Meeting Report

Fifth Biregional Meeting on Japanese Encephalitis Prevention and Control

Vientiane, Lao People’s Democratic Republic
30 May–1 June 2011
REPORT

FIFTH BIREGIONAL MEETING ON JAPANESE ENCEPHALITIS PREVENTION AND CONTROL

Convened by:
WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC
Vientiane, Lao People's Democratic Republic
30 May–1 June 2011

Not for sale
Printed and distributed by:
World Health Organization
Regional Office for the Western Pacific
Manila, Philippines
March 2013
NOTE

The views expressed in this report are those of the participants of the Fifth Biregional Meeting on Japanese Encephalitis Prevention and Control and do not necessarily reflect the policies of the World Health Organization.

This report has been prepared by the World Health Organization Regional Office for the Western Pacific for governments of Members States in the Region and for those who participated in the Fifth Biregional Meeting on Japanese Encephalitis Prevention and Control, which was held in Vientiane, Lao People's Democratic Republic from 30 May to 1 June 2011.
SUMMARY

The Fifth Biregional Meeting on Japanese Encephalitis (JE) Prevention was held in Vientiane, Lao People's Democratic Republic, from 30 May to 1 June 2011. The meeting was attended by participants from countries in the Western Pacific and South-East Asia regions; temporary advisers from the United States Centers for Disease Control and Prevention (CDC) and the India National Institute of Mental Health and Neurosciences (NIMHANS); and observers and representatives from international partner organizations.

The objectives of the meeting were:

1. to review progress in establishing the WHO JE surveillance and laboratory networks and to develop action plans for strengthening quality of surveillance, networks coordination and their sustainability;

2. to review findings from JE surveillance and country plans for JE vaccine introduction or expansion, and to identify ways to improve the use of JE surveillance data to inform programme decision-making; and

3. to review experiences of countries implementing JE vaccination programmes, share the lessons learnt with countries planning vaccine introduction, and to develop action plans for evaluating programme impact.

The meeting consisted of country presentations, technical presentations by WHO, and work group discussions. Participants shared experiences and lessons learnt in JE surveillance and vaccine introduction. They formulated country action plans to improve surveillance, laboratory testing, data use, vaccine implementation or vaccine programme evaluation to be conducted over the six to 12 months.

The following were identified as key areas of progress in JE surveillance:

1. improved data quality, increased number of surveillance sites and expansion of laboratory confirmation;

2. initiation of JE surveillance in the Philippines and establishment of concrete plans to establish JE surveillance in Papua New Guinea and Bhutan;

3. increased and continuing integration of JE surveillance into national surveillance systems; and

4. use of standard WHO case definition in most countries.

However, there are challenges in JE surveillance that remain. The overall challenges include:

1. underreporting to surveillance systems from remote areas, the private and laboratories, at both the national level to the regional level;

2. inadequate sample collection, difficulties in sample transport, and limited access to JE laboratory testing in some countries;

3. incomplete use of data to guide programmatic decisions and monitor the impact of vaccination;
(4) limited data for projecting population-based estimates of the disease burden; and 

(5) inconsistent political commitment and funding when reported numbers of cases are low, both before the disease burden is defined and after the vaccination programme has had a major impact. 

In terms of implementing JE vaccination programmes, examples of challenges faced by countries included:

(1) developing immunization strategies: campaign or routine immunization (or both), and selection of age groups and geographic areas to target; 

(2) impact monitoring: lack or inadequate use of retrospective analysis of surveillance data or case-control studies; 

(3) adverse events following immunization (AEFI) monitoring: standardized methodology developed in some countries but only planned in others; and 

(4) programmatic issues: vaccination potentially requiring an additional contact, integration with school health programmes, and whether to co-administer the vaccine with measles or other vaccines. 

In country groups, participants developed country action plans to improve JE surveillance and JE vaccination programmes over the coming year. Common themes in the country plans are described below:

(1) Resources: identifying increased and sustainable funding for surveillance, and integrating with other types of surveillance, where feasible. 

(2) Surveillance quality: training staff, increasing coordination among laboratory and surveillance staff, improving data completeness, using new data systems and ensuring that surveillance meets the WHO standards. 

(3) Decision-making: using surveillance data to determine target areas and age groups for introducing JE vaccine, and incorporating economic evaluation into decision-making. 

(4) Strengthening immunization systems: addressing gaps in vaccine management, training staff, and improving AEFI surveillance systems. 

(5) JE vaccination programme strategy: planning for JE vaccination campaigns by incorporation into routine immunization, as recommended by WHO. 

(6) JE vaccine: considering a shift to live attenuated SA 14-14-2 vaccine for countries using mouse brain-derived vaccine. 

(7) Improving programme monitoring and using surveillance and special studies to evaluate vaccine impact.
**LIST OF ACRONYMS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AFRIMS</td>
<td>US Armed Forces Research Institute of Medical Sciences</td>
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<tr>
<td>AEFI</td>
<td>adverse events following immunization</td>
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<td>AES</td>
<td>acute encephalitis syndrome</td>
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<tr>
<td>AMES</td>
<td>acute meningitis and encephalitis surveillance</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>CDIBP</td>
<td>Chengdu Institute of Biological Products</td>
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<td>CSF</td>
<td>cerebrospinal fluid</td>
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<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<td>GSL</td>
<td>global specialized laboratory</td>
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<tr>
<td>Hib</td>
<td><em>Haemophilus influenzae</em> type b</td>
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<td>JE</td>
<td>Japanese encephalitis</td>
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<td>LP</td>
<td>lumbar puncture</td>
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<td>ME</td>
<td>meningitis-encephalitis</td>
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<td>NCLE</td>
<td>National Center for Laboratory and Epidemiology</td>
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<td>NIH</td>
<td>National Institute of Health</td>
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<td>NIHE</td>
<td>National Institute of Hygiene and Epidemiology</td>
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<td>NIID</td>
<td>National Institute of Infectious Diseases</td>
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<td>NIMHANS</td>
<td>National Institute of Mental Health and Neurosciences</td>
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<td>NIP</td>
<td>National Immunization Programme</td>
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<td>NIPH</td>
<td>National Institute of Public Health</td>
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<td>NL</td>
<td>national laboratory</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>PRNT</td>
<td>plaque reduction neutralization test</td>
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<tr>
<td>RRL</td>
<td>regional reference laboratory</td>
</tr>
</tbody>
</table>
CONTENTS

1. INTRODUCTION .................................................................................................................. 1

1.1 Objectives ....................................................................................................................... 2
1.2 Organization .................................................................................................................... 2
1.3 Opening remarks .............................................................................................................. 2

2. PROCEEDINGS .................................................................................................................... 3

2.1 Overview and updates of JE surveillance and JE vaccination programmes
in the WHO Western Pacific and South-East Asia regions ......................................................... 3
2.2 Country presentations on progress and challenges in implementation of JE
surveillance ............................................................................................................................... 4
2.3 Progress with the JE laboratory network ........................................................................ 9
2.4 Update on JE vaccines .................................................................................................. 11
2.5 Progress on JE vaccine introduction and impact monitoring ........................................ 12
2.6 Work groups: improving and sustaining JE surveillance
and JE vaccination programmes ........................................................................................... 16
2.7 Partners in JE prevention and control .......................................................................... 17
2.8 Action plans for applying lessons learnt to future plans .................................................. 18

3. CONCLUSIONS .................................................................................................................... 22

3.1 Conclusions .................................................................................................................... 21
3.2 Closing remarks ............................................................................................................. 24

ANNEXES:

ANNEX 1 - TIMETABLE

ANNEX 2 - LIST OF PARTICIPANTS

Keywords:

Encephalitis, Japanese – epidemiology, prevention and control / Vaccination / Laboratories
– standards, utilization /Regional health planning
1. INTRODUCTION

Japanese encephalitis (JE) is an important cause of death and disability and a pressing public health problem for many countries in Asia. Vaccination programmes have been a successful tool for the control of JE in some countries but were limited for many years by the high cost of vaccine, limited availability, multiple dose requirements and concerns about safety. Recent advances have led to the development of new JE vaccines that are more effective, require fewer doses, appear to be very safe and, in some cases, are much cheaper than older vaccines.

Surveillance data are critical to defining the burden of JE disease and to identifying the most important target populations for vaccination. The recent commercial availability of sensitive, highly specific, and easy to perform JE antibody tests has facilitated the implementation of JE surveillance in low-resource settings. WHO and several partners have provided support to capitalize on the technical advances in laboratory diagnosis and vaccine availability by initiating and strengthening JE surveillance in suspected endemic countries, and by initiating and expanding JE vaccination programmes in demonstrated endemic areas.

In 2002, the WHO South-East Asia and Western Pacific regions, in collaboration with PATH, organized a joint South-East Asia and Western Pacific working group meeting on Japanese encephalitis. The meeting was instrumental in raising global awareness of the public health importance of JE in the two WHO regions. A series of biregional meetings in 2005, 2007 and 2009 provided a forum for coordination of global work on JE, dissemination of technical updates and country exchange of experiences. Key achievements during this time were the finalization of WHO JE surveillance guidelines, initiation or strengthening of laboratory-confirmed JE surveillance as part of integrated surveillance systems in many countries, development of regional JE vaccine introduction guidelines, and introduction of the live attenuated SA 14-14-2 JE vaccine by several countries.

