



Approaching vaccination from end to end

Five lessons from more than
15 years of advancing Japanese
encephalitis vaccination



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Introduction

Starting at the end



A comprehensive approach for vaccine introduction and sustainability enables unprecedented success.

From early-stage research and development to navigating regulatory hurdles and vaccine introduction policies, PATH's Japanese encephalitis (JE) project was unique. It arose from an unanticipated need, faced unforeseen challenges, and developed several unexpected solutions.

In 2000, JE, a mosquito-borne viral infection of the brain, was relatively unknown as a global health issue. Unlike polio or measles, which are globally distributed, JE is a regionally endemic disease in Asia and parts of the Western Pacific. Although more than 3 billion people live in at-risk areas, many are unaware of JE because encephalitis can be caused by several different pathogens, JE diagnosis can be complex and expensive, and there is no specific treatment for JE. As a result, a specific JE diagnosis was rarely sought, disease surveillance was limited, and there were no large-scale JE interventions being implemented. JE was truly a neglected tropical disease.

Then, in 2003, after local public health officials in India raised concerns about JE to PATH staff, PATH got involved.

At the start of the project, safe and affordable JE vaccines were out of reach for most low- and lower-middle-income countries. Over the course of nearly 20 years of working on JE—along with lessons from other vaccine projects such as the Meningitis Vaccine Project¹—PATH and its partners developed a new and much needed approach to introducing a previously unavailable JE vaccine.

PATH's JE vaccine project began with an end goal and worked backward, conducting end-to-end activities that spanned from improving the quality and production of the vaccine to conducting additional clinical trials to country-specific introduction activities.

It started with clear alignment and shared understanding of the need to save lives from JE, ended with sustainable country-led programs, and fostered comprehensive thinking by integrating diverse perspectives at all points along the way. It was unprecedented, and it worked. Through support from PATH and its partners, since 2003, ten countries have introduced a now more widely available JE vaccine. Over that time, more than 300 million children have been protected from the disease through vaccination.

Sharing a common end goal

From the project's start, the end goal was clear—save lives from JE now. Having a shared end goal allowed for flexibility and creativity when considering multiple solutions and approaches,

¹For more information about the Meningitis Vaccine Project, please visit: <https://www.path.org/articles/about-meningitis-vaccine-project/>



including those that did not involve development of a new JE vaccine. If the project had solely focused on creating and developing a new JE vaccine, it would have missed an opportunity to save time and resources by scaling an existing, but largely unknown vaccine. It also would have missed an opportunity to support the development of a Chinese vaccine manufacturer as a producer of low-price, high-quality vaccines for public health application. Agreement on the end goal allowed acceptance of this alternative approach.

In addition, a clear and common end goal made it easier for diverse partners and stakeholders from across many technical areas to work together to solve a common problem. From the outset, the JE project team developed one comprehensive plan with several paths, all leading to decreased death and disability due to JE. These included but were not limited to:

- Elevating global, regional, and national awareness of JE and disseminating evidence through advocacy and communications.
- Supporting countries' JE surveillance and diagnostics efforts.
- Ensuring safety and quality of a suitable vaccine through clinical trials and chemistry, manufacturing, and controls (CMC) activities.
- Supporting stable and predictable vaccine supply and demand through demand forecasting.
- Informing country decision-making with evidence from clinical trials and health economics.
- Supporting countries' data-based decision-making, planning, and logistics for smooth and sustainable vaccine introduction.
- Coordinating global efforts by convening a global resource center for JE.

Because experts from many technical areas worked together, PATH's JE team was able to make connections and identify gaps and opportunities that may have been missed if this

work was done piecemeal. For example, if this project had narrowly focused on CMC without broader perspective or input from experts in vaccine introduction, we might have risked developing a JE vaccine with very little country demand because of a presentation incompatible with country delivery systems.

Similarly, countries preferred a vaccine that resulted in immunity for life after a single dose and could be obtained at an affordable price. PATH's experts in health impact, new vaccine policy, health economics, financing, cold chain, and other key areas listened to experts in vaccine introduction regarding these country needs and made it happen together.



Over nearly 20 years, the partnerships forged through the effort to introduce JE vaccination have had an impact that goes beyond JE in the Asian and Western Pacific regions. Not only did these partnerships result in more than 300 million children being protected from JE, they also strengthened health systems across multiple countries.

Developing an end-to-end approach

Just as a clear end goal informed the JE project's initial approach, the end results continue to inform other efforts at various points along the development-to-delivery spectrum. For example, early-adopter countries emphasized that a new vaccine must use the existing cold chain infrastructure, resources, and personnel from other vaccination programs in order to make a new introduction feasible, affordable, and sustainable. In this way, the JE project's end goal also became a beginning, not only for other vaccine efforts that can learn from the JE experience, but also for country-

owned vaccination program sustainability. It became a true end-to-end approach to vaccine introduction, with cycles of feedback, learning, and recalibrating from multiple points of view along the way.

About this report

Over nearly 20 years, the partnerships forged through the effort to introduce JE vaccination have had an impact that goes beyond JE in the Asian and Western Pacific regions. Not only did these partnerships result in more than 300 million children being protected from JE, they also strengthened health systems across multiple countries. Additionally, China is now positioned as a global vaccine manufacturer as a result of this project. As JE immunization gained steam throughout the JE-endemic region, these lessons learned emerged as potential tools for future delivery of vaccines.

So, what factors led to the project's success? As the world faces new challenges with climate change, migration, and emerging infections, how can the global community adapt to continue ensuring protection from JE? How can partners use the JE project experience to inform current and future efforts to take on other health challenges?

This report tries to answer those questions. PATH and its partners have compiled five key lessons learned from the project that they hope will inform, challenge, and inspire ongoing efforts against JE, as well as other vaccination projects, to ensure impact and sustainability.

This high-level summary of lessons from the project is not meant to capture every detail or important learning. If you have questions or would like additional information about any of the lessons or examples shared throughout the report, please reach out by emailing us at jeproject@path.org.



Lesson 1

Meet countries where they are

Successful new vaccine introduction requires listening and appropriately tailoring responses to a country's specific needs and priorities.

PATH has worked on vaccines against Japanese encephalitis (JE) for nearly two decades, but the work came about unexpectedly. This work did not begin by responding to a donor request for proposals. It began by listening to the concerns of local public health officials in India, where PATH learned that JE was having a devastating impact, and deciding to do something about it.

As the project progressed, PATH encountered unique circumstances and challenges in each country considering JE vaccine introduction. In response to these challenges, PATH and its partners first asked what is best for each specific country, then, with the country and other stakeholders, set out to co-develop a remedy. Today, thanks to nearly two decades of using this approach, ten additional countries have added childhood vaccination programs and hundreds of millions of children who would not have been vaccinated are now protected against JE.

Hearing an unanticipated need

JE mainly strikes poor, rural communities throughout Asia and the Western Pacific, and it historically received little attention compared to other vaccine-preventable diseases. By the end of 2000, this began to change thanks to concerned public health officials in Andhra Pradesh, India, and a PATH team that heard their need and decided to help.

In 2000, PATH was working with the government of Andhra Pradesh to strengthen routine immunization services and introduce urgently needed hepatitis B vaccines. Conversations with district- and state-level public health officials revealed a deep concern about “brain fever,” the local term for JE. PATH staff observed the situation and listened to the local concern. While continuing to prioritize work to prevent hepatitis B, PATH also began simultaneous efforts to better understand JE, the scope of the problem, and how to control it. PATH quickly learned that the broader global health community knew little about JE.

First, PATH assessed the magnitude of the problem. JE is caused by a mosquito-borne virus, and, although fewer than 1% of people infected with the virus become ill, infection can progress to life-threatening encephalitis, causing paralysis, seizures, inability to speak, and coma. Nearly 30% of people who fall ill with JE die and nearly half of all survivors have severe, life-long neurological damage. There is no treatment for JE, so the only solution is prevention through immunization. More than 3 billion people live in areas at risk for JE, and as of 2011, an estimated 70,000 cases occurred each year. Although this 70,000 is likely an underestimate due to surveillance limitations, these 70,000 encephalitis cases translate to more than 7 million human JE viral infections per year. Because the risk factors for progression are unknown,



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vaccination programs would have to develop a strategy that includes all children living in risk areas in the 24 JE-endemic countries.

