# BACKGROUND PAPER ON

# JAPANESE ENCEPHALITIS VACCINES

Prepared by the SAGE Working Group on

Japanese encephalitis vaccines

October 1, 2014

## Contents

# 1. Introduction

## *1.1 Background*

Japanese encephalitis (JE) is the leading cause of viral encephalitis in Asia. The pathogen is a mosquito-borne flavivirus, and its transmission is maintained through a enzootic cycle with *Culex* mosquitos, pigs and water birds. Symptomatic JE, most commonly manifest as encephalitis, is rare and thought to occur in approximately 1 in 250 infections. However, of JE cases, the case fatality rate can be as high as 30%, and permanent neurologic or psychiatric sequelae can occur in 20-30% of survivors, such as paralysis, recurrent seizures, or inability to speak. There is no antiviral treatment for patients with JE, and clinical care is supportive to relieve symptoms and stabilize the patient.

Among available control strategies, such as vector control and animal vaccination, human vaccination is the most effective tool against JE. Although human vaccines have been available since the early 1960s, there are still unnecessary JE morbidity and mortality due to a lack of vaccination programs in high risk areas. Of the 24 countries considered endemic to JE, half have no routine JE vaccination program (Figure 1).

The last WHO vaccine position paper (VPP) on JE vaccines was published in 2006. A number of developments have occurred that require revision of the JE VPP, including widespread availability of inactivated Vero cell vaccines, a GMP-compliant live attenuated vaccine, and a live chimeric vaccine. While previously inactivated mouse brain-derived vaccines were the primary product used globally, there are now a number of other products that were either previously limited to local production or not yet licensed. Three products are now WHO prequalified vaccines and eligible for UN procurement.

As a result of the recent availability of WHO prequalified vaccines, Gavi, the Vaccine Alliance, has opened a financing window to support vaccination campaigns among those aged 9 months to 14 years in at-risk areas. This support is contingent upon countries then introducing JE vaccine into the routine vaccination program in these areas.

This changing product landscape and improved access to JE vaccines necessitates a revised WHO VPP on JE vaccines. In addition, many countries have gained experience with JE vaccination, and these experiences were reviewed. This Background Paper describes the relevant data reviewed by the SAGE Working Group on JE Vaccines (Appendix 1) and the resulting proposed recommendations for JE vaccine use (Section 7), for SAGE deliberation and consideration.

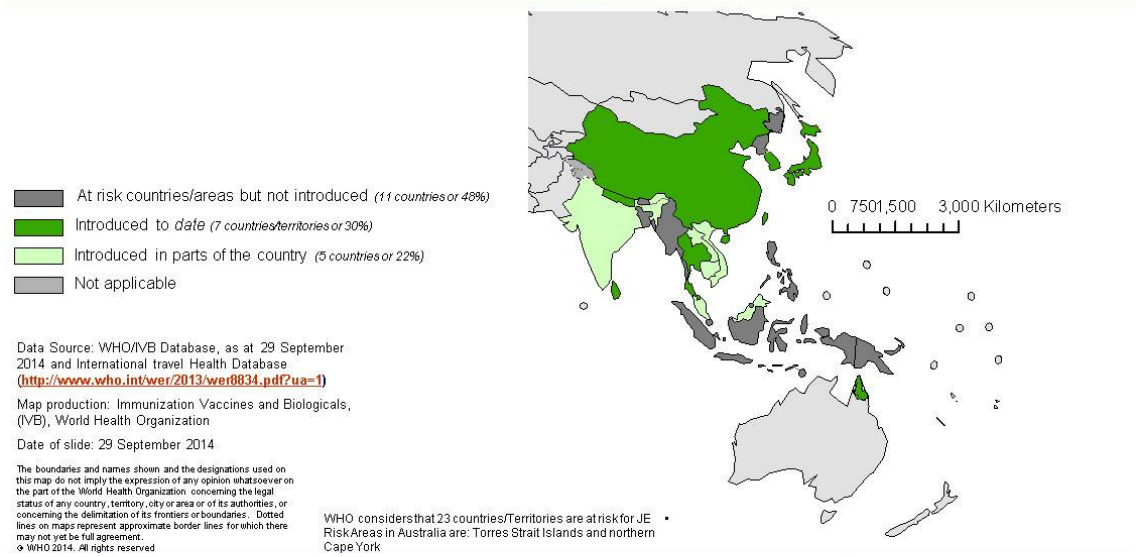



**Figure 1.** Areas at risk of JE and use of JE vaccines, 2014

## 2. JE epidemiology and burden of disease

A recent systematic review of the literature estimates 67,900 cases of JE each year, with approximately 13,600 to 20,400 deaths, and an overall incidence rate of 1.8/100,000 (Campbell 2011). An estimated 3 billion people live in the 24 countries in the WHO South East Asia and Western Pacific regions at risk of JE. Most infections are asymptomatic or mild, such as fever and headache. Although severe clinical disease is rare (about 1 case per 250 infections), JE disease can be devastating. The case-fatality rate can be as high as 30%, with 20-30% of survivors suffering permanent intellectual, behavioral, or neurological problems.

Japanese encephalitis is a single-stranded RNA virus in the family *Flaviviridae*. Genetic sequences of JE are categorized into five genotypes. While genotype 3 used to be the predominantly circulating genotype, there has been a shift towards circulation of genotype 1, with genotype circulation associated with temperate and tropical climates (Schuh 2013).

JE is transmitted by *Culex* mosquitos (primarily *Culex tritaeniorhynchus*) and circulates in an enzootic cycle between mosquitos, pigs, and/or aquatic birds that serve as amplifying hosts. With these animal reservoirs, JE cannot be eliminated but can be controlled with universal human vaccination. Humans are considered dead-end hosts, with viraemia too low for further transmission.

The first case of JE was documented in 1871 in Japan. Because JE is predominantly, although not exclusively, a rural disease, and laboratory confirmation is challenging, the true reach of the virus and burden of disease is not well understood. The current estimate of nearly 68,000 cases, which took into account similar ecological zones and existing vaccination programs to predict incidence in areas without data, is a rough estimate. Incidence estimates are dynamic as the level of virus transmission varies from year to year, but vaccination programs are increasingly helping to control disease. Better surveillance is needed to improve the estimate of the burden of disease. Underreporting is a key problem for understanding the burden of JE disease, but attempts were made to address this to the extent possible in the Campbell 2011 estimate. Some studies used in the

Campbell estimate relied on an incomplete network of sentinel hospitals and were subject to underreporting, which could result in a biased estimate. There were other potential sources of error including (i) a lack of standardized laboratory testing methods (ii) incomplete collection of clinical samples (e.g. failure to collect and test both acute- and convalescent-phase samples); and (iii) the co-circulation of other cross-reactive flaviviruses (especially dengue viruses) in some JE-endemic areas. Surveillance data are needed to fully understand the local and global burden of JE and better identify areas at risk of disease. Epidemiology of JE in neighboring countries (States or Provinces in large countries) with similar ecological profiles may be useful to determine JE disease burden.

Some countries are identifying JE in new areas, suggesting expansion due to changing land use patterns or vector adaptation. Cases have even been detected in cities such as Kathmandu, Nepal, and New Delhi, India, in the absence of rural travel (Partridge 2007, Kumari 2013).

Annual incidences vary by age group, and have been estimated to be in the range of 5.4 per 100,000 in the 0-14 year age group, and 0.6/100,000 in the ≥15 year age group (Campbell 2011). These values mask tremendous variation across regions, with incidence in the younger age group estimated as high as 12.6/100,000 in some high incidence areas (e.g. parts of China, Democratic People's Republic of Korea). While traditionally considered a childhood disease, available data suggest that in many areas of the world it is a disease of all ages. As the numbers of cases in children decrease due to successful vaccination programs, there is frequently a shift to a greater proportion of cases in older, unvaccinated age groups. But even in some areas without vaccination programs, such as Bangladesh, over 50% of cases are in the adult age groups (Hossain 2010). In Thailand, 69% of individuals 20-24 years had protective levels of neutralizing antibody, and by 40 years of age, approximately 10% of the population did not have protective levels of antibody titers. (Yoocharoan 2009). Among a sample of 12-18 year-olds in the Philippines (unvaccinated), the seroprevalence rate was just 44% (Dubischar-Kastner 2012b). These data suggest an important proportion of adults are still susceptible. How severity differs by age group is not well understood, in part because of the lack of follow up of many cases. The age-specific incidence may be considered when designing immunization programs, and some countries, such as Nepal, have chosen to conduct campaigns in which all individuals over one year of age were vaccinated in select areas.

WHO guidelines for JE surveillance are available[1]. Because there are no clinical signs of JE that distinguish it from other causes of encephalitis, acute encephalitis syndrome (AES) cases should be laboratory-tested for JE. WHO recommends testing for the presence of JE virus-specific IgM antibody in a single sample of CSF or serum, using an IgM-capture ELISA specifically for JE antibody, as the preferred method for laboratory confirmation. A more detailed approach to diagnostics for surveillance is outlined in the WHO guidelines.

## *2.1 Risk of JE in the context of immunization programs*

Because JE virus transmission is preserved in the enzootic cycle, elimination is not currently possible and susceptible individuals will continue to be at risk of disease even when few cases are observed due to good vaccination programs. As human are believed to be dead end hosts, vaccination has no impact on transmission and thus offers no indirect protection. Environmental sampling has

[1] http://whqlibdoc.who.int/hq/2003/who_v&b_03.01.pdf

demonstrated continued virus circulation despite few apparent cases, e.g. in Japan, highlighting the importance of continued vaccination.

## 3. Methods for Working Group Evidence Review

### *3.1 Key topics for consideration*

Per the SAGE Guidelines for the Development of Evidence-Based Vaccine-Related Recommendations[2], important questions were identified for review to inform proposed recommendations. Eleven policy questions were identified (Appendixes 2 and 3), which were further stratified into three critical questions and eight important questions. Available evidence for the three critical questions was identified through a systematic literature search (see section 3.2).

**Box 1.** Critical and important policy questions for JE vaccine recommendations

**Critical policy questions**

1. What is the effectiveness (including immunogenicity) of JE vaccines?
2. What is the risk of serious adverse events following JE vaccination?
3. Is there need for a booster dose following immunization with the primary series of JE vaccination?

**Important policy questions**

4. Can JE vaccines be safety and effectively co-administered with other vaccines?
5. Can JE vaccines be safety and effectively use in special populations?
6. What is the role of inactivated mouse brain-based JE vaccines in the context of other products?
7. What is the appropriate age of administration for JE vaccines in the routine immunization schedule?
8. What is the appropriate JE vaccine introduction strategy in an endemic country without a vaccination program?
9. What is the impact of JE vaccine introduction on JE disease at a country or regional level?
10. What is the cost-effectiveness of JE vaccination?
11. What is the global prevalence and disease burden of JE?

### *3.2 Data retrieval and synthesis*

The primary method to identify relevant data was a systematic search of the literature using PubMed, Embase, the Cochrane Clinical Trial Database, Index Medicus for South-East Asia Region (IMSEAR), and the Western Pacific Region Index Medicus (WPRIM). A convenience search of the China Academic Journals Full-text Database was also done (The systematic review protocol is available upon request). The search was completed initially on February 27, 2014 and updated on June 4, 2014. The search was general for JE vaccines and so covered all topics in the critical questions. The search was also capitalized upon for data to address the non-critical questions. Articles in non-English languages were reviewed by native speakers when possible. No articles were excluded due to the study population or type of study. Animal studies were excluded.

[2] http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf

Two independent reviewers screened all abstracts for inclusion, followed by a full text screen. References were categorized by the type of vaccine studied and the data available to answer policy questions. Working Group members and/or the Secretariat reviewed the evidence and presented the data and key conclusions at a face-to-face meeting of the Working Group 10-12 June, 2014.

Additional data not yet published were sought and provided to the WG by PATH, Chengdu Institute of Biological Products, Valneva, and Sanofi Pasteur. A catalogue of clinical trials and results available on clinicaltrials.gov was also done. WHO-HQ with WPRO and SEARO also conducted a survey of JE-endemic countries to determine if countries had additional unpublished data that could be useful to the recommendation development process. These multiple data inputs were further reviewed and considered by the WG in their formulation of proposed JE vaccine recommendations.

## 4. Overview of JE vaccines

Approximately 15 JE vaccines are currently in use globally (Appendix 4). All vaccines are based on genotype 3 virus strains. Given the large number of vaccines in use, focus was placed on vaccines that are internationally distributed and/or WHO prequalified. Given a shift in the vaccine landscape away from mouse brain-derived vaccines, emphasis was also placed on non-mouse brain vaccines. The four major types of JE vaccines are:

1. Inactivated Vero cell vaccines
2. Live attenuated vaccines
3. Chimeric vaccines
4. Inactivated mouse brain-derived vaccines

### *4.1 Inactivated Vero cell vaccines*

A number of inactivated Vero cell JE vaccine products have become available in the last five years (Appendix 4). The most widely marketed inactivated Vero cell vaccine is the IC51 inactivated Vero cell-derived vaccine, developed by Valneva Scotland Limited (formerly Intercell Biomedical) and known as IXIARO in the US and Europe (JESPECT in Australia and New Zealand), and first licensed in 2009. A vaccine manufactured by Biological E was developed through a technology transfer agreement with Intercell; this vaccine, JEEV, was WHO pre-qualified in July, 2013, for 18-49 year-olds, and in June, 2014, for 12-35 month olds. Clinical studies in support of an indication for 3-17 year olds are on-going. Other inactivated Vero cell products include two from Japan (JEBIK V manufactured by Biken, and ENCEVAC manufactured by Kaketsuken), one from China (JEVAC manufactured by Liaoning Chengda Bioltechnology Co), and a second from India (JENVAC manufactured by Bharat Biotech). These different vaccine products are based on different JE strains and are recommended for use based on different schedules, frequently with boosters. JEBIK V and ENCEVAC have no adjuvant, while the others contain aluminium hydroxide adjuvant.

IXIARO is based on the JE SA14-14-2 vaccine virus produced in Vero cells, and consists of inactivated, purified virus antigen. It is alum-adjuvanted and contains phosphate buffered saline as excipient and protamine sulphate in residual amounts (in contrast to inactivated mouse brain-derived vaccines, which contain gelatin and murine proteins). It is licensed for individuals from 2 months onwards in non-endemic settings.

### 4.2 Live attenuated vaccines

The live attenuated SA 14-14-2 vaccine is manufactured by the Chengdu Institute of Biological Products (CDIBP) and has been licensed in China since 1988. It is frequently referred to as the live attenuated SA 14-14-2 vaccine, or its trade names CD.JEVAX or RS.JEV (for the rest of this document it will be referred to as CD.JEVAX). It is licensed and used in several countries in Asia (Table 1, Appendix 4). The SA 14-14-2 vaccine virus is produced in primary hamster kidney cells. It contains gelatin, saccharose, human serum albumin, and sodium glutamate as excipients. A standard dose is not less than 5.7 log plaque forming units (PFU) per ml.

In partnership with PATH, CDIBP built a new GMP-compliant facility (approved by the Chinese Food and Drug Administration in 2011), and in October 2013, the CDIBP live attenuated vaccine was WHO prequalified for individuals starting at 8 months of age. Two other live attenuated vaccines are manufactured in China but are not exported (and were not reviewed).

### 4.3 Chimeric vaccines

Only one product in this class has been licensed. Sanofi Pasteur developed a live attenuated chimeric viral vaccine, marketed as IMOJEV, prequalified by WHO in September 2014. It was created using recombinant DNA technology by replacing the premembrane (prM) and envelope (E) coding sequences of the yellow fever live attenuated 17D vaccine virus with the SA 14-14-2 live attenuated JE vaccine virus. The vaccine was first licensed in Australia in 2012 and is now also in use in the public sector in Malaysia and Brunei and licensed in the Philippines, Thailand, and Myanmar. It is licensed in individuals 9 months of age and older. Each dose contains 4.0-5.8 log PFU. Mannitol, lactose, glutamic acid, potassium hydroxide, histidine, human serum albumin, and sodium chloride are excipients.

### 4.4 Inactivated mouse brain-derived vaccines

Inactivated mouse brain vaccines were first developed in the 1960s. Many countries have produced or continue to produce their own mouse brain-derived vaccine products (e.g. Vietnam, Thailand and the Republic of Korea). In 2006, Biken, formerly a major producer of a globally-distributed mouse brain-derived JE vaccine (JEVAX) discontinued manufacture of the product, leading to a major shift in the product use across the globe (Table 1).

In 2006, the WHO position paper stated that mouse brain-derived vaccines should be gradually replaced by new generation JE vaccines. Given this, and the continued agreement with this statement, mouse brain-derived vaccines were not reviewed systematically, in contrast to the other categories of products.

**Table 1.** Overview of JE vaccine use by country, sector, and scale. Results are based on a 2014 country survey, a WER/MMWR joint report (Baig 2013), and expert information. This table reflects commercialization of products, not just licensure.

| Current JE-Endemic Country Vaccine Use | | | |
|---|---|---|---|
| **Country** | **Vaccine (Public market)** | **National/ Subnational** | **Vaccine (Private market)** |
| Australia | Chimeric | Subnational | Chimeric, Vero cell (inactivated) |
| Bangladesh | None | NA | None |
| Bhutan | None | NA | None |
| Brunei Darussalam | Chimeric | Subnational | Chimeric |
| Cambodia | Live attenuated | Subnational | Mouse brain (inactivated) |
| China | Live attenuated | National* | Vero Cell (inactivated)<br>Live attenuated |
| Democratic People's Republic of Korea (the) | None | NA | Unknown |
| India | Live attenuated<br>Inactivated Vero cell (adults) | Subnational | Mouse brain (inactivated)<br>Vero Cell (inactivated) |
| Indonesia | None | NA | None |
| Japan | Vero Cell (inactivated) | National | Vero Cell (inactivated) |
| Lao People's Democratic Republic (the) | Live attenuated | Subnational | None |
| Malaysia | Chimeric | Subnational | None |
| Myanmar | None | NA | Chimeric (expected 2015) |
| Nepal | Live attenuated | Subnational | Live attenuated |
| Pakistan | None | NA | Unknown |
| Papua New Guinea | None | NA | None |
| Philippines (the) | None | NA | Chimeric |
| Republic of Korea | Mouse brain (inactivated)<br>Live attenuated | National | Vero Cell (inactivated)<br>Live attenuated |
| Russian Federation (the) | None | NA | Unknown |
| Singapore | None | NA | Vero Cell (inactivated) |
| Sri Lanka | Live attenuated | National | Mouse brain (inactivated) |
| Thailand | Mouse brain (inactivated)<br>Live attenuated** | National | Live attenuated<br>Chimeric |
| Timor Leste | None | NA | None |
| Vietnam | Mouse brain (inactivated) | Subnational | None |

*Excluding non-endemic provinces

**Distribution limited geographically

## 5. Review of the evidence for critical issues

### *5.1 General principles*

The following three topics were identified as critical to be reviewed for the policy decision: protection against disease, vaccine safety, and duration of protection. For vaccine protection, three measures are theoretically acceptable: vaccine efficacy, vaccine effectiveness, and immunogenicity. There have only been two efficacy trials of a JE vaccine in the past (Hsu 1971, Hoke 1988), both of which enrolled over 65,000 children. Clinical trials of JE vaccines currently use immunological endpoints as a surrogate of protection, because the rarity 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 ($PRNT_{50}$). Seroconversion is defined as $PRNT_{50}$ titer <10 at baseline and ≥10 post vaccination at time of serum sampling, or a 4-fold rise from a baseline titer of ≥10 (Hombach 2005, WHO TRS 2014). Immunogenicity analyses are influenced by the virus strain used in the $PRNT_{50}$ assay (homologous vs. non-homologous) as well as the cell substrate (e.g. use of LLC-MK2 cells elicit higher GMTs than Vero cells). **Immunogenicity results should be considered in the context of the serological assay reagents, and caution should be exercised in doing any cross-study comparisons for these reasons.** 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. International reference reagents for standardizing $PRNT_{50}$ titers are urgently needed, and a collaborative study has been initiated. Vaccine effectiveness studies have been undertaken for mouse brain-derived vaccines and the live attenuated vaccine but have not been possible for inactivated Vero cell vaccines or chimeric vaccine. In the following review, the $PRNT_{50}$ neutralization assay results reported are done using homologous virus unless otherwise specified.

Another important issue is the relevance of natural boosting (i.e. boosting the vaccine-induced immune response by exposure to wild circulating virus), and implications for booster doses. Particularly for newer vaccines with limited follow up time in endemic areas, it is unclear how long protective level of antibodies will last, and whether natural boosting contributes to maintaining protective antibody level. Due to this ambiguity, data from endemic areas were the primary source for recommendations, without presumption that natural boosting will be sufficient. However, data available from some settings in which vaccinated children who are followed longitudinally found some vaccinees were seronegative at one visit and seroprotected at a subsequent visit (e.g. Sohn 2008). This observation suggests that natural boosting occurs but whether these children were protected prior to the boost cannot be determined. **In summary, the Working Group concluded that there should be positive evidence of vaccine breakthrough cases to justify a global recommendation for booster doses given the programmatic and financial implications**. However, policy makers should base their national recommendations on a careful assessment in their own epidemiologic situation and should have mechanisms in place to monitor for vaccine failure to feedback into national recommendations for booster doses.

**Table 2.** Currently available evidence by vaccine type

| | Immunogenicity data | Efficacy data | Effectiveness data |
|---|---|---|---|
| Inactivated mouse brain vaccines | ✘ | ✘ | ✘ |
| Inactivated Vero cell vaccines | ✘ | | |
| Live attenuated vaccines | ✘ | | ✘ |
| Chimeric vaccines | ✘ | | |

For safety monitoring, a better definition of cases of serious adverse events, using standard case classifications, such as the Brighton Collaboration definitions, and more active case investigation

would be valuable. Future immunization campaigns should be accompanied by strengthened AEFI monitoring and investigation activities.

Encephalitis has not been established as causally related to vaccination with live attenuated, including chimeric, JE vaccines. However, it is important to thoroughly investigate any occurrence of a neurological illness that occurs in temporal association with JE vaccination to rule out this possibility. Coincidental cases of encephalitis should be expected (and have been reported), especially during mass campaigns. An appropriate investigation will help maintain confidence in the vaccination program.

## *5.2 Inactivated Vero cell-based vaccines*

### 5.2.1 Available data

The vast majority of publically available data on inactivated Vero cell-based vaccines have been generated for a single product, IXIARO, developed by Valneva. Ten studies have contributed immunogenicity data, eight of which were among adults from non-endemic settings up to 3 years after the primary series. Two observational studies have also been done collecting immunogenicity data from travelers and military personnel. There are no effectiveness data at this time.

There are only limited data available for the WHO prequalified product JEEV (Biological E), which for pre-qualification purposes was considered "sufficient given the acceptance of the degree of similarity between JEEV and IC51 (IXIARO) in terms of same raw materials (cell banks and virus seed banks), same process flow and compliance of the two vaccines with the same in-process controls and release specifications."[3] Therefore, the review of the evidence was entirely based on IXIARO, the only vaccine currently with broad international distribution. There are additional locally produced and distributed inactivated Vero cell vaccines such as JENVAC (Bharat Biotech), JEBIKV (Biken), ENCEVAC (Kaketsuken), and JEVAC (Liaoning Chengda Biotechnology Co). Any extension of recommendations to other products should be done with careful consideration and caution.