In 2008-2009, the JE laboratory network was established to expand capacity for JE case confirmation and improve the quality of JE testing among countries either known or suspected to be endemic for JE in the Western Pacific Region, as recommended by the Technical Advisory Group on Immunization and Vaccine-Preventable Diseases in 2008. The JE laboratory network also evaluates commercial test kits for JE antibody to increase the standardization and quality of testing.

The JE laboratory network was formed based on the WHO polio and measles/rubella laboratory network models. The network consists of one global specialized laboratory (GSL) in Japan, two regional reference laboratories (RRLs) in China and the Republic of Korea, and seven national laboratories (NLs) in Cambodia, the Lao People’s Democratic Republic, Malaysia, Papua New Guinea, the Philippines and Viet Nam (north and south).

JE laboratory network meetings were held in 2009 and 2010 during the first and second meetings on vaccine-preventable disease laboratory networks in the Western Pacific Region. To build regional laboratory capacity for JE testing, three regional hands-on training workshops were organized in 2009, 2010 and 2011. The Papua New Guinea laboratory, which was the last of 10 laboratories to join the regional network, participated in the second hands-on training workshop in 2010.
To consolidate the gains in JE surveillance and vaccination programmes and the JE laboratory network, and to build on past achievements to form a solid foundation for future JE control, WHO held the Fifth Biregional Meeting on JE Prevention and Control and the Third JE Laboratory Network Meeting in the Western Pacific Region.

This report pertains to the activities at the Fifth Biregional Meeting on JE Prevention and Control. The Third Japanese Encephalitis Laboratory Network Meeting in the Western Pacific Region is reported separately. Joint sessions of the two meetings are included in both reports.

1.1 Objectives

(1) To review progress in establishing the WHO JE surveillance and laboratory networks, and to develop action plans for strengthening the quality of surveillance, coordination through the networks, and sustainability in the future.

(2) To review findings from JE surveillance and country plans for JE vaccine introduction or expansion, and to identify ways to improve the use of JE surveillance data to inform programme decision-making.

(3) To review experiences of countries implementing JE vaccination programmes, share lessons for the benefit of countries planning to introduce JE vaccine, and to develop action plans for evaluating programme impact.

1.2 Organization

The timetable of the meeting and list of participants are given in Annex 1 and Annex 2.

1.3 Opening remarks

Professor Bounkong Sihavong, Deputy Minister of Health, the Lao People's Democratic Republic, welcomed the participants to Vientiane. He noted the importance of JE in causing death and disability, especially among children under 15 years old. It is estimated that at least 50,000 cases occur each year in countries across Asia, causing 10,000 deaths. Dr Bounkong said that by sharing experiences, countries can help each other find the best way to control the disease in the future.

Dr Yunguo Liu, WHO Representative for the Lao People's Democratic Republic, presented opening remarks. Dr Liu noted the importance of JE as a cause of encephalitis in Asia. While vaccination has been a successful tool for the control of JE in some countries, its use has been limited by high cost, unavailability and other issues. Dr Liu also noted the importance of surveillance data in defining the burden of JE and identifying the most important populations to vaccinate. Recent advances in JE vaccines and in surveillance technology have created new opportunities to detect and prevent the disease. Dr Liu acknowledged the achievements of the ministries of health and partners in the two WHO regions in taking advantage of the technological advances to strengthen surveillance and vaccination programmes. Dr Liu also noted that past biregional meetings in provided a forum for coordinating and sharing experiences. In closing, Dr Liu expressed his appreciation to the Lao People's Democratic Republic Ministry of Health for welcoming the group to Vientiane, and wished the group a successful and productive meeting.
2. PROCEEDINGS

2.1 Overview and update of JE surveillance and JE vaccination programmes in the Western Pacific and South-East Asia regions

2.1.1 Overview and update of JE surveillance and JE vaccination in the Western Pacific Region

Dr Kimberley Fox, Technical Officer, Expanded Programme on Immunization (EPI), WHO Regional Office for the Western Pacific, presented an overview of the current status of JE surveillance and vaccination in the Western Pacific Region. In countries with limited data on JE disease burden, progress has been made by training surveillance officers (the Lao People’s Democratic Republic), establishing sentinel surveillance plans (Papua New Guinea), and establishing meningitis-encephalitis (ME) surveillance and notification (the Philippines). Cambodia, a country with demonstrated disease burden and a pilot vaccination programme, has established sentinel ME surveillance. In countries with established vaccination programmes but incomplete disease control (China, Malaysia and Viet Nam), there is a need to monitor vaccine impact so surveillance is necessary on a national or broad geographic scale. Regional WHO support for JE surveillance has included the development of generic case investigations forms and databases, and establishment of the WHO JE laboratory network in the Western Pacific Region.

Eleven per cent of the population of JE-endemic areas of the Western Pacific Region live in countries where JE is almost eliminated (Australia, Japan, the Republic of Korea), 82% live in countries where immunization programmes have been implemented but the disease still occurs (China, Viet Nam, Malaysia), 6% live in countries with unclear disease burden and no vaccination programme (Brunei Darussalam, the Lao People’s Democratic Republic, Papua New Guinea, the Philippines), and 1% live where there is demonstrated burden and pilot vaccination (Cambodia). For countries newly introducing JE vaccination, WHO recommends a two-pronged strategy of a vaccination campaign for a broad age group based on local JE epidemiology plus integration into the routine immunization schedule. Since the last JE biregional meeting in 2009, Viet Nam has continued to expand JE vaccination coverage, and Cambodia has initiated pilot JE vaccination in three provinces. Issues that need to be addressed in the future include investigation of JE cases in countries with national JE vaccination programmes, provision of a WHO-prequalified JE vaccine, and financing vaccine support for low- and middle-income countries.

2.1.2 Overview and update of JE surveillance and JE vaccination in the South-East Asia Region

Dr Patrick O’Connor, Regional Advisor, Polio and Vaccine-Preventable Disease Surveillance, WHO Regional Office for South-East Asia, presented an overview of JE surveillance and immunization programmes in the South-East Asia Region. Four countries have JE vaccination programmes and surveillance systems (India, Nepal, Sri Lanka and Thailand), while seven countries (Bhutan, the Democratic People’s Republic of Korea, Maldives, Timor Leste, Bangladesh, Indonesia and Myanmar) only have JE surveillance systems. JE surveillance is implemented as acute encephalitis syndrome (AES) surveillance with laboratory confirmation. The objectives of AES surveillance are to estimate and monitor trends in the proportion of hospitalizations caused by AES, to describe the demographics and vaccination histories of JE cases, to obtain data for new vaccine
introduction, and to identify the effectiveness of the AES immunization programmes. In 2009, 8.5% of cerebrospinal fluid (CSF) and 10.1% of serum samples from AES cases were JE-positive (2010 data were not yet complete). The South-East Asia Regional JE/AES Laboratory Network consists of 13 AES/JE labs and one AES/JE regional reference laboratory under the National Institute of Mental Health and Neurosciences (NIMHANS) in Bangalore, India. Standards for data flow in this system require that AES cases be reported within 14 days after onset, and that samples be shipped within three days after collection to the national laboratory, where JE IgM testing is conducted and results reported within seven days. All results from testing at the national level are reported to the WHO Regional Office for South-East Asia by the 15th of the following month.

2.2. Country presentations on progress and challenges in implementation of JE surveillance

2.2.1 China

Dr Yin Zundong, Research Associate, National Immunization Programme, China CDC, presented the status of JE surveillance in China. JE is one of 38 notifiable diseases, and surveillance is conducted through 13 sentinel sites located in selected epidemic provinces. Eight provinces have been using enhanced JE laboratory testing since 2004. In two counties in Henan province, a survey was conducted to test for JE antibodies in healthy people using the plaque reduction neutralization test (PRNT) method. Prefectures in four additional provinces have conducted acute meningitis and encephalitis surveillance (AMES) since 2006. Annual incidence rates of ME have been similar among prefectures, ranging from nine to 14 per 100,000 population. Combining passive and active surveillance resulted in an incidence rate two to three times higher than that with passive surveillance alone. The China JE laboratory network comprises local CDCs, where most JE antibody testing is done, provincial CDCs and the China CDC, where quality control and other tests such as viral isolation are performed. In 2008, the China CDC JE laboratory was accredited as a WHO regional reference laboratory. According to passive surveillance data, incidence, case fatality, and mortality due to JE have steadily declined since the availability of inactivated mouse brain-derived JE vaccine in 1968, live attenuated vaccine in 1989, and Vero cell-derived inactivated vaccine in 2003. Data from the years 2008 to 2010 show a consistent peak in reported cases during the months of July and August. For the year 2010, more than 80% of reported JE cases were children under 15 years old, and 76% of cases were laboratory-confirmed. AMES data indicate that many JE cases are not initially diagnosed as encephalitis and therefore JE may be missed in the absence of active surveillance testing.

