

# Rotavirus Vaccine Solutions

Each year, an estimated 1.3 million children die from severe, dehydrating diarrhea.<sup>1</sup> The most common cause of severe infantile diarrhea—accounting for two million hospitalizations and more than 500,000 deaths each year—is rotavirus. Due to limited access to adequate health care, these rotavirus deaths occur predominantly among children in the poorest countries.<sup>2</sup>

Rotavirus is highly contagious and resilient and, regardless of water quality and available sanitation, nearly every child in the world is at risk of infection.<sup>3</sup> Traditional diarrheal disease prevention measures are not enough to limit its impact, and vaccination is the best hope for protecting infants against severe dehydration and death from rotavirus infection. Commercial rotavirus vaccines exist, but they are not yet widely available in or affordable for low-resource countries. PATH is working on two fronts to address these gaps: increasing access to and effectiveness of existing commercial vaccines worldwide and accelerating the development of safe, effective, and more affordable new vaccines. PATH is also pursuing an advocacy strategy to increase awareness of diarrheal disease and how an array of interventions, including vaccines, can save lives.

## Existing commercial vaccines

Two live, oral vaccines against rotavirus—manufactured by GlaxoSmithKline and Merck & Co., Inc.—are saving lives today. In June 2009, the World Health Organization (WHO) recommended global use of rotavirus vaccines,<sup>2</sup> citing data from pivotal clinical studies conducted by PATH and partners that demonstrated vaccine efficacy in high-burden, impoverished settings. More than 20 countries to date have introduced these vaccines in the public sector, mostly in North America, Latin America, and Europe. The GAVI Alliance, a global health partnership that works to increase access to vaccines, has received a number of applications from countries in the developing world that are interested in introducing the vaccines. PATH continues to partner with global health leaders to provide technical support to countries in Africa and Asia preparing for rotavirus vaccine introduction.

Although these vaccines were proven to significantly reduce severe disease in developing-country settings, they demonstrated lower efficacy in comparison to results from developed countries.<sup>4</sup> PATH is conducting studies to examine why this may be happening and to identify ways to improve or enhance rotavirus vaccine performance so that the lifesaving benefits of vaccination can be maximized in countries where the burden is greatest.

## New vaccines in development

Because bringing new rotavirus vaccines to the global market is key to improving affordability and ensuring a sustainable supply, PATH is supporting the development of several promising rotavirus vaccine candidates.

### 116E vaccine candidate

The 116E human monovalent vaccine candidate contains a naturally occurring reassortant human strain originally isolated from an asymptomatic rotavirus-infected neonate in a hospital in New Delhi, India. This live, oral vaccine is being developed by the Indian manufacturer Bharat Biotech International, Ltd. (BBIL). In June 2008, BBIL and India's Society for Applied Studies (SAS) announced encouraging data from a Phase 1/2 clinical trial of 116E in New Delhi. The trial evaluated two different dosages (approximately 10<sup>4.0</sup> and 10<sup>5.0</sup> FFU) of 116E in nearly 400 infants. The vaccine was well tolerated with no adverse events observed, and it was immunogenic with 62.1 and 89.7 percent of the infants seroconverting after three doses of the approximated 10<sup>4.0</sup> and 10<sup>5.0</sup> dosages, respectively.<sup>5</sup>

PATH has been part of a collaborative effort to develop and evaluate 116E since 2001, supporting BBIL to conduct early-stage clinical trials and build manufacturing and quality control systems, including establishing a Good Manufacturing Practices (GMP)-compliant laboratory and manufacturing facility. Currently, the Government of India's Department of Biotechnology (DBT), BBIL, and PATH are working together to assess 116E in a Phase 3 efficacy study. The trial, which will last for three years, is enrolling 6,800 infants at three sites in India: the Centre for Health Research and Development at SAS in New Delhi, Shirdi Sai Baba Rural Hospital at the King Edward Memorial Hospital Research Centre in Pune, and Christian Medical College (CMC) in Vellore. Other organizations involved in the study include the Research Council of Norway, DBT's Translational Health Science and Technology Institute, and Quintiles.

