

SEA-CD-142
Distribution: Limited

Report of the Bi-Regional Meeting on Japanese Encephalitis

(WHO SEA/WPR AND /PATH's JE Project)

Bangkok, Thailand, 30 March – 1 April 2005



World Health Organization
Regional Office for South-East Asia
New Delhi
July 2005

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1. OPENING SESSION

Dr William L. Aldis, WHO Representative to Thailand, inaugurated the Bi-Regional Meeting on Japanese Encephalitis (JE) by reading out a message from Dr Samlee Plianbangchang, WHO Regional Director for South-East Asia. The Regional Director recognized that “although vaccination seems to be the most viable option in the fight against JE,” the challenge at present is the lack of a vaccine against JE that is affordable and easily available. He was happy to note that while South-East Asia and the Western Pacific are two different regions, JE is a common public health issue and, therefore, a joint effort to tackle the problem is a sensible approach. He was confident that the partnership between WHO and PATH’s JE Project would go a long way to push the JE agenda globally and also provide countries with the resources and technical support to enable them to frame a rational strategic approach to the prevention and control of JE.

Dr Brent Burkholder, Regional Adviser for Immunization and Vaccine Development (IVD), stated that JE is an urgent health problem and needs to be addressed. He highlighted the expected outcomes of this meeting as follows:

- Share country experiences in JE control;
- Update countries on the current status of JE vaccines and options for the future, including programmatic implications for vaccination;
- Provide opportunity to discuss country-specific immunization strategies and identify what support individual countries may require;
- Discuss and agree on the draft JE surveillance standards;
- Discuss and identify options for linking of JE surveillance with other existing surveillance systems, including vaccine safety monitoring;
- Discuss and identify options for JE laboratory strengthening, networking and integration;
- Review diagnostic options and make recommendation on their use/ further evaluation, as well as quality assurance.

He emphasized that a multi-pronged approach is needed for JE control that would include not only immunization but strong public health surveillance for programme planning and monitoring impact.

Dr Julie Jacobson, Director, PATH's JE Project, outlined the progress made on action items since the 2002 GAVI JE meeting in Thailand. Progress has been made on all fronts with JE included as an Agenda item in the SEA Regional Committee meeting with strong leadership from Nepal. JE has also been included for consideration by GAVI in the next round of funding. Coordination of JE efforts at the global level have been improved with a JE Core Working Group.

National action points from 2002 included establishing national surveillance of JE to better define the at-risk population and begin discussions on the use of JE vaccine for disease control. The highlights of progress in this include Cambodia being ready to start a national surveillance programme for JE and Nepal's decision to introduce JE vaccine into their routine immunization.

In general, additional action items included support for surveillance with progress including:

- Draft WHO guidelines for JE surveillance to be reviewed at the meeting;
- New simplified diagnostic tools under evaluation;
- Integrated JE surveillance into the AFP surveillance system in Nepal.

Support for vaccine availability:

- WHO guidelines for live JE vaccine production completed and published;
- Clinical trial end-points defined for evaluating new JE vaccines now going into press for publication;
- Regulatory authority in China recognized by WHO opening the opportunity for pre-qualification of the live JE vaccine.

Support for JE vaccine and immunization:

- Vaccines derived from nerve (brain) tissue are increasingly disfavoured, which has implications for the inactivated JE vaccine.

Several of the international producers of JE vaccine are stopping production of this vaccine;

- An international team has reviewed the live attenuated vaccine and production in Chengdu, China with a positive report. The vaccine is now licensed in South Korea, Sri Lanka, and Nepal;
- Several candidate vaccines are in late stage development (Phase III trials);
- The JE project was funded to help accelerate the availability of a second generation vaccine;
- China has now integrated JE into the routine EPI system in most of its endemic provinces.

To continue the progress new tools are available:

- Immunization training tool, AIM e-learning on considerations for JE vaccine introduction (available at <http://aim-e-learning.stanford.edu/en/vaccines/je/index.html>);
- The new JE Prevention Network linking JE-affected countries together to share information and tools to analyse and use national data (available soon at www.jepn.org);
- An advocacy film on JE about the human toll of JE disease (available through the JE project at PATH).

2. OVERVIEW OF JE IN THE SEA AND WPR REGIONS

2.1 JE Situation in the South-East Asia Region

Japanese encephalitis is a disease of public health concern, mainly for the WHO South-East Asia (SEA) and the Western Pacific (WP) regions. It is estimated that annually more than 50 000 cases of JE and more than 10 000 deaths from JE occur in the countries of these two regions.

