ADVOCACY FOR JAPANESE ENCEPHALITIS

Japanese encephalitis (JE), a mosquito-borne viral brain infection, afflicts an estimated 35,000 to 50,000 inhabitants of Asia and the western Pacific annually.[1] The disease most often strikes children, who have not yet built up a natural immunity. One-third of JE infections are fatal, and another third leave survivors with severe neurological sequelae. There is no treatment for JE; vaccination is the only defense. Funded by the Bill & Melinda Gates Foundation, PATH's JE project (2003–2009) worked with international partners and developing countries to increase the information available for understanding the extent of the disease and how best to control it.

Background

PATH's advocacy work raised the prominence of JE within the global health dialogue. Efforts at regional and national levels also helped prioritize JE immunization, fostering collaboration and country-level control strategies.

The importance of advocacy was revealed in the early stages of the PATH JE project. In Andhra Pradesh, India, officials working with PATH to support routine immunization and hepatitis B vaccine introduction voiced concerns about JE. Voices rose from several other states, citing repeated outbreaks and seeking a solution. By 2003, PATH had secured a grant from the Bill & Melinda Gates Foundation to tackle JE not just in one state in India, but in the entire Southeast Asia and Pacific region. Since then, focused advocacy has sensitized stakeholders and raised awareness among decision-makers so they may set appropriate policies in support of JE control efforts.

Local conversations and global outreach

Information-sharing was a key element of the JE project's accomplishments in all technical areas. To disseminate data on surveillance studies and clinical trials or to discuss country experiences using JE vaccine, PATH presented at international meetings and local workshops. Conversations with ministries of health identified information gaps, such as details on the safety of JE vaccines, and guided the JE project's communications and outreach efforts.

PATH raised awareness of JE control at key conferences, ensuring it was included on the agendas of various meetings, including the World Health Organization (WHO) Global Vaccine Research Forum, the United Nations Children's Fund Global Immunization Meeting, and the WHO Global Meeting on New and Underutilized Vaccines Implementation. Presentations to WHO's Strategic Advisory Group of Experts and Global Advisory Committee on Vaccine Safety brought new data for review by experts setting global recommendations. Every two years, PATH and WHO co-sponsored a Bi-regional Meeting on Control of JE, bringing together country representatives, officers from the WHO's Southeast Asia and Western Pacific regions, and other partners to share lessons learned and set priorities for the coming years.

Established as a primary resource for information on JE disease and vaccines, PATH was a major contributor to an effort initiated by the GAVI Alliance to identify vaccines for future support. PATH and its partners compiled crucial information that informed GAVI's evaluation and eventually led to the designation of JE vaccines as a future funding priority (along with vaccines against human papillomavirus, rubella, and typhoid).[2]

Laying a foundation for continued advocacy, PATH assembled a coalition of partners to develop a JE global control plan with communications and advocacy as primary components. *Japanese Encephalitis Morbidity, Mortality, and Disability: Reduction and Control by 2015* outlines priority activities that must be sustained, including improved understanding of disease burden, technical assistance for vaccine introduction, procurement support, and advocacy.[3] Multiple organizations—including PATH, WHO, UNICEF, the US Centers for Disease Control and Prevention, research institutions, universities, and others—helped develop the plan and have committed to working together to maintain progress, catalyze fundraising, and provide assistance to countries in need.

Multiple channels to reach multiple audiences

To raise awareness of clinical information about JE, PATH created training presentations on vaccine storage and administration, surveillance, and diagnostics (available on the Vaccine Resource Library—see sidebar). Provided in a generic format, these materials allow for adaptation according to local settings. Other training materials produced by the University of Liverpool with funding from the JE Project focus on clinical evaluation of patients at hospital admission and follow-up—important tools to assess the burden of JE disability.

Talking points and Q&As distributed to partners ensured consistent messaging, particularly regarding clinical trials, vaccine quality and safety, and public-sector pricing. In 2006, the importance of clear and accurate messaging was illuminated by inaccurate press reports that questioned the safety of the SA 14-14-2 JE vaccine and threatened mass campaigns in India. With clear and thorough responses already prepared, PATH and the Government of India were able to quell rumors and provide accurate information.

ONLINE RESOURCES

***JE Newbriefs* archives**: A quarterly newsletter on the field's latest developments, supplemented by *JE Flash*, a timely email announcement to distribute breaking news. **http://www.path.org/projects/japanese_encephalitis_project_newsletter.php**

The PATH Vaccine Resource Library: An archive of scientific documents published by PATH and partners on surveillance and disease burden, immunization financing, vaccine safety, and more. **http://www.path.org/vaccineresources/japanese-encephalitis.php**

The PATH Advanced Immunization Management (AIM) e-Learning module: An interactive learning tool that compiles technical information on JE disease and vaccines to enable national immunization managers to plan vaccine introduction. **http://aim.path.org/en/vaccines/je/index.html**

Shadow Lives, a film produced by the JE project in 2005, demonstrated the impact of JE on families and communities and is a powerful advocacy tool. Two additional films produced in partnership with Rockhopper TV—*Japanese encephalitis* and *Vaccine of Hope*—documented the burden of JE and the promise of vaccines and captured the first images of Indian children receiving JE vaccine. Aired on BBC World, these documentaries were broadcast in more than 200 countries.

