Japanese Encephalitis Morbidity, Mortality, and Disability

REDUCTION AND CONTROL BY 2015

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If you want to go fast, go alone.
If you want to go far, go together.

African proverb

Japanese Encephalitis Morbidity, Mortality, and Disability: Reduction and Control by 2015 was prepared by:

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United States Centers for Disease Control and Prevention
World Health Organization

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Executive summary

Japanese encephalitis (JE) is the leading cause of viral encephalitis and a significant cause of disability in Asia. In addition to thousands of deaths each year—most of which occur among children and the rural poor—JE causes lifelong disability in survivors, taking a long-term social and economic toll on families and communities. Progress over the past five to seven years, however, has stimulated momentum and commitment toward a control target.

JE control is feasible. Japan, China, and the Republic of Korea have JE immunization programs that span several decades. Others, such as India and Nepal, have recently introduced JE vaccine, with Cambodia planning to introduce the vaccine in the near future.

JE immunization is cost-effective. A cost-effectiveness analysis for 14 GAVI Alliance–eligible countries estimated that, from 2007 to 2021, immunization provided through campaigns and routine immunization programs would be a very cost-effective intervention. Taking into consideration nonmedical costs and costs due to sequelae, vaccination may also result in cost savings.

A JE control target is consistent with the goals and objectives of all major health and development partners: the World Health Organization, the United Nations Children's Fund, the GAVI Alliance, and the World Bank. It would contribute to meeting the Millennium Development Goals and is also supported by a 2005 World Health Assembly resolution on disability.

A change of strategy is imminent. The achievements of the past five to seven years toward JE control have been managed by a vigorous alliance of many partners, including the World Health Organization, the United States Centers for Disease Control and Prevention, the Armed Forces Research Institute of Medical Sciences, endemic countries, the International Vaccine Institute, vaccine manufacturers, and several universities. Many activities and collaborations were spearheaded by the PATH JE project, with funding provided by the Bill & Melinda Gates Foundation. The PATH JE project, however, operated under a time-limited grant (2003 to 2009), and the Gates Foundation has indicated that future funding for continuation—or the establishment of a similar type of project focused strictly on JE—is unlikely. Therefore, from mid-2009 a new coalition is needed to raise funds, take on the roles left open by PATH's departure, and to continue the work stimulated by the Gates Foundation's support.

This document outlines a strategic framework for advancing JE control by building on progress and addressing priorities for future efforts—identified in collaboration with the partners listed previously. This is an evolving document, and future collaboration will continue to refine the JE control target and the activities necessary to reach it. The document is broken out into two sections:

1. Background describes the public health significance of JE and the rationale for its control. This is followed by a description of the status of JE control in 2008 and finally, a basis for a future control target, by 2015, of fewer than 0.5 cases per 100,000 children under 15 years of age in each endemic country.

2. Strategic plan, 2009–2015 includes objectives, strategies, and priorities, followed by a description of anticipated opportunities and challenges. The section concludes with an estimate of the total cost of achieving JE control by 2015. These costs include those that would need to be borne by the countries themselves and the donor community. The cost of controlling JE in the 14 GAVI-eligible, endemic countries is estimated at US$338 million over seven years to 2015.

Six annexes describe:

- **Annex 1:** Role of partners
- **Annex 2:** Cost implications
- **Annex 3:** Strategic milestones
- **Annex 4:** Status and estimated future vaccine implementation, 2006–2015
- **Annex 5:** Status of JE disease and control plans in endemic countries
- **Annex 6:** Contributors

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Acronyms

Acronym	Definition
AEFI	adverse events following immunization
AES	acute encephalitis syndrome
AFP	acute flaccid paralysis
AFRIMS	Armed Forces Research Institute of Medical Sciences
AusAID	Australian Agency for International Development
CDIBP	Chengdu Institute of Biological Products
CSF	cerebrospinal fluid
DALY	disability-adjusted life year
ELISA	enzyme-linked immunosorbent assay
EPI	Expanded Program on Immunization
GIVS	Global Immunization Vision and Strategy
IgM	immunoglobulin M
IPA	International Pediatric Association
IVI	International Vaccine Institute
JE	Japanese encephalitis
JICA	Japanese International Cooperation Agency
KOICA	Korean International Cooperation Agency
ME	meningoencephalitis
MOH	ministry of health
NRA	national regulatory authority
QA	quality assurance
QC	quality control
SEAR	Southeast Asia Region
SEARO	Southeast Asia Regional Office (WHO)
UNICEF	United Nations Children's Fund
US CDC	United States Centers for Disease Control and Prevention
USAID	United States Agency for International Development
WHO	World Health Organization
WPR	Western Pacific Region
WPRO	Western Pacific Regional Office (WHO)

Preface

The World Health Organization has developed a theoretical framework for Japanese encephalitis control, defined by a World Health Organization position paper. The purpose of this document is to provide a more detailed implementation strategy through 2015 and to provide a strategic direction—which may be revised after the first few years of implementation—for Japanese encephalitis control by 2015.

1. Background

1.1 Public health significance of Japanese encephalitis and rationale for control

This first section of this plan describes the public health significance of Japanese encephalitis (JE) and the rationale for its control. This is followed by a description of the current status of JE control in 2008, and finally presents a basis for a future control target, by 2015, of fewer than 0.5 cases per 100,000 children under 15 years of age in each endemic country.

1.1.1 Disease burden is high

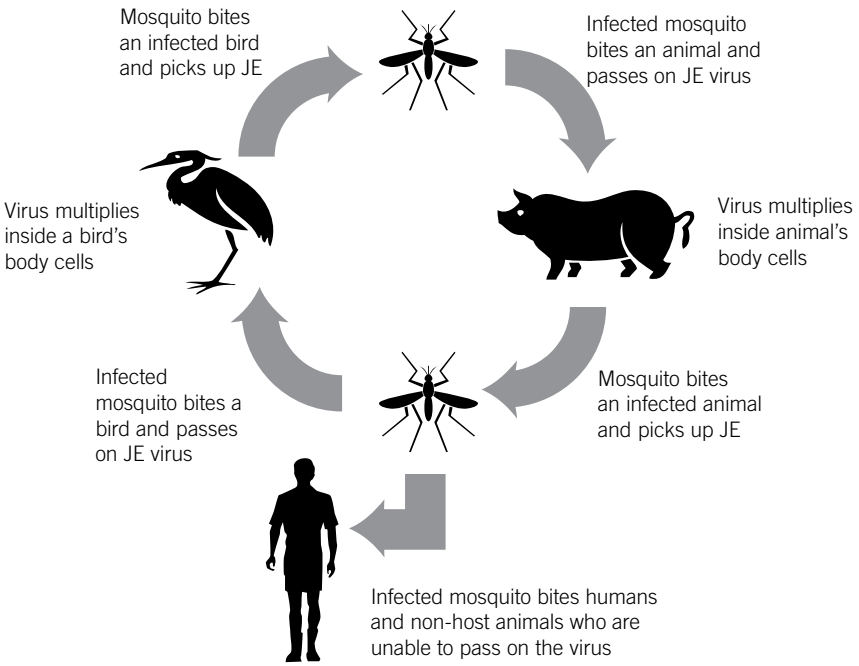
JE is the leading cause of viral encephalitis and a significant cause of disability in Asia. The severity of sequelae, together with the volume of cases, makes JE the most important cause of viral encephalitis in the world.[1] Approximately 3 billion people—including 700 million children under 15 years of age—live in the countries at risk of JE in Southeast Asia and the Western Pacific.[2] The World Health Organization (WHO) estimates that JE causes at least 45,000 cases of clinical disease each year, mostly among children under 15 years of age, resulting in about 10,000 deaths and 15,000 cases of long-term, neuropsychiatric sequelae.[3] While knowledge of the burden of disease varies by country, the presence of JE is increasingly being recognized in countries in Southeast Asia and the Western Pacific,[4] and these figures are believed to underestimate the disease burden that actually exists.

At least 50 percent of children who survive illness are left with disabilities, including physical, cognitive, or psychiatric problems.[5] These disabilities are typically lifelong[6] and cause significant burden within affected families and communities. With the near-eradication of poliomyelitis, JE has gained increasing prominence as an important cause of disability of children in Asia.

The greatest disease burden occurs in vulnerable groups—children and the rural poor. JE is most common in children between 1 and 15 years of age.[7] In areas where JE is hyperendemic, about half of all cases occur in children younger than four years of age, and nearly all cases occur in children younger than ten years of age.[8] As the JE virus transmission cycle involves mosquitoes that typically breed in rice fields, with pigs and birds as amplifying hosts (Figure 1), exposure to the virus is highest in rural areas.

Extensive and devastating outbreaks are a feature of JE disease in many countries. For example, in just five months, 5,737 cases and 1,344 deaths were reported from seven districts of Uttar Pradesh, India, when an epidemic occurred in 2005.[9] Such cyclical epidemics predominantly kill young children who are susceptible because of lack of previous exposure to the virus.

FIGURE 1. **Transmission cycle of Japanese encephalitis**



1.1.2 Recent developments mean JE control is feasible

Vector control for JE has had limited effectiveness in most settings and is expensive and resource-intensive, leaving immunization as the most important and effective control measure.[10] Although a JE vaccine was first used for disease control in the 1960s and has been used extensively in countries such as Japan, the Republic of Korea, and Thailand, its use remained limited or negligible in the poorest countries in Asia. The high cost of the mouse brain–derived vaccine, an insufficient vaccine supply, poor disease surveillance, and limited advocacy hindered control efforts.

However, recent progress, stimulated by funding from the Bill & Melinda Gates Foundation, has led to improved documentation of disease burden and initiatives to control disease in many Asian countries. A newer, safe, effective, live JE vaccine is now available, and a price has been negotiated to allow vaccine introduction in public-sector immunization programs in lower-income JE-endemic countries. Other JE vaccine candidates are in late-stage development. It now appears feasible that JE can be controlled as a public health issue in all endemic countries where this has not yet been achieved.

1.1.3 JE control through immunization is cost-effective

A cost-effectiveness analysis for 14 countries eligible for funding from the GAVI Alliance (GAVI-eligible)[a] estimated that from 2007 to 2021, 193,676 cases, 43,446 deaths, 77,470 cases with sequelae, 6,622,932 disability-adjusted life years (DALYs), and US$19 million in acute

a GAVI-eligible JE-endemic countries include Bangladesh, Bhutan, Cambodia, India, Indonesia, Democratic People's Republic (DPR) of Korea, Lao People's Democratic Republic (PDR), Myanmar, Nepal, Pakistan, Papua New Guinea, Sri Lanka, Timor Leste, and Vietnam. Non–GAVI-eligible countries include Australia (Torres Strait Islands), Brunei Darussalam, China, Japan, Republic of Korea, Malaysia, Philippines, Thailand.

hospitalization costs could be avoided by immunization with the live, attenuated SA 14-14-2 JE vaccine through campaigns and implementation of routine immunization programs. At US$28 per DALY averted, vaccination is a very cost-effective intervention. Taking into consideration nonmedical costs and costs due to sequelae, vaccination may also result in cost savings.[11]

A recent cost-effectiveness analysis conducted using data from Bali, Indonesia indicated that an immunization program in the birth cohort is highly cost-effective, at US$31 per DALY averted.[12]

Economic evaluations of the live, attenuated SA 14-14-2 vaccine conducted in China, India, and Thailand demonstrate that JE vaccination is a cost-effective intervention. A cost-effectiveness analysis of routine immunization to control JE in Shanghai, China, demonstrated that routine vaccination with inactivated P3 JE vaccine or live, attenuated SA 14-14-2 vaccine was cost-saving. The SA 14-14-2 vaccine, however, had a 47 percent greater financial saving than the P3 vaccine.[13] A cost-effectiveness analysis of JE control strategies in Andhra Pradesh, India, estimated that implementing campaign and routine vaccination programs using the inactivated, mouse brain–derived JE vaccine would result in US$1,247 per DALY averted. Vaccination with SA 14-14-2 vaccine compared to no vaccination was a cost-effective intervention with US$76 per DALY averted. In Thailand, a study estimated the cost and benefit of the routine JE immunization program with inactivated mouse brain–derived vaccine and predicted that the program would cost US$15,715 to US$21,661 per prevented JE case; there would be 124 cases and 31 deaths averted and direct medical cost savings of US$72,922 in treatment expenses, disability care, and loss of future earnings per prevented JE case.[14]

1.1.4 JE control is aligned with international goals

JE control is aligned with WHO and UNICEF priorities

In response to challenges in global immunization, the WHO and United Nations Children's Fund (UNICEF) developed the *Global Immunization Vision and Strategy (GIVS), 2006–2015*. GIVS aims to immunize more people, from infants to seniors, with a greater range of vaccines. Its chief goal is, by 2015 or earlier, to reduce illness and death due to vaccine-preventable diseases by at least two-thirds compared to 2000 levels. The GIVS document was adopted by governments meeting at the World Health Assembly in 2005.[15] It has four main aims:

- To immunize more people against more diseases.
- To introduce a range of newly available vaccines and technologies.
- To provide a number of critical health interventions and surveillance with immunization.
- To manage vaccination programs and activities within the context of global interdependence.[b]

Furthermore, JE control is aligned with the *WHO Plan of Action for New and Under-utilized Vaccines Implementation, 2007–2010*.[16]

WHO Global Plan to Combat Neglected Tropical Diseases, 2008–2015

JE control is an initial focus within the global targets of WHO's plan to address neglected tropical diseases, which the organization cites as an important element of reaching the Millennium Development Goals.[17] The plan applies an intersectoral and interprogrammatic

b The GIVS document lists five strategies: 1. Ensure a reliable supply of affordable vaccines of assured quality; 2. Assure adequate and sustainable financing; 3. Improve communication and dissemination of information; 4. Recognize the roles, responsibilities, and accountability of partners; and 5. Include vaccines in global epidemic preparedness plans and measures.

strategy to eliminate or eradicate these diseases in impoverished communities, which reflects the collaborative approach needed to overcome disability and death caused by JE.

