In 2003, several countries of the WHO South-East Asia Region had routine JE reporting and vector control measures, but immunization programmes were not prioritized. Only two countries of the Region had successful JE immunization programmes (Sri Lanka and Thailand). In the last six years, the SEA Region has seen significant activity and progress towards JE control, with sustained long-term immunization programmes and ever more countries considering vaccine introduction. In recent years, India and Nepal introduced the live, attenuated SA 14-14-2 JE vaccine, increasing to four the number of countries in the Region with sustained JE immunization programmes. Broad-based laboratory surveillance in the Region is supported and enhanced through a regional laboratory network, which has helped identify JE in many countries with previously limited information on the JE disease burden.

In WHO's Western Pacific Region, 11 countries with a total population of 1.74 billion are at risk for JE infection. Progress over the last two decades shows inequities in control, with human disease almost eliminated in the developed countries — namely, Australia, Japan, Singapore and the Republic of Korea. China, a lower middle-income country, has made significant advancements in JE control but still needs further improvement in immunization coverage.

Despite these successes, JE remains a significant public health problem in countries of both regions. The biregional meeting on JE control (7-8 June 2009) focussed on the progress made since the last biregional meeting held in 2007 in expanding surveillance activity, measures towards JE control, including establishing routine JE immunization. The report summarizes the proceedings of the meeting, and updates on progress in JE control, defining disease burden, assessing outcome after JE infection, JE laboratory network and diagnostic initiatives, JE vaccine clinical trials, planning for expansion of introduction of vaccine in JE endemic countries, and future goals and challenges in JE control.
Fourth Biregional Meeting on the Control of Japanese Encephalitis (JE)

Report of the Meeting
Bangkok, Thailand, 7-8 June 2009
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1. Introduction

The Fourth Biregional Meeting on the Control of Japanese Encephalitis (JE) for the WHO South-East Asia and Western Pacific regions of WHO was held, in collaboration with the Programme for Appropriate Technology in Health (PATH), on 7-8 June 2009 in Bangkok, Thailand. The objectives of the meeting were to:

1. Review progress in endemic countries towards JE control through immunization;
2. Provide updates and identify challenges for JE surveillance, laboratory diagnostics, and immunization strategies; and
3. Develop a future strategy for mobilizing donor support to countries to facilitate JE prevention and control.

Approximately 70 participants attended the meeting, including immunization officials from 11 JE-endemic countries and technical officers from WHO and UNICEF headquarters and regional and country offices. Industry and nongovernmental organizations, public health and academic institutions, and the Bill and Melinda Gates Foundation also were represented. The meeting’s agenda is provided in Annex 1, and a complete list of participants is provided in Annex 2.

Dr Myint Htwe, Director, Programme Management, WHO South-East Asia (SEA) Region, welcomed the participants and presented a message from the Regional Director of the SEA Region, Dr Samlee Plianbangchang, and the Director of the Western Pacific Region (WPR), Dr Shin Young-Soo. Dr Plianbangchang pointed out that “developed countries have successfully controlled the disease through a combination of better living conditions, early diagnosis and prompt treatment, immunization, and effective vector control. However, in many developing countries JE still continues to be a major public health problem with billions of people at risk of contracting the disease.”

He was pleased to see the tremendous progress made in the last few years to tackle this disease in the two regions, highlighting efforts to
accelerate JE control activities in endemic countries. However, resilient challenges remain, including financing JE programmes in resource-limited countries that bear the greatest burden—an obstacle that is particularly emphasized in the current global recession. But there is hope. Key advances include the publication of standard guidelines for JE surveillance and vaccine introduction; integration of JE within vaccine-preventable disease surveillance programmes; greater availability of standardized diagnostic kits; and the establishment of laboratory networks providing expert technical guidance.

While vaccines have proven to be superior in controlling JE in many countries, he encouraged stronger collaboration for integrated vector control, to enable us to mount comprehensive and integrated disease control that also includes effective vector control in addition to vaccination.

Finally, the Regional Director acknowledged the strong partnership that WHO and PATH have built and appreciated the support given by the Bill and Melinda Gates Foundation through PATH for the control of JE in the Asia-Pacific regions.

2. Updates on progress in JE control

2.1 Overview and progress in the South-East Asia Region

In the last six years, the SEA Region has seen significant activity and progress towards JE control, with sustained long-term immunization programmes and ever more countries considering vaccine introduction. In 2003, only two countries had successful JE immunization programmes (Thailand and Sri Lanka). Several countries had routine JE reporting, but immunization programmes were not prioritized. Many other countries considered JE to be non-existent within their borders.

In recent years, India and Nepal introduced the newly available live, attenuated SA 14-14-2JE vaccine, increasing to four the number of countries in the SEA Region with sustained JE immunization programmes. Beginning with vaccination campaigns introduced in 2006, followed by integration of JE vaccine into routine immunization services, India plans to reach 104 districts by 2010. Sixty districts were reached through 2008, and more than 40 million children were immunized. In Nepal, campaigns beginning in 2006 targeted 18 of 24 JE-endemic districts along the border with India in the lowlands, the terai. The government plans to complete
campaigns in all endemic districts and introduce the vaccine through routine immunization given at one year of age in the same areas.

Sri Lanka transitioned from the inactivated, mouse-brain-derived vaccine to the SA 14-14-2 vaccine this year, and the Democratic People’s Republic of Korea introduced this vaccine for a pilot project targeting nearly half a million children and adolescents in 2009.

In Sri Lanka and Thailand, sustained JE control efforts have demonstrated progressive declines in JE morbidity and mortality. Nepal and India also are beginning to see early signs of vaccine impact that will be formally recorded and published in the months to come.

Broad-based laboratory surveillance in the SEA Region is supported and enhanced through a regional network, which has helped identify JE in many countries with previously limited information on JE disease burden. Global surveillance standards guide countries recording JE cases.¹ Regional introduction guidelines are available for countries ready to implement JE control programmes.²

Despite these successes, JE remains a significant public health problem in the SEA Region. To carry forward the unfinished agenda, several issues must be addressed:

- Routine immunization must be sustained and supported by commitment and investment from governments and partners.
- Access to a safe and affordable vaccine must continue, and financing options must be explored for developed countries not eligible for special pricing.
- New and improved candidate vaccines must be accessible when their development is complete.
- Lingering challenges in JE diagnostics must be overcome.

➢ Surveillance must be sustained beyond donor funding.
➢ Globally, JE must remain high on the development agenda, otherwise countries will not prioritize JE control.

2.2 Overview and progress in the Western Pacific Region

Eleven countries with a total population of 1.74 billion are at risk for JE infection in the WP Region. These include six countries with known epidemics and background endemic transmission, where human disease has been partially or fully controlled with human vaccination (Australia, China, Japan, Malaysia, Republic of Korea, and Viet Nam). Cambodia and the Lao People’s Democratic Republic (PDR) are demonstrated to have endemic JE transmission but have not yet introduced JE vaccine. In addition, three countries are presumed to have endemic transmission, but the disease burden is not clearly documented — Brunei, Philippines and Papua New Guinea (PNG). Transmission may be geographically limited in some countries, as in Australia and Malaysia.

The number of JE cases reported in the WP Region has declined substantially since the 1990s. In 2008, the number of cases reported (4633) was less than one-fifth of cases reported in 1991 (25 451) (Figure 1). Since 2000, five of the region’s 11 at-risk countries have cumulatively reported less than 50 cases annually (Japan, Republic of Korea, Brunei, Australia, and Malaysia).

Figure 1: Reported JE (viral encephalitis) cases in the WP Region: 2001-2008
The greatest reduction in cases has occurred in China and Viet Nam (Figure 2), both of which have long-term JE immunization programmes. However, there may be substantial underreporting, and the actual number of total annual cases in the region may vary from 20,000 to 40,000.

Figure 2: Reported JE cases, China

Based on two prospective studies in Japan and Malaysia, the average JE case fatality rate is estimated to be about 15%. Only about 200 deaths were reported from the region in 2008, as compared to an expected number of 700 (15% of 4633), demonstrating substantial underreporting. Based on a case fatality rate of 15% and expected annual cases (20,000–40,000), the number of deaths from JE in the region may vary from 3000–6000 each year. The same studies in Japan and Malaysia estimated a disability and neuropsychiatric sequelae rate of 50%; accordingly, 10,000–20,000 children may be left disabled for life each year by JE.

Major progress has been made in JE control in the WP Region in the 1990s and 2000s. Human disease has largely been eliminated in Australia, Japan and the Republic of Korea through sustained vaccination programmes, and in the case of Singapore by elimination of pig farming and strong vector control programmes. China also has recorded a more than 90% decline in JE cases since the 1980s with the introduction of government-supported, low-fee JE immunization in high-risk provinces. (Most of China’s current JE cases occur in southern and central areas,
particularly Guizhou, Chongqing and Henan provinces.) User fees for Expanded Programme on Immunization (EPI) vaccinations, including JE vaccine, were abolished in China in 2005, and a decision was taken in December 2007 to introduce JE vaccine nationwide for eligible children by 2010. A similar decision was taken by Viet Nam, which reports the second-highest number of JE cases in the Western Pacific Region. Immunization programme expansions in these two countries will ultimately protect 82% of the region's population from JE.

However, progress over the last two decades shows inequities in control, with human disease almost eliminated in the developed countries—namely, Australia, Japan, the Republic of Korea and Singapore. China, a lower middle-income country, has made significant advancements in JE control but still needs further improvement in immunization coverage. However, almost all the region's at-risk, low-income countries have yet to achieve an optimal level of control. Viet Nam, a low-income country, is able to provide only the primary vaccination schedule of the inactivated, mouse brain-derived vaccine and has been introducing vaccine in a phased manner, with plans to provide the vaccine nationwide in 2010. Cambodia, another low-income country, is only currently able to introduce the live, attenuated SA 14-14-2 vaccine in routine services in three provinces, due to both vaccine supply and financing issues. The disease burden is yet to be established in other low-income countries due to poor disease surveillance infrastructure.

Low-income countries demonstrate the greatest need for JE control support. In many, there is no routine surveillance and, in those that do have surveillance activities, there are few resources to introduce vaccine when JE disease is demonstrated. However, political will is encouraging. Cambodia plans to introduce routine immunization with the live, attenuated SA 14-14-2 vaccine in three provinces in 2009 as a phase I introduction, with nationwide expansion in coming years. Philippines is establishing sentinel hospital surveillance. Efforts are being made to restart surveillance in Lao PDR and Papua New Guinea. Efforts also are under way to establish a WP Region regional laboratory network.

To achieve the ambitious target of eliminating clinical human JE, several obstacles will need to be overcome:

- Countries without surveillance must institute routine activities to gather data on disease burden to inform control strategies.
Many countries must recognize the geographic diversity of JE and develop or expand immunization programmes accordingly.

Vaccine financing and supply must be addressed at both country and donor levels.

Upon vaccine introduction, surveillance must be sustained and/or enhanced to demonstrate the clear impact of immunization.

Countries must continue to strengthen systems for monitoring adverse events following immunization (AEFI) in order to build data on vaccine safety.

Finally, more data must be made available to assist countries developing a policy on co-administration of JE and measles vaccines to simplify programme logistics and increase immunization coverage.

3. Update on global policies and programmes

WHO’s global activities related to JE aim to take stock of immunization efforts and identify countries that deserve specific attention by regionally defining strategies, assuring vaccine supply, confirming vaccine safety, and sharing resources. In 2006, WHO updated its position paper on JE vaccines, accounting for advances in vaccine availability and the development of recommended immunization strategies. Since then, understanding of issues in JE control has evolved further, introduction experiences have provided greater evidence on particular strategies and their impact, and new vaccines are reaching final stages of development. In November 2008, the WHO Strategic Advisory Group of Experts heard an update on JE control in the WP Region, which emphasized the global prioritization of JE control. Given this growth of understanding and the progress made over the last few years, an updated WHO position paper could be developed in the near future.

To maintain the momentum and growing attention to JE control at the global level, partners met in February 2009 to discuss continued partnership and country support beyond the PATH JE projects closure in October 2009. Participants agreed that key efforts should focus on mobilizing funds, sustaining and building awareness, advancing the
technical agenda on surveillance and diagnostics, and coordinating partners.

Among potential new funding sources, the GAVI Alliance Vaccine Investment Strategy has identified JE immunization as a priority for future support (other priority diseases include cervical cancer, rubella and typhoid). GAVI funds for JE have not been assigned, however, and it is estimated that JE prioritization activities could mirror the timeline for WHO prequalification of JE vaccine, expected by 2011. At its October 2009 meeting, the GAVI Board is expected to discuss the way forward based on assessment of possible immunization strategies, vaccine readiness and introduction challenges.

4. Progress on action points from the 2007 biregional meeting

The PATH JE project, established in 2003 with funding from the Bill and Melinda Gates Foundation, has served as a focal point in coordinating strategic activities or complementing partner programmes towards JE control. Effort to address action items identified at the 2007 biregional meeting were presented, summarizing activities conducted with PATH support (Table 1).