In the SEA Region, India, Nepal, Thailand and Sri Lanka have, since 1985, regularly reported JE to WHO. From Bangladesh, Bhutan, Indonesia, Myanmar, and Timor-Leste, there are only anecdotal reports of JE or small-scale studies to demonstrate the occurrence of the disease. The epidemiology

of JE remains fairly stable in India, whereas dramatic reduction is seen in Thailand and Sri Lanka after JE vaccination campaigns, followed by the introduction of JE vaccine into routine immunization programmes. In the SEA Region, only Sri Lanka and Thailand have introduced JE vaccine as part of routine immunization. Nepal carried out a pilot project with the Chinese-produced SA 14-14-2 vaccine. In India, JE vaccine is now used extensively in Andhra Pradesh only, based on risk approach. In the past, JE vaccine has been used sporadically to pre-empt potential outbreaks of JE. The rest of the other countries have no experience with the use of JE vaccine.

The vaccine commonly used is the inactivated mouse-brain derived vaccine of Nakayama or Beijing strain, except in Nepal, where the live, attenuated SA 14-14-2 vaccine was used. Only Thailand and India have capacity to produce the inactivated vaccine, albeit on a limited scale. There are no producers of the live vaccine in the SEA Region.

2.2 JE situation in the Western Pacific Region

In the Western Pacific Region (WPR), China, in the past, accounted for the maximum number of cases and deaths from JE. However, in the past decade or more, China, Japan and South Korea have been able to achieve significant reduction of JE disease burden due to the widespread use of vaccines against JE. Cambodia, Brunei, Laos, Malaysia, Philippines, and Papua New Guinea (PNG) are still considered endemic, although there is no clear disease burden data. Viet Nam, despite the use of JE vaccine, still reports periodic outbreaks of JE. More recently, even Australia had reports of introduction of JE in the outer Torres Straits Islands and Cape York from nearby Papua New Guinea.

Regular JE vaccination, as part of routine immunization, is carried out in China, Japan, South Korea, and Viet Nam. Immunization in identified population at risk is conducted in Malaysia, and no specific programme is in place in Cambodia, Laos, Philippines and PNG. As in the SEA Region, the vaccine commonly used is the inactivated mouse-brain derived. However, the live, attenuated SA14-14-2 vaccine is used extensively in China. South Korea has experience with the use of both the inactivated and live vaccines. Despite the high number of doses of the vaccine used without any major adverse events, currently this vaccine is not pre-qualified and, consequently, the export and use of this potentially effective and safe vaccine is constrained due to lack of evidence of its efficacy and safety ascertained by international bodies.

2.3 Common issues and Challenges in the Control and Prevention of JE in the Two Regions

Despite notable progress in the prevention and control of JE in some of the Asia-Pacific countries, there are also notable challenges for many JE-endemic countries. Some of the key issues are summarized below.

(a) Surveillance

- There is a lack of a common surveillance standard;
- Most countries use a syndromic approach by considering a 'suspect JE case' from a range of encephalitis reported in their routine reporting systems. However, laboratory confirmation is limited.

(b) Epidemiology

- Difficult to compare epidemiological data due to lack of common surveillance standards;
- There is little research on JE, thereby, making it difficult to understand the epidemiology of the disease.

(c) Laboratory

- Although laboratories exist for testing for JE, there is a lack of regional/global quality control systems and affordable reagents for JE tests;
- There is no laboratory network for JE.

(d) Vaccine

- The most commonly-used JE vaccine is the mouse brain-derived inactivated one. However, it is expensive and not available in sufficient quantities to meet the demands of all JE countries; it is also not WHO pre-qualified;
- The live, attenuated SA14-14-2 vaccine has the potential for being both affordable and available. The vaccine is yet to undergo WHO pre-qualification¹.

(e) Financing

- JE control programmes lack financial resources;

¹ Prequalification is the procedure by which WHO evaluates vaccines for UN supply based on stringent quality and safety standards.

- Countries do not have sufficient disease burden data to enable rational decision-making process for financing JE control activities. Consequently, political commitment to JE prevention and control is either weak or lacking.

3. COUNTRY EXPERIENCES

The state of *Andhra Pradesh (AP), India*, has a population in excess of 79 million, and 12 out of its 23 districts are considered endemic for JE. Japanese encephalitis has been reported since 1979 and outbreaks of JE are known to occur on a regular basis. Like anywhere else, JE is seen primarily in rural areas, affecting predominantly those under 15 years of age.

