Japanese Encephalitis Vaccines; WHO Position Paper Aug 2006: Selected references

Epidemiology of Japanese Encephalitis

Mackenzie JS, Gubler DJ, Petersen LR. Emerging flaviviruses: The spread and resurgence of Japanese encephalitis, West Nile and dengue viruses. Nature Medicine. Vol. 10(12 SUPPL.)(pp S98-S109), 2004.

Mosquito-borne flaviviruses provide some of the most important examples of emerging and resurging diseases of global significance. Here, we describe three of them: the resurgence of dengue in tropical and subtropical areas of the world, and the spread and establishment of Japanese encephalitis and West Nile viruses in new habitats and environments. These three examples also illustrate the complexity of the various factors that contribute to their emergence, resurgence and spread. Whereas some of these factors are natural, such as bird migration, most are due to human activities, such as changes in land use, water impoundments and transportation, which result in changed epidemiological patterns. The three examples also show the ease with which mosquito-borne viruses can spread to and colonize new areas, and the need for continued international surveillance and improved public health infrastructure to meet future emerging disease threats.

JE vaccines, general

Monath TP. Japanese encephalitis vaccines: current vaccines and future prospects. Curr Top Microbiol Immunol. 2002;267:105-38.

Vaccination against JE ideally should be practiced in all areas of Asia where the virus is responsible for human disease. The WHO has placed a high priority on the development of a new vaccine for prevention of JE. Some countries in Asia (Japan, South Korea, North Korea, Taiwan, Vietnam, Thailand, and the PRC) manufacture JE vaccines and practice childhood immunization, while other countries suffering endemic or epidemic disease (India, Nepal, Laos, Cambodia, Bangladesh, Myanmar, Malaysia, Indonesia and the Philippines) have no JE vaccine manufacturing or policy for use. With the exception of the PRC, all countries practicing JE vaccination use formalin inactivated mouse brain vaccines, which are relatively expensive and are associated with rare but clinically significant allergic and neurological adverse events. New inactivated JE vaccines manufactured in Vero cells are in advanced preclinical or early clinical development in Japan, South Korea, Taiwan, and the PRC. An empirically derived, live attenuated vaccine (SA14-14-2) is widely used in the PRC. Trials in the PRC have shown SA14-14-2 to be safe and effective when administered in a two-dose regimen, but regulatory concerns over manufacturing and control have restricted international distribution. The genetic basis of attenuation of SA14-14-2 has been partially defined. A new live attenuated vaccine (ChimeriVax-JE) that uses a reliable flavivirus vaccine--yellow fever 17D--as a live vector for the envelope genes of SA14-14-2 virus is in early clinical trials and appears to be well tolerated and immunogenic after a single dose. Vaccinia and avipox vectored vaccines have also been tested clinically,

but are no longer being pursued due to restricted effectiveness mediated by anti-vector immunity. Other approaches to JE vaccines--including naked DNA, oral vaccination, and recombinant subunit vaccines--have been reviewed.

Zanin MP, Webster DE, Martin JL, Wesselingh SL. Japanese encephalitis vaccines: moving away from the mouse brain. Expert Rev Vaccines. 2003 Jun;2(3):407-16.

Japanese encephalitis (JE) is a severe disease that is widespread throughout Asia and is spreading beyond its traditional boundaries. Three vaccines are currently in use against JE but only one is available internationally, a mouse-brain-derived inactivated vaccine first used in the 1930s. Although this vaccine has been effective in reducing the incidence of JE, it is relatively expensive and has been linked to severe allergic and neurological reactions. Cell-culture-derived inactivated and attenuated vaccines have been developed but are only used in the People's Republic of China. Other vaccines currently in various stages of development are DNA vaccines, a chimeric yellow fever-JE viral vaccine, virus-like particle vaccines and poxvirus-based vaccines. Poxvirus-based vaccines and the chimeric yellow fever-JE vaccine have been tested in Phase I clinical trials. These new vaccines have the potential to significantly reduce the impact of JE in Asia, particularly if used in an oral vaccine delivery strategy.