2.2.2 Malaysia

Dr Faridah binti Amin, Head, Epidemiology Division, National Public Health Laboratory, presented the current situation of JE surveillance in Malaysia. AES, not specifically JE, is a notifiable disease. Specimens from outbreak investigations and from clinical AES cases are tested at the Ministry of Health’s Institute for Medical Research and National Public Health Laboratory. Clinical cases are also tested at the University of Malaysia Medical Centre and the University of Malaysia-Sarawak. The main JE test used is IgM capture ELISA. JE vaccination programmes have been in place in high-risk areas near pig farms in Sarawak since 1999; since then, reported laboratory-confirmed JE cases in Malaysia have dropped from 84 per year to less than 10 per year. In 2010, there were eight laboratory-confirmed JE cases in Malaysia, all in Sarawak. The mean age of JE cases has increased from 6.3 to 9.0 years. Challenges for the future include addressing diagnostic difficulties due to cross-reaction of dengue antibodies and determining whether to continue using the current vaccine or switch to another available vaccine.
2.2.3 Viet Nam

Dr Nguyen Dac Trung, Programme Officer, National Expanded Programme on Immunization, National Institute of Hygiene and Epidemiology (NIHE), gave an update on JE surveillance in Viet Nam. Viet Nam has two ME sentinel sites at paediatric hospitals in Hanoi and Ho Chi Minh City, where samples from clinical AES cases are tested with IgM ELISA. In addition, there are two national laboratories participating in the WHO JE laboratory network. These laboratories perform referral testing for AES cases from provincial hospitals in Viet Nam. Both sentinel surveillance and JE referral laboratory testing in 2010 found that 12% of tested cases were JE IgM-positive. Most cases were children five to 14 years old, and there was a peak in reported cases during June and July. Challenges include addressing underreporting, and the lack of population-based data, collecting vaccination history of JE cases and investigating cases before hospital discharge.

2.2.4 India

Dr Vinod Kumar Raina, Joint Director, National Vector-Borne Disease Control Programme, India Ministry of Health and Family Welfare, presented an overview of JE surveillance in India. AES sentinel surveillance is performed in 50 sentinel sites and four WHO-National Polio Surveillance Project supported sites. AES cases are reportable and laboratory confirmation with JE IgM ELISA is done when feasible, in twelve laboratories. Data are reported to the district level, to the state level, and then to the National Vector-Borne Disease Control Programme. In 2010, 5149 AES/JE cases and 677 AES/JE deaths were reported, an increase from 4482 and 774, respectively, in 2009. Over 50% of reported cases were in the state of Uttar Pradesh. Age distribution of AES cases varied widely from state to state. For example, most cases in Uttar Pradesh were between ages one and five years whereas most cases in Assam were over 15 years old. Seasonality also varied, with Uttar Pradesh having a peak of cases from August to November and Assam experiencing a peak in June and July. Surveillance challenges include improving infrastructure and increasing manpower, promoting adherence to surveillance guidelines, and increasing the timeliness of sample processing and data reporting.

2.2.5 Nepal

Dr Shyam Raj Upreti, Director, Child Health Division, Department of Health Services, presented on JE surveillance in Nepal. The sentinel surveillance system uses the WHO case definition for AES with weekly reports from 97 sentinel sites in all 75 districts. In addition, there are weekly active surveillance visits to most sites by surveillance medical officers. Laboratory confirmation is conducted at the National Public Health Laboratory and BP Koirala Institute of Health Sciences, using JE IgM capture ELISA. XCyton kits are used for CSF, and Panbio kits for serum. In 2010, there were 196 laboratory-confirmed JE cases in 41 districts, as compared to 147 cases in 34 districts in 2009 and 339 cases in 48 districts in 2008. Cases occur mostly in the terai (lowland) region of the country, with peaks each year from July to September. Cases in the hill and mountain regions have been increasing. The five- to nine-year age group account for more cases than any other age group spanning five years; approximately one-third cases occur in persons 15 years and older. The annual number of JE cases has decreased since the initiation of JE vaccination campaigns in high-risk districts in 2006, and the large majority of cases have occurred in non-vaccinated persons. Challenges include addressing the lack of entomological surveillance, lack of stock of test kits, funding gaps, availability of only two laboratories for testing, and the occurrence of cases in districts that have completed JE campaigns.
2.2.6 Sri Lanka

Dr Pushpa Ranjan Wijesinghe, National Surveillance Focal Point, Epidemiology Unit, Ministry of Health, presented on JE surveillance in Sri Lanka. AES is a notifiable disease and all laboratory-confirmed JE cases are investigated and recorded in the national JE registry. JE sentinel surveillance is also performed at designated sites, with JE IgM testing of serum and CSF at the accredited National JE Reference Laboratory. Out of 215 suspected JE cases in 2010, 27 (12.5%) confirmed. At the sentinel surveillance sites, 6.4% of CSF samples and 6.9% of serum samples were JE-positive. Seasonal peaks occur annually between December and January, and occasionally on a smaller scale, between May and July. Confirmed JE cases occurred mostly in coastal districts, especially in the west. Cases varied in terms of age, with only 10% to 30% occurring in children under 15 years. Challenges included addressing the waning interest of policy-makers as disease burden decreases, sustaining logistics supply to the national reference laboratory, ensuring coverage of JE testing for AES cases, and establishing sustainable private sector reporting. Strategies to improve surveillance include quarterly surveillance reviews and increased communications with clinicians and professional bodies.

2.2.7 Thailand

Ms Surapee Anantapreecha, Medical Technologist, National Institute of Health (NIH), Department of Medical Sciences, presented the status of JE surveillance in Thailand. AES cases, using the WHO case definition, are reportable weekly to the Bureau of Epidemiology under the National Notifiable Diseases Surveillance system. Specimens are sent to the Thai NIH laboratory for testing, and cases are considered JE-confirmed if the JE IgM ELISA on CSF or serum is $>40$ units and the JE IgM to dengue IgM ratio is $>1$. Data from 2000 to 2010 showed that 18.1% of 469 suspected JE cases were laboratory-confirmed as JE and two-thirds were children ages five to 14 years. Seasonal peaks occurred from May to August but cases occurred in all months of the year. JE occurred primarily in the central, northern and northeastern regions of the country, with few cases in the south.

2.2.8 Cambodia

Dr Ya Nareth, Programme Officer, National Immunization Programme (NIP), presented the Cambodia JE surveillance situation. Clinical ME cases are notifiable through an early warning and response system. In addition, the NIP maintains a sentinel surveillance site for ME in six provinces, with plans to increase coverage in Battambang and Banthay Meanchey provinces to achieve population-based surveillance. An ME case is defined as a child 15 years of age or younger with a sudden onset of fever and a change in mental status, new onset of seizures, movement disorder, flaccid paralysis, or meningial signs. Samples are transported weekly to the WHO- accredited National Institute of Public Health (NIPH) laboratory, which tests with the Panbio JE-Dengue IgM Combo ELISA kit. Case reports from hospitals are sent to local NIP offices, then to the central NIP, and finally to the NIPH. In 2009, 11.9% of 201 ME cases from sentinel sites were laboratory-confirmed JE, compared to 31.4% of 124 ME cases in 2010. More than half of the cases in the two years occurred in children one to 10 years old are ensuring timeliness of specimen shipment, and efficient data management and communications among the many offices and levels involved in the surveillance.
2.2.9 Lao People’s Democratic Republic

Dr Bouaphanh Khamphaphongphane, Chief, Epidemiology Division, National Centre for Laboratory and Epidemiology (NCLE), presented the JE surveillance system for the Lao People’s Democratic Republic. NCLE serves as the reference laboratory and surveillance unit with Mahosot Hospital and Welcome Trust providing laboratory testing. AES is a notifiable condition, and is defined as the acute onset of fever with change in mental status or new onset of seizures. To confirm JE, CSF and serum specimens are sent to NCLE or Mahosot Hospital and tested with the JE IgM ELISA test. In 2010, 184 suspected cases were reported and 122 were laboratory-confirmed JE. Most cases occurred in the rainy season from June to September, and more than 50% of suspected cases were children aged one to 15 years. Almost 80% of suspected cases were from the northern provinces. One of the challenges is to obtain reports and specimens from non-cluster-associated AES cases and from hospitals in the southern part of the country.

2.2.10 Papua New Guinea

Dr Evelyn Lavu, Director, Central Public Health Laboratory, presented on JE surveillance plans in Papua New Guinea. The Paediatric Society of Papua New Guinea plans to lead the establishment of JE sentinel surveillance in five hospitals, three of which already participate in the country’s paediatric bacterial meningitis sentinel surveillance. Central Public Health Laboratory has been designated as the national JE laboratory. A recent study of meningitis and encephalitis at Port Moresby General Hospital found that two of 146 ME cases in young children were JE IgM-positive. Several other studies have identified JE virus in mosquitoes in and JE cases among humans in other areas of Papua New Guinea. Challenges include transporting CSF under the appropriate conditions, staffing the national laboratory, and encouraging all paediatricians to participate in public health surveillance.

2.2.11 Philippines

Ms Dulce Elfa, Vaccine-Preventable Disease Surveillance Coordinator, National Epidemiology Center, presented on JE surveillance in the Philippines. JE surveillance was established to assess the burden of disease and determine whether the JE vaccine should be included in the routine immunization programme. ME sentinel surveillance among children 15 years old and younger was established in five hospitals in 2009, with CSF and serum specimens from suspected ME cases tested for JE IgM by the Research Institute for Tropical Medicine (RITM). AES is also a notifiable condition under the Philippines Integrated Disease Surveillance and Response (PIDS) system which collects reports from 200-350 health facilities. AES reports in PIDS use the WHO case definition but are usually not laboratory-confirmed. At the five ME sentinel surveillance hospitals in 2009 and 2010, 23% of suspected ME cases were laboratory-confirmed JE. A challenge is to coordinate cases detected from the sentinel surveillance with PIDS. There is insufficient laboratory capacity to diagnose AES cases in hospitals, and there are financial and other barriers to CSF collection. Plans are being developed to integrate laboratory-confirmed JE surveillance into PIDS.