Table 1: Recommendations from the 2007 biennial meeting and actions taken with support from PATH’s JE project

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Follow-up action</th>
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<tr>
<td><strong>Surveillance</strong></td>
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<tr>
<td>Refine and distribute JE surveillance standards.</td>
<td>Standards distributed and implemented in both regions (print and online versions).</td>
</tr>
<tr>
<td>Integrate surveillance into other vaccine preventable diseases and etiologies of [meningo-encephalitis] ME.</td>
<td>Integrated ME surveillance in Cambodia.</td>
</tr>
<tr>
<td>Increase collaboration on disease surveillance throughout regions.</td>
<td>Training materials and manuals for laboratory procedures developed and distributed through regional laboratory networks.</td>
</tr>
<tr>
<td><strong>Recommendations</strong></td>
<td><strong>Follow-up action</strong></td>
</tr>
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<td>----------------------------------------------------------</td>
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</tr>
<tr>
<td>Increase disability reporting/monitoring.</td>
<td>Disability assessments demonstrated the importance of preventing economic and social burdens of JE (Cambodia, Indonesia and Viet Nam).</td>
</tr>
<tr>
<td>Evaluate available diagnostic methodologies.</td>
<td>Diagnostic tests, including commercial test kits, evaluated in field conditions.</td>
</tr>
<tr>
<td>Vaccine assessment</td>
<td>Studies conducted to evaluate immunogenicity and safety (Philippines and Sri Lanka), safety (India), co-administration with measles vaccine (Philippines and Sri Lanka), cost-effectiveness (Cambodia), use of SA 14-14-2 as booster after administration of inactivated vaccine (Sri Lanka). More information on study details and results is available in the “JE vaccines and clinical studies” section of this report.</td>
</tr>
<tr>
<td>Collect post-marketing surveillance data, ensuring AEFI reporting in parallel with vaccine introduction.</td>
<td>AEFI system enhanced and post marketing survey data collected (India).</td>
</tr>
<tr>
<td>Prioritize WHO prequalification of SA 14-14-2 JE vaccine.</td>
<td>Clinical studies gathered needed data, and production facility constructed according to WHO good manufacturing practices (estimated to be completed in 2010).</td>
</tr>
<tr>
<td>Advocacy</td>
<td>JE vaccines are included among GAVI Alliance priorities for future support.</td>
</tr>
<tr>
<td>Identify donor support for introduction.</td>
<td>Partners developed a strategic plan for JE control by 2015 and are establishing a working group to assume and sustain strategic activities beyond the PATH JE project.</td>
</tr>
<tr>
<td>Document lessons learned from country introduction activities.</td>
<td>Fact sheets and publications posted on enhanced PATH Vaccine Resource Library (<a href="http://www.path.org/vaccineresources/japanese-encephalitis.php">http://www.path.org/vaccineresources/japanese-encephalitis.php</a>). The online Advanced Immunization Management (AIM) e-Learning module for decision-makers and programme managers has been updated, with new content including case studies summarizing country experiences (<a href="http://aim.path.org/en/vaccines/je/index.html">http://aim.path.org/en/vaccines/je/index.html</a>).</td>
</tr>
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</table>
Beyond these specific recommendations, additional activities since 2007 have advanced JE control in several countries. India continued campaigns that had reached more than 40 million children by 2008. Sri Lanka transitioned from the mouse-brain-derived vaccine to the live, attenuated SA 14-14-2 vaccine in 2009. Cambodia plans to introduce the SA 14-14-2 vaccine in routine programmes of three provinces in October 2009. Discussions are under way for pilot vaccination campaigns to be held in July 2009 in the Democratic People’s Republic of Korea to reach nearly 500,000 children in 2009. And Bangladesh officials are planning development of a strategic plan for JE control.

As the PATH JE project moves towards close-out by December 2009, it is important to maintain its guiding principles for future activities: generating data for decision-making; ensuring access to an affordable high-quality vaccine supply; assisting countries with vaccine introduction strategies; and advocating for JE control at country, regional and global levels.

5. Defining the JE disease burden

5.1 Assessing the outcome following JE infection

Evaluating the outcome among JE survivors is a crucial step in defining the importance of sequelae, guiding treatment of children with disability following JE, and assessing the overall disease burden. However, follow-up to determine patient outcome after JE is not often conducted.

The University of Liverpool, with support from PATH, developed the Liverpool Outcome Score, a tool that is applicable across a wide range of settings and cultures, usable by non-specialists, and easy to access. The tool, which incorporates a series of motor skill observations and care-giver questions, can be used to assess children’s status at discharge and at follow-up. For each question, a score of 1-5 is applied (Table 2).
Table 2: Score applied to questions/observations using the Liverpool Outcome Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>5</td>
<td>Completely normal</td>
</tr>
<tr>
<td>4</td>
<td>Minor sequelae often not noticed by the child</td>
</tr>
<tr>
<td>3</td>
<td>Moderate sequelae, which affect function but are probably compatible with independent living</td>
</tr>
<tr>
<td>2</td>
<td>Severe sequelae, which impair function sufficiently to make the child dependent</td>
</tr>
<tr>
<td>1</td>
<td>Child died</td>
</tr>
</tbody>
</table>

To evaluate the score, researchers measured the redundancy and inter- and intra-observer variability of questions, and compared score results with a “silver” standard of assessment by a specialist clinician and an occupational therapist. The tool was piloted in Karnataka, India, in 2007. The evaluation found that the tool worked well: sensitivity was good, and specificity very good.

Through field experience and evaluation, the tool has been validated and proven to be a relatively good indicator of outcome when compared with assessment by a multidisciplinary team. Applied in Bangladesh, India, Indonesia and Malaysia, it has proven to be useful in a variety of settings. A further study using the tool in Indonesia, for example, found that half the patients died or had severe sequelae upon follow-up, and 25% recovered fully. There was a trend towards more severe sequelae in younger children, and behavioural problems were common. A long-term evaluation in Sarawak, Malaysia—with an average of 2-3 years between discharge and follow-up—found that severe or mild sequelae sometimes appeared in children who were classified as fully recovered at discharge. Children with severe sequelae at discharge also sometimes either recovered or their sequelae were reduced.

Defining the nature of disability following JE is an important first step, but increased attention to follow-up of children with sequelae is needed. There are simple, practical solutions for rehabilitation even in resource-limited settings. Many are outlined in the Liverpool guide to rehabilitation and long-term care of patients with encephalitis. Both the tool and
rehabilitation guide are available on the University of Liverpool’s website: http://www.liv.ac.uk/braininfections.

Discussion

Discussion among participants about the outcome following JE infection focused on future research needs and opportunities, including the potential of studying whether clinical predictors in the acute infection phase (severe seizures, sodium levels, quality of care) are related to long-term outcome. Use of the Liverpool Outcome Score for evaluation after other brain injuries is another potential area of study to compare with the outcome after JE infection.

5.2 Defining the JE disease burden in the SEA Region

Bangladesh

Though awareness is high among clinicians, JE is not well known to stakeholders in the Ministry of Health (MoH) in Bangladesh. Surveillance has been conducted since 2007, with support from WHO, the US Centers for Disease Control and Prevention (CDC), and the International Centre for Diarrhoeal Disease Research, Bangladesh. However, there is no immunization program for JE.

Beginning in 2007, the US CDC provided support for the acute meningoencephalitis surveillance project (AMES), with the following objectives:

- Include meningoencephalitis (ME) and JE in disease surveillance.
- Strengthen capacity for detection and reporting of ME cases.
- Estimate JE incidence rates.

The ME patients were evaluated at three hospitals, where data were collected on JE, Nipah, and etiologies of bacterial meningitis. Between October 2007 and May 2009, 1200 ME cases had been identified in 35 of 64 districts. The mean age of cases was 20 years old. JE was laboratory-confirmed in 4.66% cases. Other etiologies identified in < 3% cases were Nipah virus infection, Haemophilus influenzae type b, Streptococcus
pneumonia, Neisseria meningitidis, and Group B streptococcus. Among JE cases, 38% were < 15 years of age and 62% were male.

Acknowledging that hospital-based surveillance underestimates the total burden of JE disease, researchers in Bangladesh applied a low-cost approach to provide a better estimate of population-based JE incidence to help evaluate vaccine cost-effectiveness. To help define the denominator for incidence calculation, the researchers evaluated the proportion of patients with ME symptoms in the hospital catchment area who sought care at surveillance hospitals. Instead of costly visits to each house, they relied on community awareness of serious health events among health providers and community members to identify possible cases, then visited these houses to confirm if they were ME cases. In the three catchment provinces, they found JE incidence to be 3 cases per 100 000 in Rajshahi, 1.7 cases per 100 000 in Khulna, and 0.3 cases per 100 000 in Chittagong.

Gathering additional evidence of disease burden through continued surveillance will be a priority as Bangladesh moves towards planning for JE control through immunization. Other challenges include limited funding and a need for greater engagement with policy-makers.

**India**

The first case of human JE in India was recorded in 1955, with the first outbreak reported in 1973 in West Bengal. Since 1978, India has conducted national-level monitoring of JE.

In 2006, India strengthened syndromic acute encephalitis syndrome (AES) surveillance efforts, expanding the network and increasing diagnostic capacity. Sentinel JE surveillance is conducted at 50 sites throughout the country (Figure 3), with four sentinel sites currently supported by WHO and US CDC and to be supported by the Government of India beginning 2010. In 2007-2008, clinicians at the WHO-supported sites collected CSF, serum or both in 97% of identified AES cases.
More than 80% of AES cases are reported from Uttar Pradesh (UP), and the majority of these are from unknown causes, emphasizing the need for evaluation of etiologies other than JE. It was suggested that a greater focus on AES surveillance could be the indirect cause of an increase in reported cases, as expanded efforts have built awareness.

Most AES cases throughout India occur in children younger than 15 years old, except in Assam, where 60% cases are older than 15 years. This could be the result of vaccination campaigns targeting children and adolescents, but this has not been confirmed.

Mass JE vaccination campaigns with the live, attenuated SA 14-14-2 JE vaccine were initiated in 2006, and India has recorded an overall 7% reduction in AES/JE cases since 2007, along with a 31% reduction in deaths. The challenges to continued progress include resilient incidence of AES in UP; a marginal (16.7%) reduction in AES deaths in UP; and the higher age
group of JE cases in Assam. The coverage achieved in immunization campaigns should be evaluated and appropriate corrective measures taken.

**Discussion**

Challenges persist in efforts to determine disease burden, including difficulties in sample collection, specifically routine collection of CSF and collection of both acute and convalescent samples. Typically, JE antibodies are detected in 70%–80% of clinical JE cases upon admission to hospital. Convalescent sample collection can be very difficult, however; if using only an acute CSF or serum sample to confirm JE infection, programmes are likely to miss cases. A negative diagnosis on one acute serum or CSF sample only should actually be categorized as “AES unknown,” and a “JE negative” classification should be used only for cases that have a full set of samples collected.

Participants also discussed the potential impact of community-based rehabilitation among survivors. In Karnataka, India, for example, simple interventions for children with disability following JE have had an impact. In Sarawak, Malaysia, interventions are coordinated through a local rehabilitation centre.

The pattern of JE among older cases in Bangladesh, with 62% of cases >15 years of age, mirrors a similar trend of JE among adults in Nepal and parts of India. The definitive causes are unknown, but recent introduction of virus in new areas and migration in and out of these regions may be among the causes. These new data will have implications for control strategies in the future, particularly since the target populations for immunization and surveillance have typically been limited to children and adolescents.

**5.3 Defining the JE disease burden in the WP Region**

Representatives from select countries provided an update on surveillance activities, plans and future needs for defining the disease burden in order to inform control strategies. One study has laid a solid foundation for the establishment of routine surveillance in Lao PDR, while Viet Nam looks towards expanding JE surveillance nationwide.
Lao PDR

Little is known about JE in the Lao PDR, but it is surrounded by endemic countries. Unpublished data from Vientiane have demonstrated laboratory-confirmed, hospitalized cases. The Culex mosquito also has been identified in Lao PDR. The national government is considering vaccine introduction, but data are insufficient, and information on JE epidemiology is urgently needed.

In June 2003, researchers initiated a study on causes of central nervous system infections at Mahosot Hospital. Both cerebrospinal fluid (CSF) and serum were collected. In December 2006, with support from the WP Region and the Wellcome Trust, Mahosot Hospital and provincial hospitals expanded efforts to achieve the following:

- Determine JE incidence among AES patients (using the WHO AES syndromic case definition for identification of cases, and with confirmation of JE based on JE IgM positivity in CSF).
- Determine accuracy of the Panbio JE/dengue IgM ELISA kit.
- Develop and validate filter paper diagnostic techniques.

In addition, patient follow-up was conducted at least one year after discharge, including a complete neurological examination and use of the Liverpool Outcome Score.

Interim results (2003-2009) demonstrate that JE occurs in Vientiane and northern, central and southern Lao PDR, and incidence peaks during the rainy season. Based on CSF anti-JEV IgM results, 13% AES patients (39 of 335) had JE infection. Among JE patients, 60% were children less than 15 years of age. The most common clinical symptoms of patients with JE were fever, headache and neck stiffness. The follow-up (median 23 months after discharge) found that 8% of JE patients died in the hospital, 10% died after discharge, 15% had sequelae, 18% recovered with behavioural changes and 15% recovered fully. Thirteen discharged JE patients could not be located for follow-up.

In addition to gathering evidence on the JE disease burden, the study also found that the majority of AES is caused by other agents. Further investigation of these etiologies will be important, along with additional kit
evaluation, comparison of diagnostics using serum or CSF, filter paper serology assessment, and continued patient follow-up.

**Viet Nam**

JE immunization was introduced in Viet Nam in 1997, using a locally produced, inactivated, mouse brain-derived vaccine. The national programme expanded gradually, with the focus on high-risk districts: 520 of 686 (76%) districts were included in the programme by 2009. Routine JE immunization targets children 1-5 years old. By 2011, the government plans to expand JE immunization nationwide.