### 5.2.2 Immunogenicity of a primary series

[3] http://www.who.int/immunization_standards/vaccine_quality/pq_266_je_1dose_biologicale_updated_vpsar.pdf

**Table 3.** Clinical trials of inactivated Vero cell vaccine (IXIARO): seroprotection rates (95%CI) by time since first dose (of two dose series given 28 days apart).

| Study ID | Country | Age | N | 2M | 6M | 12M | 15M | 18M | 2Y | 3Y | Serology* | Reference/Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IC51-221** | India | 1-3Y | 24 | 95.7 (87.3-104) | | | | | | | SA 14-14-2/ Vero | Kaltenbock 2010 |
| IC51-323** | Philippines | 2-6M | 1869 | 100 (NR) | | | | | | | SA 14-14-2/ Vero | Dubischar-Kastner 2012a |
| IC51-323** | Philippines | 6-12M | | 95 (NR) | | | | | | | SA 14-14-2/ Vero | Dubischar-Kastner 2012a |
| IC51-323** | Philippines | 1-3Y | | 97 (NR) | | | | | | | SA 14-14-2/ Vero | Dubischar-Kastner 2012a |
| IC51-323** | Philippines | 3-12Y | | 94 (NR) | | | | | | | SA 14-14-2/ Vero | Dubischar-Kastner 2012a |
| IC51-323** | Philippines | 12-18Y | | 77 (NR) | | | | | | | SA 14-14-2/ Vero | Dubischar-Kastner 2012a |
| IC51-325** | Philippines | 2M-17Y | 300 | 100 (NR) | 86*** (NR) | 89.9 (NR) | | | 89 (NR) | 90.1 (NR) | SA 14-14-2/ Vero | Dubischar-Kastner Quoted with permission |
| IC51-301** | USA, Germany, & Austria | 18-80Y | 430 | 98 (NR) | | | | | | | SA 14-14-2/ Vero | Tauber 2007 |
| IC51-301 & 302W** | Austria, Germany, & Romania | 18-86Y | 181 | 99 (96.1-99.7) | 95 (90.8-97.4) | 83 (77.3-88.1) | | | 82 (75.5-86.7) | 85 (78.3-89.7) | SA 14-14-2/ Vero | Schuller 2008A / CDC 2011 / EMEA SPC |
| None** | USA | 18-49Y | 25 | 95 (NR) | 100.0 (NR) | 100.0 (NR) | | 90.0 (NR) | 87.5 (NR) | | SA 14-14-2/ Vero | Lyons 2007 |
| IC51-304/ IC51-305** | Germany & Northern Ireland | 18-76Y | 115 | 97.3 (94.4-100.0) | 82.8 (74.9-88.6) | 58.3 (49.1-66.9) | | | 48.3 (39.4-57.3) | | SA 14-14-2/ Vero | Schuller 2009/ Dubischar-Kastner 2010A |
| IC51-308** | Austria & Germany | 18Y+ | 58 | 98.2 (NR) | | | | | | | SA 14-14-2/ Vero | Kaltenbock 2009 |
| IC51-311 | Austria & Germany | 19-66Y | 198 | | | | 69.2 (62.4-75.2) | | | | SA 14-14-2/ Vero | Eder 2011 |

*Serology measured by $PRNT_{50}$ neutralization assay

**Seroconversion rates reported

***Month 7

**Table 4.** Observational studies of inactivated Vero cell vaccine (IXIARO): seroprotection rates (95%CI) by time since first vaccination (of two dose series given 28 days apart).

| Study ID | Country | Age | N | 2M | 2Y | Serology* | Reference/Notes |
|---|---|---|---|---|---|---|---|
| 382/E7/07 | Finland & Sweden | 18-69Y | 31** | 94 (NR) | 87 (NR) | Nakayama/LLC-MK2 | Erra 2012/ Erra 2013 |
| 382/E7/07 | Finland & Sweden | 18-69Y | 31** | 97 (NR) | 93 (NR) | SA 14-14-2/LLC-MK2 | Erra 2012/ Erra 2013 |
| NA | USA | 19-41Y | 70 | 93 (NR) | | SA 14-14-2/Vero | Woolpert 2012 |

*Serology measured by $PRNT_{50}$ neutralization assay

**Decreased to 15 participants at 2 years

Across multiple studies in adults, high rates of seroprotection have been found one month following completion of the two-dose primary series (Table 3). In the largest study of 430 adult vaccine recipients, the seroprotection rate was 98% and the GMT was 244 (Tauber 2007). Among children living in an endemic setting, there are two studies, one in India (N=24 vaccinees aged 1-3 years; Kaltenböck 2010) and one in the Philippines (N=1,411 IXIARO vaccinees aged 2 months - 17 years, 396 assessed for immunogenicity; Dubischar-Kastner 2012a). In the small Indian study, 95.7% (95% CI: 87.3-100) of vaccinees who received the age appropriate dose[4] were seroprotected one month following the second dose with a GMT of 201 (95% CI: 106-380). In the Philippines, the age appropriate dose[4] elicited the following titers in the 2-<6 months, 6-<12 months, 1-<3 years, 3-<12 years, and 12-<18 years age groups, respectively: 637, 367, 258, 235, and 171.

**Conclusions:** Inactivated Vero cell vaccines (based on two doses of IXIARO given in the indicated age range, generally starting at 2 or 6 months, at a one month interval) have evidence of seroprotective neutralizing antibody titers at 1 month after primary immunization. The seroprotection rates and GMTs gradually decline over the following 12 months post immunization.

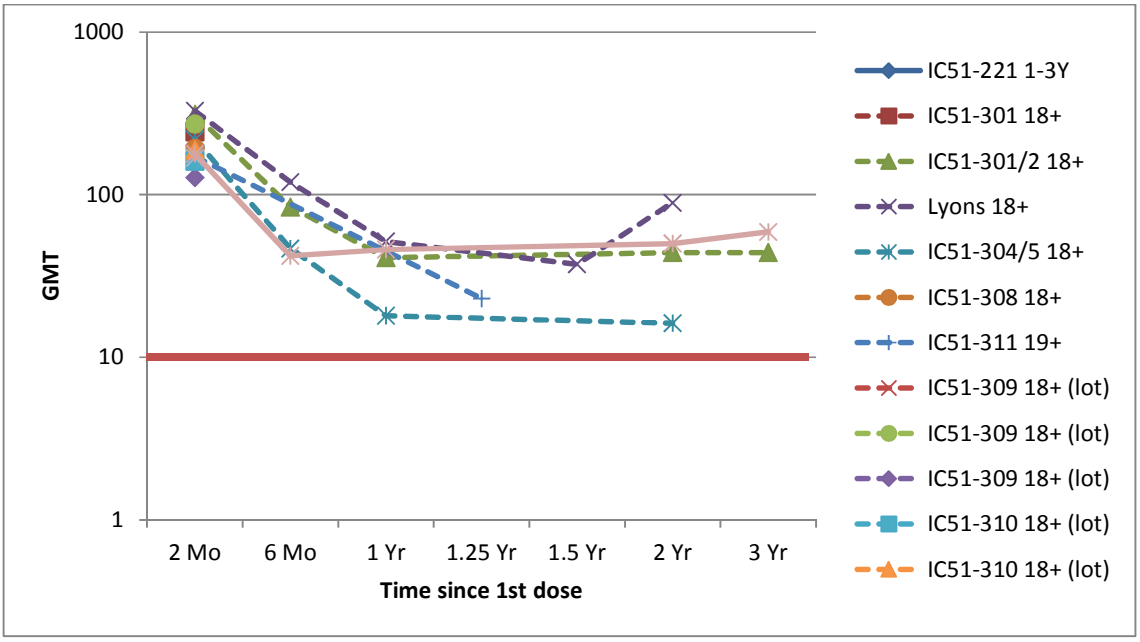



**Figure 2.** Reported GMTs from clinical trials by time since first dose (participants received 2 doses of IXIARO administered 28 days apart). No co-administration and no booster doses were given. Red line at GMT of 10 represents the accepted threshold of protection.

### 5.2.3 Long-term protection

Data in adults from non-endemic settings suggest a decline in seroprotection rates and GMTs in the 24 months following primary immunization (Tables 3 and 4). One study in Austria, Germany, and Romania found seroprotection rates dropped from 99% (95% CI: 96.1-99.7) at one month following the primary series to 82% two years later and 84.9% (95% CI: 78.3-89.7) three years later (Schuller

[4] 0.25ml 2 months to <3 years of age, 0.5ml 3-18 years of age.

2008a; CDC 2011); however, these results were obtained from a study population among which some had previously been exposed or vaccinated against tick-borne encephalitis (TBE). Another study compared participants who tested positive by TBE ELISA to assess the impact of previous TBE vaccination: one month following completion of the primary series 96% were seropositive (GMT 573.9) compared to 91% (GMT 186.7) among TBE ELISA negative participants (Schuller 2008b). Another study in Germany and Northern Ireland (where there is no TBE) found seroprotection rates dropped from 97.3% (95% CI: 94.4-100.0) to 48.3% (95% CI: 39.4-57.3) over a two-year period (Schuller 2009; Dubischar-Kastner 2010a). A booster dose is indicated >12 months after the primary series in non-endemic settings for longer protection.

In a follow-on from a clinical trial in European adults, 198 subjects were given a booster dose 15 months following primary vaccination (Eder 2011). While 69% were seroprotected prior to the booster dose, 100% were seroprotected one month after the booster, and 98.5% were seroprotected 12 months after the booster. The GMTs were 22.5 pre-booster, and 900, 487, and 361 at 1, 6, and 12 months after the booster.

In another small study, adult participants not seroprotected at 6 or 12 months following primary vaccination were given a booster dose at month 11 or 23, respectively; one month following the booster dose 100% were seroprotected with high GMTs (Dubischar-Kastner 2010a). Among those boosted at 11 months, the seroprotection rate was still 100% at 13 months after the booster.

There are limited data for IXIARO in children and in endemic settings. In the Philippines study, follow-up was continued for 36 months after the primary series (Dubischar-Kastner 2014 and unpublished, quoted with permission from Valneva). One hundred 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 three years was 90%. The GMT decreased between 2 month and month 7, but then was relatively stable through the 3 years of follow up (49-52). Data by age is 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. There are some limitations, as it was a small study with a small number of children across a broad age range.

**Conclusions:** Available data on IXIARO given to adults in non-endemic settings suggest a booster will be needed if the primary series was completed more than 1 year previously, consistent with the manufacturer's indication. Booster doses elicit a rapid and robust immune response when given 11-23 months post primary series, and high levels of seroprotection persist for at least one year following the booster. Based on preliminary data from one study of 150 children in the Philippines adequate seroprotective titers may persist for at least three years after the primary immunization. Further studies across a variety of transmission settings and a more detailed assessment of the Philippines study will provide further evidence on the booster needs of IXIARO when used in children living in endemic settings.

### 5.2.4 Safety

Two pooled safety analyses of adult vaccination have been published. In the first pooled 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) (Dubischar-Kastner 2010b; Table 5). For solicited local adverse events up to six days after first vaccination, frequencies were comparable; however, following the second and third doses, they were higher in the JE-VAX

group, particularly for hardening, swelling, and redness. Severe local reactions occurred at a rate of 3.2% in the IXIARO group, 3.1% in the placebo group, and 13.8% in the JE-VAX group. Solicited systemic adverse events occurred within a week after the first dose in a similar proportion of participants across the three groups (33% IXIARO, 29% JE-VAX, 31% placebo). There was a higher incidence of systemic reactions after the first dose than after the second or third doses. Three and one half percent of participants experienced a hypersensitivity reaction or allergy-associated adverse events in the IXIARO group, 5.5% in the JE-VAX group, and 3.7% in the placebo group. One case of death of a 70-year old woman diagnosed with adenocarcinoma of the lung was reported in the IXIARO group after the second vaccination, which was judged unrelated to the vaccine. In summary, in adults there was comparable tolerability and reactogenicity with placebo (adjuvant alone) and mouse brain-derived JE vaccine except for local reactions. A significantly lower frequency of severe local reactions was reported for IXIARO compared to mouse brain-derived JE vaccine.

**Table 5.** Overview of adverse events (AE) in subjects with at least one AE following IXIARO, JE-VAX, or placebo across 7 clinical trials (from Dubischar-Kastner 2010b). AEs were graded by the investigator as follows: *mild*: awareness of signs or symptoms, but easily tolerated; *moderate*: discomfort enough to interfere with usual activity; *severe*: incapable of work or usual activity. Serious AEs were defined based on the standard ICH-E6 guideline from July 2002.

| **Subjects with at least one of:** | **IXIARO (N=3558)** | **JE-VAX (N=435)** | **Placebo (N=657)** |
|---|---|---|---|
| Any AE | 64.1% | 64.1% | 61.2% |
| Severe AE | 5.8% | 4.4% | 6.4% |
| AE leading to withdrawal | 0.8% | 1.8% | 0.8% |
| Serious AE | 1.1% | 0.7% | 2.0% |
| Death* | 0.0% | 0.0% | 0.0% |
| AE considered related to vaccine | 38.3% | 34.3% | 38.8% |
| Severe AE considered related to vaccine | 2.4% | 1.4% | 2.7% |
| AE leading to withdrawal considered related to vaccine | 0.4% | 0.9% | 0.2% |
| Serious AE considered related to vaccine | 0.0% | 0.0% | 0.0 |

*One death occurred in IXIARO group but considered unrelated

The most recent analysis includes a summary of safety data across 10 clinical trials in 4,043 adult vaccinees as well as the first 12 months of post-licensure passive reporting data (Schuller 2011). Sixty-six percent of all clinical trial participants experienced any adverse events (39% considered vaccine related). The most common vaccine-related adverse events were headache (19%), myalgia (13%), fatigue (10%), flu-like illness (9%), and nausea (5%).

In reviewing post-marketing data for the first 12 months following vaccination in Europe, the US, and Australia, 25 reports of AEFIs were submitted, with an overall rate of reporting of 10.1/100,000 doses distributed (consistent with reporting rates for other new vaccines). The most frequently reported AEFIs were rash, fever, and headache. The reporting rate for serious AEFIs was 1.6 per 100,000 doses distributed (4 serious AEFIs: neuritis, meningism, oropharyngeal spasm, and iritis). Hypersensitivity reactions were observed at a rate of 3.6 per 100,000 doses compared to 8.4 per 100,000 doses reported for the mouse brain-derived vaccine JE-VAX in the USA.

In a clinical trial of children aged two months to one year in the Philippines, a similar percentage of participants receiving IXIARO (N=131) or Prevnar (N=64) experienced solicited (58.0% vs. 59.4%),

unsolicited (72.5% vs. 65.6%), and serious (0% vs. 1.6%) adverse events up to Day 56 after the first vaccination (European Assessment Report 2013).

**Table 6.** Rates of serious adverse events or medically attended adverse events up to day 56 (28 days post dose 2). Total numbers were back-calculated from percentages when not reported.

| Age group | Ixiaro 0.25 mL | Ixiaro 0.5 mL | Prevnar | HAVRIX 720 |
|---|---|---|---|---|
| ≥ 2 months to < 1 year | 50/131 (38.2%) | - | 27/64 (42.2%) | - |
| ≥ 1 year to < 3 years | 171/640 (26.7%) | - | - | 47/213 (22.1%) |
| ≥ 3 years to < 12 years | 7/100 (7.0%) | 24/301 (8.0%) | - | 6/100 (5.9%*) |
| ≥ 12 years to < 18 years | - | 4/240 (1.7%) | - | 3/80 (3.8%) |

*Discrepancy between back-calculation (6/100) and reported percentage (5.9%).

For IXIARO, in children and adolescents from two months to <18 years the safety profile is comparable with licensed vaccines (pneumococcal conjugate and hepatitis A vaccines) in regards to frequency and severity of local and systemic adverse events.

GACVS has reviewed data on IXIARO (and JEEV) and determined it has an acceptable safety profile (GACVS 2013).

**Conclusions:** Inactivated Vero cell vaccine (specifically IXIARO) has an acceptable safety profile based on currently available data. According to the WHO prequalification assessment, these data can be considered to support the safety of JEEV. However, because of the potential for minor differences in the manufacturing process, which may accumulate over time for the two vaccines, the safety data reported from IXIARO might not apply to the safety of JEEV in the future. Safety of JEEV should be monitored.

## *5.3 Live attenuated vaccines*

### 5.3.1 Available data

As the live attenuated SA 14-14-2 vaccine (CD.JEVAX) has been licensed and in use in China since 1988, studies in China have contributed to the acceptance of the safety and effectiveness profile (e.g. Zhou 2001, Zhou 1999, Ma 1993, Wang 1993). However, due to the passage of time since the studies were completed, the non-randomized design, limited detail in the methods sections, possible minor variations in the vaccine, and use of a 2-dose schedule in some studies, focus was given to studies of the CDIBP live attenuated vaccine that have been published more recently, especially those employing GMP compliant vaccine lots. In addition to studies primarily focused on the live attenuated vaccine, it has also been used as a control in investigational studies of other products. In total, seven RCTs and three observational studies contributed to the immunogenicity and safety data. Four effectiveness studies, public regulatory assessments, and post-licensure safety monitoring data that contributed to the evidence review. All trial data are limited to infants and children; there are no clinical trial data on immunization of adults.

### 5.3.2 Immunogenicity of a single dose

**Table 7.** Clinical trials of live attenuated JE vaccine: seroprotection rates (95%CI) by time since vaccination.

| Study ID | Country | Age | N | 28D | 6M | 1Y | 2Y | 3YR | Serology | Reference/Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| JEV01/02 | Philippines | 8M | 70 | 92.1 (84.3-96.7) | | 90.4 (81.9-95.8) | 81.1 (71.5-88.6) | 79.3 (69.3-87.2) | Beijing-1/LLC-MK2 | Victor 2014, clinicaltrials.gov |
| JEV01/02 | Philippines | 10M | 173 | 90.6 (85.3-94.4) | | 86.1 (80.6-90.6) | 80.7 (74.6-85.9) | 81.9 (75.8-87.0) | Beijing-1/LLC-MK2 | Victor 2014, clinicaltrials.gov |
| JEV05 | Bangladesh | 10-12M | 146 | 86.3 (79.8-91.0) | | | | | Beijing-1/LLC-MK2 | Zaman 2014 (original facility) |
| JEV05 | Bangladesh | 10-12M | 195 | 82.1 (76.1-86.8) | | | | | Beijing-1/LLC-MK2 | Zaman 2014 (GMP lot 1) |
| JEV05 | Bangladesh | 10-12M | 192 | 80.2 (74.0-85.2) | | | | | Beijing-1/LLC-MK2 | Zaman 2014 (GMP lot 2) |
| JEV05 | Bangladesh | 10-12M | 194 | 84.5 (78.7-89.0) | | | | | Beijing-1/LLC-MK2 | Zaman 2014 (GMP lot 3) |
| JEC07 | Thailand | 9-18M | 150 | 99.3 (96.3-100.0) | 97.2 (93.1-99.2) | 97.3 (93.1-99.2) | | | JE-CV/Vero | Feroldi 2014 |
| JEC07 | Thailand | 9-18M | 150 | 97.3 (93.1-99.2) | 89.0 (82.7-93.6) | 87.5 (81.0-92.4) | | | SA 14-14-2/LLC-MK2 | Feroldi 2014 |
| JEC12 | Korea | 12-24M | 136 | 99.1 (NR) | | | | | JE-CV/Vero | Kim 2013 |

**Table 8.** Observational studies of live attenuated JE vaccine: seroprotection rates (95%CI) by time since vaccination.

| Study ID | Country | Age | N | 28D | 90D | 4Y | 5.5Y | Serology | Reference/Notes |
|---|---|---|---|---|---|---|---|---|---|
| NA | Korea | 1-3Y | 68 | 96 (NR) | | | | SA 14 (UTMB) | Sohn 1999 |
| NA | Thailand | 9-15M | 140 | 89.3 (83.1-93.4) | 95 (90.0-97.6) | | | Beijing-1&SA 14-14-2/LLC-MK2 | Chotpitayasunodh 2011 |
| NA | Thailand | 9-11M | 93 | | 95.7 (NR) | | | Beijing-1&SA 14-14-2/LLC-MK2 | Chotpitayasunodh 2011 |
| NA | Thailand | 12-15M* | 47 | | 93.6 (NR) | | | Beijing-1&SA 14-14-2/LLC-MK2 | Chotpitayasunodh 2011 |
| NA | Nepal | 1-15Y | 69 | | | 89.9 (NR) | 63.8 (NR) | Beijing-1&SA 14-14-2/LLC-MK2 | Sohn 2008 |

*Subset of 9-15M study reported above

PATH has sponsored two RCTs in children administered a single dose of vaccine at ages 8-12 months, in the Philippines and in Bangladesh (Victor 2014, Zaman 2014). Seroprotection rates[5] at 28 days post-vaccination in the Philippines study were 92.1% (95% CI: 84.3-96.7) and 90.6 (95% CI: 85.3-94.4); the latter result was in the group administered measles vaccine one month prior. In a lot-to-lot consistency study in Bangladesh with vaccine from a new GMP-compliant facility, seroprotection rates ranged between 80.2% (95% CI: 74.0-85.2) to 86.3% (95% CI: 79.8-91.0)[6]. Two lots were not equivalent with a seroprotection rate difference of -4.33 (-11.94-3.31). When reviewed for WHO prequalification, the results were considered sufficient to support the consistency of the lots (WHO PSAR 2013). The seroprotection rate was 97.3% (95% CI: 93.1-99.2) for the live attenuated vaccine when used as a control in a chimeric JE vaccine RCT in children aged 9 months to 18 years in Thailand (Feroldi 2014). In a similar study in children 12-24 months in Korea, the seroprotection rate was 99.1% (Kim 2013)[7]. These results are consistent with immunogenicity results from observational studies in children in Korea and Thailand (Sohn 1999; Chotpitayasunondh 2011)[8].

GMTs measured from these studies are more variable (Figure 3), although GMTs and the lower bound of associated 95% confidence intervals are always magnitudes above the accepted protection threshold of 10. At 28 days post-vaccination GMTs were 203 (95% CI: 141-293) and 139 (95% CI: 110-178) in the Philippines (Victor 2014), while GMTs ranged from 52.8 (95% CI: 42.9-65.1) to 77.3 (95% CI: 59.6-100.4) in Bangladesh (Zaman 2014). GMTs were 370 (95% CI: 291-470) in 9-18 month-olds in Thailand (Feroldi 2014). Due to variable challenge viruses and serological assays, and the lack of standardized reagents, overall, it was considered critical that the GMT and confidence intervals were above the accepted correlate of seroprotection.

**Conclusion:** Live attenuated vaccine (CD.JEVAX) has evidence of seroprotective neutralizing antibody titers post-immunization. This is based on an age of administration of ≥8 months.

[5] $PRNT_{50}$ using the non-homologous Beijing-1 strain in LLC-MK2 cells
[6] GMP lot B and original facility, respectively
[7] $PRNT_{50}$ using JE chimeric virus strain in Vero cells
[8] $PRNT_{50}$ using Beijing-1 and SA 14-14-2 in LLC-MK2 cells

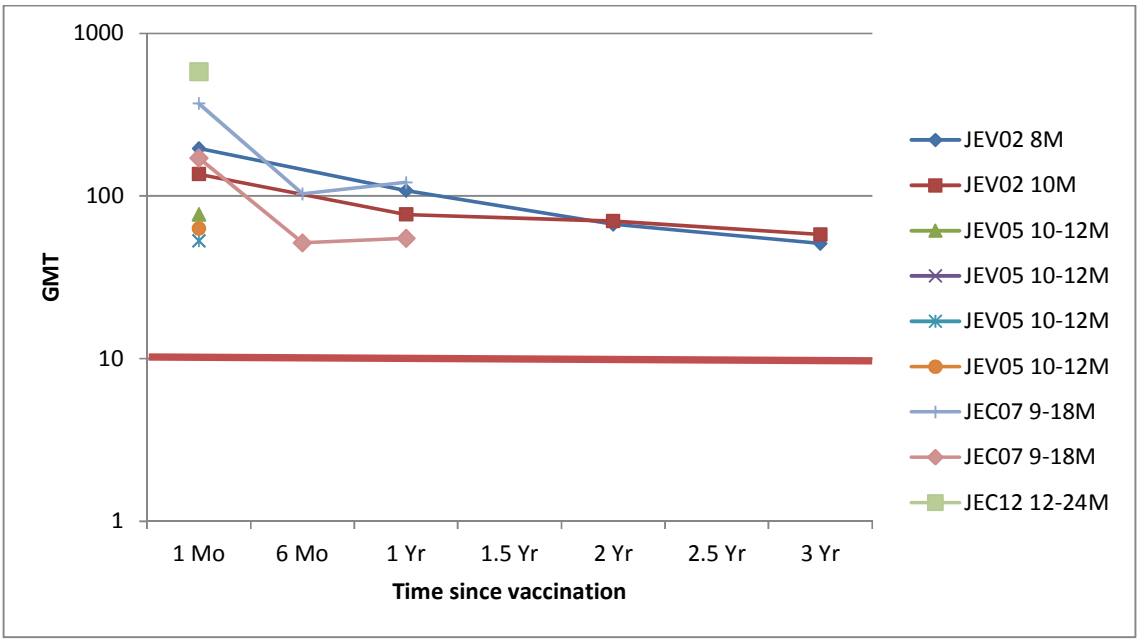



**Figure 3.** Reported GMTs for live attenuated vaccines (CD.JEVAX) from clinical trials by time since vaccination. No co-administration and no booster doses were given. Red line at GMT of 10 represents the accepted threshold of protection.