Second, because there is no treatment for JE, PATH realized that childhood vaccination was the most sensible and economically feasible way to control the disease. Because the illness

primarily occurs in children, and survivors may live for another 50 to 60 years, JE results in many more disability-adjusted life-years (DALYs), or healthy years of life lost, per reported case compared to many other vaccine-preventable diseases. To assess the potential impact and feasibility of JE vaccination, PATH performed an

early cost-effectiveness analysis of JE vaccination for 14 endemic countries.² The analysis found that not only would a one-dose, live attenuated JE vaccine given through the routine Expanded Programme on Immunization (EPI) schedule likely be cost-effective in all JE-endemic countries, if the full costs of long-term consequences were included, such an intervention could be cost-saving in many countries.



Third, PATH sought to help countries better understand their JE burden. Investigation of encephalitis outbreaks and improved disease surveillance and diagnostics suggested a previously unrecognized high incidence of JE, prompting the government of Andhra Pradesh to pursue JE vaccination. Andhra Pradesh's success with JE vaccination was shared across India and prompted Indian government ministries, the World Health Organization (WHO), UNICEF, and PATH to establish a cross-sectoral India JE working group to coordinate technical support and information sharing. The working group developed a roadmap for planning JE vaccination programs. JE vaccines were eventually implemented in all of India's JE-endemic states, and lessons from India informed efforts to tackle JE globally. PATH hoped to replicate this model in other JE-endemic countries.

Listening and learning

Every country was different in terms of their awareness about JE and their efforts to control the disease. While India was increasingly aware of JE's impact, other countries had little-to-no awareness of their JE burden and had no way to identify and track cases. Similarly, countries like Japan and Thailand had already evolved solutions for JE over decades. Creating situations to share the awareness and the approaches to

JE control in India, Japan, and Thailand would be an important step to improve JE control throughout the region.

Listening does not end after the initial contact meeting or with vaccine introduction. After introduction, decision-makers often faced additional, unexpected challenges that required a

²Suraratdecha C, Levin C, Jacobson J, La Force M. Demand-driven and affordable next generation vaccines for preventing Japanese encephalitis in Asia and meningococcal meningitis in Sub-Saharan Africa. Presented at: Sixth International Health Economics Association World Congress; Explorations in health economics, July 2007; Copenhagen, Denmark.

continuous and iterative method to identify these challenges and develop country-specific and innovative solutions to address them. For example:

- In Laos, vaccine uptake declined rapidly following the initial introduction. Country decision-makers met with PATH staff to figure out why. Upon investigation, the team found two major problems: parents had little knowledge about JE, and the government had difficulty procuring and distributing the vaccine within the country. To address these concerns, PATH worked with partners to develop short, animated cartoons delivered to parents' phones via social media messaging apps as well as an interactive online training for JE vaccine procurement. This work is ongoing as Laos prepares for nationwide expansion of JE vaccination.
- In Vietnam, the initial JE immunization program was limited to areas thought to have higher incidences of JE cases. In 2007, PATH-supported enhanced hospital-based surveillance that showed many JE cases in areas not reached by the current JE immunization program, prompting officials to plan national expansion.

By incorporating countries' input throughout the entire course of a project, teams could help ensure that programs met countries' needs.





Building a continuous feedback and adjustment cycle

JE prevention and control efforts have been successful largely because of PATH's desire to hear country concerns and partner with them to develop a tailored solution. A key factor in this success was a dedicated network of public health partners who jumped in and brought their own strengths and experiences to the problem-solving table. PATH worked with WHO, Centers

for Disease Control and Prevention, UNICEF, country and local governments, civil society, and public-sector partners to communicate, collaborate, and solve commonly shared problems that could pose challenges to getting the vaccine to at-risk children. Sometimes that meant changing tactics to focus on an unanticipated need or investing in surveillance infrastructure. Other times, it meant finding a way

to deliver vaccines to remote locations or focusing on public and healthcare worker education and communications.

The JE project would not have been successful in helping to protect so many children from JE without initially and continually collecting, seeking, and implementing feedback from countries and many partners over the nearly two decades of its work on JE. Listening and responding appropriately to the needs, priorities, and concerns of beneficiaries is a valuable way to ensure participation and sustainability. Meeting countries where they are is a lesson that can be applied not just to other vaccine programs, but to all public health and development initiatives.

Meeting countries where they are is a lesson that should be applied not just to other vaccine programs, but to all public health and development initiatives.

Country spotlight

Indonesia

In Indonesia, meeting countries where they are meant addressing the need to challenge some long-held assumptions. Surveillance data suggested a greater JE burden than previously appreciated. JE vaccine introduction in Bali led to questions about further introduction, and addressing community cultural concerns about the vaccine required social mobilization.

Many in Indonesia's Ministry of Health (MOH) did not believe that JE was endemic in multiple provinces. Although sporadic human JE virus infections in Indonesia have been well documented on multiple islands since the 1970s, the actual JE burden remained unknown until a 2001 surveillance study conducted by the International Vaccine Institute (IVI) found a significant number of cases in the province of Bali. In 2005, the MOH expanded surveillance with PATH support and found that, although the greatest JE incidence was in Bali, endemic JE cases occurred in eight other provinces, establishing Indonesia as a JE-endemic country.³

After a decade of building political will and planning, subnational JE vaccine introduction in Bali became a reality. In March 2018 with Gavi and PATH support, the MOH vaccinated over 890,000 Balinese children against JE, and JE vaccination is now included in Bali's routine immunization for children. But while Bali's JE control is underway, the eight other JE-endemic provinces in Indonesia remain unprotected. Because the burden varies by province, ongoing cost-effectiveness analyses supported by PATH are informing decisions about which provinces to prioritize.

Another lesson from Bali's experience has been in addressing vaccine hesitancy such as community cultural or religious concerns about the processes or ingredients used to make CD-JEV and other vaccines. To ensure demand for JE vaccine and reduce vaccine hesitancy, the MOH and other stakeholders worked together with Balinese religious and cultural leaders and conducted advocacy and social mobilization campaigns. As the MOH considers scaling up JE vaccination to the rest of Indonesia, these lessons from Bali may help guide the way.



Indonesian Ministry of Health

³ Maha MS, Moniaga VA, Hills SL, et al. Outcome and extent of disability following Japanese encephalitis in Indonesian children. *International Journal of Infectious Disease*. 2009;16(6):e389-393.



Lesson 2

Prioritize public health and simple solutions

Public health benefit must be the foremost goal when developing, identifying, or delivering solutions, and those solutions should be as simple as possible to deliver.

Widespread Japanese encephalitis (JE) vaccination is, first and foremost, a public health solution to JE control. PATH's JE project sought to prioritize public health benefit when identifying and advancing a JE vaccine for global use. Because public health was always the primary goal, the project had a remarkable impact on communities suffering from JE. Finding a JE vaccine that could be optimized for use in a public health setting was an important driver of the JE project's priorities and strategies. And because price, logistics, ease of use, long-term immune protection, and time required are all important factors in determining public health benefit, solutions that are the simplest to deliver are usually the

ones with the highest public health benefit. Therefore, our second lesson learned is to prioritize both public health benefit and simplicity as the foremost goals when developing, identifying, evaluating, or delivering vaccines for public health use.

Finding a safe, effective, and affordable vaccine

After listening to country decision-makers and learning more about the JE burden and need for a vaccine, PATH conducted a landscape analysis of vaccine manufacturers. The goal was to develop or identify a vaccine that was safe, effective, and had a minimal impact on the existing cold chain. In addition, the vaccine had to be affordable for low- and lower-middle-income countries without donor



support. Several inactivated JE vaccines derived from infected mouse brains were used in various countries, but these had safety concerns, required numerous doses, and were unaffordable in many JE-endemic countries—all major obstacles for a public health solution.

