

The PATH Rotavirus Vaccine Program
SUMMARY REPORT



LETTER FROM THE DIRECTOR

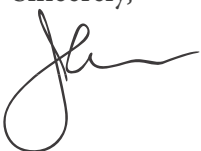
Six years ago, the GAVI Alliance undertook a bold experiment: fund and empower a time-limited partnership to close the gap between the availability of rotavirus vaccines in the industrialized and developing worlds. At that time, new rotavirus vaccines were still in clinical development and many questions were unanswered about the disease and the potential of vaccination to save lives in resource-poor settings. Today, children in developed and developing countries alike benefit from rotavirus vaccines. Expanding use in Latin America is currently making that region a model for developing-country introduction, and many more countries in other parts of the world are poised to access this lifesaving intervention.

The Rotavirus Vaccine Program (RVP) harnessed the respective strengths of PATH, the World Health Organization (WHO), and the US Centers for Disease Control and Prevention (CDC) to generate and communicate the evidence required by global and national policymakers to make critical decisions about rotavirus vaccines. To solve the disparity between the timelines of availability in resource-rich and resource-poor settings, the partners collaborated on several activities in parallel, seeking answers to outstanding questions of disease burden, vaccine efficacy in developing countries, cost-effectiveness, and the role of rotavirus vaccines in the management of diarrheal disease. The principles of developing effective partnerships, pursuing rigorous science, and listening to country needs were instrumental in the accomplishments of RVP and its partners around the world.

The end of RVP's timeline has come, but its spirit, energy, and momentum live on. Several ongoing activities to further understand the efficacy, effectiveness, and safety of rotavirus vaccines in developing countries will continue under the banner of the Rotavirus Vaccine Trials Partnership. And many of the partners involved with RVP will contribute to GAVI's Accelerated Vaccine Introduction initiative (AVI) —the next chapter in accelerating global access to rotavirus vaccines.

From clinics to conference rooms, the collective vision of countless partners is becoming a reality. It has been a privilege for me to be a part of this bold experiment and to witness the rapid changes that have occurred over the past six years. The future is a place where children everywhere need not suffer and die from diarrheal disease, and rotavirus vaccines are a vital step to reach that reality.

Sincerely,



Dr. John R. Wecker
Director, PATH Rotavirus Vaccine Program



Dr. Jean-Marie Okwo-Bele, director of the WHO Department of Immunization, Vaccines, and Biologicals, and Dr. John Wecker, director of PATH's Immunization Solutions, solidify a key partnership at the outset of the Rotavirus Vaccine Program.

Rotavirus is the most common cause of severe, dehydrating diarrhea among children worldwide, and it is the leading culprit of the nearly two million unnecessary and preventable deaths caused by diarrheal disease each year.

RVP, a partnership with WHO and the US CDC, was established in 2003 through a generous grant from the GAVI Alliance. RVP aimed to generate and disseminate information on the worldwide burden of rotavirus and the potential impact of safe and efficacious vaccines. Key collaborations allowed RVP to simultaneously pursue several strategic activities toward accelerating vaccine access in the developing world.

This report provides highlights and lessons learned from each area of technical, scientific, and collaborative pursuit. While these activities yielded several important milestones, continued dedication of global partners will be essential to sustaining momentum and ensuring that the prevention of rotavirus through immunization remains a global health imperative.



