

Japanese Encephalitis Vaccines

WHO Position Paper, Feb 2015

Selected References

- **Alberer M et al. Co-administration of a meningococcal glycoconjugate ACWY vaccine with travel vaccines: A randomized, open-label, multi-center study. Travel Med Infect Dis.2014.**
BACKGROUND: Potential interactions between vaccines may compromise the immunogenicity and/or safety of individual vaccines so must be assessed before concomitant administration is recommended. In this study, the immunogenicity and safety of travel vaccines against Japanese encephalitis (JEV) and rabies (PCECV) administered together with or without a quadrivalent meningococcal glycoconjugate ACWY-CRM vaccine were evaluated ([NCT01466387](#)).**METHOD:** Healthy adults aged 18 to ≤60 years were randomized to one of four vaccine regimens: JEV + PCECV + MenACWY-CRM, JEV + PCECV, PCECV or MenACWY-CRM. Immunogenicity at baseline and 28 days post-complete vaccination was assessed by serum bactericidal assay using human complement or neutralization tests. Adverse events (AEs) were collected throughout the study period. **RESULTS:** JEV + PCECV + MenACWY-CRM was non-inferior to JEV + PCECV. Post-vaccination seroprotective neutralizing titers or concentrations were achieved in 98-99% (JE) and 100% (rabies) of subjects across the vaccine groups. Antibody responses to vaccine meningococcal serogroups were in the same range for MenACWY-CRM and JEV + PCECV + MenACWY-CRM. Rates of reporting of AEs were similar for JEV + PCECV and JEV + PCECV + MenACWY-CRM. **CONCLUSIONS:** MenACWY-CRM was administered with an inactivated adjuvanted JE and a purified chick embryo cell-culture rabies vaccine without compromising immunogenicity or safety of the individual vaccines. These data provide evidence that MenACWY-CRM could be effectively incorporated into travel vaccination programs.
- **Australian Public Assessment Report for Japanese Encephalitis Chimeric Virus, 2010.**
Available at <https://www.tga.gov.au/file/1158/download>
- **Background paper on JE Vaccines- SAGE working group. Available at**
http://www.who.int/immunization/sage/meetings/2014/october/1_JE_Vaccine_Background_Paper.pdf, accessed November 2014.
- **Bista MB et al. Efficacy of single-dose SA 14-14-2 vaccine against Japanese encephalitis: a case control study. Lancet,2001;358(9284):791–795.**
BACKGROUND: In China, since 1989, an estimated 120 million children have been immunised with the SA 14-14-2 live-attenuated Japanese encephalitis (JE) vaccine at ages 1, 2, and 6 years. A case-control study of licensed vaccine found two doses to be 98% effective. Subsequently, researchers found that single-dose vaccine efficacy was high; we aimed to confirm this result. **METHODS:** During July 11-24, 1999, 160000 doses of JE vaccine were given to children aged 1-15 years, resident in three districts of Nepal. Several cases of JE were admitted to hospital from early August. We obtained names and addresses of cases with serological evidence of a recent infection from Bheri Zonal Hospital, Nepalgunj. We did a matched case-control study and calculated the odds ratio of vaccination among JE cases and age-sex matched village controls. **FINDINGS:** 20 children, aged 1-15 years, were identified whose illness conformed with the JE case definition and were resident in villages receiving the vaccine. None of 20 JE cases had received JE vaccine compared with 326 of 557 age-sex

matched village controls. The efficacy of a single dose of JE vaccine was 99.3% (CI 94.9-100%). **INTERPRETATION:** A single dose of JE vaccine is highly efficacious in preventing Japanese encephalitis when administered only days or weeks before exposure to infection.

- **Campbell GL et al. Estimated global incidence of Japanese encephalitis: a systematic review. Bull World Health Organ. 2011;89(10):766–774.**

OBJECTIVE: To update the estimated global incidence of Japanese encephalitis (JE) using recent data for the purpose of guiding prevention and control efforts. **METHODS:** Thirty-two areas endemic for JE in 24 Asian and Western Pacific countries were sorted into 10 incidence groups on the basis of published data and expert opinion. Population-based surveillance studies using laboratory-confirmed cases were sought for each incidence group by a computerized search of the scientific literature. When no eligible studies existed for a particular incidence group, incidence data were extrapolated from related groups. **FINDINGS:** A total of 12 eligible studies representing 7 of 10 incidence groups in 24 JE-endemic countries were identified. Approximately 67 900 JE cases typically occur annually (overall incidence: 1.8 per 100 000), of which only about 10% are reported to the World Health Organization. Approximately 33 900 (50%) of these cases occur in China (excluding Taiwan) and approximately 51 000 (75%) occur in children aged 0–14 years (incidence: 5.4 per 100 000). Approximately 55 000 (81%) cases occur in areas with well established or developing JE vaccination programmes, while approximately 12 900 (19%) occur in areas with minimal or no JE vaccination programmes. **CONCLUSION:** Recent data allowed us to refine the estimate of the global incidence of JE, which remains substantial despite improvements in vaccination coverage. More and better incidence studies in selected countries, particularly China and India, are needed to further refine these estimates.

- **Choi UY et al. Is a booster dose necessary in children after immunization with live attenuated Japanese encephalitis vaccine? J Trop Pediatr. 2013 Oct;59(5):423-5.**
Japanese encephalitis virus is a common cause of encephalitis in Asian children; therefore, maintenance of immunity against Japanese encephalitis virus is essential. Although many countries recommend booster vaccination, some trials have concluded that administration of one or two vaccinations is sufficient. The current study was conducted to evaluate immunogenicity and safety after a booster vaccination with live attenuated vaccine. For 68 study subjects, measurement of antibody titer was performed before and at 4-6 weeks after administration of a booster dose. Adverse reactions occurring at the injection site and systemic adverse reactions were documented. The percentages of subjects with seroprotective neutralizing antibody titers was 100% before and after booster vaccination, and the geometric mean titer increased after booster vaccination. Thus, we predict that immunity will be maintained for a long time by an amnestic response. Low percentages of adverse reactions indicated the safety of the immunizations.

- **Chokephaibulkit K et al. A comparative study of the serological response to Japanese encephalitis vaccine in HIV-infected and uninfected Thai children. Vaccine, 2010;28(20):3563–3566.**

We report a prospective study of mouse brain derived inactivated Japanese encephalitis (JE) vaccine, given in 3-dose EPI program to human immune deficiency virus (HIV)-exposed Thai infants. 18 HIV-infected receiving antiretroviral therapy with median baseline CD4 of 33.1%, and 92 HIV-uninfected children were studied. All but one HIV-infected child seroconverted after the second dose. The geometric mean titers (GMTs) 3 months after the second and third doses in HIV-infected vs HIV-uninfected children were 247 vs 938 ($p=0.022$), and 2273 vs 24069 ($p=0.009$), respectively. Urticaria or angioedema found in 4% and 6% in HIV-infected

and -uninfected children, respectively ($p=1.0$). The vaccine was safe and immunogenic but antibody response in HIV-infected children was not as high as in uninfected children.

- **Chokephaibulkit K et al. 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;29(12):1111–1117.**

BACKGROUND: Safe and effective Japanese encephalitis (JE) vaccines are needed to protect populations living in or visiting endemic areas. A live-attenuated JE-chimeric virus vaccine (JE-CV) has been developed with a single-dose regimen. **METHODS:** In an open-label, crossover study, 100 children aged 2 to 5 years with a history of 2-dose primary vaccination with mouse-brain derived inactivated JE vaccine according to the Thai Expanded Program for Immunization schedule, and 200 JE vaccination-naïve 12- to 24-month-old toddlers were randomized 1:1 to receive JE-CV, containing ≥ 4 log₁₀ plaque forming units, 1 month before or after hepatitis A control vaccine. Neutralizing antibody titers were assessed using PRNT₅₀ (titers expressed in inverse of dilution) before and 28 days after JE-CV, and at months 7 and 12. **RESULTS:** All 2- to 5-year-olds and 96% of 12- to 24-month-olds were seroprotected (titer ≥ 10) 28 days after JE-CV administration, and geometric mean titers (GMT) (95% confidence interval) in these age groups were 2634 (1928-3600) and 281 (219-362), respectively. One year later, seroprotection rates in the 2 age groups were 97% and 84% and GMTs were 454 and 62.3, respectively. Vaccine-induced antibodies neutralized a panel of wild-type JE isolates. There were no vaccine-related serious adverse events. Reactogenicity of JE-CV was comparable with that of the inactivated hepatitis A vaccine. **CONCLUSIONS:** A single administration of JE-CV has a good safety profile and elicits a protective immune response in both JE-naïve toddlers and JE-primed young children.

- **Determining Long-Term Safety and Efficacy of Japanese Encephalitis Vaccine When Given With Measles Vaccine. Available at <https://clinicaltrials.gov/ct2/show/NCT00412516?term=Nct00412516&rank=1>, accessed February 2015.**

Detailed Description: Japanese encephalitis is the leading cause of viral neurological disease and disability in Asia. The severity of sequelae, together with the volume of cases, make JE the most important cause of viral encephalitis in the world. Approximately 3 billion people—including 700 million children—live in Asian areas at risk for JE. JE most commonly infects children between the ages of 1 and 15 years, and can also infect adults in areas where the virus is newly introduced. More than 50,000 cases are reported annually and cause an estimated 10,000 to 15,000 deaths. This figure is believed to represent only a small proportion of the disease burden that actually exists.

An effective vaccine has existed since 1941, but has not reached the poorest countries in Asia. During the 60 years that the vaccine has been available, JE has infected an estimated 10.5 million children, resulting in more than 3 million deaths and more than 4 million children living with long-term disabilities. Control of this disease has been limited due to poor disease surveillance, a limited and unstable vaccine supply, lack of guidance and programmatic support for immunization, and limited advocacy.

A successful vaccine should be safe, efficacious, affordable, administered in a single dose, and easily incorporated into the routine Expanded Programmes on Immunization (EPI) programs. This trial is designed to determine the potential interference between the measles vaccine and the Japanese encephalitis vaccine at 12, 24, and 36 months post-vaccination. As these vaccines will be used in routine EPI systems at the same time, similar to how measles and yellow fever vaccine (also a Flavivirus) are administered, it is imperative to collect long-term data showing that neither vaccine interferes with seroconversion of the other when co-administered. This

information will help to ensure subject safety and facilitate programmatic efficiency, reducing the number of immunization visits for both parents and health care workers.

- **Ding D et al. Cost-effectiveness of routine immunization to control Japanese encephalitis in Shanghai, China. Bull World Health Organ. 2003;81(5):334–342.**

To assess the cost-effectiveness of inactivated and live attenuated Japanese encephalitis (JE) vaccines given to infants and children in Shanghai.

A decision-analytical model was constructed in order to compare costs and outcomes for three hypothetical cohorts of 100,000 children followed from birth in 1997 to the age of 30 years who received either no JE vaccine, inactivated JE vaccine (P3), or live attenuated JE vaccine (SA 14-14-2). Cumulative incidences of JE from birth to 30 years of age in the pre-immunization era, i.e. before 1968, were used to estimate expected rates of JE in the absence of vaccination. The economic consequences were measured as cost per case, per death, and per disability-adjusted life year (DALY) averted for the two JE immunization programmes.

In comparison with no JE immunization, a programme using the P3 vaccine would prevent 420 JE cases and 105 JE deaths and would save 6456 DALYs per 100,000 persons; the use of the SA 14-14-2 vaccine would prevent 427 cases and 107 deaths and would save 6556 DALYs per 100,000 persons. Both kinds of immunization were cost saving but the SA 14-14-2 vaccine strategy resulted in a saving that was 47% greater (512,456 US dollars) than that obtained with the P3 vaccine strategy (348,246 US dollars).

Both JE immunization strategies resulted in cost savings in comparison with no JE immunization. This provides a strong economic rationale for vaccinating against JE in Shanghai and suggests that vaccination against JE might be economically justifiable in other parts of China and in certain other developing countries of Asia where the disease is endemic.