After several months of research, a simple solution emerged.

The team identified that one JE-endemic country, China, had developed an effective live attenuated vaccine that met many of the public health requirements. The Chengdu Institute of Biological Products' (CDIBP's) SA 14-14-2 vaccine—now referred to as CD-JEV—had safely and effectively protected 200 million Chinese children over nearly 20 years. It only required one dose for lifelong immunity. Most importantly, CDIBP was willing to work with PATH and other global partners to make this vaccine more available for public health benefit.

The first obstacle was gaining international approval so that countries other than China could readily use the CDIBP vaccine. CD-JEV was not widely used outside of China and, because it did not initially meet international manufacturing standards, it could not be procured using global funding mechanisms. In fact, no Chinese vaccine had previously achieved the World Health Organization's (WHO) prequalification, an international signal of quality and safety.

Facilitating China's entrance into the global vaccine market

To be procured through international mechanisms like WHO, UNICEF, other United Nations-associated health programs, and Gavi, the Vaccine Alliance, vaccines need to be WHO-prequalified. Prequalification required a strong evidence base regarding the vaccine's safety, efficacy, and manufacturing quality and was an important step in providing CD-JEV to low- and lower-middle-income countries. PATH partnered with CDIBP and other partners to build the evidence base and take the steps needed for prequalification. PATH supported

capacity building, demand forecasting, contingency planning, construction of a new manufacturing facility, and development of a Quality Management System and a Pharmacovigilance System.

New facility construction immediately tripled CDIBP's vaccine production capacity. In addition, this new facility was deemed compliant with Good Manufacturing Practices (GMP), a system for ensuring vaccines are consistently produced and controlled according to international quality standards. In 2012, CDIBP began producing CD-JEV in its new facility, which underwent comprehensive

inspections to ensure the vaccine and manufacturing site met international standards.

One of the requirements for prequalification was a "bridging" clinical trial, a scientific study that shows that the vaccine made in the new GMP-compliant facility had the same efficacy, safety, and quality of the vaccine made in the previous manufacturing facility and used in previous clinical studies.

Alongside efforts to build the evidence for prequalification, PATH continued to perform demonstration projects and post-licensure clinical trials outside of China. This was done to leverage buy-in from JE-endemic countries and increase product confidence in China's first WHO-prequalified vaccine. Although China has been exporting several vaccines to low-

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income countries for decades through bilateral aid programs, changing global perception of vaccine quality was an important step.

To help facilitate these demonstration projects, PATH secured millions of CD-JEV doses that could be donated to countries. CDIBP provided these vaccines as part of a collaborative agreement whereby PATH provided CDIBP with technical assistance in strengthening and increasing its vaccine manufacturing capabilities in exchange for access to this donated vaccine. In addition, CDIBP agreed to provide CD-JEV at a lower price to several JE-endemic low- and lower-middle-income countries. By demonstrating the safety, effectiveness, quality, and value of CD-JEV in JE-endemic countries, these projects and trials laid the groundwork for countries to introduce the vaccine.

In 2013, WHO prequalified CD-JEV—the first-ever prequalification for a vaccine made in China. Prequalification opened the door for CD-JEV to be supported by Gavi for introduction in low-income countries. Just as important, the prequalification symbolized China’s entry as a contributor to the global vaccine market and as a benefactor of global public health.

Ensuring affordability

While partners were working to increase vaccine availability through WHO prequalification, PATH and CDIBP addressed another key bottleneck in vaccine access—affordability. If the vaccine was prequalified but remained unaffordable for the countries that needed it, it would be difficult to achieve public health impact. Early in the JE project, PATH negotiated

with the manufacturer to secure a maximum public-sector price for the vaccine for the JE-endemic region. This public health pricing mechanism, which is in place until 2033, allows vaccine introduction in countries with limited public health resources, while still supporting CDIBP’s business goals even in the absence of support from other donors such as Gavi.

Achieving a vaccine price that was sustainable for CDIBP and low- and lower-middle-income countries alike was a critical step. Providing a vaccine for widespread public health impact should not have a negative financial impact on a manufacturer; instead, it should have both public health impact and a positive business impact to keep private-sector partners engaged. Through the pricing agreement, PATH and CDIBP opened new markets for CD-JEV, increased access to the vaccine for many countries, and ensured a sustainable supply for the foreseeable future.

While Gavi-eligible countries now benefit from Gavi support for JE vaccination, the price negotiations greatly benefited several low- and middle-income countries in the JE-endemic region before Gavi support was available, and the low price will continue to benefit non-Gavi-eligible, Gavi-graduated, and middle-income countries who do not receive donor support for childhood vaccination programs.

PATH also supported CDIBP through demand forecasting projections, which provided useful data for the manufacturer and global partners like Gavi.

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Prioritizing public health and sustainability

PATH's JE project showed the potential benefits of multi-sector partnerships that prioritize vaccines for low- and lower-middle-income countries. Vaccine manufacturers may be hesitant to invest in vaccines for low-income countries, where profits will be minimal, unless another group—like a donor, non-profit, or public institution—are committed to sharing the investment. Although PATH prioritized public health and the availability of vaccine for low-income countries throughout this project, the partnership also sought to maintain an acceptable profit margin that would keep CDIBP engaged in producing vaccine for international export.

Country spotlight

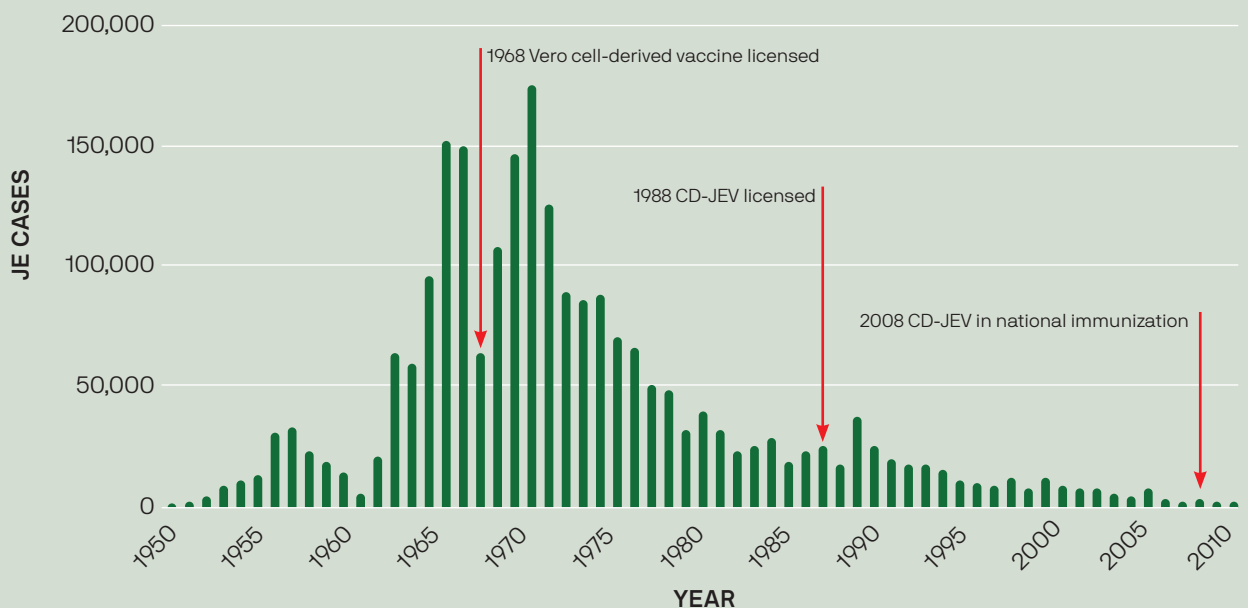
China

In addition to its leadership role in developing and distributing the CD-JEV vaccine, China was an early leader in national JE control. A highly JE-endemic country, the first clinical case of JE in China was confirmed in 1943. A national JE case reporting system was established in 1951, and in the decades that followed, China saw several major JE epidemics.

