REPORT

THIRD BIREGIONAL MEETING ON CONTROL OF JAPANESE ENCEPHALITIS

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NOTE

The views expressed in this report are those of the participants of the Third Biregional Meeting on Control of Japanese Encephalitis and do not necessarily reflect the policies of the World Health Organization and Program for Appropriate Technology in Health.

Keywords:

Immunization / Poliomyelitis – prevention and control / Measles – prevention and control / Hepatitis B – prevention and control / Tetanus – prevention and control

This report has been printed by the Regional Office for the Western Pacific of the World Health Organization for the participants of the Third Biregional Meeting on Control of Japanese Encephalitis, which was held in Ho Chi Minh City, Viet Nam, from 26 to 27 April 2007.
# LIST OF ACRONYMS

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<tr>
<td>AEFI</td>
<td>adverse event following immunization</td>
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<tr>
<td>AES</td>
<td>acute encephalitis syndrome</td>
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<tr>
<td>AFP</td>
<td>acute flaccid paralysis</td>
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<td>AFRIMS</td>
<td>Armed Forces Research Institute of Medical Sciences</td>
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<tr>
<td>CDIBP</td>
<td>Chengdu Institute of Biological Products</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<tr>
<td>EWARS</td>
<td>Early Warning and Reporting System</td>
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<td>GACVS</td>
<td>Global Advisory Committee on Vaccine Safety</td>
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<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunization</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>HMIS</td>
<td>Health Management Information System</td>
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<td>IgM</td>
<td>Immunoglobuline M</td>
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<td>JE</td>
<td>Japanese encephalitis</td>
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<td>JeVa</td>
<td>Japanese Encephalitis Vaccine Planning Tool</td>
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<td>ME</td>
<td>meningoencephalitis</td>
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<td>NIPH</td>
<td>National Institute of Public Health</td>
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<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>PRNT</td>
<td>Plaque Reduction Neutralization Testing</td>
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<td>SAE</td>
<td>serious adverse events</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<td>US CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
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<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>VPD</td>
<td>vaccine preventable disease</td>
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<tr>
<td>WARUN</td>
<td>Walter Reed/AFRIMS Research Unit Nepal</td>
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<td>WHO</td>
<td>World Health Organization</td>
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SUMMARY

The Third Biregional Meeting on Control of Japanese Encephalitis (JE) was held in Ho Chi Minh City, Viet Nam from 26 to 27 April 2007. Efforts to control JE through immunization have grown significantly since the second biregional meeting in 2005, which was also hosted by the World Health Organization (WHO) and Program for Appropriate Technology in Health (PATH). Despite significant advances, the burden of JE is still great in many countries of the Western Pacific and South-East Asia regions.

The objectives of the workshop were:

1. to review progress made by countries in JE control through immunization;
2. to share, update and develop a consensus on the latest developments in surveillance standards, laboratory diagnostics and immunization strategies; and
3. to reach an agreement on activities over the next two years towards JE control in individual countries.

Defining the burden of JE illness through routine surveillance is the first step towards informing country-level decisions about JE vaccine introduction. Several countries have initiated or enhanced JE surveillance by integrating it in routine reporting systems, and WHO’s standards for acute encephalitis surveillance have facilitated this process. Participants offered valuable input towards the further refinement of these surveillance standards. Challenges still remain, however, in particular with regard to the collection and testing of samples and the complexities of laboratory diagnostics. The recent development of the JE laboratory network will assist in providing support and guidance to countries. The impact of long-term disability on those that survive JE infection was recognized as very important in regard to understanding overall JE disease burden. Methods for evaluating disability were discussed, and a related tool developed by the University of Liverpool is currently being refined through field evaluation.

The response to a significant JE outbreak in 2005 in Nepal and India helped lay groundwork for planning and implementation of new JE immunization programmes in these two countries. Responding with unprecedented speed, the national governments of both countries introduced the SA 14-14-2 vaccine through campaigns before the onset of the monsoon season. More than 11 million children were vaccinated in 2006. These experiences—coupled with the affordability of the SA 14-14-2 vaccine—are encouraging other endemic countries throughout the two regions to introduce JE vaccine. Lessons learnt and continued implementation of long-term strategies, in which campaigns are followed by inclusion of JE vaccine in the country’s routine EPI, were among several important presentations made to the group.

Investigators presented data that are expanding the safety and efficacy profiles of available JE vaccines and providing information on how JE vaccine can best be included in routine immunization programmes. Recent studies have yielded crucial information on the SA 14-14-2 vaccine, including the acceptability of co-administration with measles vaccine, demonstrating that the SA 14-14-2 vaccine can be given at a routine EPI visit; long-term efficacy; and extended safety, reactogenicity, and immunogenicity data following introduction in new areas. Information was presented on several other JE vaccines in development, including tentative timelines for their availability in the global market.

Identifying financial support for JE vaccine introduction is an important element of developing control plans. Representatives from several countries presented their individual strategies. Countries considering the introduction of JE vaccine felt their national governments could support the costs of a routine programme given the affordable price of the SA 14-14-2 vaccine, but initial campaigns would require external financial support. Donor support will be key to advancing the agenda. As such, options for identifying external resources and fostering partnerships were central elements of discussion.
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1. INTRODUCTION

The Third Biregional Meeting on Japanese Encephalitis (JE), organized by the Program for Appropriate Technology in Health (PATH) and World Health Organization (WHO), was held from 26 to 27 April 2007 in Ho Chi Minh City, Viet Nam. The first biregional JE meeting was held in 2002, and a second meeting was organized in March 2005. Since then, much progress has been made towards generating new empirical data, developing new standards and manuals in laboratory diagnostics and surveillance, and assessing alternative JE vaccines. Key accomplishments in each area are listed below.

(1) Surveillance

- WHO JE surveillance standards were published as a field-test version and used to initiate or enhance surveillance activities in Indonesia, India, Cambodia, Viet Nam and Nepal. The standards will be fine-tuned based on feedback and suggestions from this meeting.

(2) Diagnostics and laboratory

- A laboratory network was established in the WHO South-East Asia Region to provide technical assistance, training, quality assurance and diagnostic confirmation. A similar resource is planned for the Western Pacific Region.
- Studies were completed on comparison of diagnostic kits—under reference laboratory and field conditions—with results pending publication.
- A laboratory manual was developed.

(3) Immunization strategies

- Surveillance was intensified in several countries to collect data for immunization planning purposes. Key data included age, geographic location of patient, and disease outcome.
- JE vaccines were introduced in selected endemic districts of India and Nepal using the recommended strategy of one-time preventive campaigns, followed by the planned introduction into the Expanded Programme on Immunization (EPI). More than 11 million people in high-risk districts were reached in one-time preventive campaigns in 2006.
- Operational guidelines were published for the introduction of SA 14-14-2 JE vaccine in the South-East Asia Region.
- Systems were strengthened in India and Nepal for monitoring adverse events following immunization (AEFIs).

(4) Coordination and promotion of JE control

- Documents and data were collected for preparation of an investment case for JE vaccines.
- A demand model was developed to inform programme planning at global and country levels.
National capacities for JE control were strengthened and international awareness grew.

The WHO Advisory Committee on Flavivirus and Dengue Vaccines and other advisory groups presented clinical trial data on SA 14-14-2 vaccine. Several studies were completed or were in progress based on guidance provided.

1.1 Objectives

(1) Review progress made by countries in JE control through immunization.

(2) Share, update and develop a consensus on the latest developments in surveillance standards, laboratory diagnostics and immunization strategies.

(3) Reach an agreement on activities over the next two years towards JE control in individual countries.

1.2 Participation

More than 90 participants attended the meeting, with representation from several endemic countries in the Western Pacific and South-East Asia Regions. Technical officers, investigators, and other staff represented research and academic institutions, nongovernmental organizations, United Nations Children's Fund (UNICEF), the United States Agency for International Development (USAID), the United States Centers for Disease Control and Prevention (US CDC) and PATH, among others. A complete list of attendees and the meeting’s agenda are provided in Annexes 1 and 2, respectively.

1.3 Opening remarks

A joint message presented on behalf of Dr Shigeru Omi and Dr Samlee Plianbangchang, WHO Regional Directors for the Western Pacific and South-East Asia, respectively, emphasized the importance of vaccination as the most effective strategy for prevention and control of JE. It also noted that limited vaccine options, a lack of WHO pre-qualified vaccines for JE, and a lack of appreciation of public health importance and disease burden of JE due to weak surveillance systems have constrained the expansion of JE immunization in endemic countries.

Partnerships are key to overcoming these challenges. The future of JE control is promising, boosted by the ongoing development of several vaccine candidates, increased availability of a safe and affordable vaccine, updated recommendations from WHO, and improved disease burden data.

2. PROCEEDINGS

2.1 Overview of JE in the Western Pacific and South East Asia Regions

2.1.1 JE in the Western Pacific Region

The Western Pacific Region, with a total population of 1.8 billion, comprises 36 countries and areas. None of the 20 Pacific island countries and areas is considered endemic for JE. Out of the other 16 countries and areas, six are not considered endemic (Australia, Brunei Darussalam, New Zealand, Hong Kong [China], Macao [China], and Mongolia) and Singapore
has reported few sporadic cases in last few years. The total number of cases reported by the endemic countries has declined by almost 72% from 25,431 cases reported in 1991, to 7,130 cases reported in 2005. More than 99% of these reported cases come from China and Viet Nam (99.9% in 1991 and 99.3% in 2005). The cases reported from China varied from 23,618 (93% of regional cases) in 1991 to 5,217 (73% of total regional cases) in 2005. The cases reported from China increased in 2006 to 7,643. On the other hand, the number of cases reported from Viet Nam varied from 1,795 in 1991, to 1,866 in 2005. Fewer than 10 cases were reported annually from Japan and the Republic of Korea—the two countries that reported a very high number of cases between the 1950s and 1980s but controlled the disease successfully with nationwide immunization programmes. Data are not routinely collected by some countries considered to be endemic, including the Lao People's Democratic Republic, Cambodia, Papua New Guinea and the Philippines, and therefore regional estimates are not complete. Cases reported may underestimate disease burden in countries where surveillance systems are poorly functioning. On the other hand, reporting from some countries (e.g. China, Viet Nam) may overestimate JE disease burden by including all cases of viral encephalitis. Several challenges inhibit accurate measurement of disease burden of JE disease in the Western Pacific Region, including limited laboratory capacity and a lack of awareness in countries where outbreaks are not common but the disease is potentially endemic.

Almost all the countries in the Western Pacific Region with reported JE outbreaks are using vaccines nationwide or in selected high-risk provinces. Japan and the Republic of Korea have implemented comprehensive JE immunization programmes, and the related impact is apparent in surveillance figures. For example, targeted vaccination in Japan began as early as 1954 and expanded into a universal immunization programme. Today, fewer than 10 cases are reported annually. The Republic of Korea has achieved a similar decline in JE cases.

China, Viet Nam and Malaysia have also introduced immunization programmes. As of 2006, China has provided JE immunization as part of its EPI in 16 of 31 provinces. Different vaccines and schedules are employed, but continuing progress is being made. Almost 50% of districts in Viet Nam have introduced the JE vaccine for children under five years of age since phased introduction commenced in 1997; nonetheless, Viet Nam still reports the second highest number of cases in the Region with no consistent declining trends in the reported number of viral encephalitis cases since 1991. In Malaysia, immunization is provided in select provinces to children one to 15 years of age living within two kilometres of a pig-rearing farm and to all persons living on pig farms.

Progress is underway to strengthen control of JE in the Western Pacific Region, including addressing challenges to measuring the disease burden in countries considered to be endemic but with no systematic estimates of annual disease incidence (Cambodia, Lao People's Democratic Republic, Philippines, Papua New Guinea). Additional progress is evident in increased accurate case reporting, strengthened laboratory capacities, and the establishment of a regional laboratory network. Disease burden data from countries considered to be endemic will be critical to providing decision-makers with the information they need to determine the appropriateness of introducing JE vaccines. There is also consideration or planning for expansion of JE immunization in countries with programmes that target only select areas for vaccination (e.g. Viet Nam, China, Malaysia), based on demonstration of disease burden in other areas. Other than challenges with collection of disease burden data and therefore lack of disease visibility, other barriers to expansion of JE control through immunization in the Western Pacific Region include competing disease priorities, lack of strong routine immunization services in some countries, and the need to mobilize resources for new vaccine introduction, although the affordable price for the SA 14-14-2 JE vaccine is an advantage.
The next steps for JE control in the Region include: (1) raising awareness of disease among policy-makers, supported by data collected through strengthened surveillance; (2) assessing the cost-effectiveness of JE immunization programmes; (3) using disease burden and disability data to mobilize resources for JE control; and (4) strengthening routine immunization systems to improve coverage.

2.1.2 JE in the South-East Asia Region

The South-East Asia Region comprises 11 countries with almost 1.5 billion total populations. The public health importance of the disease in the South-East Asia Region was illustrated by the 2005 JE season in India and Nepal. Between the two countries, almost 9000 acute encephalitis syndrome (AES) cases were reported with more than 1700 deaths. Official reported data underestimate disease burden in the Region, as currently only three of 11 countries report cases to the WHO Regional Office through Vaccine Preventable Disease (VPD) monthly reporting: Nepal, Sri Lanka and Thailand. In 2006, these three countries reported a total of 1921 AES cases: 1477 in Nepal, 131 in Sri Lanka, and 313 in Thailand.

