OBJECTIVE 2:
ADVANCE AVAILABILITY OF AN IMPROVED VACCINE

Several endemic countries have successfully controlled JE with a vaccine available for over 60 years.[2] However, most manufacturers of the inactivated, mouse brain–derived vaccine had decreased or halted production, as it was difficult and expensive to produce. PATH joined others in seeking a solution. Several vaccine candidates were in development, but the SA 14-14-2 JE vaccine manufactured by the Chengdu Institute of Biological Products (CDIBP) in China offered the greatest potential. This live, attenuated vaccine had been safely used for over 20 years,[12] a reliable supply was available, and the manufacturer was willing to provide it at an affordable price for developing countries.

Because the live, attenuated SA 14-14-2 vaccine had not been widely used outside of China, international- and country-level officials called for specific clinical studies. Collaborating with the manufacturer, WHO, and ministries of health, PATH conducted pivotal clinical trials to add to a growing collection of data on the vaccine. Recommendations from the WHO Global Advisory Committee on Vaccine Safety and the Strategic Advisory Group of Experts also informed research activities.

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 live, attenuated SA 14-14-2 JE vaccine and the Expanded Programme on Immunization (EPI) measles vaccine. The WHO Global Advisory Committee on Vaccine Safety reviewed the data and concluded that the short-term safety profile was acceptable.[13] With advances in plaque-reduction neutralization testing (PRNT) as the emerging 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.

Photo: Chengdu Institute of Biological Products

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

PATH and the Ministry of Healthcare and Nutrition, 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.[14]

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 2- and 5-year-old children who had previously received doses of the mouse brain–derived, inactivated vaccine used in the national program. The study was completed in 2008, and results showed a booster effect of JE antibodies at one month that persisted one year after receipt of SA 14-14-2 vaccine.[14]

Adult viremia (India)

Sponsored by the Indian Council on Medical Research and the National Institute of Virology 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 live, attenuated SA 14-14-2 JE vaccine.[15]

Vaccine effectiveness (India)

PATH is assisting the Government of India in conducting a case control study to evaluate the effectiveness of the live, attenuated SA 14-14-2 vaccine in preventing clinical JE.

Vaccine quality

Data from these studies also expanded the vaccine's dossier for submission to WHO toward prequalification, which allows for medical products to be procured through United Nations agencies. This status is granted to products and/or manufacturers that demonstrate quality, acceptability, and reliability of supply. To ensure that vaccine production at CDIBP meets these requirements, PATH is providing support and technical assistance for construction of a new facility that will help meet regional demand and produce JE vaccine according to international standards for current Good Manufacturing Practices.

OBJECTIVE 3:
INTRODUCE AND INTEGRATE VACCINE

In recent years, numerous projects and studies have demonstrated regional and national incidence of JE as never before. With this new information—and with the availability and reliable supply of a safe, affordable JE vaccine—comes the increasing need for strategies to control JE and protect populations at risk. Progress has been rapid; countries that were only beginning to understand their JE burden a few years ago are now implementing immunization programs. Furthermore, their experiences are being carefully documented to benefit the future planning of their neighbors.

Introduction of the live, attenuated SA 14-14-2 JE vaccine

India and Nepal were among the first to introduce the SA 14-14-2 vaccine from CDIBP through mass campaigns and routine immunization services. A severe outbreak in 2005 spanned the two countries, raised significant community demand, and accelerated plans already under way for JE vaccine introduction. 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.[8]

Nepal had conducted sporadic campaigns a few years earlier, but committed to a sustained effort after the 2005 outbreak. Campaigns beginning in 2006 aimed to protect not only vulnerable children, but also adults. Surveillance data had revealed cases of JE in new areas. Adults in these districts would most likely not have previously been exposed to JE in the environment, and thus would not have natural immunity. Following campaigns in endemic districts, JE vaccine was provided through routine immunization services as well.[8]

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.

Photos: PATH/Julie Jacobson

VACCINE OF HOPE

West Bengal is one of India's most high-risk states for JE and was among those hit hard by an outbreak in 2005. Thousands of families were affected, among them the Hansda family, who lost their oldest son to JE. Malati Hansda remembers her son's fever and severe headache, which developed into convulsions. His father brought him to the hospital by bicycle and bus, but the boy died soon after. "A vaccine against JE," said Malati Hansda, "definitely could have saved my son."