Mouse-brain derived vaccine

Hoke CH, Nisalak A, Sangawhipa N, Jatanasen S, Laorakapongse T, Innis BL, Kotchasenee S, Gingrich JB, Latendresse J, Fukai K, et al. Protection against Japanese encephalitis by inactivated vaccines. N Engl J Med. 1988 Sep 8;319(10): 608-14

Encephalitis caused by Japanese encephalitis virus occurs in annual epidemics throughout Asia, making it the principal cause of epidemic viral encephalitis in the world. No currently available vaccine has demonstrated efficacy in preventing this disease in a controlled trial. We performed a placebo-controlled, blinded, randomized trial in a northern Thai province, with two doses of monovalent (Nakayama strain) or bivalent (Nakayama plus Beijing strains) inactivated, purified Japanese encephalitis vaccine made from whole virus derived from mouse brain. We examined the effect of these vaccines on the incidence and severity of Japanese encephalitis and dengue hemorrhagic fever, a disease caused by a closely related flavivirus. Between November 1984 and March 1985, 65,224 children received two doses of monovalent Japanese encephalitis vaccine (n = 21,628), bivalent Japanese encephalitis vaccine (n = 22,080), or tetanus toxoid placebo (n = 21,516), with only minor side effects. The cumulative attack rate for encephalitis due to Japanese encephalitis virus was 51 per 100,000 in the placebo group and 5 per 100,000 in each vaccine group. The efficacy in both vaccine groups combined was 91 percent (95 percent confidence interval, 70 to 97 percent). Attack rates for dengue hemorrhagic fever declined, but not significantly. The severity of cases of dengue was also reduced. We conclude that two doses of inactivated Japanese encephalitis vaccine, either monovalent or bivalent, protect against encephalitis due to Japanese encephalitis virus and may have a limited beneficial effect on the severity of dengue hemorrhagic fever.

Nimmannitya S, Hutamai S, Kalayanarooj S, Rojanasuphot S.
A field study on Nakayama and Beijing strains of Japanese encephalitis vaccines. Southeast Asian J Trop Med Public Health. 1995 Dec;26(4):689-93.

A field study to compare the immune response of children aged 1-6 years to Nakayama and Beijing strains JE vaccines was carried out in Mae Hong Son Province, northwest Thailand, where there was low incidence of JEV infection. The first and second dose of each vaccine was given 1-2 weeks apart and the third dose was 1 year after the second dose. Seroconversion rate was similarly high, about 94% in both groups of vaccinees. At 6 and 12 months after 2 doses of vaccines, the seroconversion rates dropped in both groups of vaccinees, so there were 10-20% of children (50-65% if cross protection was considered) susceptible to JEV infections during this period. After the third dose of vaccine, the seroconversion rate rose to 100% in both groups. The GMT in Bejing strain vaccinees were slightly higher than Nakayama strain JE vaccines. To reduce the number of susceptible children during 6-12 months after the second dose and for longer protection, the primary JE immunization should be 3 doses and the timing for the third dose should be at 6 months after the second dose. Either Nakayama or Beijing strain vaccine could be used in Thailand.

Aihara H, Takasaki T, Toyosaki-Maeda T, Suzuki R, Okuno Y, Kurane I.T-cell activation and induction of antibodies and memory T cells by immunization with inactivated Japanese encephalitis vaccine. Viral Immunol. 2000;13(2):179-86.

Mouse brain-derived inactivated Japanese encephalitis (JE) vaccine is the only currently internationally accepted vaccine against JE virus. We analyzed cellular and humoral immune responses to the JE vaccine in healthy adults in order to understand the protective immunity induced by this vaccine. Immunization with the JE vaccine induced T-cell activation in vivo, demonstrated by increase in the plasma levels of interleukin (IL)-2 and soluble CD8. JE virus-specific antibodies determined in radioimmunoprecipitation (RIP), hemagglutination inhibition (HI), and neutralization assays were also induced by immunization with the JE vaccine. JE virus-specific memory T cells were detected 60 days after immunization. These results suggest that protective immunity induced by the inactivated JE vaccine includes JE virus-specific T cells as well as antibodies with multiple biological activities.

Hanna JN, Smith GA, McCulloch BG, Taylor CT, Pyke AT, Brookes DL. An assessment of the interval between booster doses of Japanese encephalitis vaccine in the Torres Strait. Aust N Z J Public Health. 2005 Feb;29(1):44-7.

