WHO assists Member States to periodically review and discuss various topics concerning national immunization programmes. Deliberations on these issues lead to tangible improvements in managing these national programmes.

With this objective, the sixth Bi-regional Meeting on Prevention and Control of Japanese Encephalitis (JE) was held in Bangkok, Thailand, on 27–29 May 2014. The objectives of the meeting were to support JE endemic countries of South-East Asia and Western Pacific Regions to reap the benefits of recent technical advances in JE laboratory diagnosis, vaccine availability and to gain benefits from new opportunities. This publication reports on the aforesaid meeting.

This publication includes recommendations for Member States’ next steps in implementing strategies for prevention and control of JE. The report also contains a summary of progress, key issues and challenges in implementing JE control measures for Member States that have introduced JE vaccines. Member States that have not introduced the vaccine are encouraged to proceed with decision making, planning vaccine introduction, programme implementation, and monitoring and evaluation of the impact of existing JE vaccine programmes. The support required by countries to implement the next steps including establishing or strengthening JE surveillance is also discussed.
Prevention and control of Japanese encephalitis (JE)

Report of the sixth bi-regional meeting
Bangkok, Thailand, 27–29 May 2014
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# Acronyms

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<th>Description</th>
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<tr>
<td>AMES</td>
<td>acute meningoencephalitis syndrome</td>
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<tr>
<td>AEFI</td>
<td>adverse events following immunization</td>
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<tr>
<td>AES</td>
<td>acute encephalitic syndrome</td>
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<tr>
<td>CDIBP</td>
<td>Chengdu Institute of Biological Products, Chengdu, China</td>
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<tr>
<td>CFR</td>
<td>case-fatality ratio</td>
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<tr>
<td>cMYP</td>
<td>comprehensive multi-year plan</td>
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<tr>
<td>CSF</td>
<td>cerebrovascular fluid</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<tr>
<td>GAVI</td>
<td>Global Alliance for Vaccine and Immunization</td>
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<tr>
<td>HCW</td>
<td>health-care worker</td>
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<td>JE</td>
<td>Japanese encephalitis</td>
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<tr>
<td>JE VISP</td>
<td>JE Vaccine Investment Strategy Project</td>
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<tr>
<td>JRF</td>
<td>joint reporting form</td>
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<tr>
<td>MR</td>
<td>measles and rubella</td>
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<tr>
<td>NSSNSD</td>
<td>Nationwide Surveillance System of Notifiable Selected Diseases</td>
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<tr>
<td>VPD</td>
<td>vaccine-preventable diseases</td>
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<tr>
<td>PATH</td>
<td>Programme for Appropriate Technology for Health</td>
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<tr>
<td>PNG</td>
<td>Papua New Guinea</td>
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<tr>
<td>SEAR</td>
<td>South-East Asia Region</td>
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<tr>
<td>TAG</td>
<td>Technical Advisory Group</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children Fund</td>
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<tr>
<td>UP</td>
<td>Uttar Pradesh, India</td>
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<tr>
<td>VP3</td>
<td>vaccine product, price and procurement</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1. Introduction

In 2002, the WHO South-East Asia and Western Pacific regions in collaboration with Programme for Appropriate Technology for Health (PATH) organized a Joint South-East Asia and Western Pacific Working Group Meeting on Japanese encephalitis (JE). That meeting was instrumental in raising global awareness of the public health importance of JE in the Asian region. Since then, WHO has been supporting Member States in vaccine safety and regulatory authority oversight, guidelines development, surveillance and vaccine introduction.

Subsequently, a series of bi-regional meetings held in 2005, 2007, 2009 and 2011 provided a forum for coordination of the global work on JE, technical updates, country exchange of experiences, and monitoring the progress of the JE work. Key achievements have been the finalization of WHO JE surveillance guidelines; evaluation and standardization of commercial test kits for JE diagnosis; establishment of the JE laboratory network; expanding and strengthening of JE surveillance; development of regional JE vaccine introduction guidelines; and introduction of the live attenuated SA 14-14-2 JE vaccine by several countries.

The sixth bi-regional meeting on prevention and control of Japanese encephalitis (JE) for the WHO South-East Asia and Western Pacific regions of WHO was held on 27–29 May 2014 in Bangkok, Thailand.

The general objective of the meeting was to support endemic countries to reap the benefits of recent technical advances in JE laboratory diagnosis, vaccine availability and new opportunities.

The specific objectives of the meeting were to:

(1) review the current status of the disease, surveillance and vaccine introduction including:
– magnitude of the problem as well as identification of high risk areas;
– overview of current surveillance approaches and capacity (using a template pre-filled by countries); and
– vaccine introduction experiences, vaccine coverage, and the impact of vaccination

(2) update participants on new developments in prevention and control of JE including WHO prequalified vaccines, Global Alliance for Vaccine and Immunization (GAVI) support and other new opportunities; and

(3) discuss and identify the necessary steps for strengthening JE surveillance and vaccine introduction/expansion in the two Regions including discussion on financing and budgeting, as well as vaccine coverage, monitoring and evaluation.

