Live and Inactivated Japanese Encephalitis Vaccine Interchangeability in Travelers: Review of Evidence and Recommendation to Travelers

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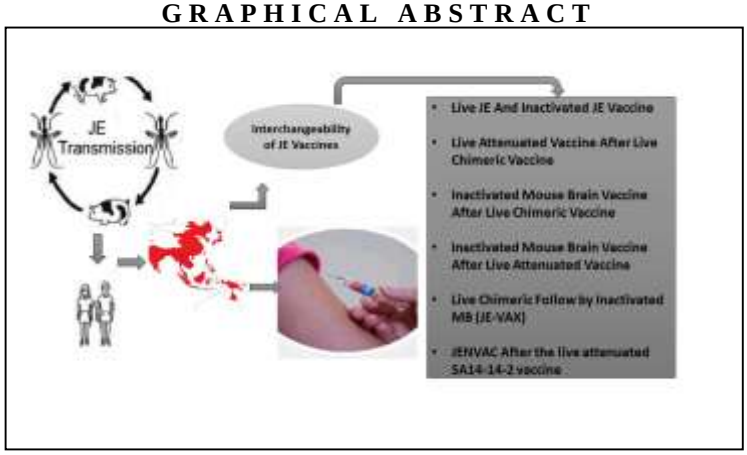
Abstract:
Japanese encephalitis (JE) is a vector borne zoonotic disease caused by the virus belongs to Flaviviridae family. Japanese encephalitis virus is known as a major etiological agent of encephalitis in Asia, few western pacific nations and in northern Australia. JE has case fatality rate of 20-30% and 30-50% of the survivors have neurological sequalae. It is estimated that's almost 67,900 cases occur annually, and overall incidence is 1.8 per 100000. There is no treatment available for JE and it cause significant mortality and morbidity in infected people. JE can be prevented by using vaccines. Different types of vaccines like mouse brain derived inactivated vaccine (MBJEVs), inactivated primary hamster kidney cells (PHK) derived vaccine, live attenuated SA14-14-2 virus, and chimeric live attenuated JE vaccine (ChimeriVax, JE-CV). Vaccination against JE has been carried out extensively in Asian countries from past few decades. JE vaccines are highly recommended for travellers to the endemic regions, this gives to the rise of the question of Interchangeability of JE vaccines. Interchangeability of inactivated, live and chimeric JE vaccines has been studied in different regions. According to all these case studies discussed in the review it is possible to interchange JE vaccine because after booster dose they gave significant Sero-protection in terms of geometric mean titer GMTs and plaque reduction neutralizing test PRNT against JE virus. But present data is limited and further large-scale studies are recommended.

Keywords: Japanese Encephalitis Live JE Vaccines Inactivated JE vaccines Interchange of JE Vaccine

G R A P H I C A L A B S T R A C T



INTRODUCTION

Japanese encephalitis (JE) is a zoonotic vector borne disease[1]which is caused by Japanese encephalitis virus. It is a single stranded positive sense RNA virus[2] and belongs to Flaviviridae family [3] and is transferred from animals to human by mosquito known as Culex [4, 5]. Japanese encephalitis virus is known as major etiological agent of encephalitis in Asia [6], few western pacific nations and in northern Australia [7].Transmission cycle of JEV includes the Culex triaeniorhyncus or Culex vishnui mosquito species, they act as vectors and breed in rice fields stagnant water[8, 9]. Birds and pigs act as their replicating hosts and humans act as dead end hosts [10, 11]. First JEV epidemic of 6000 cases were reported in 1924 in japan[12]. JEV was first isolated in 1934 in Japan from the post-mortem brain sample and initially named as Japanese B encephalitis virus[13]. In Japanese encephalitis humans act as dead-end host and rarely develop viremia to feeding mosquitoes. Less than 1% of all infected humans would develop symptomatic disease. JE has case fatality rate of 20-30% and 30-50% of the survivors have neurological sequalae[14, 15]. This disease primarily infects adult and children. In endemic countries most of the population has natural immunity against JE after childhood infections. JE is more prevalent in temperate region and is transmitted during warm seasons. It is the time of the year when most of