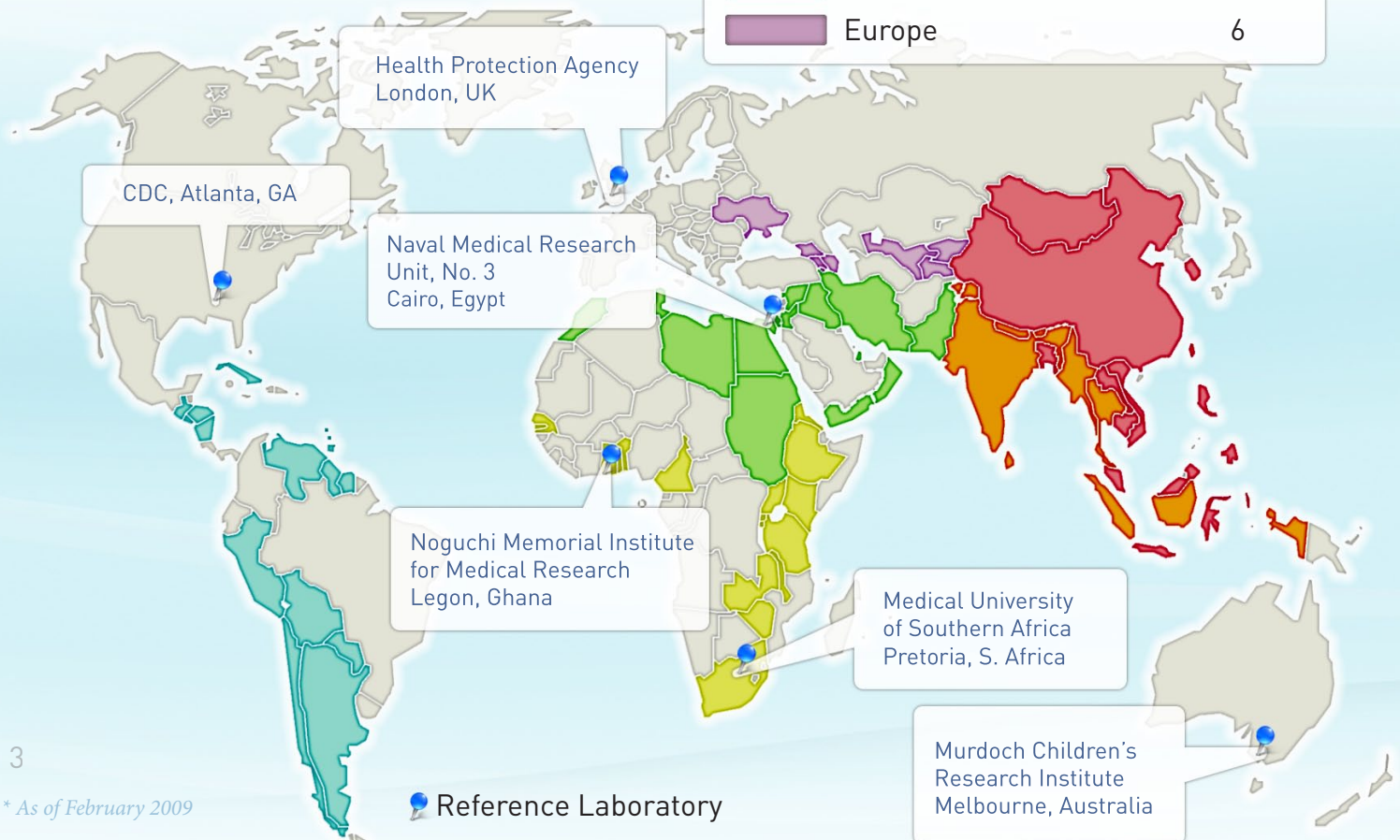
DISEASE SURVEILLANCE

While the severe impact of diarrheal disease is widely recognized, country officials often reveal limited awareness about rotavirus. Under the leadership of WHO and CDC, RVP support to surveillance efforts allowed for expansion to multiple countries and the development of regional networks to standardize procedures, deliver training, and provide technical assistance. National and international stakeholders now have a clearer picture of rotavirus's impact. For example, the latest findings from a hospital-based global surveillance network representing 35 countries indicate that rotavirus accounts for approximately 40 percent of diarrhea hospitalizations among children under five years of age. This significant worldwide burden emphasizes the need for vaccination to control rotavirus and for attention to rotavirus within a comprehensive approach to prevent and control diarrhea.

Investigators around the world continue to generate pivotal data on rotavirus disease burden. New journal supplements on global efforts, as well as activities in Africa, will become available in the coming months. Please see the Additional Resources page at the end of this report for a list of key rotavirus surveillance publications from the past few years.

Routine, standardized surveillance collects data on rotavirus disease burden throughout the world.

Region	# countries*
Americas	14
Eastern Mediterranean	13
Africa	11
Southeast Asia	5
Western Pacific	10
Europe	6



REFLECTIONS

Dr. Kathy Neuzil, Senior Clinical Advisor, PATH

I had been with PATH for about three weeks when I traveled to Africa for the first time, headed to Malawi to evaluate potential study sites. We landed at a tiny airport outside of Blantyre and, as we drove into town on a two-lane road, I watched women walk by carrying tremendous loads, their bare-footed children running and playing not far off. I sensed an immediate difference between their world and my own.