The next year, Malati and Dasarath Hansda brought their surviving son and daughter to a local school serving as a temporary vaccination center, determined that they would be protected before the 2006 monsoon season struck. They were one of millions of families now empowered to provide lifesaving protection to their children, thanks to the national government's prompt response to the devastating JE outbreak just one year earlier.

Image from the video *Vaccine of Hope* (Rockhopper)

The Hansdas' daughter Seva received JE vaccine in 2006, one year after the virus claimed her older brother.

Transition to SA 14-14-2 JE vaccine

The Government of Sri Lanka first introduced phased vaccination campaigns using the inactivated, mouse brain–derived JE vaccine in 1988. Surveillance data revealed the need for national expansion, but cost considerations, unreliable supply, and reports of adverse events with the inactivated vaccine prompted a search for a better alternative.

Upon review of recommendations from the WHO Strategic Advisory Group of Experts, scientific literature, cost-effectiveness data, evidence of impact in other countries, and local studies on safety and immunogenicity, national immunization managers suggested transitioning to the SA 14-14-2 vaccine. PATH assisted with local studies on the vaccine's safety and immunogenicity, 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 derived from this transition will allow for program sustainability, budget for other new vaccines, expansion of childhood JE immunization nationwide and targeting of vulnerable adults in high risk areas, and the potential to add a second dose of JE vaccine, if necessary.[16]

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 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

Other countries are planning or expanding JE immunization programs as well, boosted by crucial surveillance data. In Cambodia, the SA 14-14-2 JE vaccine was introduced on a small scale in October 2009, with plans for national expansion. The Government of Vietnam plans to expand its geographically targeted JE immunization program nationwide by 2011.[4]

OBJECTIVE 4:
EXPAND OUTREACH THROUGH ADVOCACY

Throughout the lifetime of the JE project, PATH engaged stakeholders and shared information to raise awareness at national, regional, and global levels. Advocacy efforts helped prioritize JE immunization, foster collaboration, and inform country-level control strategies.

Vehicles for spreading the message of JE control included key conferences convened by WHO, United Nations Children's Fund (UNICEF), and others. Every two years, PATH and WHO co-sponsored the Bi-regional Meeting on Control of JE, bringing together country officials from the Southeast Asia and Western Pacific regions and other public health partners. National-level events in endemic countries, such as annual pediatric association meetings, also featured JE.

PATH also worked closely with the GAVI Alliance to collate crucial information on JE burden, cost-effectiveness, and future vaccine demand. This evidence ultimately led to GAVI's inclusion of JE vaccines among those to be considered for future support (along with vaccines against human papillomavirus, rubella, and typhoid).[17]

PATH's JE resources

Several different types of resources helped educate various audiences about key issues in JE control. A series of training presentations—adaptable to local settings—addressed vaccine storage and administration, surveillance, and diagnostics (available on the Vaccine Resource Library—see sidebar). Talking points and Q&As distributed to partners ensured consistent messaging, particularly regarding clinical trials, vaccine quality and safety, and vaccine pricing.

PATH also developed three films for use by partners and health officials in advocacy efforts. *Shadow Lives* is a short film demonstrating the impact on families and communities when a child is left with severe disability after JE. Two documentaries produced in partnership with Rockhopper TV—*Japanese Encephalitis* and *Vaccine of Hope*—illustrated 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 helped disseminate the scientific evidence of JE disease burden and vaccine safety gathered through the JE project's research endeavors. Publications addressed country-level disease burden, cost-effectiveness, characteristics of the SA 14-14-2 JE vaccine, disability among JE survivors, and evaluation of available diagnostic kits. A complete list of these publications is available at the end of this report.

Photos: PATH/Julie Jacobson

ONLINE JE RESOURCES

***JE Newbriefs* and *JE Flash* archives**: A quarterly newsletter on the latest developments and a supplemental email announcement for breaking news. Available at: http://www.path.org/projects/japanese_encephalitis_project_newsletter.php

The PATH Vaccine Resource Library: An archive of scientific documents and training materials published by PATH and its partners on surveillance and disease burden, immunization financing, vaccine safety, and more. Available at: 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. Available at: http://aim.path.org/en/vaccines/je/index.html

THE FUTURE OF JE CONTROL

PATH's JE project has provided an important model for applying donor funds toward a neglected disease. Made possible by the vision and support of the Bill & Melinda Gates Foundation, this special effort has raised awareness to an unprecedented level and achieved lifesaving impact on countries burdened by JE. But the work is not complete. Moving forward, partners and stakeholders must continue to convene in order to sustain progress and mobilize resources.