PATH's Childrends Vaccine Programme (CVP), in collaboration with the Government of AP, initiated a JE control programme in 2000. The programme focused on strengthening surveillance, establishing laboratory diagnostic capacity, vaccination with the inactivated JE vaccine, and improved case management. Due to insufficient vaccine availability, the vaccine was administered only to children aged 2 to 12 years in the high-risk villages. Criteria used for prioritization included case rates, deaths, consistent reports of outbreaks and villages with vector or ecological conditions favouring transmission. For example, the district of Kurnool accounted for almost 35% of the total case-load of the state. Therefore, villages in Kurnool became a priority focus on immunization efforts.

Since the introduction of the vaccine and improved case detection and management, there has been a dramatic reduction in the mortality and morbidity due to JE. The case-fatality from JE dropped from 50.4% in 1994 to 12.9% in 2003. For example, in the district of Kurnool, the incidence dropped from 369/100 000 cases before immunization to 84/100 000 cases barely three years after immunization began in the state - a 77% reduction in disease incidence. Not only has immunization been successful, but a cost-effectiveness analysis showed that the JE immunization programme in AP was cost-saving. In comparison to vaccination, other measures, such as vector control and environmental modifications, have had little effect.

Although India used JE vaccine in the past, there has been no national attempt to use JE vaccine at the national level, either as a high risk targeted campaign or as an integrated part of routine immunization. This is primarily

due to the poor information on the disease epidemiology as well as lack of sufficient quantities of JE vaccine. India produces the inactivated vaccine, but only in limited amounts.

Sri Lanka saw a major outbreak of JE in 1985 and JE immunization was started in 1988, targeting children aged 1 to 10 years with four doses of the vaccine. JE vaccination began as a risk-based, phased approach to start with, but immunization had to expand as the disease continued to spread into other areas; by now 14 districts have JE immunization as part of the routine immunization programme. The number of cases and deaths from JE in the districts where vaccine is used declined dramatically over the years. However, JE continues to present as an important public health concern as the disease continues to spread into districts where the vaccine is yet to be introduced.

The major challenge to the government in JE immunization is the huge cost of the vaccine. Sri Lanka does not produce its own vaccine, and has been purchasing the vaccine from Thailand. There has been a steady rise in the cost of the vaccine. For 2005, the total projected cost of all other EPI vaccines is roughly \$ 1.548 million, whereas the cost of JE vaccine alone is \$ 3.117 million, two times more than the combined cost of all EPI vaccines. The SA 14-14-2 vaccine, which is cheaper, is recently licensed in the country and is being considered by the programme. Sri Lanka, in collaboration with PATH, will undertake an immunogenicity and co-administration of JE and measles vaccines trial for the SA 14-14-2 vaccine, starting in 2005.

Sri Lanka's experience is a demonstration of the constraints that countries face in the control of JE, particularly in the face of absence of an affordable and available vaccine. Without donor support, most developing countries will find it impossible to introduce and sustain JE vaccination at current prices.

Thailand is one of the few countries in the Asia-Pacific Region with a model JE control programme. JE was recognized in the early 1970s. From the early 1980s technology transfer for the local production of the inactivated mouse brain-derived vaccine was done. From the 1990s onwards, stepwise introduction of the nationally-produced JE vaccine began. Three doses of the vaccine are given to children between the ages of 18 months to 3 years as part of routine immunization programme, resulting in impressive decline in the number of cases and deaths due to JE.

Surveillance in Thailand is based on reporting of cases of encephalitis. Laboratory confirmation is done only on a subset of cases to determine the percentage due to JE. Using this information, an overall national estimate of disease burden is produced. The experience of Thailand in the control of JE has lessons that may be relevant to other countries too. Some of these are:

- Decision-making on vaccine introduction needs sufficient data and careful consideration;
- Planning and implementation of vaccine introduction must take into account local factors such as a country's economy, programme capacity, manpower capability, health service situation, community acceptance, and political support;
- External assistance is extremely helpful for vaccine introduction; however, long-term sustainability is based on strengthened national capacity and infrastructure.

China developed the live, attenuated SA14-14-2 JE vaccine and used it extensively since it was licensed in 1989. The number of manufacturers increased from one at the beginning of 1989 to 3 in the early 1990s. The availability of the SA14-14-2 JE vaccine increased from several million in the early 1990s to approximately 20-30 million in the late 1990s and over 50 million doses annually in recent years. In the past 15 years, approximately 300 million doses of attenuated vaccines have been produced and 200 million children have been vaccinated with the vaccine. This experience has shown the live vaccine to be immunogenic and efficacious. More recently, WHO and PATH's JE Project have been assisting the producers to develop a file in order for their product to be considered for pre-qualification.

