both inactivated JE vaccine and hepatitis A vaccine in the per-protocol analysis, all had protective neutralizing antibodies compared with 98% (57 of 58) of persons who received inactivated JE vaccine alone. GMTs also were similar at 203 (95% CI = 154–261) and 192 (95% CI = 148–250), respectively.[62] When rabies vaccine and inactivated JE vaccine was given simultaneously, seroprotection against rabies virus (i.e., ≥0.5 IU/mL) at 28 days after the third rabies vaccine dose was 100% (157 of 157) in the concomitant administration group and 99% (203 of 204) in the group administered rabies vaccine alone. Non-inferiority of the immunologic responses to inactivated JE vaccine and rabies vaccine was established for concomitant administration compared with separate administration of either vaccine.[63]

No significant differences were found in the percentage of participants who achieved human serum bactericidal assay antibody titers ≥1:8 against meningococcal serogroups A, C, W, or Y when inactivated JE vaccine was given simultaneously with meningococcal vaccine.[64] The live-attenuated JE vaccine coadministered with measles vaccine at 9 months of age showed no significant differences between groups in immunogenicity or safety concerns when the vaccines were given on the same day or separated by 1 month, with high seroprotection rates of measles vaccine as 91.8% (95% CI 87.3–95.1) and 90.5% (95% CI 85.9–94.1), respectively.[65]

Pregnancy and Lactation

No controlled studies have assessed the safety, immunogenicity, or efficacy of inactivated JE vaccine in pregnant women. Pre-clinical studies of inactivated JE vaccine in pregnant rats did not show evidence of harm to the fetus.[66] No studies have investigated the safety or immunogenicity of inactivated JE vaccine in breastfeeding women, and no data are available on whether inactivated JE vaccine is excreted in human milk. ACIP general guidelines for best vaccination practices indicate inactivated vaccines administered to breastfeeding women do not affect the safety of breastfeeding for women or their infants.[67]

Current Recommendations of IAP Advisory Committee on Vaccines and Immunization Practices

Individual Use

The vaccination against JE is not recommended for routine use but only for individuals living in endemic areas. Although occasional cases have been reported from urban areas in a few districts, JE is predominantly a disease of rural areas. Government of India has identified around 268 districts to be endemic for JE in India so far. JE vaccine is also recommended for longer term (e.g., ≥1 month) travelers to JE endemic areas, and frequent travelers to JE endemic areas. JE vaccine also should be considered for shorter term (e.g., <1 month) travelers with an increased risk for JE on the basis of planned travel duration, season, location, activities, and accommodations and for travelers to JE endemic areas who are uncertain about their specific travel duration, destinations, or activities.

Live-Attenuated SA 14-14-2 Vaccine

Two doses are given in NIP in endemic districts of India. First dose of the vaccine can be administered at 9 months along with measles and rubella vaccine and second at 16–18 months at the time of 1st booster of DTP vaccine.

JEEV® by Biological E Ltd

The committee believes that although Biological E India Ltd. has used the same strain, adjuvant and technology in production of JEEV® as used by Intercell AG in the development of IXIARO®, the two vaccines cannot be treated as the same product. Considering the proven efficacy and safety profile of its parent vaccine in many countries over past many years, and demonstration of good seroprotection in Indian trial, the committee endorses use of this vaccine in India and recommends a primary schedule of two doses as single dose is not immunogenic. It should be given in a dose of 0.25 mL for children aged ≥1–≤3 years and 0.5 mL for children >3 years, adolescents and adults administered intramuscularly on days 0 and 28.

Further boosting at later time points may be beneficial. More studies across a variety of transmission settings and a more detailed assessment of the effect of inapparent infection leading to natural boosting will provide further evidence on the booster needs of IXIARO when used in children living in endemic settings. Inactivated JE vaccine is found to be safe when coadministered with the vaccines and no interference of immunogenicity of either is found.

No controlled studies on safety, immunogenicity, or efficacy of inactivated JE vaccine in pregnant and breastfeeding women are available and no data are available on whether inactivated JE vaccine is excreted in human milk. Pre-clinical studies of inactivated JE vaccine in pregnant rats did not show evidence of harm to the fetus. ACIP general guidelines for best vaccination practices indicate that inactivated vaccines given to breastfeeding women do not affect the safety of breastfeeding for women or their infants. Considering all the facts, inactivated JE vaccines may be given to pregnant and nursing mothers, if needed, with reasonable safety.

Jenvac ® by BBIL

The committee reviewed the data provided by the manufacturer on the clinical trials of JENVAC® in India. Results of two studies conducted in India, one Phase II/III study in 2011[54] and another Phase 4 study with interchangeability data[55] from 2014 to 2016 show, following single dose, very good seroprotection for 720 days post-vaccination, exponential response to booster after 2 years, and safety of interchangeability with other vaccines. Since seroprotection rates and GMTs were significant even after 720 days post-vaccination and endemic nature of infection in our country with high chance of exposure to natural infection and very good response to boosters, exact timing, and need of booster is to be defined at a later time.

Interchangeability Of JE Vaccines

NTAGI has already opined that live-attenuated JE vaccine (SA-14-14-2) can be administered interchangeably with JEEV as well as JENVAC vaccine in interest of the immunization program. It was also expressed that the issue of interchangeability is not only of completion of the primary series of vaccination but also of replacing a vaccine product in an area where another product was being used earlier with different dose recommendation. Another Phase 4, multicenter, open-label, randomized, control trial with interchangeability data showed favorable response with good safety profile between JENVAC and live attenuated JE vaccine. However, there is a need to generate data on the interchangeability between JEEV and JENVAC vaccines.

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