The first use of JE vaccine in China was with an earlier, inactivated mouse brain-derived vaccine that was licensed in 1968. Development of the live attenuated SA14-14-2 vaccine (CD-JEV) began in the 1970s under the leadership of Dr. Yu Yongxin at the National Institutes for Food and Drug Control. In the early 1980s, his team transferred the vaccine technology to the Chengdu Institute of Biological Products (CDIBP), one of several vaccine manufacturing institutes in China, for further development. After undergoing safety and efficacy testing, CD-JEV was licensed in China in 1988. Because of its improved safety and fewer required doses compared to the inactivated vaccine, it was introduced in immunization programs starting in 16 provinces and gradually expanded to the national EPI starting in 2008, with over 200 million children vaccinated in a 20-year period.⁴

Due to the commitment of Chinese health authorities and CDIBP to reducing JE's toll through vaccination, JE incidence in China decreased from 21 cases per 100,000 in 1971 to an estimated 0.12 cases per 100,000 in 2011. Later, this same commitment by CDIBP would help make CD-JEV available to save lives not just in China, but across the entire JE-endemic region in Asia and the Western Pacific.

China's control of Japanese encephalitis, 1951-2011.



⁴ Gao X, Li X, Li X, et al. Vaccine strategies for the control and prevention of Japanese encephalitis in mainland China, 1951-2011. *PLoS Neglected Tropical Diseases*. 2014;8(8):e3015. doi: 10.1371/journal.pntd.0003015.



Lesson 3

Work together

Global partnership and coordination are essential for new vaccine introduction.

What does it take to identify, evaluate, introduce, scale, and sustain a safe, effective, and low-cost vaccine to millions of children? In the case of the Japanese encephalitis (JE) vaccine, a diverse set of partners—governments, civil society, local immunization champions, multilateral organizations, and the private sector—working toward a common goal were essential.

Using advocacy to raise awareness and reach consensus

At the start of the project, JE and its burden were not well understood at global and national levels. To gain and maintain the necessary support from global, regional, and local partners to tackle JE, PATH used advocacy to raise awareness and build consensus for JE control throughout the project.

The first priority was partnering with the World Health Organization (WHO) to raise awareness of JE and gain consensus on regional priorities through the bi-regional meetings on JE control. These regional meetings brought together partners and country

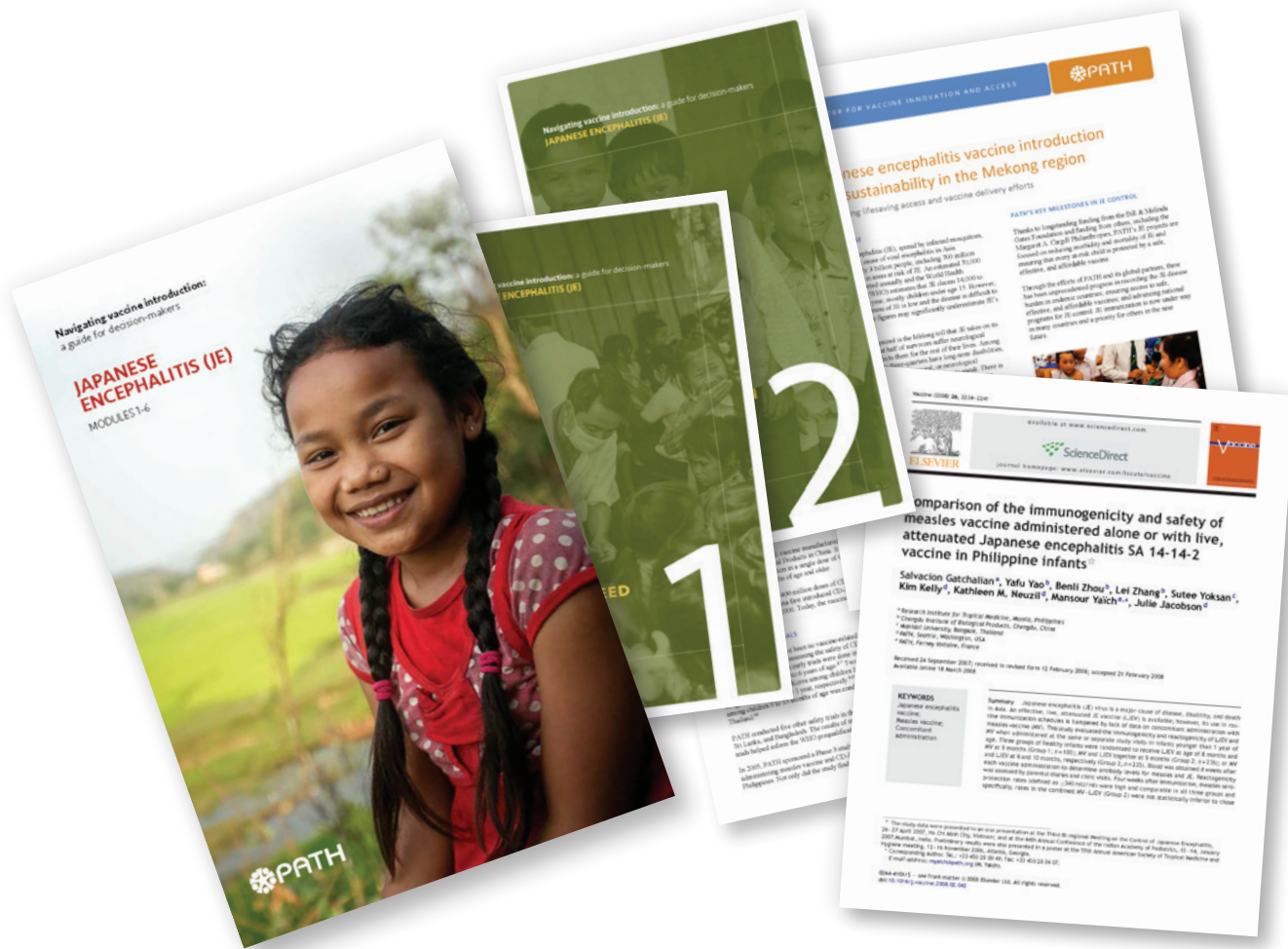
officials from countries in South Asia, Southeast Asia, and the Western Pacific and became a strategic venue for JE advocacy and communications. PATH also worked to ensure that national convenings in endemic countries, such as annual pediatric association meetings, included JE.

Another priority for advocacy and awareness-raising was the collection of new and existing

data and information on the burden and control of JE from a variety of resources, which were reconfigured and disseminated to various audiences. These included a series of training presentations, messaging, fact sheets, newsletters, case studies, peer-reviewed publications, a vaccine introduction decision-making guide, social media resources, and media outreach. Early in the project, the team and its partners also developed three films for use by stakeholders and health officials in advocacy efforts—two of which aired on BBC World and were broadcast in more than 200 countries.

Advocacy and communication efforts to highlight JE's burden and the impact of vaccination helped prioritize JE immunization, build consensus, foster collaboration, and inform strategy decisions from WHO, Gavi, and country governments. Working together requires starting on the same page, and advocacy and communications about the issue is a critical way to ensure consensus.

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Making it possible with partnership

Bringing together partners makes progress possible. Several key partners played crucial roles throughout the course of the JE project, including:

- Country stakeholders:** Country decision-makers, advisors, implementers, health workers, and immunization champions—from Cambodia, India, Laos, Nepal, Sri Lanka, and other JE-endemic countries—were the crucial change-makers to protect their countries' children from JE. Country advocates and experts were a key part of helping to determine the burden of disease, conducting and supporting clinical trials to build the evidence base, raising local and global awareness around JE, convincing country governments to introduce JE vaccine into routine immunization, and increasing country demand. Countries also learned from each other's experiences and expertise and took a leadership role in driving momentum in global discussions.
- World Health Organization (WHO):** WHO is a critical partner for setting global JE standards and recommendations for countries. WHO regional offices played a key role in seeing and responding to countries' needs, hosting the bi-regional



meetings on JE, and communicating with regional and national immunization technical advisory groups and in-country stakeholders. PATH also worked with the global WHO office in several ways, including helping develop global surveillance standards for JE and forming a JE laboratory network. PATH helped inform the WHO Prequalification team in order to achieve prequalification for CD-JEV in 2013 and worked with the WHO Strategic Advisory Group of Experts on Immunization (SAGE) JE working group, which led to a new JE vaccine position paper recommending vaccination in 2015.