### 5.3.3 Long-term immunogenicity

Long-term immunogenicity data are limited. The PATH study in the Philippines measured immunogenicity of a single dose of CD.JEVAX (and no other vaccine administered for at least 28 days) for three years (quoted with permission from PATH, publication pending)[9]. Among 8 month-olds administered a single dose of CD.JEVAX, seroprotection was measured at 90.4% (95% CI: 81.9-95.8), 81.1% (95% CI: 71.5-88.6), and 79.3% (69.3-87.2) at 1 year, 2 years, and 3 years post vaccination. Among 10 month-olds, the corresponding seroprotection rates were 86.1% (95% CI: 80.6-90.6), 80.7% (95% CI: 74.6-85.9), and 81.9% (95% CI: 75.8-87.0). These figures are consistent with 12-month immunogenicity results from a study of Thai children aged 9-12 months (Feroldi 2014). A convenience study in Nepal of 69 individuals vaccinated at ages 1-15 years found seroprotection rates of 89.9% and 63.8% at four and five years after vaccination, respectively (Sohn 2008).

GMTs appear to decrease gradually over the first 1-2 years post vaccination. In the Philippines study, GMTs among 8 month-old vaccines declined from 108 (95% CI: 70-167) to 67 (95% CI: 46-99) to 51 (95% CI: 37-71) at 1, 2, and 3 years after vaccination (NCT00412516 results). Among 10 month-old vaccinees, the corresponding GMTs were 77 (95% CI: 60-98), 70 (95% CI: 54-92), and 58 (95% CI: 45-73). Data beyond three years is not currently available. In Thailand (Feroldi 2014; NCT01092507 results), immunogenicity dropped from 171 (95% CI: 138-212) 28 days post-vaccination to 51.4 (95% CI: 41.6-63.6) six months post-vaccination and 54.8 (95% CI: 43.9-64.8) one year post-vaccination. These data may be suggestive of a plateauing in immune response.

[9] $PRNT_{50}$ using the non-homologous Beijing-1 strain in LLC-MK2 cells

Available data suggest a good anamnestic response in individuals given a second dose (booster) of live attenuated vaccine (Choi 2013, Sohn 2008). In the Sohn study conducted in Nepal described above, those who were seronegative 5.5 years after primary immunization were given a booster dose. The GMTs among these seronegative children were 169 and 392 at seven days and one month after the booster, respectively. The seroprotection rate was 76% and 82% at these same time points.

### 5.3.4 Effectiveness

Following a mass vaccination campaign in Nepal in 1999 (in children aged 1-15 years), effectiveness using case-control studies was measured at different time points after the campaign. Shortly after the campaign, an outbreak of JE occurred that allowed for an immediate assessment of effectiveness. Between one week and one month post-campaign, vaccine effectiveness was estimated at 99.3% (95% CI: 94.9-100) (Bista 2001). Vaccine effectiveness was then estimated at 98.5% (95% CI: 90.1-99.2) (Ohrr 2005) and 96.2% (95% CI: 73.1-99.9) (Tandan 2007) at one year and five years post-campaign. The outbreak experienced shortly after the campaign may have boosted immunization. A case-control study in India estimated vaccine effectiveness at 94.5% (95% CI: 81.5-98.9) six months following a mass campaign (Kumar 2009). A more recent case-control study in India estimated vaccine effectiveness at 84% (95%CI: 53-95) at 0-38 months post-vaccination (Murhekar 2014). All of these studies were based on a relatively small number of cases (20-35). A study conducted more than 20 years ago in China estimated vaccine effectiveness at 80% (95%CI: 44-93), which covered cases identified up to 14 years post-vaccination (Hennessy 1996). This same study estimated vaccine effectiveness at 97.5% (95%CI: 86- 99.6) with two doses. Children had received JE vaccine as part of the routine immunization program in China, and the study authors noted the quality of the program at that time, in terms of maintenance of the cold chain and vaccine administration techniques, was unknown.

Some countries, including China and recently India, administer CD.JEVAX as a two-dose series. Informal discussions with countries suggest much of the rationale for a two-dose schedule comes from programmatic reasons, primarily enhancing coverage and vaccinating missed children rather than a concern about protection with one dose.

**Conclusion:** Available immunogenicity data indicate children vaccinated with a single dose at ≥8 months have adequate seroprotective titers at three years. Good vaccine effectiveness up to five years was demonstrated in children vaccinated at 1-15 years of age in an endemic area. Studies and continued monitoring when used in vaccination programs are needed to assess whether a booster dose is warranted. Based on available but limited data, currently no booster is recommended. Careful long-term follow up is needed to monitor for potential vaccine failure (i.e., the need for a booster dose), in particular because one study in Bangladesh utilizing vaccine from the new GMP compliant facility showed somewhat lower levels of seroprotection one month following vaccination compared to results using vaccine from the old facility. Program monitoring and/or special studies should be considered in different endemic settings where the level of natural boosting may vary. Continued monitoring of seroprotective titers beyond year three is encouraged. Individuals given a booster dose respond rapidly with a good anamnestic response.

### 5.3.5 Safety

Data from multiple RCTs (including primary vaccination, booster vaccination, and co-administration studies) as well as post-marketing surveillance data and available case reports were reviewed. In

children aged nine months to six years, live attenuated vaccine had moderately higher frequency and severity of local and systemic adverse reactions, including fever, compared to chimeric vaccine (Feroldi 2014; Kim 2013). No vaccine-related serious adverse reactions or deaths were reported in RCTs (up to 7 months follow up) except for two cases of pyrexia in children aged 12-23 months (Table 9, Study 2).

**Table 9.** Comparison of chimeric vaccine IMOJEV and live attenuated vaccine CD.JEVAX in 2 observer-blind RCTs (Feroldi 2014, Kim 2013). Study 1 included children 9-18 months, study 2 included children 12-23 months.

| | **IMOJEV** | | **CD.JEVAX** | |
|---|---|---|---|---|
| | **Study 1** | **Study 2** | **Study 1** | **Study 2** |
| | **N=146** | **N=137** | **N=152** | **N=137** |
| **Children experiencing at least one:** | **%** | **%** | **%** | **%** |
| **Solicited injection site reaction (day 0-7)** | **37.7** | **32.8** | **44.1** | **40.9** |
| - Injection site tenderness | 30.1 | 25.5 | 37.5 | 27.7 |
| - Injection site erythema | 17.8 | 16.8 | 23.0 | 24.1 |
| - Injection site swelling | 6.2 | 4.4 | 7.9 | 7.3 |
| **Solicited systemic reaction (day 0-14)** | **45.2** | **52.6** | **57.9** | **53.3** |
| - Fever | 16.4 | 24.6 | 21.7 | 25.0 |
| - Vomiting | 14.4 | 6.6 | 26.3 | 10.2 |
| - Crying abnormal | 19.2 | 19.7 | 25.7 | 25.5 |
| - Drowsiness | 17.1 | 16.8 | 25.0 | 24.1 |
| - Appetite loss | 21.9 | 27.7 | 35.5 | 29.2 |
| - Irritability | 28.1 | 22.6 | 38.2 | 26.3 |
| **Unsolicited AE** | **34.7** | **-** | **50.0** | **-** |
| -related injection site reactions | 1.4 | - | 0.7 | - |
| -related systemic reactions | 0 | - | 0 | - |
| **SAEs** | **9.5** | **12.4** | **11.8** | **13.1** |
| - related SAEs | 0 | 0 | 0 | 1.5 (pyrexia in 2) |

In an older trial in China (Liu 1997) among 26,239 participants aged one, two, or six years, health centers were randomized to vaccinate (13,275 children) or to not vaccinate (12,964 children). Study participants were followed up for one month post vaccination. All illnesses prompting a health center visit during the 30-day study period including the diagnosis were recorded. At day 30 parents underwent a structured interview regarding hospitalizations and illnesses that occurred since the initial visit. Rates of adverse health outcomes reporting to the health center were comparable between groups.

Passive reporting of adverse events following vaccination with the live attenuated vaccine has been undertaken in China (Liu 2014). Based on 23 million doses distributed between 2005-2012, 1426 adverse events were reported (61 per million doses), although this is likely an underestimate as is typical with all passive surveillance systems. Nearly forty percent of reports were allergic reactions, usually generalized rash. The most frequently reported event was fever greater than 38.6$^{o}$C (22.37 reports per million doses), followed by generalized rash (21.86 reports per million doses). There were 36 SAEs and 31 neurologic events reported including three cases of viral encephalitis, two

cases of encephalopathy, and two cases of ADEM. Reports on cases of encephalitis and 2 deaths following administration of CD.JEVAX were found non-conclusive but were judged unrelated to the vaccine (Jia 2011; Liu 2014). However, this emphasizes the need for more complete investigations of neurological illness following vaccination.

GACVS has reviewed data on the live attenuated vaccine on multiple occasions and determined it has an acceptable safety profile (GACVS 2013, GACVS 2008, GACVS 2007, GACVS 2005).

**Conclusion:** Live attenuated (CDIBP) vaccine has an acceptable safety profile based on currently available data.

## *5.4 Chimeric vaccines*

### 5.4.1 Available data

As a new vaccine, the chimeric JE vaccine (IMOJEV®) is well characterized in clinical trials. In total, seven RCTs for safety and immunogenicity were conducted with published results in endemic countries (three additional RCTs from non-endemic settings). No observational studies are yet available. Data from the endemic setting ranges from 9 months to 10 years, however the number of vaccinees in the 9-12 month age group was limited to around 60 across two studies.

### 5.4.2 Immunogenicity of a single dose

**Table 10.** Clinical trials of chimeric JE vaccine: seroprotection rates (95%CI) by time since vaccination.

| Study ID | Country | Age | N | 28-30d | 42d | 6 M | 1YR | 2YR | 3YR | 4YR | 5YR | Serology | Reference/Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| JEC07 | Thailand | 9-18M | 149 | 99.3 (96.2-100,0) | | 94.5 (89.4-97.6) | 88.1 (81.6-92.9) | | | | | JE-CV/Vero | Feroldi 2014 |
| JEC07 | Thailand | 9-18M | 149 | 97.2 (93.1-99.2) | | 84.1 (77.2-89.7) | 76.8 (68.9-83.4) | | | | | SA 14-14-2/LLC-MK2 | Feroldi 2014 |
| JEC12 | Korea | 12-24M | 137 | 100.0 (NR) | | | | | | | | JE-CV/Vero | Kim 2013 |
| JEC01 | Thailand | 12-24M | 200 | 96 (92-98) | | 87 (NR) | 82 (NR) | 80 (NR) | 75 (NR) | 74 (NR) | 65.6 (NR) | JE-CV/Vero | Chokephaibulkit 2010a / Quoted with permission from Sanofi Pasteur |
| JEC02* | Thailand & Philippines | 12-18M | 1059 | 95.0 (93.3-96.3) | | | | 80.3 (NR) | | | | JE-CV/Vero | Feroldi 2012 & 2013 |
| JEC02 (subset) | Thailand & Philippines | 12-18M | 591 | 100 (99.4-100.0) | | | 88.2 (85.3-90.7) | | | | | JE-CV/Vero | Feroldi 2010 |
| JEC04* | Taiwan | 12-18M | 110 | | 97.9 (NR) | | 96.6 (NR) | | | | | JE-CV/Vero | Huang 2014 (JE-CV followed by MMR) |
| JEC04* | Taiwan | 12-18M | 220 | | NR | | 96.8 (NR) | | | | | JE-CV/Vero | Huang 2014 (MMR followed by JE-CV) |
| JEC15 | Philippines | 36-42M | 46 | 89.7 (75.8-97.1) | | | | | | | | JE-CV/Vero | Feroldi 2013 |
| H-040-004*† | India | 9M-10Y | 33 | 100 (NR) | | | | | | | | JE-CV/Vero | clinicaltrials.gov |
| H-040-004*† | India | 9M-10Y | 33 | 25 (NR) | | | | | | | | Nakayama/? | clinicaltrials.gov |
| H-040-004*† | India | 9M-10Y | 33 | 82 (NR) | | | | | | | | Indian WT/? | clinicaltrials.gov |
| H-040-009* | USA & Australia | 18-65Y | 410 | 99.1 (97.5-99.8) | | | | | | | | JE-CV/Vero | Torresi 2010 |
| H-040-009* | USA & Australia | 18-65Y | 410 | 80.9 (76.4-84.9) | | | | | | | | Nakayama/Vero | Torresi 2010 |
| H-040-005* | Australia | 18-55Y | 202 -> 93 | 99 (96-100) | | 97 (93-99) | 95 (87-99) | 90 (81-96) | | | 94# (82-99) | JE-CV/LLC-MK2 | Nasveld 2010a |
| H-040-008*† | USA | 18-65Y | 30 | 100 (NR) | | 92 (NR) | 92 (NR) | | | | | JE-CV/Vero | clinicaltrials.gov |

*Seroconversion rate reported at 28-30d and 42d

# Only 45% of original study population remained in the study at this time point

†Used data from clinicaltrials.gov and calculated percentage

High seroprotection rates one month post-vaccination were reported. In the lowest age group (9-18 months), the seroprotection rate was estimated at 99.3% (95% CI: 96.2-100.0) (Feroldi 2014) . Similar results were found in Korea (Kim 2013) among 12-24 month-olds (seroprotection 100%, 95% CI: NR) and in Thailand and the Philippines among 12-18 month-olds (seroprotection 95.0%, 95% CI: 93.3-96.3) (Feroldi 2012). Among 36-42 month-olds, 89.7% (95% CI: 75.8-97.1) were seroprotected one month post vaccination. Lower seroprotection rates were found with some serological assays in a small study in India (e.g., against Nakayama strain and Indian strains, both genotype 3); however, similar results were obtained with the comparator vaccine, a Nakayama mouse brain-derived vaccine, and the virus stock used for testing was reportedly not good (NCT00441259 results, G. Houillon personal communication). Seroprotection rates were also high in three trials among adults in non-endemic settings (e.g. 99.1% seroprotected (95% CI: 97.5-99.8) adults aged 18-65 in the US and Australia (Torresi 2010); see Table 10).

GMTs were also very high in the month following vaccination (Figure 4). Among 9-18 month-olds, GMTs were 507 (95% CI: 395-651) when PRNT was conducted with chimeric virus in Vero cells, and 198 (95% CI: 158-247) when PRNT used SA 14-14-2 in LLC-MK2 cells (Feroldi 2014; NCT01092507 results). In children, GMTs as high as 908 (95% CI: 656-1256) were generated in Korean children aged 12-24 months (Kim 2013).

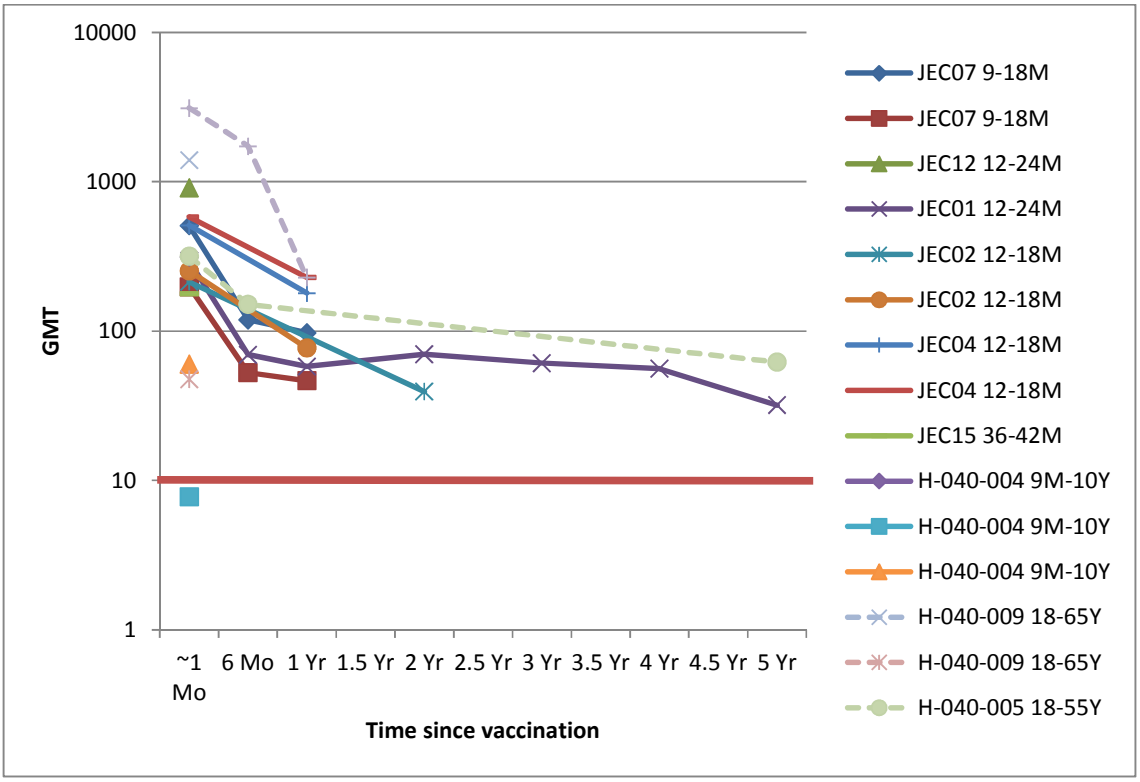



**Figure 4.** Reported GMTs for chimeric vaccine (IMOJEV) from clinical trials by time since vaccination. No co-administration and no booster doses were given. Red line at GMT of 10 represents the accepted threshold of protection.

**Conclusion:** Chimeric vaccine (IMOJEV) has evidence of seroprotective neutralizing antibody titers post-immunization. This is based on an age of administration of ≥9 months.

### 5.4.3 Long-term protection

Among children in endemic settings, four trials followed up participants for 1 year or longer. In one study, between six months and one year post-vaccination, the percent seroprotected dropped from 94.5% (95% CI: 89.4-97.6) to 88.1% (95% CI: 81.6-92.9) (Feroldi 2014). A recent study followed Thai participants vaccinated at 12-24 months for five years of age (quoted with permission from Sanofi Pasteur, data to be presented ACPID 2014). Seroprotection rates fell from 82.2% one year post-vaccination to 80.2%, 75.2%, 74.1%, and 65.6% at two, three, four, and five years post-vaccination, respectively. The corresponding GMTs were 58, 70, 61, 56, and 64 at years one, two, three, four, and five post-vaccination. Long-term protection in adults from another study was much higher. Seroprotection rates among Australia military participants aged 18-55 years were 99% (95% CI: 96-100) one month after vaccination, followed by 95% (95% CI: 87-99), 90% (95% CI: 81-96), and 94% (95% CI: 82-99) at one year, two years, and five years post-vaccination (Nasveld 2010a). However, only 46 participants (45% of the original study population) remained in the study at the final time point. In Australia and Malaysia, IMOJEV is licensed as a two-dose vaccine for the pediatric population and as a single-dose vaccine for the adult population.

Individuals given a booster dose respond rapidly with a good anamnestic response with GMTs quickly rising to levels much higher than with primary immunization. In a study among children 12-18 months in the Philippines, a booster was given two years following the first dose (Feroldi 2013). The seroprotection rate was 80% (GMT 39) just prior to the booster dose, 96% (GMT 231) seven days after the booster dose, 100% (GMT 2242) one month after the booster dose, and 99% (GMT 596) 12 months after the booster dose. Five year follow up data are pending.

In this same study, 68 participants who did not have seroprotective titers two years following primary immunization were re-vaccinated with IMOJEV. In comparing their responses to IMOJEV-naive participants, 82.4% (95% CI: 71.2; 90.5) were seroprotected seven days after vaccination compared with 15.4% (95% CI: 5.9; 30.5) in group receiving IMOJEV as a primary immunization. The seroprotection rate in the boosted group was 100% at day 28 (95% CI: 94.7, 100.0) while it was 89.7% (95% CI: 75.8, 97.1) in the naïve group. These data suggest that although some children did not have seroprotective antibody titers two years after one dose of IMOJEV, they did have a strong anamnestic response following a second dose. Whether or not those children were protected in between the two doses is unknown.

**Conclusion:** Available immunogenicity data indicate children vaccinated at ≥12 months of age have adequate seroprotective titers at two years. One small study shows adequate seroprotective titers up to five years in adults. One study shows some evidence of declining seroprotection rates up to five years after a single dose in children. There are no vaccine effectiveness data available. Based on the data available, including long-term immunogenicity data and anamnestic booster responses in children seronegative after one dose, it is unclear whether a booster is needed for individuals living in endemic areas. It is considered acceptable for countries to introduce IMOJEV as a single dose as long as they carefully monitor for vaccine failures. More data are needed to fully assess the need for a booster dose of IMOJEV in endemic settings. Program monitoring and/or special studies should be done in different endemic settings where the level of natural boosting may vary.

### 5.4.4 Safety

In children 12 months to 18 years IMOJEV chimeric vaccine had a safety profile comparable with licensed vaccines (hepatitis A and varicella zoster) in terms of frequency and severity of local and systemic adverse reactions (Table 11; Chokephaibulkit 2010a, Feroldi 2012, Feroldi 2013). There was lower frequency of fever, injection site erythema and swelling after the first compared to second dose. Table 9 also shows the comparability in safety profiles between CD.JEVAX and IMOJEV. IMOJEV also has a comparable safety profile to MMR vaccine when administered to children 12-18 months old in Taiwan (Huang 2014).

**Table 11.** Rates of solicited injection site reactions, systemic reactions, unsolicited AE, and SAEs among children from two studies in Thailand and the Philippines.

| | IMOJEV | | HEP A | |
|---|---|---|---|---|
| | **Study 1*** | **Study 2**** | **Study 1*** | **Study 2**** |
| | **N=199** | **N=1097** | **N=199** | **N=102** |
| **Children experiencing at least one:** | **%** | **%** | **%** | **%** |
| **Solicited injection site reaction (day 0-7)** | 41 | 39.3 | 36 | 36.3 |
| - Injection site tenderness | 32 | 22.2 | 27 | 17.6 |
| - Injection site erythema | 23 | 24.4 | 20 | 25.5 |
| - Injection site swelling | 9 | 6.9 | 7 | 3.9 |
| **Solicited systemic reaction (day 0-14)** | 49 | 51.0 | 51 | 45.1 |
| - Fever | 21 | 20.5 | 21 | 20.6 |
| - Vomiting | 20 | 19.1 | 22 | 15.7 |
| - Crying abnormal | 23 | 18.5 | 20 | 20.6 |
| - Drowsiness | 18 | 18.4 | 15 | 19.6 |
| - Appetite loss | 26 | 25.9 | 29 | 26.5 |
| - Irritability | 28 | 28.6 | 23 | 27.5 |
| **Unsolicited AE** | - | 48.8 | - | 53.9 |
| - Vaccine-related unsolicited adverse reactions | - | 1.2 | - | 1.0 |
| **SAEs** | - | 3.4 | - | 4.9 |
| - Vaccine-related | 0 | 0 | 0 | 0 |

*Study 1: children aged 12-24 months in Thailand (Chokephaibulkit 2010a)

**Study 2: children aged 12-18 months in Thailand, Philippines (Feroldi 2012)

There are limited data in 9-12 month group to affirm the safety of the vaccine in this youngest age group. More data on the safety of IMOJEV in this age group should be generated.

In adults in two RCTs, comparable tolerability and reactogenicity with placebo and a mouse brain-derived JE vaccine were seen with the exception of local reactions (Torresi 2010). Significantly lower frequency of local adverse reactions was reported for IMOJEV than mouse brain-derived vaccine JE-VAX. The majority of adverse events was mild to moderate and resolved within a few days. Only one vaccine related serious AEFI (high-grade pyrexia) was reported within the first month of vaccination and none during a 6-month follow-up. No case of death occurred (Torresi 2010).

In addition, two serious adverse events (acute viral illness) possibly related to vaccination with IMOJEV were reported during clinical development in adults (Australian Public Assessment Report 2010). Post-marketing safety data were not available to evaluate whether there is risk of rare neurologic adverse events. The chimeric vaccine IMOJEV is based on the Yellow Fever 17D backbone, so yellow fever vaccine-associated viscerotropic disease (AVD) and acute neurotropic disease (NVD) are considered Adverse Events of Special Interest by the company and are being monitored in their

Risk Management Plans. Post-marketing surveillance for rare adverse events is important, especially for the newer products recently introduced to the market.

As IMOJEV is a live, recombinant vaccine, a variety of non-clinical and clinical studies have been undertaken to establish genetic stability, low risk of reversion to a neurotropic virus, low levels of viraemia in vaccinated subjects, lack of transmission by mosquitoes, and lack of replication in JE animal hosts (Guy 2010). Adult subjects demonstrated short duration and low titer viraemia (Monath 2003). In children, JE vaccine-naive children had low virema, while JE vaccine- primed children had no detectable viraemia (Chokephaibulkit 2010a).

GACVS has reviewed data on the chimeric vaccine and determined it has an acceptable safety profile (GACVS 2014).

**Conclusions:** Chimeric vaccine (IMOJEV) has an acceptable safety profile based on currently available data. Safety data in the 9-12 month age group are limited.