The typical challenges to surveillance are confronted in the Region, including the need for laboratory diagnostics to differentiate JE from other AES aetiologies, the cross reactivity of JE virus with other flaviviruses in most immunological tests, the high asymptomatic–symptomatic ratio, and the characteristic cyclical pattern of JE outbreaks, which means that surveillance for JE must be a year-round, long-term effort. Current activities at various levels of intensity throughout the Region include syndromic AES surveillance, sentinel site surveillance for JE, and entomological surveillance, as well as serosurveys.

Control efforts vary widely among countries in South-East Asia Region. Thailand, Nepal, Sri Lanka and India have all taken steps to control disease through immunization and have surveillance data to support and inform the immunization programme. Thailand and Sri Lanka have strong immunization programmes, and data from integrated surveillance systems direct programme decision-making. Nepal conducted JE vaccination campaigns in July/August 2006, immunizing more than 2.2 million population in JE endemic districts in the Terai region. Likewise, India conducted JE vaccination campaigns in 2006, reaching more than 9.0 million children. Bangladesh is developing a sentinel surveillance system. Unfortunately, other countries in the Region do not have specific surveillance systems or control programmes.

Initiatives to improve control of JE in the South-East Region have included the development of regional guidelines for JE surveillance and vaccine introduction, the addition of AES as a reportable condition in the monthly VPD reporting system, support for the development of global standards for laboratory diagnosis, and the establishment of a regional laboratory network to develop skills and capacity for JE diagnosis (further information on this network may be found in Section 4.5). Improving capacity for identifying other AES aetiologies beyond JE will be a next step. Future efforts to improve reporting and data management will include integrating JE with other VPD reporting systems and establishing a regional system for case investigation and data management.

2.2 Defining disease burden through surveillance for JE diseases

2.2.1 Assessment of the JE surveillance standards

WHO published a field-test version of the JE surveillance standards in 2006, with input collected through previous biregional meetings and interaction with country-level stakeholders. Several countries have already adapted the standards as a way to enhance or establish JE surveillance.
The standards use AES as the basis for JE surveillance and define a case of AES as “a person of any age, at any time of the year, with the acute onset of fever and a change in mental status or new onset seizures (excluding simple febrile seizures)”\(^1\). Since clinical signs of JE are indistinguishable from other causes of AES, laboratory confirmation is essential for further classification of AES cases as “confirmed”, “probable”, “AES – other agent” or “AES – unknown.” An AES case is confirmed as JE by the “detection of JE virus-specific antibody in a single sample of cerebrospinal fluid (CSF) or serum.”

To evaluate the sensitivity and specificity of using AES as the starting point for assessing JE disease burden, as well as the appropriateness of the definition’s laboratory component, a team from the University of Liverpool applied the case definition, with single blinding, to an existing cohort of patients with suspected central nervous system (CNS) infections in southern Viet Nam, where JE and dengue are endemic. The patients had a detailed clinical and virological work-up as part of previous prospective studies. Out of 380 patients reviewed, 54 children and nine adults were confirmed to be positive for JE. Some important findings were as follows:

- The AES clinical case definition identified JE-infected children with neurological disease with a sensitivity of 65% and specificity of 39%. Adding limb paralysis and meningism to the case definition would have identified 53 of 54 JE-infected children, but would have lowered the specificity. Among adults, the definition was 100% sensitive but specificity was only 16%.

- Not all the recommended samples (paired sera and CSF, as per the surveillance standards) were collected in 63 cases diagnosed as JE positive. An acute serum sample diagnosed 41 of 60 JE-positive patients (68%), and a CSF sample taken upon admission diagnosed 33 of 46 patients (72%), including seven that were serum negative. Examining a second serum sample at day 10 would have diagnosed 61 of 62 patients. One case was diagnosed only by immunohistochemistry.

- For patients who had both serum and CSF collected on the same day and for whom CSF was JE IgM positive, serum JE IgM was positive for 24 of 31 (i.e. 77% sensitive).

- Five patients with suspected CNS infection had positive serum for JE as well as dengue IgM. In fact, the levels of dengue IgM were higher than those of JE IgM. These cases would have been misdiagnosed if tests for dengue antibodies were not run in parallel, or if only CSF was tested (as CSF in all these five cases was negative). Hence the surveillance standards should include parallel testing for dengue, especially in dengue-endemic countries.

Input from meeting representatives was encouraged. These discussions, as well as the findings from the University of Liverpool’s evaluation, will guide refinements to the WHO standards.

2.2.2 Country experiences in the Western Pacific Region

Cambodia

Several research studies conducted since the 1990s have demonstrated the presence of JE disease in Cambodia; however, most were limited in duration or extent. In 2005, the Communicable Disease Control (CDC) Department of the Ministry of Health introduced national weekly reporting of clinical meningoencephalitis (ME) cases along with 11 other diseases and/or clinical syndromes, as part of a national outbreak surveillance and response system. The system was geared towards the detection of epidemics rather than measurement of disease burden.

In May 2006, the CDC Department launched JE sentinel site surveillance, involving six hospitals from six different provinces and focusing on children under 15 years of age, using the clinical case definition of ME as used in the outbreak surveillance and response (OSR) system. The hospitals are responsible for collecting epidemiological data and samples (CSF and two serum samples). The National Institute of Public Health (NIPH) then tests the samples for dengue and JE using the Panbio JE-dengue combo enzyme-linked immunosorbent assay (ELISA) test kits. Among 240 cases reported during the first 11 months of surveillance, JE-positive cases were reported from all six sites, and 17% of recruited ME cases tested positive for JE. Most JE-positive cases (80%) occurred in children under 10 years of age. In addition, about 18% of cases tested positive for dengue, mostly from serum samples. The CDC Department plans (1) to strengthen routine and JE-specific surveillance to enable better determination of national JE incidence, and (2) to actively follow up cases to better measure the mortality and disability resulting from JE disease. Coupled with a study on the cost-effectiveness of vaccine introduction, data collected through surveillance will help develop future policy on JE control through immunization.

Viet Nam

In Viet Nam, JE is one of 24 notifiable communicable diseases to be reported weekly by all hospitals based on the clinical diagnosis of acute viral encephalitis (both cases and deaths). Only 10 out of 64 provinces have capacity to confirm a diagnosis with laboratory testing, and even in these provinces not all cases of viral encephalitis may be laboratory tested. The majority of testing is performed at regional or national facilities. Reporting is still considered to be incomplete, and significant challenges with JE surveillance in Viet Nam include limited resources and the high incidence of disease in hard-to-reach, mountainous provinces.

In 2005-2006, three JE sentinel surveillance sites were established in northern Viet Nam, and laboratory testing demonstrated that approximately 30% of all viral encephalitis cases were due to JE. Two additional sites, one in the north and another in the south, are piloting new surveillance guidelines developed by the national EPI, with support from PATH. These two additional sites are using the Panbio JE-dengue combo ELISA test kits. Between September 2006 and February 2007 (non-JE season), 88 AES patients were enrolled and four (4.5%) tested positive for JE IgM. All sentinel surveillance sites used the standard WHO clinical case definition for AES to enrol patients. Data indicate that approximately two-thirds of all cases occurred in males, and only about 70% of all cases recover completely.

Viet Nam has seen little reduction in the overall incidence of viral encephalitis since 1991, although the age distribution of JE cases has shifted with the introduction of a targeted immunization programme. Approximately two-thirds of cases are now seen in five- to 14-year-olds, compared with 84% of cases in children one to nine years of age prior to the commencement of immunization. Future plans include extending JE sentinel site surveillance and improving the capacity for diagnostic testing at province level.
**Malaysia (Sarawak state)**

Sarawak is the largest of 16 states in Malaysia. It is also one of a few states considered endemic for JE, with interspersed epidemics. Since 2001, the EPI has been administering inactivated, mouse brain-derived JE vaccine in Sarawak to 12-month-old infants living within 2 km of a pig farm, as well as to household contacts (aged one to 15 years) of JE cases. The decision to introduce JE vaccine was made based on surveillance data collected between 1997 and 2000. Surveillance has been conducted since 1997 through a hospital-based study in Sibu and through passive surveillance at all other hospitals in the state since 1998. The data show occurrences of cases year-round, with a peak in the fourth quarter each year. Surveillance for JE in Malaysia has demonstrated the impact of targeted vaccine introduction in Sarawak. Since 2001, data have revealed a reduction in annual JE incidence by more than half (from 9.8 to 4.3 cases per 100 000 children 12 years of age and under) in central Sarawak. Close monitoring has provided insight into gaps in the surveillance programme. For example, after an outbreak of Nipah virus in 1999, awareness among community members and health workers was significantly heightened. Over several months during the outbreak, the surveillance system marked a dramatic increase in JE cases reported—up to four times the normal figures—illustrating the need for improvement in routine surveillance.

2.2.3 Country experiences in the South-East Asia Region

**Nepal**

Nepal established passive surveillance for viral encephalitis in 1978 as part of the Early Warning and Reporting System (EWARS) and Health Management Information System (HMIS), following the country’s first recorded epidemic of JE disease. Between 1978 and 2004, a total of 27 584 cases of viral encephalitis and 5382 deaths were reported through HMIS. In 2004, it was integrated with acute flaccid paralysis (AFP) surveillance, and the WHO standard case definition for AES was adopted. A total of 93 sentinel sites were developed throughout all districts in the country. Sentinel sites from 71 of 75 districts submit weekly reports on number of AES cases, with monthly reports from the four remaining districts in inaccessible areas. In addition, medical officers assigned for AFP surveillance review AES cases during weekly active surveillance visits to 83 sites. Two laboratories (one national and one regional) confirm diagnoses using IgM capture ELISA, and in 2006, an 86% testing rate of AES cases was achieved. In 2004, 2005 and 2006, laboratory-confirmed JE cases as a percentage of total AES cases were 36%, 34%, and 23%, respectively. JE cases increase seasonally with a peak in August and are primarily recorded in the Terai region of the south, but incidence has recently begun to increase in Kathmandu Valley. Interestingly, data from Nepal reveal a high percentage of cases among adults, with 44% of all cases occurring in persons 15 years of age and older from 2004 to 2006. Among the patients followed up, the case-fatality rate was about 15% in 2004 and 2006 and slightly lower (11%) in 2005. Issues to be resolved in strengthening AES surveillance include collection of properly timed specimens, collection of CSF samples (current surveillance mostly uses single serum samples), establishing the aetiology of JE-negative AES cases, and ruling out cross-reactivity with other flaviviruses, including dengue.

**Indonesia**

Research studies indicating the presence of JE disease in Indonesia have been undertaken since the 1970s, including inclusion of reporting of ME cases through the routine surveillance system. Systematic, longer-term surveillance studies were initiated more recently in nine pilot provinces on six islands through partnerships with PATH and International Vaccine Institute.
Results from a six-province surveillance study, conducted from 2005 to 2006, proved JE to be endemic in Indonesia, with cases confirmed in all sites, stretching from Sumatra in the west to Papua in the east. The total number of confirmed JE cases as a proportion of AES cases varied from 1.7% to 17.8% in different provinces, with an average of 5.5% over two years. Disease burden in children under five years of age was high, with 71% of confirmed JE cases occurring in this age group, and the impact was serious. Data show a case fatality rate of 16%, and preliminary results of case follow-up show 33% of surviving JE patients were unlikely to be able to lead an independent life. Indonesia uses the WHO AES case definition to ensure that cases are not missed. In less than 50% of cases, “viral encephalitis” was clinically diagnosed by physicians on discharge, before JE ELISA results were available (see Figure 1). Indonesia plans to strengthen routine ME surveillance and continue sentinel JE surveillance at specific sites. However, challenges include the vast geographical extent of the country, which creates difficulties for specimen transport and testing, as well as a limited capacity for CSF collection and testing in more peripheral areas.

The impact of disease burden data on informed programme decision-making is well-illustrated in Indonesia. For example, with the implementation of surveillance in Bali, the Ministry of Health was able to determine that JE vaccine introduction would be a cost-effective measure. It is planning to introduce JE live attenuated SA 14-14-2 vaccine in Bali through the public sector in 2008.

Figure 1. Clinical diagnosis of JE positive cases prior to laboratory test results (n=82)

Note: This chart emphasizes the importance of using the WHO standard case definition for JE rather than relying solely on physician diagnosis. Without application of the case definition, more than half of JE cases would have been misdiagnosed. It also emphasized that JE symptoms are not specific and laboratory confirmation is necessary to confirm cases.

Source: Dr Jane Soepardi, Indonesia Ministry of Health
2.2.4 Measuring the burden of JE disability

Efforts are growing to determine the mortality associated with JE in endemic regions, but the impact of disability among JE survivors has long been a neglected area of an already neglected disease. The generally accepted rate of neurological sequelae following JE is around one-third of survivors, but studies show wide variations depending on a number of factors including the age group of those assessed, the time after illness, the quality of acute care, selection biases and lack of a standard tool to measure disability. The need for guidelines and directed efforts for evaluating and caring for those disabled by JE is great. The measurement of JE morbidity can also offer important information for decision-makers on the potential benefits of JE vaccine introduction.

Investigators from the University of Liverpool’s Viral Brain Infections Group developed the Liverpool Outcome Score to quantify JE disability with a standardized measurement of outcomes, primarily focused on whether a survivor will be able to live independently. The tool was developed to be used in several different cultural settings by health care workers and non-specialists in order to identify a patient’s needs.

The Liverpool Outcome Score is generated through interviews with caregivers and observations of children regarding various indicators of child development, in addition to a simple examination of function. For example, questions are posed on speech, feeding, dressing, and behaviour, and children are observed performing simple physical tasks. Answers are scored on a scale of 1 to 5, with 1 indicating death and 5 indicating normal function as compared to the child’s peers (Table 1).