The JE control plan is aligned with GAVI Alliance principles

Specific activities of the strategy for JE control outlined in this document further reflect the priorities of the GAVI Alliance:[18]

- Make vaccines and related technologies more affordable for poor countries.
- Focus on new and underutilized vaccines.
- Encourage country-driven approach[es].
- Promote equity in access to immunization services between and within countries.
- Support nationally defined priorities.
- Align the institutional obligations and mandates of partners.
- Contribute to achieving the Millennium Development Goals.
- Be catalytic and time-limited.

JE control is aligned with a World Health Assembly resolution

In 2005, the World Health Assembly passed a resolution on disability, including prevention, management, and rehabilitation. JE control will not only reduce the number of disabled persons in Asia, but will result in improved awareness and management of those disabled by the disease.[19]

JE control is aligned with four of the Millennium Development Goals

- *Reduce under-five child mortality*. Based on an estimated 45,000 cases annually, at least 10,000 to 15,000 children die from JE each year. This figure is believed to underestimate the amount of disease burden that actually exists.[20]
- *Eradicate extreme poverty and hunger*. At least one-half of children who survive JE suffer long-term disabilities, leading to adverse social, psychological, and economic consequences for the child, their family, and the community. Lifelong physical, cognitive, and psychiatric sequelae often require permanent care and limit the survivor's ability to lead an independent life.
- *Achieve universal primary education*. Each year, many children affected by JE either never return to school after illness or do not perform as well at school due to sequelae of illness. Data from a review of disability after JE in Cambodian children showed that only 5.6 percent of children recovered to a similar condition as prior to illness. Twenty-three percent were not doing as well at school or with routine activities, and 6 percent had dropped a grade or were no longer attending school.[21] Many others had behavioral problems that could potentially interfere with school performance.
- *Promote gender equality and empower women*. Every year, at least 15,000 new families have their economy destroyed or disrupted when a family member is disabled by JE. Since women and girls are most frequently the caregivers of disabled family members, JE burdens women and girls with yet another responsibility in the family.

1.1.5 JE incidence will not be reduced without immunization

JE virus is maintained in the environment in a cycle that involves mosquitoes and vertebrate amplifying hosts—primarily pigs and wading birds. The *Culex* mosquitoes that transmit the virus commonly breed in rice paddies and ground pools. Over the past 40 years, the total area under rice cultivation in all JE-endemic countries (excluding the Russian Federation and Australia) has risen to 1,234,000 km^2—an increase of 22 percent—with a concomitant increase in rice production of 134 percent. Pig farming in Asia has increased by 17 percent in the last 10 years. The rural population living in areas considered at risk for JE has increased by 66 percent in the last 40 years.[22] JE has occurred in new geographical regions and in new areas within existing JE-endemic countries.[23,24] Taking these factors into account, it is clear that exposure to JE virus can only be increasing. Natural environmental or living factors are unlikely to lead to any reduction in risk in the foreseeable future. Furthermore, climate changes may further influence spread of the virus.

Interventions other than immunization have not significantly reduced morbidity and mortality from JE disease. Although good quality care improves outcome, there are no antiviral medications available to treat JE. Mosquito- and pig-control methods have shown very limited impact, have significant limitations, and are not recommended as a focus for JE control.[25]

Immunization is the only reliable and effective method to control disease. Experience from countries including Australia, Japan, Republic of Korea, and Thailand has shown that immunization has been a critical factor in achieving JE control.[10,26–28]

1.2 Status of JE control, 2008

The intensity of a range of activities necessary for JE control varies among endemic countries. Some countries are establishing or strengthening surveillance while others are implementing vaccination campaigns and adding JE vaccine to routine immunization programs. A handful of countries have achieved great success in JE control with programs that span several decades. Many of the poorest countries in Southeast Asia and the Western Pacific, however, have not been able to evaluate the level of JE disease burden among their populations and determine whether control through immunization is appropriate. In these settings, identifying resources and generating commitment from policymakers and funding agencies will be crucial. Meanwhile, routine vaccine introduction and outbreak control activities under way throughout the region are informing future planning and raising awareness of the burden of JE and the potential impact of vaccination. The status of surveillance and vaccine introduction activities in 2008 follows.

1.2.1 Determination of disease burden

Surveillance

WHO JE surveillance standards have been prepared, evaluated,[29] and published in a final version. In the Southeast Asia Region (SEAR), countries are requested to routinely report viral encephalitis/JE cases, and four of ten JE-endemic countries currently report these figures (Bangladesh, Nepal, Sri Lanka, and Thailand).[c] Other countries include viral encephalitis as a reportable disease but have not provided data routinely to WHO. In the Western Pacific Region (WPR), many countries have established reporting of viral encephalitis/JE as part of national communicable disease surveillance systems. Though there is no regular mechanism requesting countries to report viral encephalitis cases to the regional WHO office, data are collected annually in the WHO–UNICEF Joint Reporting Form. Additional progress in standardizing and expanding JE surveillance includes the following:

- JE case numbers have recently been included in the annual WHO–UNICEF Joint Reporting Form.[d]
- A tool for measuring disability after JE illness has been developed and evaluated (Liverpool Outcome Score).[30]
- Training materials are routinely developed and updated at www.path.org/je.

Diagnostics and laboratory capacity to support surveillance

WHO JE laboratory networks have been created to establish standards for the laboratory diagnosis of JE, provide support and technical assistance, establish reference and quality control mechanisms, and provide training resources and facilities.

- SEAR established a laboratory network in 2006 that includes 11 national and subnational laboratories from six countries (Bangladesh, India, Indonesia, Myanmar, Nepal, and Sri Lanka), a regional reference laboratory (National Institute of Mental Health and Neurosciences, Bangalore, India), and a global specialized laboratory (United States Centers for Disease Control and Prevention [US CDC], Fort Collins, USA).
- The WPR laboratory network is under development with the identification of seven national laboratories in six countries (Cambodia, Lao PDR, Malaysia, Papua New Guinea, the Philippines, Vietnam [2]), two regional laboratories (China, Japan), and a global specialized laboratory (South Korea).
- A WHO JE laboratory manual has been prepared (2007 version, for evaluation purposes) and a final version is soon to be published.
- A WHO-led Laboratory Working Group of global experts convenes regularly to share information and formulate advice on diagnostics and laboratory needs for JE.

c *Weekly Vaccine-Preventable Disease Surveillance Bulletin* is published by WHO Regional Office for Southeast Asia. Current and past issues are available at: www.searo.who.int/en/Section1226/showfiles.asp.

d The latest JE incidence reporting can be found at the WHO Immunization surveillance, assessment, and monitoring web page, available at: www.who.int/immunization_monitoring/en/globalsummary/timeseries/tsincidencejap.htm.

Three commercial JE immunoglobulin M (IgM) antibody enzyme-linked immunosorbent assay (ELISA) diagnostic kits are commercially available and in limited use in national laboratories in JE-endemic countries. However, crucial analyses involving these kits remain in progress.

- Determination of the sensitivity, specificity, and usability of the kits is not yet complete.
- Determination of the appropriateness of their use with cerebrospinal fluid (CSF) and serum is ongoing.
- Two assays have undergone field evaluations and all three will be assessed with a standard panel of specimens currently under development.

Several in-house ELISAs are in use in many countries, and plans are under way to evaluate these with a standard panel of specimens. Other diagnostic assays have been developed for research purposes or are in the development phase, but are not routinely accessible for country-level use. Finally, other methodologies for specimen collection (for example, filter paper to facilitate specimen testing) have been investigated, but there are insufficient data to make conclusions on their applicability for use.

Information on JE disease burden at country level

Many countries have initiated or strengthened surveillance in recent years. However, in at least 10 of 25 JE-endemic countries, the level of JE disease burden is unclear due to limited data collection. Annex 5 provides information on the status of surveillance in the 25 JE-endemic countries[e] as of 2008. In summary:

- Five countries conduct case-based JE surveillance with excellent laboratory support: Australia, Japan, Republic of Korea, Singapore, and Chinese Taiwan.
- Three countries have surveillance systems with access to laboratory diagnosis for the majority of cases: Nepal, Sri Lanka, and Thailand.
- Seven countries have ministry of health (MOH)–established JE surveillance systems, but strengthening or expansion is required to ensure collection of accurate data for decision-making: Cambodia, China, India, Malaysia, Myanmar, Timor Leste, and Vietnam.
- Two countries are in the early stages of developing or modifying existing surveillance systems to establish JE disease burden: Indonesia and the Philippines.
- Three countries have research-based projects at one or more sentinel hospitals to investigate JE disease burden: Bangladesh, Papua New Guinea, and Lao PDR.
- One country has strong encephalitis surveillance but limited JE surveillance due to the lack of an in-country facility for JE diagnosis: Brunei Darussalam.
- Four countries have not yet taken steps to establish the burden of JE disease and disability: Bhutan, Democratic People's Republic of Korea, Pakistan, and southeast Russian Federation.

e Brunei Darussalam and Pakistan have no JE data from the last five years.

1.2.2 Availability of vaccines

There are two types of JE vaccines currently available internationally: the inactivated, mouse brain–derived JE vaccine and the live, attenuated SA 14-14-2 JE vaccine. In addition, several other JE vaccines are in late-stage development. Features of the existing vaccines approved for pediatric use and those in development are provided in Tables 1 and 2, respectively.

The mouse brain–derived, inactivated vaccine has been available for over 40 years. However, due to its complex schedule, difficult production process, supply issues, safety concerns, and expense, there is increasingly a move away from use of this vaccine.[31]

The live, attenuated SA 14-14-2 vaccine has been used in China since 1988, and internationally for the last ten years. It has been demonstrated to be safe and efficacious, has a simple schedule, and data on coadministration with measles vaccine reflect an acceptable short-term safety profile.[32] An affordable public-sector price was negotiated with manufacturer Chengdu Institute of Biological Products (CDIBP) to enable introduction in immunization programs of lower-income endemic countries.[33]

TABLE 1. **JE vaccines available internationally for pediatric use, 2008**

	Live, attenuated, SA 14-14-2 vaccine (CDIBP)	Inactivated, mouse brain–derived vaccine
Primary series	Single dose.	Two doses given at an interval of 1–4 weeks.
Boosters	Studies have documented ongoing protection from a single dose for five years in a JE-endemic area.[34] Boosters are unlikely to be required; monitoring of ongoing protective efficacy is needed.	First booster dose required after one year. Repeated boosters are required. Schedules vary from country to country.
Presentation	5-dose or single-dose vial.	10-dose or single-dose vial.
Use in routine EPI*	Can be safely coadministered with measles vaccine at 9 months of age.[32] Data on non-inferiority of immunological response are under review.	Primary series commonly commences at 12 months of age, but schedules vary from country to country. Schedule generally does not allow the vaccine to be given within routine EPI schedule.
Manufacturers	Single manufacturer, CDIBP, is authorized to export this vaccine from China.	Manufacturers in Republic of Korea, Chinese Taiwan, Thailand, and Vietnam.
Availability of supply	Guaranteed supply for 20 years to meet market needs.	The primary producer (BIKEN, Japan) has stopped producing bulk (filling only). The Indian manufacturer has stopped production. Increasing supply problems are expected in the coming years.
Countries with experience using vaccine	China, Nepal, India, Republic of Korea, and Thailand.	Australia, India, Japan, Republic of Korea, Malaysia, Sri Lanka, Chinese Taiwan, Thailand, and Vietnam. Also in travelers.
Cost	CDIBP established a maximum public-sector price for lower-income endemic countries (Gross National Income per capita <US$1,000 in 2006) through 2026. The ex-works price per dose for GAVI-eligible countries in 5-dose vials is similar to measles vaccine (excluding costs of freight, insurance, etc.).	The price varies widely between manufacturers; some countries in Asia reported paying about US$4.50 per dose in 2007, including shipping and transport costs.

	Live, attenuated, SA 14-14-2 vaccine (CDIBP)	Inactivated, mouse brain–derived vaccine
WHO prequalification and licensure	Not prequalified yet, but planned pending approval of the Chinese national regulatory authority (NRA) and vaccine file submission to WHO. Licensed in China, India, Lao PDR, Nepal, Republic of Korea, Sri Lanka, and Thailand.	Not prequalified and no plans for prequalification. Licensed in many Asian countries, including India, Japan, Malaysia, Republic of Korea, Sri Lanka, Chinese Taiwan, Thailand and Vietnam.

* Expanded Program on Immunization

In early 2009, Intercell received regulatory approval of IC51—its inactivated, Vero cell–derived vaccine (SA 14-14-2 strain) for adult travelers—in Australia (JESPECT®) and the European Union and US (Ixiaro®).[35] Intercell is transferring the technology to Biological E., which will produce the vaccine for India, Pakistan, Nepal, Bhutan, and countries of Southeast Asia. Novartis is the marketing and distribution partner for most other countries worldwide, with the exception of Australia and New Zealand (CSL Biotherapies). Both adult and pediatric Phase 2 trials of IC51 have been completed. The vaccine will be available for adult use in 2009, with pediatric label extension planned in 2012. The IC51 vaccine requires two doses (day 0 and day 28); booster studies are ongoing.

Several other JE vaccine candidates are in late-stage development (Table 2). Three are likely to be licensed for use in adults in at least one country by 2009, but only one is likely to initially be available for use in children—the primary target population for JE immunization in Asia—and it will initially only be available in Japan. However, clinical trials are ongoing for each of the candidate vaccines to accelerate progress toward availability for children.