Despite insufficient quantities of vaccine, low coverage and incorrect vaccination dosage and schedules in some provinces and districts, the widespread use of the live, attenuated vaccine has resulted in a dramatic reduction in the burden of JE in China. The JE morbidity decreased from 2.5/100 000 in 1990 to less than 0.5/100 000 in 2004.

In *Viet Nam*, JE has spread throughout the country and, like in other JE-endemic countries, the disease affects primarily the younger age group. Viet Nam started its own vaccine production in 1991 with the inactivated vaccine and, by 2004, the production capacity had reached 4.5 million doses. JE immunization in Viet Nam targets 1-5 year olds and, since 1997, the

government has provided the vaccine free of cost to high-risk areas. Primary immunization is two doses, separated by a week's interval, and a booster is given one year after the second dose.

Although vaccine production capacity exists, the EPI Programme is unable to purchase the needed quantities of the vaccine due to financial constraints. Therefore, vaccination is limited only to the high-risk districts. Surveillance in Viet Nam is poor, and was identified as an area that needs strengthening.

Box 1: Summary of key lessons from country experiences

- The understanding of the epidemiology of JE in most is limited. More efforts and investment are needed in JE endemic countries to study and define better the epidemiology of JE and to enable a rational decision process in the introduction of JE vaccine. Where data exist, it clearly shows that JE is a cyclical disease with epidemic potential, affecting primarily rural and the poor, with the maximum disease burden borne by the young.
- A national control strategy needs to be specific for each country, given the diverse nature and capacity that exist in different countries. Further, starting with campaigns focused on high-risk groups and geographical areas, followed by progressive introduction of regular vaccination into routine immunization, seems to be the best approach for the control and prevention of JE.
- It is also clear that vaccination in some form is necessary for control. Other measures such as environmental and vector control efforts have not been demonstrated to be effective at country level.
- The use of inactivated mouse brain-derived vaccine has had a dramatic impact, but there are major challenges in production capacity, scheduling concerns as well as cost of the vaccine. The SA 14-14-2 live attenuated vaccine offers great promise as an alternative to the killed vaccine.
- A strong JE surveillance system is needed for all JE-endemic countries.

4. SURVEILLANCE FOR JE

Countries such as Japan, South Korea, Thailand and Sri Lanka, where effective JE immunization programmes exist, also have JE-specific surveillance systems in place. However, in most other JE-endemic countries, JE may be listed on their required routine communicable diseases reporting forms, but no special attention is given to JE. The general approach to JE surveillance seems to be more generic encephalitis surveillance, using primarily a syndromic definition rather than a JE-specific definition. Where capacity and facilities exist, a diagnosis of JE is considered either only after other potential causes of encephalitis is ruled out, or where laboratory tests clearly demonstrate the diagnosis.

In Japan, JE reporting is mandated by law; the Infectious Diseases Control Law enacted in 1999, requires JE to be reported immediately upon diagnosis. In addition to the immediate reporting of confirmed cases, JE is also tracked by studying the prevalence of JE antibody among general populations as well as regular monitoring of seroconversion rate of sentinel pigs. The sentinel pig system clearly demonstrates that the virus remains active in the environment even if human disease is prevented through effective vaccination.

Several countries have initiated steps to either enhance or establish surveillance for JE in their countries.

- A prospective study in Bali, Indonesia, showed the disease to be endemic in all districts. A National Institute of Health Research and Development (NIHRD), CDC and PATH collaborative work, initiated in January 2005 will study the epidemiology of JE in Indonesia. It is a hospital-based surveillance where 15 hospitals in six provinces (West Sumatra, East Java, West Kalimantan, East and West Nusa Tenggara, Papua) and several health centres in Lombok, West Nusa Tenggara Province, will participate.
- In Cambodia, meningo-encephalitis has recently been included as one of the diseases on the weekly report of outbreak-prone diseases; however surveillance for JE is still weak.

- Bangladesh had an outbreak of JE in 1977 and since then no JE has been reported. However, initial results of an ongoing two year prospective, hospital-based surveillance study for encephalitis cases showed the proportion of JE to be 6-11%, suggesting JE as an important cause of encephalitis. However, even with intensive laboratory support the etiology in the study can be determined in only approximately 50% of encephalitis cases.
- An ongoing study in Thailand shows that, despite successful JE immunization efforts in the country, JE still remains an important cause of encephalitis. Comparison of symptoms and signs in patients with JE and with other causes of encephalitis indicated no clear way to distinguish etiologies based on clinical characteristics.
- Nepal integrated JE with AFP surveillance and has more than 80 active surveillance sites.

