PATH's Japanese encephalitis project

COLLABORATION AND COMMITMENT TO PROTECT ASIA'S CHILDREN

PATH
A catalyst for global health

Japanese encephalitis transmission area

Source: US Centers for Disease Control and Prevention

INTRODUCTION

Japanese encephalitis (JE) is the leading viral cause of disability in Asia.[1] The mosquitoes that transmit JE breed in areas of standing water—such as rice paddies—and rural communities of Asia are particularly vulnerable. The disease primarily affects children and begins with flu-like symptoms, sometimes progressing to abnormal behavior, confusion, and agitation. As the illness advances, seizures may occur, and patients often become comatose. Approximately 70 percent of those who develop JE illness either die or suffer long-term neurological disabilities.[2]

Immunization is the best method for prevention of JE, but control efforts have been hindered by inadequate disease surveillance, a limited and unstable vaccine supply, lack of guidance and programmatic support, and insufficient advocacy.

Focused efforts from PATH and its partners over the past several years, however, have shifted the landscape of JE control. Dedicated endeavors have resulted in unprecedented progress in recording JE disease burden in endemic countries, ensuring access to safe and affordable vaccines, and advancing national programs for JE control. JE immunization is now under way in many developing countries and a priority for others in the near future.

Photo: PATH/Julie Jacobson

PATH'S JAPANESE ENCEPHALITIS PROJECT

PATH first heard the call for JE control directly from within one of the countries suffering its greatest burden. In 2000, health officials in Andhra Pradesh, India, working with PATH to introduce hepatitis B vaccine and boost general immunization services, raised concerns about JE. Voices rose from several other states, weary from repeated outbreaks and in search of a solution. The JE project set its goals and carried out a broad array of activities that responded directly to the needs, priorities, opportunities, and challenges in endemic countries.

Through a generous grant from the Bill & Melinda Gates Foundation, PATH's JE project was established in 2003 with the goal of eliminating clinical JE and avoiding the unnecessary death and disability caused by this disease. The project focused on providing technical support to JE-endemic countries and operated according to the following objectives:

- Improve data for decision-making.
- Advance the availability of an improved vaccine.
- Introduce vaccine to immunization systems.
- Expand outreach through advocacy.

This report summarizes the accomplishments gained and challenges faced through the JE project's work with partners and endemic countries to meet these objectives. Fact sheets on each technical area, included with this report, provide further details and offer lessons learned to benefit future JE control efforts.

OBJECTIVE 1:
IMPROVE DATA FOR DECISION-MAKING

Disease surveillance

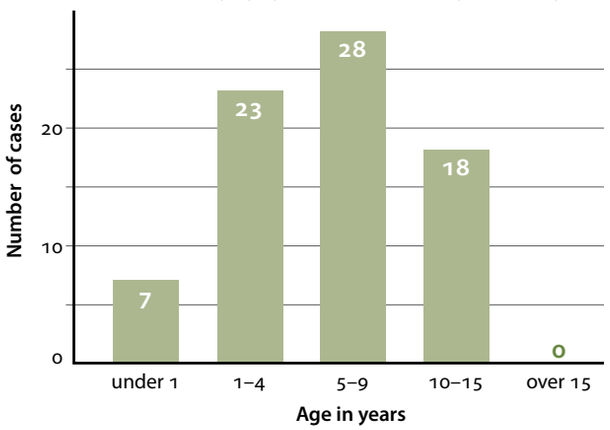
To consider the appropriateness and potential impact of JE vaccine introduction, decision-makers need information on JE incidence, case fatality rate, age distribution, and more. Reliable, routine surveillance activities are critical to gathering these important data. Their value also extends beyond program planning. Continued surveillance reveals the ultimate results of JE immunization and helps inform program evolution and management.

PATH and its partners collaborated to initiate or strengthen encephalitis surveillance in several countries, and these activities often provided crucial insights:

- In Indonesia, a sentinel surveillance study revealed JE throughout the country rather than just in pig-rearing areas, as prevailing wisdom had held.[3]
- In Vietnam, hospital-based surveillance showed that JE cases were persistent in areas not reached by the geographically targeted JE immunization program, and officials are now planning national expansion.[4]
- In Cambodia, sentinel surveillance showed clear evidence of disease burden, with children younger than 12 years of age at highest risk (see chart below). These results were pivotal to health officials' decision to introduce the live, attenuated SA 14-14-2 JE vaccine in October 2009.[5]

These and similar efforts in other countries were facilitated by the publication of the World Health Organization (WHO) JE surveillance standards, which provide a clinical case definition for acute encephalitis syndrome (AES) and criteria for laboratory confirmation of JE. A version of the surveillance standards was distributed in 2006 for field testing. Feedback from country-level activities, combined with input from the JE Core Working Group—an advisory group of experts in public health, clinical and laboratory issues, and other aspects related to JE disease—helped refine an updated version published in August 2008.[6]

Distribution of JE cases by age group (Cambodia, May 2006–May 2007)



JE diagnostics

Beyond clinical case evaluation, the next step in surveillance activities is confirmation of JE through sample collection and laboratory testing. But major challenges have prevented streamlined and reliable JE diagnostic testing in developing countries.