TABLE 2. **JE vaccines in late-stage development, 2008**

Company	Vaccine type	Initial licensure	Anticipated availability in children	Schedule
Sanofi Pasteur/ Acambis (France)	Live, recombinant Vero cell–derived vaccine (SA 14-14-2 strain).	Adults and children: Expected 2010 (Australia and Thailand).	Studies in progress in India, Thailand, and Philippines. Available: expected 2010 (Australia and Thailand).	1 dose. Boosters may not be needed (studies ongoing).
BIKEN (Japan)	Inactivated, Vero cell–derived vaccine (Beijing strain).	Adults and children: Expected 2009 (Japan initially).	Studies in progress in Japan. Available: Expected 2009 (targeted for Japanese market initially, but plans also exist for use outside Japan).	3 doses. Boosters to be determined.
Kaketsuken (Japan)	Inactivated, Vero cell–derived vaccine (Beijing strain).	Infants/young children: Expected 2011 (Japan initially).	Studies in progress in Japan (target age 6–90 months). Available: Expected 2011 (targeted for Japanese market initially).	3 doses. Boosters to be determined.

1.2.3 Introduction and integration of vaccine into immunization systems

Country status of JE control through immunization varies throughout the region. Annex 4 describes, country by country, the status of both campaign and routine vaccine introduction in 25 endemic[f] countries. In summary:

- Six countries have comprehensive immunization programs with vaccine offered to all at-risk individuals as appropriate: Australia–Torres Strait Islands, Cambodia, Japan (temporarily halted),[36] Republic of Korea, Chinese Taiwan, and Thailand.
- Five countries have a program with plans for expansion or development: China, India, Nepal, Sri Lanka, and Vietnam.
- Two countries have limited or geographically targeted immunization programs: Democratic People's Republic of Korea and Malaysia, respectively.
- Eleven countries do not yet have JE immunization programs: Bangladesh, Bhutan, Brunei Darussalam, Indonesia, Lao PDR, Myanmar, Pakistan, Papua New Guinea, Philippines, southeast Russian Federation, and Timor Leste. In many of these countries, JE is currently not perceived as a public health problem by the ministry of health (MOH).
- One country does not consider an immunization program necessary based on ongoing surveillance and disease burden data: Singapore.

Several tools are available to guide countries in decision-making and implementation of JE vaccine introduction plans, including:

- *Introduction of Japanese Encephalitis Vaccine in the Southeast Asia Region (With Focus on SA 14-14-2 JE Vaccine)—Operations Guidelines* (WHO–SEAR): This resource provides practical, hands-on operational guidelines for the introduction of JE vaccine. The guidelines assume that disease epidemiology has been defined, appropriate national consultations have taken place, necessary funding has been secured, and other administrative and policy decisions have been made.[37]
- *The Advanced Immunization Management e-Learning module* (PATH): This online resource provides training necessary for informed decision-making on JE control, as well as guidance on program implementation. Available since 2004, the module is currently being updated. This interactive tool is available online at: http://aim.path.org/en/vaccines/je/index.html.
- *PATH JE project website:* This site describes project activities and links to films, PowerPoint presentations, and other information. Materials are available at: www.path.org/je.
- *PATH's Vaccine Resource Library:* This resource provides important scientific articles on surveillance and vaccine safety, clinical training materials, and training materials on topics from diagnostics to vaccine administration. The library's JE materials are available at: www.path.org/vaccineresources/japanese-encephalitis.php.

f Pakistan and Brunei Darussalam have no JE data from the last five years but are presumed endemic (see Annex 5).

1.2.4 Treatment and management of individuals diagnosed with JE

There are currently no specific antiviral or other curative medications for JE. Treatment consists of supportive care and management of complications that may be treatable, such as seizures. Therefore, awareness-building should focus on early detection and diagnosis, good quality medical and nursing care, and management of sequelae. The following materials have been developed to assist in this area:

- *JE Clinical Care Guidelines* (PATH). This resource presents guidelines for management of children presenting with symptoms or signs of acute encephalitis syndrome. It is currently available in the PATH Vaccine Resource Library: www.path.org/vaccineresources/files/JE_clinical_care_guidelines_PATH.pdf.
- *Liverpool Guide to Rehabilitation and Long-term Care of Patients With Encephalitis* (University of Liverpool Viral Brain Infections Group). This resource for physicians in resource-poor settings in Asia aims to guide follow-up of children recovering from acute brain injury, and JE in particular. Available in the PATH Vaccine Resource Library: http://www.path.org/vaccineresources/details.php?i=417.

Additional training and educational materials are available from the University of Liverpool Viral Brain Infections Group (www.liv.ac.uk/braininfections) and through the PATH Vaccine Resource Library (www.path.org/vaccineresources/japanese_encephalitis.php).

1.2.5 Research and development

The aim of ongoing research studies is to improve the control of JE through, for example, better systems for diagnosis or refinement of systems logistics to facilitate JE introduction. However, there are no outstanding research activities that should delay vaccine introduction. Current research activities focus on technical elements of vaccination toward preparing and submitting the SA 14-14-2 JE vaccine file for WHO prequalification:

- *Coadministration of measles and SA 14-14-2 JE vaccines.*
  - — Philippines: Research Institute of Tropical Medicine/PATH; commenced 2005.
  - — Sri Lanka: Sri Lanka Ministry of Healthcare & Nutrition/PATH; commenced 2007.
  - — Preliminary discussions with CDIBP to investigate the feasibility of developing a combined measles-JE and/or a combined rubella-JE vaccine.
- *Ability of live, attenuated SA 14-14-2 vaccine to replace booster doses of mouse brain–derived vaccine.*
  - — Sri Lanka; Sri Lanka Ministry of Healthcare & Nutrition/PATH; commenced 2007.
- *Vaccine effectiveness case-control study of live, attenuated SA 14-14-2 vaccine.*
  - — India; India Ministry of Health and Family Welfare/PATH; commenced 2009.
- *Human viremia study of SA 14-14-2 vaccine.*
  - — India; India Ministry of Health and Family Welfare; commenced 2007.
- *Development of an outcome assessment tool to help quantify disease burden.*
  - — India, Malaysia; University of Liverpool; commenced 2005.

- *Cost-effectiveness or cost-of-illness studies.*
  - — Cambodia; PATH and the Communicable Disease Control Department, National Immunization Program, National Institute of Public Health; commenced June 2007.
  - — China; PATH and the China Center for Disease Prevention and Control, Shaanxi Center for Disease Prevention and Control; commenced 2006.
  - — Indonesia; PATH and the Center for Research and Program Development for Disease Control, National Institute of Health Research and Development; commenced 2007.

1.2.6 Communications and advocacy

Awareness of JE among key audiences has grown significantly in the past few years. Surveillance activities have been a major factor toward increasing knowledge about JE disease burden and have highlighted its regional importance. For example, the establishment of the JE laboratory network is an important step in helping countries share information while learning from each others' best practices.

Country experiences with vaccine introduction, including the 2006 initiation of campaigns in high-risk districts of India, have been important vehicles for spreading messages about JE among stakeholders at all levels. As other countries, including Sri Lanka[g] and Cambodia, plan their own JE immunization introduction activities, discussions around JE will further increase at regional meetings and global conferences. WHO has established itself as an important resource for recommended policies and practice on JE control, with vaccine safety and new data discussed in several issues of the *Weekly Epidemiological Record* and at key meetings of the Strategic Advisory Group of Experts and the Global Advisory Committee on Vaccine Safety. Held every two years, the Biregional Meeting on Control of JE has become an important forum for sharing country experiences and informing national planning.

Media coverage in the past has primarily focused on JE outbreaks, but with more children receiving protection through vaccination, this coverage is poised to reflect a more positive perspective in spreading news about successful efforts toward JE control.

Reinforcing and communicating value of immunization versus other interventions

Along with advocacy, information-sharing is necessary to ensure appropriate decision-making at all levels. For example, the comparison of vaccination impact to that of vector control, which has been shown to be both expensive and ineffective, will continue to be a key message.

The WHO position paper on JE vaccination makes reference to the relative values of immunization against other interventions, specifically, improved economic conditions in the countries, changed lifestyles, centralized pig production, and the use of insecticides and impregnated mosquito nets. The position paper recognizes that *"while permethrin-impregnated mosquito nets have been shown to provide some protection in one study, […] mosquito nets and other adjunctive interventions should not divert efforts from childhood JE vaccination."*[1]

g Sri Lanka plans to transition from mouse brain–derived to SA 14-14-2 vaccine in 2009.

1.3 Basis for a control target

JE virus is maintained in the environment in an enzootic cycle between birds and pigs. Therefore, human exposure to the virus cannot be eliminated and control of JE relies on establishment of immunization programs to provide protection. As humans are an incidental host and play no role in the maintenance or amplification of JE virus, human immunization programs will not influence the transmission cycle or reduce JE virus levels in the environment, so maintenance of high immunization rates is essential for long-term disease control.

The five countries[h] that have good estimates of disease burden and have comprehensive JE immunization programs have managed to substantially reduce disease incidence rates and maintain low levels of disease. While other developmental factors are also likely to have influenced the incidence of JE, a comparison between two 10-year periods pre- and post-immunization in Japan and the Republic of Korea shows a reduction in disease incidence of over 99 percent (Table 3).

TABLE 3. **Impact of JE vaccines in Japan and the Republic of Korea, 1950s to 1990s**

Country	JE incidence rate per 100,000 pop. (1955–1966)	JE incidence rate per 100,000 pop. (1990–2000)	Percent reduction
Japan	2.5[10,28]	0.01[28]	99.6%
Korea	7.3[28]	<0.01[38,39]	99.9%

The first consideration for a control target is the age group for which the target should be set. The at-risk age group for JE is typically considered to be up to 15 years of age. Cases of JE sometimes occur in non-immune adults, but immunization programs rarely target older age groups. The majority of adults living in endemic areas will have acquired natural immunity, and as cases are infrequent, programs targeted at this population are unlikely to be cost-effective. Ensuring mosquito protection measures for older people is not feasible, and mosquito control to prevent cases is neither cost-effective nor likely to be successful.

The control target should therefore focus on the same group for which the intervention is targeted and for which control is achievable: those aged 15 years and under. The age group for surveillance for vaccine-preventable diseases in most JE-endemic countries includes children up to 15 years of age, which will facilitate monitoring of the control target.

To establish an ambitious yet achievable control target, thought was given to incidence rates in countries or regions that are considered to have already successfully controlled JE. Total population incidence rates in recent years in these areas range from 0 to 0.12 laboratory-confirmed JE cases per 100,000 population (Table 4). In areas with childhood JE immunization programs, the age distribution of disease shifts, resulting in a higher percentage, if not almost all, of cases occurring in older age groups.[40,41] Although incidence in the under-15 age group was not available for these countries, assuming half of all cases occurred in this age group, incidence rates would range from 0 to 0.3 JE cases per 100,000 children under 15 years of age (Table 4).

h Australia–Torres Strait islands, Japan, Korea, Chinese Taiwan, and Thailand.

It is important to note that these figures represent rates from wealthier countries, and several factors may differ from conditions in other, less-developed countries. For example, living conditions in wealthier settings may result in less exposure to virus as a result of screened or air conditioned houses, and there may not be as close proximity to amplifying hosts as occurs in other parts of Asia. In addition, access to health care and immunization may be better. As a result, applicability of the figures to other countries in Asia must be considered.

Accordingly, a similar analysis has started to assess the achievements to date—and anticipated achievements that can be expected over the coming years—in Thailand and Sri Lanka, two countries that have implemented successful JE immunization programs for many years. In Thailand in 2007, the annual incidence of JE in children under 15 years of age was 0.2/100,000.[42] In Sri Lanka, incidence rates have been decreasing for many years, as the JE control program has expanded and strengthened. In 2006 to 2008, incidence of laboratory-confirmed JE in children under 15 years of age was 0.06 to 0.18 per 100,000 children.

Based on these experiences, a control target of 0.5 confirmed JE cases per 100,000 children under 15 years is proposed for discussion.[i]

TABLE 4. **Recent JE incidence rates in selected countries considered to have controlled JE**

Country	Number of cases (years)	Rate in total population (per 100,000)	Rate in population under 15 years of age (per 100,000)
Australia–Torres Strait Islands[43]	0 (2001–2006)	0	0
Japan[44]	5.5 (average) Range 1–7/year (2000–2005)	0.004	0*
Republic of Korea[33]	2.3 (average) Range 0–6/year (2001–2006)	0.005	N/A (0.01)**
Chinese Taiwan+	29 (2006)	0.12	N/A (0.3)++
Sri Lanka	28 (average) Range 18–39/year (2006–2008)	0.14	0.13‡ (Avg. from 2006–2008)
Thailand	43 (2007)	0.07	0.2‡‡ (2007)

* Kurane I (personal communication). Note: one case in a three-year-old occurred in 2006.
** Age of cases is not available. Rate calculated based on conservative figure of 50% cases in this age group.
+ Centers for Disease Control, Chinese Taiwan. Available at: www.cdc.gov.tw.
++ Age of cases is not available. If half of all cases were in children under 15 years of age, incidence would be 0.3/100,000. Note: In 1999, 24 cases were reported and all were over 15 years of age.
‡ Epidemiology Unit, Ministry of Healthcare and Nutrition, Sri Lanka.
‡‡ Ministry of Public Health website, Thailand. Available at: http://eng.moph.go.th/.

i A rate of 0.5 confirmed JE cases per 100,000 children under 15 years of age is equivalent to about two confirmed cases each year in the under–15 years of age population in each endemic district in India; this target is ambitious, but probably achievable.

2. Strategic plan, 2009–2015

This second section of the plan presents objectives, strategies, and priorities, followed by a description of the anticipated opportunities and challenges, as discussed among the 17 organizations contributing to the development of this plan (Annex 6).