the JE epidemics occur. In tropical and subtropical regions JE epidemics occur throughout the year but raining season supports more epidemics [16, 17]. Worldwide incidences of JE are unknown because the quality and intensity of JE surveillance and availability of diagnostic tests vary around the world. In 1980s, it was reported that almost 50,000 new cases of JE occurred annually among almost 2.4billion population of 16 Asian JE endemic countries [18]. Different factors like urbanization, population growth, agricultural practices change, vaccination in endemic countries have influenced the number of incidences per year. It is estimated that's almost 67,900 cases occur annually, and overall incidence is 1.8 per 100000[18].

There is no treatment available for JE and it cause significant mortality and morbidity in infected people. JE can be prevented by using vaccines [19, 20]. First generation of vaccine has been available since 1950s in routine use in endemic areas. Different types of vaccines like mouse brain derived inactivated vaccine known as (MBJEVs). This vaccine was made from Beijing-1 or Nakayama virus strain. MBJEV was propagated on mouse brain tissue. This was one of the most effective JE vaccine that's why it was prominently used Asia, USA and Europe. MBJEV vaccine had reduced the number of incidences of JE in japan and Taiwan[21]. Other vaccine against JE is an inactivated vaccine cultivated on primary hamster kidney cells (PHK). Live attenuated SA14-14-2 virus vaccine has been developed in China in 1988. Live attenuated SA14-14-2 was a wild type SA14 strain [22]. Second generation vaccines are chimeric live attenuated JE vaccine known as (ChimeriVax, JE-CV) [21]. Other example is IXIARO also known as JESPECT formalin based inactivated whole virus JE vaccine propagated on Vero cells [23]. Inactivated Vero cells derived JE vaccine was approved as substitute of MBJEVs in 2011[24]. Vaccination against JE has been carried out extensively in Asian countries from past few decades. JE vaccines are highly recommended for travellers to the endemic regions. Main concerns related previously manufactured mouse brain JE vaccines are their side effects like neurological and allergic reactions. New generation purified inactivated JE vaccines produced using Vero cell lines are safer and more effective [25].

JE Vaccine Distribution According to Regions

Different types of JE vaccine are available in different regions. JE vaccines include live attenuated, inactivated JE vaccines and chimeric JE vaccines [26]. There are several factors those effect the choice of vaccine in different regions including vaccine efficacy, safety, local disease prevalence, regulatory authority and availability [27].

Mouse Brain Inactivated JE Vaccine

Mouse brain inactivated JE vaccine was a first-generation inactivated vaccine known as JE-VAX or Biken. JE-VAX had Nakayama strain derived from mouse brain, manufactured in japan and licensed in 1954[28]. JE-VAX was used in the USA and Europe for decades[29]. Trails for this vaccine were conducted in Taiwan in1965 and it showed 80% effectiveness. Several studies were conducted in Japan, India, Thailand and USA reported 80-100% sero-protection after this inactivated purified vaccine. Later Nakayama strain was replaced by Beijing-1 strain as it showed more and better cross-protection and boarder coverage on different JEV strains in 1988[19]. JE-VAX had several disadvantages like requirements of multiple doses of vaccine as it was a killed vaccine. It had a complex manufacturing process. It also had several safety related issues as it is derived from mouse brain and also animal ethic issues. Although it had impressive efficacy and was used till 2000. It was discontinued by the manufacturer after the appearance of single case of disseminated encephalomyelitis in vaccinated individuals. It's all lots were exhausted in 2011[30, 31]. Thailand is still using this JE-VAX vaccine and it is the part of Thai National Immunization Program [32]. Primary hamster kidney (PHK) cell culture vaccine having Beijing-3 strain was produced in 1965 in China, but it had some adverse effects[28]. The vaccination against JE was recommended by Centre for Disease Control and Prevention (CDC) for all ages[30]. For age 1-3 years, three doses at 0,7,30 days had displayed better neutralizing antibodies in all recipients in 6 months. Immunity remain persistent in individual for two years, than booster dose is required and recommended [33]. The Nakayama JEV strain had been the most prominent strain used in mouse brain derived inactivated vaccine production in Asia since it was identified from the cerebrospinal fluid of a patient and was propagated using mouse brain passages[34]. However, mouse brain derived JE vaccine is replaced by cell culture-based vaccine[35, 36]. Another inactivated vaccine against JE is known as JENVAC, produced using Vero cell line in India. JENVAC contains an Indian Kolar strain (821564XY). It is produced by Bharat Biotech international Limited, Hyderabad, India and licensed in 2014. JENVAC provides 90-96% seroconversion and sero-protection in 28 days of immunization in trails[37]. Two doses of JENVAC with 24 months of intervals and showed highest antibody titer. JENVAC provides better immunogenicity over live attenuated vaccines. It is recommended for all age groups [38].