One significant obstacle is the lack of standardized JE test kits. 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 cerebrospinal fluid. PATH and its partners conducted studies to evaluate the accuracy and usability of currently available commercial kits (the Panbio JE-Dengue IgM Combo ELISA by Inverness [Brisbane, Australia], the JE IgM ELISA by InBios International, Inc. [Seattle, USA]; and the JEV CheX kit by XCyton Diagnostics Ltd. [Bangalore, India]):

- An evaluation in partnership with the Armed Forces Research Institute for Medical Sciences (AFRIMS) found high sensitivity among all three kits but low specificity of the kits manufactured by InBios and XCyton when dengue is also present—both had limited capacity to distinguish between JE and dengue infections. The Panbio kit includes both JE and dengue antigens.[7]
- A field evaluation of the Panbio and XCyton kits, in partnership with Nepal's National Public Health Laboratory and AFRIMS, showed that both kits had good predictive values using single serum samples from AES cases, and either kit could be used for laboratory-based JE surveillance in similar epidemiologic settings.[8]

Future efforts will need to ensure that evaluations of diagnostic kits are standardized and that all countries at risk of JE have access to qualified national or regional reference laboratories. Regional laboratory networks in WHO's Southeast Asia and Western Pacific regions will provide training, protocols, and technical assistance to national laboratories as they continue to build capacity in JE diagnostics.

Disability after JE

An often-unrecognized burden of JE is the neurological disability it causes in more than one-third of survivors, which can be as severe as paralysis or as mild as lingering learning disabilities and behavioral changes.[2] A complete definition of disease burden would include not just deaths caused by JE, but also the social and economic impact of disability on families and communities. Thus, data on JE disability comprise another important element to be considered by decision-makers.

Image from the video *Shadow Lives* (PATH)

Mahesh suffered long-term neurological disability as a result of JE infection and requires constant supervision and care from his family.

SHADOW LIVES: A HIDDEN TOLL

Mahesh was a typical boy from a rural village in southern India. He went to school, played with friends, and helped with household chores. Today, he is a shadow of his former self.

Two years ago, Mahesh contracted JE. Although he has fared better than most—he survived and has no physical disability—the infection damaged his brain so badly that he no longer recognizes his own parents. Today, Mahesh attends school, but he sits passively in the back of the classroom, unable to concentrate for any stretch of time. He will never be able to work, and his illness has been emotionally and financially devastating to his family.

JE vaccination is the only way to avoid such tragedy. Determined to overcome the toll of JE on children like Mahesh, the Government of India made an unprecedented commitment to spare vulnerable children. Mass vaccination campaigns were initiated in 2006, and by 2010 more than 100 million children will be protected.

PATH supported the University of Liverpool's efforts to develop a tool for assessing disability after JE that would be simple, adaptable, and easy to use in resource-limited settings. The Liverpool Outcome Score met these criteria, incorporating a set of questions posed to caregivers along with observation of the child performing simple tasks such as walking and grasping an object.[9]

Small-scale studies in several countries revealed the tool to be a valuable method for gathering data on the burden of JE disability while estimating the likelihood of a JE survivor ultimately leading an independent life:

- In Cambodia, among 38 survivors who were assessed, researchers applying the tool at home visits found that 11 percent had severe sequelae, 38 percent had moderate sequelae, and 45 percent had minor sequelae.[10]
- In Indonesia, 65 children were evaluated, and half either died or were left with serious disabilities.[3]
- In Vietnam, among 26 laboratory-confirmed JE cases, 2 cases had severe sequelae, 5 had moderate sequelae, and 8 had mild sequelae.[4]

The disability studies clearly show the devastating impact of JE. Among the cases assessed in these studies, up to one-quarter died, and almost half of JE survivors suffered severe or moderate disabilities, requiring constant support from their families and communities. As few as four percent of JE survivors recovered completely.

Cost-effectiveness of JE immunization

Immunization is one of the most cost-effective health interventions available. It is universally accepted that adopting vaccines is among the very best uses of scarce health care dollars. But even though immunization is universally recognized as a good use of health resources, many countries have limited resources to invest in new vaccines. When faced with competing priorities and limited resources, economic evaluations can help determine appropriate resource allocation and design services.

In 2006 in Andhra Pradesh, India, investigators compared the cost-effectiveness of (1) two strategies: a one-time catch-up campaign or a catch-up campaign combined with routine immunization, and (2) two vaccines: inactivated, mouse brain–derived JE vaccine and live, attenuated SA 14-14-2 JE vaccine. Results demonstrated that the WHO-recommended JE vaccine introduction strategy (catch-up campaigns plus routine immunization) using the live, attenuated SA-14-14-2 JE vaccine is 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 were found to be more cost-effective.[11] It is important to note that this analysis was completed prior to the availability of public-sector pricing for the SA 14-14-2 vaccine, which further improves its cost-effectiveness.

Similarly, PATH launched a study in 2007 to analyze cost-effectiveness of JE vaccines in Cambodia, collaborating with the Communicable Disease Control Department and the National Immunization Program of the Ministry of Health. Results helped guide decision-making and inform the JE immunization strategy.[5]