<table>
<thead>
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<th>Table 1: Liverpool Outcome Score</th>
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<tbody>
<tr>
<td><strong>Ask the parent or caregiver:</strong></td>
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<tr>
<td>• Speech and communication</td>
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<tr>
<td>• Feeding</td>
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<tr>
<td>• Whether the child can be left alone</td>
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<tr>
<td>• Behaviour</td>
</tr>
<tr>
<td>• Recognition of people and things</td>
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<tr>
<td>• School and/or work</td>
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<tr>
<td>• Epilepsy</td>
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<tr>
<td>• Dressing</td>
</tr>
<tr>
<td>• Bladder and bowel control</td>
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<tr>
<td>• Hearing</td>
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<tr>
<td><strong>Observe the child:</strong></td>
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<tr>
<td>• Sitting</td>
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<tr>
<td>• Standing</td>
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<tr>
<td>• Walking</td>
</tr>
<tr>
<td>• Putting hands on head</td>
</tr>
<tr>
<td>• Picking things up (pincer grip)</td>
</tr>
<tr>
<td><strong>For each of the 15 questions/observations, provide a score of 1, 2, 3, 4 or 5:</strong></td>
</tr>
<tr>
<td>5 = Completely normal</td>
</tr>
<tr>
<td>4 = Minor sequelae often not noticed by the child</td>
</tr>
<tr>
<td>3 = Moderate sequelae, which affect function but are probably compatible with independent living</td>
</tr>
<tr>
<td>2 = Severe sequelae, which impair function sufficiently to make the child dependent</td>
</tr>
<tr>
<td>1 = Child died</td>
</tr>
<tr>
<td><strong>Overall outcome score: The single lowest score for any item for that child:</strong></td>
</tr>
<tr>
<td>5 = Full recovery and normal neurological examination</td>
</tr>
<tr>
<td>4 = Minor sequelae not affecting function or personality change on medication</td>
</tr>
<tr>
<td>3 = Moderate sequelae mildly affecting function compatible with independent living</td>
</tr>
<tr>
<td>2 = Severe sequelae, greatly impairing function, likely to make patient dependent</td>
</tr>
<tr>
<td>1 = Death</td>
</tr>
</tbody>
</table>

Source: Dr Penny Lewthwaite, University of Liverpool (www.liv.ac.uk/braininfections).
The tool is being validated among children in India and Malaysia. The results from the tool are being compared with results from a detailed assessment by a multidisciplinary team that includes a neurologist or paediatrician and an occupational therapist. Preliminary results reveal high sensitivity and specificity in identifying those that are likely to be dependent or independent. Inter- and intra-observer variability is also being evaluated. Complete results are expected to be published in 2007. A field-test version is available for use in JE endemic countries, and the score’s developers are collecting feedback to further refine the tool.

2.2.5 The JE laboratory network and resource development

Laboratory testing plays an important role in diagnosis of JE. The case definition for JE surveillance has low specificity and includes all AES cases, making laboratory confirmation essential. However, there are many challenges to laboratory diagnosis, including serological cross-reactivity within the flavivirus family, a JE antibody response where 95% IgM positivity is only reached 10 days after disease onset, the lack of usefulness of virus or antigen detection methods, and the small number of validated assays available commercially.

The recently established JE laboratory network will therefore play a critical role in strengthening and supporting JE diagnostic work. The network is being developed based on best practices and infrastructure of other WHO laboratory networks for vaccine-preventable diseases, such as measles and polio. An important element of a laboratory network is to ensure standardization of procedures. The newly developed JE laboratory manual will include standards for specimen collection and transport, principles of testing and data management, the roles and responsibilities of the laboratory in JE control, etc. Other benefits provided through the laboratory network include facilitated communication, enhanced coordination, training, quality assurance, infrastructure development, and differential diagnosis. A JE laboratory working group is an integral part of the network and includes participants from WHO, US CDC, PATH, University of Liverpool, and other experts.

In the last two years, several JE assay evaluations with serum and CSF were conducted to facilitate the availability of standardized, validated IgM ELISA assays. Results showed that for serum samples collected in non-dengue endemic areas, any of the three commercial kits demonstrated good sensitivity and specificity; however, in dengue-endemic areas, the Panbio assay discriminated best between recent dengue and JE infections. For CSF samples, the Xcyton JEV Chex assay showed good correlation with the CDC ELISA assay. Further evaluation of assays is required, including field assessments and evaluations with larger panels of CSF samples. The importance of referral laboratories to enable confirmatory testing also was emphasized in these evaluations.

**JE laboratory network in the South-East Asia Region**

Since 2005, significant progress has been made with the development of a JE laboratory network in South-East Asia. Potential network laboratories have been identified, and in most countries, these laboratories are already a part of the WHO Measles Laboratory Network. A JE training workshop was held in October 2006, followed by two rounds of quality assurance and proficiency testing. Six countries (11 laboratories) are currently represented in the network (Figure 2), and it is anticipated that several more will soon join.

The functions of network laboratories are: (1) serologically confirm clinically suspected AES cases and outbreaks using validated JE IgM ELISA kits, (2) report laboratory results to the country programme and WHO, (3) perform quality assurance including annual proficiency testing and internal quality control standards, (4) appropriately store and maintain an inventory of samples, and (5) dispatch samples to regional reference laboratories. These laboratories will
perform confirmatory testing and testing for other aetiologies, while also providing technical support and training. Global specialized laboratories will offer high-level laboratory services, technical consultation, technology updates, and general resources. The US CDC is providing support to the network at a global level.

Ongoing activities for the network in the South-East Asia Region include (1) development of a laboratory information system to facilitate data management and reporting, (2) identification of regional reference laboratories, and (3) ongoing quality assurance activities including preparation of proficiency panels. Despite challenges in these and other areas, including the need to ensure sufficient resources and sustainability, significant achievements have been made.

**Figure 2. JE Laboratory Network, South-East Asia Region, 2006-2007**

![JE Laboratory Network, South-East Asia Region, 2006-2007](image)

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2005. All rights reserved.

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2.2.6 JE diagnostics

Ensuring the availability of validated and reliable JE IgM ELISA diagnostic kits for use within JE surveillance systems is important. In 2004, PATH contracted the Armed Forces Research Institute of Medical Sciences (AFRIMS) to evaluate three commercial IgM capture assays under reference laboratory conditions. AFRIMS used the kits to test 360 acute-phase
serum samples that contained either JE, dengue or no IgM antibody; were collected in 2001 in Thailand or in 2004 in Nepal; and were stored at -20°C. The in-house JE MAC ELISA from AFRIMS was used as the practical gold standard. The kits, manufactured by Panbio Limited, Inbios International Inc, and XCyton Diagnostics Ltd, use a cell-culture derived recombinant particulate antigen; the Panbio test also uses recombinant dengue 1-4 antigens. The kits were observed to have sensitivities of 89.3%, 99.2%, and 96.7%, respectively. Specificities were 99.2% for the Panbio assay, 56.1% for the Inbios assay, and 65.3% for the XCyton assay. When dengue IgM positive samples were excluded, the kits had specificities of 98.4%, 96.1%, and 96.1%, respectively. Since the Panbio kit is the only one to include both JE and dengue antigens, it appears to have an advantage in settings where dengue virus co-circulates. However, it was apparent that further assessment in a field setting was warranted. If dengue infection was not common in patients presenting with AES, cross-reactivity would be less of an issue and the positive predictive value of all kits should be high. Other factors to be considered in selecting a test kit include ease of use, affordability and field capability, which varied across the three kits.

The Walter Reed/AFRIMS Research Unit Nepal (WARUN) and PATH conducted a follow-up study in 2007 at the National Public Health Laboratory in Nepal. Two commercially available kits (XCyton and Panbio) were evaluated. The 350 blood samples used were randomly selected from samples collected in 2005 from Nepali patients presenting with encephalitis symptoms, and the evaluation was performed blinded. The AFRIMS JE IgM MAC ELISA, performed at AFRIMS laboratory in Bangkok, served as the practical “gold standard” for comparison. Preliminary results revealed high positive predictive values for both kits and greater than 80% concordance with the “gold standard”. Further testing and analysis is required before results can be finalized.

The China CDC’s Institute for Viral Disease Control and Prevention conducted a study to evaluate two locally produced JE kits, using an immunofluorescence assay as the gold standard. Investigators tested a total of 266 sera and 31 CSF samples and determined that both IgM-capture kits evaluated—manufactured by Yueda and Beixi—were suitable for JE diagnosis, but the Beixi kit demonstrated slightly higher specificity. During a JE outbreak in Yuncheng in 2006, the opportunity was also taken to conduct a small evaluation of the PanBio kit, which demonstrated good comparability to locally produced kits.

2.2.7 Discussion

- **Case definition used for surveillance**: The participants discussed the possible expansion of the definition used for surveillance, such as the inclusion of meningitis, AFP or fever cases. The critical aspects of this consideration include whether an expanded definition would help with decision-making and would be justified based on the additional resources needed (e.g. human, financial). It was thought, for example, that adding “meningism” to the encephalitis case definition may increase case load by 20% to 40%. However, some countries indicated that integrated ME surveillance was more justified to streamline the surveillance system and enable consideration of several vaccine-preventable diseases (e.g. *Haemophilus influenzae* type B [Hib], *Streptococcus pneumoniae*, and *Neisseria meningitidis*).

- **Laboratory testing for JE**: Countries are very interested in WHO providing technical assistance in relation to laboratory strengthening for JE diagnosis, including advice on standard kits and a system to assure quality. Country participants noted that for diagnostic kits to be useful they must not only be reliable and easy to use, but also cost-effective. Affordability is a critical factor that will influence the extent of testing in any country. The standard recommendation on number of specimens to collect (CSF and acute and convalescent serum) was also discussed. Three specimens may not always be required. For example, if a CSF specimen is positive, further confirmation is not necessary. Likewise if a
convalescent serum specimen is positive, it is not necessary to test the acute specimen. However, the danger of more specific recommendations is that samples may not be collected and a diagnosis missed. Another issue discussed was that if a single sample is collected at less than seven days after onset, the interpretation of a negative result should be “JE unknown” and not “JE negative”. The JE laboratory manual may be able to address specific testing issues in more detail.

− **Testing methodologies other than ELISA**: Participants discussed the use of viral culture, polymerase chain reaction (PCR) and plaque reduction neutralization testing (PRNT) for diagnosis of JE. Positive culture or PCR results are helpful, but it is well known that viraemia at the time of presentation with JE is very rare, so these methodologies should not be considered in standard practice. PRNT requires paired samples, as a single result is not diagnostic, and a level 3 laboratory is needed to grow the virus, so this is not appropriate as a routine testing methodology.

− **Further evaluation of currently available JE diagnostic kits**: There is a need for validation of CSF versus sera, as well as for a gold standard. Field data from use of the Panbio kit within the JE laboratory network will also add to a more comprehensive evaluation of this tool.

− **The identification of cross-reactive flaviviruses**: This is crucial to improving diagnostics and validating commercial assays. The Pediatric Dengue Vaccine Initiative and AFRIMS have been collecting such samples, and others could be submitted from endemic countries where other flaviviruses routinely circulate, such as Viet Nam, India and Cambodia.

### 2.3 JE vaccines

Several studies are generating data on the safety and efficacy of existing and new JE vaccines. This information is critical for country decision-makers and programme managers as they consider the introduction or expansion of JE immunization. As new vaccines become available, they may help establish a robust and competitive market and make vaccines more accessible for developing countries.

#### 2.3.1 WHO guidelines, policies and recommendations

In light of new and updated information on JE vaccines, WHO’s mandate is to develop norms, policies and other related resources in order to offer technical guidance to programme managers, national regulatory authorities and manufacturers. Several documents on WHO’s website address topics related to JE disease burden and surveillance, vaccine development, safety and efficacy, and recommendations for introduction. Expert groups such as the Strategic Advisory Group of Experts and the Global Advisory Committee on Vaccine Safety provide guidance in relation to vaccination policy and safety, respectively. A list of WHO documents and websites relevant to JE disease and vaccines can be found in Annex 3.