Vero Cell Culture Derived Inactivated JE Vaccine JE-VC

Vero cell derived cell culture JE vaccine made up of an inactivated JEV strain known as SA 14-14-2. JE-VC uses 0.1% of aluminium hydroxide as an adjuvant.[33, 39]. JE-VC is marketed as IXIARO in the USA and other countries. In Australia and New Zealand, it is marketed as JESPECT and in India its brand name is JEEV[40]. Intercell biomedical. Austria was the initial manufacturer of JE-VC and licensed in 2009 for 17 or above aged persons. In 2013 it was licensed for less than 2 months to 16 years [41]. It has been reported that JE-VC has 100% seroconversion in vaccinated individuals with the boosters. Some studies have reported decreased in seroconversion with time[42, 43]. There are several advantages

of JE-VC over mouse brain derived inactivated vaccine like higher immunogenicity and antibody titer. It has several side effects like myalgia, headaches, influenza like sickness and fatigued in 13-26% in clinical trial participants in first week of immunization[33].

JE-VC vaccine has a variant, which has inactivated Beijing-1 strain of JEV without adjuvant. It is licensed and marked as JEBIK-V and ENCEVAC in 2009 and 2011 respectively in Japan. Other vaccine known as TC-JEV also have Beijing-1 strain and was manufactured in Korea and licensed in 2013[40].

Recombinant Chimeric JE Vaccine (JE-CV)

Recombinant live chimeric JE vaccine is known as IMOJEV. JE-VE vaccine is based on the 17D-204 yellow fever vaccine, where structural genes (prM, E) were replaced by JEV (prM. E) genes of SA 14-14-2 attenuated strain[40]. IMOJEV is a safe and effective live attenuated JE vaccine for children up to 6 years. The median protection duration of IMOJEV is 30 years after booster dose[44]. This vaccine was designed by Chamber's group in 1999 and then by Guirakhoo's group as ChimeriVAX^{TM}-JE vaccine. It was licensed in USA, Europe and Australia with the brand name IMOJEV in 2009 [45]. The advantage of IMOJEV is that it induces a significant immune response with approximately 95% of the seroconversion rate of its single dose. IMOJEV is recommended to the age group like from 9 months to 18 years with a booster dose after 1-2 years of primary dose. Later IMOJEV was recommended to the people above 18 years followed by one optional booster dose after 5 years of JEV endemic areas[46]. Some side effects like myalgia, headache, weariness in 17-24 of the clinical trial candidates. JE-CV is approved in 14 countries including Thailand, Philippines, Australia, Malaysia, Hong Kong and Singapore[45].

