



International Social Innovation Partnership Leads to Lifesaving Vaccine

ROTAVAC[®] (also known as 116E) has travelled a long and unique road to reach its current status as a vaccine that is proven safe and effective in protecting infants against severe rotavirus diarrhoea. This vaccine is the product of an innovative international model of collaboration across agencies, sectors, continents, and cultures.

Over the years, the global team contributing to the development of *ROTAVAC*[®] has included scientists and health experts at the Government of India's Department of Biotechnology (DBT), the Indian Council of Medical Research, the Indian Institute of Science (IISc), the All India Institute of Medical Sciences (AIIMS), the National Institute of Immunology in India (NII), the Society for Applied Studies (SAS) in India, Bharat Biotech International, Ltd. (Bharat Biotech), Stanford University School of Medicine, the US National Institutes of Health (NIH), the US Centers for Disease Control and Prevention (CDC), and the nonprofit organization PATH.

Simultaneous discoveries

The idea for an Indian-based rotavirus vaccine sparked in the mid-1980s, when two different groups of scientists working in India discovered unusual strains of rotavirus that infected newborns in hospital nurseries without making them sick. Dr M.K. Bhan, who later became the Secretary of DBT, was among the scientists at AIIMS who discovered one of these strains (116E) during his routine testing of newborns in New Delhi. He brought in Dr Roger Glass, a diarrhoeal expert working at the CDC's rotavirus laboratory, to join in the study of the strain. (Dr Glass has since moved to the NIH's National Institute of Allergy and Infectious Disease [NIAID].) Meanwhile, Dr Durga Rao contacted Stanford University's Dr Harry Greenberg, a rotavirus and vaccine expert, to collaborate on a discovery of a similar strain (I321) by IISc in newborns at hospitals in Bangalore and Mysore.

The neonatal strains 116E and I321 showed much promise for use as vaccines because all of the infants naturally infected with these strains demonstrated a strong immune response to rotavirus when they were exposed to the pathogen again, meaning that they did not experience severe diarrhoea. Both of these strains were human-bovine gene reassortants, which means that they included genetic elements from both human and bovine rotavirus strains. The disease-causing component of the human virus had been swapped with a strain of rotavirus that only infects cows, which is likely why the infants did not experience any symptoms of illness.

For more than two decades, the two independent research teams worked in parallel under the auspices of the Indo-US Vaccine Action Programme (VAP), a bilateral program implemented since 1987 by DBT and NIAID/NIH, to study the two different naturally occurring, weakened strains and develop new rotavirus vaccines for infants. NIH contracted with DynCorp to produce clinical-grade pilot lots of the vaccines in 1997 and evaluate those lots in US adults and children prior to shipping them to India. In 1998, VAP solicited commercial partners in India for the next stage of development and identified Bharat Biotech to develop both vaccine candidates. A vaccine development committee comprising of senior scientific advisory group of experts including Dr Roger Glass, Dr Harry Greenberg and Dr George Curlin was established to guide all aspects of product development and clinical development.

Early clinical testing

In 2000, a consortium of partners including Bharat Biotech, CDC, NIH, AIIMS, Stanford University, and IISc, submitted a proposal to PATH and DBT for support to move the two vaccine candidates through production, testing, and surveillance. Through the Bill & Melinda Gates Foundation-funded

Children's Vaccine Program, PATH joined the collaborative effort in 2001. Since then, PATH has provided technical assistance to Bharat Biotech and the consortium on issues like vaccine stability, the development of special harvesting techniques, using cleaner preparation methods, and designing and implementing clinical trials that meet international standards.

In 2003, Bharat Biotech convened the various partners to discuss strategies for clinical studies of the 116E and I321 vaccine lots and to develop specific decision rules to guide the progress of the trials. After the Institutional Review Boards (IRBs) at AIIMS, CDC, PATH, and Stanford, as well as NIAID's clinical trials committee, cleared the protocol for a Phase I trial of both vaccines in adults, the first Indian trial began in May 2003 at AIIMS. Dr Bhan served as the Principal Investigator and Dr Pratima Ray managed clinical immunology testing (also at AIIMS), and the trial was completed in July 2003 with no major adverse events reported.