### *5.5 Inactivated mouse brain-derived vaccines*

Due to the shift away from mouse brain vaccines, little data have been generated on mouse brain-derived vaccines since the 2006 vaccine position paper. Per the 2006 vaccine position paper:

*In several Asian trials, primary immunization based on 2 doses given at an interval of 1–2 weeks has induced protective concentrations of neutralizing antibodies in 94–100% of children aged >1 year. Although experience from Thailand shows that JE vaccination of children aged 6–12 months may be highly efficacious as well, in most epidemiological settings primary immunization should be given at the age of 1–3 years. Given the mostly infrequent occurrence of JE in infancy and the likely interference with passively acquired maternal antibodies during the first months of life, vaccination is not recommended for children before the age of 6 months. In immunogenicity studies in the USA, seroconversion occurred only in approximately 80% of adult vaccinees following an equivalent 2-dose schedule. In contrast, in US soldiers, a schedule based on vaccination on days 0, 7 and 30 resulted in 100% seroconversion. Following a booster injection approximately 1 year after the primary 2 doses, protective antibody levels have been achieved in practically all children and adults, regardless of geographical region. In people whose immunity is unlikely to be boosted by natural infection, repeated boosters are required for sustained immunity. Australian studies following the outbreak of JE in the Torres Strait demonstrated that in the majority of children the level of neutralizing antibody declines to non-protective concentrations within 6–12 months following primary immunization. About 3 years after the primary series of 3 doses, or the last booster, only 37% of adults and 24% of children had protective antibody levels.*

*In general, the mouse brain-derived JE vaccine has been considered safe, although local reactions such as tenderness, redness and swelling occur in about 20% of vaccinated subjects. A similar percentage of vaccinees may experience mild systemic symptoms, including headache, myalgia, gastrointestinal symptoms and fever. Acute disseminated encephalomyelitis (ADEM) temporally coinciding with JE immunization using the mouse brain-derived vaccine has been reported at frequencies corresponding to 1 case per 50 000–1 000 000 doses administered, but no definitive studies are available. Based on observations of a case of ADEM temporarily associated with JE vaccination, the recommendation for routine childhood JE vaccination has been withdrawn in Japan. However, the Global Advisory Committee on Vaccine Safety concluded recently that there was no*

*definite evidence of an increased risk of ADEM temporally associated with JE vaccination and that there was no good reason to change current recommendations for immunization with JE vaccines. Occasionally, hypersensitivity reactions, in some cases serious generalized urticaria, facial angioedema or respiratory distress, have been reported, principally in vaccine recipients from non-endemic areas. The reported rates of such reactions in prospective and retrospective studies are usually in the range of 18–64 per 10 000 vaccinated subjects. A complicating factor is that such reactions may occur as late as 12–72 hours following immunization. Sensitization to gelatin, a vaccine stabilizer, has been suspected in some cases in Japan, but the underlying cause remains uncertain.*

**Conclusions:** Ideally, mouse brain-derived vaccines should be replaced by newer generation JE vaccines. Manufacturers have been moving away from production of mouse brain-derived vaccines in favor of newer technologies. Mouse brain-derived vaccines may continue to play a role in combatting JE in some countries, but overall these products have a less favorable profile due to the increased reactogenicity compared to newer JE vaccines. In addition, inactivated mouse brain-derived vaccines may be less preferable due to variability of manufacturing, cost, and compared to some other products, number of doses required and need for repeat boosters.

## *5.6 Vaccine Interchangeability*

As countries transition from the use of one product to another, or use multiple products requiring more than one dose, the potential exists for vaccinees to receive more than one product to finish out a series or for the purposes of a booster. Limited data exist on vaccine interchangeability; there have been few studies with small numbers.

**Table 12.** Overview of available data on JE vaccine interchangeability.

| | | **Booster vaccine** | | | |
|---|---|---|---|---|---|
| | | **Inactivated MB** | **Inactivated Vero** | **Live attenuated** | **Chimeric** |
| **Primary vaccine** | **Inactivated MB** | NA | Erra 2012; Erra 2013; Woolpert 2012 | PATH JEV04; Sohn 1999 | Chokephaibulkit 2010a |
| | **Inactivated Vero** | No published data | NA | No published data | No published data |
| | **Live attenuated** | No published data | No published data | NA | No published data |
| | **Chimeric** | Monath 2003 | No published data | No published data | NA |

Of most relevance to endemic countries is likely inactivated mouse brain vaccine followed by vaccination with either live attenuated or chimeric vaccine. Of note, the studies of inactivated mouse brain vaccine followed by inactivated Vero cell vaccine suggested a strong anamnestic response and no serious safety signals (Erra 2012, Erra 2013, Woolpert 2012).

#### 5.6.1 Inactivated mouse brain vaccine followed by live attenuated vaccine

In an open-label non-randomized single-arm trial, 294 two and five year-olds previously immunized with 2-3 doses of inactivated mouse brain vaccine in Sri Lanka were re-vaccinated with live attenuated vaccine CD.JEVAX (quoted with permission from PATH). At day 0, 98.6% (95%CI 96.6-99.6) of participants were seropositive. By day 28 post-vaccination with live attenuated vaccine, 100% (95% CI: 98.8-100) were seropositive, and at one year post vaccination, 99.7% (95% CI: 98.1-100) were seropositive. GMTs ranged from 804 (95% CI: 681-949) at day 0 to 2968 (95% CI: 2679-3289) at day 28 and 2863 (95% CI: 2518-3256) at day 365. There were no safety concerns identified in this study. Another study included 10 children in Korea who had received either two or three doses of inactivated mouse brain vaccine previously (at variable time points and number of doses) and were vaccinated with CD.JEVAX (Sohn 1999). The GMT was 3378 four weeks after re-vaccination with CD.JEVAX, more than 18-fold higher than participants who received live attenuated vaccine for the first time. This strong anamnestic response was seen regardless of whether the participant had detectable neutralizing antibodies prior to boost. No safety data specific to the children who received CD.JEVAX following inactivated mouse brain-derived vaccine were reported.

#### 5.6.2 Inactivated mouse brain vaccine followed by chimeric vaccine

In a prospective, randomized open-label cross-over study in Thailand, 100 2-5 year-olds who had received 2 doses of inactivated mouse brain vaccine as part of the routine immunization program were randomized to receive one dose of chimeric JE vaccine or inactivated hepatitis A vaccine (Chokephaibulkit 2010a). Eighty-six percent of participants were seropositive at baseline. One hundred percent were seropositive 28 days post-vaccination with chimeric vaccine, with a GMT of 2634 (95% CI: 1928-3600). GMTs in previously immunized children decreased to 1055 at seven months (100% seroprotected) and 454 at 12 months (97% seroprotected). There were no vaccine-related serious adverse events and no safety concerns identified in this study. Reactogenicity following chimeric vaccine was comparable to that experienced with hepatitis A vaccine.

## 6. Consideration of other key issues

### *6.1 Recommendations for Introduction*

JE vaccination should be extended to all areas where JE is recognized as a public health priority. Even if the number of JE-confirmed cases is low, vaccination should be considered where there is a suitable environment for JE transmission (e.g., presence of animal reservoirs, ecological conditions supportive of virus transmission, and proximity to other countries/regions with known JE transmission).

It is advisable that countries deciding on JE vaccine introduction have at least some minimal local data on the burden of JE disease, such as information collected through sentinel sites. More refined country-specific data are useful to identify target age groups and areas of highest risk. The latter is particularly important if a phased or only subnational vaccine introduction is considered. An absence of confirmed cases from suboptimal surveillance and case detection should not be taken as sufficient to exclude JE vaccination. Appropriate data should be available to policy makers to inform decisions about introduction, strategy, and scope of the program.

## 6.2 Age of administration and vaccine schedules

The following principles were used to identify the optimal age of administration for JE vaccination:

1. to provide protection as early as possible, taking into account local JE epidemiology;
2. to avoid interference with passively acquired maternal antibodies that can lower or impair the immune response; and
3. to take advantage of opportunities to co-administer with other vaccines rather than add additional vaccination visits

**Table 13.** Overview of currently recommended schedules and age of administration

| Vaccine | Recommended schedule and age of administration based on currently available data | Supporting evidence |
|---|---|---|
| Inactivated Vero cell vaccine | Primary series per manufacturer's recommendations (vary by product). Generally,<br>• ≥6 months of age in endemic settings<br>• ≥2 months of age in non-endemic settings<br>In endemic settings, the need for a booster has not been established. | • Immunogenicity and safety data from clinical trials of IXIARO down to 2 months of age in the Philippines and US/Europe |
| Live attenuated vaccine | Single dose administered at ≥8 months of age<br>In endemic settings, the need for a booster has not been established. | • Immunogenicity and safety data from clinical trials down to 8 months of age<br>• Post-marketing surveillance in China |
| Chimeric vaccine | Single dose administered at ≥9 months of age<br>In endemic settings, the need for a booster has not been established. | • Immunogenicity and safety data from clinical trials down to 9 months of age, with limited data available in the 9-12 month age group. |

The risk of infection will clearly differ by setting. In a metropolitan area in Manila, Philippines, where the incidence of JE would be expected to be lower than in rural settings, the seroprevalence rate jumped from 2.9% in the 1 to <3 year age group to 22.6% in the 3 to <12 year age group (Dubischar-Kastner 2012b). These data, in addition to case-based data in young children, emphasize the need for early vaccination (Country data presented at 2014 WHO Bi-Regional Meeting on JE).

## 6.3 Co-administration with other vaccines

Many countries currently co-administer JE vaccines with other vaccines for programmatic reasons despite a lack of robust data supporting safety or non-inferiority of immune responses (Table 14). The WHO measles position paper currently states that measles and JE vaccines may be co-administered at the same time but at different sites (WHO 2009).

**Table 14.** Comparison of country practices for co-administration with JE vaccines and published data on co-administration.

| Co-Administered Vaccines | Inactivated Vero cell JE vaccine | Live attenuated JE vaccine | Chimeric JE vaccine |
|---|---|---|---|
| **M** | | P R | |
| **MR** | | R | |
| **MMR** | | | P |
| **OPV** | | R | |
| **YF** | | | P |
| **Inactivated HepA** | P | R | |
| **Td/DT/DTP** | | R | |
| **Influenza** | | R | |
| **Rabies** | P | | |
| **Rabies + Mening** | P | | |

P= Data published; R= ≥1 country reported routine co-administering, or co-administered during campaign; travelers not considered. Vaccines not listed: no indication of study or practice of co-administration with JE vaccines.

### 6.3.1 Co-administration with inactivated Vero cell vaccines

Co-administration of inactivated Vero-cell JE vaccine and hepatitis A vaccine in healthy adults showed comparable seroconversion and GMTs for all groups at 56 days post-JE and 28 days post-Hepatitis A (Kaltenböck 2009). Seroconversion for JE was between 98.2-100%. Another study in European adults demonstrated good and comparable GMTs and seroprotection for JE and rabies in JEV+PCECV+MenACWY and JEV+PCECV groups (Alberer 2014). Comparable seroprotection was seen for MenACWY + JE compared to MenACWY-alone groups. No short-term safety concerns were shown for either of these studies.

### 6.3.2 Co-administration with live attenuated vaccine

For the live attenuated vaccine, a study was conducted comparing the immunogenicity and safety of measles vaccine co-administered with CD.JEVAX in children aged 9 months in the Philippines (Gatchalian 2008, Victor 2014). At day 28 there were no significant differences between groups in both measles (86.5-91.8%) and JE seroprotection (90.5-92.1%) rates. There were no short-term safety concerns, and this conclusion was supported by GACVS. Long-term follow up from this study is ongoing (serology available only for JE due to a measles campaign that occurred in the study area). Another study in Sri Lanka also did not identify any safety concerns when measles and JE vaccine were co-administered; however, there was no control group (Wijesinghe 2014). Post-marketing surveillance in Guangdong, China (2005-2012) showed no increased sign of neurological-related events associated with co-administration of live attenuated JE vaccine with other vaccines (Liu 2014).

### 6.3.3 Co-administration with chimeric vaccine

For the chimeric JE vaccine, a study with MMR co-administration in Taiwanese children (12-18 months) demonstrated comparable immune responses for all antigens at 6 weeks (Huang 2014). At one year the JE seroprotection rate was slightly lower (seroprotection rates for measles, mumps and rubella were not significantly different between groups) in the co-administration group compared to single administration groups (88.6% vs 96.6-98.8%), however, no non-inferiority test was shown. Of the 29 children who experienced a skin and subcutaneous tissues AE (e.g. rash), 22 were in the co-

administration group (N=220). Another study of concomitant administration with yellow fever (YF) vaccine in Australian adults showed comparable YF seroconversion rates across groups (Nasveld 2010b). JE GMT was significantly decreased in the co-administration and YF/JE groups compared to JE/YF group (seroprotection 91-96% vs 100%). No short-term safety concerns were found.

**Conclusions:**

Data support co-administration of live attenuated JE vaccine with measles vaccine. Immunogenicity studies are needed for co-administration with MR and MMR. However, for programmatic reasons it may be considered acceptable to co-administer live attenuated JE vaccine with MR or MMR vaccines, although data are not yet available. Following the same rationale, co-administration of MMR and chimeric vaccine is acceptable although slightly lower anti-JEV GMT values, but nonetheless seroprotective, were obtained in the co-administration group at 12 months after vaccination. Immunogenicity studies, including long-term studies, are needed for co-administration of chimeric vaccine with M and MR vaccines.

Experience with inactivated mouse brain vaccines does not suggest reduced seroconversion rates or an increase in adverse events when mouse brain JE vaccine is given simultaneously with vaccines against measles, DPT and oral polio as part of the EPI program. The same is true for trials of co-administration of IXIARO with a range of vaccines given to travelers. While the possible impact of co-administration of inactivated JE vaccines with other vaccines of the childhood immunization program has not been systematically studied, co-administration of inactivated Vero cell vaccines with other vaccines for programmatic reasons seems acceptable.

Vaccine co-administration is a preferred programmatic approach. Further studies on co-administration are encouraged. Program monitoring and/or special studies are warranted to assess immunogenicity and/or effectiveness.

## *6.4 Use in special populations*

### 6.4.1 Immunocompromised

There are very limited data in immunocompromised persons for inactivated Vero cell, live attenuated, or chimeric JE vaccines. Four studies were conducted in Thailand with mouse brain-derived vaccine in HIV-infected persons. In the one small study of HIV-infected children not receiving anti-retroviral therapy (ART) no safety concerns were identified but the seroprotection rate was approximately half the rate in HIV-uninfected children (Rojanasuphot 1998). In the other studies in which participants were receiving ART, seroprotection was comparable to that seen in HIV-negative children; GMTs were lower, but within an acceptable range (Chokephaibulkit 2010b; Puthanakit 2007; Puthanakit 2010). Adverse events were similar between HIV-infected and HIV non-infected participants. An older study from Japan in which two doses of mouse brain-derived vaccine were given to children with neoplastic diseases demonstrated similar responses among the seven children with neoplastic diseases and the other children who were healthy or had non-neoplastic diseases (Yamada 1986). No adverse events were reported. A recent study was conducted in post-hematopoietic stem cell transplant subjects given live attenuated vaccine ≥2 years post-transplant and ≥6 months post-immunosuppressants (Pakakasama 2014, abstract only). Among the 18 children not seroprotected prior to JE vaccination, nine had seroprotective titers after one dose (only three

sustained protection for at least 12 months), seven had seroprotective titers after two doses, and two had no response.

Experience with yellow fever (YF) vaccine administered to HIV-infected persons may also inform the possible experience with chimeric JE vaccine, both because it is a live attenuated flaviviral vaccine and because the YF17D virus is the backbone for the chimeric vaccine. In a review done by GACVS in 2010, no clear evidence was available to suggest that hypothetical risk should preclude use of YF vaccine in HIV-infected persons (WHO 2011). Recent data suggest immune response wanes more rapidly in HIV-infected persons (Veit 2009). The WHO YF position paper states that YF vaccine may be offered to asymptomatic HIV-infected persons with CD4 T-cell counts ≥200 cells/mm (WHO 2013). YF vaccine is contraindicated in immunocompromised persons based on historical experience with live vaccines.

**Conclusions:** Based on indirect evidence with use of inactivated mouse brain vaccines in immunocompromised persons, inactivated Vero cell JE vaccine can be used in HIV-infected and immunocompromised persons, but the immune response may be lower than in healthy persons. Inactivated vaccines should be used preferentially over live or chimeric vaccines in immunocompromised persons. However, it is not necessary to use screening tests prior to vaccinating and it should not be a deterrent to using live or chimeric vaccines during campaigns.

### 6.4.2 Pregnant women

There are no studies on inactivated Vero cell vaccines, live attenuated vaccine, and chimeric vaccine in pregnant women. Preclinical studies of IXIARO in pregnant rats did not show evidence of harm to the mother or foetus. According to the European Public Assessment Report, 24 pregnant women were inadvertently vaccinated in clinical studies with no untoward findings (EMA 2009).

Experience with the YF vaccine administered to pregnant women may also inform the possible experience with chimeric JE vaccine for the same reasons stated above. The WHO YF position paper recommends a risk-benefit assessment be undertaken for pregnant and lactating women but noted in areas where YF is endemic or during outbreaks the benefits of vaccination likely outweigh potential risks to the fetus (WHO 2013).

**Conclusions:** Inactivated vaccines should be used preferentially over live or chimeric vaccines in women known to be pregnant out of the same precautionary principle against using any live attenuated vaccine in pregnant women. However, it is not necessary to do pregnancy testing before JE vaccination.

### 6.4.3 Travelers

Travelers are potentially at risk, and there are specific recommendations issued by various national authorities. Most authorities recommend vaccination for travelers going to endemic countries, particularly but not exclusively rural areas, for more than one month, or repeat travel to such areas. As noted by WHO guidelines for International Travel and Health, “the risk varies according to season, destination, duration of travel and activities. Vaccination is recommended for travelers with extensive outdoor exposure...during the transmission season” (2014).

### 6.4.4 Health care workers

WHO defines health care workers as all persons involved in patient care such as health care professionals, residents, students, laboratory staff, administrative and service staff, as well as persons in public health acts such as field workers, epidemiologists, laboratory staff and community health workers. Health care workers at high-risk in JE-endemic areas, e.g. those involved in vector control, should be vaccinated.

## *6.5 Vaccination strategies*

JE vaccination strategies include campaigns in locally defined target groups, introduction into the routine immunization program, or a combination. Little empiric assessment of various strategies has been conducted, and mathematical modelling may help to refine the vaccination approach.

The most effective immunization strategy in JE endemic settings is a one-time campaign in the primary target population, as defined by local epidemiology (typically children <15 years of age), followed by incorporation of the JE vaccine into the routine immunization program. This approach has a greater public health impact than either strategy separately. When possible, campaigns should be scheduled outside periods of high JE disease activity to avoid any coincidental association of vaccination with encephalitis.

Some countries may have a sufficient burden of disease in the adult population to warrant vaccination of older age groups. JE vaccination does not induce any herd immunity.

There are no data documenting the impact of vaccination when initiated as a response to a JE outbreak. If an outbreak occurs, an assessment needs to be made about whether it is appropriate to implement an immediate vaccine response, including considerations such as size of outbreak, timeliness of the response, population affected, programmatic capacity, etc. Due to the need for rapid production of protective antibodies, single dose live attenuated or chimeric vaccines should be used. The use of JE vaccine during an outbreak should not deter countries from introducing JE vaccine into routine programs if they have not already done so, and occurrence of an outbreak further strengthens the case that routine immunization is needed.

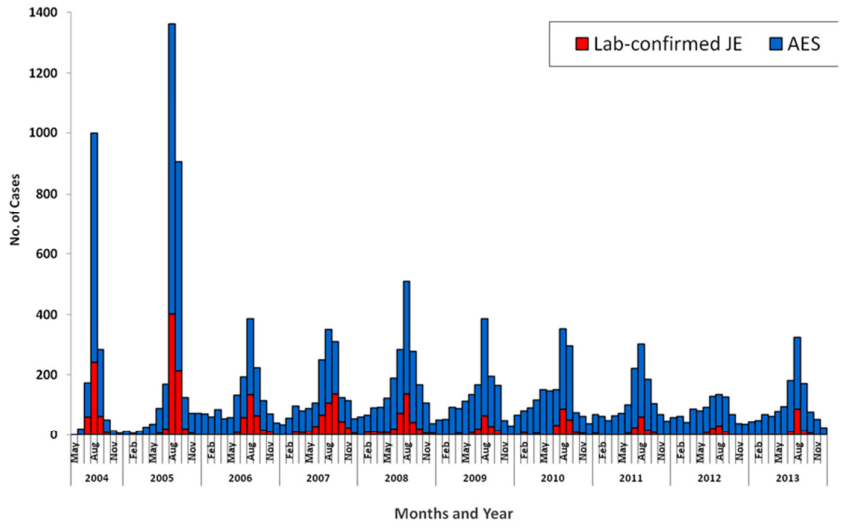
## *6.6 Public health and economic impact*

SAGE guidelines for evidence-based vaccine recommendations include considering the population impact of the vaccine and cost-effectiveness of immunization programs.

Many countries with JE surveillance systems have been able to track JE trends over time, before and after vaccination. There is clear evidence of significant impact on JE disease of population vaccination with live attenuated and inactivated mouse brain JE vaccines (Liu 2006, Upreti 2013, Zhou 2001, Chen 1992, Wong 2008, Japanese Surveillance Report 1999, Wu 1999). Disease impact studies exclusively for inactivated Vero cell vaccines and chimeric vaccines are not yet available due to the lack of widespread use; chimeric vaccine impact studies may now be possible in some of the endemic countries in which they are now being used. In Nepal, mass vaccination campaigns were conducted between 2006 and 2009 among those aged 1-15 years in some districts and among all persons ≥1 year of age in other districts, with high coverage (94% of the target population) achieved (Upreti 2013). Surveillance data from 2004-2009 were analyzed, and showed the incidence of laboratory-confirmed JE incidence following the campaigns was 1.3 per 100,000, which was 72% lower than the expected incidence of 4.6 per 100,000 had no campaigns occurred. The incidence

difference was greatest in the high-risk districts and when the vaccinated population was all individuals greater than 1 year of age. When the burden in adults is considered sufficiently high, vaccinating adults increases the impact on JE disease.

**Figure 5.** AES and lab-confirmed JE cases by month and year in Nepal (courtesy of S. Upreti).




The cost-effectiveness of JE vaccination, either when introduced directly into the routine program, or when introduced through mass campaigns followed by routine introduction, has been assessed for live attenuated, inactivated mouse brain, and inactivated PHK cell vaccines in a variety of countries (Yin 2012, Touch 2010, Liu 2008, Suraratdecha 2006, Ding 2003, Siraprapasiri 1997). The cost per case averted ranged from -$1200 USD (live attenuated vaccine introduced into routine schedule in China; Ding 2003) to $21,928 (inactivated mouse brain vaccine introduced through mass campaigns followed by routine in India; Suraratdecha 2006). The cost per DALY averted ranged from $22 (live attenuated vaccine introduced into the routine program in Cambodia; Touch 2010) to $1,247 (inactivated mouse brain vaccine introduced through mass campaigns followed by routine in India; Suraratdecha 2006).

JE vaccination, even with more expensive inactivated products requiring multiple doses, was nearly always cost-effective regardless of the vaccination strategy. One dose of live attenuated JE vaccine was typically very cost-effective by WHO criteria[10] or cost-saving. The cost per DALY averted was highly sensitive to the pre-vaccination incidence and the cost of the vaccine.

Gavi supports endemic countries in one-time JE vaccination campaigns for children under 15 years old, including phased campaigns until all areas have had vaccination opportunity. As part of the application to Gavi, countries must have a plan for sustaining routine immunization. This is a good strategy for public health and economic impact.

[10] Following the recommendations of the Commission on Macroeconomics and Health, CHOICE uses gross domestic product (GDP) as a readily available indicator to derive the following three categories of cost-effectiveness: (1) highly cost-effective (less than GDP per capita), (2) cost-effective (between one and three times GDP per capita), and (3) not cost-effective (more than three times GDP per capita). Available at: http://www.who.int/choice/costs/CER_thresholds/en/.

**Conclusions:**

Data on the population impact of vaccination programs show significant reductions in JE cases. When high coverage is achieved in populations at risk of disease, JE in humans can be virtually eliminated while the virus remains in circulation. Due to the continued enzootic cycle of JE virus, sustained high coverage vaccination programs are critical.

Although cost-effectiveness studies are highly dependent upon parameters such as incidence of disease and vaccine price, it has been demonstrated that vaccination programs can be highly cost effective. A variety of vaccination strategies, including campaigns plus routine introduction, have been shown to be cost effective or highly cost effective. Vaccination impact studies, including demonstration of sustained low incidence of disease following a product switch, would be valuable in particular for newer vaccines.