2.2.12 Bangladesh

Dr Md. Shafiquur Rahman, Medical Officer, Directorate General of Health Services, presented on JE surveillance in Bangladesh. JE surveillance was initiated to define the geographic areas with JE cases and to identify areas where JE vaccination may be of value. A study in four medical college
hospitals during 2003-2005 identified JE in 4% of AES cases. Subsequently, the AMES study established systematic surveillance in the same four hospitals, with JE IgM testing of serum and CSF at the Institute of Public Health. Several other laboratories conduct polymerase chain reaction (PCR) testing for JE virus, no laboratory has been designated as a national JE laboratory. Since the reduction in AMES funding in 2010, surveillance continues in two of the four hospitals. From 2007 to 2010, the annual number of laboratory-confirmed JE cases has ranged from 15 to 77. Sixty percent of JE cases were among those 15 years old or older. Challenges include lack of provider awareness of JE, difficulties in obtaining permission to collect a CSF specimen, logistical constraints of donor dependency for supplies, and incomplete data collection.

2.2.13 Bhutan

Mr Tobgyel, Senior Program Officer, Vector-borne Disease Control Program, presented on the establishment of JE surveillance in Bhutan. Due to its proximity to countries with JE and presence of the vector mosquito, Bhutan may have endemic JE. To monitor trends in AES cases and determine the proportion of JE cases due to JE in Bhutan, sentinel surveillance at five sites started in 2011. Cases to be reported were defined as febrile illness with altered sensorium with or without convulsions. The case investigation form was developed, roles of the site and central surveillance and laboratory were determined, and procedures for specimen management defined. Sentinel sites were to submit data monthly to district health offices, which would then provide data to the national office. CSF and acute and convalescent serum samples were to be tested by IgM ELISA at the national reference laboratory using XCyton for CSF and Panbio JE-Dengue IgM Combo ELISA for serum. Future expansion of sentinel surveillance will be considered based on implementation at the five initial sites.

2.2.14 Indonesia

Dr Endang Burni Prasetyowati, Directorate of Vector-borne Disease Control, presented the current situation of JE surveillance in Indonesia. Clinical ME surveillance is part of routine surveillance in the country, and JE sentinel surveillance studies have been performed in many regions of the country over the past two decades. Most recently, a six-site study from 2005-2006 found that 6% of AES cases were JE-positive. After a study demonstrated the disease burden in all nine districts in Bali has comparable to other endemic Asian countries, a plan to introduce JE vaccine was developed but the plan has not been implemented. JE is not considered a priority disease as it occurs in scattered areas; surveillance is limited by the lack of laboratory capacity for JE diagnosis. However, it may be feasible to strengthen AES surveillance as part of existing ME surveillance. Plans to strengthen JE laboratory capacity and to pilot test JE vaccination may also be considered.

2.2.15 Summary of issues in country presentations on JE surveillance

Dr Susan Hills, Medical Epidemiologist, United States Centers for Disease Control and Prevention, summarized the progress and challenges in the implementation of JE surveillance. Key areas of progress have been the following:

(1) improved data quality, increased number of surveillance sites, and expansion of laboratory confirmation;

(2) initiation of JE surveillance in the Philippines and concrete plans to establish JE surveillance in Papua New Guinea and Bhutan;
(3) increasing integration of JE surveillance into national surveillance systems; and

(4) standard WHO case definition being used by most countries.

However, the following challenges remain:

(1) under-reporting from remote areas and the private sector, from laboratories to surveillance systems, and from the national to the regional level;

(2) inadequate sample collection, difficulties in sample transport, and limited access to JE laboratory testing in some countries;

(3) need to increase use of data to guide programmatic decisions and monitor impact of vaccination;

(4) sentinel site data does not allow for population-based estimates of the disease burden; and

(5) ensuring sustained political commitment and funding when reported numbers of cases are low, both when the disease burden is not yet defined and after the vaccination programme has had a major impact.

2.3 Progress with the JE laboratory network

2.3.1 JE laboratory network in the WHO Western Pacific Region

Dr Youngmee Jee, EPI Laboratory Coordinator in WHO Regional Office for the Western Pacific, presented the progress and challenges of JE laboratory network in the Western Pacific Region. The WHO JE laboratory network in the Western Pacific Region consists of one global specialized laboratory (GSL), two RRLs, and seven national JE laboratories (NL). Most JE network laboratories were designated in the national public health institute where the laboratory testing for measles and rubella is also performed. To build regional laboratory capacity for JE testing, two regional hands-on training workshops were organized in 2009 and 2010. The Papua New Guinea laboratory, which was the last of ten laboratories to join the regional network, participated in the second hands-on training workshop in 2010. China has held its own annual training workshops and proficiency panels since 2006. For the quality assurance of the JE laboratory network, the first and second proficiency tests for JE were successfully conducted in 2009 and 2010, and a confirmatory testing mechanism was also established in the Region. The China CDC JE laboratory also provides annual proficiency testing samples to provincial laboratories but confirmatory testing mechanism is not yet placed for China provincial JE laboratories. The concordance rates for confirmatory testing were more than 90% for most network laboratories. The WHO accreditation programme, which uses a WHO JE laboratory checklist, was initiated in 2010. Seven out of 10 laboratories have been accredited as of June 2011. Three JE network laboratories in the Region, namely the National Institute of Infectious Diseases Japan, the National Institute of Hygiene and Epidemiology and Pasteur Institute in Viet Nam use their own in-house assays. China CDC uses locally-produced JE commercial kits, and the six remaining network laboratories use the Panbio JE-Dengue IgM Combo ELISA kits. Regional data were presented for 2009 to 2010, showing that in 2010, 14.2% of 1308 cases tested were JE-positive, an increase from 8.8% of 520 samples tested in 2009. The countries with the highest proportion of positive JE samples were Cambodia and the Lao People's Democratic
Republic. Both of these countries, as well as the Philippines, demonstrated an increase in JE cases during the months of March to October. Malaysia and Viet Nam showed increased JE incidence during the months of September to March. Challenges for the laboratory network are the following: i) JE laboratories do not fully collaborate with national EPI since JE surveillance is not established at the national level and JE vaccination is not available in some countries; ii) some difficulties in comparing the results and implementing quality assurance since different assays are used; and iii) unstable funding for JE surveillance and laboratory network. Data from JE laboratory network in this region provided some evidence of JE incidence in Cambodia, the Lao People’s Democratic Republic and the Philippines. These countries should consider introduction of JE vaccines. For quality assurance of national JE laboratories, confirmatory samples should be sent twice a year, and annual proficiency testing and onsite reviews should continue.

2.3.2 JE laboratory network in the WHO South-East Asia Region

Dr Ravi Vasanthapuram from NIMHANS, Bangalore, India, presented the progress and challenges of the JE laboratory network in the South-East Asia region on behalf of Dr Nalini Ramamurti of the WHO Regional Office for South-East Asia. The network consists of one RRL and 13 NLs. The regional training workshops were held in 2006 and 2008. As of 2010, nine laboratories were WHO-accredited, and WHO supported 14 laboratories in eight countries in 2011. The regional reference laboratory in NIMHANS provided confirmatory testing and samples for proficiency testing for quality assurance and also hosted training workshops. NIMHANS also tested samples received for bacterial pathogens for AES. In 2009, concordance rates of confirmatory testing varied from 73.3% to 100%. Concordance rates of serum samples (86.1%) were lower than CSF samples (90.1%) in general. NIMHANS also established the real-time PCR for bacterial meningitis pathogens and JE virus. Laboratory testing data from 2007 to 2009 showed that in 2009, 8.5% of 3036 CSF samples tested were JE IgM-positive while 10.1% of 2881 serum samples were positive for JE IgM. The strengths of the JE laboratory network in the Region are the use of the same tests and protocols for quality assurance, data management and reporting and the integration of the JE laboratory network into the existing EPI laboratory network ensuring cost-effectiveness from shared infrastructure and expertise. Challenges for the JE laboratory network in the Region include linking surveillance and laboratory data, ensuring the use of validated diagnostic kits, preparing JE proficiency panels, and sustaining the network with financial and technical support from partner organizations, WHO and national governments.