The section concludes with an estimate of the total cost of achieving JE control by 2015—meant to serve as a general guide for gauging potential funding needs. These costs include those that would need to be borne by the countries themselves, as well as the donor community. The cost of controlling JE in 14 GAVI-eligible, endemic countries is estimated at US$338 million dollars over the seven years through 2015 (Annex 2B).

2.1 Objective

By 2015, to control disease, death, and disability attributable to JE at a level at which they no longer constitute a significant public health problem.

➲ ***PROPOSED TARGET:*** 0.5 cases per 100,000 in the under-15 population by 2015.

2.2 Priorities

This section presents the highest-priority activities necessary to reach JE control by 2015, followed by a section on future leadership and funding needs. The four highest-priority activities are:

- Improve data for decision-making.
- Secure prequalification of at least one affordable JE vaccine for international procurement.
- Support countries with vaccine introduction.
- Identify adequate funding to support the governments' and partners' work in the future.

2.2.1 Improve data for decision-making

About half of all countries within the areas that are perceived to be JE-endemic currently consider that they have insufficient information to enable decision-making on introduction of an immunization program to control JE.[45] Several do not consider JE a public health concern. Offering technical assistance for JE surveillance, improving access to laboratory testing for JE diagnosis, ensuring data gathered are used for awareness-building, and providing financial support for priority activities (if required) will all be essential to enable country-level understanding of the national burden of JE disease. Awareness of burden, in turn, can establish

JE as a public health priority and inform decision-making on JE control. In addition to information on reported cases, data on seasonality, periodicity of outbreaks, and presence of high-risk areas may also be useful.

WHO recently published a surveillance strategy for new vaccines.[46] JE surveillance is incorporated in this strategy to ensure system integration and best use of resources.

2.2.2 Secure WHO prequalification of at least one affordable JE vaccine

There is currently no WHO-prequalified JE vaccine, which constrains procurement in countries that normally rely on UNICEF systems for vaccine supplies and also in countries with weak national regulatory authorities (NRAs). Three manufacturers have indicated that they will seek WHO prequalification for their JE vaccines; however, timelines are still several years long:

- CDIBP: Estimated 2011–2012 (conditional on WHO approval of NRA in China).
- Intercell/Novartis/Biological E: Estimated 2011.
- Sanofi Pasteur/Acambis: Estimated 2011.

As of 2009, the live, attenuated SA 14-14-2 vaccine from CDIBP is the only vaccine available in a reliable supply for use in immunization programs. While this vaccine has been widely used in China for many years and recently in large campaigns in India and Nepal, and is licensed in the Republic of Korea, Sri Lanka, and Thailand, it has not yet been submitted for WHO prequalification and may not be procured through UNICEF. Until a JE vaccine is prequalified, countries committed to JE control through immunization will have to face logistical and financial procurement challenges.

By current estimates, WHO prequalification of SA 14-14-2 JE vaccine will not occur until 2011 at the earliest.

The issue has the following implications for country programs:

- UNICEF does not routinely procure vaccine that is not WHO-prequalified.
- UNICEF has only procured non-prequalified vaccine where alternative quality criteria could be established in liaison with WHO, and the recipient country government has taken the responsibility for quality of the vaccine.

WHO will not accept a prequalification file from a manufacturer in a country without an approved NRA. The Chinese NRA was previously recognized by WHO as having reached an acceptable level of performance of the six critical control functions of an NRA,[47] but did not meet new WHO NRA standards introduced in 2004.

WHO's estimated timeline from submission to prequalification is a minimum of 12 to 18 months.

Accelerated WHO prequalification of SA 14-14-2 vaccine is currently the highest priority for progress with JE control.

WHO headquarters in Geneva is currently reviewing this issue. One potential alternative is GAVI-eligible countries' purchase of JE vaccine themselves through a non-United Nations procurement agency with the vaccine licensed in a third country that has a WHO-certified NRA, such as the Republic of Korea.

2.2.3 Support countries with vaccine introduction

JE control can be achieved only through introduction of human immunization programs. To assist planning and technical assistance for vaccine introduction, this plan categorizes countries into four groups: current users, early adopters, medium adopters, and later adopters (Annex 4). The assignment of countries to these groups is based on a judgment of their readiness and willingness to consider vaccine introduction, their capacity to adopt a new vaccine into their existing immunization program, and the amount of technical assistance that may be available to support decision-making and implementation of vaccine introduction.

Annex 4 shows estimated timelines for introduction of JE vaccine in individual countries. Annex 2 (Part B) indicates estimated resource requirements.

2.2.4 Identify adequate funding

Although many countries have indicated that a routine JE immunization program is feasible if an affordable vaccine is available, an initial campaign to cover all at-risk groups in the country can be relatively expensive.[33] WHO recommends the most appropriate strategy for vaccine introduction is a one-time catch-up campaign followed by incorporation of JE vaccine into the routine immunization program.[1] Many countries are likely to require funding to assist with campaigns, and some may also need assistance with costs associated with implementation of routine immunization programs. The manufacturers of the other JE vaccines newly developed (Intercell/Novartis/Biological E.) and in late-stage development (Sanofi Pasteur/Acambis, BIKEN, and Kaketsuken) have not yet published prices, but external funding support may be needed for these vaccines, too.

2.3 Future leadership

Following a successful Bill & Melinda Gates Foundation–funded project to strengthen immunization in Andhra Pradesh State, India, which included JE vaccine introduction, the Gates Foundation supported PATH for a five-year project to explore JE control challenges and opportunities throughout the rest of Asia. The PATH JE project comes to a close in 2009, and follow-on funding to PATH for continuation of the project is not expected. With PATH stepping back from its management role in advancing the JE control agenda, questions now arise as to which organizations have the skills and capacity to lead the control effort in the future and which will support the effort financially.

At present there are several organizations that have some of the capacities needed to carry the priority activities forward, including technical skills, the capacity to manage a public-private project, a strong presence in JE endemic countries, and above all the vision to lead the collaborative efforts. Several organizations can each do part of the work, but there is not a single institution that can reasonably take the responsibility for all components. The following paragraphs present a collaborative solution.

- A broad *JE control coalition*, supported by a small secretariat, could provide the breadth and depth of scientific, management, and technical assistance skills needed to work with governments and manufacturers. This plan has assembled, under a common set of objectives and targets, all the major organizations that can contribute to JE control: WHO, UNICEF,

US CDC, the Bill & Melinda Gates Foundation, GAVI Alliance, vaccine manufacturers, academic institutions, and civil society organizations.

- PATH is leading an effort to evaluate alternative forms and functions of a future coalition and to consider where a secretariat may be located to best support the contributions of all partners.
- As activities progress and specific roles are completed, organizations may close out their contributions to the coalition. Similarly, others may join as the JE control target gets closer and follow-on activities are initiated. But the initial critical management task is to come to a common agreement on three items: the goal, the roles of each of the partners, and a plan that will be useful for each of the partners to raise funds for respective activities.

There are at least four coalition-like organizations for vaccine-preventable disease control that may serve as models for the JE coalition: the Measles Initiative, the Yellow Fever Partnership, the Global Alliance to Eliminate Lymphatic Filariasis, and the Stop TB Partnership. In its own way, each coalition:

- Monitors funding needs of the principal implementing partners.
- Identifies potential funding sources.
- Supports communication between the partners.
- Manages promotional and technical meetings between the partners.

2.3.1 Future funding

There are currently limited sources of funding for JE control. In view of the relatively low cost of supporting JE control, the highest priority is to find financial support for implementation of JE catch-up campaigns in endemic countries that have not already conducted them.

In 2008, the GAVI Alliance Secretariat determined that JE immunization should be included as a priority in its future vaccine support strategy.[48] A further decision is expected in early 2009 regarding the extent of future support that may be provided.

Additional prospective donors may include the Australian Agency for International Development (AusAID), the Japanese International Cooperation Agency (JICA), the Korea International Cooperation Agency (KOICA), the United States Agency for International Development (USAID), and other bilateral government organizations with either a regional focus or a country focus in one or more of the endemic countries (for example, the Netherlands' support to Indonesia, and US support to the Philippines).

2.4 Strategies and targets

> "If you're not keeping score, you're just practicing."
>
> —Tadataka Yamada, President, Global Health Program
> Bill & Melinda Gates Foundation

This section of the plan describes six strategies that together will ensure that JE control is achieved by the target date of 2015. Each section contains a list of planned activities to be

performed and target dates by which they should be completed. All the target dates are summarized year-by-year from 2009 to 2015 in Annex 3.

2.4.1 Improve data for decision-making

An understanding of disease burden is essential to enable programmatic decisions about JE vaccine introduction. Not only will establishing disease burden in known endemic areas be important, but monitoring for disease in new areas will also be required. As mentioned previously, the last four decades have seen an increase in rural populations considered to be living in areas at risk for JE.[12] This change, historical patterns of the spread of JE disease, and the possible impact of climate change, all suggest that new areas within countries—and new countries in Asia, the Pacific, and perhaps elsewhere—could become JE-endemic in the future.

Improve systems for gathering and reporting surveillance data

Technical assistance will be necessary to help countries establish or ensure the quality of routine JE surveillance systems to better define disease burden.

➲ ***TARGET:*** Routine surveillance will have reached WHO-recommended standards in 7 of 14 GAVI-eligible countries by 2010. All 14 GAVI-eligible countries will have reached WHO standards by 2012.

Increased frequency, reliability, and extent of routine reporting to national and regional public health authorities will enable monitoring of disease and impact of immunization. Technical assistance will be necessary to help countries improve analysis, reporting, and appropriate use of surveillance data.

➲ ***TARGET:*** Seven of 14 GAVI-eligible countries will be reporting JE cases in a timely manner by 2010, and all 14 by 2012. The remaining 11 countries in the JE-endemic zone will be reporting JE cases (including zero reporting) by 2012.

Including measurement of disability within JE surveillance efforts will improve understanding of disease impact.

➲ ***TARGET:*** Select GAVI-eligible countries will include use of standardized disability assessment tools within routine surveillance activities.

With the availability of vaccines for *Haemophilus influenzae* type B and pneumococcus, as well as JE, several countries in Asia are considering or implementing integrated meningoencephalitis (ME) surveillance. Integrated surveillance is in line with the *Global Framework for Immunization Monitoring and Surveillance*—WHO's strategy for vaccine-preventable disease surveillance.[49] A standard case definition and WHO standards to support this are required.

➲ ***TARGET:*** Draft ME surveillance standards by Q1 2010.

Integrating JE surveillance, using existing surveillance infrastructure as appropriate, can improve efficiencies and result in cost savings. For example, JE surveillance is integrated with acute flaccid paralysis (AFP) surveillance in Nepal and with meningitis surveillance in Cambodia. Bangladesh, China, and India also have started small-scale JE surveillance projects integrated with AFP and measles surveillance. To support this, WHO's recently published

surveillance strategy document should be modified to outline how JE surveillance aligns and can be included with surveillance for other diseases.[50]

➲ ***TARGET:*** Incorporate JE into WHO new vaccine surveillance strategy document by Q1 2010.

With JE surveillance overseen by public health programs that manage plans for vaccine-preventable diseases rather than departments assigned to manage vector-borne disease control, countries may more efficiently improve human disease surveillance and provide crucial feedback for future JE vaccine introduction.

➲ ***TARGET:*** Incorporate management of JE programs within divisions of ministries of health that have responsibility for human immunization in all GAVI-eligible countries by 2011.

Strengthen the laboratory component of surveillance

Increase the use of fully validated JE assays—if possible, standardized, commercially available IgM ELISA test kits. Commercial diagnostic kits have an element of quality control and assurance built into their production and utilization, ensuring standardization in different settings. Routine use of these fully validated JE assays has the potential to significantly enhance the volume and reliability of disease burden data collected at the country level. An increased demand for commercial kits would also encourage competition and potentially reduced prices.

➲ ***TARGET:*** All 20 national and subnational laboratories in the JE laboratory networks will use fully validated assays by 2009; all national laboratories in 22 JE-endemic countries will use fully validated assays.

More frequent and reliable laboratory confirmation of JE is crucial to building the evidence base on disease burden. A greater proportion of acute encephalitis syndrome (AES) cases must undergo laboratory testing to improve estimates of laboratory-confirmed JE. As coverage with JE vaccines increases in endemic areas, the proportion of encephalitis cases that are JE should decrease, and it will thus be important to have confirmed etiology of AES to measure vaccine impact.

➲ ***TARGET:*** 50 percent of all sporadic AES cases in endemic countries will have serum or CSF tested for JE by 2009; 60 percent by 2010; 75 percent by 2011; and 90 percent by 2012.

JE case confirmation through evaluation of CSF rather than serum only can help to reduce misdiagnoses due to cross-reactivity in dengue-endemic areas. Additionally, JE vaccination produces an IgM antibody response in serum that is identical to that caused by natural infection with the virus. Therefore, to distinguish true JE disease among AES cases and vaccinations, it will be necessary to test CSF.

➲ ***TARGET:*** 30 percent of all AES cases have CSF collected for testing by 2009; 40 percent by 2010; 60 percent by 2011; and 75 percent by 2012.

The JE laboratory networks have established a strong start in supporting uniform diagnostic standards and protocols, personnel training, quality assurance/quality control (QA/QC), proficiency testing, and accreditation of laboratories. Enhancement and continued support of the networks will ensure high-quality laboratory testing capacity for JE, which will aid surveillance efforts and collection of disease burden data.

➲ ***TARGET:*** Establish an accreditation program by 2010 and have it fully functioning by 2012.