But at the sites, when we began talking with local researchers, the similarities came to the surface and it felt very natural.

At the outset of each site visit, we spent long days together, and throughout the studies stayed in touch through phone calls, e-mail, and periodic visits. I had tremendous respect for the work and commitment of everyone I met. Their dedication amazed me. In trials in the US, we would follow up with a phone call.

These site staff make weekly visits to homes then follow up with more visits. They travel by foot, bike, and motorcycle. Almost everyone works 12- to 14-hour days, from investigators to field workers to administrators. Our basic methods may have been different, but quality always prevailed.



Children in Malawi offer a warm welcome.

The trials were quite collaborative in a number of ways, not only with the seven sites across Africa and Asia, but also with WHO, country leaders, and the manufacturers. We were from vastly different walks of life, but we had a common goal: to collect the data that would inform a global policy on rotavirus vaccines. It is hard to describe the feeling of being part of a group that has the capacity to save children's lives. It's wonderful and overwhelming. But the steps to get here required diligence, consistency, partnership, and hard work. Delivery can't happen without a policy recommendation, policy cannot be set without evidence, and high-quality evidence cannot be generated without a dedicated team at the top of their game.

CLINICAL TRIALS

RVP's support of rotavirus vaccine clinical trials in the developing world began in 2004, building off the foundation laid by the Rotavirus Action Program for Immunization and Development (RAPID), a public-private partnership involving RVP partners WHO and PATH among others, which initiated Phase 1 and 2 trials in South Africa and Bangladesh. These studies gathered crucial data:

- Infants demonstrated significant immune response to rotavirus vaccines.
- Co-administration of rotavirus vaccine with oral polio vaccine did not lower the polio immune response.
- Vaccine response with three doses was not superior to two doses.
- Rotarix™ vaccine was well tolerated and immunogenic in HIV-infected infants and showed no safety concerns with respect to the HIV status of the child.

Vaccine efficacy in Europe, Latin America, and the United States had been demonstrated through large-scale Phase 3 trials conducted by vaccine manufacturers Merck & Co., Inc., and GlaxoSmithKline Biologicals. A recommendation in 2005 from the WHO Strategic Advisory Group of Experts (SAGE) emphasized the

urgent need for generating data on the vaccines' efficacy in Africa and Asia, where the disease burden is very high. RVP and its partners met the challenge, launching trials that enrolled 10,000 children from seven countries across the two continents. Interim data showed the vaccine was efficacious in preventing severe rotavirus gastroenteritis among infants in South Africa. When complete results become available in 2009, they may warrant consideration by SAGE toward a global recommendation for rotavirus vaccines (see *Weekly Epidemiological Record*, 84[1-2]). Acknowledging that the evidence generated from these clinical trials will be key to informing global policy and country-level introduction decisions, RVP and its partners designed and conducted the studies to the highest international standards and in populations representative of developing-world settings. Please see the Additional Resources page for a list of publications generated through clinical trials conducted by RVP in close collaboration with country partners, global stakeholders, and vaccine manufacturers. The Additional Resources also include a list of documents detailing WHO recommendations related to rotavirus vaccines.



World Health Organization first prioritized development of a rotavirus vaccine for infants in the early 1980s and, since then, we have been working together as a global community to meet this need.