Live Attenuated JE Vaccine (JE-LV)

The live attenuated JE vaccine contains attenuated JE strain SA 14-14-2 and produced using primary hamster kidney cell culture [47, 48]. JE-LV was initially produced by the Chengdu Institute of Biomedical products (CDIBP), China in 1988. A single dose of JE-LV is recommended in children ages from 8-9 months with the booster dose after 3-12 months. This vaccine has an efficacy of 85-95% with a single dose. It produces neutralizing antibodies in 90 % of the vaccinated individuals, reported by WHO[46]. JE-LV produces protection in vaccinated individuals for almost 5 years. Since 1988 almost 700 million doses of JE-LV have been given out globally. This vaccine produces some side effects like drowsiness, irritability, fever, nasopharyngitis, conjunctivitis, rhinitis and gastroenteritis in clinical trials[49]. There is a common safety concern related to all live attenuated vaccines like reversion to the wild type and failure in attenuation process. One study has found that Live attenuated JE vaccine JE-LV does not lead to the transmission of the vaccine virus through mosquito biting or virus amplification in pigs [50]. Almost 50% of the total JE vaccine is JE live attenuated vaccine in Asian countries like Sri Lanka, Nepal, India Korea and in Western Pacific Regions. It is suspected to be used more widely in endemic areas in future [51, 52].

Difference Between South Asian and Western JE Vaccines

Different type of JE vaccine is administered in South Asian and western Pacific countries. They differ in the type of vaccine formulation, administration schedules and type of immune response it generates. Recommendation of the particular vaccine to the travelers is critical and impacts their vaccination strategies and requirements[53].

South Asian JE Vaccines (Live Attenuated JE Vaccines)

South Asian countries administer live attenuated JE vaccines. JEV strain used in live attenuated JE vaccines is SA14-14-2. It provides high sero-conversion and sero-protection. Its single dose is given subcutaneously[54]. As they are live attenuated viral particles, the stimulate immune response effectively but do not cause disease. As they do not produce a long-lasting immune response, so booster dose is required in case of traveling to the endemic area.

Western JE vaccines (Inactivated JE vaccines)

Western JE vaccines contain killed JE virus or viral components. Inactivated JE vaccines use rendered non-pathogenic JE virus strains that ensures safety. It requires 2-3 doses depending upon the vaccine used. Its typical schedule is one initial dose along with booster doses too enhances the immune response. The interval between doses depend on the type of vaccine used. In case of IXIRO JE vaccine second dose is given after 28 days of the primary dose[55].

Challenges Faced by Western Travelers

Western travellers receive inactivated JE vaccines face many challenges like limited no. of doses received, limited availability of second dose in endemic areas, risk associated and its consequences[56]. Single inactivated JE vaccine dose like of IXIRO may not provide long term immunity against JE. This is the reason travellers may contract JEV and develop disease. Travelers visiting endemic JE areas may find it difficult to find an inactivated JE vaccine as these areas have live attenuated JE vaccines. There may be a change in the vaccine regulations[57]. There are several challenges faced by Western travellers having JE vaccine that include the need of a person's decision making based on the travel plan, duration and risk factors[58]. Guidelines for travellers for JE vaccination vary and needs several implodents[59-61].

Vaccination Needs for Endemic and Non-Endemic Travelers

JEV has two epidemiologic patterns: endemic, non-endemic[62]. There is a seasonal pattern of JE outbreak in temperate regions like Japan, China, Nepal, northern India[63]. Non- endemic countries usually don't have JE vaccination programs as there are almost no incidences of JE. When individual travel from non-endemic to JE endemic countries, it is necessary for them to get vaccinated. As vaccination is the only way to get themselves protective against JE. There are several types of vaccine are available against JE. Type of vaccine and doses depend on the area and the vaccine type available in that region[64]. JE vaccine is highly recommended to the international travellers visiting endemic regions in raining season, especially if they are visiting for more than a month [65, 66].

Guidelines for Endemic Region Travelers

With the availability of safer JE vaccines, the Expert committee advice comprised of two categories, either consider vaccination or advise vaccine[67]. The Advice category states as follows: health professional or provider should advise all travellers to endemic areas like Southeast Asia about the risk and consequences of JE and characteristics of available vaccines [68]. JE vaccines are recommended to all expatriates, repeat and prolong duration travellers, to the ant traveller with travel itinerary including rural areas, travellers looking for maximum protection[68]. The second category to consider one states that all travellers visiting exotic JE areas should consider vaccination against JE especially during rainy season. All those travellers those have maximum outdoor exposure, are of age more than 50 years, has a history of a chronic condition, history of solid transplant, hypertension, chronic renal disease, anti-TNF therapy, diabetes mellites etc. should take JE vaccination in consideration[1].