Finally, peer-reviewed publications were a priority for the JE project, with clinical trials and surveillance studies generating new information. Publications addressed cost-effectiveness, co-administration of JE and measles vaccines, country-level disease burden, disability among JE survivors, and evaluation of available diagnostic kits.

Key lessons learned

- Advocacy efforts must highlight the impact of regional diseases, which may be underappreciated by funding agencies and global health bodies. The total disease burden of JE may be less overall than for diseases found around the world, but the impact of JE on an individual country can be catastrophic.
- Close attention must be paid to media reports and communications outlets within the global public health community. Inaccurate and/or incomplete news reports from even local publications can quickly become available on the Internet. It is crucial to develop a crisis communications plan to ensure immediate clarification and responses when appropriate.
- The decision of a national government to introduce a new vaccine can significantly influence decisions in other countries of the region. Vaccine introduction experiences can be valuable in a regional and global context, and it is important to document these experiences and support the sharing of lessons learned and best practices.

ENDNOTES

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COST-EFFECTIVENESS OF JAPANESE ENCEPHALITIS VACCINATION

Japanese encephalitis (JE), a mosquito-borne viral brain infection, afflicts an estimated 35,000 to 50,000 inhabitants of Asia and the western Pacific annually.[1] The disease most often strikes children, who have not yet built up a natural immunity. One-third of JE infections are fatal, and another third leave survivors with severe neurological sequelae. There is no treatment for JE; vaccination is the only defense. Funded by the Bill & Melinda Gates Foundation, PATH's JE project (2003–2009) worked with international partners and developing countries to increase the information available for understanding the extent of the disease and how best to control it.

Background

Immunization is one of the most cost-effective health interventions: most childhood vaccines are inexpensive and so effective that vaccination can be cost-saving to health systems. However, in countries with limited resources and competing public health priorities, it is important to determine whether new vaccine introduction is an appropriate financial investment. Economic evaluations, including cost-effectiveness analyses, can help in decision-making by comparing resource costs to public health outcomes when choosing one health intervention over another.

Cost-effectiveness analysis

Cost-effectiveness analysis is often used to inform decisions about the use of health care resources, including those related to vaccines and immunization strategies. In simple terms, cost-effectiveness analysis helps determine how much will be spent on an intervention to gain health improvement, such as saving one life or other measures of health outcomes, as compared with existing or other interventions.

Epidemiology patterns and vaccine characteristics determine both the inputs (costs) and the outcomes (e.g., cases, deaths, sequelae, or disability-adjusted life-years averted) for a cost-effectiveness analysis associated with any intervention. Outcomes of cost-effectiveness analysis of new vaccines can vary according to the characteristics of the country health system as well as vaccine characteristics.

Cost-effectiveness analysis of JE vaccines

Studies on cost-effectiveness of JE vaccination were undertaken throughout the life of the JE project. In 2006, PATH and local investigators studied cost-effectiveness of JE immunization in Andhra Pradesh, India, by (1) comparing implementation of a one-time vaccination campaign with an intervention that combined campaign plus routine immunization, and (2) comparing use of either the inactivated, mouse brain–derived JE vaccine or the SA 14-14-2 JE vaccine. Results demonstrated that the World Health Organization (WHO)-recommended combined JE vaccine introduction strategy (catch-up campaigns plus routine immunization) using the live, attenuated SA 14-14-2 JE vaccine was very cost-effective. This same strategy using the inactivated, mouse brain–derived JE vaccine was considered not cost-effective. Given limited resources, immunization strategies targeting high-risk areas also were found to be more cost-effective.[2] (It is important to note that this article was completed prior to the availability of SA 14-14-2 vaccine with a public-sector price. Introducing the lower public-sector price will further improve its cost-effectiveness.)

In 2007, the National Institute of Health Research and Development of the Indonesia Ministry of Health, the Directorate General of Communicable Disease Control and Environmental Health, and PATH linked an assessment of the economic burden of JE with a study on hospital-based surveillance in six Indonesian provinces, collecting data on hospital costs associated with JE infection and financial implications for families. Similarly, PATH and investigators from the China Center for Disease Control gathered information on costs associated with JE illness in Shaanxi Province in order to perform an economic evaluation of the JE vaccination program and identify strategies to improve JE immunization.

Additionally, the Communicable Disease Department of Cambodia launched a study to analyze cost-effectiveness of JE vaccine in 2007, collaborating with the National Immunization Program, National Institute of Public Health, PATH, and WHO. Five hospital sentinel sites collected data on treatment costs associated with JE cases identified through the meningo-encephalitis syndromic surveillance system. Results helped guide decision-making and inform immunization policy.[3]

Future directions

Studies have demonstrated that JE imposes a significant economic burden on households and JE vaccination is considered a cost-effective intervention for endemic populations. The public-sector price set by the manufacturer of the SA 14-14-2 JE vaccine also increases affordability and access for countries that must allocate limited public health resources. As countries continue to introduce vaccine, data on immunization program impact also will be important in refining cost-effectiveness analyses and planning future immunization strategies.

Key lessons learned

- Some elements of cost-effectiveness analyses can be comparable among countries, but it is important to consider potential variations in epidemiology patterns, target populations, and characteristics of the country health system.
- Hospital-based surveillance activities offer an opportunity to simultaneously collect information on costs of clinical treatment for JE.
- Cost-effectiveness analysis is just one piece of information that helps inform decision-making. It should be considered within a broader context of disease burden, vaccine supply, and sustainable financing.
- Countries often underestimate the programmatic costs of vaccination. It is important that countries budget time and resources for these programmatic costs, which include transportation of vaccine, training and supervision, surveillance, waste management, monitoring for adverse events following immunization, and cold chain maintenance.