➲ ***TARGET:*** Twenty-two JE-endemic countries (90 percent) are served by fully functional and proficient laboratories [that pass proficiency testing and meet other WHO QA indicators] by 2010; and all JE-endemic countries are served by 2012.

2.4.2 Advance the availability and use of JE vaccines

A market that includes several options for JE vaccine will stimulate price competition and ensure stable supply. In the interim, further data that address long-term immunity and optimal dosing schedules for the SA 14-14-2 vaccine will continue to add to the evidence base and inform a submission to WHO for prequalification and, thus, greater accessibility in developing countries.

Support expansion of the evidence base on the SA 14-14-2 JE vaccine and build product dossier toward WHO prequalification.

The live, attenuated SA 14-14-2 vaccine is currently available internationally, is safe and efficacious, has a simple schedule, is considered affordable by most countries for use in their routine immunization programs, and has a reliable, established supply.

➲ ***TARGET:*** Finalize expert review and recommendations on coadministration of the live, attenuated SA 14-14-2 vaccine with measles vaccine by Q4 2009.

➲ ***TARGET:*** Finalize recommendations on primary schedule for SA 14-14-2 vaccine by Q4 2009.

➲ ***TARGET:*** Finalize recommendations on need for boosters with SA 14-14-2 vaccine by Q4 2011.

Support access to safe and effective new vaccines as they become available

Other JE vaccines are in late-stage development, and their forthcoming inclusion on the international market will be crucial for driving down price and providing additional options for national immunization programs. As noted in section 1.2, several vaccines are undergoing clinical trials aimed at the pediatric populations, and manufacturers plan to seek prequalification within the next few years.

For new JE vaccines, collaboration with manufacturers will ensure that the vaccines are:

- Affordable.
- Appropriate for use in endemic countries (that is, are safe for coadministration with measles vaccine in EPI schedule).
- Available in presentations that support safe injection policies.
- Available with packaging that considers the limitations of cold chain capacity in developing countries.
- Available in an affordable, reliable supply.

➲ ***TARGET:*** Ensure quality management system for each developing country manufacturer by 2011.

➲ ***TARGET:*** One or more JE vaccines will be prequalified by Q4 2011.

➲ ***TARGET:*** All new JE vaccines intended for use in EPI programs in developing countries will have a negotiated price for public-sector use.

2.4.3 Support countries with vaccine introduction

Implement catch-up campaigns

> The most effective immunization strategy in JE-endemic settings is one-time catch-up campaigns including child health weeks or multiantigen campaigns in the locally defined primary target population, followed by incorporation of the JE vaccine into the routine immunization program. This approach has a greater public health impact than either strategy separately.[1]
>
> —World Health Organization, 2006

When introducing JE vaccine into the routine childhood immunization program, a one-time preventive, or catch-up, campaign should also be conducted. This will ensure the maximum reduction of disease. The preventive campaign should cover the at-risk group who would not otherwise receive vaccine through the routine immunization program (that is, children older than those in the routine immunization target population). The at-risk group can be defined by the epidemiology of disease in a specific area, but usually includes children 1 to 15 years old.

If JE vaccine is introduced through the routine childhood immunization program only, it will take up to 15 years to protect most of the at-risk population. A single preventive or mass catch-up campaign helps protect the at-risk population initially, but with the strategy of a catch-up campaign alone, infants born after the campaign would be unprotected. However, when integration into routine immunization is added to the strategy, the complete at-risk population is able to access vaccine and JE can be successfully controlled over the long term.

➲ ***TARGETS:*** Country-specific targets are presented in Annex 4. These targets have been used as the basis for future cost estimations and vaccine demand forecasting.

Where possible, other child health interventions should be provided in parallel with campaigns as well as with routine JE immunization. These other activities could, for example, be an opportunity for a second dose of measles vaccine, a fourth opportunity for diptheria–tetanus–pertussis immunization, vitamin A supplementation, and deworming.

Introduce routine immunization

> With increasing availability of efficacious, safe, and affordable vaccines, JE immunization should be integrated into the EPI programs in all areas where JE constitutes a public health problem.[1]
>
> —World Health Organization, 2006

A challenge for national governments and immunization program managers is to maintain the momentum for routine immunization after a campaign, particularly if the campaign was stimulated by an outbreak. Reaching high routine immunization coverage within a year or two following a campaign will be important to protect children who were too young to be included in the campaign and to sustain protection among the at-risk population.

The activities necessary to introduce a new routine vaccine and achieve high coverage rates are well known by national immunization program managers: obtaining the funding for routine vaccine supplies; training frontline workers to administer the vaccine; ensuring sufficient cold chain capacity; and updating the recording and reporting systems.

➲ ***TARGETS:*** Country-specific targets are presented in Annex 4. These targets have also been used as the basis for future cost estimations and vaccine demand forecasting.

Coordinate monitoring and evaluation post-introduction

A well-functioning surveillance system to monitor and record adverse events following immunization (AEFIs) will allow programs to investigate and appropriately respond to all reported AEFIs, whether they are coincidental, caused by program errors, or caused by the vaccine.

➲ ***TARGET:*** At the time of JE vaccine introduction, each country will have incorporated JE into the AEFI system.

Routine surveillance after introduction of JE vaccine also is essential to monitor the impact of immunization. It also will detect any issues needing follow up; for example, JE cases occurring in new areas or significant numbers of cases occurring in children in an area with a JE immunization program, indicating program concerns.

➲ ***TARGET:*** All 14 GAVI-eligible countries will provide timely and reliable surveillance reports to the WHO–UNICEF Joint Reporting System by 2012.

Implement policy on JE control in outbreak situations

A WHO policy document is currently under development to ensure proper management of JE outbreaks. This document should provide a basis for development of national outbreak control policies.

➲ ***TARGET:*** WHO policy on JE immunization response during an outbreak will be published by 2009.

2.4.4 Improve clinical care of JE patients

Early detection and diagnosis of JE cases, good standards of inpatient care, and appropriate post-discharge management are all important to improve outcomes for JE patients, and thus reduce disease burden.

Improve early detection and diagnosis of JE

Early detection and diagnosis require appropriate samples to be taken, including CSF collected by lumbar puncture. Sample collection is vitally important, not only for JE diagnosis, but for recognition of potentially treatable central nervous system (CNS) infections, such as bacterial meningitis.

➲ ***TARGET:*** All hospitals that receive and manage patients with CNS infections will be able to perform a lumbar puncture and have facilities for basic evaluation of CSF by 2013.

Promote better care

The accessibility of clinical care guidelines must be improved through publication on the WHO website.[51] Additionally, strategies for implementing the guidelines and determining their impact should be developed. Furthermore, hospital physicians should be trained how to assess, investigate, and manage children with suspected CNS infections, including JE.

➲ ***TARGET:*** Clinical care guidelines will be posted on the WHO website by 2009.

➲ ***TARGET:*** National guidelines that reflect best practice management of encephalitis will be available in 7 of 14 GAVI-eligible countries by 2011, and in all by 2013.

Improve follow-up and management of sequelae

Patient outcomes at hospital discharge and at follow-up should be assessed properly to inform estimates of disease burden and ensure the best outcome for the individual patient, including minimizing the handicaps caused by disability.

➲ ***TARGET:*** All patients will be assessed at least once at three to six months after discharge, and then regularly as needed, by 2012.

2.4.5 Support research

Research activities are needed that are relevant to developing countries, feasible and affordable for implementation, and that will result in improved control of JE. Objectives for such research include improved diagnosis and management of JE patients and improved ease and safety of immunization.

Evaluate and improve JE diagnostics

New diagnostic options are needed to improve sensitivity and reduce cross-reactivity.

➲ ***TARGET:*** At least one commercial diagnostic kit with both sensitivity and specificity > 85 percent will be available by 2012.

In addition to commercialization of diagnostic kits, research also should evaluate new methodologies to improve access to and feasibility of sample testing where laboratory capacity is limited.

➲ ***TARGET:*** Sufficient data will exist to determine feasibility of use of filter paper for sample testing and confirmatory testing by 2010; evaluations/field trials for use of dried blood and dried serum/CSF completed by 2011.

Evaluate and improve clinical management

Various interventions to improve clinical management and outcomes for JE patients should be studied to determine the most appropriate, feasible, and impactful approaches.

➲ ***TARGET:*** Data from intervention trials will be reviewed and any positive findings (interventions that can improve outcome) are disseminated annually and are accessible in JE-endemic countries.

Explore options for JE combination vaccines

The development of a measles-JE, measles-JE-rubella, or other relevant combination vaccine could improve feasibility of administration of multiple antigens with fewer needles and enhance routine immunization service delivery in general.

➲ ***TARGET:*** Combination vaccine will be developed by 2015.

Track country progress in meeting JE control target

During the period between 2009 and 2011, efforts will be needed to develop a method for verifying whether countries or states have reached the agreed-upon control target. The strategy developed and used for verifying the elimination of neonatal tetanus may provide a useful model on which to build.

➲ ***TARGET:*** Methodology will be developed for verifying whether control target has been reached, tested in at least one country, and modified as needed by the end of 2011.

2.4.6 Expand outreach through communications and advocacy

Awareness of JE and successful introduction experiences are crucial to maintaining momentum toward global JE control. Importantly, the 2006 WHO position paper on JE vaccines noted that "The need for increased regional and national awareness of JE and for international support to control this disease is urgent."[1]

Continued advocacy at global and regional levels is necessary to maintain attention to and funding for support of activities up to and following JE vaccine introduction.

➲ ***TARGET:*** JE will be on the agenda of at least three international and regional conferences each year, with number of presentations increasing annually by 2011.

Sharing successes of new programs and remaining needs with funders, decision-makers, and audiences at state, district, and clinic levels will ensure sustainability of national immunization programs.

➲ ***TARGET:*** Information will be disseminated through global means, such as WHO's *Global Immunization Newsletter* and similar publications, at least three times each year to ensure JE control remains a high priority among all national stakeholders and beneficiaries.

Technical information should be shared at all levels to ensure appropriate decision-making and application of lessons learned.

➲ ***TARGET:*** At least three articles will be published annually in peer-reviewed journals. Already achieved but should continue each year until at least 2015.

Consistent messaging about JE disease burden, surveillance activities, and introduction will allow for dissemination of accurate information and appropriate awareness-building.

➲ ***TARGET:*** Publications, such as the WHO position paper, are updated as needed, and new information is disseminated annually so national partners are equipped to answer questions from a variety of audiences—including media—and are prepared to respond appropriately to crisis communications situations.

The JE coalition is an essential element for building consensus about partner roles and responsibilities, mechanisms for future funding, and a detailed action plan for the next two years.

➲ ***TARGET:*** Coalition will be established by the end of 2009.

2.5 Opportunities

Significant momentum toward JE control has been generated in recent years. Individual countries have made substantial progress and it is vital this momentum is not lost. Both India and Nepal, for example, recently introduced JE immunization campaigns and are establishing routine immunization programs; the national government in China decided to provide funding for a national JE immunization program; and Indonesia and Cambodia have gathered data establishing disease burden—as a result, Cambodia is planning a national immunization program. Such country achievements can act as stimulus for other countries.

Secondly, and sadly, the "opportunity" provided by an outbreak can be a powerful stimulus for increasing management support and funding for introducing JE vaccine. JE is a disease that is known and feared by the public in countries where regular outbreaks occur, and they and the press can stimulate health officials to call for mass vaccination campaigns.

2.6 Financial resource requirements, 2009–2015

Current and future funding

Many organizations have contributed efforts and funds over the past five to seven years toward JE control. These organizations are listed in Annex 2A and, where known, the extent of their funding support is included.

Annex 2B presents details of an estimate of the future funding needed to implement this control plan in the 14 GAVI-eligible countries that are JE-endemic, or believed to be endemic. In summary, a total of US$338 million will be needed between 2009 and 2015.

This total breaks down as follows:

Routine vaccine costs	6%
Routine immunization start-up costs	16%
Campaign vaccine costs	6%
Campaign operations	22%
Surveillance and laboratory costs	35%
Technical assistance	15%

Conclusion

Over the past several years, achievements at national and global levels have generated significant momentum toward JE control, spurred by improved and expanded surveillance in endemic countries; increased availability of a safe, effective, and affordable vaccine; the development of new candidate JE vaccines; and the successful introduction of JE immunization programs efforts in several countries.

Global partners need to build on this momentum and ensure that this progress represents a sustainable shift in addressing this often-neglected disease. With clear roles and responsibilities defined, committed partnerships leading the charge, and international donors engaged, JE can be controlled, relieving the economic burden on national health systems and protecting vulnerable children and families in communities at greatest risk.

Annex 1. Role of partners

This annex describes, in the organizations' own words, what each believes it can best contribute to JE control by 2015.

World Health Organization: Geneva, SEAR, and WPR

WHO–Geneva and the SEAR and WPR offices in JE-endemic areas undertake technical assistance in controlling a variety of endemic diseases, including JE. The headquarters office in Geneva provides leadership on multiple fronts, and fosters a wide array of partnerships that confront organizational, technical, and policy issues facing JE-endemic countries. Each regional office works semi-autonomously to engage the governments of its respective member states in cooperative efforts to advance surveillance and control of JE.

As an indicator of its objective (or "Expected Result") to support evidence-based recommendations and policies for optimal use of vaccines, the WHO Immunization, Vaccines and Biologicals strategic plan for 2005 to 2009[52] includes JE vaccines.