2.3.3 Standardization of JE diagnosis and evaluation of JE assays

Dr Barbara W. Johnson from the Division of Vector-Borne Infectious Diseases, US CDC, gave a presentation on the development of reference serological panels for standardization of JE diagnosis and evaluation of JE assays. There is a need to standardize JE testing throughout the laboratory network, as well as validation of JE ELISA kits. Two reference panels were developed to standardize JE testing for the WHO JE laboratory network and to validate commercial JE kits or reagents to make recommendations for the JE laboratory network to use, and to harmonize data from reference laboratories. Commercial kits such as Panbio, XCyton, InBios, Shanghai Beixi and in-house assays from the National Institute of Infectious Disease (NIID), Japan, NIMHANS of India, the National Institute of Virology of India, University of Malaysia Sarawak, Pasteur Institute in Ho Chi Minh City, Viet Nam, the National Institute of Hygiene and Epidemiology (NIHE) in Hanoi, Viet Nam, US Armed Forces Research Institute of Medical Sciences (AFRIMS) of Thailand, and US CDC were included in the evaluation. To create reference serological panels, samples from JE reference and laboratory network laboratories were compiled and tested by US CDC with in-house
assays. Samples were tested for anti-JE IgM with ELISA, and plaque reduction neutralization test (PRNT) was used for confirmation. Preliminary reference panel samples (406) were tested in five laboratories (US CDC, NIMHANS India, AFRIMS Thailand, NIH Japan, and University of Malaysia Sarawak). There was 88%-95% agreement between the in-house assays and US CDC in-house assays using the preliminary reference panel. All laboratories had sensitivities ranging from 95% to 99%. It was also noted that samples classified as dengue infection had a high rate of cross-reactivity with JE antigen in IgM ELISA, and that reference laboratories with JE/dengue differential diagnostic testing formats had higher specificity than laboratories testing for JE IgM only. Based on the results of preliminary reference panel, samples from five laboratories were used to select final reference panel samples for evaluation of additional in-house or commercial assays. Two in-house assays from Institute Pasteur in Ho Chi Minh City and NIHE in Hanoi, Viet Nam, and a commercial Shanghai Beixi kit were also evaluated with the final reference serological panel. Analysis showed all three assays had sensitivities of more than 92% and specificities more than 94%. Cross-reactivity of dengue IgM and JE IgM was about 20%, and differential JE/dengue IgM detection assays had a high specificity for dengue IgM, with no false positive JE result.

2.3.4 Global JE laboratory network update

Mr David Featherstone from the WHO presented on the global JE network update. He discussed the process in the establishment of JE laboratory network and the role of the JE ad hoc laboratory working group in establishing JE laboratory surveillance. Since 2006, more than 100 JE laboratory staff were trained at three training workshops in the South-East Asia Region and two training workshops in the Western Pacific Region. The WHO laboratory accreditation process and quality assurance mechanisms also promoted communication with national immunization programmes and surveillance authorities in the two regions. Next steps include ensuring laboratory network sustainability, as well as surveillance programme integration and assay assessment.

2.4 Update on JE vaccines

2.4.1 Vaccine development and global policies

Dr Joachim Hombach, Scientist, WHO Initiative for Vaccine Research, presented updates on current global policies for vaccine development. The 2006 WHO position paper on JE vaccine recommended that JE vaccination be extended to all areas where JE is a public health problem. The recommended vaccination strategy is a one-time campaign for the primary target population followed by incorporation into routine immunization. In 2008, the Strategic Advisory Group of Experts on Immunization recognized JE vaccine to be an underutilized vaccine, and the GAVI Alliance deemed JE vaccine a priority for future investment. For future priority vaccines, the GAVI Alliance has established groups to review essential technical issues necessary for countries to consider when applying for support and policy issues that may require resolution. Although there is no WHO-prequalified vaccine, the March 2011 WHO accreditation of the Chinese national regulatory authority to regulate vaccine production represents a major step towards an assured JE vaccine supply.

Data on recently licensed JE vaccines were presented. Live recombinant vaccine (JE-CV) by Sanofi-Pasteur (Imojev) is given as single dose and co-administration with measles vaccine co-administration is being evaluated. The vaccine is licensed in Australia and Thailand for use in children aged 12 months and older. Inactivated purified cell culture-derived vaccine (IC51) from Intercell (Ixiaro) is licensed as a two-dose primary series with doses 28 days apart, for persons 17
years of age and older. Ongoing studies include Phase 2 and 3 trials for a paediatric indication. The vaccine is currently licensed in the European Union, the United States of America, and Canada. Inactivated purified cell culture-derived vaccine from Biken and Kaketsuken is licensed as a 3-dose series to be administered on days 0, 7 and 30, for those six months of age or older. The vaccine is currently licensed and available in Japan only. Three JE vaccines (JE-CV, IC51, and the live attenuated cell culture-derived SA 14-14-2 vaccine made by Chengdu Institute of Biological Products [CDBIP]) have been targeted for 2013 WHO prequalification. For the live attenuated SA 14-14-2 vaccine, immunogenicity in children at least eight months old is confirmed. Studies of long-term effectiveness, booster doses, and vaccine safety and immunogenicity in special target groups are needed, along with post-marketing surveillance for adverse events following immunization (AEFI).

2.4.2 SA 14-14-2 vaccine activities and WHO prequalification preparation

Dr. Mansour Yaich, Vaccine Development Advisor, PATH, presented an update of the live attenuated SA 14-14-2 JE vaccine known as RS.JEV produced by CDBIP. RS.JEV is licensed for infant use and is given as one or two primary doses. Since it has been used in China on a large scale for 20 years, so safety and efficacy are proven. Nine other countries have licensed this vaccine between 2001 and 2010. Advantages of this vaccine include the affordability similar to the measles vaccine, the option of a single-dose primary series, stability up to 18 months at 2°C -8°C, and potency for at least six hours after reconstitution at 37°C. Negotiations in 2005 between PATH and CDBIP established a maximum public sector price for the vaccine. Studies have demonstrated the long-term effectiveness of a single dose of RS.JEV (98.5% at 12-15 months and 96% at 5 years, in different studies). Several trials have documented the safety and immunogenicity of the vaccine. Immunogenicity when co-administered with measles vaccine was studied in the Philippines and Sri Lanka. Results from the Philippines trial indicate similar seroconversion rates at 1, 12, 24, and 36 months; Sri Lanka data are pending. A full review of this SA 14-14-2 vaccine was presented in 2007 to the WHO Global Advisory Committee on Vaccine Safety (GACVS), which concluded that the short-term safety profile appeared satisfactory. CDBIP has constructed ten new buildings for RS.JEV production and support according to WHO and Chinese good manufacturing practices (GMP). To demonstrate that the comparability of products from the new and existing facilities, a study involving 1000 children was scheduled to be conducted in Bangladesh starting in October 2011. Data from this trial are expected to be submitted to WHO by September 2012. All other pertinent data and product summary forms for WHO prequalification are planned to be submitted by January 2012.

2.5 Progress on JE vaccine introduction and impact monitoring

2.5.1 Cambodia

Dr. Ya Nareth, Programme Officer, NIP, presented on vaccine introduction in Cambodia. The decision to introduce JE vaccine was based on several factors: sentinel surveillance from 2006-2008 showing that 19% of ME cases were due to JE, an analysis showing that JE vaccination was cost-effective and an outcome assessment showing 13% case fatality and sequelae among 81% of surviving children. In 2009, the live attenuated SA 14-14-2 JE vaccine was introduced into routine immunization in three provinces comprising 23% of the national population. The target population was children 10 to 24 months old and a single-dose was administered one month after measles vaccination. After eleven months of vaccination, target population coverage was 97% across the three provinces, higher than measles and pentavalent vaccination in the same areas; wastage was 8%. No adverse events were identified. An evaluation conducted by NIP in collaboration with PATH
found 100% coverage among children aged 10-12 months, while coverage among children aged 13-24 months was low. Children from other provinces had come to the pilot provinces to receive JE vaccination, and the demand for JE vaccine had increased opportunities to administer the measles vaccine. The evaluation found that refrigerators at all sites were functioning, daily temperature was recorded, and all vaccine vial monitors were in stage 1. Challenges included the absence of a WHO-prequalified vaccine, limited vaccine supply, and no financial resources for scaling up the programme.

2.5.2 China

Dr Donglei Liu, China CDC, presented on the China JE vaccination programme in China. In 2008, JE vaccine was integrated into the national immunization programme. Prior to 2008, 16 provinces had included JE vaccine in their provincial immunization programmes. Two JE vaccines are used in the country, live attenuated SA-14-14-2 vaccine in a two-dose schedule at ages eight and 24 months, and inactivated Beijing P-3 Vero cell-derived vaccine in a four-dose schedule at ages eight months (two doses), 24 months and six years. In 2010, reported JE vaccine coverage was 98%. AEFI surveillance was initiated in 2005 and expanded to all mainland provinces in 2008 with 50% of counties covered. The most common AEFI was rash in 16 children per one per million doses for inactivated vaccine and five per one million doses for live vaccine. An economic evaluation in Guizhou province in 2009 concluded that incorporating JE vaccination into routine immunization would cost US$ 95.5 per disability-adjusted life-year averted, making it highly cost-effective. Next steps include improving JE coverage in rural areas and considering the use of JE vaccine in high-risk populations such as adults in rural areas.

2.5.3 Malaysia

The JE vaccination programme in Malaysia was presented by Dr Faridah binti Amin, Head, Epidemiology Division, National Public Health Laboratory. JE vaccination targets all residents of and workers at commercial pig farms who are at least one year old, and all children aged one to 15 years living within 2 km of a commercial pig farm. The programme uses inactivated mouse brain-derived vaccine (Biken) given in a two-dose primary series (7-14 days apart) with boosters at 12 months followed by every three years. Coverage targets are 80% for the first dose and 90% for the first booster. Vaccination is performed at health centres and in Sarawak as part of the school health programme. In 2010, coverage in Sarawak for the first two doses and first booster were greater than 90%, while coverage for the second booster was about 50%. JE cases in Sarawak have gradually declined and only four cases were reported in 2010. A major issue for the future is switching to a new vaccine as the Biken mouse brain-derived vaccine is no longer produced, but clarification is needed on the live attenuated vaccine dose requirements and whether it should be co-administered with the measles vaccine.