- **Dubischar-Kastner K et al. 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.**

Available at <http://nectm.com/wp-content/uploads/2015/01/NECTM5Bergen2014.pdf>

BACKGROUND: Vero cell-derived, inactivated Japanese Encephalitis (JE) vaccine (Valneva SE), JE-VC, is licensed for children above 2 months in US and EU. In adults, booster is recommended 12-24 months after primary immunization. Antibody persistence in children with and without booster needed further study. **MATERIALS:** Open-label, randomized Phase 3 study. 300 children from Philippines (≥ 2 months to < 17 years at primary series) were randomized 1:1 to receive a booster dose 12 months after initiation of primary series, or no booster. Neutralizing antibody titers were assessed by PRNT up to Month 24 (12 months after booster). Unsolicited Adverse Events were collected up to Month 24. **RESULTS:** A booster of JE-VC led to pronounced increase in PRNT titers (100% SCR and GMTs 890 – 4076 one month after booster, highest in youngest children). One year after the booster, titers in booster group remained above the cut-off defined for seroprotection (PRNT₅₀ $\geq 1:10$) in all subjects (SPR 100%, GMTs 231 – 623 depending on age), and GMTs remained elevated compared to pre-booster GMTs 1 year after primary series (pre-booster GMTs 26 – 69). In the non-booster group, titers also remained above the threshold for seroprotection in a substantial proportion (SPR 81 - 100%, GMTs 39 – 92) at Month 24. The booster was well tolerated, with no apparent long term Adverse Events. **CONCLUSION:** A booster of JE-VC 12 months after primary series was highly immunogenic and well tolerated in pediatric population. One year after booster, 100% of subjects retained protective titers and GMTs were still considerably higher than after primary series. Without booster, antibody titers had declined considerably by Month 24, but seroprotection rates were still high. These data suggest a booster may not be required in children for at least 2 years, but 3-years persistence data and data from JE non-endemic population are awaited for a comprehensive conclusion on timing of a booster in children.

- **Dubischar-Kastner K, et al. Long-term immunity and immune response to a booster dose following vaccination with the inactivated Japanese encephalitis vaccine IXIARO, IC51. Vaccine, 2010;28(32):5197–5202.**

IC51 (IXIARO, JESPECT) is a recently approved prophylactic Japanese encephalitis virus vaccine with a two-vaccine primary immunization regimen. In this phase 3 trial, after primary immunization with a Day 0/28 dose schedule, seroprotection rates were 83%, 58% and 48% at Month 6, Month 12 and Month 24, respectively. A booster dose at Month 11 and/or Month 23 in subjects with neutralizing antibody titers below the limit of detection (defined as a serum dilution giving a 50% reduction of plaque counts in a plaque reduction neutralization test [PRNT₅₀] < 1:10) led to 100% seroconversion. After a single-dose immunization (incomplete primary immunization), only 9% of subjects were seroprotected at Month 6; however, a booster dose at Month 11 led to seroconversion in 99% of subjects. Hence, subjects with incomplete primary immunization can complete their schedule within at least 11 months.

- **Dubischar-Kastner K et al. Long Term Immunity and Safety Following Vaccination with inactivated Japanese Encephalitis Vaccine in a Pediatric Population in Non endemic Countries. Submitted for presentation at the 14th Conference of the International Society of Travel Medicine, May 2015.**

(Revised title: Dubischar-Kastner et al. Antibody Persistence in Children from JE Non-Endemic and JE-Endemic Countries and After a Booster Dose of Inactivated Japanese Encephalitis Vaccine. CISTM14 (oral communication, 14th Conference of the International Society of Travel Medicine, Quebec, May 2015))

BACKGROUND: Protection lasts at least 12 months after a JE-VC booster (Vero cell-derived, inactivated Japanese Encephalitis vaccine, Valneva) in adults. Antibody persistence without booster and after a JE-VC booster in children (currently unlicensed) needed further study. **OBJECTIVES:** To evaluate antibody persistence after primary series or booster of JE-VC in children aged 1 to <18 years. **METHODS:** One randomized, controlled open-label study in the Philippines: 300 children, mean age at primary JE-VC series approx. 4.6 years, received either no booster or a booster (3 mcg/0.25 ml < 3 years, 6 mcg/0.5 ml ≥ 3 years) 12 months after the primary series. A second small open-label follow-up study in 23 children from Europe, USA and Australia without booster. Neutralizing antibody titers were assessed by PRNT before and 1, 12 and 24 months after the booster and 12, 24 and 36 months after primary series. **SUMMARY OF RESULTS:** Study One: A JE-VC booster increased PRNT titers substantially (100% SPR and GMTs 890 – 4076, highest in youngest children). Two years after boosting, titers remained above the seroprotection threshold (PRNT₅₀ ≥ 1:10): SPR 100%, GMTs 231 – 535 depending on age. Without booster, 3 years after the primary series, a substantial proportion retained protective titers (SPR 81 - 100% depending on age), but GMTs (45 – 81) were substantially lower without booster. Study Two: In traveling children (mean age 14.3 years, one child <3 years at priming), seroprotection rate was 91.3% (21/23 subjects) at month 24 after the primary series, with a GMT of 75. **CONCLUSIONS:** A booster dose of JE-VC in children was highly immunogenic. Two years after the booster, 100% of subjects retained protective titers. Without booster, SPRs were still high (> 80%) in all age groups for two years (traveling children) / three years (endemic areas), but titers declined considerably. Data, although limited for traveling children, suggest a booster may not be required in children for a minimum of 2 years after the primary series; natural boosting through JEV exposure may however have contributed to persistence of immunity in the Philippines study. Pending 36-months data from traveling children will allow a comprehensive conclusion on antibody persistence in children.

- **Dubischar-Kastner K et al. Safety analysis of a Vero-cell culture derived Japanese encephalitis vaccine, IXIARO (IC51), in 6 months of follow-up. *Vaccine*,2010;28(39):6463–6469.**

Japanese encephalitis (JE) is the most common viral encephalitis in Asia. IXIARO is a Vero cell-derived, inactivated JE virus vaccine which has recently been approved in the US, Europe, Canada and Australia (trade name JESPECT). This overview of the safety and tolerability of IXIARO, for 6 months after the first vaccination in 7 Phase III trials, includes: 3558 subjects with at least one IXIARO vaccination, 435 subjects with a JE-VAX (manufactured by BIKEN, distributed by Sanofi Pasteur) vaccination, and 657 with phosphate-buffered saline solution with 0.1% Al(OH)₃ (PBS+Alum) control vaccination. The percentage of subjects reporting solicited local adverse events (AEs) with IXIARO (54%) was similar to PBS+Alum vaccination (56%) as were solicited systemic adverse events (40% IXIARO; 40% PBS+Alum vaccination). JE-VAX showed a higher frequency of subjects with solicited local adverse events (61%) but a slightly lower frequency of subjects with solicited systemic adverse events (36%). The frequency of subjects with any solicited and unsolicited AE with IXIARO (64%) was also similar to PBS+Alum vaccination (61%) and JE-VAX (64%); as for subjects with serious AEs (1% IXIARO; 2% PBS+Alum vaccination, 1% JE-VAX). No serious allergic reactions were observed in any group. This safety analysis indicates that IXIARO has a favourable safety profile, comparable to PBS+Alum control vaccination and appears to have a better local tolerability profile than JE-VAX.

- **Dubischar-Kastner K et al. 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.**

INTRODUCTION: IXIARO, a Vero cell-derived, inactivated Japanese encephalitis (JE) vaccine manufactured by Intercell AG, is licensed for adults but investigational for pediatric use. Favorable Phase II data supported initiating pivotal pediatric studies. **OBJECTIVES:** To confirm safety and immunogenicity of IXIARO in children aged 2 months to < 18 years. **METHODS:** Randomized, active-controlled, open-label Phase III study in 1869 children aged 2 months (m) to < 18 years (y) in the Philippines. 1,411 children were randomized to two i.m. doses (Day 0, 28) of IXIARO: 0.25ml (half adult dose, ages < 3y) or 0.5ml (adult dose, ages ≥12y). For ages 3 to < 12y the full adult dose was found appropriate in a dose-confirmation sub-study. As control, 64 children received PrevnarR (depending on age, 3 or 4 i.m. doses Day 0, (28), 56 and Month 7-13) and 394 children received HavrixR (2 i.m. doses Day 0, Month 7). Systemic and local adverse events (AEs) were solicited for 7 days post vaccination, unsolicited AEs were collected up to Month 7. Antibody titers were assessed by PRNT in a subgroup of 496 children. **SUMMARY OF RESULTS:** Up to Day 56, AEs (solicited or unsolicited) were reported by 84% (110/131) IXIARO vs. 88% (56/64) Prevnar in children < 1y, and 62% (794/1280) IXIARO (both dose groups) vs. 60% (235/394) Havrix in children ≥1 y; Medically attended or Serious AE were reported by 38% IXIARO vs. 42% Prevnar (< 1y); and 16% IXIARO vs. 14% Havrix (≥1 y). Most local and systemic reactions were mild. Within 7 days of the first dose, local reactions were reported by 19% IXIARO vs. 32% Prevnar of children < 1y, mainly redness. For children 1-< 18 yrs, the rates were 11% IXIARO 0.25 ml, 17% IXIARO 0.5ml and 14% Havrix, mainly pain and tenderness. Solicited systemic reactions after the first dose were reported by 36% IXIARO vs. 40% Prevnar of children < 1y, mainly fever, diarrhea and irritability; for children 1-< 18 yrs, the rates were 28% IXIARO 0.25 ml (vaccinees aged 1-< 12y), 16% IXIARO 0.5ml (ages 3-< 18y) and 19% Havrix (ages 1-< 18y), also mainly fever. Pre-vaccination JEV immunity ranged from 3% (children 1-< 3 yrs) to 44% (12-< 18y). On Day 56, >99% of children who received the age appropriate dose had protective antibody titers (PRNT₅₀≥1:10). For the 0.25 ml dose, GMTs by age group were 637 (2-6 months, N=10), 367 (6-12 months, N=20) and 258 (1-3 yrs, N=125), and for the 0.5 ml dose, 235 (3-12 yrs, N=101) and 171 (12-18 yrs, N=140); the corresponding rates of subjects who achieved a ≥4-fold titer increase were 100%, 95%, 97%, 94% and 77%,

respectively. **CONCLUSIONS:** The safety profile of IXIARO was comparable to the control vaccines PrevnarR and HavrixR and in line with expectations for a pediatric population. Safety in children >12 years of age resembled the adults profile. IXIARO was highly immunogenic at both doses tested in the pediatric population, leading to protective antibody titers at Day 56 in >99% of children receiving the age-appropriate dose.

- Eder S et al. Long term immunity following a booster dose of the inactivated Japanese Encephalitis vaccine IXIARO®, IC51. Vaccine,2011;29(14):2607–2612.**
INTRODUCTION: IXIARO (IC51), a recently approved inactivated Japanese Encephalitis vaccine, is immunogenic and safe in a 0/28 days primary immunization schedule. Neutralizing antibody titers decline with time and booster doses are likely needed to enhance persistence of immunity. **OBJECTIVES:** To assess the effect of a booster dose on neutralizing JE antibody titers for up to 12 months after boosting. **METHODS:** In this phase III trial, 198 subjects, who had received primary immunization in a preceding randomized trial, were boosted with IXIARO 15 months after the primary immunization. Neutralizing antibody titers were assessed by plaque-reduction neutralisation test, PRNT. **RESULTS:** Prior to the booster dose, 69.2% (137/198) of subjects had PRNT50 titers $\geq 1:10$. One month after the booster, the rate of subjects with PRNT50 $\geq 1:10$ (recognized as a protective titer) was 100%. This rate remained high at 98.5% at 6 and 12 months; GMTs were 22.5 before the booster and 900, 487 and 361 at 1, 6 and 12 months after the booster, respectively. **CONCLUSION:** A booster dose of IXIARO at 15 months after primary immunization was highly immunogenic with GMTs >5-fold higher than those seen immediately after primary immunization, and remained at high levels for at least 12 months after the booster.
- EMA. European Public Assessment Summary Report, 2009. Available at** http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/001016/WC500036359.pdf, accessed February 2015.
- 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
- Erlanger TE et al. Past, present, and future of Japanese encephalitis. Emerg Infect Dis,2009;15(1):1–7.**
 Japanese encephalitis (JE), a vector-borne viral disease, is endemic to large parts of Asia and the Pacific. An estimated 3 billion people are at risk, and JE has recently spread to new territories. Vaccination programs, increased living standards, and mechanization of agriculture are key factors in the decline in the incidence of this disease in Japan and South Korea. However, transmission of JE is likely to increase in Bangladesh, Cambodia, Indonesia, Laos, Myanmar, North Korea, and Pakistan because of population growth, intensified rice farming, pig rearing, and the lack of vaccination programs and surveillance. On a global scale, however, the incidence of JE may decline as a result of large-scale vaccination programs implemented in China and India.
- Erra EO et al. 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;55(6):825–834.**
BACKGROUND: A significant part of the world population lives in areas with endemic Japanese encephalitis (JE). For travelers from nonendemic countries, Vero cell-derived vaccine (JE-VC; Ixiaro) has replaced traditional mouse brain-derived vaccines (JE-MB) associated with safety concerns. The 2 vaccines are derived from different viral strains: JE-VC from the SA14-

14-2 strain and JE-MB from the Nakayama strain. No data exist regarding whether JE-VC can be used to boost immunity after a primary series of JE-MB; therefore, a primary series of JE-VC has been recommended to all travelers regardless of previous vaccination history.