Sentinel JE surveillance in Viet Nam was initiated, with PATH support, in 2006 at three sentinel hospital sites in the northern, central and southern regions. Reporting of JE cases is integrated into the EPI surveillance system, and syndromic viral encephalitis surveillance is reported monthly from all provinces. At sentinel surveillance sites, which have variable coverage rates with JE vaccine, 6% of AES cases were found to be JE positive. By 2011, the government will support expansion of JE surveillance to 8-10 sentinel sites in four regions; however, constraints remain in terms of availability of local test kits, limited budget, and limited human resources for training and supervision.

Viet Nam has also conducted disability assessments of patients following JE infection. A study in 2 sentinel provinces assessed 28 cases at an average of 15 months after discharge. Of these, 2 cases died; 2 had severe sequelae; 13 cases had slight or moderate disabilities; and 11 cases recovered fully.

6. **JE laboratory and diagnostics initiatives**

6.1 **Progress on JE laboratory and diagnostics in the SEA Region**

Since 2005, AES surveillance has been integrated into acute flaccid paralysis (AFP) surveillance in some countries of the Region. With support from the United States’ CDC Global Disease Detection (GDD) project and PATH, JE laboratory-based surveillance has been built on the existing VPD surveillance infrastructures for polio and measles, which are extensive and already well established in most countries. However, inaccurate data are
still an issue, due to lack of good population-based surveillance systems in JE endemic countries with adequate capacity for laboratory-based confirmation of JE.

The first regional WHO JE Laboratory Network (LabNet) was launched in the SEA Region in 2006, comprising six countries (Bangladesh, India, Indonesia, Myanmar, Nepal and Sri Lanka) and 13 national and sub-national laboratories. The National Institute of Mental Health and Neurosciences (NIMHANS) in Bangalore, India, serves as the regional reference laboratory for AES testing for JE and bacterial pathogens. The United States’ CDC serves as the global specialized laboratory, and the National Institute of Virology (NIV), Pune, India is designated as the reference laboratory for detection of other viral pathogens from JEV-negative AES cases. Investment in a robust regional network allows for improved sample collection and case data; standardization of testing protocols and data management to ensure comparable results; and shared infrastructure and expertise, resulting in cost-effective resource management.

Data are reported monthly from LabNet laboratories to the programme and to WHO using a standardized format with a specified communication flow. Analysis of data from 2007 and 2008 shows that only around 10% AES cases are confirmed as JE, therefore bacterial testing has also been initiated on CSF samples. A handful of commercial kits have recently become available and are used in the LabNet for the detection of JEV IgM but, in general, availability of good quality, robust, affordable commercial kits for JEV IgM detection remains a problem for JEV diagnostics.

The greatest challenge for surveillance activities in the SEA Region is ensuring long-term sustainability of the laboratory network and enabling countries to integrate JE/AES into other VPD surveillance. The remaining challenges include:

- Expansion of LabNet to other countries, including Bhutan and Timor-Leste.
- Uninterrupted supplies of validated kits.
- Sample availability for preparation of proficiency test panels.
- Ensuring proficiency in bacterial testing for AES.
Improved linkage of surveillance and laboratory data.

In addition to addressing these challenges, plans for 2009 include development of a comprehensive tool for accreditation of laboratories, which will include monitoring of proficiency test results and other performance and timeline indicators. Efforts also will aim to improve capacity for conducting molecular assays for invasive bacterial diseases in AES cases. Finally, additional funding will need to be identified as CDC and PATH support comes to a close.

6.2 Progress on JE laboratory and diagnostics in the WP Region

Several JE-endemic countries in the WP Region conduct routine laboratory diagnosis of JE. In Malaysia, Viet Nam, China, Japan, and Korea, these efforts are well-established. Cambodia, Lao PDR and Philippines recently introduced AES/JE surveillance. However, there is an overarching need to strengthen and improve laboratory capacity across the Region.

In 2008, the WPR EPI Technical Advisory Group recommended further development of a regional network to enhance laboratory capacity and increase access to AES diagnostics (Figure 4). To date, six countries (China, Cambodia, Viet Nam, Malaysia, Lao PDR, Philippines), two regional reference laboratories (China CDC and Korea CDC), and one global specialized laboratory (Japan National Institute of Infectious Diseases) have been designated and are participating in the network. The initial training for national laboratories was held in June 2009 at the Korea CDC in Seoul. The first JE PT panels were distributed during the training and results received from laboratories have been finalized. After the training in Korea CDC, JE laboratories in the WP Region initiated monthly laboratory reports, though the monthly JE laboratory reporting form needed to be finalized by the end of 2009.
An informal JE laboratory meeting hosted by China CDC was held on 18 October 2009 to discuss the current status, challenges and future plans of the newly established JE laboratory network in the WP Region.

Several challenges to diagnostic capacity in the Region still remain, however, particularly with regard to standardization of methodology:

- Various ELISA kits—including in-house assays (e.g., Japan, Malaysia and Viet Nam) and locally-produced kits (e.g. China)—are in use with different testing algorithms that make comparisons and interpretation of results difficult.
- Some countries have decentralized systems for JE diagnosis, which complicates standardization and reporting.
- Availability and reliability of supply of commercial kits is not consistent.

Looking ahead, a monthly JE laboratory reporting system will be finalized in 2009, along with a confirmatory testing mechanism at designated JE reference laboratories and annual proficiency testing. In 2010, bacterial testing of CSF samples collected from AES cases will be
established to diagnose *Haemophilus influenzae* type b (Hib), pneumococcus, and meningococcus.

### 6.3 Standardization of JE diagnostic kits

Standardized ELISA assays are essential for use in laboratory networks to ensure comparability of data and quality assurance. Laboratories currently use several different kits, including commercial kits (Panbio, XCyton, Inbios, and Beixi) and “in-house” assays (AFRIMS, US CDC, NIID, NIMHANS, NIV, University of Malaysia, Sarawak, National Institute of Hygiene and Epidemiology [Viet Nam], and Pasteur Institute [Viet Nam]).

Assessments and field evaluations of the commercial kits by the United States’ CDC have identified a range of issues, including insufficient reagents supplied for testing small batches of samples, leakage of reagents, low sensitivity, lot-to-lot variability and delays in supply. Manufacturers are working with WHO to resolve these problems. Encouragingly, these assessments have found high specificity among all of the commercial kits, which is a key point for surveillance activities.

Quality control remains a critical focus, due to variability of kit use in field settings. It is essential that assays have undergone evaluation. Referral structures to confirm positives and subsets of negatives are also important. With funding assistance from PATH, the United States’ CDC and WHO are developing a validation panel composed of a well-characterized set of samples from AES cases in several countries. The panel will contain 200 samples of both CSF and sera, either JE IgM positive, JE IgM negative, flavivirus IgM positive, or all flavivirus IgM negative. The panel will be used to validate the various in-house kits used in the SEA Region and LabNets in the WP Region to better understand how they compare to each other.

### 6.4 Evaluation of JEV IgM ELISA kits

The United States CDC arbovirus diagnostic and reference laboratory recently completed an evaluation of JEV IgM ELISA kits manufactured by Panbio, XCyton, Inbios and NIV. A specimen panel of more than 400 serum and CSF samples collected from AES patients in Bangladesh and India, as part of the CDC’s GDD project on AES surveillance, were classified according to the United States’ CDC arbovirus serological testing
algorithm, which included JEV and DENV IgM ELISA, with confirmation by JEV and DENV plaque reduction neutralization test (PRNT). A subset of specimens were also tested by WNV IgM ELISA and PRNT, as there was evidence of false JE positives due to antibody cross-reactivity with other flaviviruses. Using the United States’ CDC results as the reference standard, the kits had sensitivities ranging from 17%–75% and specificities of 85%–100% (Table 3).

Table 3: Kit performance based on the United States’ CDC reference standard

<table>
<thead>
<tr>
<th>Assay</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSF</td>
<td>Serum</td>
</tr>
<tr>
<td>NIV</td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>Panbio</td>
<td>75</td>
<td>32</td>
</tr>
<tr>
<td>XCyton</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Inbios</td>
<td>75</td>
<td>61</td>
</tr>
</tbody>
</table>

Generally, the kits had high specificity. However, although the kits had higher sensitivities with CSF than sera, overall results of this evaluation show that kit sensitivity is an issue. Further analyses were done in an attempt to determine if there was an association between the ability of the kits to detect JEV IgM and the level of JEV IgM in the specimen. Included in the analyses were specimens collected within the first few days following the onset of symptoms, when IgM is first elicited; those diluted to endpoints of JEV IgM detection; and those grouped as high or low JEV IgM positives based on CDC ELISA positive-to-negative (P/N) ratios. No factors were evidently common to all kits that would account for the significantly lower sensitivities. Further analyses of the kits is necessary and ongoing at CDC.

Researchers recommend that manufacturers consider modifying elements such as cut-off values and stability of reagents during transportation to improve kit performance. Publication of complete results is forthcoming.
Discussion

Discussion among attendees emphasized that identification of etiologies and bacterial testing among JE negative samples will be important as JE vaccine use is expanded. Also, since specificity and sensitivity issues remain with several kits, additional evaluations were suggested. Because commercial assays are problematic, confirmation through reference laboratories in regional networks is the only current option. But the validation panel will help for in-house evaluation.

A question was raised regarding why viral detection by polymerase chain reaction (PCR) was still conducted when it had not proven worthwhile. At NIV, for example, JEV IgM positive and RT-PCR positive are found in equal numbers. The United States’ CDC found no positives in more than 100 CSF samples collected less than three days post-onset of symptoms. These samples had undergone numerous freeze–thaw cycles and had been stored at or near room temperature for unknown periods of time, which likely degraded the RNA.

It is recommended that virus detection assays should only be done on CSF in designated specialized laboratories to enhance diagnosis of very acute JE cases with possible false-negative IgM results. The CSF specimens should be collected within the first few days of illness and maintained in good condition. Even under these conditions, virus detection assays are not useful for diagnostic purposes due to their low sensitivity in JE cases, in which the low-level, transient viremia is generally cleared, or below the level of detection, soon after onset of symptoms.

7. JE vaccines and clinical studies

7.1 Current vaccines and future candidates

There are three JE vaccines currently or soon to be available for international paediatric use (Table 4). In addition, inactivated, mouse brain-derived vaccines are produced in limited supply mainly for domestic use in Korea, Thailand and Viet Nam. In India and Japan, production of the inactivated, mouse brain-derived vaccine has resumed, at least temporarily. An inactivated, Vero cell-derived vaccine is produced and used exclusively in China. Two vaccine candidates have been developed in Japan based on
the Beijing strain: BK-VJE by Biken and KD-287 by Kaketsuken. The Biken product was registered in Japan in early 2009.

New JE vaccines close to entering the commercial market include Ixiaro®, a two-dose inactivated, cell culture-derived vaccine manufactured by Intercell. In early 2009, Ixiaro® received approval from the US Food and Drug Administration, the European Medicines Agency, and the Australian Therapeutic Goods Association. The current licensure is for the traveller, military and adult markets only, but paediatric trials of Ixiaro evaluating safety and dosage are ongoing in India in collaboration with Biological E.

Sanofi Pasteur is developing Imojev®, a live, cell culture-derived vaccine with a yellow fever/JE chimera. Clinical studies demonstrated safety and immunogenicity among children and adults, and licence applications have been submitted in Australia and Thailand.

Table 4 presents characteristics of the three JE vaccines that are or will soon be available on the international market.

**Table 4**: Characteristics of JE vaccines currently or soon to be available for international use

<table>
<thead>
<tr>
<th></th>
<th>Live, attenuated SA 14-14-2</th>
<th>Ixiaro®</th>
<th>Imojev®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Prevention of JE, beginning at nine months of age</td>
<td>Prevention of JE in adults (paediatric trials ongoing)</td>
<td>Prevention of JE, beginning at 12 months of age</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Chengdu Institute of Biological Products.</td>
<td>Intercell AG (partnership with Biological E in India)</td>
<td>Sanofi Pasteur.</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>Varies by country: single dose only or booster after one year.</td>
<td>Two doses, days 0 and 28, compressed schedules studied.</td>
<td>Single dose, reconstituted in 0.5ml diluent.</td>
</tr>
<tr>
<td></td>
<td><strong>Live, attenuated SA 14-14-2</strong></td>
<td><strong>Ixiaro®</strong></td>
<td><strong>Imojev®</strong></td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Case control study demonstrated &gt;95% after five years.</td>
<td>Seroconversion at day 28 post-primary: 98.9% (Intention to treat population) (non-inferiority trials against inactivated, mouse brain-derived vaccine).</td>
<td>Seroconversion at day 28: 99% (CI 97.5;99.8) (non-inferiority trials against inactivated, mouse brain-derived vaccine); High seroprotection rate against wild-type strains.</td>
</tr>
<tr>
<td><strong>Long-term immunogenicity</strong></td>
<td>Five years and more, according to case-control studies.</td>
<td>Confirmed up to 24 months (adults).</td>
<td>Confirmed up to 60 months (adults).</td>
</tr>
<tr>
<td><strong>Sero-protection against wild-type viruses</strong></td>
<td>Confirmed for all four genotypes.</td>
<td>Confirmed for all four genotypes.</td>
<td>Confirmed for all four genotypes.</td>
</tr>
<tr>
<td><strong>Booster needs</strong></td>
<td>To be confirmed</td>
<td>To be determined.</td>
<td>To be determined.</td>
</tr>
<tr>
<td><strong>Coadministration</strong></td>
<td>Acceptable short-term safety profile of coadministration with measles vaccine.</td>
<td>Studied for hepatitis A vaccine, others to follow.</td>
<td>Studied for hepatitis A vaccine, others to follow.</td>
</tr>
<tr>
<td><strong>Safety/tolerability</strong></td>
<td>No safety signals.</td>
<td>Similar to placebo, better than comparator vaccine.</td>
<td>No safety signals, better than comparator vaccine.</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Currently available internationally.</td>
<td>Adult availability in US, EU, Australia; paediatric trials ongoing; Indian licensure expected after Phase 3 trial starting in 2009.</td>
<td>Application for paediatric and adult licensure submitted in 2009 in Thailand and Australia; targeting endemic countries.</td>
</tr>
<tr>
<td><strong>Prequalification</strong></td>
<td>Targeted</td>
<td>Targeted</td>
<td>Targeted</td>
</tr>
</tbody>
</table>
**Vaccine demand**

At the request of the GAVI Alliance, Applied Strategies developed a forecast of JE vaccine need and adoption, estimating that the majority of introductory catch-up campaigns in endemic countries would occur from 2011–2013. Future demand would level out at around 24 million doses per year in 2018–2020, taking into account the needs of late-adopting countries, integration of the vaccine into routine programmes, and booster schedules.