Fifty three participants attended the meeting, including immunization officials from 12 JE-endemic countries and technical officers from UNICEF and WHO headquarters, as well as regional and country offices. Industry and nongovernmental organizations, public health and academic institutions, and the Bill and Melinda Gates Foundation also were represented. The agenda and list of participants is provided in Annexes 1 and 2.

Dr Pradeep Haldar, Deputy Commissioner (Immunization), Ministry of Health and Family Welfare, Government of India was nominated Chair of the meeting and Dr Vito Roque, Chief, Public Health Surveillance and Informatics Division, Department of Health, Philippines, the Co-chair, with Dr Samitha Ginige, Consultant Epidemiologist, Ministry of Health, Sri Lanka as Rapporteur.

2. Updates on JE

2.1 Global update

An estimated 67 900 JE cases occur globally per year. The overall incidence is 1.8 per 100 000 population. Approximately 75% of the cases are in
children in the 1–14 years age group (incidence 5.4/100 000). The number of fatal cases is around 13 600–20 400 and another 14 300–27 200 survive with long-term neuropsychological sequelae following JE infection.

Further work is needed to strengthen and standardize surveillance procedures to ensure quality data. In 2012, only 4171 JE cases were reported globally to WHO, thus demonstrating that the joint reporting form does not adequately capture the JE burden.

A number of strategies exist worldwide to control JE including:

- adult mosquito control;
- mosquito-breeding control;
  - water management; intermittent irrigation
  - using natural enemies of mosquitoes, predators such as Gambusia Affinis
- pig vaccination and separating pigs, the amplifier host from humans;
- improving living conditions; and
- human vaccination.

Human vaccination has been by far the most successful control strategy. However, the occurrence of substantial numbers of JE cases in countries with national or targeted national vaccination programmes requires further evaluation to understand the epidemiology of the disease. In addition, waning immunity leading to a rebound of the disease also needs to be further investigated.

A number of developments have occurred since the last biregional meeting held in 2011. These include the changing product landscape of JE vaccine, availability of two WHO prequalified JE vaccines (live attenuated SA 14-14-2, inactivated vero cell SA 14-14-2) and the introduction of GAVI funding for JE vaccine.
2.2 Regional updates

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

The Member countries of South-East Asia Region began JE surveillance in the early 1980s and introduced mouse brain-derived JE vaccine into high risk populations in the late 1980s. While four countries have national or sub-national JE vaccination programmes, seven countries have not yet introduced JE vaccine. The history and current status of JE vaccination programmes in India, Nepal, Sri Lanka and Thailand were summarized.

JE was a significant public health problem in these countries and they introduced vaccine following large outbreaks. Thailand and Sri Lanka introduced JE vaccine into their routine national EPI programmes throughout the country, while India and Nepal introduced it in the routine vaccination programme in the high risk areas following mass campaigns for all high-risk populations of 1–15 years. In addition, in several districts, Nepal introduced vaccine in all ages above one year followed by routinely annually for new birth cohorts. India and Nepal have introduced and continue to administer live attenuated SA 14 14 2 vaccine in the districts the campaigns were conducted, while Sri Lanka started with mouse brain vaccine in 1988 and shifted to SA 14 14 2 live vaccine in 2009. Thailand is still using its own production of mouse brain-derived inactivated vaccine and recently introduced SA 14 14 2 live vaccine in eight provinces as a pilot introduction.

Seasonal outbreaks occur in certain states of India and with high case-fatality rates (CFR), while disease incidence and sequelae data are not well documented. Diagnosis and case management are not well-established in some settings. A network of laboratory-based surveillance is in place with many sites serving as WHO-supported sentinel sites. The risk of JE is not uniform and ecological changes are associated with change in high-risk areas.

Data from Nepal, Sri Lanka and Thailand suggests that the increase in JE vaccination coverage among children has led to a shift in disease burden among adults. However, the overall incidence has come down in the vaccinated cohorts of the three countries.
**JE in the Western Pacific Region**

Substantial progress in the establishment or strengthening of JE surveillance has occurred in recent years in the Western Pacific Region. Surveillance has been implemented in some form in all countries with JE risk, so that sufficient data are available for countries to make decisions about vaccine introduction. China, Cambodia, Philippines, Papua New Guinea and Viet Nam have case-based surveillance with laboratory confirmation at sentinel site hospitals. Australia, Brunei, Japan, Republic of Korea, Lao People’s Democratic Republic, Malaysia and Singapore have case-based surveillance and laboratory confirmation in the whole country.

According to estimates published in 2011, WPR has 40 400 JE cases annually (incidence -2.3/100 000) and out of these, 77% of the cases occur among children 0–14 years of age (8.9/100 000). The number of reported cases is only 5–10% of the estimated cases. The highest number of cases is reported from China. Of note is that a significant reduction of reported cases has been observed in the Region during 2006–2013. JE vaccine is used nationally or sub-nationally in nine of the 12 countries of the the Western Pacific Region with JE risk. The supply of JE vaccines has improved in recent years. JE vaccination programmes face constraints in terms of vaccine financing. Only three countries in the Region are eligible for GAVI support for broad age-range campaigns; however, only two of the three (Cambodia and Lao People’s Democratic Republic) will be applying to GAVI, as Viet Nam produces its own vaccine.