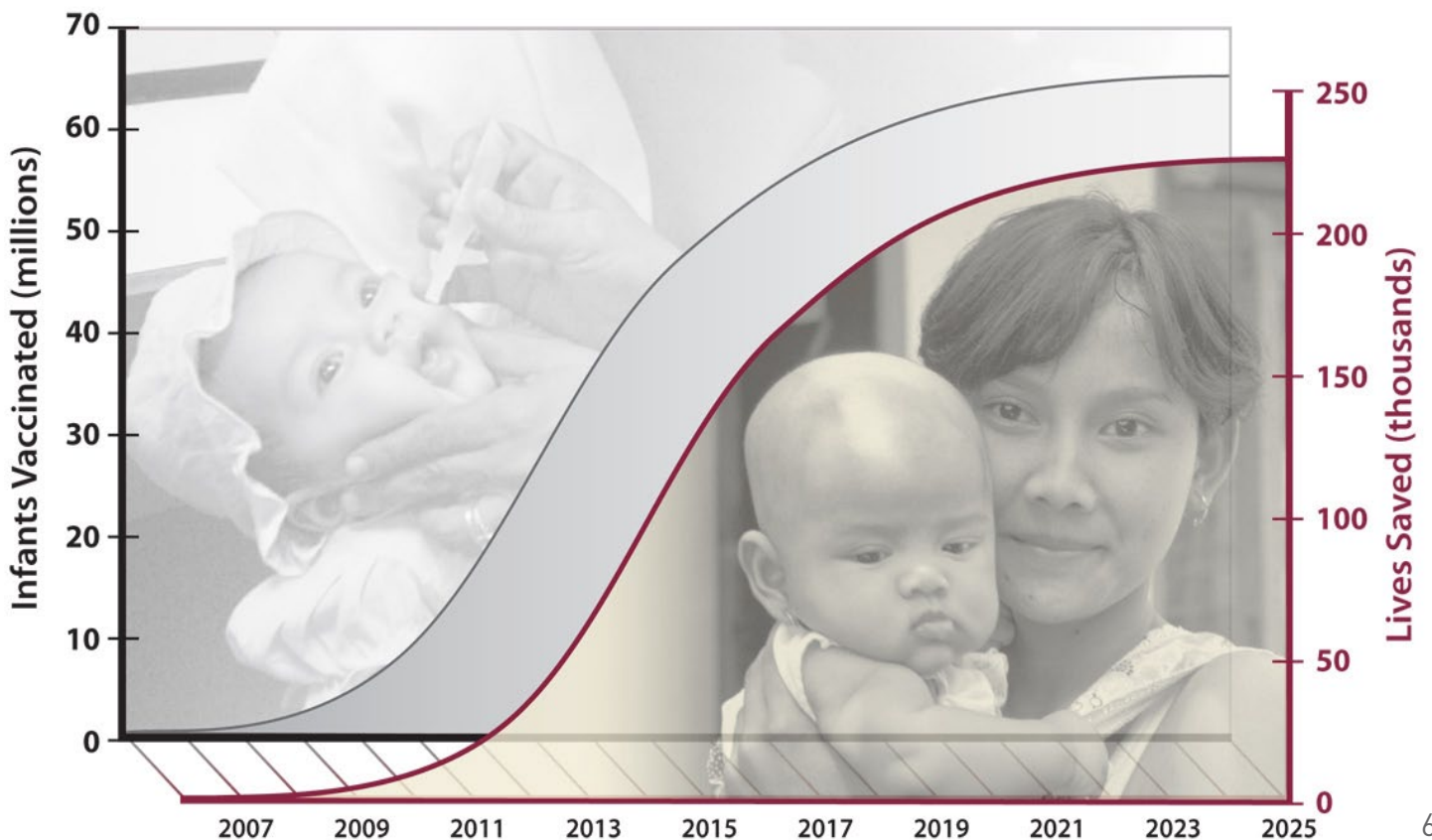
Dr. Duncan Steele
Scientific Officer
World Health Organization

DEMAND FORECASTING

To make sure that rotavirus vaccines are accessible in the settings that carry the greatest disease burden, RVP needed to bring the right information to the right stakeholders. RVP's Investment Case to the GAVI Alliance for its consideration of rotavirus vaccine introduction support compiled a wealth of information, including disease burden data, vaccine characteristics, a global demand forecast, current and future supply and pricing scenarios, and cost-effectiveness analyses.

Partnerships with global stakeholders and a focus on the challenges of settings with limited financial infrastructure were key to developing the Investment Case. As rotavirus vaccine introduction progresses and candidate vaccines become available, it will be critical for stakeholders to closely monitor market-related conditions, align incentives among public and private sectors, update forecast estimates, and ensure that supply meets the growing demand.

The RVP Investment Case estimated that subsidized vaccine support could bring rotavirus vaccines to 716 million children and save 2.4 million lives over the next 20 years.



VACCINE INTRODUCTION

When RVP initiated conversations with health officials in the world's poorest countries, awareness about rotavirus—and thus demand for a vaccine—were relatively low. The gap between vaccine development and feasible introduction in the developing world presented a significant challenge, due in part to the availability of several new health technologies, including vaccines as well as prevention and treatment interventions, that make for difficult decisions by policymakers allocating limited resources. Close communications with public health stakeholders at both national and subnational levels provided RVP with insight into unique challenges and helped develop partnerships that prioritized country needs and opportunities.