**Remaining challenges**

Future issues regarding JE vaccine availability include licensing strategies of new vaccines, as well as targeting of public or private sectors or both. Additionally, pricing schedules and the availability of support from donors including GAVI will need to be resolved.

As prequalification is contingent on a high-quality, well-functioning National Regulatory Authority in the country of manufacture, the WHO Strategic Advisory Group of Experts at its November 2008 meeting “encouraged the regulatory agency in China and the Chinese manufacturer of the SA-14-14-2 vaccine to take the necessary steps to facilitate prequalification of the vaccine”.

**7.2 Recent clinical studies**

*Live, attenuated SA 14-14-2 vaccine (Chengdu Institute of Biological Products)*

Recent clinical studies of the live, attenuated SA 14-14-2 vaccine have primarily addressed programmatic issues including coadministration with measles vaccine to facilitate introduction into routine services and the ability of the SA 14-14-2 vaccine to be provided to children who already have received doses of the inactivated mouse brain-derived vaccine. As the vaccine’s use becomes more widespread (Table 5), these studies will provide important information for developing country control strategies.
Table 5: Current registration status of live, attenuated SA 14-14-2 JE vaccine

<table>
<thead>
<tr>
<th>Year of registration</th>
<th>Country</th>
<th>Usage and projected demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988 China</td>
<td></td>
<td>15 million (m) doses/year</td>
</tr>
<tr>
<td>2001 Republic of Korea</td>
<td></td>
<td>0.7 m doses/year</td>
</tr>
<tr>
<td>2003 Sri Lanka</td>
<td></td>
<td>0.9 m doses (2009)</td>
</tr>
<tr>
<td>2006 India</td>
<td></td>
<td>28m doses (2008), 34 m (2009), (40 m planned for 2010)</td>
</tr>
<tr>
<td>2007 Thailand</td>
<td></td>
<td>0.1 m (2008), 0.3 m (2009)</td>
</tr>
</tbody>
</table>

A clinical study initiated in Philippines in 2005 evaluated the safety and immunogenicity of coadministering the SA 14-14-2 JE vaccine and the EPI measles vaccine. After two years of follow-up, in 2007, there was no significant difference in immunogenicity. The WHO Global Advisory Committee on Vaccine Safety had previously reviewed the short-term data and concluded that the short-term safety profile of live JE vaccine given with measles vaccine was acceptable, even though coadministration suggests a minor but statistically significant drop in measles vaccine GMT and seroconversion.

Another study in Sri Lanka, initiated in 2007, also evaluated the safety and immunogenicity of coadministering the EPI measles vaccine and the SA 14-14-2 JE vaccine. In both studies, the seropositivity rates for both JE and measles were high after follow-up at one year and demonstrated no interference. Safety assessments found no severe local reactions, and no severe systemic reactions were considered by the investigators to be related to vaccination.

A second part of the study in Sri Lanka aimed to determine the safety and immunogenicity of the SA 14-14-2 JE vaccine among two- and five-year-old children who had previously received doses of the mouse brain-derived, inactivated vaccine. At one year follow-up, the titre for JE seroconversion increased among the group receiving the SA 14-14-2 booster. Complete data were received in Q2 2009 and are currently being analysed.
**Imojev® (Sanofi Pasteur)**

The Imojev® vaccine by Sanofi Pasteur is progressing through clinical development, and recent studies are yielding important data on its use among adult and paediatric populations. A Phase 3 safety study among adults compared the safety profile of Imojev with that of the inactivated JE-VAX® vaccine and placebo. Seroprotection was recorded in 99% subjects after 28 days, and 88% are expected to be protected 48 months following a single dose. The frequency of mild systemic reactions were comparable among the vaccines and placebo, and injection site reactions to Imojev occurred less frequently than with JE-VAX.

A paediatric study among Thai children found Imojev to produce a high seroprotection rate after 28 days against JE-CV and wild-type strains. Imojev demonstrated efficient booster ability among children who previously received inactivated vaccine, and a single dose conferred seroprotective level of antibodies equal to approximately 95% of naïve toddlers. No serious adverse events were reported.

Lot-to-lot consistency also has been demonstrated. Finally, the manufacturer Sanofi Pasteur will target the endemic-country market and does not plan to target traveller markets for the United States and Europe.

The manufacturer submitted the vaccine for registration in Thailand and Australia in mid-2009.

**Ixiaro® (Intercell)**

Immunogenicity and dosing of the Ixiaro vaccine from Intercell was studied among paediatric populations in India. Among children aged one to three years of age, the vaccine demonstrated excellent safety and immunogenicity when administered in both full and half adult doses. Ixiaro also demonstrated a lower rate of adverse events as compared to the inactivated JenceVac™ vaccine. Phase 3 clinical trials among children are planned to begin in India in 2009.

Ixiaro has received regulatory approval in the United States, the European Union and Australia. Intercell has partnered with Biological E. Ltd. (India) for manufacturing and marketing in Bangladesh, Bhutan, India and Nepal; and with Novartis for other markets in Asia.
7.3 JE control experiences (International Vaccine Institute)

A key partner in the Region, the International Vaccine Institute (IVI) supports JE activities in Bangladesh (assessing disease burden), Viet Nam (refining national immunization), and DPR Korea (prevention of JE and Hib).

Bangladesh

To determine the extent of JE and inform future introduction strategies, IVI is supporting surveillance at three hospitals. Activities were initiated in November 2008, and results will identify age distribution and the possible need for a JE immunization programme, based on recorded disease burden. Initial results will be available by August 2009.

Viet Nam

In Viet Nam, IVI partnered with the National Institute of Hygiene and Epidemiology (NIHE) to establish a case-referral system to track JE in Ha Tay province, where large numbers of AES cases have been reported consistently. To support this work, IVI established a JE diagnostics laboratory and trained staff.

IVI evaluated the current JE immunization programme, which is conducted through campaigns for children aged 12 months. A case control study determined the locally produced JE vaccine to be 93% effective, but children aged six to 23 months who were not covered in the annual campaign bore the greatest burden of JE cases. The incidence among older children (5 to 14 years of age) was 2.5/100 000. Based on these findings, IVI recommended the following policy updates, which will be scientifically evaluated once implemented:

- Administer one booster dose to children at age six.
- Vaccinate as early as six months of age.
- Explore transition to live, attenuated vaccine requiring a single dose.
Democratic People’s Republic of Korea

Activities supported by IVI and the Democratic People’s Republic of Korea Ministry of Unification include capacity building for laboratory staff and improvement of laboratory facilities, which will support surveillance set to begin in 2010. A pilot vaccination campaign against Hib and JE brought the live, attenuated SA 14-14-2 JE vaccine to nearly 3000 children, and no severe adverse events were reported. The cold chain was well maintained, and the vaccines were highly accepted by the target population, with 100% coverage achieved.

Discussion

Participants discussed additional topics to be addressed in future research, including a further study on the interaction between flaviviruses, as demonstrated in lower JE vaccine titres among dengue-positive children in Sri Lanka. Another suggestion was evaluation of the mouse brain-derived vaccine administered at six months, in order to facilitate introduction into routine immunization services. However, there are currently no data on this vaccine given to this age group.

8. Introduction of JE vaccine: country experiences

8.1 Transition from mouse brain-derived to live, attenuated JE vaccine (Sri Lanka)

Japanese Encephalitis outbreaks in Sri Lanka were suspected since 1948, and the first recorded outbreak occurred in 1985, with a case fatality rate of 16.6%. In subsequent years, additional outbreaks recorded case fatality rates of 19.8% and 23.6%, respectively. In response, the Government of Sri Lanka introduced phased vaccination campaigns in 1988 using the inactivated, mouse brain-derived JE vaccine. The JE vaccine became part of the routine programme in 18 of 26 health districts in 1994, based on the endemicity of JE, and morbidity and mortality rates declined as coverage increased (Figure 4).
New challenges have emerged, with sporadic outbreaks in districts without immunization, demonstrating a need for national expansion. The AEFI surveillance system also has recorded a growing trend of AEFIs with the inactivated vaccine. Cost is an additional issue, as inactivated JE vaccine supply comprises three quarters of the national vaccine budget. Given these challenges, sustainability of the JE immunization programme was threatened. Upon review of SAGE recommendations, scientific literature, evidence of impact in China, India, and Nepal cost-effectiveness, national EPI managers suggested transition to the live, attenuated SA 14-14-2 vaccine.

The Advisory Committee on Communicable Diseases called for local safety and immunogenicity data, and a safety and immunogenicity study was conducted. With the positive preliminary results of the study the committee’s approval of transition to the SA 14-14-2 JE vaccine was given. In July 2009, the SA 14-14-2 vaccine was introduced into the routine immunization services in the 18 districts. Cost-savings derived from the negotiated pricing from the vaccine’s manufacturer will allow for programme sustainability, budget for the introduction of other new vaccines, expansion of JE immunization to vulnerable adults in high-risk areas, and the potential to add a second dose of JE vaccine, if necessary.

Sri Lanka’s future JE control strategy will focus on expanding vaccination to all districts nationwide, intensifying post-introduction
surveillance, and vaccinating cohorts missed due to limited supply of the inactivated vaccine in 2007-2008.

8.2 Adjusting the dosing regimen and refining national strategy (China)

Japanese Encephalitis is one of 39 notifiable diseases in China, and detailed information on suspected clinical and laboratory-confirmed cases have been reported online since 2007 under the National Notifiable Disease Reporting System. Sentinel surveillance is conducted at 26 sites that record acute viral encephalitis cases. Pig and mosquito surveillance supplements these efforts.

The current JE incidence in the country is 0.3 cases per 100,000; 4000 cases were reported from 24 provinces in 2007, mostly among children younger than 15, with a peak at two to six years old. Since 2007, the CDC’s GDD has supported the Acute Meningitis and Encephalitis (AMES) project in four provinces. Annual AES cases are about 10 per 100,000 population. Combining passive and active surveillance resulted in two to three times more incidence recorded than passive surveillance alone.

The inactivated, mouse brain-derived JE vaccine was introduced in 1968; the live, attenuated SA 14-14-2 vaccine was introduced in 1988, and vaccination expanded nationwide in 2008. A domestically produced, inactivated, Vero-cell-derived vaccine is used in some districts, with no significant immunological difference recorded between two doses of this vaccine and one dose of the live vaccine.

The use and study of the SA 14-14-2 vaccine has yielded important evidence:

- Current schedule is first dose at 8 months of age, second dose at 2 years.
- Efficacy is 98% with this schedule; 96% in the long term. (Zhou B. A large-scale study on the safety and epidemiological efficacy of Japanese encephalitis [JE] live vaccine (SA14-14-2) in the JE endemic areas. Chinese Journal of Epidemiology. 1999; 20[1]:38-41)
A case control study showed 80-99% efficacy after one dose and >95% after two doses (see Table 6 for complete references).

Six years after the booster dose, antibody detection rate was 57 or 75%. (Jia Lili. Observation on persistence of neutralizing antibody after inoculation of JE live vaccine in volunteers. *Chinese Journal of Vaccine and Immunization*. 2003; 9[2]:111-113)

Based on this review, China modified its existing three-dose SA 14-14-2 JE vaccine schedule to the current schedule, which is first dose at 8 months of age and second dose at 2 years. The current inactivated JE vaccine schedule in China is 4 doses (2 primary doses at 7-10 day interval at 8 months and boosters at 2 and 6 years of age).

Further research is needed on efficacy of the Vero cell vaccine. Future activities also will involve surveillance strengthening, prevention of adult cases, and continued research on the immunogenicity and safety of JE vaccines.