METHODS: One hundred twenty travelers were divided into 4 groups: Volunteers with no prior JE vaccination received primary immunization with (group 1) JE-MB or (group 2) JE-VC, and those primed with JE-MB received a single booster dose of (group 3) JE-MB or (group 4) JE-VC. Immune responses were tested before and 4-8 weeks after vaccination using plaque reduction neutralization test (PRNT) against both vaccine strains. **RESULTS:** In vaccine-naïve travelers, the vaccination response rate for test strains Nakayama and SA14-14-2 was 100% and 87% after primary vaccination with JE-MB and 87% and 94% after JE-VC, respectively. Antibody levels depended on the target virus, with higher titers against homologous than heterologous PRNT(50) target strain ($P < .001$). In travelers primed with JE-MB, vaccination response rates were 91% and 91%, and 98% and 95% after a booster dose of JE-MB or JE-VC, respectively. Subgroup analysis revealed that a higher proportion of primed (98%/95%) than nonprimed (39%/42%) volunteers responded to a single dose of JE-VC ($P < .001$).

CONCLUSIONS: A single dose of JE-VC effectively boosted immunity in JE-MB-primed travelers. Current recommendations should be reevaluated.

- **Feroldi E et al. Long-term neutralizing antibody following a booster dose of JE-CV (IMOJEV®), a novel live attenuated Japanese encephalitis vaccine, in children previously primed with a JE vaccine. 4th ASVAC, 2013.**

Introduction: A live attenuated Japanese encephalitis vaccine (JE CV, IMOJEV®, Sanofi Pasteur, Lyon, France) was developed to broaden the choice of JE vaccines for at-risk populations. Immunogenicity and safety of JE-CV up to 28 days after vaccination have been previously reported. **Objective/s:** To assess the persistence of antibody responses after a JE CV booster vaccination in children primed with different JE vaccines in two ongoing trials. **Study design:** Follow-up of children vaccinated in two open label trials. **Methodology:** In an open Phase II trial in Thailand (trial #1; ClinicalTrials.gov: NCT 00621764), 100 children aged 2–5 years who had been primed 12 months earlier with 2 doses of inactivated mouse brain derived JE vaccine (MBDV), were enrolled and given a JE-CV booster injection. In an open Phase III trial in the Philippines (Trial #2, ClinicalTrials.gov: NCT 01190228) 349 children who had received a first dose of JE CV 2 years previously (ClinicalTrials.gov: NCT 00735644), were enrolled and given a JE-CV booster injection. PRNT50 antibody titres against the vaccine virus were assessed in both trials: before the booster, on D28, then yearly up to 5 years after the booster. Children with titres ≥ 10 (1/dil) were considered seroprotected against JE. **Results:** Before the JE CV booster, 86.0% [95% confidence interval: 77.6; 92.1] of children in trial #1 and 80.3% [75.7; 84.4] of those in trial #2 presented with neutralizing antibody titres ≥ 10 (1/dil). Seroprotection on D28 after the booster dose of JE CV was 100% in both studies (100% [96.3; 100] in trial #1; 100% [98.9; 100] in trial #2); and the geometric mean titre (GMT) increased from 44.7 [34.0; 58.7] to 2,707 [1988; 3687] in trial #1 (1) and from 39.3 [33.7; 45.8] to 2,259 [1,930; 2,645] in trial #2 (2). The seroprotection rate remained 97.5% [91.2; 99.7] or higher until Year 4 in trial #1, and 98.8% [97.0; 99.7] or higher until Year 2 in trial #2. The GMT was comparable in the two trials at Year 1: 454 [327; 632] in trial #1; 596 [502; 708] in trial #2. The most recent data from trial #1 show that the GMT remains stable up to Year 4 (395 [265; 588]). The most recent data from trial #2 show a GMT of 368 [313; 432].

Conclusion/recommendations: A booster dose of JE CV given 12 to 24 months after primary JE vaccination elicited robust, persistent, neutralizing antibody responses, suggesting long-lasting protection. These results indicate that JE CV can be used as a booster dose following primary immunization with either JE-CV or inactivated JE vaccine. ClinicalTrials.gov: NCT 00621764 and ClinicalTrials.gov: NCT 01190228

- **Feroldi E et al. 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;9(4):889–897.**

Japanese encephalitis chimeric virus vaccine (JE-CV) is a licensed vaccine indicated in a single dose administration for primary immunization. This controlled phase III comparative trial enrolled children aged 36-42 mo in the Philippines. 345 children who had received one dose of JE-CV in a study two years earlier, received a JE-CV booster dose. 105 JE-vaccine-naïve children in general good health were randomized to receive JE-CV (JE-vaccine naïve group; 46 children) or varicella vaccine (safety control group; 59 children). JE neutralizing antibody titers were assessed using PRNT50. Immunological memory was observed in children who had received the primary dose of JE-CV before. Seven days after the JE-CV booster dose administration, 96.2% and 66.8% of children were seroprotected and had seroconverted, respectively, and the geometric mean titer (GMT) was 231 1/dil. Twenty-eight days after the JE-CV booster dose seroprotection and seroconversion were achieved in 100% and 95.3% of children, respectively, and the GMT was 2,242 1/dil. In contrast, only 15.4% of JE-CV-vaccine naïve children who had not received any prior JE vaccine were seroprotected seven days after they received JE-CV. One year after receiving the JE-CV booster dose, 99.4% of children remained seroprotected. We conclude that JE-CV is effective and safe, both as a single dose and when administrated as a booster dose. A booster dose increases the peak GMT above the peak level reached after primary immunization and the antibody persistence is maintained at least one year after the JE-CV booster dose administration. Five year follow up is ongoing.

- **Feroldi E et al. 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;33(6):643–649.**

BACKGROUND: The live, attenuated Japanese encephalitis (JE) chimeric virus vaccine (JE-CV) is licensed in Thailand and Australia for prophylaxis of JE in individuals at the age of 12 months. JE-CV has not yet been compared with the SA14-14-2 JE vaccine, which is also licensed in Thailand. **METHODS:** In this phase 3, observer-blinded trial, 300 children at the age of 9-18 months were randomized 1:1 to receive 1 dose of JE-CV or SA14-14-2. JE neutralizing antibody titers were assessed using PRNT50. The primary endpoint was the noninferiority of seroconversion against JE on Day 28 after JE-CV compared with SA14-14-2, as assessed using the 95% confidence interval of the difference between the groups. Safety and reactogenicity were described in each group using conventional methods, including the reporting of solicited and unsolicited adverse events. **RESULTS:** The seroconversion rate on Day 28 was 99.2% in each group. Noninferiority was demonstrated as the difference between the JE-CV and SA14-14-2 groups was -0.012 percentage points (95% confidence interval: -3.6 to 3.6), which was above the required -10%. The seroprotection rate remained very high at Month 6 and comparable between groups, but a slight decrease was observed in the JE-CV group between Months 6 and 12. Current recommendations for both vaccines call for a booster dose 12-24 months after primary immunization to maintain high seroprotection rates in the long term. Geometric mean titers (GMTs) on Day 28 after vaccination were 507 (1/dil) in the JE-CV group and 370 (1/dil) in the SA14-14-2 group, decreasing by 4.3-fold and 3.6-fold, respectively, to Month 6 before remaining stable to Month 12 and comparable between groups. Solicited reactions were all reported at lower rates after vaccination with JE-CV compared with SA14-14-2. **CONCLUSIONS:** A single dose of JE-CV elicited a noninferior immune response compared with SA14-14-2 and had a satisfactory safety profile.

- **Feroldi E et al. 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;8(7):929–937.**

This trial in 1200 JE-vaccination naïve children (age 12-18 mo) in Thailand and the Philippines aimed to demonstrate consistency of three successive industrial scale manufacturing lots of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and consistency between industrial scale manufacturing lots and a fourth, development lot. Children received JE-CV from one of three successive industrial scale lots produced in Thailand (n = 899), or from a fourth development lot produced in the USA (n = 199), or hepatitis A control vaccine (n = 102). Antibodies were assessed by 50% plaque reduction neutralization test (PRNT(50)) at screening and Day 28. Seroconversion rates (titer of < 10 at baseline and ≥ 10 on Day 28, or a four-fold rise from a baseline titer of ≥ 10) were determined per group. Lot-to-lot consistency of seroconversion rate and GMT was demonstrated between the 3 industrial scale lots, and between these lots and the US lot. Seroconversion rate on pooled data 28 d after JE-CV vaccination (Thai lots) was 95.0% [95% confidence interval (CI); 93.3-96.3]. The safety profile of JE-CV was favorable and comparable with hepatitis A vaccine. There were no serious adverse events related to vaccination. This study demonstrated the consistency of three successive industrial scale JE-CV vaccine lots, as well as consistency with a development lot. The study also demonstrated that a single dose of JE-CV is well tolerated and elicits a high protective immune response, seroconverting 95% of JE-naïve Asian children aged 12-18 mo.

- **Feroldi E et al. 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).**

Available at

http://www.astmh.org/AM/Template.cfm?Section=Abstracts_and_Education1&Template=/CM/ContentDisplay.cfm&ContentID=2841

Live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) was developed to replace first mouse-brain derived JE vaccines. An adult trial has shown that 87% of the participants who were seroprotected at month 6 after JE-CV vaccination were still protected at month 60. The objective of this study was to document persistence of JE-CV-induced antibodies in children. In a 5-year follow-up to a phase 3 trial where 1200 JE-naïve Thai and Filipino children aged 12-18 months were randomized 11:1 to receive a single injection of JE-CV (Sanofi Pasteur, Lyon, France) or a control, we are following a cohort of ~600 JE-CV-vaccinated children to assess long term antibody persistence. Plaque reduction neutralization test (PRNT50) antibody titers against homologous JE-CV will be tested in annual samples. Children with titers $\geq 1:10$ are considered seroprotected against JE. Here we present the first data, obtained one year after vaccination. The seroprotection rate in all 1100 children vaccinated with JE-CV in the phase 3 trial was 95% 28 days after vaccination. Of these, 591 children were enrolled in this follow-up trial in August and September 2009. In this subset, the seroprotection rate 28 days after JE-CV vaccination was 100% (95%CI: 99.4-100) and the geometric mean titer (GMT) was 253 (95%CI: 225-284). One year after vaccination (12 \pm 1 month), 88.2% (85.3-90.7) of the 591 children were still seroprotected and the GMT was 77.2 (67.7-88.0). No cases of Japanese encephalitis and no vaccine related SAEs occurred during the year after vaccination. In conclusion, all the subjects enrolled in this long-term follow-up presented with seroprotective antibody titers one month after a single injection of JE-CV between the ages of 12 and 18 months; more than 88% of them were still seroprotected one year later. This ongoing follow-up study is documenting the long term persistence of antibodies against JE after a single injection of the new JE-CV vaccine. Data obtained each successive year will enable us to refine the antibody persistence curve

- Feroldi E. Immunogenicity after one dose of IMOJEV in naïve toddlers and children primed with MBDV. ACPID 2014. (Revised title: Choekphaibulkit K et al. Long-term neutralizing antibody response to a booster dose of a novel live attenuated Japanese encephalitis vaccine (IMOJEV® in a pediatric population). ACPID 2014.**

Purpose: IMOJEV® (Sanofi Pasteur, Lyon, France) is a novel live attenuated Japanese encephalitis vaccine licensed in Asia. Immunogenicity and safety have been previously reported. We assessed the persistence of antibody response after an IMOJEV booster vaccination in children primed with a JE vaccine. **Methods:** A booster injection of IMOJEV was administered to 449 children in 2 open clinical trials. Trial 1 (NCT 00621764) was a Phase II trial in Thailand in 100 children (2 to 5 years) primed with 2 doses of inactivated mouse brain derived (MBDV) JE vaccine 12 months earlier. Trial 2 (NCT 01190228) was a Phase III trial in the Philippines in 349 children (36 to 42 months) primed with JE-CV 2 years earlier. PRNT antibody titers against the vaccine virus were measured before the booster, 28 days later then each year up to 5 years post-booster. Children with titers ≥ 10 (1/dil) were considered seroprotected against JE. **Results:** Pre-booster seroprotection rates were 86.0% [95% CI: 77.6; 92.1] in Trial 1 and 80.3% [75.7; 84.4] in Trial 2. On D28 after the booster, seroprotection reached 100% in Trial 1 [96.3; 100] and Trial 2 [98.9; 100] with GMTs increasing from 44.7 [34.0; 58.7] to 2,707 [1988; 3687] in Trial 1 and from 39.3 [33.7; 45.8] to 2,259 [1,930; 2,645] in Trial 2 (60- and 57-fold increase, respectively). Seroprotection rates remained high at 97.5% [91.3; 99.7] until Year 5 in Trial 1 and 99.1% [97.4; 99.8] until Year 3 in Trial 2. GMTs remained stable up to Year 5 in Trial 1 (228 [167; 313]) and up to Year 3 in Trial 2 (301 [257; 352]). **Conclusions:** Regardless of the JE vaccine received in toddlers as primary vaccination, a booster dose of IMOJEV 12 to 24 months later induces a robust and persistent neutralizing antibody response demonstrating long-lasting protection.
- Gatchalian S et al. 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.**