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JAPANESE ENCEPHALITIS DIAGNOSTICS

Japanese encephalitis (JE), a mosquito-borne viral brain infection, afflicts an estimated 35,000 to 50,000 inhabitants of Asia and the western Pacific annually.[1] The disease most often strikes children, who have not yet built up a natural immunity. One-third of JE infections are fatal, and another third leave survivors with severe neurological sequelae. There is no treatment for JE; vaccination is the only defense. Funded by the Bill & Melinda Gates Foundation, PATH's JE project (2003–2009) worked with international partners and developing countries to increase the information available for understanding the extent of the disease and how best to control it.

Background

A paradox of JE is that it most significantly burdens resource-limited settings in which capacity to diagnose JE infections is often severely limited. JE is clinically indistinguishable from several other causes of acute encephalitis syndrome (AES), and a diagnosis can only be confirmed through laboratory testing of cerebrospinal fluid (CSF) or serum samples, the latter taken during both the acute and recovery phases of illness.[2]

In addition to logistical challenges, including collection and transportation of samples, other obstacles hinder JE diagnostic testing in the developing world. The most significant barriers are a lack of standardized test kits, inadequate quality assurance and quality control, and significant gaps in resources and capacity. However, reliable diagnostics are essential to JE surveillance for determining overall disease burden and informing policymaking on JE control.

The WHO JE Laboratory Working Group

With support from PATH, the World Health Organization (WHO) regularly convened experts to address challenges and advances in JE diagnostics and surveillance and to share information, prepare guidelines, and develop recommendations for endemic countries. Members of this WHO JE Laboratory Working Group represented WHO headquarters, the WHO Western Pacific Region (WPR), the WHO Southeast Asia Region (SEAR), the US Centers for Disease Control and Prevention (CDC), the Armed Forces Research Institute for the Medical Sciences (AFRIMS), the University of Liverpool, and PATH. In addition to routine technical assistance and evaluation of JE diagnostic assays (see below), the working group informed the development of a WHO JE laboratory manual, released as a field-test version in April 2007.[2] The manual provides guidelines to ensure quality control of diagnostic activities, facilitate training, and standardize laboratory procedures; feedback from its use at country facilities will inform a final edition.

The WHO JE laboratory networks

The JE Laboratory Working Group also provided guidance for the development and evolution of regional JE laboratory networks, which aim to ensure quality control and standardize protocols and methodology so that data are comparable over time and across geographic areas. With support from PATH and the US CDC, WHO established laboratory networks in both SEAR and WPR to provide training, protocols, and technical assistance to national laboratories. The networks leverage existing measles laboratory networks and, where appropriate, integrate with the national polio surveillance system for collecting and transporting patient samples.

The SEAR laboratory network (LabNet) was established in 2006. Eleven national and subnational labs participate, and the National Institute of Mental Health and Neuro Sciences (Bangalore, India) serves as the designated regional reference laboratory. Training workshops have addressed performance review, good laboratory practices, proficiency testing, and reporting and data management. To ensure quality control, all JE-positive samples and 10% of JE-negative samples are sent for confirmatory testing at the regional reference laboratory. The US CDC serves as the global specialized laboratory, providing technical assistance and training and maintaining proficiency test panels for annual accreditation of national laboratories.

The WPR laboratory network was established in mid-2009, with designation of seven national laboratories in six countries (Cambodia, Laos, Malaysia, Papua New Guinea [pending as of September 2009], the Philippines, and Vietnam [2]), two regional reference laboratories (China, South Korea), and a global specialized laboratory (Japan). The first training workshop was held in June 2009, and data were being reported as of July 2009.

JE diagnostic kit evaluations

The platform for JE virus laboratory diagnosis is the immunoglobulin M (IgM) antibody capture enzyme-linked immunosorbent assay (ELISA), which detects antibody in

serum and CSF. Several research institutions and reference laboratories around the world have "in-house" IgM ELISAs, but these have shown variable performance, especially when used in field settings.[3] To ensure predictable performance and allow comparability among labs, in-house assays must be validated, and standardized test kits for JE diagnosis must be accessible. Currently, there are three IgM ELISA assays commercially available for JE diagnostics:

- Panbio JE-Dengue IgM Combo (Inverness; Brisbane, Australia).
- JE Detect™ (InBios International, Inc.; Seattle, USA).
- JEV CheX (XCyton Diagnostics Ltd.; Bangalore, India).

PATH supported two evaluations of the validity, reliability, and standardization of results among these kits. The first was conducted in 2005 at AFRIMS using a panel that included JE-positive, JE-negative, and dengue-positive samples. Results from all kits were compared to results from the reference standard AFRIMS IgM ELISA kit. Sensitivity was high for all kits, but the specificity of the InBios and XCyton kits was found to be low, as they had limited capacity to distinguish between JE and dengue antibodies. The Panbio kit includes both JE and dengue antigens and appeared to present an advantage in settings where dengue virus co-circulates with JE virus.[3]

The second study was a field evaluation of the Panbio and XCyton kits, using serum samples collected as part of routine AES/JE surveillance in 2005 in Nepal. Again, the AFRIMS JE IgM ELISA served as the reference standard. Laboratory testing was undertaken at Nepal's National Public Health Laboratory with assistance from the Walter Reed/AFRIMS Research Unit Nepal. Results demonstrated that both kits had good predictive values when single serum samples from AES cases were tested for JE in a national laboratory; it was concluded that either kit can be used for laboratory-based JE surveillance in a similar epidemiologic setting.[4]

The WHO JE Laboratory Working Group continues to evaluate the commercial kits using serum and CSF samples from AES patients in various endemic countries. The group also is establishing a framework based on a global validation panel of samples for future kit evaluation so that results may be comparable between different assays. In-country labs will be able to further evaluate and improve in-house and commercial kits by testing a panel of standardized, well-characterized specimens comprising bulk serum and CSF samples, currently under development by the US CDC, with support from PATH and WHO.