There is a need for standardized guidance on how to approach JE vaccine assessments such as effectiveness and impact studies. This should address data source and analysis issues for using surveillance data to measure impact, data collection and analysis for observational studies to measure vaccine effectiveness, and designing surveillance and special studies to measure JE vaccine impact. There are many complexities relating to JE case diagnostics that make such studies complicated. WHO should take the lead on developing this guidance and making it available to countries and stakeholders.

### *6.7 Non-vaccine interventions*

There is little evidence to support a reduction in JE disease burden from interventions other than vaccination of humans. Other attempted strategies have included pig vaccination, environmental management for vector control, and chemical control of vectors (Erlanger 2009). Pig vaccination is limited by the high turnover in pig populations continuously throughout the year and reduced effectiveness of live attenuated vaccine in young pigs due to maternal antibodies (Igarashi 2002). It also does not affect other amplifying hosts (i.e. aquatic birds). Environmental management, although possible to reduce vector breeding along with other benefits such as saving water and reducing methane emission, is challenging, and not always feasible. It is difficult to cover all mosquito habitats with insecticides, such as rice paddies and ground pools of water, especially during the rainy season. Insecticide use, including for reasons other than JE, has promoted insecticide-resistance. Permethrin-impregnated mosquito nets were shown to provide some protection against JE in one study (Luo 1994), but several other studies showed no reduction in the risk of JE when bed nets were used (Liu 2010, Rayamajhi 2007, Phukan 2004, Lowry 1998); nonetheless bed nets may be important to reduce the risk of other vector-borne diseases. Adjunctive interventions should not divert efforts from childhood JE vaccination.

## 7. WG key conclusions and proposed recommendations

### *7.1 Key conclusions*

A. Japanese encephalitis is major public health problem in many countries in South East Asia and the Western Pacific.

B. Safe and effective (immunogenic) vaccines are available.

C. With greater access to products, including new vaccines and WHO prequalified vaccines, and with Gavi funding support for eligible countries, there are many opportunities to initiate or expand JE vaccination programs.

D. Surveillance strengthening is needed to assess the burden of JE, inform vaccination strategies, and monitor the impact and effectiveness of JE vaccines.

E. Assessments of the public health and economic impact of vaccination programs show significant reductions in JE cases and economic burden of JE. When high coverage is achieved in populations at risk of disease, JE disease in humans can be virtually eliminated while the virus remains in circulation.

### *7.2 Proposed JE vaccine recommendations*

1. JE vaccination should be extended to all areas where JE is recognized as a public health priority. Even if the number of JE-confirmed cases is low, vaccination should be considered where there is a suitable environment for JE transmission (i.e. presence of animal reservoirs, ecological conditions supportive of virus transmission, and proximity to other countries or regions with known JE transmission).

2. It is advisable that countries deciding on JE vaccine introduction have at least minimal local data on the burden of JE disease, such as information on confirmed cases collected through sentinel sites. More refined country-specific data are useful to identify target age groups and areas of highest risk. The latter is particular important if a phased or only subnational vaccine introduction is considered. An absence of confirmed cases in the context of suboptimal surveillance and case detection should not be taken as sufficient to exclude the need for JE vaccination.

3. All JE-endemic countries should have at least sentinel surveillance with laboratory confirmation of JE. Acute encephalitis syndrome (AES) surveillance is an important tool for understanding all causes of encephalitis. Even in the absence of JE-confirmatory testing, reporting of AES cases can have value in demonstrating impact of vaccination programs. However, low impact of JE vaccination programs on AES may reflect the burden of non-JE causes of AES.

4. The most effective immunization strategy in JE endemic settings is a onetime campaign in the primary target population, as defined by local epidemiology (typically children <15 years of age), followed by incorporation of the JE vaccine into the routine immunization program. This approach has a greater public health impact than either strategy separately. When possible, campaigns should be scheduled outside periods of high JE disease activity. Older age groups may be considered for vaccination if the disease burden in such groups is sufficiently high.

5. Due to the continued enzootic cycle of JE virus (and thus no herd immunity), sustained high-coverage vaccination programs are critical.

6. The following vaccine dosing schedules and age of administration are recommended in **endemic settings**. For all vaccines, the need for a booster dose in endemic settings has not been established.
    a. Inactivated Vero cell vaccine: Primary series per manufacturer's recommendations (these vary by product). Generally starting the primary series at ≥6 months of age in endemic settings
    b. Live attenuated vaccine: Single dose administered at ≥8 months of age
    c. Chimeric vaccine: Single dose administered at ≥9 months of age

7. Countries are strongly encouraged to conduct rigorous vaccine failure monitoring to assess the need for eventual booster doses.

8. Vaccine co-administration is a preferred programmatic approach. There are some data on co-administration of JE vaccines with some other vaccines, particularly live attenuated measles vaccine. However, many countries are already co-administering JE vaccines with vaccines not yet tested, such as combination measles-rubella vaccine. While the possible impact of co-administration of JE vaccines with measles-rubella vaccine as well as other vaccines of the childhood immunization program has not been systematically studied, co-administration for programmatic reasons seems acceptable. However, program monitoring and/or special studies are warranted to assess immunogenicity and/or effectiveness.

9. The value of reactive JE campaigns has not been studied. If an outbreak occurs in a country or region having not yet introduced JE vaccination, an assessment needs to be made about whether it is appropriate to implement an immediate vaccine response, including considerations such as size of outbreak, timeliness of the response, population affected, and programmatic capacity. Due to the need for rapid production of protective antibodies, single dose live attenuated or chimeric vaccines should be used. When outbreak response immunization is conducted, planning for routine immunization should follow.

10. Special populations:
    a. Immunocompromised persons: Inactivated Vero cell JE vaccine can be used in HIV-infected and immunocompromised persons, but the immune response may be lower than in healthy persons. Inactivated vaccines should be used preferentially over live or chimeric vaccines in immunocompromised persons.
    b. Pregnant women: If JE risk is sufficient to vaccinate pregnant women, inactivated vaccines should be used preferentially over live or chimeric vaccines based on the general precautionary principle against using any live attenuated vaccine in pregnant women. It is not necessary to do pregnancy testing before JE vaccination.
    c. Travelers: JE vaccination is recommended for travelers to endemic areas with extensive outdoor exposure during the transmission season.
    d. Health Care Workers: WHO defines health care workers as all persons involved in patient care such as health care professionals, residents, students, laboratory staff,

administrative and service staff, as well as persons in public health acts such as field workers, epidemiologists, laboratory staff and community health workers. Health care workers at high-risk in JE-endemic areas, such as those involved in vector control, should be vaccinated.

11. Adjunctive (non-vaccine) interventions, in particular vector control, should not divert efforts from childhood JE vaccination.

### *7.3 Research Priorities and Data Gaps*

*In no particular order*

I. Long-term immunogenicity studies to inform optimal dosing schedules for long-term protection, which may vary by location (based on natural boosting or other factors).

II. Vaccine effectiveness and impact studies (particularly for newer vaccines).

III. Development of standardized neutralization assay reagents.

IV. Further development of sensitive, specific, affordable commercial serological assays to ensure access to diagnostic testing in JE-endemic countries.

V. Co-administration of live attenuated and chimeric vaccines with other live vaccines, including MR and MMR. Co-administration of any JE vaccine with other vaccines not yet studied may also be warranted.

VI. Better description of disease severity by age, including long-term sequelae from JE disease.

VII. Guidance on how to approach JE vaccine impact assessments. This guidance should address surveillance data sources and analysis to measure JE vaccine impact, design of surveillance and special studies for impact measurement, JE laboratory diagnostics, and data collection and analysis for observational studies to measure vaccine effectiveness. WHO should take the lead on developing this guidance and making it available to countries and stakeholders.

VIII. Development of case-investigation protocols and field tools to enable strong monitoring and assessment of vaccine failures.

IX. The safety of live and chimeric vaccines when administered to pregnant women and immunocompromised persons is a data gap.

## References


1. Alberer M, Burchard G, Jelinek T, Reisinger E, Beran J, Meyer S, Forleo-Neto E, Gniel D, Dagnew AF, Kumar Arora A. Co-administration of a meningococcal glycoconjugate ACWY vaccine with travel vaccines: A randomized, open-label, multi-center study. Travel Med Infect Dis. 2014 May 9.
2. Australian Public Assessment Report for Japanese Encephalitis Chimeric Virus,2010. Available at http://www.tga.gov.au/pdf/auspar/auspar-imojev.pdf
3. Baig S, Fox K, Jee Y, O'Connor P, Hombach J, Wang S, Hyde T, Fischer M, Hills S. Japanese encephalitis: status of surveillance and immunization in Asia and the Western Pacific, 2012. Wkly Epidemiol Rec. 2013 Aug 23;88(34):357-64.
4. Bista MB, Banerjee MK, Shin SH, Tandan JB, Kim MH, Sohn YM, Ohrr HC, Tang JL, Halstead SB. Efficacy of single-dose SA 14-14-2 vaccine against Japanese encephalitis: a case control study. Lancet. 2001 Sep 8;358(9284):791-5.
5. Campbell GL, Hills SL, Fischer M, Jacobson JA, Hoke CH, Hombach JM, Marfin AA, Solomon T, Tsai TF, Tsu VD, Ginsburg AS. Estimated global incidence of Japanese encephalitis: a systematic review. Bull World Health Organ. 2011 Oct 1;89(10):766-74, 774A-774E.
6. Centers for Disease Control and Prevention (CDC). Recommendations for use of a booster dose of inactivated vero cell culture-derived Japanese encephalitis vaccine: advisory committee on immunization practices, 2011. MMWR Morb Mortal Wkly Rep. 2011 May 27;60(20):661-3.
7. Chen P, Zhou B, Ma W, Li Z, Zhu J, Zhang J, Weng Z, Jiang X. Observation of Epidemiological Effect of Japanese Encephalitis (JE) Live Vaccine Strain SA 14-14-2. Chin Biologicals. 1992; 5: 135.
8. Choi UY, Lee SY, Kim KH, Kim DS, Choi KM, Cha SH, Kang JH. Is a booster dose necessary in children after immunization with live attenuated Japanese encephalitis vaccine. J Trop Pediatr. 2013 Oct;59(5):423-5
9. Chokephaibulkit K, Sirivichayakul C, Thisyakorn U, Sabchareon A, Pancharoen C, Bouckenooghe A, Gailhardou S, Boaz M, Feroldi E. Safety and immunogenicity of a single administration of live-attenuated Japanese encephalitis vaccine in previously primed 2- to 5-year-olds and naive 12- to 24-month-olds: multicenter randomized controlled trial. Pediatr Infect Dis J. 2010 Dec;29(12):1111-7. (A)
10. Chokephaibulkit K, Plipat N, Yoksan S, Phongsamart W, Lappra K, Chearskul P, Chearskul S, Wittawatmongkol O, Vanprapar N. A comparative study of the serological response to Japanese encephalitis vaccine in HIV-infected and uninfected Thai children. Vaccine. 2010 Apr 30;28(20):3563-6. (B)
11. Chotpitayasunondh T, Sohn YM, Yoksan S, Min J, Ohrr H. Immunizing children aged 9 to 15 months with live attenuated SA14-14-2 Japanese encephalitis vaccine in Thailand. J Med Assoc Thai. 2011 Aug;94 Suppl 3:S195-203.
12. Ding D, Kilgore PE, Clemens JD, Wei L, Zhi-Yi X. Cost-effectiveness of routine immunization to control Japanese encephalitis in Shanghai, China. Bull World Health Organ. 2003;81(5):334-42.
13. Dubischar-Kastner K, Eder S, Buerger V, Gartner-Woelfl G, Kaltenboeck A, Schuller E, Tauber E, Klade C. Long-term immunity and immune response to a booster dose following vaccination with the inactivated Japanese encephalitis vaccine IXIARO, IC51. Vaccine. 2010 Jul 19;28(32):5197-202. (A)

14. Dubischar-Kastner K, Kaltenboeck A, Klingler A, Jilma B, Schuller E. Safety analysis of a Vero-cell culture derived Japanese encephalitis vaccine, IXIARO (IC51), in 6 months of follow-up. Vaccine. 2010 Sep 7;28(39):6463-9. (B)
15. Dubischar-Kastner K, Kadlecek V, Eder S, Sablan Jr. B, Borja-Tabora CF, Gatchalian S, Westritschnig K. Safety and Immunogenicity of the Inactivated Japanese Encephalitis Vaccine IXIARO®, IC51, in Filipino Children Aged 2 Months to < 18 Years. Presented at the Asia Pacific Travel Health Conference, 2012. (A)
16. Dubischar-Kastner K, Kadlecek V, Sablan Jr.B, Borja-Tabora CF, Gatchalian S, Eder S, Spruth M, Kiermayr S, Westritschnig K. Prevalence of Neutralizing Antibodies against JEV in the Metropolitan Manila Area, the Philippines. Presented at the American Society of Tropical Medicine and Hygiene, 2012. (B)
17. Dubischar-Kastner K, Kadlecek V, Bézay N, Sablan Jr. B, Borja-Tabora CF, Gatchalian S, Eder S, Westritschnig K. 24-Months Antibody Persistence in Children With and Without a Booster Dose of an Inactivated Japanese Encephalitis Vaccine, JE-VC, IC51. Presented at the Northern European Conference on Travel Medicine, 2014.
18. Eder S, Dubischar-Kastner K, Firbas C, Jelinek T, Jilma B, Kaltenboeck A, Knappik M, Kollaritsch H, Kundi M, Paulke-Korinek M, Schuller E, Klade CS. Long term immunity following a booster dose of the inactivated Japanese Encephalitis vaccine IXIARO®, IC51. Vaccine. 2011 Mar 21;29(14):2607-12.
19. EMEA. European Public Assessment Summary Report, 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000963/WC500037286.pdf
20. EMEA. European Public Assessment Summary Report, 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000963/WC500142252.pdf
21. EMEA. Summary of Product Characteristics. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000963/WC500037287.pdf
22. Erlanger TE, Weiss S, Keiser J, Utzinger J, Wiedenmayer K. Past, present, and future of Japanese encephalitis. Emerg Infect Dis. 2009 Jan;15(1):1-7.
23. Erra EO, Askling HH, Rombo L, Riutta J, Vene S, Yoksan S, Lindquist L, Pakkanen SH, Huhtamo E, Vapalahti O, Kantele A. A single dose of vero cell-derived Japanese encephalitis (JE) vaccine (Ixiaro) effectively boosts immunity in travelers primed with mouse brain-derived JE vaccines. Clin Infect Dis. 2012 Sep;55(6):825-34.
24. Erra EO, Askling HH, Yoksan S, Rombo L, Riutta J, Vene S, Lindquist L, Vapalahti O, Kantele A. Cross-protection elicited by primary and booster vaccinations against Japanese encephalitis: a two-year follow-up study. Vaccine. 2013 Dec 17;32(1):119-23.
25. Feroldi E, Pancharoen C, Watanaveeradej V, Bouckenooghe A. Persistence of antibodies one year after a single injection of live attenuated Japanese encephalitis chimeric virus vaccine at 12-18 months of age. Presented at the American Society of Tropical Medicine and Hygiene, 2010. Am J Trop Med Hyg. 2010. 83:5 (abstract only).
26. Feroldi E, Pancharoen C, Kosalaraksa P, Watanaveeradej V, Phirangkul K, Capeding MR, Boaz M, Gailhardou S, Bouckenooghe A. Single-dose, live-attenuated Japanese encephalitis vaccine in children aged 12-18 months: randomized, controlled phase 3 immunogenicity and safety trial. Hum Vaccin Immunother. 2012 Jul;8(7):929-37.

27. Feroldi E, Capeding MR, Boaz M, Gailhardou S, Meric C, Bouckenooghe A. Memory immune response and safety of a booster dose of Japanese encephalitis chimeric virus vaccine (JE-CV) in JE-CV-primed children. Hum Vaccin Immunother. 2013 Apr;9(4):889-97.
28. Feroldi E, Pancharoen C, Kosalaraksa P, Chokephaibulkit K, Boaz M, Meric C, Hutagalung Y, Bouckenooghe A. Primary immunization of infants and toddlers in Thailand with Japanese encephalitis chimeric virus vaccine in comparison with SA14-14-2: a randomized study of immunogenicity and safety. Pediatr Infect Dis J. 2014 Jun;33(6):643-9.
29. GACVS. Global Advisory Committee on Vaccine Safety, 11-12 December 2013. Wkly Epidemiol Rec. 2014 Feb14; 89(7):53-60.
30. GACVS. Global Advisory Committee on Vaccine Safety, 12-13 June 2013. Wkly Epidemiol Rec. 2013 Jul19; 88(29):301-312.
31. GACVS. Global Advisory Committee on Vaccine Safety, 12-13 December 2007. Wkly Epidemiol Rec. 2008 Jan25; 83(4):37-44.
32. GACVS. Global Advisory Committee on Vaccine Safety, 29-30 November 2006. Wkly Epidemiol Rec. 2007 Jan19; 82(3):18-24.
33. GACVS. Meeting of the Global Advisory Committee on Vaccine Safety, December 2010. Wkly Epidemiol Rec. 2011 Jan 28;86(5):38-43
34. GACVS. Global Advisory Committee on Vaccine Safety, 9-10 June 2005. Wkly Epidemiol Rec. 2005 Jul15; 80(4):241-7.
35. Gatchalian S, Yao Y, Zhou B, Zhang L, Yoksan S, Kelly K, Neuzil KM, Yaïch M, Jacobson J. Comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants. Vaccine. 2008 Apr 24;26(18):2234-41.
36. Guy B, Guirakhoo F, Barban V, Higgs S, Monath TP, Lang J. Preclinical and clinical development of YFV 17D-based chimeric vaccines against dengue, West Nile and Japanese encephalitis viruses. Vaccine. 2010 Jan 8;28(3):632-49.
37. Hennessy S, Liu Z, Tsai TF, Strom BL, Wan CM, Liu HL, Wu TX, Yu HJ, Liu QM, Karabatsos N, Bilker WB, Halstead SB. Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case-control study. Lancet. 1996 Jun 8;347(9015):1583-6.
38. Hoke CH, Nisalak A, Sangawhipa N, Jatanasen S, Laorakapongse T, Innis BL, Kotchasenee S, Gingrich JB, Latendresse J, Fukai K, et al. Protection against Japanese encephalitis by inactivated vaccines. N Engl J Med. 1988 Sep 8;319(10):608-14.
39. Hombach J, Solomon T, Kurane I, Jacobson J, Wood D. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2-3 September, 2004. Vaccine. 2005 Nov 1;23(45):5205-11.
40. Hossain MJ, Gurley ES, Montgomery S, Petersen L, Sejvar J, Fischer M, Panella A, Powers AM, Nahar N, Uddin AK, Rahman ME, Ekram AR, Luby SP, Breiman RF. Hospital-based surveillance for Japanese encephalitis at four sites in Bangladesh, 2003-2005. Am J Trop Med Hyg. 2010 Feb;82(2):344-9.
41. Hsu T, Chow L, Wei H, et al. A controlled field trial for an evaluation of effectiveness of mouse-brain Japanese encephalitis vaccine. J Formosa Med Assoc. 1971;70:55–61
42. Huang LM, Lin TY, Chiu CH, Chiu NC, Chen PY, Yeh SJ, Boaz M, Hutagalung Y, Bouckenooghe A, Feroldi E. Concomitant administration of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and measles, mumps, rubella (MMR) vaccine: Randomized study in toddlers in Taiwan. Vaccine. 2014 Mar 12. pii: S0264-410X(14)00312-0.

43. Igarashi A. Control of Japanese encephalitis in Japan: immunization of humans and animals, and vector control. Curr Top Microbiol Immunol. 2002;267:139-52.
44. Kaltenböck A, Dubischar-Kastner K, Schuller E, Datla M, Klade CS, Kishore TS.Immunogenicity and safety of IXIARO (IC51) in a Phase II study in healthy Indian children between 1 and 3 years of age. Vaccine. 2010 Jan 8;28(3):834-9
45. Kaltenböck A, Dubischar-Kastner K, Eder G, Jilg W, Klade C, Kollaritsch H, Paulke-Korinek M, von Sonnenburg F, Spruth M, Tauber E, Wiedermann U, Schuller E. Safety and immunogenicity of concomitant vaccination with the cell-culture based Japanese Encephalitis vaccine IC51 and the hepatitis A vaccine HAVRIX1440 in healthy subjects: A single-blind, randomized, controlled Phase 3 study. Vaccine. 2009 Jul 16;27(33):4483-9.
46. Kim DS, Houillon G. A randomized study of the immunogenicity and safety of Japanese encephalitis chimeric virus vaccine (JE-CV) in comparison with SA 14-14-2 vaccine in children in South Korea. 8th World Congress of the World Society for Pediatric Infectious Diseases (WSPID) - Nov. 19-22, 2013, Cape Town, South Africa.
47. Kumar R, Tripathi P, Rizvi A. Effectiveness of one dose of SA 14-14-2 vaccine against Japanese encephalitis. N Engl J Med. 2009 Apr 2;360(14):1465-6.
48. Kumari R, Kumar K, Rawat A, Singh G, Yadav NK, Chauhan LS. First indigenous transmission of Japanese Encephalitis in urban areas of National Capital Territory of Delhi, India. Trop Med Int Health. 2013 Jun;18(6):743-9.
49. Jia N, Zhao QM, Guo XF, Cheng JX, Wu C, Zuo SQ, Dai PF, Zhao JY, Zhang JS. Encephalitis temporally associated with live attenuated Japanese encephalitis vaccine: four case reports. BMC Infect Dis. 2011 Dec 14;11:344.
50. Liu W, Clemens JD, Yang JY, Xu ZY. Immunization against Japanese encephalitis in China: a policy analysis. Vaccine. 2006 Jun 12;24(24):5178-82.
51. Liu W, Clemens JD, Kari K, Xu ZY. Cost-effectiveness of Japanese encephalitis (JE) immunization in Bali, Indonesia. Vaccine. 2008 Aug 18;26(35):4456-60.
52. Liu W, Gibbons RV, Kari K, Clemens JD, Nisalak A, Marks F, Xu ZY. Risk factors for Japanese encephalitis: a case-control study. Epidemiol Infect. 2010 Sep;138(9):1292-7.
53. Liu Y, Lin H, Zhu Q, Wu C, Zhao Z, Zheng H. Safety of Japanese encephalitis live attenuated vaccination in post-marketing surveillance in Guangdong, China, 2005-2012. Vaccine. 2014 Mar 26;32(15):1768-73.
54. Liu ZL, Hennessy S, Strom BL, Tsai TF, Wan CM, Tang SC, Xiang CF, Bilker WB, Pan XP, Yao YJ, Xu ZW, Halstead SB. Short-term safety of live attenuated Japanese encephalitis vaccine (SA14-14-2): results of a randomized trial with 26,239 subjects. J Infect Dis. 1997 Nov;176(5):1366-9.
55. Lowry PW, Truong DH, Hinh LD, Ladinsky JL, Karabatsos N, Cropp CB, Martin D, Gubler DJ. Japanese encephalitis among hospitalized pediatric and adult patients with acute encephalitis syndrome in Hanoi, Vietnam 1995. Am J Trop Med Hyg. 1998 Mar;58(3):324-9.
56. Luo D, Zhang K, Song J, Yao R, Huo H, Liu B, Li Y, Wang Z. The protective effect of bed nets impregnated with pyrethroid insecticide and vaccination against Japanese encephalitis. Trans R Soc Trop Med Hyg. 1994 Nov-Dec;88(6):632-4.
57. Lyons A, Kanesa-thasan N, Kuschner RA, Eckels KH, Putnak R, Sun W, Burge R, Towle AC, Wilson P, Tauber E, Vaughn DW. A Phase 2 study of a purified, inactivated virus vaccine to prevent Japanese encephalitis. Vaccine. 2007 Apr 30;25(17):3445-53.