Japanese encephalitis (JE) virus is a major cause of disease, disability, and death in Asia. An effective, live, attenuated JE vaccine (LJEV) is available; however, its use in routine immunization schedules is hampered by lack of data on concomitant administration with measles vaccine (MV). This study evaluated the immunogenicity and reactogenicity of LJEV and MV when administered at the same or separate study visits in infants younger than 1 year of age. Three groups of healthy infants were randomized to receive LJEV at age of 8 months and MV at 9 months (Group 1; n=100); MV and LJEV together at 9 months (Group 2; n=236); or MV and LJEV at 9 and 10 months, respectively (Group 3; n=235). Blood was obtained 4 weeks after each vaccine administration to determine antibody levels for measles and JE. Reactogenicity was assessed by parental diaries and clinic visits. Four weeks after immunization, measles seroprotection rates (defined as ≥ 340 mIU/ml) were high and comparable in all three groups and specifically, rates in the combined MV-LJEV (Group 2) were not statistically inferior to those in Group 3 receiving MV separately (96% versus 100%, respectively). Likewise, the LJEV seroprotection rates were high and similar between the three groups. The reactogenicity profiles of the three vaccine schedules were also analogous. LJEV and MV administered together are well tolerated and immunogenic in infants younger than 1 year. These results should facilitate incorporation of LJEV into routine immunization schedules with MV.

- **Griffiths MJ et al. Japanese encephalitis virus infection. In Tselis A, Booss J, editors. Handbook of Clinical Neurology. Vol 123 (3rd series) Neurovirology, pp. 551–576. Available at http://www.researchgate.net/publication/263863336_Japanese_encephalitis_virus_infection**

Japanese encephalitis is the most important epidemic encephalitis in the world, responsible for a higher burden of disability than any other arthropod-borne virus. Twenty-four countries, home to over 2.5 billion people, within Asia and the Western Pacific rim are endemic for Japanese encephalitis. In these countries the burden of disease is mostly on children. The adult population is typically immune following childhood exposure. Although only a minority of people exposed to the virus develop disease, Japanese encephalitis is estimated to be responsible for nearly 70 000 cases and 20 000 deaths annually. Patients develop a febrile illness followed by headache, vomiting, impaired consciousness, and often seizures. A wide range of neurologic abnormalities are observed. Typically 20-30% of patients die, and 30-50% of survivors have severe neuropsychiatric sequelae. There are no proven effective therapies and treatment is supportive; however, Japanese encephalitis can be prevented by vaccination.

- **Guy B et al. Preclinical and clinical development of YFV 17D-based chimeric vaccines against dengue, West Nile and Japanese encephalitis viruses. Vaccine, 2010;28(3):632–649.**
Dengue viruses (DENV), West Nile virus (WNV) and Japanese encephalitis virus (JEV) are major global health and growing medical problems. While a live-attenuated vaccine exists since decades against the prototype flavivirus, yellow fever virus (YFV), there is an urgent need for vaccines against dengue or West Nile diseases, and for improved vaccines against Japanese encephalitis. Live-attenuated chimeric viruses were constructed by replacing the genes coding for Premembrane (prM) and Envelope (E) proteins from YFV 17D vaccine strain with those of heterologous flaviviruses (ChimeriVax technology). This technology has been used to produce vaccine candidates for humans, for construction of a horse vaccine for West Nile fever, and as diagnostic reagents for dengue, Japanese encephalitis, West Nile and St. Louis encephalitis infections. This review focuses on human vaccines and their characterization from the early stages of research through to clinical development. Phenotypic and genetic properties and stability were examined, preclinical evaluation through in vitro or animal models, and clinical testing were carried out. Theoretical environmental concerns linked to the live and genetically modified nature of these vaccines have been carefully addressed. Results of the extensive

characterizations are in accordance with the immunogenicity and excellent safety profile of the ChimeriVax-based vaccine candidates, and support their development towards large-scale efficacy trials and registration.

- **Halstead S et al. Japanese Encephalitis Vaccines. In Plotkin S, Orenstein W, Offit P, editors. Vaccines 6th: Saunders Elsevier; 2013, pp. 312–351**
- **Hennessy S et al. Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case-control study. Lancet. 1996 Jun 8;347(9015):1583-6.**
BACKGROUND: Japanese encephalitis is a major cause of death and disability throughout Asia, including the Indian subcontinent. Although an effective vaccine for Japanese encephalitis is available, hundreds of millions of susceptible individuals remain unimmunised because of the vaccine's cost. In 1988, an inexpensive live-attenuated vaccine (SA14-14-2) was licensed in China. We have measured the effectiveness of this vaccine. **METHODS:** In a case-control study in rural Sichuan Province, China, the 56 cases consisted of children admitted to hospital with acute Japanese encephalitis, and were confirmed serologically. 1299 village-matched and age-matched controls were identified, and vaccination histories obtained from pre-existing written records. **FINDINGS:** The effectiveness of one dose was 80% (95% CI 44 to 93%); that of two doses was 97.5% (86 to 99.6%). Controlling for multiple potential confounders did not alter these results. **INTERPRETATION:** We conclude that a regimen of two doses of live-attenuated Japanese encephalitis vaccine, administered 1 year apart, is effective in the prevention of clinically important disease. Subsequent study is needed to assure the safety of this vaccine.
- **Hills S et al. Japanese Encephalitis Core Working Group. Evidence and rationale for the World Health Organization recommended standards for Japanese encephalitis surveillance. BMC Infect Dis,2009;9:214.**

BACKGROUND: Japanese encephalitis (JE) is the most important form of viral encephalitis in Asia. Surveillance for the disease in many countries has been limited. To improve collection of accurate surveillance data in order to increase understanding of the full impact of JE and monitor control programs, World Health Organization (WHO) Recommended Standards for JE Surveillance have been developed. To aid acceptance of the Standards, we describe the process of development, provide the supporting evidence, and explain the rationale for the recommendations made in the document. **METHODS:** A JE Core Working Group was formed in 2002 and worked on development of JE surveillance standards. A series of questions on specific topics was initially developed. A literature review was undertaken and the findings were discussed and documented. The group then prepared a draft document, with emphasis placed on the feasibility of implementation in Asian countries. A field test version of the Standards was published by WHO in January 2006. Feedback was then sought from countries that piloted the Standards and from public health professionals in forums and individual meetings to modify the Standards accordingly. **RESULTS:** After revisions, a final version of the JE surveillance standards was published in August 2008. The supporting information is presented here together with explanations of the rationale and levels of evidence for specific recommendations. **CONCLUSION:** Provision of the supporting evidence and rationale should help to facilitate successful implementation of the JE surveillance standards in JE-endemic countries which will in turn enable better understanding of disease burden and the impact of control programs.

- **Hombach J et al. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2-3 September, 2004.**

Vaccine, 2005;23(45):5205–5211.

The World Health Organization (WHO) is undertaking consultations on immunological responses as parameters for evaluation and licensure of new Japanese encephalitis (JE) vaccines. Immunological markers could be used by vaccine developers and regulatory authorities to assess vaccine efficacy in absence of clinical efficacy data. The consultation which is reported here reviewed current data on mechanisms of protective immunity gathered from animal experimentation, clinical data from licensed vaccines and from vaccine candidates still in clinical development. Immunological assays and readouts for use in evaluation of candidate vaccines were also discussed. The consultation made a series of recommendations for specifications on immunological criteria to assess JE vaccine efficacy. More detailed recommendations will be drafted following further consultations to serve as WHO guidelines for evaluation and licensure for new JE vaccines.

- **Hossain MJ et al. Hospital-based surveillance for Japanese encephalitis at four sites in Bangladesh, 2003–2005. Am J Trop Med Hyg, 2010;82(2):344–349.**

We investigated the epidemiology and etiology of encephalitis at four tertiary hospitals in Bangladesh during 2003–2005. Patients who met a clinical case definition for acute encephalitis and had cerebrospinal fluid (CSF) pleocytosis were eligible for enrollment; a standardized sampling pattern was used to enroll eligible patients. Recent Japanese encephalitis virus (JEV) infection was defined by presence of IgM antibodies against JEV in CSF or serum. Twenty (4%) of 492 cases had laboratory evidence of recent JEV infection; two died. All JE cases occurred during May–December, and cases were identified among all age groups. All cases resided in rural areas. Fifteen patients were re-assessed 4–6 weeks after hospitalization; 5 (33%) patients had physical disabilities and 7 (47%) reported cognitive difficulties. Infection with JEV is clearly an etiology of encephalitis in Bangladesh. Population-

based studies to quantify burden of disease could assess options for targeted immunization programs.

- **Huang LM et al. 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;32(41):5363–5369.**
BACKGROUND: Japanese encephalitis (JE) is the most important cause of viral encephalitis in Asia. **METHODS:** In this randomized, open-label, multicenter trial in 550 children aged 12 to 18 months in Taiwan, children received one dose of JE-CV and one dose of MMR vaccine. Vaccines were either administered separately 6 weeks apart (Groups 'JE-CV' and 'MMR', named after which vaccine was given first), or concomitantly (Group 'Co-Ad'). JE neutralizing antibody titers were assessed using PRNT50. MMR antibody levels were determined by ELISA. **RESULTS:** All groups had low seroprotection/seropositivity rates (<10%) before vaccination for all antigens. Forty two days after vaccination, on either Study Day 42 or 84, seroconversion rates for all antigens were high in all groups, irrespective of the order of vaccinations. Seroconversion for JE ranged from 96.9% in Group Co-Ad on D42 to 100% in Group MMR. Non-inferiority was demonstrated for all analyses as the lower bound of the 95% CI of the difference in seroconversion rates between groups was above the pre-defined limit of -10.0%. The immune responses remained high for all antigens and well above the level of protection 12 months after vaccination in all groups. There were no safety concerns. **CONCLUSIONS:** JE-CV is safe and induces a strong protective immune response which persists over 1 year when co-administered with MMR vaccine.
- **Japanese encephalitis (JE) vaccines. Available at http://www.who.int/vaccine_safety/committee/topics/japanese_encephalitis/en/, accessed January 2015.**
- **Jelinek T et al. Immunogenicity and safety of an accelerated dosing regimen of Japanese Encephalitis inactivated absorbed vaccine for travelers: A phase III randomized study in healthy adults. Abstract P 2.9 presented at the 5th Northern European Conference on Travel Medicine,2014,Norway.**
Available at <http://nectm.com/wp-content/uploads/2015/01/NECTM5Bergen2014.pdf>
BACKGROUND: Primary immunization regimen for Japanese Encephalitis (JE) inactivated absorbed vaccine is a 2-dose series that requires 1 month to complete, which may not always be feasible for travel at short notice to JE endemic areas. An accelerated JE dosing regimen allowing completing vaccination within one week before travel would be advantageous. **MATERIALS:** In this phase III randomized, observer-blind study, the non-inferiority of the immune response to JE vaccine accelerated dosing regimen [administered concomitantly with a purified chick-embryo cell rabies vaccine], as compared to the conventional schedule was established. A total of 661 healthy adults were randomized to four groups, 440 subjects were enrolled in one of the three JE regimens (see Table). **RESULTS:** Non-inferiority was established as the lower limit of the 2-sided 97.5% confidence interval for the group difference (R/JE-Acc minus JE-Conv) of the percentage of subjects with a titer of $\geq 1:10$ in a 50% Plaque Reduction Neutralization Test (PRNT50) measured 28 days after the last vaccination was -4.8% (pre-specified margin set at -10%), with rates being 99% (R/JE-Acc) and 100% (JE-Conv). GMTs at Days 36 and 57 were 695 and 368 in the R/JE-Acc group and 377 and 345 in the JE-Conv group, respectively. Solicited reactions and unsolicited AEs were generally comparable between groups and mostly mild to moderate in severity. There was 1 possibly/probably vaccine-related SAE in the JE-Conv (eyelid edema and generalized pruritus, resolved in 1 day without treatment). Concomitant administration of JE and Rabies vaccines did not interfere with the tolerability and immune responses against JE. **CONCLUSION:** JE inactivated absorbed vaccine

administered according to the accelerated 2-dose regimen within one week induced strong immune response similar to that obtained with the conventional schedules, with a satisfactory tolerability profile. This accelerated regimen could be a valid alternative schedule for the pre-exposure prophylaxis of JE (NCT01662440).