JE surveillance is critical for characterizing the epidemiology, measuring the burden of the disease, identifying high-risk areas and documenting the impact of control measures. Realizing the need to harmonize JE surveillance efforts in different countries, WHO is developing JE surveillance standards. The guidelines also outline the laboratory criteria for diagnosis, and recommend minimum data elements for reporting, as well as indicators and targets for performance indicators to assess surveillance quality.

The efforts to strengthen surveillance for JE must link with the existing systems and integrate into them instead of setting up a parallel surveillance system. This is possible as most countries have a notifiable diseases reporting system in place. Further, for several of the polio-endemic countries, the AFP surveillance system has developed a network of skilled surveillance workforce. And experience with yellow fever in Africa clearly indicates that surveillance for a specific disease can be linked with other regular surveillance systems already in place.

Box 2: Summary of discussions and action items on surveillance standard and linking of JE surveillance to existing disease surveillance systems

- The draft surveillance standards should be finalized after a peer review and published on the web by end June 2005.
- A companion document also needs to be prepared to provide the background information and rationale for the surveillance standards.
- The objectives and methods of surveillance in individual countries may vary based on the stage of vaccine implementation and JE control:
 - For countries still endemic for JE, it is agreed that surveillance should be syndromic with only aggregate reporting; it is NOT necessary to subject all suspected cases to laboratory confirmation; doing so in selected sentinel sites and for the first few cases (5-10 cases per geographic area per outbreak) is sufficient.
 - For those countries where JE control has been achieved to a great extent, surveillance will be case-based with all cases being subjected to laboratory confirmation tests.
- The sensitivity and specificity of the AES case definition should be reviewed by applying the definition to existing data sets from JE patients and/or by monitoring results when the definition is used in ongoing prospective surveillance, as in Indonesia.
- Performance indicators must be relevant, simple, and not in variance with a normal, integrated disease surveillance system of a country.
- Countries reiterated their interest in utilizing surveillance at this time for JE control rather than elimination or eradication.
- Where strong AFP or other relevant surveillance networks already exist, all efforts should be made to explore the feasibility of integrating JE surveillance into them.
- Integration of surveillance also requires integration of resources, both financial and human, to be effective.

5. IMMUNIZATION STRATEGIES

While a long-term goal of JE elimination is desirable, given that at present there is no affordable vaccine, the goal of immunization must remain prevention of outbreaks and control JE disease to reduce morbidity, mortality, and disability. For immunization programme planning purpose, disease burden needs to be further defined and demand forecasting to ensure that the vaccine supply is adequate if and when an acceptable vaccine becomes available. The strategy for disease control includes human immunization, surveillance, communication, AEFI and case management. Other interventions, such as vector control and animal immunization, have been tried but found to be ineffective in preventing human disease; they are also more expensive to implement.

(1) Immunization

Consensus on immunization strategy after discussion of country experience is that disease control starts with campaigns in high-risk populations followed by introduction of the vaccine into routine EPI programme. Advocacy is needed to raise awareness and shift attention from vector control to immunization. Additional advocacy is needed for national and regional levels to help to improve JE control. To keep momentum going JE should be a regular agenda item in immunization meetings like TAG/TCG, and national ICC. However, key issues remain to be resolved regarding full use of JE vaccines in routine EPI programmes.

(2) Post marketing surveillance of AEFI

Monitoring adverse events following immunization (AEFI) is important. Since vaccines are given to healthy individuals to protect from diseases that may potentially affect the person, a higher standard of safety is expected. Further, there are limitations in the pre-licensure safety data primarily due to the small sample sizes in clinical trials and shorter duration of follow-up. Therefore, it is essential to have post-marketing AEFI monitoring systems in place primarily to identify urgent problems for investigation and action to correct programmatic errors, but also to estimate rates for serious AEFIs (Table 1) for purpose of comparison between products, to determine risks versus benefits and to validate pre-licensure data. The role of communications in managing AEFI was referred to as being hugely important and should not be overlooked.