58. Ma W, Yu Y, Wang S, Zhou B, Ma Y, Feng S, Chen P, Hao Q, Zhang G, Guo Y. A large-scale study on the safety and serological efficacy of live attenuated Japanese encephalitis vaccine. Chin J Biologicals. 1993. 6:1.
59. Monath TP, Guirakhoo F, Nichols R, Yoksan S, Schrader R, Murphy C, Blum P, Woodward S, McCarthy K, Mathis D, Johnson C, Bedford P. Chimeric live, attenuated vaccine against Japanese encephalitis (ChimeriVax-JE): phase 2 clinical trials for safety and immunogenicity, effect of vaccine dose and schedule, and memory response to challenge with inactivated Japanese encephalitis antigen. J Infect Dis. 2003 Oct 15;188(8):1213-30.
60. Murhekar MV, Ranjan P, Selvaraju S, Pandey A, Gore MM, Mehendale SM. Low coverage and acceptable effectiveness of single dose of Japanese encephalitis vaccine, Gorakhpur division, Uttar Pradesh, India, 2013. J Infect. 2014 Jul 1. pii: S0163-4453(14)00195-9
61. Nasveld PE, Ebringer A, Elmes N, Bennett S, Yoksan S, Aaskov J, McCarthy K, Kanesa-thasan N, Meric C, Reid M. Long term immunity to live attenuated Japanese encephalitis chimeric virus vaccine: randomized, double-blind, 5-year phase II study in healthy adults. Hum Vaccin. 2010 Dec;6(12):1038-46. (A)
62. Nasveld PE, Marjason J, Bennett S, Aaskov J, Elliott S, McCarthy K, Kanesa-Thasan N, Feroldi E, Reid M.Concomitant or sequential administration of live attenuated Japanese encephalitis chimeric virus vaccine and yellow fever 17D vaccine: randomized double-blind phase II evaluation of safety and immunogenicity. Hum Vaccin. 2010 Nov;6(11):906-14. (B)
63. No Author (Japanese surveillance report). Japanese encephalitis, 1991-1998. Jpn.J.Infect.Dis.. 1999. 52:34.
64. Ohrr H, Tandan JB, Sohn YM, Shin SH, Pradhan DP, Halstead SB. Effect of single dose of SA 14-14-2 vaccine 1 year after immunisation in Nepalese children with Japanese encephalitis: a case-control study. Lancet. 2005 Oct 15-21;366(9494):1375-8.
65. Pakakasama S, Wattanatitan S, Techasaensiri C, Yoksan S, Sirireung S, Hongeng S. Immunogenicity of a live-attenuated Japanese encephalitis vaccine in children and adolescents after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2014 Jul 21.
66. Partridge J, Ghimire P, Sedai T, Bista MB, Banerjee M. Endemic Japanese encephalitis in the Kathmandu valley, Nepal. Am J Trop Med Hyg. 2007 Dec;77(6):1146-9.
67. Phukan AC, Borah PK, Mahanta J. Japanese encephalitis in Assam, northeast India. Southeast Asian J Trop Med Public Health. 2004 Sep;35(3):618-22.
68. Puthanakit T, Aurpibul L, Yoksan S, Sirisanthana T, Sirisanthana V. Japanese encephalitis vaccination in HIV-infected children with immune recovery after highly active antiretroviral therapy. Vaccine. 2007 Nov 28;25(49):8257-61.
69. Puthanakit T, Aurpibul L, Yoksan S, Sirisanthana T, Sirisanthana V.A 3-year follow-up of antibody response in HIV-infected children with immune recovery vaccinated with inactivated Japanese encephalitis vaccine Vaccine. 2010 Aug 16;28(36):5900-2.
70. Rayamajhi A, Singh R, Prasad R, Khanal B, Singhi S. Study of Japanese encephalitis and other viral encephalitis in Nepali children. Pediatr Int. 2007 Dec;49(6):978-84.
71. Rojanasuphot S, Shaffer N, Chotpitayasunondh T, Phumiamorn S, Mock P, Chearskul S, Waranawat N, Yuentrakul P, Mastro TD, Tsai TF. Response to JE vaccine among HIV-infected children, Bangkok, Thailand. Southeast Asian J Trop Med Public Health. 1998 Sep;29(3):443-50.

72. Schuh AJ, Ward MJ, Brown AJ, Barrett AD. Phylogeography of Japanese encephalitis virus: genotype is associated with climate. PLoS Negl Trop Dis. 2013 Aug 29;7(8):e2411.
73. Schuller E, Jilma B, Voicu V, Golor G, Kollaritsch H, Kaltenböck A, Klade C, Tauber E. Long-term immunogenicity of the new Vero cell-derived, inactivated Japanese encephalitis virus vaccine IC51 Six and 12 month results of a multicenter follow-up phase 3 study. Vaccine. 2008 Aug 12;26(34):4382-6. (A)
74. Schuller E, Klade CS, Heinz FX, Kollaritsch H, Rendi-Wagner P, Jilma B, Tauber E. Effect of pre-existing anti-tick-borne encephalitis virus immunity on neutralising antibody response to the Vero cell-derived, inactivated Japanese encephalitis virus vaccine candidate IC51. Vaccine. 2008 Nov 11;26(48):6151-6. (B)
75. Schuller E, Klade CS, Wölfl G, Kaltenböck A, Dewasthaly S, Tauber E. Comparison of a single, high-dose vaccination regimen to the standard regimen for the investigational Japanese encephalitis vaccine, IC51: a randomized, observer-blind, controlled Phase 3 study. Vaccine. 2009 Mar 26;27(15):2188-93.
76. Schuller E, Klingler A, Dubischar-Kastner K, Dewasthaly S, Müller Z. Safety profile of the Vero cell-derived Japanese encephalitis virus (JEV) vaccine IXIARO®. Vaccine. 2011 Nov 3;29(47):8669-76.
77. Siraprapasiri T, Sawaddiwudhipong W, Rojanasuphot S. Cost benefit analysis of Japanese encephalitis vaccination program in Thailand. Southeast Asian J Trop Med Public Health. 1997 Mar;28(1):143-8.
78. Sohn YM, Park MS, Rho HO, Chandler LJ, Shope RE, Tsai TF. Primary and booster immune responses to SA14-14-2 Japanese encephalitis vaccine in Korean infants. Vaccine. 1999 May 4;17(18):2259-64.
79. Sohn YM, Tandan JB, Yoksan S, Ji M, Ohrr H. A 5-year follow-up of antibody response in children vaccinated with single dose of live attenuated SA14-14-2 Japanese encephalitis vaccine: immunogenicity and anamnestic responses. Vaccine. 2008 Mar 20;26(13):1638-43.
80. Suraratdecha C, Jacobson J, Silvalenka S, Narahari D. A cost-effectiveness analysis of strategies for controlling Japanese encephalitis in Andhra Pradesh, India. J Pharm Fin, Econ & Policy. 2006. 15:21
81. Tauber E, Kollaritsch H, Korinek M, Rendi-Wagner P, Jilma B, Firbas C, Schranz S, Jong E, Klingler A, Dewasthaly S, Klade CS. Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. Lancet. 2007 Dec 1;370(9602):1847-53.
82. Tandan JB, Ohrr H, Sohn YM, Yoksan S, Ji M, Nam CM, Halstead SB. Single dose of SA 14-14-2 vaccine provides long-term protection against Japanese encephalitis: a case-control study in Nepalese children 5 years after immunization. Vaccine. 2007 Jun 28;25(27):5041-5.
83. Torresi J, McCarthy K, Feroldi E, Méric C. Immunogenicity, safety and tolerability in adults of a new single-dose, live-attenuated vaccine against Japanese encephalitis: Randomised controlled phase 3 trials. Vaccine. 2010 Nov 23;28(50):7993-8000.
84. Touch S, Suraratdecha C, Samnang C, Heng S, Gazley L, Huch C, Sovann L, Chhay CS, Soeung SC. A cost-effectiveness analysis of Japanese encephalitis vaccine in Cambodia. Vaccine. 2010 Jun 23;28(29):4593-9.
85. Upreti SR, Janusz KB, Schluter WW, Bichha RP, Shakya G, Biggerstaff BJ, Shrestha MM, Sedai TR, Fischer M, Gibbons RV, Shrestha SK, Hills SL. Estimation of the impact of a Japanese

encephalitis immunization program with live, attenuated SA 14-14-2 vaccine in Nepal. Am J Trop Med Hyg. 2013 Mar;88(3):464-8.
86. Veit O, Niedrig M, Chapuis-Taillard C, Cavassini M, Mossdorf E, Schmid P, Bae HG, Litzba N, Staub T, Hatz C, Furrer H; Swiss HIV Cohort Study. Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. Clin Infect Dis. 2009 Mar 1;48(5):659-66.
87. Victor J, Gatchalian S, Yao Y, Zhou B, Zhang L, Yoksan S, Yaich M, Neuzil K. Corrigendum to "Comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants." Vaccine. 2014 32(2): 306-8.
88. Wang J, Na J, Zhao S, Wang J, Zhang K, Wang W, Yang Y. An Epidemiologic Study on the Efficacy of Japanese Encephalitis Live Vaccine. Chin J Biologicals. 1993. 6:36.
89. Wijesinghe PR, Abeysinghe MR, Yoksan S, Yao Y, Zhou B, Zhang L, Yaich M, Neuzil KM, Victor JC. Safety and immunogenicity of live-attenuated Japanese encephalitis SA 14-14-2 vaccine co-administered with measles vaccine in 9-month-old infants in Sri Lanka. Vaccine. 2014 Aug 20;32(37):4751-7.
90. Wong SC, Ooi MH, Abdullah AR, Wong SY, Krishnan S, Tio PH, Pek PC, Lai BF, Mohan A, Muhi J, Kiyu A, Arif MT, Cardosa MJ. A decade of Japanese encephalitis surveillance in Sarawak, Malaysia: 1997-2006. Trop Med Int Health. 2008 Jan;13(1):52-5.
91. Woolpert T, Staples JE, Faix DJ, Nett RJ, Kosoy OI, Biggerstaff BJ, Johnson BW, Sracic M, Fischer M. Immunogenicity of one dose of Vero cell culture-derived Japanese encephalitis (JE) vaccine in adults previously vaccinated with mouse brain-derived JE vaccine. Vaccine. 2012 Apr 26;30(20):3090-6.
92. World Health Organization. Measles vaccines: WHO position paper. Wkly Epidemiol Rec. 2009 Aug 28;84(35):349-60.
93. World Health Organization. PUBLIC ASSESSMENT SUMMARY REPORT – Japanese Encephalitis Vaccine, Live (Human). 2013. Available at: http://www.who.int/immunization_standards/vaccine_quality/pq270_vpsar_jevlive_chengdu_12nov13.pdf
94. World Health Organization. International Travel and Health. 2014. Available at: http://www.who.int/ith/en/
95. World Health Organization. Vaccines and vaccination against yellow fever. WHO position paper -- June 2013. Wkly Epidemiol Rec. 2013 Jul 5;88(27):269-83.
96. World Health Organization. Recommendations to assure the quality, safety and efficacy of Japanese encephalitis vaccines (live, attenuated) for human use. Technical Report Series No 980, 2014.
97. Wu YC, Huang YS, Chien LJ, Lin TL, Yueh YY, Tseng WL, Chang KJ, Wang GR. The epidemiology of Japanese encephalitis on Taiwan during 1966-1997. Am J Trop Med Hyg. 1999 Jul;61(1):78-84.
98. Yamada A, Imanishi J, Juang RF, Fukunaga T, Okuno Y, Tadano M, Fukai K, Baba K, Yabuuchi H. Trial of inactivated Japanese encephalitis vaccine in children with underlying diseases. Vaccine. 1986 Mar;4(1):32-4.
99. Yin Z, Beeler Asay GR, Zhang L, Li Y, Zuo S, Hutin YJ, Ning G, Sandhu HS, Cairns L, Luo H; Guizhou JE Study Group. An economic evaluation of the use of Japanese encephalitis vaccine in the expanded program of immunization of Guizhou province, China. Vaccine. 2012 Aug 10;30(37):5569-77.

100. Yoocharoan P, A-neugoolpipat A, Anantapreecha S, Tharmaphornpilas P. Seroprevalence of Immunity against Japanese Encepalitis in Thai population. Disease Control Journal. 2009 Oct-Dec;35(4):276-284.
101. Zaman K, Naser AM, Power M, Yaich M, Zhang L, Ginsburg AS, Luby SP, Rahman M, Hills S, Bhardwaj M, Flores J. Lot-to-lot consistency of live attenuated SA 14-14-2 Japanese encephalitis vaccine manufactured in a good manufacturing practice facility and non-inferiority with respect to an earlier product. Vaccine. 2014 Sep 18 (epub ahead of print).
102. Zhou B, Zhang M, Chen P, Jiang X, Zhang L. An 11 Year Follow-up of Epidemiological Effect of Japanese Encephalitis Vaccine, Live (SA 14-14-2). Chin J Biologicals. 2001. 14: 183.
103. Zhou B, Jia L, Xu X. [A large-scale study on the safety and epidemiological efficacy of Japanese encephalitis (JE) live vaccine (SA14-14-2) in the JE endemic areas]. Chinese Journal of Epidemiology. 1999. 20:38.
104. Zhou B, Zhang M, Chen P, Jiang X, Zhang L. An 11 Year Follow-up of Epidemiological Effect of Japanese Encephalitis Vaccine, Live (SA 14-14-2). Chin J Biologicals. 2001; 14: 183.

## Appendix 1. SAGE Working Group on JE Vaccines: Terms of Reference and Composition

The Working Group will be asked to review the evidence, identify the information gaps, and formulate proposed recommendations on the use of Japanese encephalitis (JE) vaccines for a SAGE review. This will lead to an update of the current (2006) JE vaccine position paper. The target date for publication of the revised vaccine position paper is 2015.

The Working Group will specifically be asked to review data relating to:

1. the global prevalence and burden of disease caused by JE, including issues relating to JE surveillance
2. the role of inactivated mouse-brain based JE vaccines in the context of other products
3. the safety, effectiveness, and immunogenicity profile of JE vaccines*
4. the schedule and age of administration for JE vaccines
5. the duration of protection following immunization with JE vaccines
6. co-administration of JE vaccines with other vaccines
7. JE vaccination strategies to reduce disease in a country or region, including the possible utility of reactive campaigns during outbreaks
8. use of JE vaccines in special populations (e.g. immunosuppressed, pregnancy)
9. the disease impact and cost-effectiveness of JE immunization programs
10. additional critical issues that need to be considered in updating the current vaccine position paper

*Due to the large number of available JE vaccines with limited global use, the Working Group will focus its in-depth evidence review on products with current or likely international distribution. The Working Group will also place emphasis on inactivated cell-based, live attenuated, and live chimeric vaccines.

**Composition**

**SAGE Members**

- Piyanit Tharmaphornpilas (Working Group Chair), National Immunization Program, Ministry of Public Health, Thailand
- Paba Palihawadana, Central Epidemiological Unit, Ministry of Health, Sri Lanka

**Experts**

- Alan Barrett, Sealy Center for Vaccine Development, University of Texas Medical Branch, USA

- Susan Hills, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, USA
- Ooi Choo Huck, Sarawak Health Department, Ministry of Health, Malaysia
- Heidi Meyer, Viral Vaccines Section, Paul-Ehrlich-Institut, Germany
- Khin Saw Aye Myint, Eijkman Institute, Indonesia
- Tom Solomon, Institute of Infection and Global Health, University of Liverpool, UK
- Tomohiko Takasaki, Laboratory of Vector-Borne Viruses, National Institute of Infectious Diseases, Japan
- Shyam Upreti, Central Regional Health Directorate, Ministry of Health and Population, Nepal
- Yin Zundong, National Immunization Program, Chinese Center for Disease Control and Prevention, China

**WHO Secretariat**

- Joachim Hombach
- Kirsten Vannice

**DECLARATION OF INTERESTS**

All Working Group members completed a declaration of interests. Two members reported relevant interests. The reported relevant interests are summarized below:

**Susan Hills**

- Her organization (CDC) received a research grant from the Bill and Melinda Gates Foundation to investigate the impact of SA 14-14-2 JE vaccine in Asia. This interest was assessed as non-personal, specific, and financially significant*.

**Piyanit Tharmaphornpilas**

- Received in 2011 a travel grant from a joint venture of the Thai Government Pharmaceutical Organization - Merieux Biological Product to attend the Re-invigorating Immunisation Policy Implementation and Success: From Parent to Partner and from Broad to Engagement. This interest was assessed as personal, non-specific and financially insignificant*.

* According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single vaccine manufacturer or other vaccine-related company exceeds 5,000 USD in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of 1,000 USD would also constitute a “significant shareholding”.

## Appendix 2. Critical Policy and PICO Questions Identified by the JE WG

| Theme | Policy Question | PICO Question |
|---|---|---|
| Effectiveness CRITICAL | What is the effectiveness of JE vaccines? | **Population**: Immunocompetent individuals<br>**Intervention**: Primary series of inactivated Vero cell-based vaccine<br>**Comparator**: No vaccine, placebo, or other JE vaccine<br>**Outcome**: JE disease |
| | | **Population**: Immunocompetent individuals<br>**Intervention**: Primary series* of live attenuated vaccine<br>**Comparator**: No vaccine, placebo, or other JE vaccine<br>**Outcome**: JE disease |
| | | **Population**: Immunocompetent individuals<br>**Intervention**: Primary series* of chimeric live attenuated vaccine<br>**Comparator**: No vaccine, placebo, or other JE vaccine<br>**Outcome**: JE disease |
| Safety CRITICAL | What is the risk of serious adverse events following JE vaccination? | **Population**: Immunocompetent individuals<br>**Intervention**: Administration of inactivated Vero cell-based vaccine<br>**Comparator**: No vaccine, placebo, or other vaccine<br>**Outcome**: SAEs |
| | | **Population**: Immunocompetent individuals<br>**Intervention**: Administration of live attenuated vaccine<br>**Comparator**: No vaccine, placebo, or other vaccine<br>**Outcome**: SAEs |
| | | **Population**: Immunocompetent individuals<br>**Intervention**: Administration of chimeric live attenuated vaccine<br>**Comparator**: No vaccine, placebo, or other vaccine<br>**Outcome**: SAEs |
| Duration of protection CRITICAL | Is there need for a booster dose following immunization with the primary series of JE vaccination? | **Population**: Immunocompetent individuals<br>**Intervention**: Primary series of inactivated Vero cell-based vaccine received ≥ 1 years ago<br>**Comparator**: No vaccine, placebo, or other JE vaccine OR recipient of inactivated Vero cell-based vaccine < 1 year<br>**Outcome**: JE disease |
| | | **Population**: Immunocompetent individuals<br>**Intervention**: Primary series* of live attenuated vaccine received ≥ 1 years ago<br>**Comparator**: No vaccine, placebo, or other JE vaccine OR recipient of live attenuated vaccine <1 years ago<br>**Outcome**: JE disease |
| | | **Population**: Immunocompetent individuals<br>**Intervention**: Primary series* of chimeric live attenuated vaccine received ≥ 2 years ago<br>**Comparator**: No vaccine, placebo, or other JE vaccine OR recipient of chimeric live attenuated vaccine <2 years ago<br>**Outcome**: JE disease |

*DEFINITION: Primary series - For live attenuated/chimeric live attenuated JE vaccines, defined as one dose for all ages

## Appendix 3. Other key policy questions identified by the JE Working Group

| Theme | Policy Questions |
|---|---|
| Co-Administration NON-CRITICAL | Can JE vaccines be safety and effectively co-administered with other vaccines? |
| Special populations NON-CRITICAL | Can JE vaccines be safety and effectively use in special populations? |
| Mouse brain vaccines NON-CRITICAL | What is the role of inactivated mouse brain-based JE vaccines in the context of other products? |
| Vaccine schedules NON-CRITICAL | What is the appropriate age of administration for JE vaccines in the routine immunization schedule? |
| Vaccine strategies NON-CRITICAL | What is the appropriate JE vaccine introduction strategy in an endemic country without a vaccination program? |
| Impact on disease NON-CRITICAL | What is the impact of JE vaccine introduction on JE disease at a country or regional level? |
| Cost-effectiveness NON-CRITICAL | What is the cost-effectiveness of JE vaccine introduction? |
| Global burden of JE NON-CRITICAL | What is the global prevalence and disease burden of JE? |
| At-risk population NON-CRITICAL | How should at-risk populations be defined? |

## Appendix 4. Table of JE Vaccines

| | Names | Manufacturers | Strain | Age (first dose) | Dose Schedule | Licensure[1] |
|---|---|---|---|---|---|---|
| Inactivated (Mouse Brain) | **JenceVac** | Korea: Green Cross | Nakayama | 12-23 M | Primary: 3 doses (0/7-30D/>6M)<br>Booster: Ages 6Y and 12Y | International |
| | **JE Vaccine "Kuo Kwang"** | Taiwan: Adimmune Corp | Nakayama | 15-27 M | Primary: 3 doses (0/7-14D/1Y)<br>Booster: Age 5 Y | Taiwan |
| | **J.E. (BEIJING) – GPO** | Thailand: Government Pharmaceutical Organization | Beijing-1 | >= 1 Y | Primary: 2 doses (0/7-14 D)<br>Booster: Every 1-3 Y | Thailand |
| | **JEVAX** | Vietnam: VaBiotech | Nakayama | >=1 Y | Primary: 3 doses (0/14D/1Y)<br>Booster: Every 3 Y | Vietnam |
| Inactivated (Vero Cell) | **JEBIK V** | Japan: Biken | Beijing-1 | >= 6M | Primary: 2 doses (0/6-28D)<br>Booster: 1 Y | Japan |
| | **ENCEVAC**<br>KD-287/<br>JEIMMUGEN INJ1 | Japan: Kaketsuken<br>Korea: Boryung | Beijing-1 | >= 6M | Primary: 3 doses (0/7-14D/12M)<br>Booster: Ages 6Y and 12Y | Japan, Korea |
| | **JEVAC** | China: Liaoning Chengda Biotechnolog Co | Beijing P-3 | 6-12M | Primary: 2 doses (0/7D)<br>Booster: 1M-1Y | China, Cambodia |
| | **IXIARO**<br>IC51/JE-VC/<br>JESPECT | Austria: Intercell/Valneva, distributed by Novartis and bioCSL | SA 14-14-2 | >=17 Y (>=2 M in US) | Primary: 2 doses (0/28D)<br>Booster: 1 Y | US, EU, Canada, Australia, HK, Switzerland, Israel, Singapore, New Zealand, PNG, Pacific Islands |
| | **JEEV** | India: Biological E | SA 14-14-2 | >=18, <=49 Y<br>(India 1-3 years) | Primary: 2 doses (0/28D) | India, Bhutan,<br>Pakistan, Nepal |
| | **JENVAC** | India: Bharat Biotech | Kolar Strain (JEV 821564 XY) | >=1Y | Primary: 2 doses (0/28D)<br>Booster: >1 Y | India |
| Live Attenuated (PHK) | **SA-14-14-2**<br>CD.JEVAX | China: Chengdu Institute of Biological Products (CDIBP) | SA 14-14-2 | >=8M | Primary: 1 dose<br>*Booster: 9M-12M, or age 2Y in some countries* | India, South Korea, Thailand, Nepal, Sri Lanka,<br>DPRK, Laos, Cambodia, Burma, Malaysia, Vietnam |
| Live Chimeric (Vero) | **IMOJEV**<br>JE-CV/<br>ChimeriVax-JE | France : Sanofi pasteur | SA 14-14-2/ yellow fever 17D | >1Y | Primary: 1 dose<br>Booster (paediatric): Age 2Y | Australia, Malaysia, Thailand, Brunei |

[1]Not necessarily commercialized

## GRADE Table 1. What is the effectiveness of two doses (primary series) of inactivated Vero cell JE vaccine in preventing JE disease in vaccinees living in JE-endemic areas?

**Population :** Immunocompetent individuals living in JE-endemic areas
**Intervention:** Two doses (primary series) of inactivated Vero cell vaccine
**Comparison:** Placebo/No vaccination
**Outcome :** JE disease (immunogenicity accepted)

| *What is the effectiveness of two doses of inactivated Vero cell JE vaccine in preventing JE disease in individuals living in JE-endemic areas?* | | | | |
|---|---|---|---|---|
| | | | Rating | Adjustment to rating |
| **Quality Assessment** | No. of studies/starting rating | | 7 RCTs[1] | 4 |
| | Factors decreasing confidence | Limitation in study design | None serious[2] | 0 |
| | | Inconsistency | None serious | 0 |
| | | Indirectness | None serious[3] | -1 |
| | | Imprecision | None serious | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Large effect | Applicable[4] | +1 |
| | | Dose-response | Not applicable | 0 |
| | | Antagonistic bias and confounding | Not applicable | 0 |
| | **Final numerical rating of quality of evidence** | | | **4** |
| **Summary of Findings** | **Statement on quality of evidence** | | | **We are very confident that the true effect lies close to that of the estimate of effect on health outcome** |
| | **Conclusion** | | | **Inactivated Vero cell JE vaccines have evidence of seroprotective neutralizing antibody titers.** ***Based on a review of data on IXIARO*** |

[1]Clinical studies from 7 RCTs in approximately 2,890 IXIARO vaccinees provided short-term immunogenicity data. Across multiple studies in adults, high rates of seroprotection have been found one month following completion of the two-dose primary series. In the largest study of 430 adult vaccine recipients, the seroprotection rate was 98% and the GMT was 244 (Tauber 2007). Among children living in an endemic setting, there are two studies, one in India (N=24 vaccinees aged 1-3 years; Kaltenböck 2010) and one in the Philippines (N=1,411 IXIARO vaccinees aged 2 months - 17 years, 396 assessed for immunogenicity; Dubischar-Kastner 2012a). In the small Indian study, 95.7% (95% CI: 87.3-100) of vaccinees who received the age appropriate dose[4] were seroprotected one month following the second dose with a GMT of 201 (95% CI: 106-380). In the Philippines, the age appropriate dose (0.25ml 2 months to <3 years of age, 0.5ml 3-18 years of age) elicited the following rates of seroconversion in the 2-<6 months, 6-<12 months, 1-<3 years, 3-<12 years, and 12-<18 years age groups, respectively: 100%, 95%, 97%, 94%, and 77% (Dubischar-Kastner 2012a).
[2]Some RCTs assessed immunogenicity in vaccine-recipients, though not within the control group (or was a single-arm trial).
[3]Clinical study outcomes are based on an accepted immunological correlate of protection (Hombach 2005).
[4] High seroprotection (>80%) rates post-vaccination, a defined threshold in the WHO Guidance for the Development of Evidence-Based Vaccine-Related Recommendations.