In 2013, the Technical Advisory Group (TAG) on Vaccines and Immunization advised the Regional Office for Western Pacific to establish a JE accelerated control goal. This will be proposed at the Regional Committee for endorsement in October 2014. TAG noted the weakness and fragmentation of JE surveillance in the Region and its critical role for estimating disease burden, defining target populations for vaccination, and measuring vaccine impact.
2.3 **Country updates**

**Bangladesh**

JE surveillance is limited to five sentinel sites. In 2013, a total of 71 cases were reported of which 94% were from the north-western region. The majority of reported cases are in the age groups of 6–15 years (23%) and the 46–65 years (23%). The cases are reported more during July–November period. Currently, two research projects are underway to determine the presence of antibodies in pigs and humans in selected districts.

**Bhutan**

An acute encephalitic syndrome (AES) surveillance system is in place in five sentinel sites. It was started in 2011. A reference laboratory is available. The districts bordering India are reporting more cases. The available surveillance data are not sufficient enough to decide on JE vaccination.

**China**

JE is one of 39 notifiable diseases. The National Notifiable Disease Reporting System (NNDRS) collects basic information for all JE cases. Detailed epidemiological and laboratory testing results of JE cases have been collected online since 2007. Sentinel surveillance is being carried out in 16 provinces.

More than 50% of laboratory-confirmed JE cases are reported among children. The highest incidence is reported in the 5–10 years age group. Before national introduction in 2008, sixteen provinces already had JE vaccine integrated into their provincial EPI. Since 2008, JE live attenuated vaccine is part of the national EPI, in a two-dose schedule at ages eight months and two years. Inactivated Vero-cell P-3 vaccine is used in private clinics in a four-dose schedule also starting at age eight months. Reported JE vaccination coverage for eligible children in 2013 was >99%; however, coverage was lower in rural areas.
**India**

Massive JE outbreaks occurred in 2005, mainly in Bihar and Eastern Uttar Pradesh (UP). Around 6000 AES/JE cases/1500 deaths were reported from UP and around 6500 AES/JE cases/1600 deaths from ten other states of India were reported. JE vaccination started in 2006, with SA14-14-2 LJEV in two states (i.e. Bihar and Uttar Pradesh). A single dose was given to children in the 1–15 years age group. Later, the vaccination campaigns were extended to the other high-risk states and out of 179 JE endemic districts, the campaigns have now been conducted in 152 districts. Routine vaccination was introduced following the campaigns. Currently two doses of LJEV are given in the routine programme for the new cohorts; first dose at nine months and the second dose at one and half years. Incorrect media publicity about adverse events following immunization (AEFI) creates difficulties in achieving targeted coverage. The JE vaccination coverage is relatively low and not consistent over the years.

Sentinel site-based surveillance was started in 2005. Over the years from 2008-2013, the reported AES cases increased significantly, but only 15% of AES are due to JE. In the state of Assam in 2013, approximately 80% JE confirmed cases were among adults. In UP, this figure was 30%.

**Discussion points:**

- In 2005, the state of UP, India reported a large number of JE cases. One potential reason is that at the time, all reported AES cases were considered as JE. In 2006, the JE laboratory network was established, and thus, subsequently only 15-20% of the total number of AES cases were confirmed as JE.

- The cerebrovascular fluid (CSF) or serum samples collected before day 5 of the disease may give negative results for detection of IgM antibodies. This fact needs to be considered when interpreting the results.

- In UP, JE vaccination started in 2006, but the state continues to report a significant number of JE cases.

- It is very important to ensure the timely availability of JE vaccine to the target populations. A close monitoring and evaluation of JE surveillance system is very essential. India may think of
adopting a monitoring and evaluation mechanism that is similar to polio surveillance.

- From 2011, India has offered two doses of LJEV; the first dose at 8–9 months and the second dose at 18 months. The rationale of introducing the second dose is to compensate for the children who dropped out of the first dose.

- Due to poor documentation, it is difficult to assess the vaccination status in the campaign districts of India.

**Indonesia**

Indonesia has not yet started JE vaccination; however, the Indonesia TAG has recommended the introduction of JE and has included plans in the new comprehensive multi-year plan (cMYP) for 2015–2019. The serological studies have demonstrated the presence of JE virus in pigs and antibodies among 25% of encephalitis patients that could be attributed to JE. No burden estimates have been carried out in Bali for the past 10 years. The WHO country office will be facilitating a JE sentinel laboratory surveillance site in Bali, while there is acknowledgement that there is a need to also start JE surveillance in other provinces.