Momentum began to build in 2006, marking the first time in history that a vaccine was introduced in a developing country—Nicaragua—during the same year it was introduced in industrialized countries. As country leaders reviewed data on disease burden generated by surveillance networks and analysis from evaluations that demonstrated the cost-effectiveness of rotavirus vaccine introduction, interest grew. RVP's perspective also evolved, informed by conversations with policymakers encouraged by the forthcoming availability of rotavirus vaccines but still concerned about the broader problem of diarrheal disease in general.

This insight led to the development of PATH's Enhanced Diarrheal Disease Control Initiative, through which outreach to providers, policymakers, and the community are helping countries move toward rotavirus vaccine adoption as part of a sharpened focus on diarrheal disease control.

GAVI support will be a major vehicle in the settings where the disease carries its greatest impact. Bolivia, Guyana, Honduras, and Nicaragua have been approved by GAVI to receive rotavirus vaccine introduction support, signalling expanded use in the region. The experiences of these early adopters will provide lessons learned that will be important in informing introduction among impoverished populations around the world. Vaccine packaging, for example, presented a major challenge in settings with limited cold chain storage. Working with GAVI, RVP, and other partners, the manufacturers are implementing packaging improvements to overcome this barrier. Issues of infrastructure, financing, and implementation are crucial considerations. As global organizations consider universal recommendations in 2009 and the introduction of rotavirus vaccines continues to expand, continued engagement with countries will be essential.

We now have a wealth of information on rotavirus burden and strains from all areas of the world, collected with a common protocol and common approach.

Dr. Umesh Parashar
Epidemiologist
US Centers for Disease
Control and Prevention



REFLECTIONS

Dr. Duncan Steele, Scientific Officer, Initiative for Vaccine Research, WHO

Fewer than 10 years after the discovery of rotavirus, WHO identified it as a major cause of acute infantile gastroenteritis with high, associated infant mortality. WHO first prioritized development of a rotavirus vaccine for infants in the early 1980s, and since then we have been working together as a global community to meet this need.

WHO envisioned regional surveillance networks using standard protocols. Beginning with small studies in developing countries of Latin America, Asia, and Africa, that seed has taken root and grown into a significant body of evidence on epidemiology and strain diversity. With activities expanded through RVP support, WHO regional offices now coordinate surveillance networks that collect routine, monthly reports on rotavirus in all parts of the world. Many countries now have their own data on rotavirus disease and are aware of the potential of vaccine introduction made possible through GAVI support. But we are not yet at 100 percent—awareness-building must continue.

At WHO headquarters, the teams behind the scenes focusing on vaccine safety and quality, prequalification, regulatory strengthening, manufacturing standards, and other major areas have been another driving force. As the vaccines are introduced more broadly, the EPI team will take on the challenge of ensuring they are delivered to the children who need them most.

Looking back to 1982, when I first started working in the field of rotavirus, I feel privileged to have been on this journey—from a time when we could not even grow human rotaviruses in tissue culture to today, when two live, attenuated rotavirus vaccines are routinely used in several countries. We are on the verge of final results from clinical efficacy trials to determine how the vaccines work in Africa and Asia, and potentially a global recommendation for use.

New rotavirus vaccine candidates from developing country manufacturers represent the journey's next step. We can look forward to a future where safe and effective vaccines are produced in countries with demonstrated burden, vaccine price is declining, and a long-term commitment to a reliable supply is ensured.



Dr. Duncan Steele, left, and Dr. Joe Bresee (US CDC) were among the team who took on the task of determining global rotavirus burden in the early days of RVP. (Their “upside-down” map is a reversed version that sets Australia as the point of reference)

NICARAGUA: A MODEL FOR ACCELERATED ROTAVIRUS VACCINE INTRODUCTION

Nicaraguans experienced rotavirus' impact firsthand in the spring of 2005, when a severe outbreak overwhelmed the health system. Already working in the region to raise awareness and support surveillance, RVP had developed partnerships that enabled immediate collaboration between the Ministry of Health, the Pan American Health Organization, and child health experts, who collectively called for a strategy to address rotavirus control while renewing attention to all causes of diarrheal disease. A local consortium of nongovernmental organizations called NicaSalud, the Nicaragua Pediatric Society, and UNICEF promptly joined the effort, and partners swiftly educated health workers and caregivers about both preventive and curative interventions for managing diarrheal disease.