2.5.4 Viet Nam

Dr Nguyen Dac Trung, Programme Officer, National Expanded Programme on Immunization, NIHE, presented on the Viet Nam JE immunization programme. A locally-produced mouse brain-derived vaccine is administered in a two-dose primary series at 12 months of age and 1-2 weeks later, with a booster dose one year after the second dose. Doses are 0.5 ml for children aged on to three and 1 ml for those four to five years old. Vaccine was introduced in a few of districts in 1997, and the proportion of districts covered gradually increased each year. In 2009, 75% of districts were
covered but in 2010, only 49% of districts were covered due to vaccine shortage. In 2009, coverage for the booster dose among the target population in implemented areas was 95%.

2.5.5 Bangladesh

Dr Md. Shafiqur Rahman, Medical Officer, Directorate General of Health Services, and Dr Khorsed Ara, Principle Scientific Officer, Department of Microbiology, Institute of Epidemiology, Disease Control and Research, presented on JE vaccination in Bangladesh. The Government is considering introduction of JE vaccine based on the evidence that JE is endemic in Bangladesh and causes significant mortality. A clinical trial of the vaccine is planned before the government makes a decision on a national programme. The trial will involve administration of a single dose of the live attenuated SA 14-14-2 JE vaccine to 10- to 12-month-old infants. Vaccine recipients will undergo clinical and laboratory assessment one month after vaccination. AEFI will be closely monitored and JE surveillance and case notification will be used to assess the impact of JE vaccination. Remaining challenges are identifying stakeholders, training staff and raising community awareness.

2.5.6 India

Dr Navneet Kumar Dhamija, National Programme Manager and Assistant Commissioner for Immunization, Ministry of Health and Family Welfare, presented on JE vaccine introduction in India. Prior to 2005, there had been sporadic outbreaks of AES in several states, and some had introduced JE vaccination with inactivated mouse brain-derived vaccine produced in India. A large outbreak in 2005 led to the introduction of the live attenuated SA 14-14-2 JE vaccine through the National Universal Immunization Programme in endemic districts. In a phased manner over five years (2006-2010), each area conducted a three-week campaign for children one to 15 years old and then incorporated the JE vaccine into the routine immunization programme. In total, 111 districts and 15 states were covered and over 77 million children (80% of the target population) were vaccinated during the campaigns. AEFI were reported in 50 per million children vaccinated, with five serious AEFI per million children vaccinated. A national committee of experts, formed in 2006 to investigate AEFI, found no deaths or serious illness to be causally linked to JE vaccine. Strengthening of AEFI investigations and causality assessments were recommended. Challenges for the vaccination programme include investigating and addressing JE cases in areas both covered and not yet covered by vaccination, age shift of JE to adults in some states, and incomplete coverage through routine immunization.

2.5.7 Nepal

Nepal’s JE vaccination programme was presented by Dr Shyam Raj Uperti, Director, Child Health Division, Department of Health Services. According to JE surveillance initiated in 2004, risk for JE in Nepal is highest in the lowland (terai) area along the southern border. From 2006 to 2009, vaccination campaigns were implemented in 23 of 27 high- and moderate-risk districts, using a single-dose schedule of the live attenuated SA 14-14-2 vaccine. Campaigns targeted either children one to 15 years old (11 districts), or those one year old or older (12 districts). Vaccine impact was measured using surveillance data through 2009. Overall, the post-campaign AES incidence was 58% lower than pre-campaign AES incidence in districts that had implemented JE vaccination campaigns. The post-campaign JE incidence was 72% lower than the pre-campaign incidence in the districts that had implemented campaigns. District-level trends varied. AES incidence increased in four districts but no district had a statistically significant increase in JE incidence. Vaccination campaign impact was greatest in the districts with highest JE disease burden, and in districts that implemented
campaigns targeting all people rather than just children. The number of JE cases increased in some hill and mountain districts not included in the JE vaccination programme. Limitations of the analysis were short post-campaign observation periods in some areas, unknown true coverage rate, and the use of 2001 population projections for incidence denominators.

2.5.8 Sri Lanka

Dr Pushpa Ranjan Wijesinghe, National Surveillance Focal Point, Epidemiology Unit, presented on the JE vaccination programme in Sri Lanka. From 1988, Sri Lanka implemented campaigns targeting children one to 10 years old in high-risk areas, using the inactivated mouse brain-derived vaccine. A study estimated that 97% of JE cases were prevented with these campaigns, and that the cost per JE case averted was US$ 315. Although JE cases decreased substantially, the programme faced challenges with continued JE outbreaks, high vaccine costs, decreasing vaccine availability and poor vaccine acceptability due to a high AEFI rate compared to other routinely-used vaccines. To address these issues, the live attenuated SA-14-14-2 vaccine was introduced into the routine immunization programme in all districts starting in 2009, after completion of a local safety and immunogenicity study. The selected schedule was a single dose at 12 months of age, which shifted to nine months of age with introduction of the combination measles, mumps and rubella vaccine. Challenges during implementation included shortages of vaccine supply, higher-than-anticipated cost and difficulties in developing an operationally-useful contraindications list.

2.5.9 Thailand

Dr Pornasak Yoocharoen, Medical Officer, Bureau of General Communicable Diseases, Department of Disease Control, presented on the JE vaccination programme in Thailand. The Advisory Committee on Immunization Practice made a decision in 1990 to introduce JE vaccine based on the evidence of JE disease burden (45%-50% of encephalitis cases due to JE), a cost-benefit analysis, and consideration of safety, availability and affordability of the vaccine. A locally-produced inactivated mouse brain-derived JE vaccine was used, with a three-dose schedule between ages 18 months and 3 years. Vaccine was introduced in a phased manner starting in 1990 and reached national coverage by 2000. In 2008, national coverage with the second dose was 95%, and 89% with the third dose. A 2003 retrospective study found that urticaria occurred following 20 per 10 000 doses of JE vaccine administered, primarily after the second dose. After JE vaccination was initiated in 1990, reported JE cases decreased to 40 cases/year from 500-1000 cases/year. However, 15% of encephalitis cases are still caused by JE. Initiatives for the future include possible shifting to a Vero cell-derived or live attenuated vaccine, administering the vaccine to a younger age group, and increasing coverage in hard-to-reach areas and populations.

2.5.10 Summary of issues in country presentations of JE vaccination programmes

Dr Hardeep Sandhu, Medical Epidemiologist, Global Immunization Division, CDC, summarized the progress in JE vaccine introduction and impact monitoring in the South-East Asia and Western Pacific regions.

Key characteristics of JE vaccination programmes varied from country to country as indicated below:

(1) target populations: specific age groups, specific geographic areas, or national coverage;
(2) immunization strategies: campaign or routine immunization or both;

(3) impact monitoring: by retrospective analysis of surveillance data or case-control studies;

(4) AEFI monitoring: standardized methodology developed in some countries and planned in others; and

(5) programmatic issues: vaccination potentially requiring an additional contact, potential integration with school health programmes, and decision whether to co-administer with measles or other vaccines.

2.6 Work groups: Improving and sustaining JE surveillance and JE vaccination programmes

Four work groups were formed and asked to use information from the country presentations and their own experiences to identify challenges and propose solutions in given programmatic areas of JE surveillance and JE vaccination.

2.6.1 Work groups 1 and 2: Improving the quality and efficiency of JE surveillance and use of data for decision-making

To improve the quality of surveillance, the work groups recommended the use of standardized guidelines and formats; the use of hospital and laboratory standard operating procedures (SOPs); more extensive training of laboratory staff, surveillance officers, clinicians, and private practitioners; and strengthening relationships with professional societies. The groups also recommended increasing supervision at all levels, improving coordination of specimen transfer, providing reminders for convalescent serum collection, strengthening incentives for reporting, and providing regular and timely feedback to data providers. To implement surveillance more efficiently, the groups recommended implementing more effective data cleaning, combining data collection visits for several diseases, linking laboratory and epidemiology databases, implementing electronic notification of cases, integrating JE surveillance into national surveillance systems, integrating surveillance costing into comprehensive multi-year plans (cMYPs) and sharing laboratory equipment. To increase the use of data for decision-making, the groups recommended holding regular integrated data review meetings, providing systematic data reporting to the national programme unit, identifying effective ways to present data to decision makers, mapping disease, using cost-benefit or cost-effectiveness analyses and using data as a basis for modelling.
Recommendations to improve the communication of surveillance data included using simple messages, holding media briefings and building on community support to conduct vaccine advocacy.

2.6.2 Work groups 3 and 4: Addressing the challenges in JE vaccine introduction and monitoring the impact

The work groups identified challenges including competing priorities among vaccines, insufficient surveillance data in some countries, lack of health economic data in most countries and lack of a WHO-prequalified vaccine. The groups recommended providing scientific evidence, especially local evidence, to policy-makers through national immunization technical advisory groups (NITAGs) and immunization committees. Programmatic challenges included increasing cold chain capacity, establishing an AEFI system, educating clinicians and the general population, managing media to minimize disruptions from the anti-vaccine lobby, and in some countries shifting from mouse brain-derived vaccine to other vaccines. The groups recommended considering JE vaccine co-
administration with other vaccines as a way to increase programme efficiency. For impact monitoring, coordination among multiple partners (laboratory, surveillance and immunization programme) was identified as a central challenge. Additional challenges were collecting key data points such as vaccination status of cases, and sharing results with a wide range of stakeholders from programme staff to advisory committees to international partners and media. The group recommended that partners be engaged to help build health system capacity, that JE vaccine be viewed as a routine part of the immunization programme, and that JE surveillance be included in routine national surveillance systems. The group also recommended more frequent sharing of experiences among countries in the South-East Asia and Western Pacific regions.