OBJECTIVE: Japanese encephalitis (JE) emerged for the first time in the Torres Strait, north Australia, in 1995. The inactivated mouse-brain derived JE vaccine was offered to all residents of the outer Torres Strait Islands prior to the 1996 wet season. This study was undertaken to determine the appropriateness of the recommended three-year interval between booster doses of the vaccine. METHODS: JE neutralising antibody was measured in residents of Badu Island for whom 30-36 months had passed since either a previous booster or the completion of the primary immunisation series. RESULTS: Only 70 (32%) of 219 eligible individuals had protective antibodies; 50 (37%) of the adults were immune, compared with 20 (24%) of the children (odds ratio (OR) 1.93; 95% confidence interval (CI) 1.01-3.74). CONCLUSIONS: This low level of immunity suggests that there is little in

the way of natural boosting from either JE or other closely related viruses. Given the apparent low level of risk of exposure to the JE virus in the Torres Strait, and the logistical complexities involved in delivering the booster doses, the current recommendation of a three-year interval is not inappropriate. IMPLICATIONS: It would be advantageous to have a JE vaccine that is not only safer but also more immunogenic, so that it might be possible to further increase the booster dose interval.

Ding D. Kilgore PE. Clemens JD. Liu W. Xu Z-Y. Cost-effectiveness of routine immunization to control Japanese encephalitis in Shanghai, China. Bulletin of the World Health Organization. Vol. 81(5)(pp 334-342), 2003.

Objective: To assess the cost-effectiveness of inactivated and live attenuated Japanese encephalitis (JE) vaccine**s** given to infants and children in Shanghai. Methods: 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. Findings: 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 (US$ 512 456) than that obtained with the P3 vaccine strategy (US$ 348 246). Conclusion: 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.

Yang SE, Pan MJ, Tseng HF, Liau MY. The efficacy of mouse-brain inactivated Nakayama strain Japanese encephalitis vaccine--results from 30 years experience in Taiwan. Vaccine. 2006 Mar 24;24(14):2669-73. Epub 2005 Nov 10

An intensive mandatory vaccination program has been underway, combating Japanese encephalitis (JE) since 1968 in Taiwan. Long-term collection of immunization records has been developed from 1967 to 2000 in this study to retrospectively assess the efficacy of the mouse-brain inactivated Nakayama JE vaccine. The vaccine efficacy (VE) of completing at least two doses of the JE vaccine was 96.98%. Among 1 to 14-year-old children, the efficacy of completing 1, 2, and 3 doses of immunization was 85.59%, 91.07% and 98.51%, respectively. Furthermore, the long-term efficacy for a single dose vaccinated at least 25 years was 86.79%, and for 2 and 3 doses it was 88.10% and 95.54%, respectively. In contrast to previous studies that recommended at least two doses of JE vaccination to acquire necessary protection, the empirical results in this study indicated that even immunization with one single dose provides sufficient protection to the population.

However, a single dose of JE vaccine might still be beneficial for some JE epidemic or endemic developing countries with limited resources for infectious disease control.

Defraites RE. Gambel JM. Hoke CH Jr. Sanchez JL. Withers BG. Karabatsos N. Shope RE. Tirrell S. Yoshida I. Takagi M. Meschievitz CK. Tsai TF. Japanese encephalitis vaccine (inactivated, BIKEN) in U.S. Soldiers: Immunogenicity and safety of vaccine administered in two dosing regimens. American Journal of Tropical Medicine & Hygiene. Vol. 61(2)(pp 288-293), 1999.

The safety and immunogenicity of Japanese encephalitis (JE) vaccine (Nakayama strain, monovalent/BIKEN) was studied in 538 U.S. soldiers in 1990. Three doses of vaccine from three consecutively manufactured lots were given on days 0, 7, and either 14 or 30. Serum for antibody determination was drawn at months 0, 2, and 6. Japanese encephalitis plaque reduction neutralization tests were performed by three laboratories on each specimen. Five hundred twenty-eight (98%) participants completed the immunization series. All recipients without antibody before immunization developed neutralizing antibody against JE virus. There were no differences in geometric mean titer among the three test lots at months 2 and 6. Soldiers who received the third dose on day 30 had higher titers at both time points. Antibody to yellow fever had no significant effect on immune response to vaccine**.** Conclusions drawn from analysis of serologic data from the three labs were nearly identical. Symptoms were generally limited to mild local effects and were reduced in frequency with each subsequent does in the series (21% to 11%; $P < 0.0001$). Generalized symptoms were rare (e.g., fever = 5%) with no reported cases of anaphylaxis.