**Lao People’s Democratic Republic**

Since the year 2000, encephalitis is a notifiable disease in Lao People’s Democratic Republic. JE was introduced to the Nationwide Surveillance System of Notifiable Selected Diseases (NSSNSD) or Lao Early Warning and Reporting Network under “encephalitis” since 2000. Since February 2011, AES surveillance has been in place. Out of the 17 provinces, 6–7 northern provinces are reporting more cases than others. The age group most affected is children below 15 years of age. JE vaccination campaigns targeting children 1–14 years old in the northern part of the country were conducted in 2013 (six provinces) and 2014 (two provinces). Plans include additional JE vaccination campaigns to cover children 1–14 years old in the central and southern regions, and introduction of JE vaccine into routine EPI.
**Discussion points:**

- In China, JE vaccination coverage among young children is still <80% in some provinces.
- In 2011 and 2012, Lao People’s Democratic Republic reported fewer numbers of JE cases than previously. This may be due to underreporting, overall socioeconomic development or seasonal changes.
- In 2013, Lao People’s Democratic Republic included five vaccines in one campaign: oral polio vaccine, JE, and diphtheria in the form of pentavalent, DT or Td (depending on age). Each child received one, two, or three vaccines, including up to two injections, depending on their age.
- In China, the graph shows a reduction of JE cases even before national introduction of JE vaccination. This is because JE vaccine was widely used in the private sector and in many provincial EPIs earlier.
- In Lao People’s Democratic Republic, government commitment is very high towards the immunization programme.
- Good advocacy is a key to achieve good vaccination programmes.

**Myanmar**

In Myanmar, there is no established JE surveillance in place. A limited JE/AES surveillance and diagnostic facilities are available in the reference laboratory. At present, JE is not under national surveillance, but reporting is done under vaccine-preventable diseases (VPD) surveillance; all outbreaks of AES are investigated. The majority of laboratory-confirmed cases are among >15 years old age group. JE vaccines are not available in the public sector. There is a need to develop Standard Operating Procedures, guidelines, IEC materials and a training manual for the township medical officers, basic health staff and the private sector.
Discussion points:

- The majority of JE cases in Bangladesh are among adults. No outbreaks are reported. The possible reason to support the larger number of confirmed adult cases is that there may be more CSF samples collected from adults. The other explanation could be that adults are more exposed to the disease.

- Myanmar also reported more JE cases among adults. The same reasons may be applicable. During the entomological surveillance carried out for malaria, JE was detected.

- Countries show higher numbers of JE cases among adults; however, age-specific incidence rates may be still higher among children than adults.

- Historically, pig vaccinations take place in many countries to prevent JE transmission; however, the effectiveness of this strategy is questionable.

Nepal

JE/AES surveillance has been integrated with AFP surveillance since 2004. Vaccination campaigns started in 2006 using SA-14-14-2 vaccine and covered 31 high and moderately endemic districts by 2011. The target age group was based on disease burden:

- children 1–15 years of age (11 districts) and
- whole population ≥1 year of age (20 districts)

The vaccine was introduced into the routine immunization programme in 2009 in all post campaign districts. More than 13 million doses of JE vaccine have been administered within a period of eight years and no serious adverse event related to SA 14 14 2 vaccine has been reported.

There is a plan to conduct an impact study on JE vaccination. JE cases have shifted towards the older age groups after the vaccine was introduced to children. Approximately 10% of AES cases are due to JE. Nearly 3–5% of JE cases are reported among immunized people. There are 127 sentinel
sites throughout the country. Weekly active surveillance visits are made by the surveillance medical officers in 90 out of these 127 sentinel sites.

There has been a notable positive impact of vaccination in the four high risk Terai districts that have historically had high JE disease burden. Also the impact was higher in the districts that implemented campaigns for all the population ≥1 year of age. The incidence decreased in the Terai region where the campaigns were focused, but over the same period increased in the hill and mountain districts. There are plans to expand JE vaccination to other districts. The non-JE cases among AES have been a challenge and a research study has been planned to identify the causes for non-JE AES.

**Papua New Guinea (PNG)**

The occurrence of JE cases is mainly suspected along the PNG-Indonesian border and around Port Moresby. Sporadic cases are reported from the Western Province. Currently, sentinel site case-based surveillance is being established in five provincial hospital sentinel sites as well as in Port Moresby. No vaccination has been introduced and cMYP does not include plans to introduce JE vaccine in PNG.

**Discussion points**

- GAVI support will not be extended to expanding the routine JE vaccination; it will only be for carrying out JE catch-up vaccination campaigns.

**Philippines**

A sentinel site surveillance project for JE started in 2007 in five sites. In 2008, acute encephalitis syndrome (AES) surveillance was included in the newly-established national integrated disease surveillance system. In 2012, surveillance was enhanced to become case-based surveillance with laboratory confirmation.

Results from disease surveillance, sero-epidemiologic studies, swine and other animal surveillance as well as mosquito surveys confirm circulation of JEV across all regions of the Philippines.
The majority of confirmed JE cases are among children <15 years of age. Approximately 12–40% of meningitis/encephalitis syndrome cases are JE. The Philippines has reported a CFR of 5.6–15.3% and among those who survive, there are significant neurologic sequelae. There is a tentative plan to introduce JE vaccination in 2016.