Table 1: Frequency of adverse events for currently available JE vaccines

Reaction type	Frequency of reported adverse events		
	Inactivated mouse brain derived	Inactivated PHK-derived (P3)	Live attenuated PHK (SA14-14-2)
Local reactions – tenderness, redness, swelling	20%	4%	< 1%
Mild systemic – headache, myalgia, GI symptoms, low-grade fever	10-30%	< 1%	Fever < 0.5% Total 21%
Hypersensitivity (delayed onset common)	1-64:10,000	1:15,000	None reported
Acute encephalitis	1:50-75,000 to 1:million	None reported	None reported

Four of the 11 countries in the SEA Region (Democratic People's Republic of Korea, Indonesia, Sri Lanka and Thailand) are assessed to have a functioning AEFI system in place; three other countries (India, Myanmar and Nepal) have a functioning system but need external support to strengthen it, and three countries (Bangladesh, Bhutan and Maldives) need intensive support to strengthen their AEFI systems. Timor-Leste is the only country without an AEFI system in place as yet.

Similarly, among the non-industrialized countries in WPR, two countries (Republic of Korea and Singapore) have functioning AEFI systems in place, two more (China and Viet Nam) have a functioning system but need external support, and one (Philippines) needs intensive support. Twelve countries report a system via the WHO/UNICEF Joint Reporting Form, but no objective information is available on its level of function and seven countries report "no system" or do not report at all.

Through the Global Training Network (GTN), six countries in the Western Pacific Region, and nine countries in the South-East Asia Region have

availed training opportunities to strengthen AEFI systems in their respective countries. Further efforts are needed to strengthen the capacity of individual countries to implement post-marketing surveillance of adverse events in general, and for JE vaccination.

Box 3: Summary points from the Immunization Strategy Group

- Advocacy for JE immunization is needed at national and regional levels especially to successfully have a WHA resolution passed on JE control.
- Ensure JE is included in MLM modules prepared by EPI; use as material modules prepared by PATH like the AIM e-learning
- Additional evidence is needed to determine the most effective schedule for JE vaccines in routine EPI, including number of doses, appropriate age for immunization, and co-administration with measles.
- Support countries to strengthen their AEFI system in the context of new JE vaccine introduction, including the use training opportunities through GTN.
- Determine whether there is a need to develop a specific JE Programme Managers protocol and if so, how to address it;
- Consider communications and advocacy according to needs of the countries and their control measures.

6. DIAGNOSTICS FOR JE, AND JE LABORATORY NETWORK

There are many possible laboratory tests (Table 2) that can be used to diagnosis Japanese encephalitis. Many countries have specialized laboratories that perform one or combination of several diagnostic tests for JE; what is lacking is an internationally accepted diagnostic protocol for JE or a standardized reference for laboratory testing.

Table 2: Types of tests for diagnosis of JE

	Sample type	Test type	Comments
JE IgM antibody detected	CSF, serum	IgM capture ELISA, specific for JE	<ul style="list-style-type: none"> • Use JE specific IgM capture ELISA. 68-100% sensitivity with CSF in week post-onset. IgM in serum only, not necessarily diagnostic of JE. • Second serum required if negative result with serum collected < 10 days post-onset • Cross reactivity with other flavis * & • IgM positive post-JE vaccination
JE virus antigen detected	Tissue	Immuno histo-chemistry	Low sensitivity
JE virus genome detected	CSF, tissue	RT-PCR	<ul style="list-style-type: none"> • Can allow rapid detection • Requires advanced training of staff • Requires expensive equipment • Potential for genotyping
JE virus isolated	CSF, tissue	Virus isolation in cell culture or mice	<ul style="list-style-type: none"> • Delay in obtaining result. • Viraemia is transient.
JE sero-conversion	Paired serum	HAI, neutralization assay	<ul style="list-style-type: none"> • 4-fold rise in JE antibodies • Cross reactivity with other flavis * • Delay in obtaining result, and • Patient loss to follow-up or compliance

* JE serocomplex (WN, JE, SLE, KUN, MVE) – 65% sequence homology; Dengue viruses – 45% seq. homology

In the pursuit to establish laboratory facilities for a specific disease, it is essential to consider whether laboratory function is required for patient care or for public health purpose or for both. If it is for patient care, the test(s) need to be able to differentiate rapidly between etiologies and it is usually a health care-based establishment. If it is for a public health purpose, it may be for assessing disease burden or evaluating vaccine impact or as an early warning system to predict potential outbreaks. Each of these settings would require different diagnostic characteristics. Such considerations the type of tests, timing of collection of samples during illness, and transportation needs, etc., are important, apart from the performance of the test itself with regard to sensitivity and specificity.