Reference List

**Studies in Endemic Settings**

Dubischar-Kastner K, Kadlecek V, Eder S, Sablan Jr. B, Borja-Tabora CF, Gatchalian S, Westritschnig K. Safety and Immunogenicity of the Inactivated Japanese Encephalitis Vaccine IXIARO®, IC51, in Filipino Children Aged 2 Months to < 18 Years. Presented at the Asia Pacific Travel Health Conference, 2012. (A)

Dubischar-Kastner K, Kadlecek V, Bézay N, Sablan Jr. B, Borja-Tabora CF, Gatchalian S, Eder S, Westritschnig K. 24-Months Antibody Persistence in Children With and Without a Booster Dose of an Inactivated Japanese Encephalitis Vaccine, JE-VC, IC51. Presented at the Northern European Conference on Travel Medicine, 2014.

Kaltenböck A, Dubischar-Kastner K, Schuller E, Datla M, Klade CS, Kishore TS.Immunogenicity and safety of IXIARO (IC51) in a Phase II study in healthy Indian children between 1 and 3 years of age. Vaccine. 2010 Jan 8;28(3):834-9

**Studies in Non-Endemic Settings**

Dubischar-Kastner K, Eder S, Buerger V, Gartner-Woelfl G, Kaltenboeck A, Schuller E, Tauber E, Klade C. Long-term immunity and immune response to a booster dose following vaccination with the inactivated Japanese encephalitis vaccine IXIARO, IC51. Vaccine. 2010 Jul 19;28(32):5197-202.

Kaltenböck A, Dubischar-Kastner K, Eder G, Jilg W, Klade C, Kollaritsch H, Paulke-Korinek M, von Sonnenburg F, Spruth M, Tauber E, Wiedermann U, Schuller E. Safety and immunogenicity of concomitant vaccination with the cell-culture based Japanese Encephalitis vaccine IC51 and the hepatitis A vaccine HAVRIX1440 in healthy subjects: A single-blind, randomized, controlled Phase 3 study. Vaccine. 2009 Jul 16;27(33):4483-9.

Lyons A, Kanesa-thasan N, Kuschner RA, Eckels KH, Putnak R, Sun W, Burge R, Towle AC, Wilson P, Tauber E, Vaughn DW. A Phase 2 study of a purified, inactivated virus vaccine to prevent Japanese encephalitis. Vaccine. 2007 Apr 30;25(17):3445-53.

Schuller E, Jilma B, Voicu V, Golor G, Kollaritsch H, Kaltenböck A, Klade C, Tauber E. Long-term immunogenicity of the new Vero cell-derived, inactivated Japanese encephalitis virus vaccine IC51 Six and 12 month results of a multicenter follow-up phase 3 study. Vaccine. 2008 Aug 12;26(34):4382-6. (A)

Schuller E, Klade CS, Heinz FX, Kollaritsch H, Rendi-Wagner P, Jilma B, Tauber E. Effect of pre-existing anti-tick-borne encephalitis virus immunity on neutralising antibody response to the Vero cell-derived, inactivated Japanese encephalitis virus vaccine candidate IC51. Vaccine. 2008 Nov 11;26(48):6151-6. (B)

Schuller E, Klade CS, Wölfl G, Kaltenböck A, Dewasthaly S, Tauber E. Comparison of a single, high-dose vaccination regimen to the standard regimen for the investigational Japanese encephalitis vaccine, IC51: a randomized, observer-blind, controlled Phase 3 study. Vaccine. 2009 Mar 26;27(15):2188-93.

Tauber E, Kollaritsch H, Korinek M, Rendi-Wagner P, Jilma B, Firbas C, Schranz S, Jong E, Klingler A, Dewasthaly S, Klade CS. Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. Lancet. 2007 Dec 1;370(9602):1847-53.

## GRADE Table 2. What is the effectiveness of live attenuated JE vaccine in preventing JE disease in vaccinees living in JE-endemic areas?

**Population :** Immunocompetent individuals living in JE-endemic areas
**Intervention:** One dose of live attenuated JE vaccine
**Comparison:** Placebo/No vaccination/other JE vaccine
**Outcome :** JE disease (immunogenicity accepted)

| *What is the effectiveness of one dose of live attenuated JE vaccine in preventing JE disease in individuals living in JE-endemic areas?* | | | | |
|---|---|---|---|---|
| | | | Rating | Adjustment to rating |
| **Quality Assessment** | No. of studies/starting rating | | 4 RCTs[1] | 4 |
| | Factors decreasing confidence | Limitation in study design | None serious | 0 |
| | | Inconsistency | None serious[2] | 0 |
| | | Indirectness | None serious[3] | -1 |
| | | Imprecision | None serious | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Large effect | Applicable[4,5] | +1 |
| | | Dose-response | Not applicable | 0 |
| | | Antagonistic bias and confounding | Not applicable | 0 |
| | **Final numerical rating of quality of evidence** | | | **4** |
| **Summary of Findings** | **Statement on quality of evidence** | | | **We are very confident that the true effect lies close to that of the estimate of effect on health outcome** |
| | **Conclusion** | | | **Live attenuated JE vaccines have evidence of seroprotective neutralizing antibody titers.** ***Based on a review of data on CD.JEVAX*** |

[1]Four clinical studies with 1,256 participants receiving CD.JEVAX were assessed. Seroprotection rates at 28 days post-vaccination in the Philippines study were 92.1% (95% CI: 84.3-96.7) and 90.6 (95% CI: 85.3-94.4); the latter result was in the group administered measles vaccine one month prior (Victor 2014). The seroprotection rate was 97.3% (95% CI: 93.1-99.2) for the live attenuated vaccine when used as a control in a chimeric JE vaccine RCT in children aged 9 months to 18 years in Thailand (Feroldi 2014). In a similar study in children 12-24 months in Korea, the seroprotection rate was 99.1% (Kim 2013).
[2]In a lot-to-lot consistency study in Bangladesh with vaccine from a new GMP-compliant facility, seroprotection rates ranged between 80.2% (95% CI: 74.0-85.2) to 86.3% (95% CI: 79.8-91.0)(Zaman 2014). Two lots were not equivalent with a seroprotection rate difference of -4.33 (-11.94-3.31). No clinical consequences have been established and it was determined not to downgrade.
[3]Clinical study outcomes are based on an accepted immunological correlate of protection (Hombach 2005).
[4]High seroprotection (>80%) rates post-vaccination, a defined threshold in the WHO Guidance for the Development of Evidence-Based Vaccine-Related Recommendations.
[5]Two effectiveness studies were done in the near-term after vaccination. A case control study in Nepal estimated vaccine effectiveness to be 99.3% (95% CI: 94.9-100) in the one week to one month time period post-vaccination (Bista 2001). A second case-control study in India estimated vaccine effectiveness to be 94.5% (95% CI: 81.5-98.9) six months following vaccination (Kumar 2009).

Reference List

**Clinical Studies in Endemic Settings**

Feroldi E, Pancharoen C, Kosalaraksa P, Chokephaibulkit K, Boaz M, Meric C, Hutagalung Y, Bouckenooghe A. Primary immunization of infants and toddlers in Thailand with Japanese encephalitis chimeric virus vaccine in comparison with SA14-14-2: a randomized study of immunogenicity and safety. Pediatr Infect Dis J. 2014 Jun;33(6):643-9.

Kim DS, Houillon G. A randomized study of the immunogenicity and safety of Japanese encephalitis chimeric virus vaccine (JE-CV) in comparison with SA 14-14-2 vaccine in children in South Korea. 8th World Congress of the World Society for Pediatric Infectious Diseases (WSPID) - Nov. 19-22, 2013, Cape Town, South Africa.

Victor J, Gatchalian S, Yao Y, Zhou B, Zhang L, Yoksan S, Yaich M, Neuzil K. Corrigendum to "Comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants." Vaccine. 2014 32(2): 306-8.

Zaman K, Naser AM, Power M, Yaich M, Zhang L, Ginsburg AS, Luby SP, Rahman M, Hills S, Bhardwaj M, Flores J. Lot-to-lot consistency of live attenuated SA 14-14-2 Japanese encephalitis vaccine manufactured in a good manufacturing practice facility and non-inferiority with respect to an earlier product. Vaccine. 2014 Sep 18 (epub ahead of print).

**Vaccine Effectiveness Studies (<12 months post-vaccination)**

Bista MB, Banerjee MK, Shin SH, Tandan JB, Kim MH, Sohn YM, Ohrr HC, Tang JL, Halstead SB. Efficacy of single-dose SA 14-14-2 vaccine against Japanese encephalitis: a case control study. Lancet. 2001 Sep 8;358(9284):791-5.

Kumar R, Tripathi P, Rizvi A. Effectiveness of one dose of SA 14-14-2 vaccine against Japanese encephalitis. N Engl J Med. 2009 Apr 2;360(14):1465-6.

## GRADE Table 3. What is the effectiveness of chimeric JE vaccine in preventing JE disease in vaccinees living in JE-endemic areas?

**Population :** Immunocompetent individuals living in JE-endemic areas
**Intervention:** One dose of chimeric JE vaccine
**Comparison:** Placebo/No vaccination/other JE vaccine
**Outcome :** JE disease (immunogenicity accepted)

*Is there a need for a booster dose following immunization with a single dose of chimeric JE vaccine in vaccinees living in JE-endemic areas?*

| | | | Rating | Adjustment to rating |
|---|---|---|---|---|
| **Quality Assessment** | No. of studies/starting rating | | 10 RCTs[1] | 4 |
| | Factors decreasing confidence | Limitation in study design | None serious | 0 |
| | | Inconsistency | None serious[2] | 0 |
| | | Indirectness | None serious[3] | -1 |
| | | Imprecision | None serious | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Large effect | Not applicable[4] | +1 |
| | | Dose-response | Not applicable | 0 |
| | | Antagonistic bias and confounding | Not applicable | 0 |
| | **Final numerical rating of quality of evidence** | | | **4** |
| **Summary of Findings** | **Statement on quality of evidence** | | | **We are very confident that the true effect lies close to that of the estimate of effect on health outcome** |
| | **Conclusion** | | | **Chimeric JE vaccines have evidence of seroprotective neutralizing antibody titers.** ***Based on a review of data on IMOJEV*** |

[1]Includes approximately 3,750 IMOJEV recipients in endemic and non-endemic settings. High seroprotection rates one month post-vaccination (no simultaneous vaccination) were reported. In the lowest age group (9-18 months), the seroprotection rate was estimated at 99.3% (95% CI: 96.2-100.0) (Feroldi 2014). Similar results were found in Korea (Kim 2013) among 12-24 month-olds (seroprotection 100%, 95% CI: NR) and in Thailand and the Philippines among 12-18 month-olds (seroprotection 95.0%, 95% CI: 93.3-96.3) (Feroldi 2012). Among 36-42 month-olds, 89.7% (95% CI: 75.8-97.1) were seroprotected one month post vaccination. Lower seroprotection rates were found with some serological assays (all genotype 3 challenge viruses) in a small study in India (e.g., against Nakayama strain and Indian strains) (NCT00441259 results). Seroprotection rates were also high in three trials among adults in non-endemic settings (e.g. 99.1% seroprotected (95% CI: 97.5-99.8) adults aged 18-65 in the US and Australia (Torresi 2010); see Table 10.

[2]Lower GMTs and rates of seroconversion were seen in one small study using Nakayama strain (NCT00441259). It was communicated that the virus stock was not good (G. Houillon, personal communication). Similar results were obtained in the same study in participants vaccinated with Nakayama-based inactivated mouse brain-derived vaccine, and no downgrade was applied.

[3]Clinical study outcomes are based on an accepted immunological correlate of protection (Hombach 2005).

[4]High seroprotection (>80%) rates post-vaccination, a defined threshold in the WHO Guidance for the Development of Evidence-Based Vaccine-Related Recommendations.

Reference List

**Clinical Studies in Endemic Settings**

Chokephaibulkit K, Sirivichayakul C, Thisyakorn U, Sabchareon A, Pancharoen C, Bouckenooghe A, Gailhardou S, Boaz M, Feroldi E. Safety and immunogenicity of a single administration of live-attenuated Japanese encephalitis vaccine in previously primed 2- to 5-year-olds and naive 12- to 24-month-olds: multicenter randomized controlled trial. Pediatr Infect Dis J. 2010 Dec;29(12):1111-7.

Feroldi E, Pancharoen C, Kosalaraksa P, Watanaveeradej V, Phirangkul K, Capeding MR, Boaz M, Gailhardou S, Bouckenooghe A. Single-dose, live-attenuated Japanese encephalitis vaccine in children aged 12-18 months: randomized, controlled phase 3 immunogenicity and safety trial. Hum Vaccin Immunother. 2012 Jul;8(7):929-37.

Feroldi E, Capeding MR, Boaz M, Gailhardou S, Meric C, Bouckenooghe A. Memory immune response and safety of a booster dose of Japanese encephalitis chimeric virus vaccine (JE-CV) in JE-CV-primed children. Hum Vaccin Immunother. 2013 Apr;9(4):889-97.

Feroldi E, Pancharoen C, Kosalaraksa P, Chokephaibulkit K, Boaz M, Meric C, Hutagalung Y, Bouckenooghe A. Primary immunization of infants and toddlers in Thailand with Japanese encephalitis chimeric virus vaccine in comparison with SA14-14-2: a randomized study of immunogenicity and safety. Pediatr Infect Dis J. 2014 Jun;33(6):643-9.

Feroldi E, Pancharoen C, Watanaveeradej V, Bouckenooghe A. Persistence of antibodies one year after a single injection of live attenuated Japanese encephalitis chimeric virus vaccine at 12-18 months of age. Presented at the American Society of Tropical Medicine and Hygiene, 2010. Am J Trop Med Hyg. 2010. 83:5 (abstract only).

Huang LM, Lin TY, Chiu CH, Chiu NC, Chen PY, Yeh SJ, Boaz M, Hutagalung Y, Bouckenooghe A, Feroldi E. Concomitant administration of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and measles, mumps, rubella (MMR) vaccine: Randomized study in toddlers in Taiwan. Vaccine. 2014 Mar 12. pii: S0264-410X(14)00312-0.

Kim DS, Houillon G. A randomized study of the immunogenicity and safety of Japanese encephalitis chimeric virus vaccine (JE-CV) in comparison with SA 14-14-2 vaccine in children in South Korea. 8th World Congress of the World Society for Pediatric Infectious Diseases (WSPID) - Nov. 19-22, 2013, Cape Town, South Africa.

**Clinical Studies in Non-Endemic Settings**

Nasveld PE, Ebringer A, Elmes N, Bennett S, Yoksan S, Aaskov J, McCarthy K, Kanesa-thasan N, Meric C, Reid M. Long term immunity to live attenuated Japanese encephalitis chimeric virus vaccine: randomized, double-blind, 5-year phase II study in healthy adults. Hum Vaccin. 2010 Dec;6(12):1038-46.

Torresi J, McCarthy K, Feroldi E, Méric C. Immunogenicity, safety and tolerability in adults of a new single-dose, live-attenuated vaccine against Japanese encephalitis: Randomised controlled phase 3 trials. Vaccine. 2010 Nov 23;28(50):7993-8000.

Clinical Trials Data:

http://clinicaltrials.gov/ct2/show/results/NCT01092507

http://clinicaltrials.gov/ct2/show/results/NCT00441259

GRADE Table 4. Is there need for a booster dose following immunization with the primary series of **inactivated Vero cell JE vaccine** in individuals living in JE-endemic areas?

**Population :** Immunocompetent individuals living in JE-endemic areas
**Intervention:** Two doses (primary series) of inactivated Vero cell vaccine administered ≥12 months previously
**Comparison:** Placebo/No vaccination/other JE vaccine
**Outcome :** JE disease (immunogenicity accepted)

| *Is there need for a booster dose following immunization with the primary series of inactivated Vero cell JE vaccine in individuals living in JE-endemic areas?* | | | | |
|---|---|---|---|---|
| | | | Rating | Adjustment to rating |
| **Quality Assessment** | No. of studies/starting rating | | 4 RCTs[1] | 4 |
| | Factors decreasing confidence | Limitation in study design | None serious[2] | -1 |
| | | Inconsistency | None serious | 0 |
| | | Indirectness | None serious[3,4] | -1 |
| | | Imprecision | None serious | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Large effect | Applicable[5] | 0 |
| | | Dose-response | Not applicable | 0 |
| | | Antagonistic bias and confounding | Not applicable | 0 |
| | **Final numerical rating of quality of evidence** | | | **2** |
| **Summary of Findings** | **Statement on quality of evidence** | | | **Our confidence in the estimate of the effect on the health outcome is limited.** |
| | **Conclusion** | | | **A primary series of inactivated Vero cell JE vaccines administered to children in endemic settings has evidence of seroprotective neutralizing antibody titers for at least three years after the primary immunization.**<br><br>***Based on a review of data on IXIARO*** |

[1]Five clinical studies following participants 12 months post-primary series, 2 years, or 3 years are available, limiting the full assessment of long-term protection. Data in adults from non-endemic settings suggest a decline in seroprotection rates and GMTs in the 24 months following primary immunization. One study in Austria, Germany, and Romania found seroprotection rates dropped from 99% (95% CI: 96.1-99.7) at one month following the primary series to 82% two years later and 84.9% (95% CI: 78.3-89.7) three years later (Schuller 2008a; CDC 2011); however, these results were obtained from a study population among which some had previously been exposed or vaccinated against Tick-Borne Encephalitis (TBE). Another study in Germany and Northern Ireland (without TBE) found seroprotection rates dropped from 97.3% (95% CI: 94.4-100.0) to 48.3% (95% CI: 39.4-57.3) (Schuller 2009; Dubischar-Kastner 2010a). A booster dose is indicated >12 months after the primary series in non-endemic settings for longer protection. There are limited data in children and in endemic settings. In a study in the Philippines among children aged 2 months – 16 years, the seroprotection rate among 150 children at 3 years was 90%. The GMT decreased between month 2 and month 7, but then was relatively stable through the 3 years of follow up (49-52). (Dubischar-Kastner 2014 and unpublished, quoted with permission from Valneva)

[2]The limited duration of follow up (three years post primary series) of participants in endemic areas (300 children ages 2 months to 17 years) limits the ability to assess the duration of protection in these settings.
[3]Clinical study outcomes are based on an accepted immunological correlate of protection (Hombach 2005).
[4]Data are available from one endemic country (Philippines), with only 150 participants. Other data from adults in non-endemic settings is less applicable (not downgraded twice, as the small population and limited duration of follow up was downgraded under study design).
[5]Data from one study in the Philippines do support a high level (>80%) of effectiveness, a defined threshold in the WHO Guidance for the Development of Evidence-Based Vaccine-Related Recommendations. However, due to the other reasons for downgrading, it was not felt appropriate to upgrade.

## Reference List

**Clinical Studies in Endemic Settings**

Dubischar-Kastner K, Kadlecek V, Eder S, Sablan Jr. B, Borja-Tabora CF, Gatchalian S, Westritschnig K. Safety and Immunogenicity of the Inactivated Japanese Encephalitis Vaccine IXIARO®, IC51, in Filipino Children Aged 2 Months to < 18 Years. Presented at the Asia Pacific Travel Health Conference, 2012. (A)

Dubischar-Kastner K, Kadlecek V, Bézay N, Sablan Jr. B, Borja-Tabora CF, Gatchalian S, Eder S, Westritschnig K. 24-Months Antibody Persistence in Children With and Without a Booster Dose of an Inactivated Japanese Encephalitis Vaccine, JE-VC, IC51. Presented at the Northern European Conference on Travel Medicine, 2014.

**Clinical Studies in Non-Endemic Settings**

Dubischar-Kastner K, Eder S, Buerger V, Gartner-Woelfl G, Kaltenboeck A, Schuller E, Tauber E, Klade C. Long-term immunity and immune response to a booster dose following vaccination with the inactivated Japanese encephalitis vaccine IXIARO, IC51. Vaccine. 2010 Jul 19;28(32):5197-202.

Lyons A, Kanesa-thasan N, Kuschner RA, Eckels KH, Putnak R, Sun W, Burge R, Towle AC, Wilson P, Tauber E, Vaughn DW. A Phase 2 study of a purified, inactivated virus vaccine to prevent Japanese encephalitis. Vaccine. 2007 Apr 30;25(17):3445-53.

Schuller E, Jilma B, Voicu V, Golor G, Kollaritsch H, Kaltenböck A, Klade C, Tauber E. Long-term immunogenicity of the new Vero cell-derived, inactivated Japanese encephalitis virus vaccine IC51 Six and 12 month results of a multicenter follow-up phase 3 study. Vaccine. 2008 Aug 12;26(34):4382-6. (A)

Schuller E, Klade CS, Heinz FX, Kollaritsch H, Rendi-Wagner P, Jilma B, Tauber E. Effect of pre-existing anti-tick-borne encephalitis virus immunity on neutralising antibody response to the Vero cell-derived, inactivated Japanese encephalitis virus vaccine candidate IC51. Vaccine. 2008 Nov 11;26(48):6151-6. (B)

Schuller E, Klade CS, Wölfl G, Kaltenböck A, Dewasthaly S, Tauber E. Comparison of a single, high-dose vaccination regimen to the standard regimen for the investigational Japanese encephalitis vaccine, IC51: a randomized, observer-blind, controlled Phase 3 study. Vaccine. 2009 Mar 26;27(15):2188-93.

## GRADE Table 5. Is there a need for a booster dose following immunization with one dose of live attenuated JE vaccine in individuals living in JE-endemic areas?

**Population :** Immunocompetent individuals living in JE-endemic areas
**Intervention:** One dose of live attenuated JE vaccine administered ≥12 months previously
**Comparison:** Placebo/No vaccination/other JE vaccine
**Outcome :** JE disease (immunogenicity accepted)

| *Is there a need for a booster dose following immunization with one dose of live attenuated JE vaccine in individuals living in JE-endemic areas?* | | | | |
|---|---|---|---|---|
| | | | Rating | Adjustment to rating |
| **Quality Assessment** | No. of studies/starting rating | | 2 RCTs[1] | 4 |
| | Factors decreasing confidence | Limitation in study design | None serious | 0 |
| | | Inconsistency | None serious[2] | 0 |
| | | Indirectness | None serious[3] | -2 |
| | | Imprecision | None serious | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Large effect | Applicable[4] | +1 |
| | | Dose-response | Not applicable | 0 |
| | | Antagonistic bias and confounding | Not applicable | 0 |
| | **Final numerical rating of quality of evidence** | | | **3** |
| **Summary of Findings** | **Statement on quality of evidence** | | | **We are moderately confident that the true effect lies close to that of the estimate of effect on health outcome** |
| | **Conclusion** | | | **A single dose of live attenuated JE vaccine administered to children in endemic settings has evidence of seroprotective neutralizing antibody titers for at least three years after immunization.**<br><br>***Based on a review of data on CD.JEVAX*** |

[1]Two clinical studies are available with data on participants 12 months after vaccination, and for one of these studies, 2 years and 3 years after vaccination. A study from the Philippines measured immunogenicity of a single dose (and no other vaccine administered for at least 28 days) for three years (NCT00412516 results). Among 8 month-olds administered a single dose of live attenuated vaccine, seroprotection was measured at 90.4% (95% CI: 81.9-95.8), 81.1% (95% CI: 71.5-88.6), and 79.3% (69.3-87.2) at 1 year, 2 years, and 3 years post vaccination. Among 10 month-olds, the corresponding seroprotection rates were 86.1% (95% CI: 80.6-90.6), 80.7% (95% CI: 74.6-85.9), and 81.9% (95% CI: 75.8-87.0). These figures are consistent with 12-month immunogenicity results from a study of Thai children aged 9-12 months (Feroldi 2014).
[2] In a lot-to-lot consistency study in Bangladesh with vaccine from a new GMP-compliant facility, seroprotection rates ranged between 80.2% (95% CI: 74.0-85.2) to 86.3% (95% CI: 79.8-91.0)(Zaman 2014). Two lots were not equivalent with a

seroprotection rate difference of -4.33 (-11.94-3.31). It is not known whether the long-term seroprotection rates and effectiveness of the GMP vaccine will be consistent with those seen in studies of the non-GMP vaccine.
[3]Study outcomes are based on an accepted immunological correlate of protection (Hombach 2005).
[4] High seroprotection (>80%) rates post-vaccination, a defined threshold in the WHO Guidance for the Development of Evidence-Based Vaccine-Related Recommendations. Although data for three years is only based on one study, it is supported by three effectiveness studies done at one year or greater after vaccination. A case control study in Nepal estimated vaccine effectiveness to be 95.5% (95% CI: 90.1-99.2) one year following vaccination (Ohrr 2005). A second case-control study in Nepal estimated vaccine effectiveness to be 96.2% (95% CI: 73.1-99.9) give years following vaccination (Tandan 2007). A case control study done in China in the 1990s estimated vaccine effectiveness to be 80% (95% CI: 44-93) up to 14 years after vaccination with a single dose.