**Table 6:** Published studies on vaccine efficacy of live, attenuated SA 14-14-2 JE vaccine

<table>
<thead>
<tr>
<th>Year</th>
<th>Journal</th>
<th>Authors</th>
<th>Age of admin.</th>
<th>Dosing schedule</th>
<th>Time after vaccination</th>
<th>Efficacy (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td><em>Lancet</em></td>
<td>Hennessy, et al.</td>
<td>&lt;15y</td>
<td>≥1</td>
<td>Same year</td>
<td>80</td>
<td>44 – 93</td>
</tr>
<tr>
<td>1996</td>
<td><em>Lancet</em></td>
<td>Hennessy, et al.</td>
<td>&lt;15y</td>
<td>≥2, with 1y interval</td>
<td>Same year</td>
<td>97.5</td>
<td>90.1 – 99.2</td>
</tr>
<tr>
<td>2001</td>
<td><em>Lancet</em></td>
<td>Bista, et al.</td>
<td>1-15y</td>
<td>1</td>
<td>1 year</td>
<td>99.3</td>
<td>94.9 – 100</td>
</tr>
<tr>
<td>2003</td>
<td><em>Chinese Journal of Vaccines and Imm.</em></td>
<td>Wenge</td>
<td>1-6y</td>
<td>≥1</td>
<td>Same year</td>
<td>95.98</td>
<td>72.03 – 99.42</td>
</tr>
<tr>
<td>2005</td>
<td><em>Lancet</em></td>
<td>Ohrr, et al.</td>
<td>2-16y</td>
<td>1</td>
<td>1 year</td>
<td>98.5</td>
<td>90.1 – 99.2</td>
</tr>
<tr>
<td>2007</td>
<td><em>Vaccine</em></td>
<td>Tandan</td>
<td>6-20y</td>
<td>1</td>
<td>5 years</td>
<td>96.2</td>
<td>73.1 – 99.9</td>
</tr>
</tbody>
</table>
8.3 Planning for JE vaccine introduction (Cambodia)

The JE virus in Cambodia was first isolated in 1965, and research from 1996-2005 confirmed JE as the cause of at least 20-30% of all clinical encephalitis cases. To gather evidence for decision-making on JE control, the Government of Cambodia initiated several activities:

- Sentinel surveillance commencing in May 2006, supported by PATH and WHO, found that 16-19% of ME patients under 15 years of age admitted in sentinel hospitals were JE-positive. National incidence was estimated at 7.3 JE cases per 100,000 population in 2006 and 8.2 per 100,000 in 2007 by extrapolating the results of JE sentinel site surveillance to the overall reported cases of ME nationwide.

- A disability assessment (December 2007-March 2008) found that, at follow-up of 54 confirmed cases, 13% of children had died and 81% had sequelae.

- A cost-effectiveness analysis (June 2007-March 2009), with support from PATH, incorporated household interview and hospital data collection at five sentinel sites and found that the average medical cost during hospitalization was US$ 235. Average medical and non-medical costs during hospitalization and in the 90-day period afterwards totalled US$ 440. Out-of-pocket expenditures accounted for 80% of monthly household income.

- An analysis of averted health outcomes found that JE vaccination campaigns among children aged 1-10, followed by routine immunization, would have the highest impact on health outcomes and the highest savings in health costs. JE vaccination was determined to be very cost-effective.

The evidence gathered through these activities informed the Ministry of Health’s plan to immunize children against death and disability associated with JE. However, funds are yet to be mobilized for the campaign, and campaign activities could not be included in the initial strategy. Beginning in September 2009, routine JE immunization will be provided through a Phase I introduction in three provinces (Kampong Cham, Svay Rieng, and Takeo), with the live, attenuated SA 14-14-2
vaccine given in a single dose to children after they receive measles vaccine. Regular AEFI monitoring will follow vaccine introduction.

Along with these significant steps forward, challenges remain for the Cambodia JE immunization programme, including the need for further AEFI system strengthening. The establishment of a National Regulatory Authority (NRA) is in progress. The ME surveillance came under the oversight of the National Immunization Program in January 2009.

8.4 Challenges of integrating JE vaccine into routine immunization (India)

India has phased in JE vaccination campaigns in endemic districts since 2006, with more than 40 million children reached through 2008. The government’s strategy included administration of the live, attenuated SA 14-14-2 JE vaccine through campaigns, followed by introduction to routine immunization services at 16 to 24 months, at the time of the recommended EPI visit for DTP at 18 months. PATH supported national and state trainings, IEC and social mobilization. The Government of India (GoI) took on all other expenses for the strategy and estimates expenditures to total US$ 31 million through 2011.

Many states (Tamil Nadu, Karnataka, Maharashtra and UP) have transitioned to routine immunization (RI) following campaigns; however, others have experienced delays in introducing the vaccine in routine services for various reasons: need for capacity building among health personnel, lack of standardized guidelines, difficulties incorporating JE coverage reporting, and deficiencies in management of the cold chain. Logistics bottlenecks between district and state levels also have been challenging.

To address these issues, GoI held two national-level training workshops in 2008 and two state-level training workshops in 2009. To overcome challenges in logistics and reporting, states have established separate procurement orders for campaigns and RI and now maintain a buffer stock of 25%. Detailed guidelines for introduction and for reporting JE vaccine coverage also have been distributed. To further support the RI programme, committees were constituted at national, state and district levels for AEFI training.
Future efforts will continue to advance routine JE immunization, as well as to ultimately make the vaccine available at health centres for children up to five years who missed the campaigns.

**Discussion**

The primary discussion item involved the dosing schedule for SA 14-14-2. Guidelines from WHO currently recommend two doses, but indicate that carefully planned studies are required to establish firm recommendations on the optimal immunization schedule. Further data are needed to confirm the number of doses and best schedule for long-term protection, which also emphasizes the need for post-marketing surveillance.

**9. The future of JE control**

**9.1 Global vision**

To build on progress and define needs beyond the PATH JE project, PATH—with inputs from multiple partners—developed the strategy document *Japanese encephalitis morbidity, mortality, and disability: Reduction and control by 2015*. This control plan describes the advances made through partnerships over the last several years, moving from defining disease burden and answering research questions to assisting countries with introduction and monitoring of JE immunization programmes. Through the efforts of many and the commitment of country governments, JE control is truly feasible. However, significant disease burden remains. Activities and contributions must ensure that momentum and progress seen over the past few years is maintained.

The document is meant to evolve over the next two years, as partners convene and identify strategic activities for collaboration towards JE control. The current edition was distributed to meeting participants. Main sections of the plan are summarized below.
**Background**

The public health significance of JE is summarized, including the current status of surveillance and control in JE-endemic countries (based on country presentations from the 2007 Biregional Meeting).

**Strategic plan**

This section outlines strategies and defines targets that partners agreed were pivotal to advancing JE control, along with estimates of financial resources needed to implement them:

- Strengthen JE surveillance and define burden (including resolution of laboratory/diagnostics issues).
- Ensure access to prequalified vaccine.
- Support immunization programmes.
- Meet clinical care needs.
- Answer outstanding research questions.
- Sustain and expand awareness.

Looking ahead, WHO will be the key leader in implementing strategic efforts and coordinating partner contributions, with support from a core working group of partners. Another pivotal responsibility of this future partnership will be to ensure that JE remains a priority among funders, including the GAVI Alliance.

### 9.2 Resources available for information-sharing and advocacy

Several tools and resources are available to build and maintain awareness about JE disease and vaccine and to inform policy-making at country and global levels. Interactions with country and regional officials have revealed that the greatest gap in awareness involves the safety of JE vaccines and the status of new vaccine candidates. Over the past few years, several new publications have added to the knowledge base on JE vaccines. In addition to peer-reviewed literature, organizations focused on JE control continue to publish key materials:


WHO. Manual for the laboratory diagnosis of JE virus infection. 2007.


The PATH Vaccine Resource Library (http://www.path.org/vaccineresources) maintains an up-to-date archive of these and other resources on JE, as well as other VPDs (Figure 5). The library is searchable and sortable, categorizing content according to technical areas such as surveillance and disease burden, vaccine safety, and immunization financing.

PATH’s Advanced Immunization Management (AIM) e-Learning tool (http://aim.path.org) launched an update to the JE module in June 2009. The AIM was developed to provide comprehensive information to support immunization programme managers at all stages of country-level decision-making. Content ranges from basic disease information through immunization session planning. The 2009 JE update added new information on vaccine safety, available and forthcoming vaccines, country experiences and case studies, and advocacy.
These resources provide a good foundation for addressing advocacy needs that are important to consider in keeping JE control moving forward. It will be important for countries and partners to communicate support for control so that JE stays on national and international agendas. Knowledge gaps should continue to be identified and addressed by the development of new and updated resources, while partners and countries must document experiences to inform future activities.

10. Status of JE control activities by country

Participants convened in groups according to status of JE control activities in order to identify strategies over the next five to six years. In the groups, country representatives held frank and open discussion of existing issues and challenges. Following these discussions, officials from countries represented at the meeting presented programme status, challenges and strategies to all attendees.
<table>
<thead>
<tr>
<th>Group 1: Non-vaccinating countries with some evidence of disease burden</th>
<th>Surveillance</th>
<th>Immunization</th>
<th>Decision-making needs</th>
<th>Financial issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>ME and JE surveillance at four hospitals. 4.7% JE positive among ME cases. 62% cases ≥ 15 years old. Incidence: varies from 0.3 to 3/100 000 population.</td>
<td>Expand ME and JE surveillance to six admin. divisions. Include AES in web-based surveillance system. Record seroprevalence among pigs. Evaluate vector density.</td>
<td>None. Examine nationwide burden. Identify target population. Feasible pilot introduction by 2011.</td>
<td>Vaccine dosage. Vaccine safety. Vaccine regulatory mechanism. Lessons learned from India.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2: Non-vaccinating countries with no convincing evidence of disease burden</th>
<th>Surveillance</th>
<th>Immunization</th>
<th>Decision-making needs</th>
<th>Financial issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhutan</td>
<td>No routine surveillance; random, limited samples sent outside for testing have confirmed JE. Passive surveillance: ME and encephalitis reported, but etiology not studied (CFR</td>
<td>Active AES surveillance in southern district with laboratory confirmation, beginning by end 2009. Initial hospitals in southern border district with planned expansion. Supported by</td>
<td>None. Potential decision on vaccine introduction by end-2012, with possible RI by 2014.</td>
<td>JE burden. Burden of bacterial agents causing AES.</td>
</tr>
</tbody>
</table>

Plan to involve government, NGOs and development partners. Financial support required for strategy of campaign plus RI. Resources needed for supervision, training, logistics, and laboratory support (especially in next two years).
### Group 2: Non-vaccinating countries with no convincing evidence of disease burden

<table>
<thead>
<tr>
<th>Surveillance</th>
<th>Immunization</th>
<th>Decision-making needs</th>
<th>Financial issues</th>
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<tbody>
<tr>
<td><strong>Lao PDR</strong></td>
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<tr>
<td><strong>ME and encephalitis included in 19 notifiable diseases reported weekly to central level.</strong></td>
<td><strong>Strengthen surveillance system in all provinces using serum samples.</strong>&lt;br&gt;<strong>Refresh hospital worker training.</strong>&lt;br&gt;<strong>Expand capacity for CSF collection at some sentinel sites.</strong>&lt;br&gt;<strong>Training on surveillance and specimen collection and analysis.</strong>&lt;br&gt;<strong>Quality control from reference laboratory.</strong></td>
<td><strong>Consideration for introducing JE vaccine is in cMYP.</strong>&lt;br&gt;<strong>At least two years until data are available to inform decision-making on JE control.</strong></td>
<td><strong>Funding required for training, supplies, transportation, laboratory costs, program monitoring, and follow-up of confirmed cases.</strong>&lt;br&gt;<strong>94% of current immunization program funded externally.</strong></td>
</tr>
<tr>
<td><strong>14% in 2007.</strong>&lt;br&gt;<strong>Passive disability reporting but data not analysed.</strong>&lt;br&gt;<strong>Regional WHO laboratory in border district of (Assam)/India Assam (Gelephu hospital).</strong>&lt;br&gt;<strong>Two technicians trained, protocol for AES surveillance developed, health workers sensitized.</strong></td>
<td><strong>reference lab at national level.</strong>&lt;br&gt;<strong>Establish another public health laboratory in 2011 (supported by GoI).</strong>&lt;br&gt;<strong>World Bank support for additional laboratory capacity at central facility.</strong></td>
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### Group 2: Non-vaccinating countries with no convincing evidence of disease burden

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<tr>
<th>Surveillance</th>
<th>Immunization</th>
<th>Decision-making needs</th>
<th>Financial issues</th>
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<tr>
<td>Current</td>
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<td>Current</td>
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<tr>
<td>used for reference.</td>
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### Group 3: Vaccinating countries with need for geographical expansion

<table>
<thead>
<tr>
<th>Surveillance</th>
<th>Immunization</th>
<th>Decision-making needs</th>
<th>Financial issues</th>
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<tbody>
<tr>
<td>Current</td>
<td>Planned</td>
<td>Current</td>
<td>Planned</td>
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<tr>
<td>India 7.2% JE positivity among AES cases (&gt;90% of cases are children missed during campaigns).</td>
<td>Continue surveillance of disease burden with focus on improved coordination.</td>
<td>Campaigns among 1-15 year olds with single dose of live, attenuated SA 14-14-2 vaccine. 44.5 million immunized in 2006-2008 campaigns. Inclusion of vaccine in RI among 16-24 month olds in new birth cohorts.</td>
<td>Campaigns to cover 110 endemic districts in 11 states by 2010, targeting 86.5 million children. Expansion required due to cases reported in new states. Further strengthening of AEFI system. 2009: National workshop to review vaccination schedule and geographical coverage. 2010-11: Plan for vaccine introduction in remaining areas.</td>
</tr>
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</table>
### Group 3: Vaccinating countries with need for geographical expansion