Interchangeability of JE Vaccines

Interchangeability of JE vaccines is possible, but it depends upon certain conditions and factors like vaccines options available in that particular region and primary dose JE vaccine. The type of vaccine and vaccine availability effect the interchangeability process. It also depends on the recommended guidelines for JE vaccine in that region. Some regions only have live attenuated JE vaccines like Asian regions and some regions have inactivated vaccines[69]. Data related all JE vaccine interchangeability isn't available. Here are some reported case studies related different type of JE vaccine interchangeability:

Interchangeability of Live JE And Inactivated JE Vaccine

The Inactivated Vaccine like Vero cell derived JE vaccines (JE-VC, IXIRO) has replaced the conventional mouse brain derived JE vaccine (JE-MB) for travellers' vaccination against Japanese encephalitis. Studies had reported that a single dose of JE-VC boost the immune response efficiency in the JE-MB primed vaccinated individuals. JE-VC elicit cross protective immune response against non-vaccine JE genotypes including the emerging genotype-1. Erra and its colleagues had studied 48 travellers with categories; one group received primary JC-VC vaccine and second those received JE-MB vaccine as primary dose followed by a single JE-VC booster dose and third group JE-mb as primary and booster dose. Serum samples were collected after two years and plaque reduction neutralization test [70] against seven JE strain were performed from genotype 1-IV. PRNT 50 titer ≥10 considered protective. Primary series with JE-VC showed 87-93% cross protection again genotype II-IV and 73% against genotype-I. After homologous or heterologous single dose to JE-MB primed subjects showed 89-100% sero-protection against genotype I-VI [71].

There is no data available for the interchangeability of Vero-cell culture based JE vaccine those previously received inactivated mouse brain JE vaccine. Woolpert and colleagues had studies military personnel who received≥ 3 doses of mouse brain inactivated vaccine or naïve Je vaccine were inoculated with the 2 doses of JE-VC on 0 and 28th day. Serum samples were collected and antibody titer was measured pre-vaccination and on the 28th day after each dose. Sero-protection rate and geometric mean titer between previously vaccinated participants post dose 1 and vaccine – naïve JE participant post dose two. Seventy JE naïve and 53 previously vaccinated participants were enrolled and evaluated for GMTs. Previously vaccinated individuals had higher GMTs pre, post dose-1 and dose-2. Sero-protection in previously vaccinated and post dose -1 was 100% as compared to the vaccine naïve participant post dose-2 with is 93 %. The geometric mean titer GMTs were higher in previously vaccine participants as compare to the vaccine naïve JE participants post dose-2. The GMTs in previously vaccinated participants post dose-1 were (315; 95% Cl 191-520) as compared to the vaccine naïve post dose-2 (GMT79; 95% CL54-114). This study concluded that the military personnel previously vaccinated with ≥ 3 doses of mouse brain and a single dose of JE-CV (IXIARO) had significantly higher GMTs and 100% sero-protection rate [72].

Interchangeability of Live Attenuated Vaccine Followed by Live Chimeric Vaccine

There is limited data on the interchangeability between Japanese encephalitis chimeric virus vaccine and the SA14-14-2 strain live attenuated JE vaccine. Pakpoom and colleagues studied this interchangeability by open label clinical trial in Thai children, those have previously received the SA14-14-2 JE vaccine as primary dose. After 2 years booster dose was administered and serum samples were collected. A 50% plaque reduction neutralization test against three JE virus strains JE-VC, wild type and SA14-14-2 was measured at the time of vaccination and post 28 days of vaccination. The geometric mean titers were calculated, and adverse effects were calculated. In this study participants those hand PRNT50 pre and

post vaccination were 92% and 96% against JE-VC and 65% and 98% against SA14-14-2 against wild type JE virus respectively. This study concluded that the chimeric JE vaccine booster dose is highly immunogenic and safe in those individuals received SA14-14-2 vaccine previously**[73].**