- **Jia N et al. Encephalitis temporally associated with live attenuated Japanese encephalitis vaccine: four case reports. BMC Infect Dis. 2011 Dec 14;11:344.**

BACKGROUND: Japanese encephalitis (JE) vaccination is the most effective measure for preventing JE disease. The live attenuated JE vaccine, which has shown good efficacy and safety, has been widely used in China. **CASE PRESENTATIONS:** We report four laboratory-confirmed JE cases detected in JE-endemic areas during the JE virus (JEV) transmission season, who all received a first dose of live attenuated JE vaccine within 2 weeks prior to the onset of illness. All cases presented with acute encephalitis and rapidly reduced consciousness. All cerebrospinal fluid (CSF) samples from the patients were positive for JEV-specific immunoglobulin M (IgM) antibodies, but viral isolation and polymerase chain reaction (PCR) detection of JEV were both negative. **CONCLUSIONS:** It is difficult to identify a causal link between the disease and the vaccination, as the source of positive CSF JEV IgM antibodies might be natural JEV infection or possibly due to a traumatic lumbar puncture. Our observations highlight the need for public health officers and doctors to consider reasonable vaccination policies during the JE season. In addition, continued surveillance as well as thorough investigation of any events that occur after JE vaccination is necessary.

- **Kaltenböck A et al. Immunogenicity and safety of IXIARO (IC51) in a Phase II study in healthy Indian children between 1 and 3 years of age. Vaccine, 2010;28(3):834–839.**

For adults the standard administration of the Japanese encephalitis vaccine IXIARO is two injections of 6 microg in a 28-day interval. Immunogenicity and safety of 3 and 6 microg of IXIARO compared to JenceVac were investigated in 60 healthy Indian children aged between 1 and 3 years. JE specific neutralizing antibodies were measured at baseline and 28 days after the first and second vaccination. On Day 56 SCR of the 3 and 6 microg IXIARO and the JenceVac group were 95.7%, 95.2% and 90.9%, respectively, and GMT were 201, 218 and 230, respectively, both without statistically significant difference between the three groups. Local and systemic tolerability were captured in a diary 7 days post-vaccination. No apparent difference was seen in the safety profile between the vaccines. These first immunogenicity and safety data in children are promising and support the use of a 3 microg dose in children below the age of three for further development of IXIARO in the paediatric population.

- **Kaltenböck A et al. 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;27(33):4483–4489.**

In travellers often several pre-departure immunizations are indicated, thus data are needed about possible interactions between vaccines. This Phase 3 study investigated the immunogenicity and safety of IC51 (JE vaccine) and HAVRIX1440 (hepatitis A vaccine) when administered alone or concomitantly to healthy subjects. The immune response was compared between single and concomitant vaccination in terms of geometric mean titre (GMT) and seroconversion rate (SCR) on Days 28 and 56. Immunogenicity was comparable for the 2 vaccines whether given together or separately which suggests that travellers to such regions could receive the vaccinations concomitantly.

- **Kim DS et al. 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),2013, Cape Town, South Africa.

A new live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) has been developed based on innovative technology to give protection against JE with an improved immunogenicity and safety profile. In this phase 3, observer-blind study, 274 children aged 12–24 months were randomized 1:1 to receive one dose of JE-CV (Group JE-CV) or the SA14–14–2 vaccine currently used to vaccinate against JE in the Republic of Korea (Group SA14–14–2). JE neutralizing antibody titers were assessed using PRNT₅₀ before and 28 days after vaccination. The primary endpoint of non-inferiority of seroconversion rates on D28 was demonstrated in the Per Protocol analysis set as the difference between Group JE-CV and Group SA14–14–2 was 0.9 percentage points (95% confidence interval [CI]: –2.35; 4.68), which was above the required –10%. Seroconversion and seroprotection rates 28 days after administration of a single vaccine dose were 100% in Group JE-CV and 99.1% in Group SA14–14–2; all children except one (Group SA14–14–2) were seroprotected. Geometric mean titers (GMTs) increased in both groups from D0 to D28; GM of titer ratios were slightly higher in Group JE-CV (182 [95% CI: 131; 251]) than Group SA14–14–2 (116 [95% CI: 85.5, 157]). A single dose of JE-CV was well tolerated and no safety concerns were identified. In conclusion, a single dose of JE-CV or SA14–14–2 vaccine elicited a comparable immune response with a good safety profile. Results obtained in healthy Korean children aged 12–24 months vaccinated with JE-CV are consistent with those obtained in previous studies conducted with JE-CV in toddlers.

- **Kumar R et al. Effectiveness of one dose of SA 14-14-2 vaccine against Japanese encephalitis. N Engl J Med. 2009 Apr 2;360(14):1465-6. Available at: <http://www.nejm.org/doi/full/10.1056/NEJMc0808664>**

Japanese encephalitis remains a major cause of viral encephalitis in Asia, imposing a significant burden on poor rural families. Vaccination is an important element of disease control. Japanese encephalitis is endemic in the eastern districts of Uttar Pradesh, and these districts had a severe epidemic of the illness in 2005,¹ after which a decision was made to import the Chinese live attenuated vaccine (SA 14-14-2 strain). Since 2006, summer campaigns for mass vaccination against Japanese encephalitis have been conducted among children 1 to 15 years of age in selected districts of the state. The 2007 cycle covered several districts in the catchment area of our hospital.

We studied the efficacy of a single dose of this vaccine within 6 months after its administration in India, using a case–control design similar to that described in previously published studies.^{2,3} Our study was approved by the university's institutional review board. Informed consent was received from the parents of the patients.

Children admitted to our hospital with an illness that was consistent with encephalitis were tested for Japanese encephalitis IgM antibodies in serum or cerebrospinal fluid by means of commercial IgM antibody–capture enzyme-linked immunosorbent assay kits (Excyton).⁴ In villages where the campaign for vaccination against Japanese encephalitis had been held in the summer of 2007, children with laboratory tests that were positive for Japanese encephalitis virus were evaluated. A history of vaccination was elicited, and investigators asked for a vaccination card. After the Japanese encephalitis season, trained investigators visited the villages of patients. Parents of available age- and sex-matched controls living in the same neighborhood were interviewed regarding a history of vaccination.

Twenty patients with Japanese encephalitis were identified, of whom 4 had been vaccinated. Cerebrospinal fluid from 15 of the 20 patients, including all 4 vaccinated patients, was positive for IgM antibodies against Japanese encephalitis. A vaccination card was available for all four vaccinated patients. Of a total of 441 controls, the vaccination status could be confirmed in 429. Of these controls, 339 (79.0%) had been vaccinated, and 90 had not been vaccinated. The campaign-style vaccination program was easily recalled. The crude odds ratio for disease among vaccinated children was 0.07 (95% confidence interval [CI], 0.02 to 0.22), the exact

odds ratio was 0.055 (95% CI, 0.012 to 0.184), and the vaccine efficacy was 94.5% (95% CI, 81.5 to 98.9)

- **Kumari R et al. First indigenous transmission of Japanese Encephalitis in urban areas of National Capital Territory of Delhi, India. Trop Med Int Health. 2013;18(6):743–749.**
OBJECTIVE: Until 2010, no Japanese encephalitis (JE) had been reported from Delhi. Upon report of four confirmed cases of JE in September 2011, detailed investigations were carried out to determine whether the cases were imported or indigenous. **METHODS:** Entomological surveys were carried out and all mosquito pools were tested for the detection of JE virus by ELISA method using specific monoclonal antibody. Human blood samples from contacts of the patients were tested by IgM-captured ELISA method. Pig's blood samples were also tested for the detection of JE virus. **RESULTS:** *Culex tritaeniorhynchus*, *Culex vishnui* and *Culex pseudovishnui* mosquitoes were found. In contrast to rural areas, their breeding habitats were different in the city. 19 pools were tested. JE virus was detected in two pools of *Cx. tritaeniorhynchus* females reared from field-collected larvae, indicating vertical transmission. One pool of *Cx. vishnui* was also positive. This is the first report for the detection of JE virus in mosquitoes from Delhi. JE IgM antibodies in five contacts/residents indicate recent infection. JE virus was also detected in pigs. **CONCLUSION:** Present analysis shows that of four reported JE cases, three were confirmed indigenous, indicating that the virus is multiplying in the city. Mapping of infected JE vector mosquitoes in the cities is required for preventive measures to contain further spread of the disease.
- **Liu W et al. Cost-effectiveness of Japanese encephalitis (JE) immunization in Bali, Indonesia. Vaccine, 2008;26(35):4456–4460.**
Two hypothetical birth cohorts in Bali, each consisting of 100,000 newborns, one immunized with live, attenuated JE vaccine and the other un-immunized, were modeled for JE risk over 11 years. Cumulative JE incidence before JE vaccine introduction was used to represent JE risk in the unvaccinated cohort. Data on vaccine efficacy, vaccination and treatment costs were taken from published papers and surveys. The potential immunization program averted 54 cases, 5 deaths and saved 1224 disability adjusted life years (DALYs) at a net cost of US\$ 700 per JE case averted and US\$ 31 per DALY saved and thus was highly cost-effective.
- **Liu W et al. Risk factors for Japanese encephalitis: a case-control study. Epidemiol Infect, 2010;138(9):1292–1297.**
Japanese encephalitis (JE) has been found to be endemic in Bali, Indonesia. A case-control study was conducted to identify factors associated with JE infection. All 94 serologically confirmed JE cases (cases) and 163 cases of encephalitis or aseptic meningitis without JE (controls) identified in Bali during 2001-2004 were included in the study. Potential risk factors were surveyed at hospital admission. Univariate analyses revealed the following factors to be associated with JE: older age, referral from sub-district health centre or private hospital, playing outdoors after dinner, use of mosquito repellent or spraying, proximity of the residence to rice fields, and pig ownership by the family or next-door neighbours. Multivariate analysis identified proximity to rice fields (OR 2.93, 95% CI 1.57-5.45), pig ownership (OR 2.24, 95% CI 1.17-4.26), and older age (OR 1.21, 95% CI 1.09-1.33) as being independently associated with the risk of JE. Because rice cultivation and pig rearing are essential to the economy of Bali, JE immunization is the best intervention for prevention of JE in Bali.
- **Liu Y et al. Safety of Japanese encephalitis live attenuated vaccination in post-marketing surveillance in Guangdong, China, 2005-2012. Vaccine, 2014;32(15):1768–1773.**

We reviewed the adverse events following immunization of live attenuated Japanese encephalitis vaccine in Guangdong Province, China. During the period of 2005-2012, 23 million doses of live attenuated Japanese encephalitis vaccine were used and 1426 adverse events were reported (61.24 per million doses); of which, 570 (40%) were classified as allergic reactions (24.48 per million doses), 31 (2%) were neurologic events (1.33 per million doses), and 36 (2.5%) were diagnosed as serious adverse events (1.55 per million doses). This study suggests that the JEV-L has a reasonable safety profile, most adverse events are relatively mild, with relatively rare neurologic events being observed.