<table>
<thead>
<tr>
<th>Surveillance</th>
<th>Immunization</th>
<th>Decision-making needs</th>
<th>Financial issues</th>
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<tbody>
<tr>
<td><strong>Malaysia</strong></td>
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<tr>
<td>Case-based surveillance with lab confirmation. Incidence 0.4/100,000 population. Cases from Sarawak are 80% of all cases in Malaysia. Vector surveillance.</td>
<td>Continue surveillance. Improve clinician, laboratory, and health department communication. Mouse brain-derived vaccine provided in EPI since 2001, limited to Sarawak; two doses, followed by booster at 18 months; boosters every three years.</td>
<td>No plans for program expansion. Improve coverage. Develop functioning AEFI system.</td>
<td>Fully funded through MoH.</td>
</tr>
<tr>
<td><strong>Nepal</strong></td>
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<tr>
<td>Surveillance system at 120 sites in all 75 districts, built on AFP system with case confirmation at national laboratory. Laboratory-confirmed JE appearing in greater number of districts (now up to 40 districts), even in mountainous and hilly areas.</td>
<td>Continue surveillance. Assess protection among vaccinated population. Single dose of SA 14-14-2 vaccine provided in 22 districts since 2006, with 94% coverage (preliminary estimate). Strategy varies: targeting 1-15 year olds in some districts and all population above 1 year in others. By end 2009, all 22 districts will have RI, targeting 12-23 month olds; JE vaccination included in multi-year plan.</td>
<td>Conduct campaigns in 5 districts; continue to introduce RI. Consider expansion of vaccination into new districts. Strengthen AEFI system. Program will continue through 2015.</td>
<td>Routine schedule will be reviewed in context of co-administration of JE and measles vaccines. Plan for expansion. In 2010, National Committee on Immunization Practices will review program and make recommendations.</td>
</tr>
</tbody>
</table>

**Nepal**

- Surveillance system at 120 sites in all 75 districts, built on AFP system with case confirmation at national laboratory. Laboratory-confirmed JE appearing in greater number of districts (now up to 40 districts), even in mountainous and hilly areas.
- Continue surveillance. Assess protection among vaccinated population.
- Single dose of SA 14-14-2 vaccine provided in 22 districts since 2006, with 94% coverage (preliminary estimate). Strategy varies: targeting 1-15 year olds in some districts and all population above 1 year in others. By end 2009, all 22 districts will have RI, targeting 12-23 month olds; JE vaccination included in multi-year plan.
- Conduct campaigns in 5 districts; continue to introduce RI. Consider expansion of vaccination into new districts. Strengthen AEFI system. Program will continue through 2015.
- Routine schedule will be reviewed in context of co-administration of JE and measles vaccines. Plan for expansion. In 2010, National Committee on Immunization Practices will review program and make recommendations.

**Financial issues**
- Fully funded through MoH.
### Group 3: Vaccinating countries with need for geographical expansion

<table>
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<tr>
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<tr>
<td>Current</td>
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<tr>
<td><strong>Vietnam</strong></td>
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<tr>
<td>Surveillance system not good enough to provide information on effectiveness of immunization program. Estimated incidence level with vaccination is not clear.</td>
<td>Continue surveillance with potential expansion nationwide using serum samples. Special disease burden study.</td>
<td>Domestically produced mouse brain-derived vaccine introduced from 1997; 3-dose primary series at 1–5 years old: second dose 1-2 weeks after; third dose 1 year after. 76% of districts covered by 2008. Coverage with third dose was 92% in 2008; greater than 90% since 2003.</td>
<td>2009-2010: Include JE in cMYP. 2011: Introduce vaccine in remaining districts; monitor coverage. Through 2015: Continue to monitor immunization program.</td>
</tr>
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### Vaccinating countries with nationwide JE immunization programmes

<table>
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<tr>
<th>Surveillance</th>
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<tbody>
<tr>
<td>Current</td>
<td>Planned</td>
<td>Current</td>
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<tr>
<td><strong>China</strong></td>
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<tr>
<td>Online JE/viral encephalitis reporting system. Meningitis and encephalitis surveillance in sentinel sites. One of the regional JE network laboratories is located in China.</td>
<td>Continue surveillance. Improve surveillance sensitivity.</td>
<td>Live, attenuated and inactivated JE vaccines used in national program. 16 districts with JE vaccine integrated into EPI have &gt;85% coverage. Since 2005, &gt; 25 provinces collect AEFI and report to national level.</td>
<td>Improve coverage.</td>
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</table>
### Vaccinating countries with nationwide JE immunization programmes

<table>
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<tr>
<th></th>
<th>Surveillance</th>
<th>Immunization</th>
<th>Decision-making needs</th>
<th>Financial issues</th>
</tr>
</thead>
</table>
| **Republic of Korea** | Nationwide case-based surveillance  
Median age of JE cases since 2001 is 46, ranging from 11-85.  
Vector surveillance. | Extensive surveillance to determine imm. status of adult cases.  
Collect mosquitos in 52 sites nationwide.  
Conduct training on laboratory diagnosis (with WPR support). | Mouse brain-derived vaccine; two doses given as a nation wide program 1-2 weeks apart, third dose after one year; boosters at 6 and 12 years.  
Live, attenuated SA 14-14-2 vaccine used in private sector. | n/a | Data on adult cases.  
Program supported by national government. |
| **Thailand**    | Estimated incidence is 0.5 per 100,000 among 1-4 year olds; 0.2-0.3 per 100 000 among all ages. | Continue surveillance and continue monitoring vaccine coverage.  
Domestically produced mouse brain-derived vaccine; 2-dose primary series, with booster after 1 year.  
2008 coverage was 89% with full series and booster.  
Functioning AEFI system is in place. | 2009: Endorse vaccine policy on domestic production, strengthen AEFI system.  
2010: Develop new JE vaccine candidate with potential for export to regional market.  
2016 and beyond: Continue to develop alternative vaccine candidates. | Capacity of surveillance system to provide information on program impact: need both access to lab diagnostics for the majority of cases and strengthened link between clinical and laboratory data. | Government fully funds program.  
Resources needed for surveillance strengthening, continuing RI, needed campaigns.  
JE included in cMYP. |
11. Conclusion

Activities conducted through partnerships established by PATH’s JE project have achieved success from many perspectives. Countries have made JE a higher priority than ever. Although significant resources are still needed, countries now have a good idea of what is needed to implement and sustain JE surveillance and have access to a safe and affordable vaccine. Globally, WHO has provided leadership in defining JE control policies and strategies, as well as providing technical assistance to countries to introduce the vaccine, in addition to collaborating with partners on research and standardization of diagnostics.

Global control plan as framework for national planning

The draft JE global control plan (Japanese encephalitis morbidity, mortality, and disability: Reduction and control by 2015) will be a useful framework for national planning, and countries were encouraged to review their respective JE control plans in line with this document. Many participants stated that it would be desirable to set control targets where feasible, as they would help influence policy decisions and resource allocation for a comprehensive JE control strategy. Without a target, it will be difficult to measure progress. Targets may need to vary depending on situations and settings, and a goal at the national level may help to accelerate a control programme. Regional and global targets are useful in respect of advocacy for policy-makers, and can guide development of country targets.

Surveillance will be crucial, so that there are data to measure against a target, and the growing sensitivity of surveillance systems could call for an evolution of targets. Incidence targets should be linked with surveillance goals or perhaps a target of AES incidence, since JE diagnostics remain complex and hard to implement routinely. This is in line with the WHO surveillance standards as well, which include minimum AES incidence to determine JE burden.

Evaluating non-JE AES etiologies

As AES surveillance and access to laboratory diagnostics improves, awareness of the spectrum of AES is increasing. Not only in Asia, but in research studies worldwide, etiologies are not determined in more than half
of AES cases. However, while evaluation of AES aetiologies to address the issue of non-JE encephalitis is important, it should not detract from progress towards JE control, as the proportion of AES due to JE is preventable through vaccination. It is likely that the attributable fraction of AES due to JE is greater than the proportion determined to be JE-based on laboratory confirmation of cases. Therefore, JE control remains an important step in reducing a country’s AES burden.

**Mobilizing national and international support**

The PATH’s JE project was catalytic in advancing the JE agenda in the Asia-Pacific Region, but the project ended in October 2009. Therefore, identifying future support for JE control efforts is a critical issue. National governments’ commitment in endemic countries is an important first step to identify resources at the country level. Countries that have more advanced JE control programmes can share their experiences with others to inform strategies for advocacy to health ministers, and early engagement of the Ministry of Finance may be very helpful in generating programmatic funding support. Demonstration of the full extent of JE disease and its aftermath, including disability and associated loss of productivity, can be influential in helping national policy-makers understand the full impact of JE and the need for resource allocation for disease prevention and management. However, in many cases, external funding will still be required, and efforts are needed to identify potential resources at country, regional and global levels.

Donors may also be interested in supporting health equity, as JE is a disease that primarily impacts poor populations. A JE vaccination policy could be matched with policies to address issues of the rural poor. In addition, a portfolio approach to address diseases of public health concern, rather than a disease-by-disease approach, may prove more effective in convincing donors to support. Therefore, JE control activities should be presented within the wider context of addressing health systems and other priority public health concerns.

Some of the unfinished issues that will still need support include:

- Further refinements in the standardization of diagnostic tools and approaches.
> Evaluation of long-term effectiveness of the live, attenuated SA 14-14-2 vaccine to determine appropriate dosing schedules.

> Establishment of robust surveillance systems, integrating JE surveillance with that for other VPDs.

> Ensuring access to JE vaccine in the period prior to WHO prequalification.

12. **Acknowledgements**

The WHO Regional Office for South-East Asia gratefully acknowledges the support provided by the Ministry of Health, Thailand for hosting the Fourth Bi-regional Meeting on Japanese Encephalitis and to PATH for providing funding and administrative support.

Special thanks are also extended to representatives from Member States of the WHO South-East Asia and Western Pacific regions as well as partner agencies for their participation and contributions to proceedings.
Annex 1

Agenda

Day 1: Monday, June 8, 2009

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<thead>
<tr>
<th>Time</th>
<th>Title</th>
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<tbody>
<tr>
<td>8:00–8:30</td>
<td>Registration</td>
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Session 1: Opening and welcome remarks

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<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30–8:35</td>
<td>Welcome</td>
<td>MoH, Thailand</td>
</tr>
<tr>
<td>8:35–8:45</td>
<td>Opening remarks</td>
<td>RD Representative</td>
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Session 2: Introduction and updates

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<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:45–9:05</td>
<td>Overview and progress in JE control in the South-East Asia Region</td>
<td>Pem Namgyal</td>
</tr>
<tr>
<td>9:05–9:25</td>
<td>Overview and progress in JE control in the Western Pacific Region</td>
<td>Manju Rani</td>
</tr>
<tr>
<td>9:25–9:35</td>
<td>Global update on policies and programmes (SAGE, GIVS, GAVI)</td>
<td>Joachim Hombach</td>
</tr>
<tr>
<td>9:35–9:45</td>
<td>Progress since the last Biregional JE Meeting in 2007: PATH JE project</td>
<td>John Wecker</td>
</tr>
<tr>
<td>9:45–10.00</td>
<td>Questions, discussion</td>
<td></td>
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</tbody>
</table>
## Session 3: Defining disease burden: country experiences with acute encephalitis/JE surveillance and disability assessment

**Chair:** Manju Rani  
**Rapporteur:** Deborah Phillips

<table>
<thead>
<tr>
<th>Time</th>
<th>Agenda Item</th>
<th>Presenter/Region</th>
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</thead>
<tbody>
<tr>
<td>10:30–10:45</td>
<td>Assessing outcome in Japanese encephalitis</td>
<td>Tom Solomon</td>
</tr>
<tr>
<td>10:45–11:30</td>
<td>The WP Region country experiences:</td>
<td></td>
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<tr>
<td>10:45–11:00</td>
<td>Lao PDR: Recent evidence on disease burden and disability</td>
<td>Mayfong Mayxay</td>
</tr>
<tr>
<td>11:00–11:15</td>
<td>Viet Nam: Assessing disease burden</td>
<td>Nguyen Van Cuong</td>
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<tr>
<td>11:15–11:30</td>
<td>Discussion</td>
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<tr>
<td>11:30–12:15</td>
<td>The SEA Region country experiences:</td>
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<tr>
<td>11:30–11:45</td>
<td>A low cost method to estimate burden of JE in Bangladesh</td>
<td>Mahmudur Rahman</td>
</tr>
<tr>
<td>11:45–12:00</td>
<td>India – progress report of JE Surveillance</td>
<td>V. K. Raina (tent)</td>
</tr>
<tr>
<td>12:00–12:15</td>
<td>Discussion</td>
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## Session 4: Progress with JE laboratory initiatives and diagnostics

**Chair:** Tom Solomon  
**Rapporteur:** Asheena Khalakdina

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<tr>
<th>Time</th>
<th>Agenda Item</th>
<th>Presenter/Region</th>
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<tbody>
<tr>
<td>1:30–1:50</td>
<td>Development of JE lab network in Western Pacific Region</td>
<td>Youngmee Jee</td>
</tr>
<tr>
<td>1:50–2:10</td>
<td>JE lab network activities in the South-East Asia Region: Progress, challenges and lessons learned</td>
<td>Nalini Ramamurty</td>
</tr>
<tr>
<td>2:10–2:25</td>
<td>Standardization of JE diagnostic kits—progress, challenges, and options</td>
<td>David Featherstone</td>
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<tr>
<td>2:25–2:40</td>
<td>Evaluation of JE assays</td>
<td>Barbara Johnston</td>
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<tr>
<td>2:40–3:00</td>
<td>Discussion</td>
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</table>
### Session 5: JE vaccines and clinical studies