Indicator	Status 2005	Target for end 2007	Target for end 2009
Number of new vaccines (particularly, pneumococcal, meningococcal A, Japanese encephalitis, rotavirus, human papilloma virus [HPV]) for which evidence has been generated on the appropriateness for introduction into immunization programs	0 of 5	2 of 5[53]	5 of 5

The plan goes on to outline specific activities toward achieving this objective: "Activities in this Expected Result will include, among others, researching appropriate strategies for vaccine introduction and evaluating improved immunization schedules, regimen and delivery methods. This research will focus on the means of increasing coverage of newly introduced vaccines among the poorest segments of the population. Other activities within this Expected Result include modelling of disease burden and vaccine impact, as well as researching the cost-effectiveness of preventive interventions to allow prioritization of new vaccines in national immunization strategies."[52]

UNICEF: Copenhagen, East Asia and Pacific Regional Office, New York, and Regional Office for South Asia

UNICEF partners with national governments to ensure children's rights for access to health care, education, and protection. UNICEF's priority in the health sector is to help countries achieve the health-related Millennium Development Goals. Immunization is one of the key interventions for Millennium Development Goal 4: reducing deaths of children under five years of age. UNICEF has extensive experience supporting countries in adding new vaccines that can prevent child deaths, and also provides technical and financial assistance to strengthen routine immunization systems, facilitate program operations, and implement supplementary immunization activities.

In coordination with relevant national stakeholders, UNICEF has a role in helping countries evaluate the potential use and benefit of new vaccines compared to other health interventions and, subsequently, to facilitate the planning, implementation, and monitoring of new vaccine introduction. When a prequalified JE vaccine becomes available, UNICEF will be able to procure it on behalf of countries and in response to country requests. In addition, the future demand for JE vaccines can be included in the annual vaccine demand exercise undertaken by UNICEF as well as more strategic forecasts undertaken with WHO.

UNICEF can further assist countries with new vaccine introduction through assistance in the areas of capacity-building, communication/social mobilization, preparing and strengthening the cold chain and logistics systems, and monitoring coverage to ensure vaccine access among populations that are hard to reach—especially those at increased risk of infection.

The GAVI Alliance

In November 2008, the GAVI Alliance board agreed that fundraising for four new vaccines,[54] including JE vaccine, could begin when the board members are confident that the funds can be raised in the current uncertain financial climate. This decision is anticipated in 2009. Furthermore, the GAVI Alliance opened a new funding "window" in early 2008 for joint action by governments and civil society organizations. This new funding source might also be used for JE immunization and control.

Bilateral partners

JICA, USAID, AusAID, KOICA

Bilateral partners have played a vital role in achievements toward JE control and will remain fundamentally important for future efforts. A close partnership between these agencies' national governments is necessary to ensure that support provided—be it technical assistance, funding, or supplies—is used appropriately and transparently.

Vaccine manufacturers

BIKEN (Japan)

BIKEN has discontinued bulk production of the inactivated, mouse brain–derived JE vaccine but continued to distribute the remaining supply of vaccine in 2008. BIKEN anticipates licensure of a Vero cell–derived JE vaccine during 2009, with expected availability for use in Japanese children during the same year. Plans exist for supplying this vaccine in other JE-endemic countries beyond Japan.

Chengdu Institute of Biological Products (China)

CDIBP is working toward WHO prequalification of their SA 14-14-2 JE vaccine, to be able to guarantee an affordable and large-scale supply of vaccine to endemic areas for JE control. CDIBP will ensure close cooperation with the MOH of each JE-endemic country and help with advocacy and immunization plans. CDIBP will also work on measles-JE, rubella-JE, and other JE-based combined vaccines to make JE vaccine more easily integrated into routine immunization programs. CDIBP intends to comply with international standards and references for manufacturing.

Intercell (Austria)/Novartis (Switzerland)/Biological E. (India)

IC51, an inactivated JE vaccine using the SA-14-14-2 strain has been developed by Intercell mainly as a traveler's vaccine for the Australia/European Union/US market. It received regulatory approval in Australia, Europe, and the United States in early 2009. In order to make this vaccine accessible to low- and middle-income countries, Intercell entered into collaboration with Biological E. to develop the vaccine for both pediatric and adult use in endemic populations. The vaccine has completed both adult and pediatric Phase 2 trials, and WHO prequalification is expected in 2011. Both Biological E. and Novartis have a long history of supporting public-sector immunization and are committed to making this vaccine available.

Kaketsuken (Japan)

Kaketsuken is developing a Vero cell–derived JE vaccine with licensure for use in children expected by 2011. Kaketsuken is interested in making the vaccine available outside Japan.

Sanofi Pasteur/Acambis (France)

Sanofi Pasteur's long-term intent regarding JE vaccine is to develop a single-dose, live, recombinant JE vaccine (in collaboration with Acambis), and to license and commercialize this vaccine in JE-endemic countries (including lower- and middle-income countries), with both adult and pediatric indications.

Civil society organizations

Civil society organizations are an underused resource for JE control. Examples of civil society organizations that could potentially partner with the JE coalition are listed below.

International Pediatric Association

The International Pediatric Association (IPA) has member organizations in all JE-endemic countries. The pediatricians in these countries can be hugely influential in policymaking through partnerships with both government and private-sector health services. The IPA can work with its country member organizations, supporting various efforts by:

- Encouraging national pediatric associations to include JE in conferences or meetings, or hold national and local workshops to ensure that all members are fully informed about JE and the latest developments.
- Distributing JE information.
- Advertising available JE resources.
- Encouraging reporting of encephalitis/JE cases.
- Serving as national advocates for JE control though immunization.

In-country civil society organizations

In-country civil society organizations in many JE-endemic countries have the potential to be supportive for the long-term work needed for rehabilitation of the many thousands of people living with disabilities following JE infection. Furthermore, many indigenous civil society organizations can be valuable in preparing and managing JE vaccination campaigns and can provide support for other interventions given during the same patient contact.

- National medical associations can have a significant role in policy discussion, through technical assistance on medical practice, disease reporting, and educating the parents of young children to have their children better immunized in the second year of life.
- National nursing associations are particularly valuable since their members typically provide most of the immunizations given in both public and private health sectors.

Academic/research institutions

Armed Forces Research Institute of Medical Sciences

In association with international partners based in Cambodia and Indonesia, research at the US Naval Medical Research Unit at the Armed Forces Research Institute of Medical Sciences (AFRIMS) has helped to bring about the licensing of two new vaccines against viral diseases. JE and hepatitis A vaccines were approved by the US Food and Drug Administration following successful large-scale efficacy field trials involving upwards of 60,000 volunteers in Kamphaeng

Phet Province, Thailand. Work continues on the development and testing of vaccines to prevent dengue and hepatitis E, and to evaluate second generation JE vaccines that are safer and less expensive. AFRIMS is also working on JE surveillance in Manila and Cebu, Philippines.

AFRIMS utilizes modern molecular biology tools for the rapid detection of viruses that cause epidemics of hemorrhagic fever, hepatitis, and encephalitis throughout Asia, including polymerase chain reaction and western blotting.

AFRIMS developed and evaluated diagnostic assays for dengue, JE, and chikungunya viruses. These assays are used to characterize human immune responses to flavivirus infections as well as the epidemiology of flaviviruses in the human population and the potential use of a vaccine to prevent disease. Given this breadth of experience, AFRIMS will be an important partner in future efforts toward JE control.

International Vaccine Institute

The International Vaccine Institute (IVI) works on implementation and evaluation of JE vaccination campaigns in Indonesia and North Korea (both with live, attenuated SA 14-14-2 vaccine), and in Vietnam (with the inactivated, mouse brain–derived vaccine). In Indonesia and Vietnam, vaccine safety and effectiveness are being evaluated; in North Korea, acceptability and feasibility of vaccination are being assessed. IVI also works on surveillance of JE in Bangladesh, Indonesia, and Vietnam, and on interaction between dengue and JE immunization in Indonesia. These activities could continue to inform JE control, while developing into further contributions to the JE coalition.

Oxford University Clinical Research Unit, Ho Chi Minh City

The Hospital for Tropical Diseases and the Oxford University Clinical Research Unit are based in Ho Chi Minh City in Vietnam. The research collaboration began in 1991 focusing on—among other topics—infections of the CNS (viral encephalitis as well as pyogenic and tuberculous meningitis) with a particular interest in the interface between human and animal health.

The program conducts activities throughout Vietnam, with major centers in Ho Chi Minh City, Hanoi, and more than 20 provinces at commune, district and province levels. There also are active collaborations in Cambodia, China, Indonesia, Malaysia, Nepal, the Philippines, and several countries of Latin America.

More than 50 percent of children admitted to the Hospital for Tropical Diseases with ME have JE virus infection, and approximately 20 percent of these patients die acutely. Many survivors exhibit complex sequelae, although little information is available about specific patterns of neurological involvement, underlying mechanisms, or prognosis.

Upcoming plans include:

- Clinical and imaging studies with long-term follow up.
- Role of CNS receptors/transmitters and autoantibodies in disease.
- Role of preexisting immunity to other flaviviruses and disease.
- Epidemiology, mapping, and biology of the vectors of JE in Vietnam.
- Further independent studies on safety of JE vaccines.

United States CDC

The US CDC provides technical and financial assistance to countries and partner organizations for a variety of public health issues. US CDC participates in strategy development, consensus-building, preparation of plans of action, and the implementation and evaluation of measles control activities. Support is provided for the investigation of epidemics and the development and monitoring of surveillance systems, including laboratory networks. US CDC also assists with the implementation of supplementary immunization activities and provides long-term staff at country, regional, and global levels. An additional role for US CDC in efforts moving forward would be to identify and address specific research questions needed to improve JE surveillance and prevention efforts.

University of Liverpool

The University of Liverpool's Viral Brain Infections Group studies viral CNS/brain infections of major global significance, especially those that are important in the developing world. The group works in close partnership with academic institutions in Asia and Africa. Research areas range from epidemiological, diagnostic, and clinical studies to molecular virological and pathogenesis studies. This breadth gives the group the ability to view the needs of JE control as a whole, which is also important to advocacy efforts.

The freedom and flexibility inherent in an academic environment allows the group to focus on specific key questions that are important to advance the overall JE control agenda, and they have been instrumental in several activities to date. Examples of the group's contributions include a major role in the development of WHO JE clinical care guidelines and surveillance standards, as well as producing tools and manuals for assessing and managing disability.

Future activities could include establishing reference and QC mechanisms, preparing WHO surveillance standards for ME, and demonstrating how JE management might be implemented in a research setting.

Universiti Malaysia Sarawak, Kota Samarahan, Malaysia

Located on the island of Borneo, Universiti Malaysia Sarawak's virology group at the Institute of Health and Community Medicine investigates viral infections of the CNS, including JE. The group works closely with the Ministry of Health in Sarawak to provide laboratory support for surveillance of CNS infections throughout the state, and is thus able to provide data about important etiologies, epidemiology, and molecular evolution of important causative agents. In this way, the group ensures that etiological diagnoses are made and most cases of JE are identified, with no cases associated with non-JE etiologies mistakenly classified as JE. This is important in evaluating the effectiveness of control programs, including vaccine introduction.

Work done by this group provided the evidence base for the Malaysian Ministry of Health to implement introduction of JE vaccine in Sarawak. An IgM ELISA that distinguishes JE from dengue, a co-circulating flavivirus, is available to the group, with reagents and kits produced by Venture Technologies Sdn Bhd, a Malaysian company based in Penang. The group also collaborates with pediatricians in local hospitals, particularly Sibu Hospital in the interior of the state, where prospective clinical studies are conducted and important questions about pathogenesis can be addressed. Currently studies are under way to develop a simpler diagnostic test for JE, which can be used in peripheral hospitals and clinics.

Annex 2. Cost implications

Part A of this annex presents data on investments in JE control from various partners between 2000 and 2008 and includes, where known, how much money has been invested to support activities in evaluating JE morbidity and mortality.

Part B estimates future costs of continuing efforts to control JE in both GAVI-eligible and non-GAVI-eligible countries.

A. Funding, 2000–2008

Bill & Melinda Gates Foundation

PATH Children's Vaccine Program: JE control activities in Andhra Pradesh, India; general JE control activities. US$2.9 million, 2000 to 2007.

PATH JE project: Assistance to national policymakers for decision-making on JE control; generation and dissemination of data and other information on the JE disease burden and control. US$19.5 million (estimated), 2004 to 2008.

Wellcome Trust

University of Liverpool: Researching the role of the JE virus in neurological paralysis in Vietnam.[55]

KOICA

IVI: Implementation and evaluation of JE immunization in Indonesia, the Democratic People's Republic of Korea, and Vietnam.

USAID

Nepal: Environmental Health Project, a four- to five-year project of surveillance, operational research, and laboratory support, with some cross-border components in Bangladesh, Bhutan, and India; focused on developing a common approach to JE diagnostics (syndromic and laboratory-based) with a view to enhancing surveillance, management, and control.

JICA

China: JE control support in two provinces; laboratory capacity-building at provincial and prefecture levels in the provinces of Sichuan and Jiangxi.

United States government

US CDC: Global Disease Detection innovative projects focused on determining etiologies of meningitis and encephalitis and strengthening laboratory support for diagnosis in Bangladesh, China, and India. US$1.9 million each year, 2006–2008.

AFRIMS: Support for development of laboratory capacity for JE diagnosis in Nepal.

Asian Development Bank

Vietnam: Support for JE immunization program as part of a communicable disease control grant.

WHO

WHO–Geneva: Production and publication of the JE surveillance standards and a JE laboratory manual. Support of regional surveillance training workshops and follow-up visits to ensure effective implementation of the standardized JE confirmatory testing and reporting procedures. Communication and coordination among partners preparing policy recommendations in support of JE vaccines. Establishment of the JE Laboratory Network Working Group and reference laboratories.

WHO–SEARO: Promotion of the newly published surveillance standards among JE-endemic countries developing or strengthening their JE surveillance. Finalization of JE operations guide for JE vaccine introduction.[33] National JE surveillance workshops and technical support to Nepal and Bangladesh. Assistance with establishment and development of JE diagnostics within country laboratories and regional reference labs through training workshops, supply of diagnostic kits, reagents, and equipment and use of standardized diagnostics protocol.