### Bovine-human reassortant vaccine candidates

The US National Institutes of Health (NIH) constructed reassortants against the four most common human rotavirus serotypes (G1, G2, G3, and G4), as well as reassortants against G8 (found in Africa) and G9 (found in India), and licensed them as the bovine-human reassortant vaccine (BRV) to up to ten emerging-country manufacturers and one US company for further development. A Phase 2b efficacy study of the BRV in

Finland involving 510 infants demonstrated excellent immunogenicity (97 percent) and good efficacy (88 percent) against severe rotavirus diarrhea.<sup>6</sup>

PATH supports the manufacturers actively developing BRV candidates by giving them access to a “shared technology platform” featuring a host of technologies, training, methodologies, and material. This platform is designed to meet common needs among emerging vaccine manufacturers, providing high-level expertise, minimizing cost, and accelerating the pace of development. Elements include access to qualified Vero master cells at an early passage, qualified master seed virus that meets international quality standards, and new research on formulations, packaging systems, and clinical assays. Since 2007, PATH has also directly supported China National Biotec Group’s Wuhan Institute of Biological Products’ preparations for Phase 1 and 2 clinical trials of their BRV candidate. In addition, PATH is working closely with Serum Institute of India, Ltd. to prepare for a Phase 3 efficacy trial of their BRV candidate.

PATH is also conducting preparatory activities to establish CMC in Vellore, India—a WHO regional rotavirus reference laboratory—as a reference laboratory for the development of BRV candidates. CMC will produce, qualify, and validate three assays; prepare standards of practice and protocols; and provide training and quality assurance to the clinical immunology laboratory of each manufacturer. This standardization will ensure comparability of results from clinical trials conducted by the various manufacturers.

### RV3 vaccine candidate

The monovalent RV3 vaccine candidate was developed from a strain of rotavirus that was discovered in infants at a newborn nursery in Melbourne, Australia. Murdoch Childrens Research Institute (MCRI) in Australia is developing the RV3 candidate to include a birth dose to address the risk of rotavirus infection within the first six weeks of life. MCRI is currently testing RV3 in a Phase 1 descending-age study in Australia.

Since 2008, PATH has partnered with MCRI to fund the production of clinical lots under GMP at Meridian Life Science in Memphis, Tennessee, in preparation for MCRI’s Phase 1, 2, and 2b trials. PATH is currently providing guidance on the design and conduct of their Phase 2b trial and on the development of the production process for RV3 by the Indonesian company BioFarma.

### Non-replicating vaccine candidates

Non-replicating rotavirus vaccine (NRRV) candidates could be a promising addition to the global portfolio, potentially overcoming the efficacy limitations of live, oral vaccines. Several organizations have been developing NRRVs, but none have been evaluated in humans yet.

In 2010, PATH conducted a landscape analysis of early-stage candidates and identified four for possible advancement to proof-of-concept clinical studies. PATH is now working to confirm that process development, manufacture under current GMP, and early clinical development are warranted and feasible for the selected candidates. If so, PATH will begin preparatory activities for the advancement of one or more into preclinical and clinical development.

### Diarrheal disease advocacy

PATH is pursuing an advocacy and policy strategy that integrates information about rotavirus and other enteric diseases within the broader public health priority of diarrheal disease control. This framework connects the problem of diarrheal disease with solutions that include new and forthcoming vaccines as well as existing prevention and treatment interventions like oral rehydration therapy and safe water. PATH is working at both the global and country levels to reach key donors and policymakers to raise the priority of diarrheal disease and address the devastating toll that it takes on children, families, and communities around the world.

## References

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MAILING ADDRESS  
PO Box 900922  
Seattle, WA 98109 USA

STREET ADDRESS  
2201 Westlake Ave.  
Suite 200  
Seattle, WA 98121 USA

[pvs@path.org](mailto:pvs@path.org)  
[www.path.org](http://www.path.org)