#### 2.3.2 Status of current and future JE vaccines

The global demand for JE vaccines is coincidently growing with international licensures of the SA 14-14-2 vaccine and the development of new JE vaccines. A summary of currently available JE vaccines and those in late-stage development is provided in Table 2. Additional candidates, including a recombinant poxvirus-based JE vaccine, are in preclinical development stages.
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Status</th>
<th>Schedule</th>
<th>Efficacy and safety (if data available)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CURRENTLY AVAILABLE VACCINES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated mouse brain-derived (Nakayama and</td>
<td>Internationally registered; produced and used locally in several</td>
<td>2 doses, 1 week apart; booster</td>
<td>80% protective efficacy (&gt;90% seroconversion after 3 doses)</td>
</tr>
<tr>
<td>Beijing-1 strains)</td>
<td>countries</td>
<td>after 1 year; re-boost every</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-4 years</td>
<td></td>
</tr>
<tr>
<td>Live, attenuated by Chengdu Institute of</td>
<td>Internationally registered; used in China since 1988 and licensed in</td>
<td>In China, 1 dose at 8-9 months</td>
<td>99% effectiveness in Nepal of a single dose after 1 year</td>
</tr>
<tr>
<td>Biological Products (SA 14-14-2 strain)</td>
<td>Nepal, Republic of Korea, India and Sri Lanka</td>
<td>and boosters at ~2 yrs and 6</td>
<td>Global Advisory Committee on Vaccine Safety (GACVS) noted the reported excellent safety profile and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>years of age; single dose in</td>
<td>recommended detailed study on specific issues.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>other countries</td>
<td></td>
</tr>
<tr>
<td>Inactivated primary hamster kidney cell (P-3</td>
<td>Available in China only</td>
<td>2 doses, 1 week apart; booster</td>
<td>80% protective efficacy (95% seroconversion after 3 doses)</td>
</tr>
<tr>
<td>strain)</td>
<td></td>
<td>after 1 year; re-boost at 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>years</td>
<td></td>
</tr>
<tr>
<td>Inactivated Vero cell-derived (P-3 strain)</td>
<td>Available in China only</td>
<td>Data not available</td>
<td>Data not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VACCINES IN LATE-STAGE DEVELOPMENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated, Vero cell-derived by Intercell</td>
<td>Successful adult Phase 3 trial; initiation of Phase 2 clinical trial</td>
<td>2 doses, 4 weeks apart</td>
<td>Data not available (seroconversion rate of 96% in adult Phase 3 study)</td>
</tr>
<tr>
<td>(SA 14-14-2 strain) (IC51)</td>
<td>in children 1 to 3 years old in 2007 (India) in partnership with</td>
<td></td>
<td>Clinical safety profile good - similar to placebo</td>
</tr>
<tr>
<td></td>
<td>Biological E, Ltd.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible market launch for US travellers by 2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chimeric live, attenuated by Acambis (SA 14-14-</td>
<td>Successful adult Phase 3 trial; Phase 2 paediatric trial initiated</td>
<td>1 dose</td>
<td>Data not available (99% seroconversion rate in adult Phase 3 study).</td>
</tr>
<tr>
<td>2 strain in yellow fever 17D vector) (Chimeri</td>
<td>in early 2007 (India) in collaboration with Bharat Biotech.</td>
<td></td>
<td>Systemically and locally tolerated; one vaccine-related serious adverse event in clinical trial</td>
</tr>
<tr>
<td>Vax-JE)</td>
<td></td>
<td></td>
<td>resolved without complications</td>
</tr>
<tr>
<td>Inactivated Vero cell-derived by Biken and</td>
<td>Phase 3 trials ongoing; target market in Japan only</td>
<td>Data not available</td>
<td>Data not available</td>
</tr>
<tr>
<td>Kaketsuken (Beijing-1 strain)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Source: PATH*
2.3.3 Live, attenuated SA 14-14-2 JE vaccine: updates and recent clinical trials

The SA 14-14-2 vaccine, which was recently introduced in India and Nepal, holds great potential for meeting the Regions’ needs. A maximum price has been set for its use in the public sector of endemic countries that are eligible for Global Alliance for Vaccines and Immunization (GAVI) support. The vaccine has been used in China for nearly two decades and has demonstrated an excellent safety profile. In order to provide further evidence on safety and efficacy for the purposes of national licensure and prequalification, several clinical trials have recently been completed or are underway.

The SA 14-14-2 vaccine strain was obtained from its wild-type SA 14 parent by serial passages in cell cultures (primary hamster kidney cells) and in animals (mice, hamsters) with successive plaque purifications (in primary chick embryo cells). The master seed virus of the SA 14-14-2 JE virus strain was screened for and shown to be free of adventitious viruses. The primary hamster kidney cell line was also certified pathogen free. Animal studies have demonstrated very good protection against many different JE virus strains, and greater protection in comparison to the commonly used inactivated vaccine. The absence of neurotoxicity has been shown in several animal studies, including a recent study conducted by the Government of India.

Regarding the vaccine’s efficacy, observational data collected in China since the late 1980s reveal a range of 96% to 98% efficacy after one dose and 100% efficacy after two doses. Data from an ongoing study in Nepal also provide additional information. In July 1999, approximately 160,000 children aged under one year to 15 years in the Terai region were given a single dose of SA 14-14-2 vaccine. In the JE season that followed, a case control study showed the vaccine to be 99% effective in preventing infection at one to three months. The following year, sustained protective efficacy of 99% was demonstrated. The most recent follow-up work in Nepal shows that after five years, efficacy from a single dose of vaccine remained at 96%. It is important to note that the location of the study is JE-endemic, and environmental conditions may contribute to natural boosting of immunity over time. However, the results strongly support the vaccine’s proposed target profile of one-dose administration for infants, children and adolescents aged nine months to 15 years in JE-endemic areas.

Co-administration of live, attenuated SA 14-14-2 JE and measles vaccines

A clinical trial was carried out in the Philippines to determine non-inferiority of the response to measles vaccine when co-administered with the SA 14-14-2 vaccine, as compared to measles vaccine given alone. The results provide further support for the vaccine’s introduction to routine immunization programmes. The study, conducted by the Research Institute of Tropical Medicine in partnership with PATH, vaccine manufacturer Chengdu Institute of Biological Products (CDIBP), and Mahidol University, Bangkok, revealed that the vaccines could be safely given together at nine months of age with no significant reduction in the immunogenicity of either. The safety profile, when co-administering the two vaccines, was comparable to that for either vaccine given separately. These results demonstrate that the SA 14-14-2 JE vaccine can be provided as part of the routine EPI schedule without the need for an additional clinic visit.

Applicability of open vial policy for reconstituted vaccines

WHO recommends that reconstituted vaccines should be discarded either at the end of an immunization session or after six hours, whichever comes first. To provide data for the SA 14-14-2 vaccine, the manufacturer conducted a study on stability of reconstituted vaccine stored at different temperatures for 24 hours. It demonstrated that the vaccine remains highly potent for a minimum of six hours at 37°C (actual data demonstrate high potency for at least 14 hours). These results meet requirements of the WHO open vial policy. Data were generated
on vaccine stored at 2°C to 8°C for six months, and additional data on vaccine stored for 12 to 24 months will be collected.

Other clinical trials are underway or will be initiated shortly to further strengthen the vaccine’s dossier:

- **Indonesia**: Co-administration of JE and measles vaccines (to be initiated at the end of 2007).
- **Sri Lanka**: Ability to boost with SA 14-14-2 vaccine following previous immunization with mouse brain-derived, inactivated JE vaccine and co-administration of measles and JE vaccines (to begin enrolment in mid-2007).
- **Philippines**: Long-term (12 and 24 months) follow-up of measles/JE vaccine co-administration study, including immunogenicity data to determine seropositivity rates for the measles vaccine response (ongoing).
- **Thailand**: One-dose clinical trial assessing immunogenicity (ongoing).

### 2.3.4 Effectiveness of Vietnamese mouse brain-derived JE vaccine

Several countries continue to use the inactivated, mouse brain-derived JE vaccine in their national programmes. In Viet Nam, a locally produced vaccine has been used since 1997. The International Vaccine Institute, in partnership with the National Institute for Health and Epidemiology, is currently conducting an effectiveness study of the vaccine. The paediatric dose of the vaccine is used in all children up to five years of age in Viet Nam, which differs from the international standard of using an adult dose for children over three years of age. Three doses are given at 0, 7 and 365 days, and no boosters are given. A case control study aims to assess long-term vaccine effectiveness. Results from this study will direct the Government of Viet Nam in planning the future expansion of or revision to the current JE immunization programme.

### 2.3.5 Strengthening surveillance of adverse events following immunization (AEFIs)

As JE control through immunization expands throughout the South-East Asia and Western Pacific Regions, surveillance following introduction, including monitoring for AEFIs, will provide crucial data for decision-makers in countries developing their own national strategies. The goals of AEFI surveillance are to ensure the safe delivery of vaccines, the capacity to respond to crises, and the ability to estimate the risk of any serious adverse event, particularly in relation to newly introduced vaccines. Several systems have been developed by WHO to support and strengthen safety monitoring for vaccines, including but not limited to those for JE.

- **The WHO Programme for International Drug Monitoring** is a network of national pharmacovigilance centres in partnership with WHO Headquarters and the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre). It is a significant resource for vaccine safety; however, only about 10% of the database relates to vaccines. A WHO consultation in 2006 considered the issue of improved vaccine safety monitoring.

- **The Global Advisory Committee on Vaccine Safety** provides advice and recommendations to WHO regarding vaccine safety issues of potential global importance. Multidisciplinary experts on the committee may commission task forces and further research when needed. Reports are distributed regularly through the WHO *Weekly Epidemiological Record*, which is accessible online at [www.who.int/vaccine_safety/en](http://www.who.int/vaccine_safety/en).
• The Global Network for Post-marketing Surveillance of New Vaccines is a new initiative that will support the WHO vaccine prequalification system by providing crucial safety data following the introduction of a new vaccine. The network will engender a standardized approach to adverse-events monitoring and ensure that WHO’s vaccination policy recommendations are informed by adequate data on vaccine safety from the country level. The orientation of 10 to 12 network countries is projected for late 2007.

With particular regard to monitoring of AEFIs with the SA 14-14-2 JE vaccine, the investigation in India after campaigns in 2006 was presented as a case study, with emphasis on the importance of understanding background mortality in the context of deaths temporally associated with vaccination. For example, 22 deaths were reported among the target population during the campaigns in 2006, a rate equivalent to 0.24 deaths per 100 000. Background mortality in the same age group is actually much greater—8.6 per 100 000. The Government of India addressed limitations of the AEFI system that became apparent during the 2006 campaigns and made improvements for subsequent campaigns with the SA 14-14-2 JE vaccine (for more information on the AEFI investigation in India, see sidebar).

2.3.6 Post-marketing surveillance in India

As an adjunct to monitoring for adverse events during JE vaccination campaigns in 2006, the Government of India, in partnership with CDIBP, conducted a post-marketing surveillance study to evaluate the vaccine’s safety and immunogenicity among the target population.

For the safety branch of the study, home visits to 1438 children from age one to 15 years were conducted daily for the first week, followed by weekly visits through 28 days post-vaccination. Following that, investigators visited enrollees every three months through one year following the vaccine’s administration. Local reactions, within seven days post-vaccination, included redness (< 1%), swelling (1% to 5%) and pain (5% to 10%). The most common systemic symptom was fever (12%). By six months, preliminary data identified four serious adverse events (SAEs). One event occurred

Investigating AEFIs in India

Inaccurate media reports of concerns about the SA 14-14-2 vaccine’s safety nearly derailed the programme in India, but the Government responded promptly and convened an independent expert committee to investigate AEFIs and address any risks associated with vaccine administration.

The committee conducted an extensive investigation of 504 adverse events reported through the AEFI system (including 22 deaths) and 29 additional cases identified through active case-finding, and found no link between the vaccine and temporally associated serious illnesses or deaths. The primary recommendation of the committee’s final report states: “No direct causality has been established between the reported illnesses and the JE vaccine. Therefore, no stricture on the further use of the vaccine is warranted.”

The committee’s findings were presented in conjunction with a summary of the 2006 campaigns at key global health events, including the Global Vaccine Research Forum and a meeting of WHO’s Global Advisory Committee on Vaccine Safety.

Further conclusions from the committee's report are summarized below:
• The most common adverse events (75% of reported cases) involved mild systemic reactions (fever, acute respiratory infection, vomiting, and/or rash).
• Case investigations and laboratory tests following adverse events were inadequate, and the committee recommended strengthening case recording, sample collection, data analysis, epidemiological investigation, and causality assessment.
• The frequency of 22 deaths among the vaccinated cohort of 9.3 million children aged one to 15 years calculates to a rate of 0.00024%. By comparison, the probable frequency of death among children of this age range in the general population is 0.0086%. Therefore, adverse events following JE vaccination do not seem to cause excess mortality.
within 24 hours of vaccination and involved a child with vomiting and a related electrolyte imbalance causing weakness, who recovered with fluids. The event was determined to be unrelated to the vaccine. Three other SAEs occurred two months or more after vaccination and involved a right post-auricular abscess, dengue and appendicitis.

To determine immunogenicity, investigators followed a subset of 360 children from a single site and drew blood at the time of vaccination, followed by blood draws at 28 days, six months, and one year. The retention rate at six months was 97%, and samples are currently being stored and will be tested at the National Institute of Virology in Pune, India, after the validation process is complete.

The Government of India is also planning to conduct an adult viraemia study in 2007 in Pune, a JE-endemic area with no recent outbreak.

2.3.7 Discussion

- **WHO prequalification:** While recent vaccination campaigns have demonstrated the feasibility of using the SA 14-14-2 vaccine in endemic countries and have provided further evidence to its safety profile, programme managers remain concerned about its lack of WHO prequalification. The primary barriers to this designation are the construction and validation of a new manufacturing site in China and limitations of the Chinese National Regulatory Authority, which has not received approval by WHO, a crucial step towards prequalification of a vaccine produced within its oversight. But it is important to note that the vaccine’s prequalification has not been delayed due to safety concerns.

- **Use of different vaccines in China:** China has been the vaccine’s primary proving ground. However, it has not been used in all provinces that implement JE immunization. Though the national Government recommended a comprehensive switch to the SA 14-14-2 vaccine, regulation is decentralized and the ultimate decision remains at the provincial level.

- **Policy regarding local vaccine manufacturers:** An additional challenge to the import of the SA 14-14-2 vaccine for use throughout both regions is the existing support for local manufacture of vaccines. CDIBP has determined, however, that it would not be cost-effective to provide technological transfer for the local production of the SA 14-14-2 vaccine, particularly in light of the special public-sector pricing agreement established for endemic countries.

2.4 Immunization programmes and JE vaccines introduction

The experiences of countries in the South-East Asia and Western Pacific Regions that have successfully developed and implemented a strategy for JE vaccine introduction can offer valuable resources for other countries considering similar options for control. There are elements to consider, and factors such as licensure and funding for a new or enhanced vaccination programme are chief among them. Though all stakeholders are focused on a common goal of protecting vulnerable populations from JE, endemic countries throughout the two regions find themselves at different points along the decision-making spectrum.