**Chair:** S. D. Khaparde  
**Rapporteur:** Deborah Phillips

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>3:30–4:00</td>
<td>JE vaccines: current status, future candidates, and timelines</td>
<td>Joachim Hombach</td>
</tr>
<tr>
<td>4:00–4:30</td>
<td>Results from recent clinical studies</td>
<td>Mansour Yaïch</td>
</tr>
<tr>
<td>4:30–4:45</td>
<td>Updates and impacts of the IVI's JE programmes in Vietnam, Bangladesh, the DPRK and Indonesia</td>
<td>Florian Marks</td>
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<tr>
<td>4:45–5:00</td>
<td>Questions and discussion</td>
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</table>

### Day 2: Tuesday, 9 June

### Session 6: Progress in the introduction of JE vaccine

**Chair:** Pem Namgyal  
**Rapporteur:** Deborah Phillips

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>8:30–8:45</td>
<td>Sri Lanka: Transition from mouse-brain derived vaccine to SA-14-14-2</td>
<td>Ranjan Wijesinghe</td>
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<td>8:45–9:00</td>
<td>China: Adjusting the dosing regimen and refining the national strategy</td>
<td>Yin Zundong</td>
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<td>9:00–9:15</td>
<td>Cambodia: Plans for pilot introduction of SA-14-14-2</td>
<td>Savay Sarath</td>
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<td>9:15–9:30</td>
<td>India: Challenges of routine JE immunization post-campaign</td>
<td>S. D. Khaparde   (tent)</td>
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<td>9:30–9:45</td>
<td>Questions and discussion</td>
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### Session 7: Future of JE Control: vision, resources, planning

**Chair:** Susan Hills  
**Rapporteur:** Vivien Tsu

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<td>9:45–9:55</td>
<td>Global vision: outline of draft Global Control Plan</td>
<td>James Cheyne     (tent.)</td>
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<td>9:55–10:10</td>
<td>Update on technical and advocacy resources</td>
<td>Deborah Phillips</td>
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<td>10:10–10:20</td>
<td>Orientation to Group Work</td>
<td>Manju Rani</td>
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Session 8: Group work: Country planning session on JE control (surveillance and immunization)

10:35–12:00 National planning: small groups of countries share experience and decide on individual country priorities and needs for decision-making and work plans for next two years; finalize country presentations with template provided

Session 9: Country presentations on their work plans

Moderator: Nalini Ramamurty
Rapporteur: Deborah Phillips

1:00–2:00 Presentations from SEAR countries
2:00–2:15 Questions
2:15–3:15 Presentations from WPR countries
3:15–3:30 Questions

Session 10: Conclusion

Moderators: Joachim Hombach John Wecker

3:45–4:15 Global control plan as framework for national planning (Discussion) John Wecker
4:15–4:45 Mobilizing support at national and international level (Discussion) Diana Chang Blanc
4:45–5:00 Summary of meeting conclusions on ensuring progress in JE control Joachim Hombach
Annex 1

List of participants

<table>
<thead>
<tr>
<th>Country participants</th>
<th>Cambodia</th>
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<tbody>
<tr>
<td><strong>Bangladesh</strong></td>
<td></td>
</tr>
<tr>
<td>Dr Abdul Jalil Ahmad</td>
<td>Dr Keo Samley</td>
</tr>
<tr>
<td>Assistant Director</td>
<td>Medical Officer</td>
</tr>
<tr>
<td>CDC</td>
<td>National Immunization Program</td>
</tr>
<tr>
<td>Directorate General of Health Services</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>Mahakhali</td>
<td>151-153 Kampuchea krom Street</td>
</tr>
<tr>
<td>Dhaka 1212</td>
<td>Phnom Penh</td>
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<tr>
<td>Bangladesh</td>
<td>Cambodia</td>
</tr>
<tr>
<td>Prof Mahmudur Rahman</td>
<td>E: <a href="mailto:keos@nip.gov.kh">keos@nip.gov.kh</a></td>
</tr>
<tr>
<td>Director</td>
<td></td>
</tr>
<tr>
<td>Institute of Epidemiology, Disease Control &amp; Research (IEDCR)</td>
<td></td>
</tr>
<tr>
<td>Mahakhali, Dhaka 1212</td>
<td></td>
</tr>
<tr>
<td>Bangladesh</td>
<td></td>
</tr>
<tr>
<td>Dr A. K. F. Mozibur Rahman</td>
<td>Dr Svay Sarath</td>
</tr>
<tr>
<td>Programme Manager</td>
<td>Deputy Manager</td>
</tr>
<tr>
<td>Expanded Programme on Immunization</td>
<td>National Immunization Programme</td>
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<td>Bangladesh</td>
<td>Cambodia</td>
</tr>
<tr>
<td>E: <a href="mailto:mrahman@citechco.net">mrahman@citechco.net</a>, <a href="mailto:mrahman57@hotmail.com">mrahman57@hotmail.com</a></td>
<td>E: <a href="mailto:svays@nip.gov.kh">svays@nip.gov.kh</a></td>
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<tr>
<th><strong>Bhutan</strong></th>
<th>China</th>
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<tr>
<td>Dr Karma Lhazeen</td>
<td>Prof Liang Guodong</td>
</tr>
<tr>
<td>Chief Program Officer</td>
<td>Institute for Viral Disease Control and Prevention</td>
</tr>
<tr>
<td>Vector-Borne Diseases Control Program</td>
<td>China Centers for Disease Control and Prevention</td>
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<tr>
<td>Ministry of Health</td>
<td>100 Ying Xin Jie</td>
</tr>
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<td>Gelephu</td>
<td>Xuan Wu Qu</td>
</tr>
<tr>
<td>Bhutan</td>
<td>Beijing 100052</td>
</tr>
<tr>
<td>E: <a href="mailto:klhazeen@hotmail.com">klhazeen@hotmail.com</a></td>
<td>China</td>
</tr>
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<tr>
<td>Dr Yin Zundong</td>
<td>Dr Yin Zundong</td>
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<td>National Immunization program</td>
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<tr>
<td>China Center for Disease Control</td>
<td>China Center for Disease Control</td>
</tr>
<tr>
<td>27 Nanwei Road</td>
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<tr>
<td>E: <a href="mailto:yinzdnip@hotmail.com">yinzdnip@hotmail.com</a></td>
<td>E: <a href="mailto:yinzdnip@hotmail.com">yinzdnip@hotmail.com</a></td>
</tr>
</tbody>
</table>
India
Dr Anindya Sekhar Bose  
National Polio Surveillance Project  
World Health Organization  
RK Khanna Tennis Stadium  
Africa Avenue  
New Delhi 110029  
India  
E: anindyasbose@gmail.com, bosean@npsuindia.org

Dr Milind M. Gore  
Scientist F  
National Institute of Virology  
Gorakhpur Unit  
BRD Medical College Campus  
Gorakhpur 273013, Uttar Pradesh  
India  
E: gore.milind@gmail.com, milind_gore@hotmail.com

Dr V. K. Raina  
Director  
National Vector-Borne Diseases Control Program  
22 Sham Nath Marg  
Delhi 110054  
India  
E: vkr_20032003@yahoo.com, raina.vinod1@gmail.com

Lao People’s Democratic Republic
Dr Somvang Bouphaphanh  
Senior EPI Technical Officer  
Expanded Programme on Immunization  
Ministry of Health  
Km3 Thadeua Road  
Vientiane, Capital  
Lao People’s Democratic Republic  
E: b_somvang@yahoo.com

Dr Kongmany Southalack  
Deputy Director  
National Center for Laboratory and Epidemiology  
Ministry of Health  
Km3 Thadeua Road  
Vientiane  
Lao People’s Democratic Republic  
E: k_southalack@yahoo.com

Malaysia
Dr Mohd Hafizi Abdul Hamid  
Assistant Director (JE/Filariasis/Thypus)  
Disease Control Division  
Ministry of Health  
Level 4, Block E10, Parcel E  
62590 Putrajaya  
Malaysia  
E: dr.mhafizi@moh.gov.my

Nepal
Dr Naresh Pratap K. C.  
Regional Director  
Regional Health Directorate  
Dhankuta  
Nepal

Dr Geeta Shakya  
Senior Consultant Pathologist  
National Public Health Laboratory  
Ministry of Health & Population  
Teki, Kathmandu  
Nepal  
E: npnl@wlink.com.np

Dr Shyam Raj Upreti  
Director  
Child Health Division,  
Department of Health Services  
Ministry of Health & Population  
Pamshah Path  
Teki, Kathmandu  
Nepal  
E: drshyam@hotmail.com

Republic of Korea
Dr Myung Guk Han  
Senior Researcher  
Division of Arboviruses,  
Center for Immunology & Pathology  
National Institute of Health, Korea Centers for Disease Control and Prevention  
194 Tongil-Lo  
Eunpyung-Gu  
Seoul 122-701  
Republic of Korea  
E: mghan@nih.go.kr, greenmghan@yahoo.com
Thailand

Dr Attaya Limwattanayayingyong  
Medical Officer  
National Vaccine Committee Office  
Department of Disease Control,  
Ministry of Public Health  
Tiwanon Road  
Nonthaburi 11000  
Thailand  
E: attaya@gmail.com

Dr Piyanit Tharmaphornpilas  
EPI Program Manager  
Bureau of General Communicable Diseases  
Ministry of Public Health  
Tiwanon Road  
Muang  
Nonthaburi 11000  
Thailand  
E: piyanit@health.moph.go.th

Ms Nongyao Somdach  
Medical Scientist  
Division of Biological Products,  
Department of Medical Sciences  
Ministry of Public Health  
Tiwanon Road  
Nonthaburi 11000  
Thailand

Vietnam

Mrs. Nguyen Thi Thanh Ha  
EPI Staff  
Public Health Department  
Pasteur institute, Ho Chi Minh City  
167 Pasteur  
District 3  
Ho Chi Minh City  
Vietnam  
E: hantno@gmail.com

Dr Nguyen Van Cuong  
National Expanded Programme on Immunization  
National Institute of Hygiene and Epidemiology  
1 Yersin Street  
Hanoi  
Vietnam  
E: vancuong@fpt.vn

Organizations

AFRIMS

Dr Khin Saw Myint  
Head, Emerging Pathogens  
Department of Virology  
AFRIMS  
315/6 Rajvithi Road  
Bangkok, 10400  
Thailand  
E: MyintK@afriims.org

Bill & Melinda Gates Foundation

Dr Julie Jacobson  
Bill & Melinda Gates Foundation  
1551 Eastlake Ave  
Seattle, WA  
United States of America  
E: Julie.Jacobson@gatesfoundation.org

Chengdu Institute of Biological Products

Ms Yang Lingjiang  
Manager  
International Business and Corporation  
Chengdu Institute for Biological Products  
Baojiang Bridge, Sichuan Province  
Chengdu 610023  
People's Republic of China  
E: yanglingjiang@hotmail.com

ICDDR,B

Dr Jahangir Hossain  
ICDDR,B  
Mohakali  
Dhaka-1212  
Bangladesh  
E: jhossain@icddrb.org

International Pediatric Association

Prof Usa Thisyakorn  
Professor  
Department of Pediatrics  
International Pediatric Association  
Chulalongkorn University  
Bangkok 10330  
Thailand  
E: uthisyakorn@gmail.com,  
femeduty@md2.md.chula.ac.th
International Vaccine Institute
Dr Florian Marks
The International Vaccine Institute
Kwanak, P.O. Box 14
Seoul, 151-600
Republic of Korea
E: fmarks@ivi.int

Liaoning Cheng Da Biotechnology Co. Ltd
Mr Mao Yu
Manager for Foreign Trade
Foreign Trade Department
Liaoning Cheng Da Biotechnology Co. Ltd
No. 1 Xinfang Street
Hunnan New District
Shenyang 110179
People's Republic of China
E: maoyu@0516@sina.com,
yangxu1972@yahoo.com

Mahidol University at Salaya
Dr Sutee Yoksan
Centre for Vaccine Development
Mahidol University at Salaya
25/25 Phutthamonthon 4, Salaya
Nakhonpathom 73170
Thailand
E: grsys@mahidol.ac.th

Novartis Vaccines
Dr Theodore Tsai
Senior Vice President for Scientific Affairs
Novartis Vaccines
350 Massachusetts Ave
Cambridge, MA 02139
United States of America
E: theodore.tsai@novartis.com

Oxford University Tropical Medicine Research Unit
Dr Mayfong Mayxay
Head of Field Research
Tropical Medicine Research Unit
Oxford University
Mahosot Hospital
Vientiane
Lao People's Democratic Republic
E: mayfong@tropmedres.ac

PATH
Cambodia
Dr Samnang Chham
Project Officer
PATH
PATH, Cambodia
PO Box 1684
Phnom Penh
Cambodia
E: csamnan@path.org

France
Dr Mansour Yaïch
Vaccine Development Advisor
PATH, France
Batiment Avant Centre
13 Chemin du Levant
01210 Ferney Voltaire
France
E: myaich@path.org

India
Mr Pritu Dhalaria
Program Officer II
PATH, India
A-9, Qutab Institutional Area
New Delhi 110067
India
E: pdhalaria@path.org