Currently, there is no commercial “bedside” rapid test available for JE. From the many options available for the development of an appropriate test for JE, the ELISA format is the best and most attractive. It would be easy to establish an ELISA-based test protocol as trained staff and equipped laboratories are widely available. The ELISA test can provide results rapidly (within hours), is capable of testing multiple samples, and also has the potential to use dried blood samples or alternative samples (e.g. oral fluids), thus potentially reducing the cost and logistic demands for sample collection and transport. Unfortunately, at present there are no commercially available JE ELISA test kits or reagents. Consequently, even if there is demand, there is no supply. Centres such as Armed Forces Research Institute of Medical Sciences (AFRIMS), Thailand, and National Institute of Virology (NIV), India, make their own kits. However, these kits have not demonstrated good reproducibility when taken outside of the controlled laboratories settings of the host institutions. AFRIMS shared data of the field evaluations of their kit which were very poor. Further, ensuring quality and comparability of test results is a challenge as there are currently no standards and quality assurance systems in place.

Currently, PATH is supporting the head-to-head tests of three potential JE IgM ELISA test kits on newly-developed commercial kits. The results of these tests will be available soon. Once JE laboratory diagnosis is standardized, the next step is to integrate JE laboratory activities within existing virology laboratory networks. There is potential to effect this immediately and effectively as there already exist a network built for AFP surveillance for polio

eradication. Most of these laboratories are public health-based with strong links to ministries of health and national surveillance systems. They are structured in a tiered manner with global specialized laboratories, regional reference, and national and sub-national testing laboratories. The measles/rubella LabNet is well- equipped with ELISA readers and washers and other appropriate serological equipment. Further, most staff have undergone ELISA based training and, therefore, JE training could be easily integrated with measles/rubella training. Many of the existing JE labs or institutes are already part of the existing VPD network. However, integration of JE would require, in addition to a commercially available test kit, additional resources to expand the scope of work of existing virology laboratories.

Box 4: Summary of JE laboratory diagnostics and laboratory networks

- A commercially available standardized test kit for JE diagnosis is needed urgently to ensure predictable performance and show comparability.
- Proficiency test panels are needed to establish inter-laboratory comparability and ensure quality control.
- Cross-checking of results of currently functioning laboratories, should be established by laboratories sending a subset of samples to a reference laboratory.
- Additional resources need to be mobilized to establish and expand laboratory networks for JE.
- Interpretation of test results from a clinically compatible case
 - CSF IgM positive – diagnostic
 - Serum IgM positive -- diagnostic for surveillance purposes, if there is no recent history of vaccination.
 - With a history of ‘recent’ vaccination, if serum IgM is positive – refer to a reference laboratory for further testing if suspected AEFI. Also refer vaccine vial, if live vaccine.
- Integrating JE testing into existing laboratory networks utilizing ELISA technology is feasible, and has the potential to strengthen public health infrastructure.

7. OTHER ISSUES: SPECIAL PROJECTS

(1) Update on JE vaccines, including possible time-lines for vaccine production and supplies

At present there is no WHO pre-qualified JE vaccine. Currently, the vaccine used most widely in countries such as Japan, South Korea, Thailand, Viet Nam, Sri Lanka, India and Malaysia, is the mouse brain-derived, inactivated vaccine (Nakayama or Beijing strain). The live attenuated SA14-14-2 vaccine is used extensively in China, and to a limited extent in South Korea and Nepal. The primary hamster kidney cell or Vero-cell derived P1/P3 vaccine is produced and used exclusively in China. However, there are several potential JE vaccines in development (Table 3).

Table 3: JE Vaccines at advanced stage of development

Type	Strain	Producer	Status
Inactivated, Vero cell derived	Beijing 1	Biken, Kaketsuken	Advanced clinical (Phase 3)
Inactivated, Vero cell derived	SA 14-14-2	Intercell	Clinical (Phase 2 adult)
Live, attenuated, PHK derived, prequalified	SA 14-14-2	Chengdu Institute for Biological Products	Upgrading of facilities, dossier in preparation
Live, recombinant, Vero cell derived	SA 14-14-2 prM&E in 17D YF backbone	Acambis	Clinical (Phase 2 adult, Phase 1 paediatric in preparation)

There is great interest in the development of a novel JE vaccine, the live, recombinant ChimeriVax-JE being developed by Acambis. This vaccine used the prM +E gene of SA 14-14-2 linked to the YF17D virus genetic component as the backbone. It has potential for high yield production in Vero cells and,

most importantly, it is serum-free. Currently, this vaccine has been tested in preclinical (neurovirulence, toxicity, mosquito transmission) trials and completed four safety and immunogenicity studies (Phases I-II) in adults, and paediatric development plan is already in place but is yet to start. Therefore, there are several promising and diverse products in the pipeline with product launch possible as early as 2007. What is required is to explore the potential for technology transfer to ensure an affordable supply for developing country needs once these vaccines become available for large scale use.