- **Bill & Melinda Gates Foundation (BMGF) and other funders:** Without funding and prioritizing protection against JE through vaccination, none of these efforts would have been possible. Funders like BMGF played a crucial role in supporting, guiding, and advising the JE project from the start. The long-term commitment of BMGF and their willingness to look comprehensively at the problem in order to develop effective, country-specific solutions proved critical to long-term success.
- **Chengdu Institute of Biological Products (CDIBP):** As the CD-JEV manufacturer, CDIBP played a key role through their commitment to achieving and maintaining international quality standards and scaling up production capacity to meet demand. CDIBP's willingness to negotiate an affordable private-sector price was also integral to other countries' ability to access the vaccine. The strong partnership with CDIBP revealed the important role that emerging country vaccine manufacturers can play in helping to meet the needs for regionally targeted vaccines that large, global manufacturers may not be willing to address.
- **Gavi, the Vaccine Alliance:** From the beginning, Gavi was a pivotal and willing partner to help collate and disseminate information on JE disease and

vaccines. Gavi's decision to open a funding envelope for CD-JEV immediately after the vaccine was prequalified greatly expanded and expedited country introductions of JE vaccine. Gavi also provided crucial insights into vaccine procurement and funding as well as technical assistance, awareness raising, and monitoring for countries.

“The partnerships and the collaborations have been an absolutely essential component of the success of the JE project.”

– Susan Hills, U.S. Centers for Disease Control and Prevention

- **United Nations Children's Fund (UNICEF):** UNICEF was crucial in helping to ensure that the supply and procurement of CD-JEV was a smooth process for countries both with and without Gavi support. UNICEF also played a key role in developing information, education, and communication (IEC) materials for social mobilization in countries introducing the vaccine.
- **US Centers for Disease Control and Prevention (CDC):** The CDC's global programs made it possible to set up data and surveillance systems to track



JE cases and outbreaks, informing countries of their burden of disease, contributing to cost-effectiveness analyses, and verifying the impact of the vaccine post-introduction.

- **US Armed Forces Research Institute of Medical Sciences (AFRIMS):** AFRIMS played a key role with helping to strengthen early diagnostic capacity for JE through assay evaluations and support to countries.
- **International Vaccine Institute (IVI):** IVI's leadership in surveillance and partnership in developing cost-effectiveness models for global use of JE vaccine were pivotal for informing countries' decisions to introduce.
- **Microsoft:** An innovative partnership between Microsoft employees and PATH provided flexible funding to support ad-hoc, country-identified needs for JE vaccination efforts in Cambodia, Laos, and Vietnam.
- **Clinical trial sites:** Highly skilled clinicians and researchers at diverse institutions, such as the International Center for Diarrhoeal Disease Research,



Bangladesh (icddr,b) and the Research Institute for Tropical Medicine, conducted trials in JE-endemic countries. The trial results were pivotal to global and regional decision-making for JE vaccines.

- **Academic institutions:** Academic institutions were instrumental in the development of standards and guidelines to advance the field of JE prevention, control, and monitoring throughout the project. The University of Liverpool, for example, developed a tool for healthcare providers to assess children’s level of disability after becoming ill with JE and a guide for JE disability management in low-income countries.

The partners listed above are only a subset of all the individuals, organizations, corporations, and countries that played a part in achieving success. With this large number of important partners, PATH had to define and emphasize its role as the global coordinator of this partners network. Regular communication and meetings within this network ensured that all the partners were aligned in their direction and able to communicate challenges, remedies, and best practices. The partners’ continuous input, which required a plan to regularly collect and address, was vital to the flexibility and success of the project.

Creating trusting and supportive relationships

Because of the importance of partners, building and maintaining relationships became critical. PATH had to establish communication mechanisms, build partner capacity and buy-in, and conduct regular outreach. Large-scale projects in immunization—as in all global health and development efforts—need leadership and dedicated time to reach across national, cultural, and sectoral boundaries; forge new partnerships; and encourage participation through active, sustained engagement.

By acknowledging and building in objectives around advocacy, coordination, outreach, and/or coalition building, projects can help ensure that all the right partners are at the table. Working together means that all the right voices can not only be heard, but also acted upon.

Country spotlight Nepal

With an estimated 12.5 million people at high risk for JE and a significant historical JE burden, Nepal's efforts to control and prevent JE through surveillance and vaccination are an excellent example of how a low-income country can overcome barriers such as the lack of disease surveillance data, inadequate financial resources, competing vaccination priorities, and the need for technical assistance.

Nepal's decision-makers knew that, in order to overcome these barriers, they needed to work with many partners. To improve surveillance, Nepal worked with WHO to expand JE laboratory testing. To justify investment in a vaccination program, Nepal collaborated on a cost-effectiveness analysis with the University of Liverpool. For financial assistance, Nepal applied for a loan from the World Bank and then, years later, funding from Gavi. Nepal worked with PATH's JE program team for assistance with planning, advocacy, communications, and training materials. Nepal worked with CDC to demonstrate the impact of vaccination on the disease burden in order to justify ongoing support for JE vaccination. The government also collaborated extensively with local community, religious, and media stakeholders to increase JE awareness and build demand for the vaccine.



Information, Education, and Communication (IEC) Materials about JE vaccine were translated into local languages and shared across Nepal.

No matter the barrier, Nepal prioritized collaboration and partnership in order to protect its children from JE. With the success of its JE immunization program, Nepal then became a resource and partner for other countries, sharing best practices through peer-to-peer learning opportunities at conferences and meetings.





Lesson 4

Decide with data

Country decision-making for immunization programs requires data.

From the beginning, PATH's Japanese encephalitis (JE) vaccine project emphasized that countries need data for decision-making. Data such as JE incidence, measures of cost-effectiveness, estimates of the long-term cost of vaccination, modeling of the potential impact of vaccination, and modeling the potential impact of JE vaccine introduction on other established Expanded Programme on Immunization (EPI) vaccines are needed to make sound decisions regarding JE vaccine introduction.

At the same time, the cost, time, and logistical challenges associated with conducting surveillance or collecting these other data may be prohibitive. This means that every country

may not need its own detailed data. Although public health decisions should be based on country-specific data as much as possible, the JE project showed the potential and value of regularly sharing high-quality data between neighbors in order to make decisions on new vaccine uptake. In other words, the data does not need to be perfect, complete, or country-specific for a country to make well-informed, evidence-based decisions.

Laying a foundation for decision-making through disease surveillance

Assessing a country's disease burden through surveillance is the first and most important step for decision-making about vaccine introduction. JE surveillance, however, is complicated by many factors. First, JE is only one of several causes of acute encephalitis syndrome (AES), and it has no specific clinical presentation compared to other causes of AES.

Second, a JE diagnosis can only be made through either laboratory testing of cerebrospinal fluid, which may be difficult to collect in some settings, or testing serum samples taken during both the acute and recovery phases of illness. For countries lacking laboratory capacity, equipment, or trained personnel, these diagnostic methods present several challenges. Additionally, the JE virus has cross-reactivity with other regional flaviviruses, such as dengue and West Nile viruses, that may be co-circulating at the same time in the same



areas, resulting in diagnostic errors. Finally, a lack of reporting standards can prevent the collection of standardized and useful data. Overcoming these challenges to provide enough surveillance data for decision-making was an important part of PATH's JE project.

Assessing a country's disease burden through surveillance is the first and most important step for decision-making about vaccine introduction.