Ms Shalini Khare
Program Officer
PATH, India
A9 Qutab Institutional Area
USO Road
New Delhi 110017
India
E: skhare@path.org

Indonesia
Ms Vanda Moniaga
Technical Officer
PATH, Indonesia
Suite 1001, Tifa Building, 10th Floor
Jl. Kuningan Barat No. 26
Jakarta 12710
Indonesia
E: vanda@path
Seattle

Dr Jessica Fleming
Program Officer
Immunizations Solutions
PATH, USA
1455 NW Leary Way, Seattle
Seattle, WA 98107
United States of America
E: jfleming@path.org

Dr Amy Ginsburg
Program Officer
JE project
PATH, Seattle
1455 NW Leary Way
Seattle, WA 98107
United States of America
E: aginsburg@path.org

Ms Erin Kester
Program Assistant
Immunization Solutions
PATH, USA
1455 NW Leary Way
Seattle, WA 98107
United States of America
E: ekester@path.org

Ms Deborah Phillips
PATH, USA
1455 NW Leary Way
Seattle, WA 98107-5136
United States of America
E: dphillips@path.org

Dr Chutima Suraratdecha
Health Policy and Economics Officer
PATH, USA
1455 NW Leary Way
Seattle, WA 98107-5136
United States of America
E: csuratardecha@path.org

Ms Ginger Townsend
Project Administrator
Immunization Solutions
PATH, USA
1455 NW Leary Way
Seattle, WA 98107
United States of America
E: gtopel@path.org

Dr Vivien Tsu
Deputy Director
JE Project
PATH, Seattle
1455 NW Leary Way, Seattle
Seattle, 98107
United States of America
E: vtsu@path.org

Dr John Wecker
Director
Immunization Solutions
PATH
1455 NW Leary Way
Seattle, WA 98107
United States of America
E: jwecker@path.org

Thailand

Mr Brian McLaughlin
Country Leader
Thailand and Cambodia
PATH
37/1 Petchburi Soi 15
Petchburi Road
Bangkok 10400
Thailand
E: bmclaughlin@path.org

Dr Asheena Khalakdina
Program Officer II
PATH, Thailand
37/1 Soi Petchburi
15 Petchburi Road
Bangkok 10400
Thailand
E: akhalakdina@path.org

Vietnam

Dr Lien Tran
Program Officer II
PATH, Vietnam
Unit 01-02, Floor 2nd, Hanoi Towers
49 Hai Ba Trung, Hoan Kiem District
Ha Noi
Vietnam
E: ltran@path.org
Dr Huong Vu  
Senior Team Leader  
PATH, Vietnam  
Unit 01-02, Floor 2nd, Hanoi Towers  
49 Hai Ba Trung, Hoan Kiem District  
Ha Noi, Vietnam  
E: hvu@path.org

Sanofi Pasteur  
Dr Sabine Arnoux  
Assistant Manager of Public Affairs  
Asia Pacific Public Affairs  
Sanofi Pasteur  
2 Avenue du Pont Pasteur  
69367 Lyon Cedex 07  
France  
E: sabine.arnoux@sanofipasteur.com

WHO-TDR Clinical Coordination and Training Center (CCTC)  
Dr Thongchai Thavichachart  
Consultant for External Coordination  
WHO-TDR Clinical Coordination and Training Center (CCTC)  
Thammasat University (Rangsit Campus)  
1st Floor, Academic Affairs Building  
99 Mu 18, Phaholyothin Road  
Klongluang, Pathumthani 12121  
Thailand  
E: thongchai.ls@gmail.com

UNICEF  
Ms Diana Chang-Blanc  
Regional Immunization Advisor  
East Asia and Pacific Regional Office  
UNICEF  
PO Box 2-154  
Bangkok 10200  
Thailand  
E: dchangblanc@unicef.org

Universiti Malaysia Sarawak  
Dr Mong How Ooi  
Universiti Malaysia Sarawak  
90 Taman Top Green Literature Villa  
Jalan Kapor 93150  
Kuching, Sarawak  
Malaysia  
E: monghow@pd.jaring.my

University of Liverpool  
Dr Tom Solomon  
Medical Microbiology and Tropical Medicine  
Viral Brain Infections Group  
University of Liverpool  
8th Floor Duncan Building, Dalbby Street  
Liverpool L69 3GA, United Kingdom  
E: tsolomon@liv.ac.uk

University of Melbourne  
Mr John Grundy  
Consultant  
Nossal Institute for Global Health  
University of Melbourne  
Cambodia  
E: johnjgrundy@hotmail.com

United States Centers for Disease Control and Prevention  
Dr Susan Hills  
Medical Epidemiologist  
Arboviral Diseases Branch  
US Centers for Disease Control and Prevention  
3150 Rampart Road  
Fort Collins, CO 80521  
United States of America  
E: hri1@cdc.gov

Dr Barbara Johnson  
Research Microbiologist  
Diagnostic and Reference Laboratory, Arboviral Diseases Branch  
US Centers for Disease Control and Prevention  
3150 Rampart Road  
Fort Collins, CO 80521  
United States of America  
E: bfj9@cdc.gov

Dr Hardeep Singh Sandhu  
Medical Epidemiologist  
Surveillance and Vaccine Introduction Team, Strengthening Immunizations Branch  
US Centers for Disease Control and Prevention  
1600 Clifton Road NE  
Atlanta, GA 30329-1902  
United States of America  
E: hjs3@cdc.gov
World Health Organization

Mr David Featherstone
Lab Coordinator
Expanded Programme on Immunization
World Health Organization
Avenue Appia 20
1211 Geneva
Switzerland
E: featherstoned@who.int

Dr Keith Feldon
Technical Officer
Expanded Programme on Immunization
World Health Organization
125 Saphanthong Road, Unit 5/PO Box 343
Ban Saphanthongtai, Sisattanak District
Vientiane
Lao People’s Democratic Republic
E: feldonk@wpro.who.int

Dr Joachim Hombach
Coordinator
IMR/IVB/FCH
World Health Organization
20 Av. Appia-CH-1211
Geneva 27
Switzerland
E: hombachj@who.int

Dr Kohei Toda
Medical Officer
Expanded Programme on Immunization
WHO Representative’s Office
No. 177-179 Streets Pasteur 51 and 254
Sangkat Chak Tomouk
Phnom Penh
Cambodia
E: todak@cam.wpro.who.int

Dr Youngmee Jee
Lab Coordinator
Immunizations and Vaccine Development
World Health Organization Western Pacific Regional Office
PO Box 2932
1000 Manila
Philippines
E: Jeey@wpro.who.int

Dr Pem Namgyal
Regional Advisor
Immunization and Vaccine Development
World Health Organization
Southeast Asia Regional Office
World Health House, Indraprastha Estate
Mahatma Gandhi Marg
New Delhi 110 002
India
E: namgyalp@searo.who.int

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
E: Ramamurtyn@searo.who.int

Dr Manju Rani
Scientist
Expanded Programme on Immunization
World Health Organization
Regional Office for the Western Pacific
United Nations Avenue
1000 Manila
Philippines
E: ranim@wpro.who.int

Dr Walter William Schluter
Medical Officer
Expanded Programme on Immunization
World Health Organization
Kathmandu
Nepal

Dr Yang Baoping
Regional Adviser
Expanded Programme on Immunization
World Health Organization
Regional Office for the Western Pacific
United Nations Avenue
1000 Manila
Philippines
E: yangb@wpro.who.int
Annex 3

Message by Dr Samlee Plianbangchang,
Regional Director, WHO South-East Asia

Distinguished participants, ladies and gentlemen,

It is my pleasure to extend a warm welcome to the distinguished participants who are here today. I also take this opportunity to convey the greetings of Dr Samlee Plianbangchang, Regional Director, WHO South-East Asia, to the distinguished participants of this workshop.

The Regional Director would have been pleased to be here on this occasion. However, due to important prior commitments, he is unable to do so. It is, therefore, my privilege to deliver the Regional Director’s message.

We all are here to discuss the subject of public health importance and interest, particularly for many member countries of the WHO Western Pacific and South-East Asia Regions. Japanese encephalitis (JE), as we all know, is a dreadful disease which not only kills but also leaves debilitating sequelae, resulting in unwanted social consequences.

Developed countries have successfully controlled this disease through a combination of better living conditions, early diagnosis and prompt treatment, immunization, and effective vector-control measures. Although, developing countries are also aware of all the interventions that can be used for control of the disease but due to various reasons, we could not do so very effectively. Therefore, in many developing countries, JE still continues to be a public health problem with millions of people at risk of contracting the disease, especially in rural areas.

WHO estimates that 30,000 to 50,000 cases and more than 10,000 deaths occur annually due to JE, mainly in the countries of the Asia-Pacific Region. This biregional workshop is, therefore, very important and it is also an indication of the active collaboration between the two WHO regions, WHO headquarters, and many other collaborating agencies in helping Member countries to prevent and control this disease. This workshop takes place in a period of great uncertainty and many competing priorities in the area of health, for two reasons.
First, the JE Project supported by the Programme for Appropriate Technology for Health (PATH) is ending this year. In collaboration with the PATH project, WHO, relevant Member countries and other partners have succeeded in putting JE higher on the agenda of country health programmes and strengthened countries to move further in JE prevention and control. Several of our countries have been able to introduce the JE vaccine in their routine immunization programme.

Second, this is also happening at a time of global recession when mobilizing external resources is a major challenge. Japanese encephalitis predominantly affects the poor, especially those living in rural areas where agriculture is the mainstay of their livelihood.

In the context of equity and social determinants of health, without external assistance many developing countries are already hard-pressed for resources and with multiple and competing priorities. These countries will find it difficult to provide the necessary support to control JE. However, there is room for optimism. Since 2002 there has been tremendous progress in the efforts to control JE in many countries of the two regions.

The global WHO JE surveillance guidelines, including a guideline for the introduction of JE vaccines, were prepared and published by the WHO Regional Office for South-East Asia. The guideline is very useful and should be part of the integrated disease surveillance programme. Also, at the global level, several diagnostic test kits were assessed for possible use and many commercially available test kits have been standardized. A functioning network of high-quality laboratories has been set up across several countries and these sentinel surveillance sites help track JE occurrences. Further work needs to be done and will require more support. Through this sentinel surveillance, we are beginning to see the presence of the disease even in countries where it was thought nonexistent. The importance of an effective and responsive surveillance system, together with an integrated disease surveillance programme to generate quality data, is obvious. Data generated from these laboratories are helping countries to make evidence-based decisions on the use of JE vaccine to control this public health menace.

We also need to build capacity on epidemiological thinking skills, and critical analysis of data and transforming it into viable information. We need to extract correct information from the known epidemiology and ecology of this disease and use it appropriately for initiating effective preventive and control measures. This should be supplemented by information on JE vector bionomics and behaviour. Vector control is also key to JE prevention and control. We are generally weak in the area of vector monitoring and control. The interplay between the host, the
environment, the agent and the vector in any JE prevalent area must be fully understood before we mount a comprehensive and integrated JE prevention and control programme.

Ladies and gentlemen,

I am happy to note that the two WHO Regions of Western Pacific and South-East Asia have been working very closely on this disease and helping each other, both technically and operationally, with support from WHO headquarters. This is an excellent example of setting regional priorities and developing strategies that are relevant to the two Regions. I strongly support this regional solidarity that addresses our issues without waiting for a global consensus or guidance. On the other hand, we must also thank and acknowledge the role played by many partners that share the same vision as WHO.

We live in a world of interdependence and must seek to build alliances and support groups to support the countries in their JE control activities. I would like to put on record our appreciation and thanks to the Bill and Melinda Gates Foundation and to PATH for their collaborative endeavours to promote the cause of prevention and control of JE in our two Regions. Without their support we may not have gone this far.

Finally, I wish this workshop great success and I look forward to receiving the recommendations on how best we can carry forward the excellent work that has been done till now. I wish you all a fruitful, concrete and action-oriented outcome from the workshop.

Thank you.
In 2003, several countries of the WHO South-East Asia Region had routine JE reporting and vector control measures, but immunization programmes were not prioritized. Only two countries of the Region had successful JE immunization programmes (Sri Lanka and Thailand). In the last six years, the SEA Region has seen significant activity and progress towards JE control, with sustained long-term immunization programmes and ever more countries considering vaccine introduction. In recent years, India and Nepal introduced the live, attenuated SA 14-14-2JE vaccine, increasing to four the number of countries in the Region with sustained JE immunization programmes. Broad-based laboratory surveillance in the Region is supported and enhanced through a regional laboratory network, which has helped identify JE in many countries with previously limited information on the JE disease burden.

In WHO’s Western Pacific Region, 11 countries with a total population of 1.74 billion are at risk for JE infection. Progress over the last two decades shows inequities in control, with human disease almost eliminated in the developed countries—namely, Australia, Japan, Singapore and the Republic of Korea. China, a lower middle-income country, has made significant advancements in JE control but still needs further improvement in immunization coverage.

Despite these successes, JE remains a significant public health problem in countries of both regions. The biregional meeting on JE control (7-8 June 2009) focussed on the progress made since the last biregional meeting held in 2007 in expanding surveillance activity, measures towards JE control, including establishing routine JE immunization. The report summarizes the proceedings of the meeting, and updates on progress in JE control, defining disease burden, assessing outcome after JE infection, JE laboratory network and diagnostic initiatives, JE vaccine clinical trials, planning for expansion of introduction of vaccine in JE endemic countries, and future goals and challenges in JE control.