Sakaguchi M, Miyazawa H, Inouye S. Specific IgE and IgG to gelatin in children with systemic cutaneous reactions to Japanese encephalitis vaccines. Allergy. 2001 Jun;56(6):536-9.

BACKGROUND: Systemic allergic reactions to Japanese encephalitis (JE) vaccine that include urticaria, angioedema, and rash have been reported. In Japan, children who suffered from allergic immediate-type reactions to JE vaccine had antigelatin IgE in their sera. However, the immunologic mechanism of allergic nonimmediate-type reactions that consist of cutaneous signs appearing several hours or more after JE vaccination has not been defined. METHODS: Serum samples were taken from 28 children who showed allergic nonimmediate-type cutaneous reactions to JE vaccine. Furthermore, serum samples were taken from 10 children who showed allergic immediate-type reactions with cutaneous signs and/or respiratory symptoms to JE vaccine. We have defined an immediate-type reaction as one occurring within 1 h after vaccination. RESULTS: Of 10 children who showed immediate-type reactions, all had antigelatin IgE and IgG. Of 28 children who showed systemic nonimmediate-type reactions, one had antigelatin IgE and nine (32%) had antigelatin IgG. The child who had antigelatin IgE showed urticaria 2 h after JE vaccination. CONCLUSION: These results suggest that some children who showed allergic nonimmediate-type reactions to JE vaccine were sensitized to gelatin.

Inactivated Japanese encephalitis virus vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report, 1993, 42 (RR-1): 1-15.

WHO Global Advisory Committee on Vaccine Safety, 9-10 June 2005. Wkly Epidemiol Rec. 2005 Jul 15;80(28):242-7.
http://www.who.int/vaccine_safety/topics/japanese_encephalitis/live attenuated/June_2005/en/

Inactivated PHK cell-derived JE vaccine

Luo D, **Yin H**, **Xili L**, **Song J**, **Wang Z**. **The efficacy of Japanese encephalitis vaccine in Henan, China: a case-control study. Southeast Asian J Trop Med Public Health. 1994 Dec;25(4):643-6.**

A population based case-control study to evaluate Japanese encephalitis (JE) vaccine efficacy was carried out in Gusi County, Henan Province, China from June to September in 1991. This study showed that the JE vaccine had a strong protective effect. The estimate of the vaccine efficacy was 78% (95% CI = 16-94%). An unimmunized child was at 4.54 times greater risk of developing JE than were fully immunized children during the study period. The present study may have underestimated the vaccine efficacy due to evaluation based on routine vaccination which might have been affected by vaccination management and the local cold chain system.

Live attenuated vaccine

Tsai TF. Yong-Xin Y. Jia Li Li. Putvatana R. Ran Z. Shougui W. Halstead SB. Immunogenicity of live attenuated SA14-14-2 Japanese encephalitis vaccine - A comparison of 1- and 3-month immunization schedules. Journal of Infectious Diseases. Vol. 177(1)(pp 221-223), 1998.

Live attenuated SA14-14-2 Japanese encephalitis **(**JE) vaccine has been safe and effective in > 100 million immunized children, but its current administration schedule of two doses given a year apart does not lend itself to inclusion in established Expanded Program of Immunization (EPI) schedules of childhood immunization. Immune responses to immunization at shorter intervals were compared in middle-school-aged children immunized with two doses separated by 1 month (n = 116) or 2.5 months (n = 115). Two vaccine lots were compared. Seroconversion to the vaccine was observed in 100% of vaccine**es** immunized in the 1-month schedule and in 94% (lot 2) and 100% (lot 1) of vaccinees immunized in the 2.5-month schedule. Geometric mean titers were almost 2-fold higher with the longer schedule. The routine administration of JE SA14-14-2 vaccine to infants in an EPI schedule should be possible using either interval.

Liu Z-L. Hennessy S. Strom BL. Tsai TF. Wan C-M. Tang S-C. Xiang C-F. Bilker WB. Pan X-P. Yao Y-J. Xu Z-W. Halstead SB. Short-term safety of live attenuated Japanese encephalitis vaccine (SA14-14-2): Results of a randomized trial with 26,239 subjects. J Infect Dis. 1997 Nov;176(5):1366-9

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 <=3 days. These data attest to the short-term safety of the SA14-14-2 virus strain and the hamster kidney cell substrate.