Interchangeability of Inactivated Mouse Brain Vaccine Followed by Live Chimeric Vaccine

As JE vaccine is needed for effective control and prevention of Japanese encephalitis. Live attenuated chimeric JE virus vaccine JE-CV have been developed. This vaccine has a single dose regime. A study was conducted by using open-labelled, cross over study. Hundred children from age 2 to 5 years with the history of 2-dose primary mouse brain derived inactivated JE vaccine were screened according to the Thai Expended Program of Immunization, and 200 vaccine naïve of age 12-24 months old toddles were randomized 1:1 to receive JE-CV. They had ≥ 4 log 10 plaque forming units, one month before and after Hepatitis A control vaccine. Plaque reduction neutralization50 (PRNT50) was assessed before and after 28 days after chimeric vaccination and at 7 and 12 months. Results showed that all 2-5 years old and 96% of the 12-24 months old toddles had more than 10-unit titer protection after 28 days of chimeric vaccine administration. The geometric meat titer GMTs in theses age groups were 2633 (1928-3600) and 281 (219-362) respectively. While the sero-protection rates in these 2 age groups were 97% and 84% respectively. GMTs in these 2 groups were 454 and 62.3 respectively. Wild type virus was neutralized by this vaccine induced neutralizing antibodies. This study results showed that single dose of chimeric JE vaccine elicit good safety profile and induced significant immune response in both JE naïve toddles and in JE primed young children **[74].**

Following study was conducted to evaluate the interchangeability of Inactivated mouse brain JE vaccine followed by live chimeric JE vaccine. It was a five year follow up study of two age groups; one is of 205 years children and second one was of 12-24 months old toddlers. A single dose of live attenuated chimeric JE vaccine was given and immune response assessment was conducted over the period of time. They were initially vaccinated with mouse brain derived inactivated JE vaccine [74]. A five year follow up study was conducted to assess the immune response persistence over time. Four addition follow up visits of the children after 2,3,4,5 years were arranged, and immunological assessment was performed. It was concluded that the immune response in 2-5year old mouse brain JE vaccine primed children persisted over time. After 5 years of visit the sero-protection rate in the children was 100% with GMT of 2521/dil. No decrease in sero-protection rate over time. In vaccine naïve toddler's protective immune response persisted up to 5 years in 58.8% after single dose administration of chimeric JE vaccine with GMT (26.21/dil: sensitivity analysis) **[75].**

Interchangeability of Inactivated Mouse Brain Vaccine After Live Attenuated Vaccine

In the following study the interchangeability of inactivated mouse brain vaccine followed by live attenuated vaccine was evaluated. As live attenuated SA14-14-2 JE vaccine was administered at a very huge scale like almost 100 million children in china got vaccinated by this vaccine since 1988. So, clinical trials to evaluate its immune response were designed and carried out. Eighty-four children were assessed for side effects and immune response to the single dose JE vaccine was given at the age of 1-3 years of age. In this assessment no significant side effects seen. Serum was collected and neutralizing antibody titer was determined. Serum had neutralizing antibodies with GMTs 188 in almost 96% of the children. Previously JE vaccinated 10 children with two to three doses of inactivated JE vaccine and booster of SA14-14-2 vaccine produced an anamnestic response with GMTs of 3378. This study concluded that live attenuated SA14-14-2 JE vaccine is a suitable candidate as an alternative to the only commercially available JE vaccine for national childhood immunization programs in Asia [76].