Future steps

While there has been significant progress in building country capacity for JE diagnostic testing, there is still much to be done:

- Evaluations of validated diagnostic kits should be standardized and results disseminated.[5]
- New assays to improve sensitivity, reduce cross-reactivity, and distinguish current from previous infection should be explored, developed, and evaluated.
- Standardized procedures for clinical case evaluation, consistent specimen collection, and assessment of disability should be implemented in all endemic countries.
- Each country at risk of JE should have access to a qualified national laboratory and to regional reference laboratories to aid in confirmatory testing.

Standardized diagnostic testing and laboratory-based surveillance for JE are valuable in defining disease burden, thus enabling both advocacy for control efforts and—after vaccine introduction—monitoring of impact. Long-term sustainability needs and issues must be carefully considered, with partners continuing to provide technical assistance in building country capacity.

Key lessons learned

- Links among country-level laboratory initiatives can strengthen general capacity—for example, JE diagnostic testing and sample collection can be incorporated within existing systems for other vaccine-preventable diseases.
- Regional laboratory networks can be powerful mechanisms for developing laboratory capacity, standardizing methodologies, and addressing common challenges.
- Standardization of kit performance characteristics is important for ensuring comparability among laboratory-based surveillance data reported from various countries.

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ASSESSING THE IMPACT OF DISABILITY FROM JAPANESE ENCEPHALITIS

Japanese encephalitis (JE), a mosquito-borne viral brain infection, afflicts an estimated 35,000 to 50,000 inhabitants of Asia and the western Pacific annually.[1] The disease most often strikes children, who have not yet built up a natural immunity. One-third of JE infections are fatal, and another third leave survivors with severe neurological sequelae. There is no treatment for JE; vaccination is the only defense. Funded by the Bill & Melinda Gates Foundation, PATH's JE project (2003–2009) worked with international partners and developing countries to increase the information available for understanding the extent of the disease and how best to control it.

Background

The impact of JE disease is remarkable, with a mortality rate of as much as 30% or higher.[1] However, the lingering tragedy of JE is the burden of lifelong disability borne by as many as half of JE survivors.[2] The aftereffects can be as severe as paralysis or can take the form of more subtle learning disabilities and behavioral changes. Establishing the impact of disability from JE is an important aspect of assessing overall disease burden.[3] The data generated by disability studies provides vital information governments need to determine whether JE immunization programs are appropriate and cost-effective.

Developing a better assessment tool

Assessing disability is a complex exercise, and elaborate, multidisciplinary evaluations have long been the standard.[4] Such evaluations, requiring specialized equipment and expertise, are not practical in low-resource settings. In partnership with PATH's JE project, the University of Liverpool Viral Brain Infections Group set out to develop a new tool for disability assessment that would be simple, adaptable, and easy to use.

An initial assessment was developed and validated through studies in India and Malaysia.[5] Assessments of JE survivors were conducted by local doctors and healthcare workers and compared to a multidisciplinary team assessment. The resulting tool was the Liverpool Outcome Score (LOS).[6]

The Liverpool Outcome Score

The LOS assessment focuses on determining a JE survivor's likelihood of living independently.[6] The evaluator makes a series of observations of five functional and developmental actions of survivors: sitting, standing, walking, placing hands on the head, and using a pincer grip to pick things up. In addition, ten questions elicit caregivers' observations of the child since JE infection, including communication, behavior, continence, and recognition.

Each observation or question is scored on a scale of 1 to 5 (Table 1). The overall outcome score is the lowest score on any individual item. For example, if a child receives a score of 2 on any single item, the LOS is 2, regardless of higher scores on other items.

TABLE 1. Liverpool Outcome Score scale

Score	Interpretation
5	Full recovery
4	Minor sequelae with mild effects on function, or personality change, or on medication
3	Moderate sequelae mildly affecting function; compatible with independent living
2	Severe sequelae, greatly impairing function; likely to make patient dependent
1	Death

Training materials for the LOS assessment, as well the tools for patient assessment at hospital discharge[7] and follow-up examination,[8] are available online.[9]

Assessing the impact of disability in countries

As part of its assistance to JE-endemic countries' disease surveillance efforts, PATH provided support to Cambodia, Indonesia, and Vietnam for studies to assess the magnitude of disability from JE. The LOS was applied to allow a deeper understanding of JE's impact, generating data to help evaluate overall disease burden.