2.7 Partners in JE prevention and control

2.7.1 The Bill & Melinda Gates Foundation (BMGF)

Dr Julie Jacobson, Senior Programme Officer at the Bill and Melinda Gates Foundation, presented the BMGF’s strategy to address neglected infectious diseases, including JE. The BMGF goal for JE is to eliminate clinical JE cases through vaccination. From 2000 to 2011, the BMGF committed US$ 39 million to JE programmes which supported diagnostics development, vaccine development and countries’ implementation of surveillance and vaccine introduction. Through the BMGF’s investment, over 100 million doses of live attenuated JE vaccine have been given in Sri Lanka, India, Nepal and Cambodia. The manufacturer of the vaccine committed to providing the vaccine at an affordable price for the public sector (around US$ 0.25 per dose). BMGF currently focuses on achieving prequalification for the live attenuated SA 14-14-2 vaccine, documenting vaccine impact through CDC studies, and supporting vaccine introduction through the GAVI Alliance.

2.7.2 Wellcome Trust–Mahosot Hospital–Oxford University Tropical Medicine Research Collaboration

Dr Vilada Chansamouth presented data from a study of JE disease burden done by the Wellcome Trust–Mahosot Hospital–Oxford University Tropical Medicine Research Collaboration in Vientiane, Lao People’s Democratic Republic. The study measured the proportion of AES cases caused by JE among patients from three sites: Mahosot Hospital in Vientiane, Luang Namtha Hospital in the far north, and Salavan Provincial Hospital in the south. Diagnosis was made by identifying anti-JE IgM in the CSF or serum with XCyton JE IgM ELISA and Panbio JE-Dengue IgM Combo ELISA kits, or by a positive CSF JE viral culture or PCR. At Mahosot Hospital, from January 2003 to March 2011, 521 patients with AES were evaluated and 19% (91) were JE IgM-positive. Five additional cases were identified by JE culture or PCR. Most cases occurred between May and September, the rainy season, and more than half of patients were under 15 years old. In a clinical follow-up of 73 JE patients from Mahosot Hospital, 59% had a full recovery, 19% had a slight behavioural change, 10% had moderate sequelae, 5% had severe sequelae and 21% were lost to follow up. In Luang Namtha, anti-JE IgM was found in the serum of 43% of 49 AES cases, and in Salavan, 50% of 10 AES patients. Seasonality of JE inpatients at these hospitals was similar to that found at Mahosot. XCyton and Panbio ELISA tests of JE IgM in the CSF were evaluated on 234 AES patients, with the AFRIMS JE MAC ELISA as the reference standard. XCyton had 76.5% sensitivity while Panbio had 85.3% sensitivity; both tests had a high specificity (99%-100%).
2.7.3 US Centers for Disease Control and Prevention (US CDC)

Dr Michael Thigpen of US CDC presented an ongoing study to assess the impact of JE vaccination in Cambodia. The study involves 12 months of population-based ME surveillance among children in the neighbouring provinces of Battambang and Banteay Meanchey, followed by mass immunization of Battambang children with the SA 14-14-2 live attenuated vaccine, and then 12-18 months of continued ME surveillance in the two provinces. Battambang and Banteay Meanchey have similar ecological features and the JE vaccine has not yet been introduced in either province. The case definition used is children up to 15 years old with sudden onset fever and change in mental status, new onset of seizures, or meningeal signs. CSF and serum samples are tested at the National Institute of Public Health laboratory with the Panbio JE-Dengue IgM Combo ELISA. At the time of presentation, surveillance had started in Battambang and would commence in Banteay Meanchey in the next month.

2.7.4 Summary of issues being addressed by partners

Dr Florian Marks, International Vaccine Institute, summarized the issues being addressed by partners. The Bill and Melinda Gates Foundation has made a substantial investment in JE control over the past decade through its neglected infectious diseases programme, with an aim to eliminate clinical JE cases through vaccination. Support has been critical for diagnostics and vaccine development, and to initiate JE surveillance and vaccination in countries. Support for the WHO prequalification process for the live attenuated SA 14-14-2 vaccine will continue. The Wellcome Trust–Mahosot Hospital–Oxford University Tropical Medicine Research Collaboration has an ongoing meningitis and encephalitis study which has helped to document the importance of JE as a cause of AES in the northern part of the Lao People’s Democratic Republic, with more limited data from other regions. The US CDC is initiating a study in Cambodia to measure the impact of JE vaccination with the SA 14-14-2 vaccine through comparison of population-based surveillance before and after a JE vaccination campaign, and in neighbouring provinces without the campaign.

2.8 Action plans for applying lessons learnt to future plans

2.8.1 Bangladesh

Plans for the next six to 12 months to improve implementation of JE surveillance in Bangladesh included updating the JE surveillance SOP based on lessons learnt from the current JE surveillance efforts and knowledge gained from this meeting, improving CSF specimen collection through health care worker training and community sensitization, ensuring uninterrupted resources and supplies, and incorporating JE surveillance into an existing web-based priority communicable disease surveillance system. Additional plans are to expand JE surveillance to the rest of the country, work with a health economist to evaluate the economic impact of JE vaccination, increase JE communication on from the national to peripheral levels, and collaborate with partner organizations for technical support for both surveillance and a vaccine trial.

2.8.2 Bhutan

Plans for JE surveillance in Bhutan in the next six to 12 months include mapping of the JE vector, identifying risk populations and establishing sentinel surveillance. For surveillance laboratory support, training and an external quality assurance system are needed, along with development of SOPs. Plans for JE vaccination will depend on findings from surveillance.
2.8.3 Cambodia

Plans to improve the Cambodia's JE programmes in the next six to 12 months include training new surveillance and laboratory staff in the six current sentinel sites followed by quarterly supervisory visits, and strengthening management of data collection. Sample collection and handling needs to be improved with regard to timeliness, quality, and storage. The JE vaccination programme in three provinces would be maintained, with continued monitoring of coverage, AEFI, and the number of children from other provinces receiving JE vaccination.

2.8.4 China

Plans for the China JE programme in the next six to 12 months were presented. In terms of surveillance, plans include conducting field supervision and convening an annual JE surveillance and training workshop. Laboratory quality will be improved through hands-on training and strengthened quality control for provincial laboratories. For the vaccination programme, a coverage survey is planned.

2.8.5 India

The India JE programme plans for the next 6 to 12 months were presented. For all areas of the programme, capacity building, monitoring of funds, coordination, and communications are priorities. For surveillance, plans include close monitoring of data flow, implementing mid-term reviews, consolidating maps and developing new software. For laboratory systems, plans included holding annual refresher training; laboratory strengthening through increases in funds, personnel and equipment; and continuing internal and external quality systems. For JE vaccination, coverage through routine immunization systems will be strengthened by improving vaccine logistics and service delivery, and campaigns will be conducted to reach JE vaccination. JE vaccination will be evaluated through operational research studies.

2.8.6 Indonesia

Plans for the JE programme in Indonesia in the next six to 12 months were presented. JE sentinel surveillance will be re-started in Bali and syndromic AES surveillance will be strengthened in nine priority provinces. While the national laboratory in Jakarta is part of the WHO JE laboratory network, JE testing at the Bali provincial laboratory would be initiated. The immunization programme's comprehensive multi-year plan includes conducting a JE vaccination campaign in Bali in 2013, and incorporating the JE vaccine into routine immunization in 2014.

2.8.7 Lao People's Democratic Republic

Plans to improve JE programmes in the Lao People's Democratic Republic in the next six to 12 months were presented. For surveillance, plans include training clinicians to improve reporting and sample collection for all AES cases, strengthening linkages between laboratory and epidemiology data systems, and increasing the budget for case investigation and sample shipment. In addition, the specimen collection SOP will be revised and AES surveillance with laboratory confirmation will be integrated into influenza-like illness surveillance sites. A coordination mechanism will be developed among NCLE, EPI, and the Mahosot Hospital laboratory. For JE vaccination, plans included a catch-up campaign for children under 15 years old followed by
incorporation into routine immunization. Routine AEFI reporting will continue along with monitoring of JE cases to assess vaccine impact.

2.8.8 Malaysia

Future plans for the Malaysia JE programmes were presented. For surveillance, plans include implementing an e-notification system for infectious diseases, and continuing of current passive AES surveillance with JE laboratory confirmation. The vaccination programme in Sarawak will be continued and replacement of the currently used inactivated mouse brain-derived vaccine with the live attenuated vaccine will be considered.

2.8.9 Nepal

Future plans for the Nepal JE programmes were presented. To improve surveillance, sensitization meetings and refresher trainings for clinicians and laboratory staff are planned. To strengthen JE laboratory testing, an additional site for laboratory diagnosis is planned, along with improvements in sample collection. For the vaccination programme, plans included JE vaccination campaigns in four additional high-risk districts, strengthening immunization systems and AEFI surveillance, and developing a future strategy for vaccination in districts with emerging JE transmission. Plans for monitoring and evaluation include sustained surveillance and coverage monitoring, and possible co-administration of the JE and measles vaccines.