By early 2006, clinical trial data showed new rotavirus vaccines to be safe and efficacious in Latin American populations. The Nicaraguan Ministry of Health, well apprised of the burden of rotavirus and the potential of prevention through immunization, accepted a vaccine donation from manufacturer Merck & Co., Inc., which provided a supply of a rotavirus vaccine sufficient to immunize the entire birth cohort of Nicaragua for three years.

Then-president Enrique Bolaños administered the first dose of RotaTeq® on October 27, 2006, making Nicaragua the first GAVI-eligible country to introduce rotavirus vaccine and the first to do so during the same year as the United States.



In 2006, Nicaraguan president Enrique Bolaños administered the first rotavirus vaccine in Nicaragua.

REFLECTIONS

Dr. Umesh Parashar, Lead, Viral Gastroenteritis Epidemiology Team, US CDC

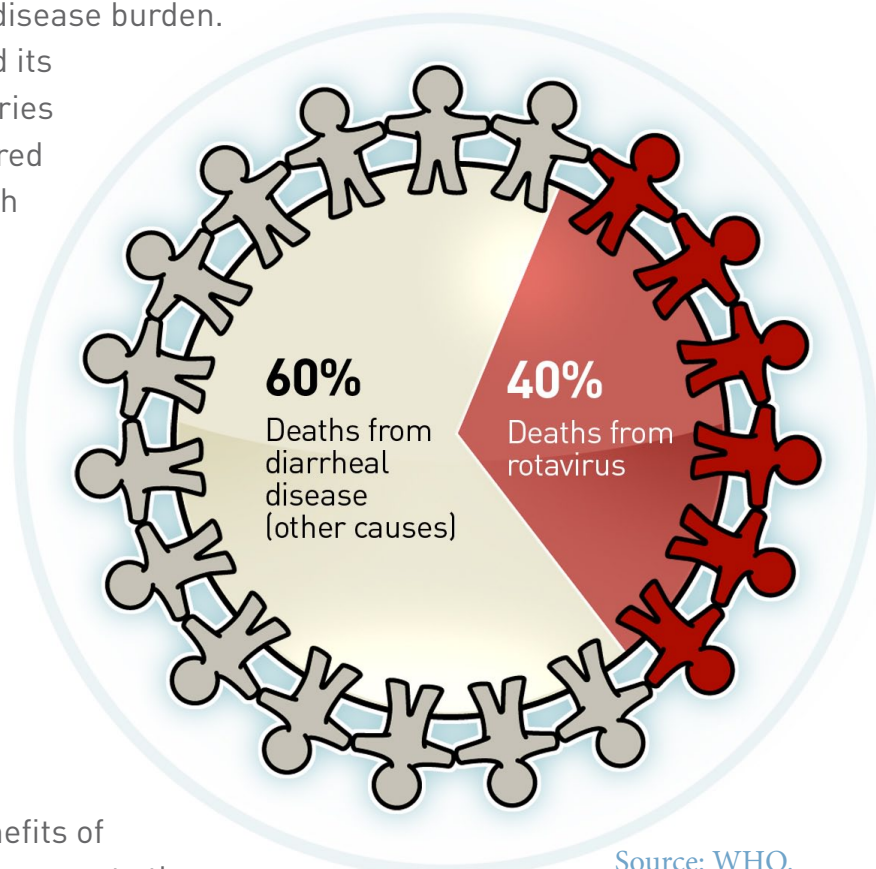
We have seen many accomplishments over the past few years, but when RVP started, we were facing a great deal of uncertainty. After two decades of research that led to the development and introduction of the RotaShield® vaccine, it was pulled from the market because of a potential association with intussusception. Would we have another rotavirus vaccine? Would the candidates in development have the same outcome? There was a lot to look forward to, but no guarantees.

CDC's partnership in RVP has allowed our team to contribute to efforts to prevent and control the global problem of rotavirus. Surveillance activities brought us together with teams around the world gathering crucial information on disease burden.