Cambodia

The LOS was used to measure the extent of disability among 47 Cambodian children who had laboratory-confirmed JE (identified through sentinel meningo-encephalitis surveillance). Children were assessed during home visits conducted a minimum of four months following hospital discharge. Seven children (13%) had died. Five (9.3%) children had severe sequelae, 18 (72.2%) had mild or moderate sequelae. Only three children (5.6%) had a full recovery.[10]

Indonesia

Data collected through the Indonesian national disease surveillance system during a two-year surveillance study (January 2005–December 2006) showed that JE occurs nationwide,[11] and a disability assessment was conducted to

further evaluate the impact of JE disease. Of 65 children followed up, half either died or were left with serious disabilities likely to impair their ability to lead independent lives. Sixteen children died in the hospital or before follow-up assessment (25%). Sixteen (25%) had severe sequelae, five (7%) had moderate sequelae, and 12 (18%) had minor sequelae. The remaining 16 children (25%) were considered to have recovered fully.[12]

Vietnam

Vietnam established a program for syndromic surveillance of meningo-encephalitis in 2006 in two provinces, expanding into a third in 2008. In a survey of disability following JE, 26 laboratory-confirmed JE cases identified through syndromic surveillance between 2006 and 2008 were assessed between 5 and 26 months after discharge from the hospital. Two (8%) cases had severe sequelae, five (19%) had moderate sequelae, and eight (31%) had mild sequelae; the remaining 11 recovered completely.[13]

Applying data to advance JE control

The disability studies in Cambodia, Indonesia, and Vietnam clearly show the devastating results of JE. Death occurred in up to one-quarter of cases, and almost half of JE survivors suffered from severe to moderate disabilities, requiring constant support from their families and creating significant emotional and financial strain. As few as 4% of JE survivors recovered completely.

Key lessons learned

- Because JE most often affects children, and the survival of a child after JE is often the first step in a long recovery, the effects of disability are magnified over time. Beyond the financial and emotional toll of hospitalization, families are faced with changes in their children that can have a long-term impact on their daily lives.
- Disease burden estimates can be made more accurate by taking into account not only the deaths from JE, but the wide-reaching and long-term impact caused by disability.
- When considering the consequences of JE, immunization emerges more clearly as the most cost-effective measure for controlling not only the death and disability caused by JE, but also the hidden emotional and economic toll on survivors, their families, and their communities.[14]

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JAPANESE ENCEPHALITIS VACCINE INTRODUCTION

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Background

New and enhanced surveillance activities, combined with increased advocacy and emerging results from clinical research studies, have increasingly prompted JE endemic countries to consider programs to protect vulnerable populations through immunization. All of this new information brings a greater awareness of JE and the solutions to control it, so countries can develop strategies for introducing safe and affordable JE vaccines.

Several countries with long-term existing JE control programs also are considering advancements in JE vaccines, as new and improved candidates move further along in clinical development. These new options may call for programmatic updates and potential transition from the traditionally used inactivated, mouse brain–derived JE vaccine, of which supply continues to decrease as international manufacturers cut back or halt production.[2]

In recent years, forward-thinking national governments have led the way in introducing or transitioning to use of the live, attenuated SA 14-14-2 JE vaccine, providing models for other countries to follow in their footsteps and learn from their experiences. Development of new JE vaccines continues, including promising products from Intercell and Sanofi Pasteur, encouraging a healthy market and eventually more options for countries ready to implement JE immunization.[3]

Introduction of SA 14-14-2 JE vaccine

Following a severe JE outbreak in India and Nepal in 2005 that roused international attention and claimed thousands of children's lives, policymakers in both countries rapidly advanced JE immunization planning. Because leaders in each country had already begun developing national JE control strategies, both were at an opportune stage to quickly initiate JE vaccination campaigns to protect vulnerable children before the next year's monsoon season struck. PATH provided technical assistance in both countries, from strategy development through program implementation and evaluation.

In India, the government committed to a five-year strategy to vaccinate more than 100 million children aged 1 to 15 years in high-risk districts. Areas that held campaigns would then begin providing the vaccine in routine immunization services to protect new birth cohorts. By the end of 2010, more than 100 million children will be vaccinated.[4] Communications barriers between state and national levels and limited vaccine supply initially prevented seamless incorporation of JE vaccine into routine immunization, but stakeholders convened to identify barriers and set guidelines. Beginning in 2009, routine immunization planning and implementation was progressing throughout the states targeted in the national JE control strategy.

Nepal had conducted campaigns in some high-risk districts during the previous few years, but committed to a sustained effort after the 2005 outbreak. An unusual element of Nepal's approach was to target adults as well as children in the campaigns, based on surveillance data showing an expansion of JE to new districts. As adults in these areas may have waning immunity or may not have developed natural immunity from exposure to JE in the environment, they also were among the at-risk population. Nepal expanded the vaccination campaigns' reach to additional districts in following years as well, and subsequently introduced JE vaccine into routine immunization services.[4]

In the Democratic People's Republic of Korea, PATH partnered with the Ministry of Health, the Academy of Medical Sciences, Christian Friends of Korea, and Global Solutions for Infectious Diseases to support JE vaccination campaigns in 2009 to immunize nearly half a million children. PATH provided supplies for safe immunization and assembled an expert team that offered technical assistance on campaign planning and monitoring. Evaluation of the campaign's success will inform the national government's future JE immunization planning.