Given the intense attention and work going on to develop and move potential JE vaccine candidates towards international certification and global production and supply, the possible time-lines for licensure for JE vaccine candidates need to be assessed, and demand and uptake of vaccines need to be forecast. This is necessary, not only to prepare countries to introduce the vaccine, but also to allow industries to plan production and marketing of their products. From the current JE vaccines in development, the possible time-lines are as follows:

- Live attenuated vaccine SA 14-14-2 – Chengdu Institute:
Prequalification expected in 2007
- Live, recombinant, Vero cell derived – Acambis:
FDA/EMA licensure: 2008 at the earliest
Prequalification expected in 2010 at the earliest
- Inactivated, Vero cell derived – Intercell:
FDA/EMA licensure: 2008 efforts are on to compress this time-line,
Prequalification expected in 2010 at the earliest.
- Inactivated, Vero cell derived – Biken:
Japan licensure 2008,
Prequalification expected in 2010 at the earliest.

(2) Assessment of cost-effectiveness of JE immunization programmes in Thailand, Viet Nam and China

The International Vaccine Institute conducted cost-effectiveness analysis in three countries, Thailand, Viet Nam and China. A decision analysis model was used that compared hypothetical cohorts of 100 000 neonates followed up to 30 years of age (China and Viet Nam) or 15 years of age (Thailand). The

model compared cohorts of children unvaccinated or vaccinated with inactivated JE vaccine. In China, the comparison also included children vaccinated with the live, attenuated SA 14-14-2 vaccine. Country level data for use in the analysis were gathered from existing surveillance records, health statistics and published studies. The cost of vaccination and costs associated with treatment and disability from JE illness were obtained from the records of the Ministry of Health.

The studies demonstrated that vaccination against JE is a cost-effective control measure in all three countries. Furthermore, in China, where the SA 14-14-2 vaccine is used, vaccination is cost saving to the health system and saves over US\$ 0.5 million in treatment costs for JE illness. In China and Viet Nam, JE vaccination was cost-effective for the range of US\$ 0.32 to US\$ 0.96 and US\$ 0.36 to US\$ 1.21, respectively. In Thailand, it was cost-effective for the range US\$ 0.95 to US\$ 2.52. Additional sensitivity analysis was used to explore the impact of changes in treatment costs and incidence rates on net costs of introducing the vaccine to the health care system. In Viet Nam and Thailand, the vaccine is cost-effective; however at current levels of treatment costs, the vaccine is not cost saving. In Viet Nam, the vaccine becomes cost-saving when treatment costs are increased from US\$560 per case to US\$785 per case.

8. RECOMMENDATIONS

8.1 Surveillance

- (1) The WHO Surveillance Standards should be finalized and published as soon as possible. Once published countries are encouraged to use the 'standards' for their surveillance activity.
- (2) Support countries to set up country-specific JE surveillance in accordance with the surveillance standards.

8.2 Laboratory

- (1) Establish a reference laboratory or laboratories and provide validation panels for tests being done in other laboratories for quality control of laboratories.

- (2) The head-to-head laboratory test kits trials by AFRIMS should be made available and reviewed prior to taking any specific standardization steps are taken.
- (3) Develop training materials and manuals for laboratory procedures and tests.
- (4) Conduct field evaluation of tests, including commercial test kits.

8.3 Immunization Strategies

- (1) All JE endemic countries considering vaccine introduction must develop a basic minimum data set that countries require for a decision on vaccine introduction. Such information may include disease burden, age and geographic distribution of cases. A proven immunization strategy for JE control seems to be to initiate preventive campaigns in high-risk areas and age groups followed by introduction of vaccine into the routine EPI programme.
- (2) Include JE in any future MLM or other training materials produced by EPI; the materials and modules produced by PATH may be used including the AIM e-learning module.
- (3) Support countries to strengthen AEFI systems in the context of new JE vaccine(s) and training opportunities through GTN may be utilized.

8.4 Coordination/promotion of JE Prevention and Control Activities

- (1) WHO and PATH-JE Project should prepare background papers, if necessary, on JE to justify it as an investment case for funding in the next GAVI Phase.
- (2) WHO's existing steering committees, particularly the ones for research and clinical trials, may serve as a useful guide to the JE Project's planned clinical trials.
- (3) The JE Project and partners should continue to invest in long term capacity building at country level if JE control and prevention activities are to be sustained.

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