**Sri Lanka**

The first recorded major outbreak occurred in 1985–1986 in the two districts of the North-Central province (385 cases with 64 deaths, CFR of 17%). The largest reported outbreak occurred in 1987–1988 (816 cases with 192 deaths, CFR 24%) which spread to adjoining districts (Kurunegala, Puttalam) of the North Central province.

Immunization against JE with the inactivated JE vaccine was introduced in a phased manner through mass vaccinations targeting high risk districts in 1988. The LJEV was introduced in 2009. LJEV was introduced into the national immunization schedule in 2011 as a routine vaccine covering the entire country at nine months of age. Before 2011, JE vaccination was limited to only 18 high risk districts.

JE/AES is a notifiable disease. Nearly 70% of all JE cases are reported in the age group of over 20 years of age, but absolute numbers are small. A well-established AEFI surveillance for all VPD including JE is in place.

**Thailand**

JE is a notifiable disease. Electronic data entry is being done and individual case reports are available. The vaccination started in 1990. A majority of JE cases are reported among 1–14 year olds. There is a plan to shift to LJEV within the next three years.

**Viet Nam**

JE surveillance with laboratory confirmation is conducted in five provinces and three national sentinel site hospitals. In addition, the national laboratories provide referral testing. The majority of confirmed JE cases
reported are among <15 years of age. In 2013, three systems found 228 JE positives in which:

- 40 cases were from five selected provinces
- 163 cases were from three sentinel hospitals and
- 25 cases from two JE laboratories (other provinces)

Viet Nam introduced JE vaccine into EPI in 1997 in high risk areas and expanded subsequently to the other areas. The country uses inactivated mouse brain vaccine and the schedule contains three doses for children aged 1–5 years. The first two doses are administered 1–2 weeks apart and the third dose one year after the second dose. Vaccination is carried out in annual campaigns. The campaigns are not yet nationwide, covering 80% of districts as of now.

### 2.4 Updates from donors

**GAVI**

In November 2013, GAVI began its support to eligible countries to introduce WHO pre-qualified JE vaccines. The support goes towards catch-up campaigns targeting children 9 months–14 years. To facilitate JE introduction into routine immunization, countries are also eligible for a vaccine introduction grant.

In addition, if a country has:

- previously conducted campaigns for a portion of the population not reaching up to 14 year olds, the country will be eligible to apply for the remaining target age group up to 14 years. This includes campaigns using donated vaccines;
- already conducted a campaign in a targeted area, with or without GAVI support, and surveillance data identify new areas at risk of JE transmission, the country will be eligible for GAVI support for another campaign; and
- conducted campaigns in the past without incorporating JE into the routine programme afterwards, the country will be eligible
for GAVI support for unreached cohorts within the nine months through 14 years-old age group.

**GAVI-eligible countries:**

SEAR: Bangladesh, Democratic People’s Republic of Korea, Myanmar, Nepal

WPR: Cambodia, Lao People’s Democratic Republic, Viet Nam, Papua New Guinea

EMR: Pakistan

To submit a GAVI application for new vaccine introduction, countries need to meet the following criteria:

- effective vaccine management assessment conducted within three years
- cMYP valid until at least one year from the proposed date of introduction

**PATH**

The main aims and working areas of PATH are facilitating assessment of the JE burden; development of JE vaccines, support to countries introducing routine vaccination against JE. The previous JE project of PATH from 2005–2012 had multiple projects to improve data for decision-making, make available affordable vaccines and introduce JE vaccine in low-resource countries. SA 14-14-2 LJEV vaccine was licensed in 11 countries. During the current project period, PATH has supported the Lao People’s Democratic Republic to submit their GAVI application.

The multicounty JE PATH project will last until 2017 (2013–2017) and will coordinate activities for achieving the financial sustainability of countries that have already started JE vaccination.
Prevention and control of Japanese encephalitis (JE)

Important milestones in JE vaccine introduction since 2000

<table>
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<th>Year</th>
<th>Event</th>
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<tr>
<td>2003</td>
<td>PATH received a grant from the Bill &amp; Melinda Gates Foundation to launch the JE project.</td>
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<td>2005</td>
<td>WHO recommended a gradual shift to new generation JE vaccines, such as the SA-14-14-2 vaccine</td>
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<tr>
<td>2006</td>
<td>PATH provided input for a WHO position paper on JE and collaborated with the Chinese manufacturer to ensure a supply of low cost SA-14-14-2 vaccine. India licensed the vaccine and began vaccination campaigns</td>
</tr>
<tr>
<td>2009</td>
<td>PATH supported construction of a new Chinese manufacturing facility</td>
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<tr>
<td>2012</td>
<td>PATH supported initiation of WHO prequalification process</td>
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<tr>
<td>2013</td>
<td>WHO prequalified the vaccine, and GAVI announced it would accept applications for support to introduce the vaccine.</td>
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PATH current JE-related projects

The current JE related projects of PA are as follows:

- Multicountry JE project (2013-2017);
- Technical assistance for JE control in UP and Bihar, India (2013-2015);
- scale-up JE vaccination within EPI in JE-endemic districts;
- Japanese encephalitis vaccine introduction/sustainability project (2014–2016);
- sustained technical support to Chengdu Institute of Biological Products;
- conduct clinical trials to further build evidence of SA-14-14-2’s effectiveness and inform policy;
- ensure adequate JE vaccine supply to meet demand;
serve as global technical resource and coordinating body; and

develop country-specific resources to enable adoption or expansion of JE vaccination programmes.