Transition to SA 14-14-2 JE vaccine: Sri Lanka

The Government of Sri Lanka introduced the inactivated, mouse brain–derived JE vaccine in 1988 through phased vaccination campaigns in high-risk districts, and the program achieved a significant decrease in JE incidence. In following years, however, outbreaks began to be recorded in districts without JE immunization and surveillance data revealed the need for national expansion. Additionally, surveillance for adverse events following immunization (AEFIs), established and enhanced in the 1990s, recorded an increasing trend of AEFIs following JE vaccination as compared to other routine vaccines.

Finally, cost considerations and an unreliable supply of the inactivated vaccine prompted a search for an alternative vaccine.

National immunization managers reviewed available information about the live, attenuated SA 14-14-2 JE vaccine, including WHO reports, scientific literature, cost-effectiveness data, and evidence of impact in other countries. PATH assisted with local studies on the vaccine's safety and immunogenicity and a cost-effectiveness analysis, which bore positive results. Beginning in July 2009, the SA 14-14-2 vaccine was introduced in routine immunization services in 18 districts. The cost-savings made possible by the vaccine transition will allow for program sustainability, budget for other new vaccines, expansion of JE immunization nationwide and to vulnerable adults in high risk areas, and the potential to add a second dose of JE vaccine, if necessary.[5]

A model project on vaccine transition: Shaanxi Province, China

In collaboration with the Chinese Center for Disease Control and Prevention, PATH assisted with a model project to transition from the inactivated JE vaccine to the live, SA 14-14-2 JE vaccine in three counties of Baoji Prefecture, Shaanxi Province. An ancillary part of the project, conducted in 2007, helped to set up active JE surveillance and strengthen JE laboratory and diagnostic testing at the county, prefecture, provincial and national levels.

Upcoming milestones

Additional countries are planning or expanding JE immunization programs, boosted by crucial surveillance data and lessons learned from the experiences of regional pioneers. In Cambodia, the SA 14-14-2 JE vaccine was integrated into routine immunization services in three provinces in October 2009, with plans for national expansion. The Government of Vietnam plans to expand its geographically targeted JE immunization program, nationwide by 2011 using a locally produced, inactivated vaccine.[6]

Key lessons learned

- The experiences of countries introducing JE vaccine can be important models for other countries in the region planning JE control strategies. Lessons learned, guidelines for implementation, and relevant data should be shared with the regional and global communities.
- When a new vaccine is introduced, communication between district, state, and national levels is critical to ensuring successful implementation and sustainability of campaigns and routine immunization services.
- New vaccine introduction and evolution of immunization strategies (including vaccine transition) offer opportunities to assess and improve health system infrastructure, enhance disease surveillance, and strengthen AEFI monitoring.

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JAPANESE ENCEPHALITIS DISEASE SURVEILLANCE

Japanese encephalitis (JE), a mosquito-borne viral brain infection, afflicts an estimated 35,000 to 50,000 inhabitants of Asia and the western Pacific annually.[1] The disease most often strikes children, who have not yet built up a natural immunity. One-third of JE infections are fatal, and another third leave survivors with severe neurological sequelae. There is no treatment for JE; vaccination is the only defense. Funded by the Bill & Melinda Gates Foundation, PATH's JE project (2003–2009) worked with international partners and developing countries to increase the information available for understanding the extent of the disease and how best to control it.

Background

JE disease can have significant consequences, with a mortality rate of as much as 30% or higher[1] and life-changing physical and cognitive disabilities borne by as many as half of JE survivors.[2] Assessment of disease burden is important for governments' decision-making about vaccine introduction, but JE surveillance is complicated by a number of factors. There are no JE-specific clinical presentations; rather, it is one of several etiologies of acute encephalitis syndrome (AES). A JE diagnosis can only be confirmed through laboratory testing of cerebrospinal fluid (CSF) or of serum samples, the latter taken during both the acute and recovery phases of illness.[3] This presents a challenge to countries with limited capacity.

Even before specimens reach a lab, endemic countries face logistical challenges of transportation while maintaining the cold chain. Compounding these difficulties is the cross-reactivity of the dengue virus (also a flavivirus), which often co-circulates in JE-endemic areas.[4] Additionally, a lack of reporting standards can prevent collection of standardized data. Overcoming these challenges has been an important part of PATH's JE project.

Setting standards for syndromic surveillance

With the variability among clinical presentations of JE infection, a standard clinical case definition for AES is a vital first step in identifying possible cases. Laboratory testing then distinguishes JE from other neurological infections. These elements are outlined in the World Health Organization (WHO) JE surveillance standards.[5]

Increasing diagnostic capacity

The refinement of JE diagnostic tests and capacity-building of regional laboratories were important efforts of the JE project. PATH assisted in the evaluation of sensitivity and specificity among diagnostic kits and the development of a validation panel to assist national-level use of in-house diagnostic kits.

Helping countries measure the extent of JE

PATH has worked to help national programs begin or enhance JE surveillance. Increased efforts in Cambodia, Indonesia, Nepal, and Vietnam provided insights into the burden of JE disease to inform decision-making on immunization.

Revealing nationwide disease burden: Indonesia

In Indonesia, the presence of JE throughout the country was in question, but a two-year surveillance study showed JE as an endemic disease nationwide.[6] Sentinel surveillance conducted by PATH and the National Institute for Health Research and Development recorded JE cases in six provinces throughout the country, with risk varying according to geographic region. Further research evaluated the additional disease burden caused by post-JE disability[7]—an often-overlooked aspect that leaves a significant impact on families and communities. Among JE survivors studied, 25% experienced sequelae so severe they were unlikely to lead independent lives.