Jia L, Wang Z, Yu Y. Protection of SA14-14-2 live attenuated Japanese encephalitis vaccine against the wild-type JE viruses. Chin Med J (Engl). 2003 Jun;116(6):941-3.

OBJECTIVE: To explore on the immunity of live attenuated Japanese Encephalitis (JE) vaccine (SA14-14-2) to different wild JE virus (JEV) strains. METHODS: The neutralizing effect of the vaccine against different wild JE virus strains was detected by plaque reduction neutralization test (PRNT), and the immunogenicity was studied on mice by vaccination - challenge protection test. In the PRNT, pooled sera from vaccinated human were tested against 10 strains of JEV, one isolated in Taiwan and 9 from other Asian countries.In the vaccination challenge test, mice received one dose of the live vaccine subcutaneously and were challenged intraperitoneally 14 days later against 22 JEV virus strains, 11 were isolated in China and the other 11 from Tailand, Vietnahailam, Indonesia, India, Philippines and Japan. RESULTS: The protection rates to all the 22 challenge virus were 90% - 100% when 340 PFU/0.1 ml vaccinate virus was administered. The neutralizing effect showed that all the JEV isolates many have neutralized by the sera. CONCLUSION: SA14-14-2 live attenuated prepared with strain SA14-14-2 is broadly immunogenic and may have effective protection against in Asian JE affected countries.

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

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.

JE - vaccines under development

Bharati K, Vrati S. Japanese encephalitis: development of new candidate vaccines. Expert Rev Anti Infect Ther. 2006 Apr;4(2):313-24.

Japanese encephalitis (JE) is the most common form of viral encephalitis that appears in the form of frequent epidemics of brain fever throughout Southeast Asia, China and India. The disease is caused by a Flavivirus named Japanese encephalitis virus that is spread to humans by mosquitoes. An internationally approved mouse brain-derived inactivated vaccine has been available that is relatively expensive, gives immunity of uncertain duration and is not completely safe. Cell culture-derived inactivated and attenuated JE vaccines are in use in China, but these are not produced as per the norms acceptable in most countries. Several new promising JE vaccine candidates have been developed, some of which are under different stages of clinical evaluation. These new candidate JE vaccines have the potential to generate long-lasting immunity at low cost.

Monath TP, Guirakhoo F, Nichols R, Yoksan S, Schrader R, Murphy C, Blum P, Woodward S, McCarthy K, Mathis D, Johnson C, Bedford P. Chimeric live, attenuated vaccine against Japanese encephalitis (ChimeriVax-JE): phase 2 clinical trials for safety and immunogenicity, effect of vaccine dose and schedule, and memory response to challenge with inactivated Japanese encephalitis antigen. J Infect Dis. 2003 Oct 15;188(8):1213-30. Epub 2003 Oct 3.

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 log(10)) 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-naive 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.

Hombach J, Solomon T, Kurane I, Jacobson J, Wood D. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2-3 September, 2004. Vaccine. 2005 Nov 1;23(45):5205-11. Epub 2005 Jul 18.

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.

WHO documents on Japanese encephalitis vaccines

Japanese encephalitis vaccine, inactivated
Title: Requirements for Japanese Encephalitis Vaccine (Inactivated) for Human Use; Adopted 1987, TRS No 771, Annex 6
http://www.who.int/biologicals/publications/trs/areas/vaccines/jap_encephalitis/WHO_TRS_771_(part2)_A6.pdf

Japanese encephalitis vaccine, live attenuated
Title: Guidelines for the production and control of Japanese encephalitis vaccine (live) for human use, Adopted 2000, TRS No 910, Annex 3
http://www.who.int/biologicals/areas/vaccines/jap_encephalitis/WHO_TRS_910_A3.pdf

WHO document: Initiative for vaccine research (IVR). Vector-borne Viral Infections. Japanese encephalitis.
http://www.who.int/vaccine_research/diseases/vector/en/index1.html

Japanese encephalitis (JE). Immunization service delivery and accelerated disease control. http://www.who.int/immunization_delivery/new_vaccines/je/en/

Report of the Bi-Regional Meeting on Japanese Encephalitis (WHO SEA/WPR and PATH's JE Project). New Delhi, 2005. SEA-CD-142
http://www.wpro.who.int/NR/rdonlyres/A62D4A75-0C28-4093-95CF-555CE379C469/0/MTGRPT_BiregionalJE2005.pdf