**PATH-CDIBP Vaccine Donation Programme**

A programme intended to supply JE vaccine only, and could be used for outbreak response, demonstration programmes, supplementary campaigns for additional age groups and changing from campaign mode to routine vaccine delivery mode for a limited period.

**Discussion points:**

- Sri Lanka has been providing JE vaccine earlier through a mass campaign for 1–10 years old children, which was followed by a campaign for all new cohorts in the high-risk areas, and since 2009, following LJEV introduction, it is being given to all children throughout the country on completion of nine months.
- How WHO receives JE data
- SEAR – Monthly VPD surveillance report, joint reporting form
- WPR – joint reporting form
- Cost of the LJEV: it subject to change; allowed to request for 10% increase annually.
- JE adult vaccination is not offered in Sri Lanka. Nepal provides vaccines to adults in selected campaign districts.
- JE among adult population is being increasingly reported, but the severity of the disease among adults has not being adequately studied.
- Post-marketing surveillance data need to assess the safety of using LJEV in paediatric age groups. India needs to improve the quality of AEFI system.
- The main priority of GAVI is to give JE vaccination opportunity to target group of <14 years. Adults are not a priority. Currently >75% of JE cases are reported among <14 years old age group.
Prevention and control of Japanese encephalitis (JE)

- JE vaccine introduction in non-GAVI countries is a challenge and needs resource mobilization.
- According to JE epidemiology data for India, JE cases are shifting towards adult ages. However, still the absolute numbers do not warrant starting vaccination in adults.
- In Nepal, mortality due to JE is high in young children and the elderly.
- Both China and Viet Nam show a downward trend in AES cases after starting of JE vaccination.

3. **JE differential diagnosis and testing algorithm**

Laboratory-based diagnosis for AES is very important, as multiple organisms can cause AES. The JE laboratory network consists of a tiered structure of national, regional and specialized laboratories. Standardized protocols and WHO JE laboratory manuals have been developed to capture JE IgM enzyme-linked immunosorbent assay (ELISA) using CSF and/or serum. Laboratory training courses are being conducted. Proficiency-testing programmes, accreditation mechanisms for quality assurance and serological reference panels to validate diagnostic assays have been developed. Laboratory-testing and reporting have been standardized.

The importance and difficulties encountered during laboratory confirmation of JE were discussed in detail. It was pointed out that the material and technical support provided by WHO is not sustainable. In 2010, SEAR AES surveillance responsibility was transferred to the countries. The countries are doing a good job to maintain sustainability of AES laboratory surveillance. However, AES is getting less priority compared to AFP/measles and therefore, laboratory coordination has become very important for maintaining the standards in the network.

**Discussion points:**

- Cross-reactivity with the dengue antigen occurs in 20–40% of samples tested for JE (using ELISA)
4. JE vaccine

4.1 New horizons

As of 2012, there are four licensed JE vaccines. The Global Advisory Committee on Vaccine Safety has endorsed the safety of all four vaccine products.

Discussion points:

- Interchangeability of different JE vaccines is currently being reviewed by the SAGE working group.
- There is a need to follow the algorithm for all specimens tested for JE to overcome the issue of cross-reactivity.
- The next SAGE meeting in October will make recommendations for JE vaccine schedule and dose requirement.
- Identification of all etiological agents responsible for non JE AES cases are not feasible.

4.2 Licensed vaccines

The major classes of licensed JE vaccines include:

- inactivated mouse brain-based JE vaccines: first licensed in Japan in 1954;
- live attenuated JE vaccines: first licensed in China in 1988;
- inactivated Vero cell-based JE vaccines: first licensed in China in 1998, Japan/US/Europe in 2009; and
- live attenuated chimeric JE vaccines: first licensed in Australia in 2010.

The table below reflects the class, company and strain of available JE vaccines on the market today:
There are a number of mechanisms in place to monitor the respective vaccine impact:

- clinical trials of JE vaccines:
  - are done under ideal conditions;
  - measure immunological outcomes; and
  - have limited follow-up time.

- vaccine effectiveness:
  - field studies to assess vaccine performance in “real world” settings;
  - measure disease outcomes; and
  - assess whether a booster dose(s) is needed.