2.4.1 The strategy for JE vaccine introduction in India

The introduction of JE vaccination in India in 2006 was a significant accomplishment in JE control, protecting more than nine million at-risk children. This undertaking marked the first year of the Government of India’s five-year plan and was possible due to the development of a deliberate strategy and collaboration between stakeholders at all levels. Public demand for a JE
vaccine was high, as awareness rose significantly following a devastating outbreak in 2005, but decision-makers still had to overcome several barriers. For example, the Ministry of Health and Family Welfare lacked experience in implementing large-scale vaccine campaigns using an injectable vaccine and in procuring an international product for the national immunization programme.

A technical advisory committee reviewed scientific data on JE surveillance, the limitations of existing vector control activities, and the experiences of other countries that had introduced JE vaccine. Because the target population for JE vaccination would be so vast, and because the local production of the inactivated mouse brain-derived vaccine was limited, the committee gathered information on alternative products, ultimately identifying the SA 14-14-2 vaccine from CDIBP as the safest and most affordable option. AES surveillance revealed that more than 85% of reported JE cases occurred in children under 15 years of age. To reach the most vulnerable children in a timely manner, the committee and national programme managers targeted high-risk districts for one-time, village-to-village campaigns. Over the span of five years, more than 100 million children, one to 15 years of age, are expected to receive a single dose of SA 14-14-2 vaccine. Following the campaign in each district, the vaccine will be integrated into the routine immunization programme. The decision-making process in India is illustrated in Figure 3.

**Figure 3. Vaccine introduction decision-making process in India**

Source: Dr Julie Jacobson, PATH

Campaigns in 2006 reached children in 11 districts of Uttar Pradesh, Assam, Karnataka, and West Bengal states, with an overall coverage rate of 88%. In 2007, 22 million children in 28 districts of nine states will be targeted for vaccination. Beyond the vaccination campaigns and implementation into the routine programme, the Government of India plans to continue strengthening its overall JE control programme through improved surveillance using national guidelines, building the JE diagnostic network, and further development of the national AEFI reporting system.
2.4.2 Financing JE introduction: country experiences

The challenge of identifying resources to finance JE vaccine introduction and a sustained immunization programme is substantial in countries that lack significant resources and are faced with additional health priorities, like human immunodeficiency virus (HIV) or diarrhoeal disease. Unfortunately, JE burden is highest in the poorest countries of the Western Pacific and South-East Asia Regions. However, a commitment to protecting children from JE infection is driving programme managers and the global donor community towards seeking out creative solutions.

India

A key element in India’s successful introduction was the vaccine manufacturer’s commitment to a maximum public-sector price, as established through negotiations led by PATH. The agreement aims to overcome financial barriers to JE vaccine introduction by setting a price to be honoured through 2026 for the vaccine’s use in countries with a gross national product less than US$ 1000. This designation is also used by GAVI for support it provides to national immunization programmes. The Government of India was able to allocate resources from within its national budget to meet the costs of procuring vaccine and implementing the programme. To ensure sustainability, budget provision was made in the national five-year plan.

Sri Lanka

Building on a robust national immunization programme that has seen dramatic uptake of new vaccines for more than two decades, Sri Lanka offers fertile ground for successful introduction. At an Immunization Summit held in early 2007, national programme managers reviewed scientific data and cost considerations (Figure 4) and decided to switch from providing an inactivated JE vaccine through routine EPI to procuring the live, attenuated SA 14-14-2 JE vaccine manufactured by CDIBP. While logistics and licensure of a new vaccine will necessitate the investment of resources, the national programme determined that the switch would, in fact, result in a cost savings that could be applied to support the introduction of a new vaccine against Haemophilus influenzae type b, or Hib—a major cause of childhood pneumonia and meningitis.

Figure 4. Cost considerations in the Sri Lankan national EPI

- Introduction of a new vaccine is always considered within the framework of the National EPI, not separately
- Total cost
  - Vaccine
  - Injection supplies
  - Other routine recurrent cost
    - Cold chain equipment
    - Transportation

Source: Dr Nihal Abeysinghe, Sri Lanka Ministry of Health
Nepal

Nepal conducted sporadic campaigns with both inactivated and live JE vaccines in 1999-2000, but stepped up efforts to immunize high-risk populations following an outbreak in 2005. As in India, the long-term strategy involves phased mass campaigns in endemic districts (with the age group targeted depending on the local epidemiology in each district and available resources), followed by the introduction of JE vaccine in the routine EPI programme in each district. In 2006, mass campaigns with the SA 14-14-2 vaccine reached almost 2.5 million in six endemic districts—89% of the target population. Financial resources were identified within the government pool fund; operational costs were low compared to previous campaigns against measles. In addition, strong political commitment and high demand resulted in little need for intensive social mobilization. In 2007, the Government planned to conduct campaigns in 18 districts with funds from the Government of Japan, but when vaccine could not be procured through UNICEF, the campaign plans were revised to immunize in four districts using available government resources. The Nepalese are confident that routine immunization can be sustained with government funds, but external support is required to support additional mass campaigns.

Viet Nam

To meet the costs of providing inactivated vaccine to the at-risk population, the Government of Viet Nam is using a phased approach in which the programme expands annually to reach children one to five years of age in endemic districts, with a goal for nationwide coverage by 2010. Beyond 2010, children aged 13 to 24 months will begin the three-dose series through the routine immunization programme, at which time programme expenses are expected to decrease significantly to US$ 2.2 million per year. Currently, all programme costs are expected to be absorbed by the Government, but external funds are also being sought. Planning challenges in the near future include determination of the appropriate vaccine for Viet Nam. The Government’s policy is to support the local vaccine manufacturer, but its price is higher and the dosing schedule is more complex than the SA 14-14-2 vaccine. Surveillance activities also must be expanded to provide better data for programme planning.

China

Nationwide expansion of JE vaccination is expected in China in coming years, building off the current programme in 16 provinces. At present, provincial-level JE immunization is supported directly from the respective provinces. But in March 2007, China’s leaders revealed plans for the central Government to support integration of EPI vaccines (including JE vaccine) throughout the country. Support for operational costs such as local health staff services will still be supplemented from the local level. Currently, three types of JE vaccines (two inactivated vaccines based on the Beijing P-3 strain and the live, attenuated SA 14-14-2 vaccine) are used in the provincial programmes.

2.4.3 Considerations of cost and impact in JE vaccine introduction

With growing awareness of the burden of JE and the availability of affordable, effective solutions to control it, global demand for JE vaccines is estimated to increase dramatically in coming years. A preliminary analysis projected that global demand may peak at 110 million doses in 2009, as more countries implement mass campaigns. The regions’ needs will be dramatically reduced once mass campaigns are replaced with routine immunization, and the annual demand should settle between 15 and 20 million doses per year. In parallel with this projection of global demand, financing needs are estimated to be greatest in 2009, when US$ 57 million will be required to cover procurement and programme costs, the bulk of which will support mass campaigns. Approximately US$ 6 million per year will be required to effectively
control JE in the 14 GAVI-eligible JE endemic countries through routine vaccination programmes.

To help programme managers distil broad assumptions, PATH and the University of North Carolina developed the Japanese Encephalitis Vaccine Planning Tool, or JeVa. Using adaptable parameters such as vaccine price, geographical area, and implementation strategies, JeVa provides a country-specific projection of vaccine doses needed, financial requirements, and the potential impact of JE vaccination in terms of cases, disabilities and deaths averted. The tool will soon be available through PATH’s Advanced Immunization Management (AIM) e-learning tool: http://aim.path.org.

2.4.4 Discussion

- Critical factors for programme planning: Countries with experience in JE vaccine introduction described factors that had been critical in their decision to introduce vaccine: good disease burden data; demonstrated high case fatality and disability rates as a result of infection; public demand; increased disease awareness as a result of outbreaks; evidence from neighbouring countries of the effectiveness of JE immunization; and political support.

2.5 Next steps

2.5.1 Country planning for JE surveillance and immunization

Meeting participants were convened in small discussion groups according to the current status of JE control in their respective countries. Discussions centred on sharing experiences and brainstorming about the way forward. One representative from each country then addressed the complete group of participants to present information regarding strengths and weaknesses of current activities, as well as plans for improvement and/or expansion in the next two years (Table 3).
### Table 3. Current status of JE control by country

<table>
<thead>
<tr>
<th>Country</th>
<th>Surveillance</th>
<th>Immunization</th>
<th>Decision-making needs</th>
<th>Financial issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>National ME syndromic surveillance &lt;br&gt;JE surveillance at six sites</td>
<td>Strengthen ME and JE surveillance</td>
<td>None</td>
<td>Conduct campaign for one- to 15-year-olds (2009) &lt;br&gt;Introduce EPI (2009-2010)</td>
</tr>
<tr>
<td>China</td>
<td>National, electronic AES and JE reporting &lt;br&gt;Special surveillance projects in some provinces &lt;br&gt;Lab. confirmation in ~half of cases &lt;br&gt;Diagnostics in 13 provinces</td>
<td>Improve case-based surveillance &lt;br&gt;Quality control training &lt;br&gt;Expand diagnostics</td>
<td>Immunization through EPI in 16 of 31 provinces &lt;br&gt;Various vaccines used, determined at provincial level &lt;br&gt;JE is public health priority</td>
<td>Expand EPI nationwide &lt;br&gt;Improve vaccine coverage &lt;br&gt;Improve monitoring and AEFI surveillance &lt;br&gt;Carry out catch-up campaigns for adults</td>
</tr>
<tr>
<td>India</td>
<td>Passive JE surveillance since 1978 with limited lab. confirmation &lt;br&gt;AES surveillance initiated in 2007 &lt;br&gt;50 sentinel laboratories identified in JE-endemic districts and 12 laboratories for advanced diagnosis</td>
<td>Strengthen AES surveillance &lt;br&gt;Build capacity for case management and rapid response to outbreaks &lt;br&gt;Develop sentinel laboratories &lt;br&gt;Diagnostics training</td>
<td>JE vaccine (SA 14-14-2) introduced in 2006 in high-risk districts &lt;br&gt;Strategy of campaigns and integration into universal immunization programme</td>
<td>Continue programme expansion through 2010 &lt;br&gt;Strengthen AEFI monitoring &lt;br&gt;Consider new vaccines as they are developed</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Encephalitis is one of 39 diseases under surveillance. &lt;br&gt;JE surveillance at selected sentinel sites</td>
<td>Strengthen ME surveillance and revise guidelines &lt;br&gt;Implement quality assurance and monitoring system</td>
<td>None</td>
<td>Set up immunization pilot in Bali in 2008 (SA 14-14-2 vaccine) &lt;br&gt;Use surveillance data and financial issues to guide plans for further introduction</td>
</tr>
</tbody>
</table>

JE – Japanese Encephalitis; ME - meningoencephalitis; EPI – Expanded Programme on Immunization; AES - acute encephalitis syndrome ; AEFI – adverse events following immunization
<table>
<thead>
<tr>
<th>Country</th>
<th>Surveillance Methodology</th>
<th>Case Reporting Requirement</th>
<th>Vaccine History</th>
<th>Surveillance &amp; Prevention Strategies</th>
<th>Future Plans</th>
<th>Funding Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>JE surveillance with laboratory confirmation Estimated ~50% all cases reported No formal AES case definition Pig surveillance</td>
<td>Mandatory human JE case reporting Continued pig surveillance</td>
<td>Vaccination introduced in 1954; universal vaccination since 1995 In 2007, the Ministry of Health recommended optional vaccination depending on local risk, based on pig surveillance data.</td>
<td>Switch to Vero cell-derived vaccine when available Awaiting further clinical trial results from new Vero cell-derived vaccine being developed in Japan</td>
<td>Funded by national government</td>
<td></td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>Year-round human JE surveillance Vector surveillance (Apr-Oct) and pig surveillance (June-Sept) National reference laboratory performs JE testing for whole country</td>
<td>Consider enhancing laboratory testing for other AES aetiologies</td>
<td>Vaccination with mouse-brain derived vaccine since 1970s</td>
<td>No additional plans Data on new cell culture-derived vaccine</td>
<td>Funded by national government</td>
<td></td>
</tr>
<tr>
<td>Lao People's Democratic Republic</td>
<td>National syndromic surveillance but insufficient data Research project initiated in 2007 at two central and two provincial hospitals</td>
<td>Expand research project (two more provincial hospitals) depending on results from initial study</td>
<td>None</td>
<td>Review surveillance data to determine need Conduct cost-effectiveness study Improved disease burden data</td>
<td>Introduction is not possible without donor support and technical assistance</td>
<td></td>
</tr>
<tr>
<td>Malaysia</td>
<td>Case-based surveillance with laboratory confirmation, although reporting probably not complete Vector surveillance</td>
<td>Improve clinician/laboratory/health dept communications Improve surveillance system to gather better data on JE incidence and mortality rate</td>
<td>Nationwide in 2001 but scaled back to Sarawak only (mouse brain derived-vaccine)</td>
<td>Integrate JE vaccine into EPI and introduce catch-up programme Information on JE vaccine alternatives, cost and availability</td>
<td>Limited funding from the Ministry of Health but strong political will</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>AES surveillance throughout country, integrated with other VPDs</td>
<td>Lab confirmation (two laboratories)</td>
<td>Sustain current surveillance strengths and improve CSF collection and follow-up of cases</td>
<td>JE vaccine formally introduced in 2006 (SA 14-14-2)</td>
<td>Campaigns in six of 24 endemic districts in first year</td>
<td>Programme expansion in phased manner in endemic districts</td>
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<tr>
<td>Nepal</td>
<td>AES surveillance throughout country, integrated with other VPDs</td>
<td>Lab confirmation (two laboratories)</td>
<td>Sustain current surveillance strengths and improve CSF collection and follow-up of cases</td>
<td>JE vaccine formally introduced in 2006 (SA 14-14-2)</td>
<td>Campaigns in six of 24 endemic districts in first year</td>
<td>Programme expansion in phased manner in endemic districts</td>
</tr>
<tr>
<td>Philippines</td>
<td>None</td>
<td>Begin AES/JE and case-based surveillance in 2007</td>
<td>None</td>
<td>Compare JE with other health priorities</td>
<td>Surveillance data Advocacy for legislators</td>
<td>No budget currently dedicated for JE vaccination</td>
</tr>
<tr>
<td>Thailand*</td>
<td>Encephalitis surveillance with JE diagnostic component for over 30 years</td>
<td>NA</td>
<td>Stepwise introduction since 1990 (locally produced mouse brain-derived vaccine) Fully integrated into routine EPI</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Timor Leste</td>
<td>Syndromic encephalitis surveillance part of integrated disease surveillance No laboratory for JE surveillance, but staff trained</td>
<td>Begin sentinel site ME surveillance</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>Disease burden data</td>
</tr>
</tbody>
</table>