Interchangeability of Inactivated mouse brain vaccine followed by live attenuated vaccine was assessed through open labelled single arm trial in the Colombo District of Sri Lanka. In these healthy children of age 2 to 5 years who received two or three doses of inactivated mouse brain JE vaccine were administered with a live attenuated JE vaccine. All candidates were monitored for side effects throughout the year. Serum samples were collected and evaluated at 28 and 365days post booster dose administration. Plaque reduction neutralization test was performed and characterized as the proportion of the participants seroconverting. Before vaccination the 98% of the 2-year old's and 99.3% of the 5-year-old children had sero-protective titer. After 28 days of vaccination, 53.7% of 2-year-old and 40.8% of 2-year-old had achieved seroconversion. GMTs rose from 697 to 3175 in 2-year-old and 926 to 2776 in 5-year-old children after 28-day post vaccination. This study concluded that administration of live attenuated JE vaccine pre-existing neutralizing antibody titers were safe and resulted in boosting of antibody level **[77].**

Interchangeability of Live Chimeric Follow by Inactivated MB (JE-VAX)

Interchangeability of Live chimeric follow by inactivated MB (JE-VAX) was assessed through double blind phase 2 trials. In this trial 99 adults received vaccine, placebo, or 17D vaccine. Chimeric JE vaccine was well tolerated with no difference in side effects among all groups. Chimeric JE vaccine and YF-VAX viremia was of short duration and of low titer. In this study, 87 adults received graded dose of vaccine from 1.8 -5.8 log (10). Second dose was administered at 30-day post vaccination and had no side effects. There was no interference was observed in YF- VAX inoculated candidates. YF-Vax didn't interfere with chimeriVAX-JE but there was a suggestion that ChimeriVAX-JE interfere with YF-VAX administered 30 days later. In another study explored immunological memory in both cases who had received ChimeriVAX-JE 9 months before and ChimeriVAX-JE naïve adults boosted with the inactivated mouse brain vaccine.

Significant immune response was observed in preimmunize individuals. According to this study ChimeriVAX-JE showed protective immune response after single dose**[3, 78].**

JE inactivated Vero cell derived vaccine JENVAC to the live attenuated SA14-14-2 vaccine

JE vaccination is recommended in endemic population and also to the travellers to the endemic areas. A Vero cell derived JE inactivated SA14-14-2 strain vaccine is recently made available for travellers from non-endemic regions. This vaccine has replaced the traditional Mouse brain derived vaccines. This vaccine licensed in 2009 and available for travellers in Europe, Australia, USA and other countries. This vaccine was approved by the European Medicine Agency and US Food and Drug Administration in 2013 for use in children[79].

Interchangeability, immunogenicity, safety of JE inactivated Vero cell derived vaccine JENVAC to the live attenuated SA14-14-2 vaccine in healthy children reported by Krishna and colleagues. This study was phase 4, open labelled, multicentre, randomized controlled trails of 360 children. In this trail all children had received a single dose of JENAVAC or SA14-14-2. They were monitored for the time frame of 2 years until 720day post vaccination. Every child had received second or booster dose of the vaccine. This study showed that single dose vaccination with JENVAC titer remained for one year of post vaccination. There is an appreciable interchangeability between both vaccines with JENVAC/JENVAC or combination exhibiting a highest immune response[80].

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CONCLUSION

In this review different types of JE vaccines are discussed. Issues faced by the western travellers visiting JE endemic regions are discussed with possible solutions. The difference between JE vaccines in Asia and Western regions are discussed with the challenges faced by Western travellers. Interchangeability of JE vaccine for travellers is a complex issue which needs more exploration. Several JE vaccine interchange case studies are discussed and they have showed significant sero-protection in all described cases. But this data isn't sufficient, more research is needed. As the wellbeing and safety of the travelers remain at the heart of the matter, addressing challenges is the need of the hour.

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All acknowledgments should be typed in one paragraph directly preceding the reference section.
The preferred spelling of the word "acknowledgment" inAmerica is without an "e" after the "g". Avoid the stiltedexpression, "One of us (R. B. G.) thanks . . ." Instead, try "R. B.G. thanks". Put sponsor acknowledgments in the unnum-beredfootnote on the first page

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