WHO–WPRO: Support of Cambodia's sentinel surveillance system; strengthening of China's national- and provincial-level laboratory network; establishment of sentinel surveillance in Lao PDR; national catch-up campaign workshops in Vietnam; assistance with advocacy in Malaysia, Philippines, and Papua New Guinea.

B. Funding, 2009–2015

The following two tables present an assessment of the funding needs for all 25 countries in the JE-endemic zone to achieve JE control by 2015, with a control target defined as fewer than 0.5 confirmed JE cases per 100,000 children under the age of 15 years.

These estimates are meant to provide a general guide on the level of funding needed, and several assumptions were made (see table notes). These funding estimates are based on introduction of the SA 14-14-2 JE vaccine only, but with availability of new JE vaccines in coming years, a growing commercial market would call for updated estimates as information on price and dosing schedules becomes available.

TABLE 1. **Estimated total resource requirements for introducing and scaling up JE immunization programs in GAVI-eligible countries, 2009–2015 (in millions US$)***

Activity	2009	2010	2011	2012	2013	2014	2015	TOTAL
Vaccine cost, campaign	5	10	15	19	22	23	5	99
Campaign operations	8	16	21	25	26	25	5	126
Vaccine cost, routine	1	3	5	5	7	10	12	43
Routine operations	1	4	5	5	6	8	8	37
Surveillance and laboratory	1	2	3	4	4	4	2	20
Technical assistance	1	1	2	2	3	3	1	13
TOTAL	**17**	**36**	**51**	**60**	**68**	**73**	**33**	**338**

ASSUMPTIONS

Geographic area: High-risk target areas in 14 GAVI-eligible countries classified into early (India, Nepal, Sri Lanka), middle (Bangladesh, Cambodia, Democratic People's Republic of Korea, Indonesia, Papua New Guinea, Timor Leste, Vietnam), and late adopters (Bhutan, Lao PDR, Myanmar, Pakistan), based on information on burden of disease, comprehensive Multi-Year Plans, and country experience in introducing other vaccines.

Immunization strategy: Catch-up campaign in children 1 to 15 years old, followed by routine in 9-month-old children (coadministration with measles).

Vaccine: Single-dose, live, attenuated SA 14-14-2 JE vaccine.

Vaccine price: US$0.17 with adjustment for change in exchange rate and inflation over the 7-year period; local distributor fees, applicable government taxes, or other related costs and charges (such as freight, transportation, etc.).

Vaccine wastage: 10% campaign, 25% routine.

Syringe wastage: 10%; safety box wastage, 30%.

Operational costs: Range from US$0.20 to US$0.30 per child administered.

Surveillance and laboratory: Assumed to be 6% of total cost.

Technical assistance: Assumed to be 4% of total cost.

* A varying proportion of these funds will be sought from external donors depending on the needs of the individual country.

In addition to applying the assumptions applied to GAVI-eligible countries, estimates of vaccine introduction timelines for non-GAVI-eligible countries are speculative and based on level of disease burden awareness and capacity of existing immunization systems.

TABLE 2. **Estimated total resource requirements for introducing and scaling up JE immunization programs in non-GAVI-eligible countries, 2009–2015 (in millions US$)***

Activity	2009	2010	2011	2012	2013	2014	2015	TOTAL
Vaccine cost (including wastage factor and safety boxes)	80	91	91	78	82	87	93	602
Operational cost	168	540	205	196	200	204	210	1,723
Surveillance and laboratory	17	42	20	18	19	19	20	155
Technical assistance	11	28	13	12	13	13	13	103
TOTAL	**276**	**701**	**329**	**304**	**314**	**323**	**336**	**2,583**

ASSUMPTIONS

Geographic area: Non-GAVI eligible countries consisting of Australia (Torres Strait Islands), Brunei Darussalam, China, Japan, Republic of Korea, Malaysia, Philippines, Thailand. Singapore and southeast Russian Federation not included, as JE incidence below control target and immunization program not required.

Vaccine strategy: Routine immunization program except in Malaysia and Philippines (routine plus campaign in 1- to 10-year-olds and 1- to 15-year-olds in Malaysia and Philippines, respectively).

Vaccine: Mouse brain–derived; Intercell's inactivated; and live, attenuated SA 14-14-2 JE vaccines.

Vaccine price: Ranges from US$0.30 to US$50, depending on pricing schedule of vaccine manufacturer.

Vaccine wastage: 10% campaign, 20% routine.

Syringe wastage: 10%; safety box wastage, 30%.

Operational cost: US$5 per child administered.

Surveillance and laboratory: Assumed to be 6% of total cost.

Technical assistance: Assumed to be 4% of total cost.

* Probably only a small proportion of these funds will need to be sought from external donors.

Annex 3. Strategic milestones

By the end of 2009:

A JE control plan and a JE coalition is established to agree on roles and responsibilities of the partners, mechanisms for future funding, and a detailed action plan for the following two years.

By the end of 2010:

Seven of 14 GAVI-eligible countries report JE cases in a timely manner.

All 14 GAVI-eligible countries provide timely and reliable surveillance reports to the WHO-UNICEF Joint Reporting System.

By the end of 2011:

Eleven of 22 JE-endemic counties have started routine JE immunization.

By the end of 2012:

All hospitalized JE patients are assessed at least once at three to six months after discharge, and then regularly as needed.

By the end of 2013:

New vaccines are available for the pediatric market in JE-endemic countries.

By the end of 2014:

Twenty-one of 22 JE-endemic countries have started routine JE immunization.

By the end of 2015:

JE incidence in all of Asia is certified at less than 0.5 cases per 100,000 children under 15 years of age.

Annex 4. Status and estimated future vaccine implementation, 2006–2015

Country† (Countries listed in bold already use JE vaccine)	**GAVI-eligible as of 2009?**	**WHO Region**	**Population under 15 years of age (%), 2006‡**	**National measles vaccine coverage (%), 2006***	**Immunization strategy: Campaign (C) and/or Routine (R)**										
					2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Australia (Torres Strait Islands)	No	WPR	-	94	R	R	R	R	R	R	R	R	R	R	R
Bangladesh	Yes	SEAR	35	81							CR	CR	CR	R	R
Bhutan	Yes	SEAR	32	90											R
Brunei Darussalam	No	WPR	29	97							R	R	R	R	R
Cambodia	Yes	WPR	37	78						R	R	R	R	R	R
China	No	WPR	21	93	R	R	R	R	R	R	R	R	R	R	R
India	Yes	SEAR	33	59		C	C	C	CR	CR	R	R	R	R	R
Indonesia	Yes	SEAR	28	72						CR	CR	R	R	R	R
Japan	No	WPR	14	99	R	**	**	**	R	R	R	R	R	R	R
Korea, DPR	Yes	SEAR	24	96							R	R	R	R	R
Korea, Republic of	No	WPR	18	99	R	R	R	R	R	R	R	R	R	R	R
Lao PDR	Yes	WPR	39	48								CR	R	R	R
Malaysia	No	SEAR	31	90							R	R	R	R	R
Myanmar	Yes	SEAR	27	78									CR	R	R
Nepal	Yes	SEAR	38	85	C	C	***	CR	R	R	R	R	R	R	R
Pakistan	Yes	EMR	36	80								CR	CR	R	R
Papua New Guinea	Yes	WPR	40	65								CR	CR	R	R
Philippines	No	WPR	36	92							CR	R	R	R	R
Sri Lanka	Yes	SEAR	24	99	R	R	R	R	R	R	R	R	R	R	R
Thailand	No	SEAR	21	96	R	R	R	R	R	R	R	R	R	R	R
Timor Leste	Yes	SEAR	45	64							CR	R	R	R	R
Vietnam	Yes	WPR	29	93	R	R	R	R	R	R	R	R	R	R	R

* WHO–UNICEF Joint Reporting System, December 2007.

** JE immunization suspended until new Vero–cell vaccine comes available (estimated 2009).

***Campaigns cancelled due to lack of WHO-prequalified vaccine.

† Excluding: Singapore—JE incidence below control level and immunization not required; Russian Federation—JE incidence presumed to be below control level.

‡ WHO Statistical Information website. Available at: www.who.int/whosis/en/.

Notes: JE routine vaccine coverage rate assumed to be similar to national measles vaccine coverage rates from 2006.
Table does not include reference to Chinese Taiwan.

Annex 5. Status of JE disease and control plans in endemic countries

This section gives details on the current status of JE control and future plans for 25 endemic countries or regions.

The purpose of this list is to document the existing level of knowledge on disease burden and status of surveillance and activities to control JE as of 2008, in order to to provide a baseline from which national MOHs will develop future plans.

Australia (Torres Strait Islands)

Human cases of JE were recorded for the first time in 1995 when three cases occurred on Badu Island in the Torres Strait.[56] Serologic surveys subsequently found widespread evidence of JE virus activity in the outer Torres Strait Islands.[56] In 1998, the first case of JE on the Australian mainland occurred. A further case occurred on Badu Island the same year. No further cases have occurred, although virus incursions during the wet season are likely an annual occurrence as far south as the central islands of the Torres Strait.

Surveillance		JE immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Case-based surveillance. Pig surveillance to detect any spread to the Australian mainland.	As previous.	JE vaccination integrated into the routine immunization schedule for residents of outer Torres Strait Islands, commencing at one year of age.	Transition from mouse brain–derived vaccine when new vaccine is available in Australia.	None.	None.

Bangladesh

JE disease was first documented in 1977 in Bangladesh during an outbreak of neurological disease.[57] In 2003, a study was initiated in three hospitals to characterize the causes of viral encephalitis. Among 266 patients enrolled, six percent (16/266) demonstrated JE infection.[58] A further hospital-based ME surveillance study commenced in mid-2007.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Sentinel surveillance at three hospitals (in collaboration with CDC, WHO). In 2008, IVI initiated three new surveillance sites: in Dhaka, the north, and the south.		None.		Disease burden data.	

Bhutan

There are currently no available data regarding JE disease burden in Bhutan, but future support from WHO–SEAR and AFRIMS may soon allow for initiation of JE surveillance in the country.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
None.	Proposal to establish surveillance at one hospital in 2009, with support provided by WHO–SEAR. AFRIMS due to start influenza surveillance that could simultaneously include JE surveillance.	None.		Disease burden data.	

Brunei Darussalam

The MOH reports no lab-confirmed cases of JE for the past five years. However, a limitation is that specimens must be sent internationally for testing. The US CDC notes that JE is presumed to be sporadic-endemic in Brunei Darussalam, as in Malaysia, with presumed year-round transmission.[59]

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Encephalitis is a notifiable disease; JE in particular is not. Passive syndromic surveillance is used, augmented by a passive laboratory-based surveillance system.	Possible introduction of JE diagnostic testing locally.	None.			

Cambodia

A series of research studies over about 15 years has identified JE as an important public health problem in Cambodia, with an estimated 1,000 cases occurring annually. A study on the causes of encephalitis at Takeo Provincial Hospital found 31 percent of pediatric cases had serological evidence of JE infection.[60] Likewise, a study from 1996 to 1998 at the National Pediatric Hospital in Phnom Penh showed 18 percent of children with encephalitis had serological evidence of JE infection.[61]

Nationwide ME surveillance is conducted, involving reporting of all clinical cases of ME from provincial and district hospitals. In 2006, sentinel site surveillance for JE, with laboratory confirmation of cases, was implemented at six sites, linked with the ME surveillance system.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
National ME syndromic surveillance; JE surveillance at six sentinel sites.	Strengthen ME and JE surveillance (completeness of reporting, laboratory QC program).	None.	Campaign in select provinces among 1- to 10-year-olds (2009). Routine EPI introduction (2010).	Vaccine prequalification or licensure required.	Need national budget provision and donor support.

China

JE immunization began in selected provinces in the 1970s and the national JE incidence rate has declined dramatically since, from 10 to 20 cases per 100,000 in the 1960s and 1970s to the current rate of about 0.6 to 0.8 cases per 100,000.[62] Some high-risk JE provinces have previously not provided JE vaccine to older age groups. According to correspondence from Dr. Xiaogeng Liang of the National Immunization Program of China (April 2008), the top priority for the future for JE control immunization is therefore to increase the coverage of JE vaccine in older children in southwestern provinces.

In 2008, China expanded JE immunization nationally. JE vaccines for the national immunization program are produced in China. Currently both a Vero cell, inactivated vaccine based on the Beijing P-3 virus strain and a cell culture–derived, live, attenuated vaccine based on the SA 14-14-2 virus strain are in use.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
National, electronic AES and JE reporting; special surveillance projects in some provinces. CDC: Sentinel surveillance for AES in four provinces with laboratory confirmation, started in 2006. PATH: AES surveillance project in one province, 2005–2007. Lab confirmation in ~half of cases; diagnostics in 13 provinces.	Improve case-based surveillance. CDC: Plan to expand sentinel surveillance to three additional sites in 1–2 years. Quality control program. Expand diagnostics.	Nationwide immunization through EPI. Various vaccines used, determined at provincial level.	Improve coverage. Improve monitoring AEFI surveillance. Catch-up campaigns for older children in southwestern provinces.		National-level funding is secured. Funding to expand diagnostic testing required.

Chinese Taiwan

Immunization against JE was introduced in Chinese Taiwan in 1968. JE has been well-controlled, and since 1985, the number of confirmed JE cases has been 35 or fewer per year. Cases occur sporadically across the country. The average age of onset has increased since immunization was introduced, with higher incidence rates commonly occurring in the 40- to 50-year-old age group.[41]

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Active surveillance.		National immunization program with mouse brain–derived vaccine.	Awaiting more effective and convenient vaccine.		