VPDs – vaccine preventable diseases; CSF - cerebrospinal fluid
| Viet Nam | Hospital-based AES surveillance since 1979  
Pilot JE surveillance in three provinces since 2005  
Capacity for JE laboratory testing in 10 provinces only | Strengthen routine syndromic system  
Expand sentinel sites to represent more geographic areas  
Capacity-building for surveillance and laboratory staff  
Improve communication between curative and preventive sectors  
Evaluate in-house diagnostic kits | Vaccination commenced in 1997 and gradually expanded in high-risk areas (locally produced mouse brain-derived vaccine) | Expand nationwide by 2010 | Programme impact  
Data on new vaccines  
WHO guidance and information on lessons learnt from other countries | Limited government resources  
Need donor support to expand sentinel surveillance and for expansion of immunization programme |

*No government representative at meeting; information available from partners*
3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

(1) Countries are at very different stages in their control programmes, from clarifying disease burden to strengthening and expanding established immunization programmes. However, one overarching theme relevant to activities in all countries is the importance of continued and improved surveillance. Excellent progress has been made in many countries in recent years, but even in countries with robust surveillance programmes, there is room for improvement (e.g. identifying outbreaks and newly affected populations, improving feedback and communication between stakeholders, or ensuring use of a uniform case definition). As JE control improves, surveillance may focus on more complete laboratory testing of AES cases, as currently only countries with very effective control programmes (about 10 cases or less per year) have laboratory testing of all reported cases. Once JE control has been achieved and human cases are minimal or absent, other forms of surveillance such as pig and mosquito surveillance may be useful.

(2) At the global level, WHO guidelines and networks are supporting and harmonizing JE data collection. A working group will address the need to further refine the JE surveillance guidelines, and it is important that this and other relevant resources are shared with stakeholders in endemic countries.

(3) Disability is recognized as an important part of JE disease burden but is not well measured or reported. JE contributes to poverty and has a large impact on affected families, particularly in relation to disability. The ability to prevent lifelong disability is an important consideration when the potential benefits of a JE immunization programme are being considered.

(4) The experiences of countries that have previously introduced JE vaccines can also provide broad lessons. For example, immunization programmes that focus only on infants or that cover only a portion of the at-risk population will not achieve the greatest impact. Monitoring impact in this situation has proven difficult, but as country programmes progress towards integration of JE vaccines into routine EPI, coverage and impact will be easier to evaluate. All country participants attending the meeting from countries currently using JE vaccine (with the exception of the Republic Korea) indicated their country is considering the use of new JE vaccines. All countries not using vaccine are either collecting data to make a decision on introduction or have plans to introduce it. Significant new information presented at the meeting that may inform country decision-making on the choice and utilization of vaccine included the safety and immunogenicity of co-administration of SA 14-14-2 JE vaccine and measles vaccine, the compliance of SA 14-14-2 vaccine with WHO’s open vial policy for reconstituted vaccines, and the safety of the vaccine in children under one year of age.

(5) Many endemic countries face challenges related to financial support and sustainability, and this is often the rate-limiting step for introduction of preventive campaigns, even when considering the maximum public-sector price that has been established for the SA 14-14-2 vaccine. Almost all countries expressed confidence that costs for routine JE immunization can be covered by the national government, but external resources may be required to cover one-time, catch-up campaign costs at the time of vaccine introduction. These constraints are being addressed through multiple approaches, including identification of donor support, advanced
planning for inclusion of JE immunization in national budgets, and wider use of a less expensive vaccine.

3.2 Recommendations

The group made the following recommendations:

3.2.1 Surveillance

(1) Increase reporting and monitoring of disability following JE infection to better understand the impact of disease beyond mortality and to provide information for advocacy purposes.

(2) Use surveillance and outbreak data to inform decision-making on JE immunization.

(3) Consider further the concept of integrated surveillance with inclusion of additional aetiologies of ME, in particular those that are vaccine-preventable (e.g. Hib, pneumococcal disease, and meningococcal disease).

3.2.2 Laboratory

(1) Provide support to national laboratories for standardization, training, quality control and quality assurance.

(2) Generate additional data on diagnostic kits and ensure information is available to countries.

3.2.3 Immunization

(1) Monitor the impact of JE vaccine introduction with surveillance and coverage data through national programmes and the WHO/UNICEF Joint Reporting Form.

(2) Ensure standardized, routine AEFI reporting in parallel with JE vaccine introduction.

(3) Continue to monitor and collect data on duration of immunity following vaccination with SA 14-14-2 vaccine.

(4) Develop outbreak response planning.

3.2.4 Coordination of JE prevention and control activities

(1) Identify funding sources for JE immunization (including GAVI and others).

(2) Prioritize WHO prequalification for JE vaccine to increase financing options.

(3) Increase collaboration on disease surveillance and control between neighbouring countries, in recognition of JE being a regional health problem.

(4) Continue to gather and disseminate data on safety and impact of SA 14-14-2 vaccine and information on other new JE vaccines to assist countries with decision-making.
4. ACKNOWLEDGEMENTS

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ANNEX 1

THIRD BIREGIONAL MEETING ON
CONTROL OF JAPANESE ENCEPHALITIS

Ho Chi Minh City, Viet Nam
26-27 April 2007

1. PARTICIPANTS

CAMBODIA
Dr HEM Sok Han, National Paediatric Hospital, #100 Federation of Russia Boulevard, Phnom Penh, Telephone: (011) 956 086, Facsimile: (012) 762 803, E-mail: hem.sokhan@yahoo.com

Dr SVAY Sarath, Deputy Manager, National Immunization Programme, Ministry of Health 151-153 Kampuchea krom Street, Phnom Penh, Telephone: (855) 12 870992, Facsimile: (855) 23 426167, E-mail: svays@nip.everyday.com.kh

CHINA
Dr LI Li, Deputy Director, National Immunization Programme, China Center for Disease Control and Prevention, 27 Nanwe Road, Xuan wu District, Beijing, Telephone: 0086 10 63027946 6, Facsimile: 0086 10 63027946 6, E-mail: llsdjn@163.com

Mr LU Ming, Programme Officer, Department of Disease Control, Ministry of Health, No. 1 Xizhimenwai Nanlu, Xicheng District, Beijing

LAO PEOPLE'S DEMOCRATIC REPUBLIC
Dr Phengta VONGPHRACHANH, Director, National Center for Laboratory and Epidemiology Ministry of Health, Km 3, Tha Deua Road, Vientiane, Telephone: 856 21 312351; 350209 Facsimile: 856 21 350209, E-mail: phengta@hotmail.com

Dr Anonh XEUATVONGSA, Manager, National Expanded Programme on Immunization, Department of Hygiene and Prevention, Ministry of Health, Simeuang Road, Vientiane, Telephone: 856 21 312352, Facsimile: 856 21 312120, E-mail: anonhxeuat@yahoo.com

MALAYSIA
Dr Mohamad Ikhsan b. SELAMAT, Principal Assistant Director, Disease Control Division Ministry of Health, Level 4, Block E10, Complex E, Federal Government Administrative Center, 52590 Putrajaya, Telephone: 603 8883 4276, Facsimile: 603 8888 6215 / 6251, E-mail: alangasan2002@yahoo.com

Dr WONG See Yin, Senior Medical Consultant, Department of Medicine, Sarawak General Hospital Jalan tun Ahmad Zaidi Adruce, 93586 Kuching, Sarawak, Telephone: 6 082 276418, Facsimile: 6 082 240767, E-mail: sywong62@yahoo.com; edkch@health.gov.my
Annex 1

PHILIPPINES
Dr Marlow NIÑAL, Chief, Public Health Surveillance, and Information Division, National Epidemiology Center, Department of Health, San Lazaro Compound, Rizal Avenue, Sta Cruz, Manila. Telephone: (632) 741 7048, Facsimile: (632) 741 7048, E-mail: marlow_ninal@yahoo.com

Dr Ma. Joyce DUCUSIN, Medical Specialist IV and EPI Programme Manager, National Center for Disease Prevention and Control, Department of Health, San Lazaro Compound, Sta Cruz, Manila. Telephone: (632) 7329956, Facsimile: (632) 7116 130, E-mail: juducusin@yahoo.com

REPUBLIC OF KOREA
Dr Hae-wol (Regina) CHO, Director, National Institute of Health, Korea Centre for Disease Control and Prevention, 195 Tongil Lo, Eunpyung-GU, Seoul 123 701, Telephone: 82-2-380-1433, Facsimile: 82-2-380-1410, E-mail: hwcho@nih.go.kr

VIET NAM
Professor Do Si HIEN, National EPI Manager, National Institute of Hygiene and Epidemiology, Ministry of Health, No. 1 Yersin Street, Ha Noi 10 000, Telephone: +844 821 4680, Facsimile: +844 821 3782, E-mail: dshien@fpt.vn

Professor Nguyen Thi Thu YEN, Chief, National AFP Surveillance, Chief, Epidemiology Department, National Expanded Programme on Immunization, National Institute of Hygiene and Epidemiology, Ministry of Health, No. 1 Yersin Street, Ha Noi 10 000, Telephone: +844 971 3433, Facsimile: +844 821 0487, E-mail: yentc@hn.vnn.vn

2. REPRESENTATIVES/OBSERVERS

ARMED FORCES RESEARCH INSTITUTE (AFRIMS), BANGKOK
Dr Khin Saw MYINT, Head, Emerging Pathogens, Department of Virology, AFRIMS, 315/6 Rajvithi Road, Bangkok, 10400, Thailand, Telephone: 662 6444674, Facsimile: 662 6444674, E-mail: MyintK@afirms.org

AFRIMS/ WARUN, NEPAL
Dr Sanjaya Kr. SHRESTHA, Head, Walter Reed/ AFRIMS Research Unit Nepal (WARUN), c/o US Embassy, Kathmandu, P.O. Box 295, Kathmandu, Nepal, Telephone: 977-9851077359 Facsimile: 977-1-4483919, E-mail: shresthask@afirms.org; swarun@mos.com.np

GATES FOUNDATION
Mr Doug HOLTZMAN, Bill & Melinda Gates Foundation, 1551 Eastlake Avenue East, Seattle Washington 98102, Telephone: 206-709-3100, Facsimile: 206-709-3170, Email: Douglas.Holtzman@GatesFoundation.org
THE INTERNATIONAL VACCINE INSTITUTE
Dr Florian MARKS, The International Vaccine Institute, Kwanak, P.O. Box 14, Seoul, 151-600 Republic of Korea, Telephone: +82-2-881-1133, Facsimile: +82-2-881-1164, E-mail: fmarks@ivi.int

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE
Dr Karen EDMOND, Senior Lecturer, Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom, Telephone: 44(0)2079588124, Facsimile: 44(0)2076374314, E-mail: Karen.edmond@lshtm.ac.uk

MAHIDOL UNIVERSITY
Dr Arunee SABCHAREON, Dept of Tropical Pediatrics, Mahidol University, Faculty of Tropical Medicine 420/6 Rajvithi Road, Bangkok 10400, Thailand, Telephone: 662-245-7197, Facsimile: 662-248-2589, Email: tmasc@mahidol.ac.th

MINISTRIES OF HEALTH
CAMBODIA
Mr Mom CHAN DARA, Chief of Immunology Unit, National Institute of Public Health, Boulevard Kim Yi Sung, Khan Toul Kork, P.O. Box 1300, Phnom Penh, Telephone: (855-23)-880 345, Facsimile: (855-23) 880 346, E-mail: chandara08@niph.org.kh

Dr Sok TOUCH, Director of Communicable Disease Control Department, Ministry of Health, #151-153 Kampuchea Krom Avenue, Phnom Penh, Telephone: (855-23) 882 317, Facsimile: (855-23) 882 317, E-mail address: touch358@online.com.kh

CHINA
Dr LIANG Guodong, Institute of Viral Disease Control, China Center for Disease Control and Prevention, No. 100, Ying Xin Street, Xuan Wu District, Beijing 100052, Telephone: 0086-10-63510124, Facsimile: 0086-10-63532053, E-mail: gdliang@hotmail.com

Dr WANG Huanyu, Department of Virus Encephalitis, Institute of Viral Disease Control, China Center for Disease Control and Prevention, No. 100, Ying Xin Street, Xuan Wu District, Beijing 100052, Telephone: 0086-10-63510124, Facsimile: 0086-10-63532053, E-mail: rainoffall@yahoo.com

Dr ZHANG Shao Bai, Shaanxi Provincial Center for Disease Control; and Prevention No. 3 Jiangdong Street, Hepingmen Wai, Xi'an City 710054, Shaanxi Province, Telephone: 86-29-82221350, Facsimile: 86-29-82251214, E-mail: maoltzhang@163.com
Annex 1