2.8.10 Papua New Guinea

Plans to initiate JE surveillance in Papua New Guinea were presented. An operational plan will be drafted and paediatricians will be sensitized to the surveillance procedures. A laboratory testing algorithm will be developed and laboratory staff will be trained in-house. The surveillance procedures would be reviewed jointly by paediatricians and laboratory staff.

2.8.11 Philippines

Plans to improve JE programmes in the Philippines were presented. Surveillance plans include integration of JE laboratory confirmation into routine AES surveillance, and expansion of sentinel surveillance from five sites to 10 sites. The surveillance guidelines and training modules will be updated and integrated monitoring and supervision visits will be conducted to the surveillance sites. Regular meetings between the surveillance and EPI staff are planned to facilitate better data analysis and feedback. Partnership with the private sector is proposed to support specimen transport. Plans for JE vaccination in the Philippines will depend on results of the sentinel surveillance.

2.8.12 Sri Lanka

Plans for JE programmes in Sri Lanka were presented. Plans for surveillance included improving the quality of case-based epidemiological AES surveillance and confirmed JE case surveillance and sustaining surveillance at a level that meets WHO standards. Plans for JE vaccination included expanding to the remaining seven districts through communications activities in these districts to reach both health care staff and the general public.
2.8.13 Thailand

Plans to improve JE programmes in Thailand through 2012 include disseminating information to physicians about the importance of JE surveillance, enhancing data coordination between the Bureau of Epidemiology and the National Institute of Health, and improving coverage data using a computer-based system. A national coverage survey is planned for 2013 and a serosurvey for 2014. Mobile teams will be used to increase vaccine coverage among migrant workers, persons in remote areas, and other hard-to-reach groups.

2.8.14 Viet Nam

Plans to improve the Viet Nam JE programmes over the next 6-12 months were presented. Responsibility for ME sentinel surveillance and separate JE surveillance in several provinces will be shifted to the national EPI, consistent with other vaccine-preventable disease surveillance. The JE surveillance guidelines, case investigation form and database will be revised, so that a single form and database can be used for JE and meningitis surveillance. JE surveillance workshops and training will be held for the two national paediatric hospitals. JE laboratory confirmation will continue at the two member laboratories of the WHO JE laboratory network, NIHE and the Institut Pasteur Ho Chi Minh City.

2.8.15 Partners work group report

Participants that attended the meeting (US CDC, Bill and Melinda Gates Foundation, International Vaccine Institute, Wellcome Trust–Mahosot Hospital–Oxford University Tropical Medicine Research Collaboration, and PATH) met to discuss major gaps in knowledge and other barriers to successful implementation of JE surveillance and vaccination programmes and to recommend ways to address these. The group recommended that access to information on vaccines and immunization planning be improved by regularly updating the Advanced Immunization Management (AIM) e-learning site available through the WHO website. The group noted that additional data on the safety and long-term efficacy of the live attenuated SA 14-14-2 vaccine is needed. A safety review paper will be published and soon. Sri Lanka could be a potential site for collection of high-quality AEFI data to establish long-term safety. There is also the opportunity for a pregnancy registry in Nepal. While the WHO position is that JE and measles vaccines may be co-administered, this practice should continue to be monitored and new data should be analyzed. Once a WHO-prequalified vaccine is available, barriers to vaccine introduction will be reduced. However, technical support will be needed for countries preparing for vaccine introduction, and planning programme monitoring and evaluation. In addition, countries currently using inactivated mouse brain-derived vaccine may need technical support to select among and administer newer vaccines given the shifts in production and loss of current supply.
3. CONCLUSIONS

3.1 Conclusions

(1) Key issues, challenges and recommendations related to JE surveillance were discussed and identified.

(a) Integrating JE surveillance with surveillance of other diseases (meningitis, routine notifiable disease, influenza-like illness) was found to be useful in many settings to improve efficiency and quality.

(b) Focussing on obtaining critical information, most importantly vaccination status, is needed to increase completeness of the data.

(c) Implementing WHO-recommended indicators and routine systems for monitoring the quality of JE surveillance are recommended.

(d) Ensuing strong communication among several groups (epidemiology, laboratory, and immunization) is necessary to effectively implement surveillance.

(e) Obtaining sufficient commitment of financial and human resources is needed for sustaining JE surveillance programmes.

(2) Key issues, challenges and recommendations related to for JE data use and decision-making were also covered at the meeting.

(a) JE positivity among AES or suspected JE cases varies widely within and between countries, for unclear reasons. Whether such data can be used to inform vaccination strategies requires further exploration.

(b) Many countries collect a combination of AES data and laboratory-confirmed JE data, from sentinel sites or sometimes larger areas. Further work is needed to determine the best analytic approaches for such data.

(c) Surveillance data reported by WHO have global implications so data quality is critical.

(d) Further guidance would be useful to help countries select the optimal approach to JE vaccine introduction (respective roles of campaigns and routine immunization, selecting target age groups, addressing newly emerging areas, etc.).

(3) The following key issues, challenges and recommendations were associated with JE vaccination implementation.

(a) Commitment from policy-makers often wanes as vaccination programmes succeed in decreasing the disease burden; solutions must be found to sustain commitment.

(b) Integrating JE vaccination into routine immunization requires decisions on the schedule to use, co-administration with another vaccine and other programmatic factors, while
taking into consideration potential impact on vaccination coverage and the financial and human resources required.

(4) In terms of JE vaccination programme monitoring and evaluation, key issues, challenges and recommendations were also discussed and identified.

(a) JE case investigation is critical to understanding why JE cases occur even with established vaccination programmes. It can determine whether new JE cases are due to vaccine failure, incomplete coverage in the target population, or a need to expand the target population or target geographic area.

(b) An increase in age among JE cases was noted in many countries after a JE vaccination programme was initiated. This is expected if the shift is in percentage of cases but the absolute number of cases decreases. The absence of such an increase after initiation of a vaccination programme targeting children is cause for careful examination of the programme.

(5) Common themes across country plans for JE surveillance are:

(a) identifying increased and sustainable funding for surveillance;

(b) integrating JE surveillance with other types of surveillance;

(c) conducting training for laboratory and surveillance staff;

(d) ensuring that JE surveillance meets WHO standards;

(e) designing new databases and web-based systems;

(f) improving data completeness for key variables; and

(g) improving communication and coordination among laboratory, epidemiology and immunization staff.

(6) Common themes across country plans for JE data use and decision-making are:

(a) incorporating economic evaluation into decision-making, are:

(b) using surveillance data to determine target areas and age groups for introducing JE vaccine.

(7) Common themes across country plans for JE vaccination programmes are:

(a) developing plans for JE vaccination campaigns followed by incorporation into routine immunization, as recommended by WHO;

(b) expanding vaccination to areas newly identified as having JE or to areas not included in initial priorities, and planning additional campaigns to increase coverage to hard-to-reach populations;
(c) considering a shift to live attenuated SA 14-14-2 vaccine by countries currently using mouse brain-derived vaccine;

(d) strengthening AEFI systems; and

(e) addressing gaps in vaccine management and providing training for service delivery.

(8) Common themes across country plans for JE programme monitoring and evaluation are:

(a) improving programme monitoring and in some cases conducting coverage surveys, and

(b) using improved surveillance and special studies to evaluate vaccine impact.

3.2 Closing remarks

Closing remarks from Dr Shin Young-soo, WHO Regional Director for the Western Pacific, were read by Dr Yunguo Liu, WHO Representative for the Lao People's Democratic Republic. The Regional Director thanked all participants for their active roles in the Fifth Biregional Meeting on JE Prevention and Control. He noted the contributions from the participants from sixteen countries and representatives from WHO, UNICEF, and other partner organizations, to develop plans of action to improve the quality and scope of Japanese encephalitis surveillance and vaccination programmes in the Western Pacific and South-East Asia regions. The Regional Director stated WHO’s commitment to assisting countries in the implementation of these plans and to improving JE programmes in the regions. Special thanks were given to the WHO Country Office in the Lao People's Democratic Republic for providing logistical support for the meeting.
<table>
<thead>
<tr>
<th>Time</th>
<th>Monday, 30 May 2011</th>
<th>Time</th>
<th>Tuesday, 31 May 2011</th>
<th>Time</th>
<th>Wednesday, 1 June 2011</th>
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<tbody>
<tr>
<td></td>
<td>1. Opening remarks</td>
<td></td>
<td>- Update on vaccine development and global policies</td>
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<td>Partner presentations on JE activities and plans</td>
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<td>Administrative announcements</td>
<td>0930-1030</td>
<td>- Questions and discussion</td>
<td>0930-1015</td>
<td>10. Applying lessons learnt to future plans</td>
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<td>- Country progress in JE vaccine introduction and</td>
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<td>- Country work groups: actions to improve JE</td>
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<td>3. Country presentations on progress and challenges in</td>
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<td>4. Cambodia, the Lao People’s Democratic Republic,</td>
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<td>7. Work groups improving and sustaining JE</td>
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<td>11. Conclusions and next steps</td>
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<td>4. Progress with JE laboratory networks</td>
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<td>8. Reports from work groups</td>
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FIFTH BIREGIONAL MEETING ON JAPANESE ENCEPHALITIS PREVENTION AND CONTROL
Vientiane, the Lao People’s Democratic Republic
30 May–1 June 2011

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