Reference List

**Clinical Studies in Endemic Settings**

Feroldi E, Pancharoen C, Kosalaraksa P, Chokephaibulkit K, Boaz M, Meric C, Hutagalung Y, Bouckenooghe A. Primary immunization of infants and toddlers in Thailand with Japanese encephalitis chimeric virus vaccine in comparison with SA14-14-2: a randomized study of immunogenicity and safety. Pediatr Infect Dis J. 2014 Jun;33(6):643-9.

*Description of methods for long-term immunogenicity study in the Philippines in*: Gatchalian S, Yao Y, Zhou B, Zhang L, Yoksan S, Kelly K, Neuzil KM, Yaïch M, Jacobson J. Comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants. Vaccine. 2008 Apr 24;26(18):2234-41.

Zaman K, Naser AM, Power M, Yaich M, Zhang L, Ginsburg AS, Luby SP, Rahman M, Hills S, Bhardwaj M, Flores J. Lot-to-lot consistency of live attenuated SA 14-14-2 Japanese encephalitis vaccine manufactured in a good manufacturing practice facility and non-inferiority with respect to an earlier product. Vaccine. 2014 Sep 18 (epub ahead of print).

**Vaccine Effectiveness Studies (>12 months post-vaccination)**

Hennessy S, Liu Z, Tsai TF, Strom BL, Wan CM, Liu HL, Wu TX, Yu HJ, Liu QM, Karabatsos N, Bilker WB, Halstead SB. Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case-control study. Lancet. 1996 Jun 8;347(9015):1583-6.

Ohrr H, Tandan JB, Sohn YM, Shin SH, Pradhan DP, Halstead SB. Effect of single dose of SA 14-14-2 vaccine 1 year after immunisation in Nepalese children with Japanese encephalitis: a case-control study. Lancet. 2005 Oct 15-21;366(9494):1375-8.

Tandan JB, Ohrr H, Sohn YM, Yoksan S, Ji M, Nam CM, Halstead SB. Single dose of SA 14-14-2 vaccine provides long-term protection against Japanese encephalitis: a case-control study in Nepalese children 5 years after immunization. Vaccine. 2007 Jun 28;25(27):5041-5.

## GRADE Table 6. Is there a need for a booster dose following immunization with a single dose of chimeric JE vaccine in vaccinees living in JE-endemic areas?

**Population :** Immunocompetent individuals living in JE-endemic areas
**Intervention:** One dose of chimeric JE vaccine administered ≥ 12 months previously
**Comparison:** Placebo/No vaccination/other JE vaccine
**Outcome :** JE disease (immunogenicity accepted)

| *Is there a need for a booster dose following immunization with a single dose of chimeric JE vaccine in vaccinees living in JE-endemic areas?* | | | | |
|---|---|---|---|---|
| | | | Rating | Adjustment to rating |
| **Quality Assessment** | No. of studies/starting rating | | 6 RCTs[1] | 4 |
| | Factors decreasing confidence | Limitation in study design | None serious[2] | -1 |
| | | Inconsistency | None serious[3] | 0 |
| | | Indirectness | None serious[4] | -1 |
| | | Imprecision | None serious | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Large effect | Not applicable[5] | 0 |
| | | Dose-response | Not applicable | 0 |
| | | Antagonistic bias and confounding | Not applicable | 0 |
| | **Final numerical rating of quality of evidence** | | | **2** |
| **Summary of Findings** | **Statement on quality of evidence** | | | **Our confidence in the estimate of the effect on the health outcome is limited.** |
| | **Conclusion** | | | **A single dose of chimeric JE vaccine administered to children in endemic settings has evidence of seroprotective neutralizing antibody titers for at least five years after immunization.**<br><br>***Based on a review of data on IMOJEV*** |

[1]Six clinical studies with data for nearly 2000 subjects provides immunogenicity data for IMOJEV vaccinees at 12 months or longer following vaccination. Among children in endemic settings, four trials followed up participants for 1 year or longer. In one study, between six months and one year post-vaccination, the percent seroprotected dropped from 94.5% (95% CI: 89.4-97.6) to 88.1% (95% CI: 81.6-92.9) (Feroldi 2014[)]. A recent study followed 200 Thai participants vaccinated at 12-24 months for five years (quoted with permission from Sanofi Pasteur, data to be presented at ACPID 2014). Seroprotection rates fell from 80.2% one year post-vaccination to 80.2%, 75.2%, 74.1%, and 65.6% at two, three, four, and five years post-vaccination, respectively. Long-term protection in adults from another study was much higher. Seroprotection rates among Australia military participants aged 18-55 years were 99% (95% CI: 96-100) one month after vaccination, followed by 95% (95% CI: 87-99), 90% (95% CI: 81-96), and 94% (95% CI: 82-99) at one year, two years, and five years post-vaccination (Nasveld 2010a). However, only 46 participants (45% of the original study population) remained in the study at the final time point.

[2]Data are only available from 2 studies with follow-up to 5 years, and there are no effectiveness data, limiting the ability to fully assess long-term protection.

[3]Immunogenicity was higher over time in adults compared with children; there may be heterogeneity in the duration of protection by age.
[4]RCT outcomes are based on an accepted immunological correlate of protection (Hombach 2005).
[5]Due to the lower seroprotection rates reported in children in endemic settings, the small number of studies, and the lack of supporting effectiveness studies, no upgrade was applied.

Reference List

**RCTs**

*Methods of long-term immunogenicity study described in:* Chokephaibulkit K, Sirivichayakul C, Thisyakorn U, Sabchareon A, Pancharoen C, Bouckenooghe A, Gailhardou S, Boaz M, Feroldi E. Safety and immunogenicity of a single administration of live-attenuated Japanese encephalitis vaccine in previously primed 2- to 5-year-olds and naive 12- to 24-month-olds: multicenter randomized controlled trial. Pediatr Infect Dis J. 2010 Dec;29(12):1111-7.

Feroldi E, Pancharoen C, Kosalaraksa P, Watanaveeradej V, Phirangkul K, Capeding MR, Boaz M, Gailhardou S, Bouckenooghe A. Single-dose, live-attenuated Japanese encephalitis vaccine in children aged 12-18 months: randomized, controlled phase 3 immunogenicity and safety trial. Hum Vaccin Immunother. 2012 Jul;8(7):929-37.

Feroldi E, Capeding MR, Boaz M, Gailhardou S, Meric C, Bouckenooghe A. Memory immune response and safety of a booster dose of Japanese encephalitis chimeric virus vaccine (JE-CV) in JE-CV-primed children. Hum Vaccin Immunother. 2013 Apr;9(4):889-97.

Feroldi E, Pancharoen C, Kosalaraksa P, Chokephaibulkit K, Boaz M, Meric C, Hutagalung Y, Bouckenooghe A. Primary immunization of infants and toddlers in Thailand with Japanese encephalitis chimeric virus vaccine in comparison with SA14-14-2: a randomized study of immunogenicity and safety. Pediatr Infect Dis J. 2014 Jun;33(6):643-9.

Feroldi E, Pancharoen C, Watanaveeradej V, Bouckenooghe A. Persistence of antibodies one year after a single injection of live attenuated Japanese encephalitis chimeric virus vaccine at 12-18 months of age. Presented at the American Society of Tropical Medicine and Hygiene, 2010. Am J Trop Med Hyg. 2010. 83:5 (abstract only).

Huang LM, Lin TY, Chiu CH, Chiu NC, Chen PY, Yeh SJ, Boaz M, Hutagalung Y, Bouckenooghe A, Feroldi E. Concomitant administration of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and measles, mumps, rubella (MMR) vaccine: Randomized study in toddlers in Taiwan. Vaccine. 2014 Mar 12. pii: S0264-410X(14)00312-0.

Nasveld PE, Ebringer A, Elmes N, Bennett S, Yoksan S, Aaskov J, McCarthy K, Kanesa-thasan N, Meric C, Reid M. Long term immunity to live attenuated Japanese encephalitis chimeric virus vaccine: randomized, double-blind, 5-year phase II study in healthy adults. Hum Vaccin. 2010 Dec;6(12):1038-46.

Clinical Trials Data:

http://clinicaltrials.gov/ct2/show/results/NCT01092507

http://clinicaltrials.gov/ct2/show/results/NCT00441259

## GRADE Table 7. What is the risk of serious adverse events following vaccination with inactivated Vero cell JE vaccine?

**Population :** Immunocompetent individuals
**Intervention:** Two doses (primary series) of inactivated Vero cell vaccine
**Comparison:** Placebo/No vaccination/Other JE vaccine
**Outcome :** Serious adverse events

| *What is the risk of serious adverse events following vaccination with inactivated Vero cell JE vaccine?* | | | | |
|---|---|---|---|---|
| | | | Rating | Adjustment to rating |
| **Quality Assessment** | No. of studies/starting rating | | 11 RCTs[1] | 4 |
| | Factors decreasing confidence | Limitation in study design | None serious[2] | -1 |
| | | Inconsistency | None serious | 0 |
| | | Indirectness | None serious | 0 |
| | | Imprecision | None serious | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Large effect | Not applicable | 0 |
| | | Dose-response | Not applicable | 0 |
| | | Antagonistic bias and confounding | Not applicable | 0 |
| | **Final numerical rating of quality of evidence** | | | **3** |
| **Summary of Findings** | **Statement on quality of evidence** | | | **We are moderately confident that the true effect lies close to that of the estimate of effect on health outcome** |
| | **Conclusion** | | | **Inactivated Vero cell JE vaccine has an acceptable safety profile.**<br>***Based on a review of data on IXIARO*** |

[1] Two pooled analyses of 7 clinical studies (N=3558 vaccinated with IXIARO) and 10 clinical studies (N=4,043 vaccinated with IXIARO) have been published. In adults there was comparable tolerability and reactogenicity with placebo (adjuvant alone) and mouse brain-derived JE vaccine except for local reactions. A significantly lower frequency of severe local reactions was reported for IXIARO compared to mouse brain-derived JE vaccine. In a clinical trial of children aged ⩾2 months to < 1 year in the Philippines, a similar percentage of participants receiving IXIARO (N=131) or Prevnar (N=64) experienced solicited (58.0% vs. 59.4%), unsolicited (72.5% vs. 65.6%), and serious (0% vs. 1.6%) adverse events up to Day 56 after the first vaccination (European Public Assessment Report 2013).

[2] This vaccine has had limited use outside of clinical trials. Post-marketing data are published for the first 12 months of use (Schuller 2011). The ability to detect less common serious adverse events is limited.

Reference List

**Pooled Safety Analyses:**

Dubischar-Kastner K, Kaltenboeck A, Klingler A, Jilma B, Schuller E. Safety analysis of a Vero-cell culture derived Japanese encephalitis vaccine, IXIARO (IC51), in 6 months of follow-up. Vaccine. 2010 Sep 7;28(39):6463-9. (B)

Schuller E, Klingler A, Dubischar-Kastner K, Dewasthaly S, Müller Z. Safety profile of the Vero cell-derived Japanese encephalitis virus (JEV) vaccine IXIARO®. Vaccine. 2011 Nov 3;29(47):8669-76.

**Clinical Studies (some only for methods, contributing to pooled analyses)**

Eder S, Dubischar-Kastner K, Firbas C, Jelinek T, Jilma B, Kaltenboeck A, Knappik M, Kollaritsch H, Kundi M, Paulke-Korinek M, Schuller E, Klade CS. Long term immunity following a booster dose of the inactivated Japanese Encephalitis vaccine IXIARO®, IC51. Vaccine. 2011 Mar 21;29(14):2607-12

European Public Assessment Summary Report, 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000963/WC500142252.pdf

Kaltenböck A, Dubischar-Kastner K, Schuller E, Datla M, Klade CS, Kishore TS.Immunogenicity and safety of IXIARO (IC51) in a Phase II study in healthy Indian children between 1 and 3 years of age. Vaccine. 2010 Jan 8;28(3):834-9

Kaltenböck A, Dubischar-Kastner K, Eder G, Jilg W, Klade C, Kollaritsch H, Paulke-Korinek M, von Sonnenburg F, Spruth M, Tauber E, Wiedermann U, Schuller E. Safety and immunogenicity of concomitant vaccination with the cell-culture based Japanese Encephalitis vaccine IC51 and the hepatitis A vaccine HAVRIX1440 in healthy subjects: A single-blind, randomized, controlled Phase 3 study. Vaccine. 2009 Jul 16;27(33):4483-9.

Schuller E, Jilma B, Voicu V, Golor G, Kollaritsch H, Kaltenböck A, Klade C, Tauber E. Long-term immunogenicity of the new Vero cell-derived, inactivated Japanese encephalitis virus vaccine IC51 Six and 12 month results of a multicenter follow-up phase 3 study. Vaccine. 2008 Aug 12;26(34):4382-6. (A)

Schuller E, Klade CS, Wölfl G, Kaltenböck A, Dewasthaly S, Tauber E. Comparison of a single, high-dose vaccination regimen to the standard regimen for the investigational Japanese encephalitis vaccine, IC51: a randomized, observer-blind, controlled Phase 3 study. Vaccine. 2009 Mar 26;27(15):2188-93.

Tauber E, Kollaritsch H, Korinek M, Rendi-Wagner P, Jilma B, Firbas C, Schranz S, Jong E, Klingler A, Dewasthaly S, Klade CS. Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. Lancet. 2007 Dec 1;370(9602):1847-53.

Tauber E, Kollaritsch H, von Sonnenburg F, Lademann M, Jilma B, Firbas C, Jelinek T, Beckett C, Knobloch J, McBride WJ, Schuller E, Kaltenböck A, Sun W, Lyons A. Randomized, double-blind, placebo-controlled phase 3 trial of the safety and tolerability of IC51, an inactivated Japanese encephalitis vaccine. J Infect Dis. 2008 Aug 15;198(4):493-9.

## GRADE Table 8. What is the risk of serious adverse events following vaccination with the live attenuated JE vaccine?

**Population :** Immunocompetent individuals
**Intervention:** One dose of live attenuated JE vaccine
**Comparison:** Placebo/No vaccination/other JE vaccine
**Outcome :** Serious adverse events

| *What is the risk of serious adverse events following vaccination with the live attenuated JE vaccine?* | | | | |
|---|---|---|---|---|
| | | | Rating | Adjustment to rating |
| **Quality Assessment** | No. of studies/starting rating | | 4 RCTs[1,2] | 4 |
| | Factors decreasing confidence | Limitation in study design | None serious | 0 |
| | | Inconsistency | None serious | 0 |
| | | Indirectness | None serious | 0 |
| | | Imprecision | None serious | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Large effect | Not applicable | 0 |
| | | Dose-response | Not applicable | 0 |
| | | Antagonistic bias and confounding | Not applicable | 0 |
| | **Final numerical rating of quality of evidence** | | | **4** |
| **Summary of Findings** | **Statement on quality of evidence** | | | **We are very confident that the true effect lies close to that of the estimate of effect on health outcome** |
| | **Conclusion** | | | **Live attenuated JE vaccine has an acceptable safety profile.**<br>***Based on a review of data on CD.JEVAX*** |

[1]Four clinical studies of 1,256 participants contributed to the safety assessment. In children 9 months to 6 years, live attenuated SA 14-14-2 had moderately higher frequency and severity of local and systemic adverse reactions, including fever, compared to chimeric vaccine (Feroldi 2014; Kim 2013). No vaccine-related serious adverse reactions or deaths were reported in RCTs (up to 7 months follow up) except for two cases of pyrexia in children aged 12-23 months.
[2]Post-marketing surveillance has also been done. Based on 23 million doses distributed between 2005-2012, 1426 adverse events were reported (61 per million doses), although this is an underestimate as is typical in particular with developing passive surveillance systems. Case reports were also reviewed, as was an observational study.

Reference List

**Clinical Studies**

Feroldi E, Pancharoen C, Kosalaraksa P, Chokephaibulkit K, Boaz M, Meric C, Hutagalung Y, Bouckenooghe A. Primary immunization of infants and toddlers in Thailand with Japanese encephalitis chimeric virus vaccine in comparison with SA14-14-2: a randomized study of immunogenicity and safety. Pediatr Infect Dis J. 2014 Jun;33(6):643-9.

Gatchalian S, Yao Y, Zhou B, Zhang L, Yoksan S, Kelly K, Neuzil KM, Yaïch M, Jacobson J. Comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants. Vaccine. 2008 Apr 24;26(18):2234-41.

Kim DS, Houillon G. A randomized study of the immunogenicity and safety of Japanese encephalitis chimeric virus vaccine (JE-CV) in comparison with SA 14-14-2 vaccine in children in South Korea. 8th World Congress of the World Society for Pediatric Infectious Diseases (WSPID) - Nov. 19-22, 2013, Cape Town, South Africa.

Liu ZL, Hennessy S, Strom BL, Tsai TF, Wan CM, Tang SC, Xiang CF, Bilker WB, Pan XP, Yao YJ, Xu ZW, Halstead SB. Short-term safety of live attenuated Japanese encephalitis vaccine (SA14-14-2): results of a randomized trial with 26,239 subjects. J Infect Dis. 1997 Nov;176(5):1366-9.

**Post-marketing surveillance and case reports**

Liu Y, Lin H, Zhu Q, Wu C, Zhao Z, Zheng H. Safety of Japanese encephalitis live attenuated vaccination in post-marketing surveillance in Guangdong, China, 2005-2012. Vaccine. 2014 Mar 26;32(15):1768-73.

Jia N, Zhao QM, Guo XF, Cheng JX, Wu C, Zuo SQ, Dai PF, Zhao JY, Zhang JS. Encephalitis temporally associated with live attenuated Japanese encephalitis vaccine: four case reports. BMC Infect Dis. 2011 Dec 14;11:344.

Choi UY, Lee SY, Kim KH, Kim DS, Choi KM, Cha SH, Kang JH. Is a booster dose necessary in children after immunization with live attenuated Japanese encephalitis vaccine? J Trop Pediatr. 2013 Oct;59(5):423-5.

## GRADE Table 9. What is the risk of serious adverse events following vaccination with the chimeric JE vaccine?

**Population :** Immunocompetent individuals living in JE-endemic areas
**Intervention:** One dose of chimeric JE vaccine
**Comparison:** Placebo/No vaccination/other JE vaccine
**Outcome :** Serious adverse events

| *What is the risk of serious adverse events following vaccination with the chimeric JE vaccine?* | | | | |
|---|---|---|---|---|
| | | | Rating | Adjustment to rating |
| **Quality Assessment** | No. of studies/starting rating | | 10 RCTs[1] | 4 |
| | Factors decreasing confidence | Limitation in study design | None serious[2] | -1 |
| | | Inconsistency | None serious | 0 |
| | | Indirectness | None serious | 0 |
| | | Imprecision | None serious | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Large effect | Not applicable | 0 |
| | | Dose-response | Not applicable | 0 |
| | | Antagonistic bias and confounding | Not applicable | 0 |
| | **Final numerical rating of quality of evidence** | | | **3** |
| **Summary of Findings** | **Statement on quality of evidence** | | | **We are moderately confident that the true effect lies close to that of the estimate of effect on health outcome** |
| | **Conclusion** | | | **Chimeric JE vaccine has an acceptable safety profile.** ***Based on a review of data on IMOJEV*** |

[1]10 RCTs contributing approximately 4,000 participants contributed safety data. In children 12 months to 18 years IMOJEV chimeric vaccine had a safety profile comparable with licensed vaccines (Hepatitis A and varicella zoster) in terms of frequency and severity of local and systemic adverse reactions (Chokephaibulkit 2010, Feroldi 2012, Feroldi 2013). There was lower frequency of fever, injection site erythema and swelling after the first compared to second dose. Table 9 also shows the comparability in safety profiles between CD.JEVAX and IMOJEV. IMOJEV also has a comparable safety profile to MMR vaccine when administered to children 12-18 months in Taiwan (Huang 2014). In adults in two RCTs, comparable tolerability and reactogenicity with placebo and a mouse brain-derived JE vaccine were seen with the exception of local reactions (Torresi 2010). Significantly lower frequency of local adverse reactions was reported for IMOJEV than mouse brain-derived vaccine JE-VAX. The majority of adverse events was mild to moderate and resolved within a few days. Only one vaccine related serious AEFI (Pyrexia) was reported within the first month of vaccination and none during a 6-month follow-up. No case of death occurred (Torresi 2010). In addition, two serious adverse events (acute viral illness) possibly related to vaccination with IMOJEV were reported during clinical development in adults (Australian Public Assessment Report 2010).

[2]This vaccine has had limited use outside of clinical trials. The ability to detect less common serious adverse events is limited.

Reference List

**Clinical Studies**

Australian Public Assessment Report for Japanese Encephalitis Chimeric Virus,2010. Available at http://www.tga.gov.au/pdf/auspar/auspar-imojev.pdf

Chokephaibulkit K, Sirivichayakul C, Thisyakorn U, Sabchareon A, Pancharoen C, Bouckenooghe A, Gailhardou S, Boaz M, Feroldi E. Safety and immunogenicity of a single administration of live-attenuated Japanese encephalitis vaccine in previously primed 2- to 5-year-olds and naive 12- to 24-month-olds: multicenter randomized controlled trial. Pediatr Infect Dis J. 2010 Dec;29(12):1111-7.

Feroldi E, Pancharoen C, Kosalaraksa P, Watanaveeradej V, Phirangkul K, Capeding MR, Boaz M, Gailhardou S, Bouckenooghe A. Single-dose, live-attenuated Japanese encephalitis vaccine in children aged 12-18 months: randomized, controlled phase 3 immunogenicity and safety trial. Hum Vaccin Immunother. 2012 Jul;8(7):929-37.

Feroldi E, Capeding MR, Boaz M, Gailhardou S, Meric C, Bouckenooghe A. Memory immune response and safety of a booster dose of Japanese encephalitis chimeric virus vaccine (JE-CV) in JE-CV-primed children. Hum Vaccin Immunother. 2013 Apr;9(4):889-97.

Feroldi E, Pancharoen C, Kosalaraksa P, Chokephaibulkit K, Boaz M, Meric C, Hutagalung Y, Bouckenooghe A. Primary immunization of infants and toddlers in Thailand with Japanese encephalitis chimeric virus vaccine in comparison with SA14-14-2: a randomized study of immunogenicity and safety. Pediatr Infect Dis J. 2014 Jun;33(6):643-9.

Huang LM, Lin TY, Chiu CH, Chiu NC, Chen PY, Yeh SJ, Boaz M, Hutagalung Y, Bouckenooghe A, Feroldi E. Concomitant administration of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and measles, mumps, rubella (MMR) vaccine: Randomized study in toddlers in Taiwan. Vaccine. 2014 Mar 12. pii: S0264-410X(14)00312-0.

Kim DS, Houillon G. A randomized study of the immunogenicity and safety of Japanese encephalitis chimeric virus vaccine (JE-CV) in comparison with SA 14-14-2 vaccine in children in South Korea. 8th World Congress of the World Society for Pediatric Infectious Diseases (WSPID) - Nov. 19-22, 2013, Cape Town, South Africa.

Nasveld PE, Ebringer A, Elmes N, Bennett S, Yoksan S, Aaskov J, McCarthy K, Kanesa-thasan N, Meric C, Reid M. Long term immunity to live attenuated Japanese encephalitis chimeric virus vaccine: randomized, double-blind, 5-year phase II study in healthy adults. Hum Vaccin. 2010 Dec;6(12):1038-46.

Torresi J, McCarthy K, Feroldi E, Méric C. Immunogenicity, safety and tolerability in adults of a new single-dose, live-attenuated vaccine against Japanese encephalitis: Randomised controlled phase 3 trials. Vaccine. 2010 Nov 23;28(50):7993-8000.