Applying surveillance data toward program planning: Cambodia

With PATH and WHO assistance, Cambodia's Communicable Disease Control Department and the National Institute of Public Health established sentinel surveillance at six sites in 2006. By 2007, the data showed clear evidence of disease burden, with children younger than 12 years of age at highest risk. At a meeting to disseminate the results, participants committed to developing a national JE control plan, with vaccine introduction in 2009. PATH collaborated with researchers in Cambodia to analyze and disseminate surveillance results through a series of publications.[8] Surveillance became the responsibility of the National Immunization Program in 2009, and JE vaccine was introduced on a small scale in October 2009, with plans for future expansion.

Gathering data to evaluate program performance: Vietnam

Vietnam began AES surveillance in 1979 and conducted several studies in the mid-1990s, including one in northern Vietnam that showed more than half of AES cases were JE.[9] The National Expanded Programme on Immunization introduced the mouse brain–derived JE vaccine in 1997 for 11 high-risk districts.

PATH provided technical assistance to strengthen the existing AES surveillance program, supporting the National Institute of Hygiene and Epidemiology in developing JE surveillance guidelines, identifying two initial sites, and conducting training. An additional sentinel site was added in 2008, creating a system that covers three provinces in the northern, central, and southern regions. Routine and standardized surveillance informed expansion of the immunization program, which now covers 267 districts in 50 provinces.

Enhancing existing surveillance systems

Funding from PATH's JE project allowed many other countries to capitalize on WHO's extensive surveillance experience. With financial support from PATH, WHO regional offices supported system enhancement through inclusion of surveillance for AES and/or JE in Bangladesh, Bhutan, Cambodia, China, India, Laos, Nepal, Papua New Guinea, Philippines, Timor L'este, and Vietnam.

These activities generated data crucial to JE control strategies. In Nepal, for example, integrated field- and laboratory-based AES surveillance within the existing vaccine-preventable diseases surveillance system resulted in greater collection of diagnostic specimens and more follow-up investigations after illness.[10] The resulting clarity on disease burden prompted Nepal to hold JE vaccination campaigns in 2007 and 2008.

Looking to the future

PATH has also focused on developing an up-to-date global incidence estimate for JE. While universal estimates have been produced before,[11,12] the most recent one is nearly 20 years old.[13] For proper health planning, a more accurate estimate of morbidity and mortality is needed. The effort has included JE experts from the US Centers for Disease Control and Prevention, WHO, and academic, governmental, and corporate entities.

JE surveillance continues to develop, with countries building diagnostic capacities, gaining experience with various surveillance models, and using what they learn in order to make life-saving decisions about JE vaccination. PATH has helped empower these governments with the skills, systems, and data they need to protect their populations from JE.

Lessons learned

- Clear surveillance standards provide critical guidance and ensure collection of accurate and useful disease burden data.
- Building surveillance and diagnostic capacity in endemic regions generates increased accuracy of disease burden data and sustainability of standardized data collection.
- Surveillance data help endemic countries learn about their own JE burden and plan targeted interventions, which can then be monitored for impact based on rates of disease incidence.
- The disease burden of JE involves not only the acute disease, but also its devastating aftereffects such as sequelae and long-term disability.

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JAPANESE ENCEPHALITIS VACCINE DEVELOPMENT

Japanese encephalitis (JE), a mosquito-borne viral brain infection, afflicts an estimated 35,000 to 50,000 inhabitants of Asia and the western Pacific annually.[1] The disease most often strikes children, who have not yet built up a natural immunity. One-third of JE infections are fatal, and another third leave survivors with severe neurological sequelae. There is no treatment for JE; vaccination is the only defense. Funded by the Bill & Melinda Gates Foundation, PATH's JE project (2003–2009) worked with international partners and developing countries to increase the information available for understanding the extent of the disease and how best to control it.

Background

Initially developed in the 1940s, an inactivated JE vaccine had been widely produced and used in several countries, but the need for new-generation JE vaccines has become apparent in recent years. Beginning in the 1990s, many manufacturers scaled back or halted production of the mouse brain–derived, inactivated vaccine, as it is expensive and difficult to produce. Countries searched for alternative vaccines that were safer, more affordable, and easier to administer.[2]

Identifying a vaccine

PATH joined the search for a solution and initially identified four promising candidates:

- The live, attenuated SA 14-14-2 JE vaccine manufactured by China's Chengdu Institute of Biological Products (CDIBP).
- IMOJEV™—a chimeric JE vaccine under development by Sanofi Pasteur.
- IXIARO®—an inactivated JE vaccine under development by Intercell.
- An inactivated vaccine under concurrent development by both Biken and Kaketsuken of Japan.

PATH entered into negotiations with each manufacturer to determine how the JE project could help accelerate clinical development and/or licensure for pediatric use in low-resource settings in return for public-sector market price considerations. After reviewing pricing structures, development progress, and production capacity, PATH moved forward in collaborating with CDIBP to increase developing country access to the live, attenuated SA 14-14-2 vaccine, which had been safely administered to more than 200 million children in China since its introduction in the late 1980s.