- **Liu ZL. 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;176(5):1366–1369.**
 The short-term safety of an effective and inexpensive new live attenuated Japanese encephalitis vaccine (SA14-14-2) was studied in a randomized trial, using block randomization. Of 26,239 children who were enrolled, half received the vaccine and half served as controls. Subjects were prospectively followed for 30 days for severe adverse events, such as encephalitis, meningitis, and "all-cause" hospitalization. No cases of encephalitis or meningitis occurred in either group. The upper 95% confidence limit for adverse events not occurring among subjects receiving their first dose was 4.1/10,000. Risk ratios and 95% confidence intervals for other adverse events were 0.70 (0.43-1.15) for all-cause hospitalization, 0.91 (0.37-2.22) for seizure, and 0.79 (0.56-1.11) for fever lasting > or = 3 days. These data attest to the short-term safety of the SA14-14-2 virus strain and the hamster kidney cell substrate.
- **Lyons A et al. A Phase 2 study of a purified, inactivated virus vaccine to prevent Japanese encephalitis. Vaccine. 2007 Apr 30;25(17):3445-53.**
 Japanese encephalitis (JE) is a serious disease caused by the JE virus. New generation JE vaccines are needed to prevent this disease. We conducted this Phase 2 randomized, open label, unblinded, single center study of a new, cell-culture derived, purified inactivated virus (JE-PIV) vaccine. The JE-PIV vaccine was administered in either two or three intramuscular (IM) doses (6.0 or 12.0 mcg each) with observation over 8 weeks. All volunteers completed the protocol without serious adverse reactions. Headache and transient tenderness at the injection site were the most common complaints. There were no laboratory abnormalities believed to be related to vaccine during the study. JE-PIV was well tolerated, resulted in high seroconversion rates [Day 56 (primary endpoint); 95-100%] and induced enduring immune responses up to 2 years after vaccination. Expanded Phase 3 trials are planned.
- **Mathers CD et al. Measuring the burden of neglected tropical diseases: the global burden of disease framework. PLoS Negl Trop Dis,2007;1(2) e114.**
 Reliable, comparable information about the main causes of disease and injury in populations, and how these are changing, is a critical input for debates about priorities in the health sector. Traditional sources of information about the descriptive epidemiology of diseases, injuries, and risk factors are generally incomplete, fragmented, and of uncertain reliability and comparability. The Global Burden of Disease (GBD) study has provided a conceptual and methodological framework to quantify and compare the health of populations using a summary measure of both mortality and disability, the disability-adjusted life year (DALY). This paper describes key features of the Global Burden of Disease analytic approach, which provides a standardized measurement framework to permit comparisons across diseases and injuries, as well as risk factors, and a systematic approach to the evaluation of data. The paper describes the evolution of the GBD, starting from the first study for the year 1990, summarizes the methodological improvements incorporated into GBD revisions for the years 2000–2004 carried out by the World Health Organization, and examines priorities and issues for the next major GBD study, funded by the Bill & Melinda Gates Foundation, and commencing in 2007.

The paper presents an overview of summary results from the Global Burden of Disease study 2002, with a particular focus on the neglected tropical diseases, and also an overview of the comparative risk assessment for 26 global risk factors. Taken together, trypanosomiasis, Chagas disease, schistosomiasis, leishmaniasis, lymphatic filariasis, onchocerciasis, intestinal nematode infections, Japanese encephalitis, dengue, and leprosy accounted for an estimated 177,000 deaths worldwide in 2002, mostly in sub-Saharan Africa, and about 20 million DALYs, or 1.3% of the global burden of disease and injuries. Further research is currently underway to revise and update these estimates.

- Monath TP et al. 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;188(8):1213–1230.**

ChimeriVax-JE is a live, attenuated vaccine against Japanese encephalitis, using yellow fever (YF) 17D vaccine as a vector. In a double-blind phase 2 trial, 99 adults received vaccine, placebo, or YF 17D vaccine (YF-VAX). ChimeriVax-JE was well tolerated, with no differences in adverse events between treatment groups. Viremias resulting from administration of ChimeriVax-JE and YF-VAX were of short duration and low titer; 82 (94%) of 87 subjects administered graded doses (1.8–5.8 log₁₀) of ChimeriVax-JE developed neutralizing antibodies. A second dose, administered 30 days later, had no booster effect. Previous inoculation with YF did not interfere with ChimeriVax-JE, but there was a suggestion (not statistically significant) that ChimeriVax-JE interfered with YF-VAX administered 30 days later. A separate study explored immunological memory both in subjects who had received ChimeriVax-JE 9 months before and in ChimeriVax-JE-naïve subjects challenged with inactivated mouse-brain vaccine (JE-VAX). Anamnestic responses were observed in preimmune individuals. ChimeriVax-JE appears to be a safe vaccine that provides protective levels of neutralizing antibody after a single dose
- Nasveld PE et al. 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;6(12):1038–1046**

In a randomized, double-blind study, 202 healthy adults were randomized to receive a live, attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and placebo 28 days apart in a cross-over design. A subgroup of 98 volunteers received a JE-CV booster at month 6. Safety, immunogenicity, and persistence of antibodies to month 60 were evaluated. There were no unexpected adverse events (AEs) and the incidence of AEs between JE-CV and placebo were similar. There were three serious adverse events (SAE) and no deaths. A moderately severe case of acute viral illness commencing 39 days after placebo administration was the only SAE considered possibly related to immunization. 99% of vaccine recipients achieved a seroprotective antibody titer ≥ 10 to JE-CV 28 days following the single dose of JE-CV, and 97% were seroprotected at month 6. Kaplan Meier analysis showed that after a single dose of JE-CV, 87% of the participants who were seroprotected at month 6 were still protected at month 60. This rate was 96% among those who received a booster immunization at month 6. 95% of subjects developed a neutralizing titer ≥ 10 against at least three of the four strains of a panel of wild-type Japanese encephalitis virus (JEV) strains on day 28 after immunization. At month 60, that proportion was 65% for participants who received a single dose of JE-CV and 75% for the booster group. These results suggest that JE-CV is safe, well tolerated and that a single dose provides long-lasting immunity to wild-type strains.

- Ohrr H et al. 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;366(9494):1375–1378.**

BACKGROUND: In July, 1999, a single dose of live-attenuated SA 14-14-2 Japanese encephalitis vaccine was given to children aged 1-15 years in the Terai region of Nepal. Cases of natural infection occurred almost immediately. Our aim was to assess the long-term protective effect of this vaccination. **METHODS:** In 2000, this same population had a second seasonal exposure to the virus. We therefore did a case-control study to measure the prevalence of vaccination against Japanese encephalitis in 35 patients hospitalised for the disease 1 year after immunisation, and in age-sex matched village controls. **FINDINGS:** Of 35 children resident in Bardiya and Banke districts admitted to the Bheri Zonal Hospital with serologically confirmed Japanese encephalitis, only one had been vaccinated in 1999. In 430 age-sex matched village controls, 234 (54.4%) were vaccinated. We calculated a median unbiased estimate of the odds ratio of 0.0155, with lower and upper confidence limits of 0.0004 and 0.0986. The protective effect of vaccine after 12-15 months was 98.5% (CI 90.1-99.2%). **INTERPRETATION:** Our study provides evidence of sustained high protection afforded by one dose of live attenuated SA 14-14-2 vaccine in Nepalese children.
- Pakakasama S et al. Immunogenicity of a live-attenuated Japanese encephalitis vaccine in children and adolescents after hematopoietic stem cell transplantation. Bone Marrow Transplant, 2014;49(10):1307–1309.**

There have been no recommendations for revaccination with the Japanese encephalitis (JE) vaccine in post-hematopoietic stem cell transplantation (HSCT) patients. This study aimed to measure the immunogenic response to a live-attenuated JE vaccine (SA 14-14-2) in post-HSCT patients. JE-specific neutralizing Ab titers were measured before and after the JE vaccination. The patients with Ab titers <10 at the 3-month time point received a second injection at 6 months. A total of 28 patients (male:female=11:17) with a median age of 13 years (4-21 years) were included. The underlying diseases were thalassemia (50%) and hematologic malignancies (50%). Ten patients (35.7%) had Ab titers above the preventive level before vaccination. Nine of 18 patients (50%) seroconverted at 3 months after a single JE vaccination, but only three of these patients had sustained protective Ab levels. Seven of nine patients (78%) seroconverted at 3 months after a second JE vaccine injection, and all of these patients sustained protective Ab levels at 12 months. In conclusion, post-HSCT patients had low seroconversion rates after a single dose of the live-attenuated JE vaccine. These patients may require at least two doses of the JE vaccine to ensure protective Ab levels.
- Partridge J et al. Endemic Japanese encephalitis in the Kathmandu valley, Nepal. Am J Trop Med Hyg. 2007;77(6):1146–1149.**

Japanese encephalitis (JE) is endemic in the Terai region of Nepal. There is little information on the occurrence of JE outside the Terai and particularly in the densely populated Kathmandu valley. Acute encephalitis syndrome (AES) cases were detected using a sentinel surveillance system that has been functioning since 2004. JE was confirmed using anti-JE IgM ELISA. All laboratory-confirmed JE cases that occurred in the Kathmandu valley during 2006 were followed up for verification of residence and travel history. JE was confirmed in 40 residents of the Kathmandu valley, including 30 cases that had no history of travel outside the valley during the incubation period. Incidence was 2.1/100,000 and the case fatality was 20% (8/40). Currently, JE prevention is focused on the Terai region in Nepal; given the evidence, this should be reviewed for the possible inclusion of the Kathmandu valley in the national JE prevention and control program.

- **Public assessment summary report update – Japanese Encephalitis Vaccine (Human) (Purified Inactivated Vaccine-Adsorbed) JEEV®.** Available at http://www.who.int/immunization_standards/vaccine_quality/pq_266_je_1dose_biological_e_updated_vpsar.pdf, accessed November 2014.
- **Puthanakit T et al . A 3-year follow-up of antibody response in HIV-infected children with immune recovery vaccinated with inactivated Japanese encephalitis vaccine. Vaccine,2010;28(36):5900–5902.**
Among HIV-infected children who had immune recovery after received antiretroviral therapy (ART), good responses to revaccination with childhood vaccines have been observed. However, the rate of long-term persistence of antibody response remains unknown. The objective of this study is to determine whether HIV-infected children still have protective antibody against Japanese encephalitis virus (JE) 3 years after receiving revaccination with two doses of inactivated JE vaccine. Plasma JE neutralizing antibody titer was determined by a plaque reduction neutralization assay. An antibody titer of more than 1:10 was defined as being protective. Fifty HIV-infected children with a mean age of 10.3 years (SD 2.2) and mean CD4 percentage of 25 (SD 5) were revaccinated with two doses of inactivated JE vaccine. Forty-three children had been followed-up for 3 years. The JE neutralizing antibody at 1 month and 3 years after revaccination were detected among 38 (88%) and 35 (81%) children, respectively. The geometric means titer significantly dropped from of 306 (min 13-max 163,617) to 106 (min 11-max 4645). This data show that the majority of HIV-infected children had persistent antibody 3 years after revaccination. JE revaccination in HIV-infected children with immune recovery after ART should be carried out in endemic areas.
- **Puthanakit T et al. Japanese encephalitis vaccination in HIV-infected children with immune recovery after highly active antiretroviral therapy. Vaccine,2007;25(49):8257–8261.**
HIV-infected children are vulnerable to infections by vaccine preventable pathogens. However, they have poorer responses to childhood immunization than healthy children. The objectives of this study are to determine the prevalence of Japanese encephalitis (JE) protective antibody in HIV-infected children with immune recovery after highly active antiretroviral therapy (HAART) and evaluate response to JE revaccination. JE neutralizing antibody titer of plasma was determined by a plaque reduction neutralization assay. An antibody titer of more than 1:10 was defined as protective antibody. Children who did not have protective antibody to JE were enrolled to receive a two-dose JE revaccination during the study. There were 96 children with mean age of 9.7 years (S.D. 2.6) and mean CD4 percentage of 25 (S.D. 5) who participated in the study. Forty-four children (46%) had protective antibody to JE. A two-dose JE revaccination was administered to 50 children who did not have JE antibody. At 1 month after revaccination, 44 children (88%) developed protective antibody. This study demonstrated that there is a low prevalence of JE protective antibody in HIV-infected children despite history of JE primary childhood vaccination. However, the majority of HIV-infected children with immune recovery after HAART can develop protective antibody after JE revaccination.
- **Rao PN. Japanese encephalitis. Indian Pediatr,2001;38: 1252–1264. Available at: <http://www.indianpediatrics.net/nov2001/nov-1252-1264.htm>**
Japanese encephalitis (JE) is a leading cause of viral encephalitis in Asia that has been controlled effectively through national vaccination programs in several countries like Japan, Korea, China and Thailand(1-3). It is endemo-epidemic in some regions in India(4,5). It is difficult to eradicate JE because it is transmitted from natural reservoirs like pigs and wading birds (herons and egrets)(3).
In many Asian Countries, the disease burden due to JE remains unclear(1). Hospital based surveillance in Malaysia revealed JE to be responsible for 38.5% of hospitalized cases of

encephalitis and 0.4% of non-specific febrile illnesses(6). Many epidemics have occurred in India since 1955(2,4). JE has been reported from 24 states/Union Territories in India so far(7,8). However, comparison of reported cases and expected cases from India indicates JE surveillance gap (difference between expected and reported cases)(1,9). Since JE deaths are always reported, but only 2% of JE cases are reported(1), Case Fatality Rate apparently increase proportionately. The case Fatality Rate (CFR) and morbidity due to JE can be reduced significantly by early diagnosis and appropriate supportive treatment(10-12).