To ensure that recent accomplishments represent a sustainable shift in JE control, PATH convened partners to develop a strategic plan for JE control by 2015 and beyond. The plan—authored in collaboration with WHO, UNICEF, the United States Centers for Disease Control and Prevention, universities, research institutions, and others—emphasizes countries' priorities and identifies the responsibilities necessary for international partners to maintain progress and generate resources to achieve an ambitious set of goals.[18] Although significant resources are still needed, JE-endemic countries are now more aware than ever of how, why, and when to plan JE control efforts and protect populations at highest risk.

PEER-REVIEWED PUBLICATIONS

Broad dissemination of the experiences and data gathered through PATH's JE project will ensure that lessons learned inform future efforts at JE control. The articles listed below represent the information collected to date by PATH and its partners. Additional publications will follow in late 2009 and beyond, addressing global JE disease burden, a summary of safety studies on the live, attenuated SA 14-14-2 JE vaccine, and experiences of regional JE laboratory networks, among other topics.

2006

Suraratdecha C, Jacobson J, Sivalenka S, Nahrahari D. A cost-effectiveness analysis of strategies for controlling Japanese encephalitis in Andhra Pradesh, India. *Journal of Pharmaceutical Finance, Economics & Policy*. 2006;15(1):21–40.

2007

Jacobson JA, Hills SL, Winkler JL, et al. Evaluation of three immunoglobulin M antibody capture enzyme-linked immunosorbent assays for diagnosis of Japanese encephalitis. *American Journal of Tropical Medicine & Hygiene*. 2007;77(1):164–168.

Zhang S, Li Y, Yang J, et al. [Analysis on surveillance data for viral encephalitis of 2005 in Shaanxi Province]. *Chinese Journal of Public Health*. 2007;23(9):1114–1116.

Zhang S, Yin Z, Wang L, et al. [Analysis of Japanese B encephalitis vaccination and a knowledge, attitude and practice survey in Shaanxi Province]. *Chinese Journal of Vaccines and Immunization*. 2007;13(4):378–380.

Photos: Patrick McHern (left) and PATH/Julie Jacobson (right)

2008

Gatchalian S, Yao Y, Zhou B, et al. Comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants. *Vaccine*. 2008;26(18):2234–2241.

Fischer M, Hills S, Staples E, et al. Japanese encephalitis prevention and control: advances, challenges, and new initiatives. In: Scheld WM, Hammer S, Hughes JM, eds. *Emerging Infections*. Vol. 8. Washington DC: American Society for Microbiology. 2008:93–124.

Ompusunggu S, Hills SL, Sembiring Maha M, et al. Confirmation of Japanese encephalitis as an endemic human disease through sentinel surveillance in Indonesia. *American Journal of Tropical Medicine and Hygiene*. 2008;79(6):963–970.

Touch S, Grundy J, Hills S, et al. The rationale for integrated childhood meningoencephalitis surveillance: a case study from Cambodia. *Bulletin of the World Health Organization*. 2009;87(4):320–324.

Wang H, Fu S, Wang L, et al. [Confirmed diagnosis for Japanese encephalitis reported cases in Shaanxi Province during 2005–2006]. *Chinese Journal of Vaccines and Immunization*. 2008;14(2):118–120.

Zhang S, Yin Z, Suraratdecha C, et al. [Analysis on data from the clinical acute viral encephalitis surveillance system in three prefectures in Shaanxi during 2005–2006]. *Chinese Journal of Epidemiology*. 2008;29(9):895–898.

2009

Elias C, Okwo-Bele JM, Fischer M. A strategic plan for Japanese encephalitis control by 2015. *Lancet Infectious Diseases*. 2009;9(1):7.

Hills S, Phillips D. Past, present, and future of Japanese encephalitis. *Emerging Infectious Diseases*. 2009;15(8):1333.

Maha MS, Moniaga VA, Hills SL, et al. Outcome and extent of disability following Japanese encephalitis in Indonesian children. *International Journal of Infectious Diseases*. 2009;13(6):e389–393.

Touch S, Hills S, Sokhal B. Epidemiology and burden of disease from Japanese encephalitis in Cambodia: results from two years of sentinel surveillance. *Tropical Medicine & International Health*. 2009. [Epub]

Yaïch M. Investing in vaccines for developing countries: How public-private partnerships can confront neglected diseases. *Human Vaccines*. 2009; 5(6):368–369.

Photos: PATH/Julie Jacobson (left) and Jacques Bablon (right)