The live, attenuated SA 14-14-2 vaccine

To further evaluate the SA 14-14-2 vaccine, PATH assembled technical experts, including representatives from the World Health Organization (WHO) Initiative for Vaccine Research, who traveled to China in 2004 to meet with regulatory authorities, the National Institute for the Control of Pharmaceutical and Biological Products, the State Food and Drug Administration, and CDIBP. The team reviewed clinical data and production methods, conducted a good manufacturing practices (GMP) inspection, and concluded that data demonstrated the vaccine's safety, efficacy, and effectiveness. In 2005, the WHO Global Advisory Committee on Vaccine Safety (GACVS) also reviewed data and acknowledged the excellent safety and efficacy profile of the SA 14-14-2 vaccine.[3]

Special pricing for developing countries

A key element of JE control in endemic, developing countries is vaccine affordability. In 2006, landmark negotiations between PATH and CDIBP established a maximum public-sector price for the SA 14-14-2 vaccine, comparable to the price of measles vaccine and available through 2026 to low-income endemic countries (gross national income per capita < US$1,000).* The availability of this pricing has allowed for JE vaccine introduction in India, Nepal, and Sri Lanka, resulting in the protection of millions of children.

Clinical trials to generate additional data

WHO and international experts recommended studies to strengthen the vaccine's file for WHO prequalification. In addition, some countries considering introduction of or transition to the SA 14-14-2 vaccine required special studies to support national licensure. PATH and CDBIP collaborated to conduct several clinical trials. Studies to demonstrate the performance of the vaccine in large-scale vaccination programs also were critical to sustaining its use and catalyzing uptake in other countries.

Co-administration of measles and JE vaccines (Philippines)

PATH and the Research Institute of Tropical Medicine initiated a study in 2005 to evaluate the safety and immunogenicity of co-administering the SA 14-14-2 JE vaccine and the measles vaccine. GACVS reviewed the results and concluded that the short-term safety profile was acceptable.[4] With advances in plaque-reduction neutralization testing (PRNT) emerging as the gold standard for antibody testing, an expert review committee in 2009 recommended re-analysis of the study samples using an ELISA test comparable to PRNT. Analysis of test results will begin in late 2009.

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* The maximum public sector price is subject to adjustment based on increases in the producer price index and wage index, and changes in currency exchange rates. The price does not include local distributor fees, applicable government taxes, or other related costs and charges (such as freight, transportation, insurance, etc).

Co-administration of measles and JE vaccines (Sri Lanka)

PATH and the Sri Lanka Ministry of Healthcare and Nutrition's Epidemiology Unit initiated a similar study in 2007. In both studies, seropositivity rates for both JE and measles were high after follow-up at one year and demonstrated no interference. Safety assessments found no severe local reactions, and no severe systemic reactions were considered by the investigators to be related to vaccination.[5]

Use of SA 14-14-2 JE vaccine after administration of mouse brain–derived vaccine (Sri Lanka)

A second study in Sri Lanka evaluated safety and immunogenicity of the live, attenuated SA 14-14-2 JE vaccine among two- and five-year-old children who had previously received the mouse brain–derived, inactivated vaccine. Results showed a booster effect of JE antibodies at one month that persisted one year after receipt of SA 14-14-2 vaccine.[5]

Adult viremia (India)

Sponsored by the Indian Council on Medical Research (ICMR) and the National Institute of Virology (NIV) with technical assistance from PATH, this study was conducted to support the licensure process and found that there was no virus shedding after 15 days in adults who received one dose of the SA 14-14-2 JE vaccine.[6]

Vaccine effectiveness (India)

Following the 2006 introduction of JE vaccination campaigns, PATH, ICMR, and NIV initiated a case control study, which completed enrollment in 2009, to evaluate the effectiveness of the SA 14-14-2 vaccine in preventing clinical JE.

Facility construction and WHO prequalification

PATH's collaboration with CDIBP extended to technical assistance in expanding manufacturing capacity and facilitating construction of a new vaccine production facility, designed to meet growing regional demand and to adhere to international manufacturing standards. Construction began in 2007 with completion anticipated in 2010. PATH has helped support procurement, testing, and qualification of major equipment. Training for CDIBP production staff has helped implement a quality management system, a validation master plan, and GMP standards. Once the new facility is online and producing vaccines, CDIBP will submit a regulatory dossier to the Chinese State Food and Drug Administration and to WHO in pursuit of vaccine prequalification, which is necessary for procurement of vaccines by United Nations agencies.

Global demand forecasting

Current and future needs for JE vaccine were identified through global demand estimates developed by PATH and disseminated to partners. Upon its evaluation of country demand, resource availability, and vaccine availability, the GAVI Alliance board committed to seek funding to expand its portfolio of support to include JE vaccines (along with vaccines against human papillomavirus, rubella, and typhoid).[7]

The future market for JE vaccines

As of 2009, both Sanofi Pasteur and Intercell have pursued licensure of their respective JE vaccines in industrialized countries, and future plans include a marketing strategy for the developing world.[8,9] Increasing availability of improved, safe, and affordable JE vaccines for use in endemic countries will create a healthy market that will regulate price and production capacity to meet the needs of vulnerable populations in all affected countries.

Key lessons learned

- Establishing the necessary quality standards and procedures to achieve WHO prequalification requires significant commitment. CDIBP's experience can inform other developing country manufacturers that have not previously submitted products for WHO prequalification.
- Licensure requirements vary among countries. For example, since the SA 14-14-2 vaccine has only recently begun to be widely used outside of China, national regulatory authorities may call for additional clinical studies to evaluate vaccine safety and performance.
- Technical assistance and the regulatory experiences of neighboring countries can be crucial for reviewing available information and generating data for product licensure.

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