- **Rojanasuphot S et al. Response to JE vaccine among HIV-infected children, Bangkok, Thailand. *Southeast Asian J Trop Med Public Health*,1998;29(3):443–450.**

Since 1990, Japanese encephalitis (JE) vaccine has been part of EPI in northern Thailand, where there is a high prevalence of JE and HIV infection. To evaluate the immunogenicity and safety of JE vaccine among HIV-infected children, we conducted a retrospective study of HIV-infected and uninfected children who received 2 doses of JE vaccine at 12 months of age. Pre- and post-immunization plasma specimens were tested by plaque reduction neutralization for antibody levels to JE and dengue(1-4) viruses; titers of ≥ 10 were considered positive. Excluding 5 children with preimmunization antibodies, 5 of 14 (36%) HIV-infected children and 18 of 27 (67%) uninfected children had positive JE antibody titers after immunization [odds ratio (OR) 0.3, $p=0.06$]; 31% absolute difference [95% confidence interval (CI) 0-61.7%]. The geometric mean titer of HIV-infected children with positive titers was lower than that of control children (15.1 vs, 23.8; $p=0.17$). No significant vaccine-associated adverse events were noted. We conclude that primary antibody response to JE vaccine was low among HIV-infected children and was approximately half of that seen among uninfected children. In endemic areas, HIV-infected children are likely to be at risk of acquiring JE despite routine immunization with 2 doses.

- **Schuh AJ et al. Phylogeography of Japanese encephalitis virus: genotype is associated with climate. *PLoS Negl Trop Dis*,2013;7(8):e2411.**

The circulation of vector-borne zoonotic viruses is largely determined by the overlap in the geographical distributions of virus-competent vectors and reservoir hosts. What is less clear are the factors influencing the distribution of virus-specific lineages. Japanese encephalitis virus (JEV) is the most important etiologic agent of epidemic encephalitis worldwide, and is primarily maintained between vertebrate reservoir hosts (avian and swine) and culicine mosquitoes. There are five genotypes of JEV: GI-V. In recent years, GI has displaced GIII as the dominant JEV genotype and GV has re-emerged after almost 60 years of undetected virus circulation. JEV is found throughout most of Asia, extending from maritime Siberia in the north to Australia in the south, and as far as Pakistan to the west and Saipan to the east.

Transmission of JEV in temperate zones is epidemic with the majority of cases occurring in summer months, while transmission in tropical zones is endemic and occurs year-round at lower rates. To test the hypothesis that viruses circulating in these two geographical zones are genetically distinct, we applied Bayesian phylogeographic, categorical data analysis and phylogeny-trait association test techniques to the largest JEV dataset compiled to date, representing the envelope (E) gene of 487 isolates collected from 12 countries over 75 years. We demonstrated that GIII and the recently emerged GI-b are temperate genotypes likely maintained year-round in northern latitudes, while GI-a and GII are tropical genotypes likely maintained primarily through mosquito-avian and mosquito-swine transmission cycles. This study represents a new paradigm directly linking viral molecular evolution and climate.

- Schuller E et al. 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;27(15):2188–2193.**

The standard administration of the investigational Japanese encephalitis vaccine IC51 is 2 doses of 6 microg with a 28-day interval. This study investigated the immunogenicity of a single-immunization, high-dose regimen (1 x 12 microg) compared to the 2-injection, standard regimen to determine the immune response that one, high-dose injection can confer. The single, high-dose regimen resulted in about 60% seroconversion rate (SCR) at 10 days after administration, but it did not reach the almost 100% SCR achieved by the 2-dose standard administration at Day 35. The standard regimen conferred essentially 100% seroconversion already 7 days after the second immunization.
- Schuller E et al. 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)**

Japanese encephalitis virus (JEV) is the leading cause of viral encephalitis in Asia with a case fatality rate up to 35% and long-term sequelae up to 75%. This active-controlled, randomized, multi-centre, observer-blind, phase III trial investigated the neutralising antibody response to the new Japanese encephalitis (JE) vaccine IC51 in subjects with (N=81) and without (N=339) pre-existing tick-borne encephalitis (TBE) vaccine induced antibodies as determined by TBE enzyme-linked immunosorbent assay IgG (ELISA). Neutralising antibody response was statistically superior in TBE ELISA-positive subjects compared to TBE ELISA-negative subjects after the first ($p<0.0001$) but not after the second vaccination with IC51. Thus, pre-existing vaccine-induced TBE immunity enhances the neutralising JEV-specific antibody response after a single IC51 vaccination.
- Schuller E et al. 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)**

Japanese encephalitis (JE) is the most common viral encephalitis in Asia. IC51 is a new Vero cell-derived, inactivated JE virus vaccine with non-inferior immunogenicity (after 2 months) compared to the US-licensed vaccine JE-VAX (mouse brain-derived, inactivated) and with a more convenient (two injections instead of three) intramuscular dose schedule. Adult subjects from two studies were followed-up for comparative immunogenicity (JE-VAX) at 6 months and long-term immunogenicity of IC51 alone at 12 months. At 6 months, immunogenicity was higher with IC51 (seroconversion rate [SCR] 95%; geometric mean titer [GMT] 84) than with JE-VAX (SCR 74%; GMT 34). At 12 months, the SCR was 83% and the GMT (41) remained above the protective titer of 1:10. Most people immunized with IC51 will have protective neutralizing antibody levels for at least a year.
- Schuller E et al. Safety profile of the Vero cell-derived Japanese encephalitis virus (JEV) vaccine IXIARO®. *Vaccine*, 2011;29(47):8669–8676.**

Japanese encephalitis (JE) is the most common cause for viral encephalitis in Asia and can be effectively prevented by vaccination. IXIARO(®) is a Vero cell-derived, inactivated JE virus vaccine which has been licensed and distributed in the US, Europe, Canada, Hongkong, Israel, and distributed in Australia under the trade name JESPECT(®). This paper reviews the safety profile of IXIARO(®) in the first 12 months after licensure and discusses the observed profile in the context of clinical trial results for IXIARO(®) and post-marketing safety data for JE-VAX(®). The clinical safety profile is derived from a pooled analysis including safety data from 10 phase

III trials in 4043 subjects who received at least one IXIARO® vaccination and were followed-up for up to 3 years after the primary immunization. Local and systemic tolerability of IXIARO® was similar to an earlier safety analysis at the time of licensure of the vaccine. In post-marketing AE reports, the system organ classes affected following vaccination with IXIARO® were similar to the previously observed clinical trial profile. No serious allergic reactions were observed in the 12-month post-marketing period. This comprehensive safety review confirms the good safety profile of IXIARO® in clinical and post-marketing use.

- Siraprapasiri T et al. Cost benefit analysis of Japanese encephalitis vaccination program in Thailand. *Southeast Asian J Trop Med Public Health*,1997;28(1):143–148.**

Using decision analysis, we estimated benefits, risks, and costs of implementing the Japanese encephalitis (JE) vaccination program in children aged 18 months and 6 years in Thailand. The costs for inclusion of JE vaccine into the routine immunization program at 18 months and 6 years are \$2.16 and \$3.68 per person, respectively. In the baseline model, the JE vaccination program will prevent 124 JE cases in the program for 18 months old children and 153 JE cases in the program for 6 years old children. The 18 month child program is more cost-effective than the 6 year child program. The cost-effectiveness ratio in the 18 month child program is \$15,715 compared with \$21,661 in the 6 year child program. The benefits of the JE vaccination program are the savings in treatment cost, disability care, and the future lifetime earnings from JE prevented. The 18 month child program will save \$72,922 per one prevented JE compared with \$66,197 in the 6 year child program. The JE vaccination program is cost-beneficial under the base-case assumption. Sensitivity analysis which alters various assumptions indicates that the JE vaccination program is worth implementing unless the incidence of JE is less than 3 per 100,000 population. Otherwise, the cost of vaccine has to be reduced.
- Sohn YM et al. 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;26(13):1638–1643.**

Out of 98 subjects who had participated in the 2000 JE vaccination campaign, 69 people were enrolled in the tests of 2004 and 2005 for the evaluation of long term immune response of a single dose of live attenuated SA14-14-2 JE vaccine. 89.9% of study subjects (62/69) had maintained a high level of neutralizing antibody until 2004 as their GMT was measured as 133 (Min 11, Max 2991). Forty-four subjects were still positive in 2005, 5 years after JE vaccination, and their neutralizing antibody positive rate was significantly higher than that of 69 age-sex matched unvaccinated control subjects: 63.8% (44/69) vs. 14.5% (10/69) ($P < 0.05$). Twenty-four subjects (Group 1) who were seronegative for neutralizing antibody at the 2005 test were given a second dose for revaccination in 2006. Also 49 seronegative (Group 2) subjects who were enrolled as a control group in 2005 were given one dose of primary JE vaccine in 2006. Seven days after vaccination, seropositive rate was discovered to be 76.5% (13/17) and 168.52 (Min 38, Max 2173) in Group 1, while no seroconversion in Group 2. On the 30th day, seropositive rate and GMT were 82.4% (14/17) and 392.01 (Min 22, Max 2197) in Group 1, while 75.7% (28/37) and 45.72 (Min 12, Max 505) in Group 2, respectively. We observed the persistence of neutralizing antibody of single dose of live attenuated SA14-14-2 JE vaccine, 89.9% after 4 years and 63.8% after 5 years, and a rapid secondary immune response on the seventh day after booster dose among those who had been seronegative in spite of the first dose of vaccine. Single dose of live JE vaccine could be effective to provide a long-term protection in JE endemic area, where natural boosting is quite probable in the vaccinees. However, further studies should be carried out to support whether one dose of live JE vaccine is sufficient for people in JE non-endemic area.

- **Solomon T et al. Seizures and raised intracranial pressure in Vietnamese patients with Japanese encephalitis. *Brain: a journal of neurology*, 2002;125:1084–1093.**

Japanese encephalitis (JE) causes at least 10 000 deaths each year. Death is presumed to result from infection, dysfunction and destruction of neurons. There is no antiviral treatment. Seizures and raised intracranial pressure (ICP) are potentially treatable complications, but their importance in the pathophysiology of JE is unknown. Between 1994 and 1997 we prospectively studied patients with suspected CNS infections referred to an infectious disease referral hospital in Ho Chi Minh City, Vietnam. We diagnosed Japanese encephalitis virus (JEV), using antibody detection, culture of serum and CSF, and immunohistochemistry of autopsy material. We observed patients for seizures and clinical signs of brainstem herniation, measured CSF opening pressures (OP) and, on a subset of patients, performed EEGs. Of 555 patients with suspected CNS infections, 144 (26%) were infected with JEV (134 children and 10 adults). Seventeen (12%) patients died and 33 (23%) had severe sequelae. Of the 40 patients with witnessed seizures, 24 (62%) died or had severe sequelae, compared with 26 (14%) of 104 with no witnessed seizures [odds ratio (OR) 4.50, 95% confidence interval (CI) 1.94-10.52, $P < 0.0001$]. Patients in status epilepticus ($n = 25$), including 15 with subtle motor seizures, were more likely to die than those with other seizures ($P = 0.003$). Patients with seizures were more likely to have an elevated CSF OP ($P = 0.033$) and to develop brainstem signs compatible with herniation syndromes ($P < 0.0001$). Of 11 patients with CSF OP ≥ 25 cm, five (46%) died, compared with seven (9%) of 80 patients with lower pressures [OR 8.69, 95% CI 1.73-45.39, $P = 0.005$]. Of the 50 patients with a poor outcome, 35 (70%) had signs compatible with herniation syndromes (including 19 with signs of rostro-caudal progression), compared with nine (10%) of those with better outcomes ($P < 0.0001$). Of 11 patients with CSF OP ≥ 25 cm, five (46%) died, compared with seven (9%) of 80 patients with lower pressures (OR 8.69, 95% CI 1.73-45.39, $P = 0.005$). The combination of coma, multiple seizures, brainstem signs and illness for 7 or more days was an accurate predictor of outcome, correctly identifying 42 (84%) of 50 patients with a poor outcome and 82 (87%) of 94 with a better outcome. These findings suggest that in JE, seizures and raised ICP may be important causes of death. The outcome may be improved by measures aimed at controlling these secondary complications.