INDIA
Dr Padmalochan BISWAL, Assistant Commissioner, Immunization, Ministry of Health and Family Welfare, Government of India, New Delhi, Telephone: 91 23062126, 23062728, E-mail: drpbiswal@rediffmail.com

Dr Roop KUMARI, Assistant Director, National Vector Borne Disease Control Programme, Ministry of Health and Family Welfare, Government of India, 33/22, Rajpur Road, Delhi – 11054, Telephone: 91 23980304, E-mail: dr_roopa@hotmail.com

INDONESIA
Dr Jane SOEPARDI, National EPI Manager, Ministry of Health, Jalan Percetakan Negara 20, PO Box 223, Jakarta 10560, Telephone: 62 21 424 9024, Facsimile : 62 21 425 7044, E-mail: janesoepardi@yahoo.com

NEPAL
Dr Sarala MALLA, Director, National Public Health Laboratory, Department of Health Services, Ministry of Health and Population, Kathmandu, Telephone: +977 1 424 0217, Facsimile : +977 1 425 2375, E-mail: nphl@wlink.com.np

Dr Shyam Raj UPRETI, EPI Section Chief, Child Health Division, Department of Health Services, Ministry of Health, Kathmandu, Telephone: 977 1 427 1324, E-mail: drshyam@hotmail.com

REPUBLIC OF KOREA
Dr Jong-Hee KIM, Public Health Researcher, Vaccine Preventable Diseases and Control, and National Immunization Program, Korea Center For Disease Control and Prevention, 5 Nokbeon-Dong, Eunpyung-Gu, Seoul, 122-701, Telephone: 822)380-1445, Facsimile: 822)352-8235, E-mail: goldpaper2@daum.net

Dr Sunk-Kyung PARK, Public Health Researcher, Vaccine Preventable Diseases and Control, and National Immunization Program, Korea Center For Disease Control and Prevention, 5 Nokbeon-Dong, Eunpyung-Gu, Seoul, 122-701, Telephone: 822)380-1445, Facsimile: 822)352-8235, E-mail: mistypak@hanmail.net

VIET NAM
Dr Tran Thanh DUONG, Head of Epidemiology Department, Preventive Medical Department, Ministry of Health, 138A Giang Vo, Ha Noi, Telephone: 84-4-8452 555, Facsimile : 84-4-7366 241, E-mail: tranthanhduong@hotmail.com

Dr Huynh Thi Kim LOAN, Japanese Encephalitis Laboratory, Pasteur Institute, Ministry of Health,167 Pasteur Street, District 3, Ho Chi Minh City, Telephone: 84-8-8296 351, Facsimile : 84-4-8231 419, E-mail: loanphuch@yahoo.com

Dr Nguyen Thi Minh PHUONG, Pasteur Institute, Ministry of Health, 167 Pasteur Street, District 3, Ho Chi Minh City, Telephone: 84-8-8295 911, Facsimile : 84-4-8202 814, E-mail: Phuong@hcm.fpt.vn
Annex 1

Dr Hoang Van TUAN, National Expanded Programme on Immunization, Ministry of Health, No. 1 Yersin Street, Ha Noi 10 000, Telephone: 84-4-8213- 764, Facsimile : 84-4-8214 782, E-mail: hoangvantuan_epi@yahoo.com; hoangvantuan@fpt.vn

NATIONAL INSTITUTE OF HEALTH, USA
Dr Patricia M. REPIK, Programme Officer for Emerging Viral Diseases, Virology Branch, National Institute of Health, NIH/ NIAID/ DMID, 6610 Rockledge Drive, Room 4063, MSC 6604, Bethesda, Maryland 20892-6604, Telephone: 301-451-3504, Facsimile : 301-480-1594, Email: prepik@niaid.nih.gov

NATIONAL INSTITUTE OF INFECTIOUS DISEASES (NIID) TOKYO
Dr Tomohiko TAKASAKI, Chief, Laboratory of Vector-borne viruses, Department of Virology 1, National Institute of Infectious Diseases, 1-23-1 Toyama Shinjuku-ku, Tokyo 162-8640, Japan, Telephone: +81-35285-1111, Facsimile : +81-35285-1188, E-mail: takasaki@nih.go.jp

OXFORD UNIVERSITY CLINICAL RESEARCH UNIT
Professor Jeremy FARRAR, Director, Oxford University Clinical Research Unit, The Hospital for Tropical Diseases, Ho Chi Minh City, Telephone: 0084 8 836 2225, Facsimile : 0084 8 923 8904, E-mail: jfarrar@oucru.org

PROGRAMME FOR APPROPRIATE TECHNOLOGY IN HEALTH (PATH)
CAMBODIA
Dr Samnang CHHAM, Project Officer, PATH, PO Box 1684, Phnom Penh, Telephone: 855-23-215 005, Facsimile : 855-23-222 330, Email: csamnan@path.org

Mr John GRUNDY, Consultant, PATH, PO Box 1684, Phnom Penh, Telephone: 855-23-215 005, Facsimile : 855-23-222 330, Email: johnjgrundy@hotmail.com

Dr Lim PICH, Senior Programme Officer, PATH, PO Box 1684, Phnom Penh, Telephone: 855-23-215 005, Facsimile : 855-23-222 330, Email: lpich@path.org

CHINA
Dr YI Tang , PATH, China, Vaccine Development Officer, Suite 718 Hua Bin Building, No. 8 Yong An Dong Li Jian Guo Men Wai, Chaoyang District, Beijing 100022, Telephone: 86-10-8528-8211, Facsimile : 86-10-8528 8210, Email: ytang@path.org

FRANCE
Mr James CHEYNE, Associate Director, Immunization Solutions, PATH, France, Batiment Avant Centre, 13 Chemin du Levant, 01210 Ferney Voltaire, Telephone: (33-450) 28-00-49, Facsimile: (33-450) 28-04-07, Email: jcheyne@path.org

Dr Jean Marie PREAUD, Senior Pharmaceutical Operations Officer, PATH, France, Batiment Avant Centre, 13 Chemin du Levant, 01210 Ferney Voltaire, Telephone: 33-450-28-00-49, Facsimile : 33-450-28-04-07, Email: jpreaud@path.org
Annex 1

Dr Mansour YAÏCH, Vaccine Development Advisor, PATH, France, Batiment Avant Centre, 13 Chemin du Levant, 01210 Ferney Voltaire, Telephone: 33-450-28-00-49, Facsimile: 33-450-28-04-07, Email: myaich@path.org

INDIA

Mr Pritu DHALARIA, Programme Officer II, PATH, India, A-9, Qutab Institutional Area, New Delhi 110 067, Telephone: 91-11-265-30080, Facsimile: 91-11-265-30089, Email: pritu@pathindia.org

Dr Rajshankar GHOSH, Senior Programme Manager, Japanese Encephalitis, India, PATH, India, A-9, Qutab Institutional Area, New Delhi 110 067, Telephone: 91-11-265-30080, Facsimile: 91-11-265-30089, Email: ghosh@pathindia.org

Ms Shilpa RAUT, Programme Officer, PATH, India, 351, Solitaire Corporate Park, 151, M. Vasani Road, Chakala, Andheri East, Mumbai 400093, Telephone: 91-22 2823 5323/4, Facsimile: 91-22 2823 5325, Email: sraut@pathindia.org

Ms Srilatha SIVALENKA, Programme Manager, Japanese Encephalitis, Andhra Pradesh, PATH, India, APHMHIDC Building, 4th Floor, DM & HS Campus, Sultan Bazaar, Koti, Hyderabad 500 095, Telephone: 91-40-2460-0192, Facsimile: 91-40-2460-0204, Email: srilatha@pathindia.org

INDONESIA

Ms Vanda MONIAGA, Technical Officer, PATH, Indonesia, Suite 1001, Tifa Building, 10th Floor Jl. Kuningan Barat No. 26, Jakarta 12710, Telephone: 62-21-520-0737, Facsimile: 62-21-520-0621, Email: vanda@path

THAILAND

Dr Asheena KHALAKDINA, Programme Officer II, PATH, Thailand, 37/1 Soi Petchburi, 15 Petchburi Road, Bangkok 10400, Telephone: 66-2-653-7563, Facsimile: 66-2-653-7568, Email: akhalakdina@path.org

UNITED STATES OF AMERICA

Dr Julie JACOBSON, Japanese Encephalitis Project Director, PATH, USA 1455 NW Leary Way, Seattle, Washington 98107-5136, Telephone: 206-285-3500, Facsimile: 206-285-6619, Email: jjacobson@path.org

Dr Susan HILLS, Programme Officer II, PATH, USA. 1455 NW Leary Way, Seattle Washington 98107-5136, Telephone: 206-285-3500, Facsimile: 206-285-6619, Email: shills@path.org

Ms Heidi JAMES, PADM Associate, PATH, USA, 1455 NW Leary Way, Seattle, Washington 98107-5136, USA, Telephone: 206-285-3500, Facsimile: 206-285-6619, Email: hjames@path.org

Ms Kim KELLY, Programme Officer, PATH, USA, 1455 NW Leary Way, Seattle, Washington 98107-5136, Telephone: 206-285-3500, Facsimile: 206-285-6619, Email: kkelly@path.org
Annex 1

Dr Kathy NEUZIL, Vaccine Development Manager, PATH, USA, 1455 NW Leary Way, Seattle, Washington 98107-5136, Telephone: 206.285.3500, Facsimile: 206.285.6619, Email: kneuzil@path.org

Ms Deborah PHILLIPS, PATH, USA, 1455 NW Leary Way, Seattle, Washington 98107-5136, Telephone: 206-285-3500, Facsimile: 206-285-6619, Email: dphillips@path.org

Dr Chutima SURARATDECHA, Health Policy and Economics Officer, PATH, USA, 1455 NW Leary Way, Seattle, Washington 98107-5136, Telephone: 206-285-3500, Facsimile: 206-285-6619, Email: csuraratdecha@path.org

Ms Jodi UDD, Senior Programme Assistant, PATH, USA, 1455 NW Leary Way, Seattle, Washington 98107-5136, Telephone: 206-285-3500, Facsimile: 206-285-6619, Email: judd@path.org

Dr Chris VICTOR, Clinical Trials Advisor, PATH, USA, 1455 NW Leary Way, Seattle, Washington 98107-5136, Telephone: 206-285-3500, Facsimile: 206-285-6619, Email: jvictor@path.org

VIET NAM

Dr Lien Thi Huong TRAN, Programme Officer II, PATH, Viet Nam, Unit 01-02, Floor 2nd, Hanoi Towers, 49 Hai Ba Trung, Hoan Kiem District, Ha Noi, Tel: 84-4-936-2215, Fax: 84-4-9362216, Email: ltran@path.org

Dr VU Huong, Senior Team Leader, PATH, Viet Nam, Unit 01-02, Floor 2nd, Hanoi Towers, 49 Hai Ba Trung, Hoan Kiem District, Ha Noi, Viet Nam, Telephone: 84-4-936-2215, Facsimile: 84-4-9362216, Email: hvu@path.org

PEDIATRIC DENGUE VACCINE INITIATIVE

Dr Scott B. HALSTEAD, Research Director, Pediatric Dengue Vaccine Initiative, 5824 Edson Lane, Rockville, Maryland 20852, USA, Telephone: 301-984-8704, Facsimile: 301-984-4423, Email: halsteads@erols.com

UNITED NATIONS CHILDREN'S FUND (UNICEF)

Dr Stephen ATWOOD, Regional Health and Nutrition Adviser, UNICEF East Asia and Pacific Regional Office, P.O. Box 2-154, Bangkok 10200, Thailand, Telephone: (66-2) 356-9427, Facsimile: (66-2) 280-3563/4, E-mail: satwood@unicef.org

UNITED STATES AGENCY FOR INTERNATIONAL DEVELOPMENT (USAID)

Annex 1

UNITED STATES CENTERS FOR DISEASE CONTROL AND PREVENTION (US CDC)
Dr Lyle R. PETERSEN, Director, Division of Vector-borne Infectious Diseases, US Centers for Disease Control and Prevention, P.O. Box 2087 (Foothills Campus), Fort Collins, Colorado 80522, Telephone: 970 221 6428, Facsimile: 970 266 3502, E-mail: LRPetersen@CDC.GOV

Mr Marc FISCHER, Medical Epidemiologist, Arboviral Diseases Branch, US Centers for Disease Control and Prevention, 3150 Rampart Road Mailstop P-02, Trailer 1-34, Fort Collins, Colorado 80522, Telephone: 970 221 6489, Email: mxf2@cdc.gov

UNITED STATES EMBASSY IN VIET NAM
Dr Michael Iademarco, Captain, US Public Health Service, Health Attaché, Department of Health and Human Services, US Embassy, Ha Noi, Telephone: 04 831 4580 (Ext 108), E-mail: iademarcoMF@state.gov

UNIVERSITY OF LIVERPOOL, UNITED KINGDOM
Dr Penny LEWTHWAITE, Clinical Research Fellow Japanese Encephalitis, Viral Brain Infections Group, University of Liverpool, 8th Floor Duncan Building, Daulby Street, Liverpool L69 3GA, Telephone: +44 151 7064381, Facsimile: +44 151 7065805, Email: Penny.Lewhtwaite@liverpool.ac.uk

Dr Tom SOLOMON, MRC Senior Clinical Fellow, Senior Lecturer in Neurology, Medical Microbiology and Tropical Medicine, Viral Brain Infections Group, University of Liverpool, UK, 8th Floor Duncan Building, Daulby Street, Liverpool L69 3GA, Telephone: +44 151 706 4603, Facsimile: +44 151 706 5805, Email: tsolomon@liv.ac.uk