Essential collaborators—including WHO and its regional offices, laboratory partners, ministries of health, and academic institutions—gathered an extraordinary amount of evidence through rotavirus surveillance. We now have a wealth of information on rotavirus burden and strains from all areas of the world, collected with a common protocol and common approach.

Ongoing surveillance will help us demonstrate the value of rotavirus vaccines in real-world settings where they are part of routine immunization. In the US and some Latin American countries, for example, we are already seeing the positive impact of vaccination in reducing rotavirus burden, including hints of unanticipated benefits of herd immunity. We can continue to gather answers to the question about intussusception and build on the evidence we have collected in the US that shows this generation of rotavirus vaccines does not pose an elevated risk.

RVP has created an exciting environment for scientific endeavors, and it has been a delightful and most satisfying experience to work with a team of highly motivated and dedicated professionals with a clear focus on the target of bringing life-saving rotavirus vaccines to children in the developing world.

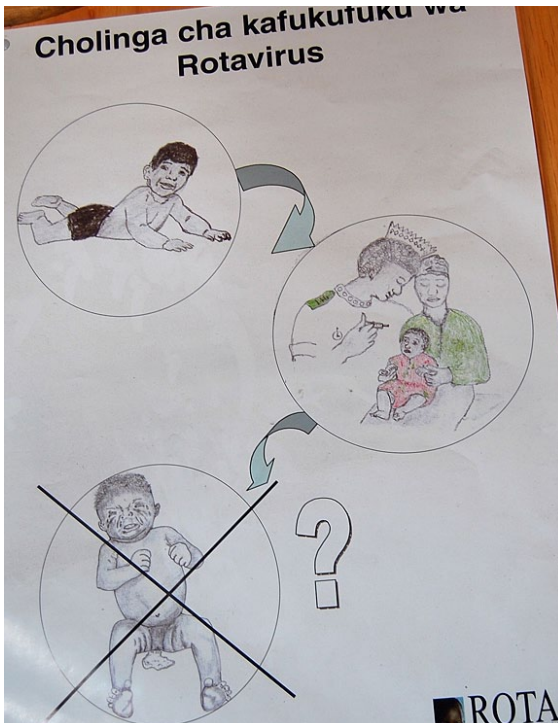
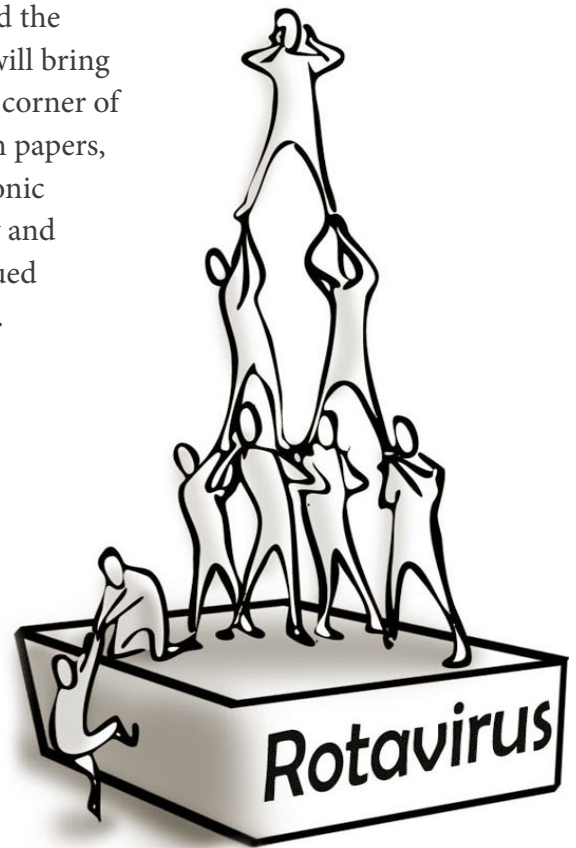


Source: WHO.
Weekly Epidemiological Record.
2008;83(47).