- vaccine impact
  - understand if/how the vaccine changes disease incidence on a population level under programme realities.
5. Options for bi-regional JE surveillance strategy

WHO headquarters commissioned a project to review the JE surveillance strategies of selected countries of the two regions and preliminary findings of this review was presented to the participants. AES surveillance systems show high variability within and between countries. There is a considerable variability in laboratory follow-up in all countries. Present surveillance systems may miss significant proportion of JE cases. No proper JE-related disability follow-up system is in place. General consensus is more towards an integrated model of disease surveillance. AES surveillance sustainability is a challenge.

It is timely to determine the existing gaps and minimum needs for JE surveillance across the two regions. JE is widely endemic across ecological zones spanning the two regions.

There is a lack of adequate baseline data on disease-associated disability, or the social and economic impacts of Japanese encephalitis/central nervous system disease. The performance of syndromic surveillance systems are highly variable within and between countries, with wide variation in detection and reporting of cases across countries. The value of syndromic surveillance (AES) is useful in alerting for outbreaks and/or high incidence locations (Bangladesh, Nepal, Viet Nam). There is considerable variability of laboratory follow-up in all countries (convalescent serum specimen collection) which obscures a critical appraisal of surveillance data. All countries report major challenges with patient follow-up. Many sentinel systems lack coverage, making estimation of national disease incidence difficult.

A general consensus exists that integrated models of disease surveillance such as acute meningoencephalitis syndrome (AMES) are desirable in many situations. They can have advantages for patient care, efficiency, feasibility/sustainability and public health decision-making. There are several models of integration:

- integration of care and follow-up systems;
- integration of logistics systems;
- integration of laboratory networks (virology, bacteriology);
➢ integration of surveillance case-definition (AMES); and
➢ integration of report systems (VPD or CDC systems).

Despite certain limitations for carrying out surveillance activities, countries have been able to demonstrate the impact of vaccine introduction. This is most commonly illustrated as a drop in the proportion of AMES/AES cases that are JE-positive post-vaccine introduction. In other words, there is reduced number of JE cases post-vaccine introduction. Surveillance systems are also able to illustrate that cases persist after achieving high immunization coverage (Viet Nam, Nepal).

Hence, it is important to consider provider and client perspectives on surveillance, and provide support accordingly for demand-side financing and provider-side financing, laboratory capacity, enhancements towards the patient–clinician interactions, and raising awareness.

**Proposed way forward**

**Guiding immunization strategy** - Using surveillance data, identify the main components of the immunization strategy – at risk geographic areas; routine and campaign strategy, age groups and the routine vaccination schedule (age and number of doses).

**Assessing vaccine impact** - Using surveillance data, assess vaccination impact; setting baselines through sentinel and syndromic surveillance; calculating the proportion of AMES cases at sentinel sites attributable to JE, and calculating incidence rates of AES/AMES through syndromic reporting.

**Assessing vaccine effectiveness** (linking immunization data and disease surveillance data)

**Discussion points**

➢ Introduction of financial incentives to improve surveillance is not advisable.
➢ Through surveillance, the system will identify the disease trend; the disease burden can be assessed by using modelling.
➢ One of the objectives of having surveillance is to assess the impact of vaccination.

➢ When considering the experiences of countries which have had JE vaccination in place for some time, it is not advisable for every country to wait until they have well-established surveillance systems to start vaccine interventions. Decisions can be taken at the country level using available information including data from neighbouring countries with similar ecologic contexts.

6. Conclusion and next steps

There has been tremendous progress since the last bi-regional JE meeting in 2011.

➢ Surveillance has been established or strengthened in several countries.

➢ Others have initiated vaccine introduction with campaigns or routine vaccination in selected areas.

➢ Some countries with well-established vaccination programmes are piloting or switching to newer vaccine technologies.

➢ Several countries with vaccination programmes are evaluating vaccine impact through surveillance or case-control studies.

New opportunities

There are several new opportunities to take advantage of.

➢ Two WHO-prequalified JE vaccines are now available – live attenuated SA 14-14-2 (liquid & Lyophilised) and inactivated.

➢ GAVI financing support is available for eligible countries.

➢ PATH has renewed its support for JE (JE VISP project).
Conclusions: Issues and challenges in countries that have not introduced JE vaccine

The conclusions were made for different strategic areas of JE prevention and control such as for decision-making, overall programme management, planning JE vaccine introduction, implementing vaccination, evaluation of vaccination programme separately both for countries that have introduced JE vaccine and those that have not introduced it.

For decision-making

- Surveillance data is not yet sufficient (in volume, breadth, quality, and/or laboratory confirmation) in a small number of countries.
- Data on JE sequelae may be needed to demonstrate the full burden of JE to policy-makers.
- It is necessary to define how country-level data is best used for designing policies and strategies including vaccine introduction.

For planning JE vaccine introduction

- Countries have very busy immunization programmes with multiple vaccines in the pipeline; so they need to carefully plan for an additional vaccine.
- Inactivated polio vaccine introduction for polio endgame and MR campaigns for measles elimination need to be initiated.
- Vaccine licensure is still needed in some countries.
- Cold-chain capacity is stretched in most countries; there is a need for expansion of capacity for this and other new vaccines.
- AEFI surveillance may need to be strengthened.
Conclusions: Issues and challenges in countries that have already introduced JE vaccine

For overall programme management

- There is a need for regional policy guidelines for JE control and a laboratory coordination mechanism in SEAR.