UNIVERSITY OF MALAYSIA, SARAWAK
Professor Dr Mary Jane CARDOSA, Director, Institute of Health & Community Medicine, Universiti Malaysia Sarawak, 94300 Kota Samarahan, Sarawak, Malaysia, Telephone: +60-82-671-730, Facsimile: +60 82 671 785, Email: jcardosa@ihcm.unimas.my

Dr Ooi Mong HOW, Institute of Health & Community Medicine, Universiti Malaysia Sarawak, Sibu Hospital, 94300 Kota Samarahan, Sarawak, Malaysia, Telephone: +60-82-671-730, Facsimile: +60 82 671 785, E-mail: monghow@pd.jaring.my

UNIVERSITY OF TEXAS
Dr D. T. Alan BARRETT, Professor, Department of Pathology, Associate Director for Basic Science, Sealy Center for Vaccine Development, Dept of Pathology, University of Texas, Medical Branch at Galveston, Texas 77555-0609, United States of America, Telephone: 409-772-6662, Facsimile: 409-772-2500, Email: abarrett@utmb.edu
4. SECRETARIAT

WHO WESTERN PACIFIC REGIONAL OFFICE (WPRO)

Dr YANG Baoping, Regional Adviser, Expanded Programme on Immunization, World Health Organization, Regional Office for the Western Pacific, United Nations Avenue, 1000 Manila, Philippines, Telephone: +632-528-8001, Facsimile: +632-521-1036, E-mail: yangb@wpro.who.int

Dr Manju RANI, Short-term Professional, Expanded Programme on Immunization, World Health Organization, Regional Office for the Western Pacific, United Nations Avenue, 1000 Manila, Philippines, Telephone: +632-528-8001, Facsimile: +632-521-1036, E-mail: ranim@wpro.who.int

WHO/CAMBODIA

Dr Kohei TODA, Medical Officer, Expanded Programme on Immunization, WHO Representative's Office, No. 177-179 corner Streets Pasteur (51) and 254, P.O. Box 1217, Sangkat Chak Tomnouk, Khan Daun Penh, Phnom Penh, Telephone: +855-23 216610, Facsimile: +855-23 216211, E-mail: todak@cam.wpro.who.int

WHO/CHINA

Dr Stephen HADLER, Medical Officer, Expanded Programme on Immunization, WHO Representative's Office – China, 401, Dongwai Diplomatic Office Building, Chaoyang District, Beijing 100600, Telephone: +8610 6532 7189 to 92, Facsimile: +8610 6532-2359, E-mail: hudlers@chn.wpro.who.int

WHO/LAO PEOPLE'S DEMOCRATIC REPUBLIC

Dr Seukpanya SOMPHAVAN, WHO Representative's Office – Lao People's Democratic Republic, Ban Phonxay, That Luang Road, Vientiane, Lao People's Democratic Republic, Telephone: (856) 21 413-431, Facsimile: (856) 21 413-432, E-mail: SeukpanyaS@lao.wpro.who.int

WHO/PHILIPPINES

Dr Howard SOBEL, Medical Officer, Expanded Programme on Immunization, WHO Representative's Office – Philippines, c/o Department of Health, San Lazaro Compound, Rizal Avenue, Sta. Cruz, Manila, Telephone: +632-338-7479, Facsimile: +632-731-3914, E-mail: sobelh@phl.wpro.who.int

WHO/VIET NAM

Dr Katsuyuki TSUKAMOTO, Medical Officer, Expanded Programme on Immunization, WHO Representative's Office, 63 Tran Hung Dao Street, Hoan Kiem District, Ha Noi, Telephone: +844 943-3734 (Ext 83833), Facsimile: +844 943-3740, E-mail: tsukamotok@vtn.wpro.who.int
Annex 1

WHO REGIONAL OFFICE FOR SOUTH-EAST ASIA (SEARO)

Dr Nalini RAMAMURTY, Scientist/Virologist, Immunization and Vaccine Development/ Family and Community Health, World Health Organization, Regional Office for South-East Asia, World Health House, Indraprastha Estate, Ring Road, New Delhi 110002, India, Telephone: 00 91 11 2337 0804, Facsimile : 00 91 11 2337 0106, E-mail: ramamurtyn@whosea.org

WHO/INDIA

Dr Anindya S. BOSE, Japanese Encephalitis Coordinator, National Polio Surveillance Project, World Health Organization, Gate # 31, 2nd Floor, Jawaharlal Nehru Stadium, New Delhi – 110 003, Telephone: +91 11 2436 7730, Cell: +91 98 18 59 59 23, E-mail: anindyasbose@gmail.com

WHO/INDONESIA

Dr Bardan Jung RANA, Medical Officer, Expanded Programme on Immunization, World Health Organization, 9th Floor, Bina Mulia Building 1, Jalan Rasuna Said, Kav 10, Jakarta 12950, Telephone: +62 21 520 4349, Facsimile : +62 21 520 1164, Mobile: +62 811 881292, E-mail: RanaB@who.or.id

WHO/NEPAL

Dr Jeffrey Michael PARTRIDGE, World Health Organization, UN House, Pulchowk Lalitpur, Kathmandu, Telephone: +977 1 5531831, Facsimile: +977 1 5530150, Email: partridgej@searo.who.int

WHO/THAILAND

Dr Somchai PEERAPAKORN, National Professional Officer (Programme), World Health Organization, c/o Ministry of Public Health, Building 3, 4th Floor, Tiwanon Road, Nonthaburi 11000, Telephone: +662 590 1524, Facsimile : +662 591 8199, E-mail: Somchai@searo.who.int

WHO/TIMOR LESTE

Dr Alex ANDJAPARIDZE, WHO Representative, World Health Organization, UN Agency House, Caicoli Streetk Dilli, Timor Lestek, Telephone: +670 723091k Facsimile: 25003 (GPN), Email: andjaparidzea@searo.who.int

WHO HEADQUARTERS, GENEVA

Dr Joachim HOMBACH, Coordinator, a.i., IMR/IVB/FCH, World Health Organization, 20 Av. Appia-CH-1211, Geneva 27, Switzerland, Telephone: +41 22 791 4531, Facsimile : +41 22 791 4865, E-mail: hombachj@who.int

Dr Adwoa BENTSI-ENCHILL, Medical Officer, QSS, World Health Organization, 20 Av. Appia-CH-1211, Geneva 27, Switzerland, Telephone: +41 22 791 4537, Facsimile : +41 22 791 3111, E-mail: bentsienchilla@who.int

Mr David FEATHERSTONE, Scientist, Expanded Programme on Immunization, World Health Organization, 20 Av. Appia-CH-1211, Geneva 27, Switzerland, Telephone: +41 22 791 1315, Facsimile: +41 22 791 3111, E-mail: featherstoned@who.int
THIRD BIREGIONAL MEETING ON CONTROL OF JAPANESE ENCEPHALITIS

Ho Chi Minh City, Viet Nam
26-27 April 2007

MEETING AGENDA

**Day 1: Thursday 26 April (Grand Hall, 2nd Floor)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>8:00–8:30</td>
<td>Registration</td>
<td></td>
</tr>
<tr>
<td>8:30–8:35</td>
<td>Opening remarks</td>
<td>Hans Troedsson</td>
</tr>
<tr>
<td>8:35–8:40</td>
<td>Welcoming remarks</td>
<td>Do Si Hien</td>
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</tbody>
</table>

**Session 1: Opening and welcome remarks**

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Presenter</th>
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</thead>
<tbody>
<tr>
<td>8:45–9:10</td>
<td>Overview of Japanese encephalitis (JE) control in the Western Pacific Region</td>
<td>Manju Rani</td>
</tr>
<tr>
<td>9:10–9:35</td>
<td>Overview of JE control in the South-East Asia Region</td>
<td>Nalini Ramamurty</td>
</tr>
<tr>
<td>9:35–10:00</td>
<td>Progress since the last Biregional JE Meeting in 2005</td>
<td>Julie Jacobson</td>
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10:00–10:30 | Group Photo and Coffee Break                                |                    |

**Session 2: Introduction and updates**

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<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>10:30–10:45</td>
<td>The WHO JE Surveillance Standards – refining and supporting the standards</td>
<td>Tom Solomon</td>
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<tr>
<td>10:45–11:00</td>
<td>WPRO country experiences: Cambodia</td>
<td>Sok Touch</td>
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<tr>
<td>11:00–11:15</td>
<td>Sarawak, Malaysia</td>
<td>Ooi Mong How</td>
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<tr>
<td>11:15–11:30</td>
<td>Viet Nam</td>
<td>Nguyen Thu Yen</td>
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<tr>
<td>11:30–11:40</td>
<td>Questions and discussion</td>
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<tr>
<td>11:40–11:50</td>
<td>SEARO country experiences: Nepal</td>
<td>Sarala Malla</td>
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<tr>
<td>12:00–12:10</td>
<td>Development of the Liverpool Outcome Score for assessing disability in JE</td>
<td>Penny Lewthwaite</td>
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12:20–12:30 | Questions and discussion                                   |                    |

12:30–1:30 | Lunch Hoa Mai Restaurant (5th floor)                       |                    |
Annex 2

<table>
<thead>
<tr>
<th>Session 4: Progress with JE laboratory initiatives and diagnostics</th>
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<tbody>
<tr>
<td><strong>Chair:</strong> Mohamad Ikhsan Selamat</td>
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<td><strong>1:30–2:00</strong></td>
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<td><strong>2:00–2:20</strong></td>
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<td><strong>3:00–3:15</strong></td>
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<tr>
<th>Session 5: JE vaccines and clinical trials</th>
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<tbody>
<tr>
<td><strong>Chair:</strong> Jane Cardosa</td>
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<td><strong>3:15–3:30</strong></td>
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<td><strong>3:30–3:55</strong></td>
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<td><strong>3:55–4:10</strong></td>
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<td><strong>4:25–4:40</strong></td>
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<thead>
<tr>
<th>Session 6: Group work</th>
<th>Participants to join groups to discuss topics and opportunity for Q and A</th>
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<tbody>
<tr>
<td><strong>Moderator:</strong> Manju Rani</td>
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<tr>
<td><strong>4:40–5:40</strong></td>
<td>Country group work:</td>
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<td></td>
<td>• Laboratory issues:</td>
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<tr>
<td></td>
<td>Chair: David Featherstone; Topics: JE laboratory network and support, diagnostics, and laboratory component of clinical trials</td>
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<tr>
<td></td>
<td>• Vaccine issues:</td>
</tr>
<tr>
<td></td>
<td>Chair: Joachim Hombach; Topics: opportunity for Q and A regarding JE vaccines</td>
</tr>
<tr>
<td></td>
<td>• Surveillance and vaccine introduction:</td>
</tr>
<tr>
<td></td>
<td>Chair: Susan Hills; Topics: opportunity for Q and A</td>
</tr>
<tr>
<td></td>
<td>Short report and conclusions from group discussions</td>
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<tr>
<td><strong>6:00–8:00</strong></td>
<td><strong>JE Biregional Reception at Binh Quoi Village</strong></td>
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<td>Meet in the lobby at 6 pm for transportation to the resort for dinner</td>
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</tbody>
</table>
Day 2: Friday 27 April (Grand Hall, 2nd Floor)

**Session 5: JE vaccines and clinical trials (continued)**
- **Chair (cont):** Jane Cardosa
- **Rapporteur:** Marc Fischer
- **9:00–9:20** Adverse events following immunization surveillance strengthening and initiatives
- **9:20–9:35** Post-marketing surveillance and studies with SA 14-14-2 vaccine in India
- **9:35–9:50** Effectiveness of mouse brain-derived inactivated vaccine in Viet Nam

**Session 7: JE vaccine introduction**
- **Chair:** Jane Soepardi
- **Rapporteur:** Jeff Partridge
- **9:50–10:10** Decision-making for vaccine introduction
- **10:10–10:25** India: implementation using a strategy of campaigns and integration into routine EPI
- **10:25–10:40** Break

**Session 8: Experience with vaccine financing**
- **Chair:** Sarala Malla
- **Rapporteur:** Chutima Suraratdecha
- **10:40–11:00** Cost and impact of JE vaccine introduction
- **11:00–11:40** Country experiences with vaccine financing (facilitated session with brief country presentations)
  - **11:00** Nepal
  - **11:10** India
  - **11:10** Viet Nam
  - **11:20** China
  - **11:20** India
  - **11:30** Viet Nam
  - **11:30** China
  - **11:40** Nepal
- **11:40–12:30** Summary discussion, conclusions, and action points on JE vaccines, introduction, and financing
  - **Rappourteurs:** Marc Fischer, Jeff Partridge

**Session 9: Group work: Country planning session. Discussion and review of country needs for decision-making in regards to JE immunization (surveillance and immunization)**
- **Moderator:** John Grundy
- **1:30–2:00** National planning: individual countries to decide on country priorities and needs for decision-making and to plan for areas of work in next two years
- **2:00–2:45** Discussion groups: country groups formed to discuss findings and activities
  - **2:45–3:00** Coffee Break
- **3:00–5:00** Report from each country
  - **Moderators:** Nalini Ramamurty, Julie Jacobson

**Session 10: Conclusion**
- **5:00–5:30** Summary of meeting conclusions on ensuring progress in JE control through improved surveillance, laboratory initiatives, vaccine development, and immunization programmes
## WHO DOCUMENT GUIDE

<table>
<thead>
<tr>
<th>TOPIC AREA</th>
<th>DOCUMENTS</th>
</tr>
</thead>
</table>