COMMUNICATIONS AND ADVOCACY

Reliable, accurate, and updated details on the burden of rotavirus and the value of vaccines are at the heart of informed decision-making that will bring the intervention to communities at risk. RVP's partnerships in every corner of the world have built a network of advocates, armed with key research papers, fact sheets that distill technical data for a broad audience, and electronic resources that make crucial information widely accessible. Advocacy and communications were major factors within each technical area pursued by RVP, ensuring that data were disseminated and voices were heard. Communications and advocacy materials developed through RVP's activities may be accessed on the following websites:

- [PATH Vaccine Resource Library](#) »
- [Resources for Diarrheal Disease Control](#) »
- [Rotavirus Vaccine Program website](#) »



This study information poster provides information for parents of potential participants in the clinical trial to evaluate safety and efficacy of GlaxoSmithKline's Rotarix™ vaccine in Malawi.



Dr. Kathy Neuzil (center), PATH's senior clinical advisor, and Dr. Penny Heaton, Merck's senior director for vaccines clinical research (third from right), join study staff including investigator Dr. Abraham Hodgson (second from right) during a visit to a site for the RotaTeq® vaccine clinical trial in Ghana.

PARTNERSHIP

By identifying the distinct resources, networks, and skills needed to meet the project's objectives, RVP tapped the strengths of several partners:

PATH: Harnessed the commitment and resources of the vaccine industry, public health organizations, donors, and governments to demonstrate and replicate a successful model for vaccine introduction.

WHO: Ensured that rotavirus stayed on the global public health agenda, considering evidence as it became available and making key recommendations on the use of rotavirus vaccines.

CDC: Facilitated development of global surveillance networks for rotavirus disease and strain monitoring so that countries had the information needed to consider vaccine introduction and platforms to assess the impact of vaccination.

GAVI Alliance: Provided financial support to fuel RVP activities; providing subsidized funding for the cost of rotavirus vaccine introduction in eligible countries, eliminating a significant financial barrier in the developing world.

Ministries of health: Considered evidence of rotavirus disease burden and vaccine efficacy and safety; catalyzed innovative introduction programs to rapidly bring lifesaving vaccines to vulnerable populations.

In-country clinical research sites: Helped to determine the safety and efficacy of rotavirus vaccines while building local research capacity and laying a foundation for future vaccine introduction planning, particularly in Africa and Asia.

Merck: Manufacturer of RotaTeq[®], a three-dose oral, liquid, pentavalent rotavirus vaccine; collaborating with RVP to evaluate vaccine safety and efficacy in Africa and Asia; donated more than one million doses to vaccinate infants born in Nicaragua over a three-year timeframe.

GSK: Manufacturer of Rotarix[™], a two-dose, live, attenuated oral rotavirus vaccine; collaborating with RVP to evaluate vaccine safety and efficacy in Africa and Asia.



An infant participant in Bangladesh receives a study vaccine for the clinical trial to evaluate safety and efficacy of Merck's RotaTeq[®] vaccine.




Dr. Dang Duc Anh of the National Institute of Hygiene and Epidemiology, and Dr. Loan, Chief of Pediatric ICU at Khanh Hoa General Hospital in Nha Trang, Vietnam, review clinical data on infants with severe diarrhea.

NEXT STEPS

In partnership with principal investigators and vaccine manufacturers, PATH is completing Phase 3 efficacy trials in Asia and Africa, and results are expected in 2009. These trials, along with vaccine effectiveness studies in Bangladesh, El Salvador, and Nicaragua, will continue to move ahead under the auspices of the Rotavirus Vaccine Trials Partnership. Results from each will be submitted for publication in peer-reviewed journals and disseminated to global stakeholders.

The GAVI Alliance will move forward with the next chapter of new vaccine introduction support that will apply the lessons learned from GAVI's Accelerated Development and Introduction Programs for rotavirus and pneumococcal vaccines. GAVI's Accelerated Vaccine Introduction initiative (AVI) will advance innovative approaches to assist country decision-making on these two vitally important interventions, while building a platform to inform future introduction of other new vaccines.



Going forward, we will need the continued dedication of all global partners to ensure that preventing rotavirus-related deaths remains a global health imperative.

Dr. John Wecker
Director Rotavirus Vaccine Program
PATH

ADDITIONAL RESOURCES

Key rotavirus surveillance publications

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Phase 3 safety and efficacy studies with RotaTeq® are ongoing in Bangladesh, Ghana, Kenya, Mali; and Vietnam, and with Rotarix™ in South Africa and Malawi.

Phase 4 vaccine effectiveness studies are ongoing in Bangladesh, El Salvador, and Nicaragua.

WHO recommendations related to rotavirus vaccines

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A catalyst for global health

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