To address diagnostic challenges, PATH worked with partners to develop WHO JE surveillance standards, evaluated and supported development of JE diagnostic tests with several manufacturers, and helped support establishment of and standards for regional JE laboratory networks. The global team of partners assisted in the evaluation of sensitivity and specificity across diagnostic kits and the development of a validation panel to assist national level use of in-house diagnostic kits. Importantly, the partners worked with national programs in collaboration with WHO regional offices to begin or enhance JE surveillance. Increased surveillance efforts led by the US Centers for Disease Control and Prevention (CDC) in Bangladesh, Cambodia, China, India, and Nepal provided insights into the burden of JE disease to inform decision-making on immunization. One key lesson from enhancing country surveillance was that JE disease burden involves not only the acute disease, but also its devastating sequelae, including long-term disability—an important factor when considering the potential value and impact of a JE vaccine.

Building in-country surveillance capacity allowed governments to generate data to answer a critical question—whether their country would benefit from introducing a JE vaccine. Having a good surveillance system in place before vaccine introduction also enabled disease burden monitoring after introduction to determine vaccine impact. One of the challenges of the JE project, however, was that not every country had the capacity to conduct nationwide disease surveillance. Often, countries only had surveillance in a handful of hospitals. Frequently, these hospitals were in urban settings as opposed to the rural settings where JE occurred more frequently. Others only had syndromic AES surveillance, with no way to confirm the proportion of cases caused by JE. Some had no surveillance at all.

At the same time, WHO, CDC, PATH, and other JE experts knew that vaccination would likely be beneficial for most countries in the JE-endemic region based on data from neighboring countries and/or the presence of the principal vector mosquito and similar ecology, geography, and agricultural practices. WHO, CDC, and PATH's JE team also helped countries determine the likelihood that JE virus transmission is occurring by investigating AES outbreaks. Although these types of data are not perfect and are often incomplete, they may provide a compelling-enough picture of likely disease burden to inform vaccine decision-making. WHO has recognized that JE surveillance data does not have to be complete or perfect before making the decision to introduce JE vaccination, which WHO recommends that countries integrate into routine immunization in all areas where JE is recognized as a public health priority or is likely present due to environmental factors.

In order to decide with data, programs must have data to use—but when enough regional and global contextual evidence exists, routine national surveillance is not necessary to justify action.



Building confidence through clinical trials

A mainstay of developing and introducing any new vaccine is ensuring its safety, efficacy, and ideally, co-administration feasibility with data from clinical trials. When PATH began working with the Chengdu Institute of Biological Products (CDIBP) to attain WHO prequalification of the live attenuated JE vaccine, CD-JEV, and help countries make decisions about introduction, the team knew that the decision-making would require data.

In order to achieve WHO prequalification, attain licensure and introduction in individual countries, inform immunization schedules, and transition from other JE vaccines, PATH and partners conducted seven clinical trials with CD-JEV in three JE-endemic countries.

Because most of the safety and efficacy studies needed for prequalification had already been completed both within and outside of China, a lot-to-lot consistency study, conducted in Bangladesh, was the only additional trial required for WHO prequalification. This trial showed that the vaccine made in the new CDIBP manufacturing facility was as safe and immunogenic as the vaccine from the previous facility.⁵ Before conducting that trial, however,



⁵Zaman K, Naser AM, Power M, Yaich M, Zhang L, Ginsburg AS et al. Lot-to-lot consistency of live attenuated SA 14-14-2 Japanese encephalitis vaccine manufactured in a good manufacturing practice facility and non-inferiority with respect to an earlier product. *Vaccine*. 2014;32(46):6061–6066.

Table 1. CD-JEV clinical trials conducted by PATH.

Trial number	Location	Purpose	Main findings
1	Philippines	Safety and immunogenicity of measles vaccine co-administered with CD-JEV	CD-JEV, when given concurrently with measles vaccines at 9 months of age, was safe, immunogenic, and non-interfering with measles vaccination.
2	Philippines	Persistence of antibody protection up to 3 years after the first study in the Philippines	The duration of CD-JEV protection 1, 2, and 3 years after vaccination is not affected by co-administration with measles vaccine.
3	Sri Lanka	Safety and immunogenicity of concurrent CD-JEV and measles vaccine	CD-JEV, when given concurrently with measles vaccines at 9 months of age, was safe, immunogenic, and non-interfering with measles vaccination—confirming this finding in a second JE-endemic country.
4	Sri Lanka	Immunogenicity of CD-JEV following mouse brain-derived JE vaccine	CD-JEV was well tolerated and elicited a strong immune response in 2- and 5-year old children who had previously received mouse brain-derived vaccine, indicating CD-JEV could replace mouse brain vaccine booster doses in the national immunization schedule.
5	Bangladesh	Lot-to-lot consistency of CD-JEV	All lots of CD-JEV manufactured in CDIBP's new manufacturing facility were well-tolerated and produced strong immune responses. This study was required for CD-JEV WHO prequalification in 2013.
6	Philippines	Safety and immunogenicity of concurrent CD-JEV and measles-mumps-rubella vaccine	CD-JEV, when given concurrently with measles, mumps, and rubella (MMR) vaccine at 9 months of age, was safe, immunogenic, and non-interfering with MMR vaccination.
7	Bangladesh	Persistence of antibody protection 3-4 years after the first study in Bangladesh and immunogenicity following a booster dose	While antibody levels may have dipped below measurable levels, CD-JEV elicits a secondary (anamnestic) response following a booster dose, which indicates long-lasting immunity.



PATH also led four other trials looking at CD-JEV co-administration with other vaccines, duration of protection, and transition from the mouse brain vaccine. PATH knew the results would be crucial for safety as well as country decision-making based on concerns about a then-unfamiliar product. Introducing a new vaccine into a country's EPI requires carving out a safe, effective, and logical space for the new vaccine into an already crowded schedule, and an important factor for finding the right place is ensuring that the new vaccine can be safely co-administered with other routine vaccines. This is an especially critical factor when live attenuated vaccines are being administered at the same time. The team needed to ensure that the new vaccine would not disrupt the schedules or effectiveness of existing vaccines—especially those driving global initiatives like measles control or polio elimination.

After the first five trials, PATH conducted two additional studies. One ensured the safety and immunogenicity of CD-JEV when co-administered with measles-mumps-rubella vaccine in the Philippines, and another confirmed the duration of protection of CD-JEV in Bangladesh after the initial trial for WHO prequalification.

All of the clinical trials provided important evidence on safety, immunogenicity, and co-administration that not only resulted in the WHO decision to prequalify CD-JEV in 2013, but also supported countries' decisions to introduce the vaccine in their national immunization programs.

Vaccine safety and efficacy trials and effectiveness studies, however, do not need to be performed in every country considering JE vaccine introduction. Building an evidence base through a limited number of high-quality clinical trials and studies can go a long way to inform decision-makers in many countries.

Informing country strategies with cost-effectiveness analyses

Although immunization is recognized as one of the most cost-effective health interventions available, many countries have limited resources to invest in new vaccines. When faced with competing priorities and limited funds, evidence from economic evaluations can help determine appropriate resource allocation and strategy designs.

Early in the project, PATH worked directly with two countries to conduct cost-effectiveness analyses of CD-JEV before the public-sector pricing agreement was in place. In 2006, the team worked with local investigators in Andhra Pradesh, India, to compare 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: an inactivated, mouse brain-derived JE vaccine and the live attenuated CD-JEV vaccine. Results showed that the WHO-recommended JE vaccine introduction strategy (catch-up campaigns, plus routine immunization) using CD-JEV would be highly cost-effective.⁶ By contrast, this same strategy using the inactivated, mouse brain-derived JE vaccine would not be cost-effective. Given limited resources, immunization strategies targeting only high-risk areas were found to be more cost-effective than vaccinating nationwide. Nationwide strategies may have been more economically favorable with current pricing, but at the time of the analysis CD-JEV's public sector price was not available.

Similarly, PATH and the Cambodian government launched a study in 2007 to analyze cost-effectiveness of JE vaccines in Cambodia. The results also supported a catch-up campaign combined with routine immunization, which helped guide decision-making and inform Cambodia's JE immunization strategy.⁷ A key result from Cambodia's analysis was that initial campaigns would have greater impact by targeting wider age ranges, leading Cambodia to conduct campaigns up to 15 years of age before transitioning into routine JE immunization.