For implementing JE vaccination

- Optimal schedules for live vaccines (number of doses) and inactivated vaccines (number and timing of primary and booster doses) are not fully defined.
- Difficulties are encountered in expanding the current routine JE vaccination programme due to resource requirements.

For evaluation of the JE vaccination programme

- A mechanism to monitor JE immunization coverage and/or verification of immunization status is required.
- Adequate AES/JE surveillance system including capacity for laboratory confirmation is needed.

Next steps were identified for the same areas of JE prevention and control for the same categories of countries.

Countries without “minimum” AES/JE surveillance need to establish at least a few sentinel sites for surveillance including:

- collating existing information on AES/JE;
- collecting data on suspected JE cases and percentage of laboratory- confirmed; and
- compiling supportive data such as presence of vectors and favourable environmental conditions for vector breeding and possible ecological changes facilitating the occurrence of JE.
Countries with a reasonable surveillance system should analyse existing AES/JE surveillance data by:

- identifying the proportion of cases that are laboratory-confirmed JE;
- defining current JE disease burden (baseline);
- determining geographic distribution, seasonality, and high-risk areas and populations;
- using data for policy development; and
- working with paediatricians, linking the need for JE vaccination with MDG (child survival), and/or include JE vaccination in the cMYP or other national plans.

**Next steps: JE vaccination**

Most countries with no JE vaccination programme or a programme that does not cover all risk areas do have sufficient data to warrant introduction or expansion of JE vaccination; others are in the process of generating this data.

**Consideration of the evidence to make decisions on JE control**

- identifying the gaps in information collection and strengthen the surveillance;
- identifying the feasibility of JE vaccine introduction including programme readiness, initiating planning for vaccine introduction if feasible; and
- identifying the gaps and taking necessary corrective measures if not feasible.

**If vaccine introduction considered:**

- Definition of policies and strategies following data review; sequelae data may be helpful in addition to data on disease occurrence; data from surrounding areas with similar ecosystems may be helpful in countries with weaker data;
Phased vaccine introduction to cover known risk areas initially while continuing to collect more information; and

Consideration of options for partner support for vaccine: GAVI, PATH donation programme.

Next steps: JE vaccine programme monitoring and impact assessment

For countries with established vaccination programmes, monitoring the programme implementation and impact is important to sustain commitment to JE vaccination:

- ensuring strong AES surveillance and laboratory confirmation;
- bi-regional JE laboratory meeting and hands-on training tentatively planned in early 2015;
- identifying mechanisms to monitor JE vaccine coverage and verifying vaccination status of JE cases; and
- conducting studies where needed:
  - vaccine effectiveness/impact studies, since existing data are still limited;
  - studies of reasons for non-vaccination to identify how to improve the vaccination programme; and
  - strengthening investigations of JE cases to determine the percentage of cases that are vaccinated (vaccine type, number of doses).

Support required by countries to achieve next steps:

- surveillance strengthening (most countries)
- inclusion of sequelae data collection in some places
- expansion of laboratory capacity
- training on clinical management, including CSF specimen collection (Lao)
- meetings to review data and initiate policy discussions
- technical assistance for vaccine introduction
- AEFI and risk communication
- support for monitoring and evaluation
- JE SIAs (India)
- vaccine impact monitoring research (Sri Lanka)
- expansion of routine vaccination - at least for a limited period (Nepal).
Annex 1

Agenda

(1) Opening session
(2) Update on global and regional JE surveillance and vaccine introduction
(3) Review of the current status of disease, surveillance and vaccine introduction
(4) Recent advances in JE vaccine availability
(5) JE surveillance consultancy project
(6) Update on GAVI and PATH support
(7) Updating country plans
(8) Next steps
(9) Conclusions and recommendations
(10) Closing session
Annex 2

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Report of the sixth bi-regional meeting

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WHO assists Member States to periodically review and discuss various topics concerning national immunization programmes. Deliberations on these issues lead to tangible improvements in managing these national programmes.

With this objective, the sixth Bi-regional Meeting on Prevention and Control of Japanese Encephalitis (JE) was held in Bangkok, Thailand, on 27–29 May 2014. The objectives of the meeting were to support JE endemic countries of South-East Asia and Western Pacific Regions to reap the benefits of recent technical advances in JE laboratory diagnosis, vaccine availability and to gain benefits from new opportunities. This publication reports on the aforesaid meeting.

This publication includes recommendations for Member States’ next steps in implementing strategies for prevention and control of JE. The report also contains a summary of progress, key issues and challenges in implementing JE control measures for Member States that have introduced JE vaccines. Member States that have not introduced the vaccine are encouraged to proceed with decision making, planning vaccine introduction, programme implementation, and monitoring and evaluation of the impact of existing JE vaccine programmes. The support required by countries to implement the next steps including establishing or strengthening JE surveillance is also discussed.