India

Cases have been reported from almost all states in the country. In 2006, the Government of India initiated a five-year strategy (2006 to 2011) of JE vaccination campaigns to immunize children and adolescents between 1 and 15 years of age in high-risk districts, followed by introduction of JE vaccine into the routine immunization program.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	**Planned**	**Current**	**Planned**		
Passive JE surveillance since 1978 with limited lab confirmation. AES surveillance initiated in 2007. 50 sentinel labs identified in JE-endemic districts and 12 labs for advanced diagnosis. CDC: AES surveillance with lab confirmation for JE at two sentinel sites in 2007.	Strengthen AES surveillance. Build capacity for case management and rapid response to outbreaks. Develop sentinel labs.	JE vaccine (SA 14-14-2) introduced in 2006 in high-risk districts. By 2009 will cover 105 districts throughout the country. Strategy of campaigns and integration into routine immunization program. Acambis/Sanofi Pasteur pediatric vaccine trial under way.	Continue program expansion through 2011. Strengthen AEFI monitoring. Consider new JE vaccines as they are developed.	Information from AES data to guide decision-making. Data from ongoing studies (safety, immunogenicity, adult viremia, vaccine effectiveness).	Funded by national government. JE vaccination included in five-year plan.

Indonesia

Recent surveillance work has shown JE is an endemic disease across Indonesia.[63] A recent study in Bali, considered high-risk for JE virus transmission, showed that for children under the age of ten the annual incidence rate was 7.1 per 100,000.[64]

Surveillance		Immunization		Decision-making needs	Financial issues
Current	**Planned**	**Current**	**Planned**		
Encephalitis is one of 39 diseases under surveillance. JE surveillance conducted at select sentinel sites.	Strengthen surveillance. Revise guidelines for surveillance. Implement QA and monitoring system.	None.	Immunization pilot program in Bali on hold (SA 14-14-2 vaccine). Surveillance data and political and financial issues will guide plans for further introduction.	Information needed for advocacy purposes as JE not currently perceived as a public health problem.	Vaccine is affordable for routine immunization but external funding required for campaigns.

Japan

Mouse brain–derived JE vaccine was first licensed in Japan in 1954, and JE rates rapidly decreased after an improved vaccine became available and more widely used in 1967. Japan now reports fewer than ten cases per year. In 2001, researchers tested 1,765 serum samples to determine the natural rate of JE infection and to answer the question of whether universal vaccination should still be recommended. The overall prevalence of NS1 antibodies (a marker for natural infection) was 4.4 percent, and annual infection rates for subjects aged 6 months to 69 years in eight prefectures ranged from 0.2 to 3.4 percent.[65]

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
JE surveillance with lab confirmation. Estimated 50% of all cases reported. No formal AES case definition. Pig surveillance.	Mandatory human JE case reporting. Continued pig surveillance.	Vaccination introduced in 1954. Universal vaccination since 1995. In 2007, MOH recommended optional vaccination depending on local risk, based on pig surveillance data.	Reinstate national recommendation for immunization and switch to Vero cell–derived vaccine when available (2008–2009).	Awaiting clinical trial results from new Vero cell–derived vaccine being developed in Japan.	Funded by national government.

Korea, Democratic People's Republic of

JE is endemic and JE vaccine is provided to children in some high-risk areas. Three thousand children were immunized in 2008 using SA 14-14-2 JE vaccine in a one-day pilot project campaign to study the feasibility of JE immunization campaigns.[66]

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
None.	JE integration into regular surveillance is expected.	JE vaccine (locally-produced) in some high-risk areas.	Decision on introduction of new JE vaccine determined by disease burden information (2009).	Disease burden information.	

Korea, Republic of

JE cases have declined since the 1980s as a result of a national JE immunization program, improved standards of living, and a vector control program. Before mass immunization, several thousand cases were reported annually. The last outbreaks occurred in 1982 and 1983 with 1,197 and 139 cases reported, respectively.[40] Currently, fewer than five cases are reported each year.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Year-round human JE surveillance. Vector surveillance (April–October); pig surveillance (June–September). National reference lab performs JE testing for whole country.		National immunization program using mouse brain–derived vaccine.	No additional plans.	Data on new cell culture–derived vaccine.	Funded by national government.

Lao, People's Democratic Republic of

Thirteen cases of JE were first confirmed from 1989 to 1991. These patients were clinically diagnosed with viral encephalitis and the cases were serologically confirmed at AFRIMS in Thailand.[67] A serosurvey conducted in 1993 collected 289 sera from Thakek and Sokyai, 350km southeast and 10km northeast from Vientiane respectively, to study neutralizing antibody seroprevalence to JE and dengue viruses. JE seroprevalence increased from childhood to reach about 50 percent seropositivity by 30 years of age.[67]

It is suspected that JE is endemic, although no official reporting of JE cases currently occurs. The country's agrarian practices (dependence on rice cultivation and pig breeding) suggest that improved information on JE disease burden would be useful.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
National syndromic surveillance but limited/ inadequate data. Research project initiated in 2007 at two central and two provincial hospitals.	Expand research project (two more provincial hospitals) depending on results from initial study.	None.	Review surveillance data to determine need. Cost-effectiveness study.	Improved disease burden data.	Introduction is not possible without donor support and technical assistance.

Malaysia

JE virus was isolated for the first time in Malaysia in 1952, and several research studies were conducted in peninsular Malaysia at that time and later in Sarawak. Outbreaks have also been reported: Pulau Langkawi in 1979, Penang in 1988, and Sarawak in 1992.[68] A review of JE cases admitted to Sibu Hospital, Sarawak, from 1997 to 2006 demonstrated the impact of a vaccination program introduced in Sarawak State in 2001.[69] Official reporting likely underestimates disease burden and extent.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Case-based surveillance with lab confirmation, although reporting probably not complete. Vector surveillance.	Improve clinician/ lab/health department communications. Improve surveillance system to gather better data on JE incidence and mortality rates.	Nationwide in 2001 but scaled back to Sarawak only (mouse brain–derived vaccine).	Integrate JE vaccine into EPI and introduce catch-up program.	Information on JE vaccine alternatives, cost, and availability.	Limited funding from MOH but strong political will.

Myanmar

Data on JE in Myanmar are limited. A total of 188 JE cases were reported in several outbreaks between 1974 and 1979 in areas close to the Thai border. Children and young adults under 20 years of age were mainly affected.[2] In 1978, serum samples from villagers in three areas near the Indian border were tested for antibodies against JE. In all areas the results indicated the presence of JE infection.[70] JE cases have been confirmed in some limited surveillance conducted since 2007.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Limited AES surveillance with laboratory confirmation.		None.		Disease burden data.	

Nepal

JE was first confirmed in Nepal in 1978. From 1978 to 2005, over 27,000 cases and almost 5,400 deaths were reported.[71] The typical disease pattern is post-monsoon seasonal increases in disease with periodic large outbreaks. Most recently, a large outbreak in 2005 resulted in almost 2,000 cases and 300 deaths. While the Terai region has been the focus of JE virus activity, in 2006 JE was confirmed in 40 residents of the Kathmandu valley, 30 of whom had no history of travel outside the valley during the incubation period.[24] In 2007 and 2008, Nepal conducted JE campaigns targeting 1.68 million children aged 1 to 15 years in seven districts, achieving 97 percent coverage.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
AES surveillance throughout country, integrated with other vaccine-preventable diseases. Lab confirmation (two laboratories).	Sustain current surveillance strengths and improve CSF collection and follow-up of cases.	JE vaccine formally introduced in 2006 (SA 14-14-2).	Program expansion in phased manner in endemic districts. Routine JE vaccination for endemic districts.	WHO policy on coadministration with measles; duration of protection; use after reconstitution; diagnostic kits; required specimens for case classification.	External support needed for campaign supply. Government can fund routine program.

Pakistan

Extent of JE disease burden in Pakistan is unclear. However, limited clinical and serological studies have suggested JE virus transmission in parts of the country. In 1992, a study of 24 patients in Karachi confirmed JE virus in a patient following isolation of virus from the CSF.[72]

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
None.		None.		Disease burden data.	

Papua New Guinea

After JE was recognized in the Torres Strait in Australia in 1995, the likelihood that the virus had come from Papua New Guinea, directly to the north, led to studies that demonstrated the presence of virus in the Western Province of Papua New Guinea and widespread evidence of antibodies to JE in humans.[56,73] The studies suggested JE has been enzootic in parts of Western Province since at least 1989, and that the virus appears to be actively and rapidly spreading. In January 2004, the first reported case of JE occurred near the capital, Port Moresby, reported in a patient of European background, diagnosed after he was evacuated for medical care to Australia.[74]

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Sentinel surveillance in one hospital in Port Moresby commenced in 2007.		None.		Disease burden data.	Need funding to continue surveillance.

Philippines

The first suggestion of JE in the Philippines came in the 1950s, and serological and clinical studies over many years provided additional data.[75] A study conducted from 2002–2004 showed 11.7 percent (72/614) of CSF samples collected from patients with AES and/or meningitis from several provinces and islands were JE positive, confirmed with a JE IgM-capture ELISA.[76] A further study conducted by AFRIMS at San Lazaro Hospital from 2005 to 2006 confirmed 40 percent (6/15) of AES cases as JE. Outbreaks have been described in Nueva Ecija, Luzon, and Manila.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Sentinel JE surveillance being established at five sites (Research Institute of Tropical Medicine, supported by WHO). AFRIMS: working in Manila and Cebu.		Sanofi Pasteur pediatric vaccine trial under way.	Compare JE immunization program with other health priorities.	Surveillance data. Advocacy for legislators.	No budget currently dedicated for JE vaccination.

Russian Federation (southeast)

Affected areas are the far eastern maritime areas south of Khabarovsk. The peak transmission season is considered to be July to September. Rare human cases are reported.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Limited information available.					

Singapore

In 1992 the government of Singapore phased out pig farming, and as a result reported JE cases decreased. However, as three locally acquired cases were detected between 2001 and 2005, the country cannot be considered risk-free.[77] A serologic survey performed in 2004 on animals (dogs, cattle, goats, birds) showed antibody prevalence of 2 to 60 percent in different animal groups, suggesting viral activity is still occurring.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Case-based surveillance.					

Sri Lanka

Sri Lanka began immunizing against JE in 1988 and gradually expanded its program to include catch-up campaigns for children from 1 to 10 years of age and a routine immunization program in 18 high-risk districts by 2007. The government is planning to transition to the live, attenuated SA 14-14-2 JE vaccine in 2009 to facilitate further expansion of the immunization program.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Clinical syndromic surveillance is implemented by all clinicians. A sentinel laboratory, the Medical Research Institute, carries out JE testing on all CSF samples received for virological tests.		18 out of 26 districts receive inactivated JE vaccine annually.	Introduce live, attenuated JE vaccine into all districts in 2009.		

Thailand

As a result of stepwise introduction of a JE immunization program since 1990, Thailand currently reports JE incidence rates of less than 1 per 100,000 population. However, cases continue to occur across the country, and coverage of the third dose of JE vaccine at 2.5 to 3 years of age was only 62 percent in 2003.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Encephalitis surveillance since 1971. Specific JE surveillance since 1976. Reporting of AES with % JE positive since 1988.		Stepwise introduction since 1990 (locally-produced, mouse brain–derived vaccine). Fully integrated into routine EPI. Sanofi Pasteur vaccine pediatric trial under way.	Sanofi Pasteur has applied for licensure of its JE vaccine. Approval anticipated in 2009.	Consideration of new JE vaccines.	Program funded by national government.

Timor Leste

A JE seroepidemiologic study was conducted in Timor Leste in 2000. The prevalence of JE antibodies in 0- to 3-year-olds was 69.2 percent, rising to 89.2 percent in the 7- to 15-year-old age group, demonstrating high JE endemicity.[50]

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Funding has been secured for JE surveillance for a limited period. Syndromic encephalitis surveillance is part of integrated disease surveillance. JE surveillance begun in 3 hospitals April 2009.	Begin sentinel site ME surveillance. Expansion to 6 hospitals by May 2009.	None.	Establish JE prevention and control plan. Gather disease burden data to be used for justification of vaccine introduction.	Disease burden data.	Need donor support.

Vietnam

National surveillance for viral encephalitis occurs in Vietnam and is complemented by laboratory testing for JE at many sites. The highest concentration of cases is in the delta regions of the Mekong and Red Rivers. Incidence can exceed 10/100,000 in certain northern areas, with an average fatality rate of 20 percent. Occurrence of JE is highest between May and July; however, the seasonal peak is less marked in the south of Vietnam.[78]

Several studies on JE were initiated in the mid-1990s to understand the cause of encephalitis syndrome in Vietnam. These included a 1995 study at the Bach Mai Hospital in northern Vietnam, which found 67 percent (31/46) of pediatric encephalitis patients had acute JE.[79]

In 1997, the national EPI introduced JE vaccine in 11 high-risk districts. In 2004, the program was expanded to 267 districts in 50 provinces, and expansion of the program is continuing. The government plans to have a nationwide program by 2010.

Surveillance		Immunization		Decision-making needs	Financial issues
Current	Planned	Current	Planned		
Hospital-based AES surveillance since 1979. Pilot JE surveillance in 3 provinces since 2005. Capacity for JE lab testing in 10 provinces.	Strengthen routine syndromic system. Expand sentinel sites to represent more geographic areas by 2009. Capacity-building for surveillance and laboratory staff. Improve communication between curative and preventive sectors.	Immunization program in high-risk districts using locally produced mouse brain–derived vaccine.	Nationwide expansion by 2010.	Program impact. Data on new vaccines. WHO guidance and information on lessons learned from other countries.	Limited government resources. Need donor support to expand sentinel surveillance and for expansion of immunization program.

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