Other cost-effectiveness analyses led by the International Vaccine Institute and partners in China,⁸ Indonesia,⁹ and other countries added to the regional knowledge base of the cost-effectiveness of JE immunization strategies.

When faced with competing priorities and limited funds, evidence from economic evaluations can help determine appropriate resource allocation and strategy designs.

⁶ Suraratdecha C, Jacobson J, Sivalenka S, Narahari 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.

⁷ Touch S, Suraratdecha C, Samnang C, et al. A cost-effectiveness analysis of Japanese encephalitis vaccine in Cambodia. *Vaccine*. 2010;28(29):4593-4599.

⁸ Ding D, Kilgore PE, Clemens JD, et al. Cost-effectiveness of routine immunization to control Japanese encephalitis in Shanghai, China. *Bulletin of the World Health Organization*. 2003;81(5):334-342.

⁹ Liu W, Clemens JD, Kari K, Xu ZY. Cost-effectiveness of Japanese encephalitis (JE) immunization in Bali, Indonesia. *Vaccine*. 2008;26(35):4456-4460.



Disseminating data for decision-making

Data helps countries make the best, most effective decisions, but for it to be useful, it must reach decision-makers. Disseminating the data and sharing information with the right audiences were key elements of PATH's JE project from the start. Data must be clearly and appropriately communicated to decision-makers and influencers in a timely manner.

Advocacy and communication efforts included translating results from surveillance studies, clinical trials, and cost-effectiveness analyses into clear and simple messages for various audiences; including messages in published materials and media resources; conference and workshop presentations, and policy briefs; and working with clinical trial teams to provide guidance and support on communicating trial results to the media. One key lesson from dissemination efforts was realizing the importance of highlighting JE's regional and country-specific impact. Because JE is a regional disease and the disease burden is much lower than many other global diseases, it was largely underappreciated by global funding agencies and international health agencies. However, in an individual country, JE's impact can be catastrophic. These findings needed to be aggregated and communicated upward

to country decision-makers and global funders who support new vaccine introduction. In order to decide with data, decision-makers must have access to and understand the data.

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Using the evidence

Data should always be an essential part of decision-making for public health interventions such as vaccines. However, it is neither feasible nor necessary for every country to have the highest-possible levels of country-specific disease surveillance and vaccine

data. A strong foundation of regional and global data on disease surveillance, vaccine safety and efficacy, and cost-effectiveness—with some country-specific verification—may be enough for a country to implement a cost-effective, lifesaving, and sustainable vaccination program. The benefit of introducing a new vaccine based on non-country-specific data usually outweighs the cost of failing to introduce the vaccine while waiting for perfect data.

Country spotlight Philippines

The burden of JE in the Philippines has been recognized for over a decade. In 2008, a national surveillance program was established to monitor cases of acute encephalitis syndrome. Disease patterns indicate that transmission in the Philippines is variable yet widespread; people living in rural regions with rice or pig farming—two of the largest agricultural outputs in the Philippines—are generally at highest risk. The Research Institute of Tropical Medicine (RITM), located in Manila, was an early and crucial partner in the JE project, recognizing the potential of CD-JEV vaccination for the Philippines. In partnership with RITM, PATH conducted three clinical trials with CD-JEV in the Philippines, vaccinating more than 1,200 children with no vaccine-related adverse events—crucial research that contributed to the WHO approval and recommendation of CD-JEV for use in all JE-endemic countries.

On a national level, data from the surveillance program and clinical trials also informed decision-making within the Department of Health (DOH). The National Immunization Program needed more information to evaluate options for CD-JEV delivery strategies—including routine nationwide vaccination only, a one-time nationwide campaign followed by routine vaccination, or subnational campaigns in high-risk regions followed by routine vaccination. To estimate the costs and benefits of each strategy, PATH conducted a cost-effectiveness analysis comparing these options. With this additional evidence to inform decision-making, in March 2019, the DOH conducted subnational immunization campaigns in four high-risk regions, vaccinating half a million children under the age of 15. Following the conclusion of the campaigns, the DOH is now evaluating the possibility of introducing the JE vaccine into its routine immunization program. PATH has provided continued support to the DOH through campaign planning and evaluation, vaccine provision, and additional cost-effectiveness analysis.

Finally, the Philippines also demonstrated the importance of communicating and disseminating data for building trust and fighting vaccine misinformation. After the completion of the most recent clinical study with CD-JEV, PATH and RITM hosted a meeting in Manila in October 2018 to present and explain the results to trial participants, their families, and other local and national stakeholders.



At the October 2018 community meeting, a presenter from RITM followed each presentation with a quiz. The answers were unanimous: Is the vaccine safe? “YES!” Is it effective? “YES!”



Lesson 5

Plan for the future

Monitoring, forecasting, and planning helps ensure sustainable immunization programs.

Transitioning from an initial vaccination campaign to a sustainable, routine vaccination program within an Expanded Programme on Immunization (EPI) schedule requires planning—and lots of it. When countries plan, the likelihood of successful and sustainable vaccination programs increases. The Japanese encephalitis (JE) project witnessed both the benefits of planning and the challenges faced by countries that had not adequately planned.

Planning ahead to enable impact monitoring

Determining the disease burden before the vaccination program starts not only helps with decision-making, but also allows comparison of the disease burden before and after vaccine introduction (vaccine impact), changes in JE epidemiology, and changes in JE vaccine performance. Plans for safety monitoring and how to respond to any safety signals (crisis communication) should also be in place before vaccine introduction. Similarly, evaluating the impact of adding JE vaccine on coverage of other routine vaccines already within the



EPI schedule should be planned for. Being able to measure and monitor these outcomes is crucial for JE vaccination program's long-term success and requires advance planning.

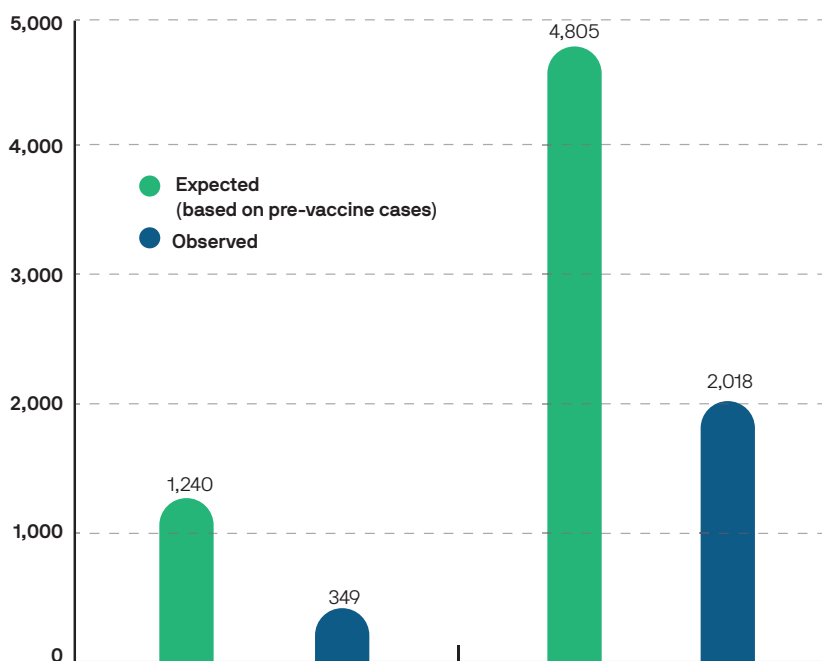
For JE, impact monitoring comes with a set of unique challenges. The JE virus is the most common vaccine-preventable cause of acute encephalitis syndrome (AES) in Asia. However, because many AES cases are caused by other pathogens, JE vaccination programs will not eliminate all AES cases. Proportions of AES cases in Southeast Asian countries due to the JE virus range from 4 to 37%. In the beginning of the JE project, some members of governments, the public, and media were concerned about why their country still had AES cases after introducing JE vaccination. When feasible, PATH helped countries set up surveillance and/or conduct laboratory testing to determine the proportion of AES due to JE both before and after vaccine introduction. Total AES cases typically do decrease following JE vaccine introduction, as seen in countries like Nepal,¹⁰ but will not completely disappear and are still subject to outbreaks and increases due to other, non-JE pathogens. The project team learned the importance of explaining the many etiologies of AES and setting the right expectations for monitoring according to each country's current surveillance system and capacity.