- **Suraratdecha C et al. A cost-effectiveness analysis of strategies for controlling Japanese encephalitis in Andhra Pradesh, India. *J Pharm Fin, Econ & Policy*, 2006;15:21.**

- **Tandan JB et al. 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;25(27):5041–5045.**

In July 1999, a single dose of live-attenuated SA 14-14-2 Japanese encephalitis (JE) vaccine was administered to children living in the Bardiya, Banke and Kailali districts of Nepal. In 2004, the original vaccinated population experienced a fifth seasonal exposure to JE. We performed a case-control study comparing the prevalence of the administration of vaccine in patients with JE hospitalized in the Bardiya and Bheri Zonal hospitals and in age-sex matched controls resident in the Bardiya district. Among the 219 village controls, 114 had been vaccinated (52.1%) while only one of 20 JE cases had received live-attenuated JE vaccine. Five years after administration of a single dose, SA 14-14-2 provided a protective efficacy of 96.2% (CI 73.1-99.9%).

- **Tauber et al. Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. Lancet, 2007;370: 1847–1853.**

BACKGROUND: Japanese encephalitis virus (JEV) is the leading cause of viral encephalitis in southeast Asia. Although no treatment is currently available, vaccination effectively prevents the disease. In a non-inferiority study, we aimed to compare the safety and immunogenicity of a novel, second-generation, inactivated candidate vaccine for JEV with a licensed, mouse-brain-derived vaccine. **METHODS:** We included 867 adults in a multicentre, multinational, observer-blinded, randomised controlled phase III trial. Study sites were located in the USA, Germany, and Austria. Volunteers received either the JEV test vaccine intramuscularly on a two-dose schedule (on days 0 and 28; n=430) or the licensed vaccine subcutaneously according to its recommended three-dose schedule (on days 0, 7, and 28; n=437). The primary endpoint was immunogenicity, with respect to neutralising JEV-specific antibodies assessed by a plaque-reduction neutralisation test, which was assessable in 725 patients in the per-protocol population. This trial is registered as a clinical trial, EudraCT number 2004-002474-36. **FINDINGS:** The safety profile of the test vaccine was good, and its local tolerability profile was more favourable than that of the licensed vaccine. Frequency of adverse events was similar between treatment groups, and vaccine-related adverse events were generally mild. The seroconversion rate of the test vaccine was 98% compared with 95% for the licensed vaccine on day 56 (95% CI for the difference –1.33 to 3.43). Geometric mean titre for recipients of the test vaccine was 244 (range 5–19 783), compared with 102 (5–1864) for the licensed vaccine (ratio 2.3 [95% CI 1.967–2.75]). **INTERPRETATION:** The test JEV vaccine has a promising immunogenicity and safety profile.

- **Tauber E et al. 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.**

BACKGROUND: Japanese encephalitis (JE) is the most important mosquito-borne viral encephalitis and has a high case fatality rate. It is caused by Japanese encephalitis virus. Improved vaccines are urgently needed for residents in countries of endemicity, travelers, and the military. The aim of the present trial was to evaluate the safety and tolerability of IC51, Intercell's Vero cell-derived, purified, inactivated JE vaccine. **METHODS:** This was a randomized (3:1), double-blind, placebo-controlled, multicenter phase 3 trial. Healthy subjects were randomized to receive 2 doses of IC51 (n=2012) or placebo (n=663) at a 4-week interval. Adverse events following immunization (AEFI) were documented over a period of 2 months. **RESULTS:** The rate of severe AEFI was similar in the IC51 group (0.5%) and the placebo group (0.9%). The rate of medically attended AEFI and all AEFI was also similar in the IC51 group and the placebo group. The same applied for all adverse events, including local and systemic tolerability. Importantly, there were no signs of acute allergic reactions. **CONCLUSION:** The Intercell JE vaccine IC51 had a safety profile similar to that of placebo. These data, together with the immunogenicity data from a recent phase 3 trial, form the basis of application for licensure of this vaccine.

- **Touch S et al. A cost-effectiveness analysis of Japanese encephalitis vaccine in Cambodia. Vaccine, 2010;28(29):4593–4599.**

This study aimed to evaluate the cost and effectiveness of introducing a live, attenuated vaccine (SA 14-14-2) against Japanese encephalitis (JE) into the immunization program. The study demonstrated that SA 14-14-2 immunization is cost-effective in controlling JE in Cambodia compared to no vaccination. Averting one disability-adjusted life year, from a societal perspective, through the introduction of SA 14-14-2 through routine immunization, or a combination of routine immunization plus a campaign targeting children 1–5 or 1–10 years

of age, costs US\$22, US\$34 and US\$53, respectively. Sensitivity analyses confirmed that there was a high probability of SA 14-14-2 immunization being cost-effective under conditions of uncertainty.

- Torresi J et al. Immunogenicity, safety and tolerability in adults of a new single-dose, live-attenuated vaccine against Japanese encephalitis: Randomised controlled phase 3 trials. *Vaccine*,2010;28(50):7993–8000.**

Japanese encephalitis chimeric virus vaccine (JE-CV) was developed to replace licensed mouse brain-derived vaccine (MBD-JE), the production of which ceased in 2005. Two randomised controlled phase 3 studies were conducted. Immunogenicity study: 410 participants received one JE-CV injection, 410 received 3 MBD-JE injections. Safety study: 1,601 participants received JE-CV, 403 received placebo. Seroconversion after a single JE-CV vaccination (99.1%) was statistically non-inferior to that after three-dose MBD-JE (95.1%) vaccination. JE-CV elicited a rapid immune response, with 93.6% of participants seroconverting within 14 days. Adverse reaction rates were significantly lower with JE-CV (67.6%) than with MBD-JE (82.2%) ($p<0.001$), and the reactogenicity profile of JE-CV was comparable with that of placebo. A single dose of JE-CV elicited rapid seroconversion in a higher proportion of vaccinees than the current vaccine with fewer reactions. The safety profile of JE-CV is good.
- Upreti SR et al. 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;88(3):464–468.**

Wider availability of the live, attenuated SA 14-14-2 Japanese encephalitis (JE) vaccine has facilitated introduction or expansion of immunization programs in many countries. However, information on their impact is limited. In 2006, Nepal launched a JE immunization program, and by 2009, mass campaigns had been implemented in 23 districts. To describe the impact, we analyzed surveillance data from 2004 to 2009 on laboratory-confirmed JE and clinical acute encephalitis syndrome (AES) cases. The post-campaign JE incidence rate of 1.3 per 100,000 population was 72% lower than expected if no campaigns had occurred, and an estimated 891 JE cases were prevented. In addition, AES incidence was 58% lower, with an estimated 2,787 AES cases prevented, suggesting that three times as many disease cases may have been prevented than indicated by the laboratory-confirmed JE cases alone. These results provide useful information on preventable JE disease burden and the potential value of JE immunization programs.
- Victor J et al. 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): 306–308.**
- WHO guidelines for JE surveillance:**
http://whqlibdoc.who.int/hq/2003/who_v&b_03.01.pdf, accessed November 2014.
- Woolpert T et al. 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;30(20):3090–3096.**

BACKGROUND: There are no data on the use of inactivated Vero cell culture-derived Japanese encephalitis (JE) vaccine (JE-VC) as a booster among individuals who previously received inactivated mouse brain-derived JE vaccine (JE-MB). **METHODS:** Military personnel who received ≥ 3 doses of JE-MB or were JE vaccine-naïve were vaccinated with 2 doses of JE-VC on days 0 and 28. Serum neutralizing antibodies were measured pre-vaccination and 28 days after each dose. Non-inferiority was evaluated for seroprotection rate and geometric mean titer (GMT) between previously vaccinated participants post-dose 1 and vaccine-naïve

participants post-dose 2. **RESULTS:** Fifty-three previously vaccinated and 70 JE vaccine-naïve participants were enrolled. Previously vaccinated participants had significantly higher GMTs pre-vaccination, post-dose 1, and post-dose 2. Seroprotection rates among previously vaccinated participants post-dose 1 (44/44, 100%) were noninferior to those achieved in previously naïve participants post-dose 2 (53/57, 93%). The GMT was significantly higher in previously vaccinated participants post-dose 1 (GMT 315; 95% CI 191-520) compared to previously naïve participants post-dose 2 (GMT 79; 95% CI 54-114). **CONCLUSIONS:** Among military personnel previously vaccinated with ≥ 3 doses of JE-MB, a single dose of JE-VC adequately boosts neutralizing antibody levels and provides at least short-term protection. Additional studies are needed to confirm these findings in other populations and determine the duration of protection following a single dose of JE-VC in prior recipients of JE-MB.

- **Yamada A et al. Trial of inactivated Japanese encephalitis vaccine in children with underlying diseases. *Vaccine*, 1986;4(1):32–34.**

Two shots of inactivated Japanese encephalitis (JE) vaccine were given to children, 139 with underlying diseases and 42 healthy, and their antibody responses were studied by the neutralization test. Before vaccination, most of the vaccinees did not have antibody against JE virus. One month after the second vaccination, they were all seroconverted and showed considerably high neutralizing titres. One healthy child developed fever on the day of vaccination without any severe symptoms afterwards, and no side reactions were observed in the handicapped children. These results suggest that the current JE vaccine is safe and can induce a strong immune response even in handicapped children.

- **Yin Z et al; 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;30(37):5569–5577.**

BACKGROUND: Historically, China's Japanese encephalitis vaccination program was a mix of household purchase of vaccine and government provision of vaccine in some endemic provinces. In 2006, Guizhou, a highly endemic province in South West China, integrated JE vaccine into the provincial Expanded Program on Immunization (EPI); later, in 2007 China fully integrated 28 provinces into the national EPI, including Guizhou, allowing for vaccine and syringe costs to be paid at the national level. We conducted a retrospective economic analysis of JE integration into EPI in Guizhou province. **METHODS:** We modeled two theoretical cohorts of 100,000 persons for 65 years; one using JE live-attenuated vaccine in EPI (first dose: 95% coverage and 94.5% efficacy; second dose: 85% coverage and 98% efficacy) and one not. We assumed 60% sensitivity of surveillance for reported JE rates, 25% case fatality, 30% chronic disability and 3% discounting. We reviewed acute care medical records and interviewed a sample of survivors to estimate direct and indirect costs of illness. We reviewed the EPI offices expenditures in 2009 to estimate the average Guizhou program cost per vaccine dose. **RESULTS:** Use of JE vaccine in EPI for 100,000 persons would cost 434,898 US\$ each year (46% of total cost due to vaccine) and prevent 406 JE cases, 102 deaths, and 122 chronic disabilities (4554 DALYs). If we ignore future cost savings and only use EPI program cost, the program would cost 95.5 US\$/DALY, less than China Gross Domestic Product per capita in 2009 (3741 US\$). From a cost-benefit perspective taking into account future savings, use of JE vaccine in EPI for a 100,000-person cohort would lead to savings of 1,591,975 US\$ for the health system and 11,570,989 US\$ from the societal perspective. **CONCLUSIONS:** In Guizhou, China, use of JE vaccine in EPI is a cost effective investment. Furthermore, it would lead to savings for the health system and society.

- **Zaman K et al. Lot-to-lot consistency of live attenuated SA 14-14-2 Japanese encephalitis vaccine manufactured in a good manufacturing practice facility and noninferiority with respect to an earlier product. *Vaccine*,2014;32(46):6061–6066.**

We conducted a four-arm, double-blind, randomized controlled trial among 818 Bangladeshi infants between 10 and 12 months of age to establish equivalence among three lots of live attenuated SA 14-14-2 JE vaccine manufactured by the China National Biotec Group's Chengdu Institute of Biological Products (CDIBP) in a new Good Manufacturing Practice (GMP) facility and to evaluate non-inferiority of the product with a lot of the same vaccine manufactured in CDIBP's original facility. The study took place in two sites in Bangladesh, rural Matlab and Mirpur in urban Dhaka. We collected pre-vaccination (Day 0) and post-vaccination Day 28 (-4 to +14 days) blood samples to assess neutralizing anti-JE virus antibody titers in serum by plaque reduction neutralization tests (PRNT). Seroprotection following vaccination was defined as a PRNT titer $\geq 1:10$ at Day 28 in participants non-immune at baseline. Follow-up for reactogenicity and safety was conducted through home visits at Day 7 and monitoring for serious adverse events through Day 28. Seroprotection rates ranged from 80.2% to 86.3% for all four lots of vaccine. Equivalence of the seroprotection rates between pairs of vaccine lots produced in the new GMP facility was satisfied at the pre-specified 10% margin of the 95% confidence interval (CI) for two of the three pairwise comparisons, but not for the third (-4.3% observed difference with 95% CI of -11.9 to 3.3%). Nevertheless, the aggregate seroprotection rate for all three vaccine lots manufactured in the GMP facility was calculated and found to be within the non-inferiority margin (within 10%) to the vaccine lot produced in the original facility. All four lots of vaccine were safe and well tolerated. These study results should facilitate the use of SA 14-14-2 JE vaccine as a routine component of immunization programs in Asian countries.