Safety monitoring is necessary for surveillance of adverse effects following immunization (AEFIs) to ensure the safety of a new vaccine and health worker compliance with proper storage, handling, and administration procedures. For JE vaccines, the availability of AEFI monitoring data from several countries went a long way toward increasing public confidence in

CD-JEV and in countries' immunization programs. Crisis communication planning—including the development of messages, independent investigation teams, and a response plan for how to address potential concerns or misinformation about vaccine safety that could circulate in local or national media—also proved invaluable for maintaining public confidence.

Finally, new vaccine introductions should also monitor the effects of the new vaccine on coverage of other routine vaccines. This is a primary purpose of post-introduction evaluations (PIEs). The JE project team observed the importance of PIEs for monitoring not only the acceptability of new JE vaccine introduction, but also the potential for subsequent new vaccines to affect coverage of JE vaccines.

Expected versus observed cases of JE and AES in Nepal following vaccination¹⁰



¹⁰ Upreti SR, Janusz KB, Schluter WW, et al. Estimation of the impact of a Japanese encephalitis immunization program with live, attenuated SA 14-14-2 vaccine in Nepal. *The American Journal of Tropical Medicine and Hygiene*. 2013;88(3):464-468.



By planning for the future of vaccination programs and the necessity of measuring impact, safety, and conducting future PIEs before a vaccine is even introduced, programs can enable monitoring of safety and impact in order to build public trust in the program.¹¹ This is true not just for JE vaccination, but for all immunization programs. If countries are not already measuring vaccine impact, programs may want to consider the reasons why—e.g., lack of awareness, lack of prioritization, lack of planning, or lack of capacity or infrastructure—and develop strategies to address these reasons across the EPI as part of a new vaccine introduction.

Setting a foundation for security of vaccine supply through forecasting and procurement

Planning for vaccine supply, demand, and procurement lays a foundation for vaccine supply security that will be crucial for preventing delayed or interrupted supplies.

Vaccine, device, and cold chain forecasting provides a projection of demand—both now and in the future—for countries, vaccine manufacturers, and procurers like UNICEF and Gavi and is the first step in establishing security for vaccine supply and demand. Having an accurate demand forecast helps ensure adequate immunization supplies free from unexpected shortages or excesses, which can increase costs and result in delays or interruptions in vaccination programs. Because PATH worked directly with the manufacturer of CD-JEV,

¹¹ For additional country guidance on vaccine monitoring, see Module 6: Is My Country's JE Vaccination Program Working? from *Navigating Vaccine Introduction: A Guide for Decision-Makers—Japanese Encephalitis*.

Planning for vaccine supply, demand, and procurement lays a foundation for vaccine security that will be crucial for preventing delayed or interrupted supplies.

the team also needed accurate forecasting to provide guidance on how much manufacturing capacity would be needed.

In order to ensure the sustainability of not just one specific vaccine, but of all vaccination programs, planning for surveillance, monitoring, demand forecasting, and vaccine procurement

must be a prioritized part of vaccine introduction products.

Procurement, the process of purchasing and shipping the vaccine and related supplies, is another step that requires careful planning to avoid delays or interruptions. For JE vaccine procurement, two main options are available to countries: (1) self-procurement, where a country takes full ownership and responsibility for procuring vaccines; or (2) delegation to a procurement agency, such as UNICEF. Pooled procurement, a third option where countries form a buying group to share supplier and pricing information and have joint tenders and contractors with vaccine manufacturers, does not yet exist in the JE-endemic region. Throughout the course of the JE project, some countries took full ownership of procurement but were not always aware of all the necessary steps involved, leading to delays with national regulatory approvals. Others, like Cambodia and Laos, delegated procurement to UNICEF. Making sure countries are aware of the options and requirements involved with each method was an important lesson learned by the project team. In the future, alternative methods such as pooled procurement for JE vaccines may merit consideration.

Looking at the road ahead for JE

While PATH's nearly 20 years of working on JE vaccines are largely coming to an end, a new story is beginning. Several challenges lie ahead. Many JE-endemic countries with large populations have yet to fully introduce JE vaccination in all endemic districts. Current efforts must be supported and sustained. Disease, demand, and vaccine supply may change

drastically in the face of climate change, urbanization, rice irrigation, and natural disasters. The global community must work together to ensure a sustainable supply of CD-JEV and other WHO-prequalified JE vaccines, listening to countries' concerns and collecting and utilizing new data around long-term protection, safety, and impact monitoring. Having multiple manufacturers and types of JE vaccines will improve sustainability and supply.

Additionally, other new vaccines and global

efforts, like the elimination of polio, will affect the demand and uptake of existing vaccines such as JE. Several countries have already seen these competing priorities rising to the surface above JE vaccines, further delaying introduction or expansion of programs.

In order to ensure the sustainability of not just one specific vaccine, but of all vaccination programs, planning for surveillance, monitoring, demand forecasting, and vaccine

In order to ensure the sustainability of not just one specific vaccine, but of all vaccination programs, planning for surveillance, monitoring, demand forecasting, and vaccine procurement must be a prioritized part of vaccine introduction projects.



procurement must be prioritized during vaccine introduction projects. Identifying the end goal and planning the steps needed to reach it are the best way to achieve desired results. The five lessons outlined in this report—meeting countries where they are; prioritizing public health; working together; deciding with data; and planning for the future—represent the keys to the success of global efforts to combat JE. Through strong partnerships and sharing lessons for others to learn from, new vaccine introductions can achieve unprecedented success for global health.

Early 2000s

In the early 2000s, PATH rallied a global team to protect the lives of people in communities at the greatest risk of Japanese encephalitis.



Country spotlight

Myanmar

After widespread JE outbreaks began in 2014 and enhanced surveillance showed wide-spread endemicity, the Myanmar Ministry of Health and Sports (MOHS) committed to introduce JE vaccination. At a 2015 stakeholder meeting organized by MOHS and PATH, Myanmar committed a bold pledge to immunize all children from 9 months to 15 years of age against JE.

Over the next year, the MOHS worked with WHO, UNICEF, and PATH—all of whom became supporting members of the central Expanded Programme on Immunization (cEPI)'s JE Vaccination Technical Task Force—on a comprehensive introduction plan and submitted a successful Gavi application for JE vaccination funding. The plan was to begin with a nationwide JE vaccination campaign of all children between 9 months and 15 years—the ages with the highest risk of contracting JE—and then subsequently integrate the vaccine into routine immunization.

Myanmar's JE vaccination campaigns took place in November and December 2017 and reached more than 12 million children in all regions, covering 92.5% of the country's children under the age of 15. School-based campaigns reached older children, and community-based campaigns reached younger children. Then, in January 2018, the cEPI transitioned JE vaccine into Myanmar's routine immunization schedule. Since then, all children have been scheduled to receive JE vaccine at 9 months of age alongside other routine vaccines.

The success and quick implementation of Myanmar's JE vaccination program is due to the commitment of its leaders to protecting children, strong support and coordination with partners, and importantly, careful planning. The campaign Technical Task Force worked diligently to develop detailed campaign guidelines, plan and monitor cold chain logistics and financial coordination, develop training and educational materials, roll out social mobilization activities, prepare crisis communications plans, and monitor campaign delivery to provide recommendations for areas in need of strengthening. The MOHS' existing surveillance program provided crucial evidence for decision-making and enabled ongoing monitoring of the vaccine's future impact. Finally, a post-introduction evaluation conducted with PATH support in early 2019 helped the National Immunization Program identify strengths and problem areas, providing valuable lessons for future vaccine introductions.



A student from Pyinnyar Youngchi school is vaccinated against Japanese encephalitis (JE) in Shan State, Myanmar, in November 2017. PATH/Thet Htoo

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