Moving ahead with 116E

With the successful evaluation of the two vaccines in adults, the consortium agreed to move both candidates into Phase I studies in Indian children and infants using the NIH-manufactured vaccine lots. AIIMS completed the trial with children in May 2004 and the trial with infants in May 2005, with Dr Bhan once again serving as the Principal Investigator for both studies. The results showed that the two vaccines had comparable safety and viral shedding profiles, but the 116E strain provided greater immunity to disease (36.6 percent of 116E recipients and 15.4 percent of I321 recipients showed an immune response attributable to the vaccine). In response to these results, the consortium decided to focus all further development efforts on the 116E vaccine candidate. This critical decision simplified and accelerated the vaccine development process. Although the I321 strain was not selected, Dr Greenberg and other researchers from that team joined the 116E development effort, remaining committed to the consortium's goal of producing a safe, effective, and affordable new rotavirus vaccine for India.

To further accelerate the vaccine's development, the consortium agreed to Bharat Biotech's proposal to next conduct a combined Phase Ib/IIa dose-escalation study of the 116E vaccine candidate in infants using lots manufactured by Bharat Biotech after NIH transferred starting material for the product. The trial, initiated in November 2006 after obtaining IRB and Drugs Controller General of India (DCGI) approvals, evaluated two different dosages ($10^{4.0}$ and $10^{5.0}$ FFU) of the vaccine in 369 infants and was conducted by SAS in New Delhi. Dr Nita Bhandari served as Principal Investigator and Dr Sudhanshu Vрати managed clinical immunology testing at NII in Delhi.

The Phase Ib/IIa trial concluded in February 2008, with no safety concerns identified, and the results demonstrated a robust immune response in 89 percent of infants after the third dose of the vaccine at the higher dosage level ($10^{5.0}$ FFU). These positive results led Bharat Biotech to propose moving the vaccine to a Phase III efficacy study, which the consortium agreed to in April 2008.

The pivotal Phase III trial

DBT, Bharat Biotech, SAS, and PATH started preparing for a pivotal Phase III trial to assess the efficacy and safety of the 116E rotavirus vaccine (now named "*ROTAVAC*[®]") with an assessment of data management options and the clinical immunology laboratory, as well as a review of epidemiological data to estimate an attack rate. Experts from across the consortium, such as biostatisticians from NIH, assisted with research and analyses to estimate the number of participants for a Phase III clinical

trial and the development of a trial design. In addition to resources provided by DBT and Bharat Biotech, PATH received funding from the Bill & Melinda Gates Foundation, the Research Council of Norway, and the United Kingdom Department for International Development to provide both financial and technical support on the trial design, trial site and laboratory preparation, and overall conduct and coordination of the Phase III study. Bharat Biotech, the trial sponsor, also provided technical support for the trial, including laboratory preparation, logistics management, provision of Universal Immunization Programme vaccines, and distribution of study materials.

The clinical trial began in March 2011 and enrolled 6,799 infants across three sites in India: the Centre for Health Research and Development at SAS in New Delhi (Principal Investigator: Dr Temsunaro Rongsen-Chandola), Shirdi Sai Baba Rural Hospital at the KEM Hospital Research Centre in Vadu, Pune (Principal Investigator: Dr Ashish Bavdekar), and Christian Medical College in Vellore (Principal Investigator: Dr Gagandeep Kang). The Phase III trial's Clinical Operations Management Unit, an internal team formed by the study partners and headed by Dr Bhandari, was charged with overseeing the day-to-day coordination and logistical complexities of this multi-site study and has played a pivotal role in the conduct of this trial.

DBT's Translational Health Science and Technology Institute was selected to perform the laboratory assays, with Dr Vrati once again leading the work. Quintiles was selected as the contract research organization responsible for monitoring all of the trial sites, medical monitoring/safety surveillance services, and data management and biostatistics services for this study. The Wellcome Trust Research Laboratory, at Christian Medical College, Vellore and headed by Dr Kang, was selected to manage strain testing of untypeable rotavirus in stool samples in the study. Extensive audits conducted at the laboratories and the trial sites demonstrated that all operations and procedures followed for the study adhered to the highest international standards.

An independent group of experts served as the Data Safety Monitoring Board (DSMB) for the Phase III study. At a meeting in February 2013, the DSMB determined that the trial met the highest standards for ethics and patient care and complied with international standards for good clinical practices. The DSMB also stated that the vaccine safety profile is excellent, and that the efficacy data met the pre-specified success criteria. The DSMB concluded that the clinical trial results warranted an application for early licensure of *ROTA VAC*[®] with the Central Drugs and Standards Control Organization headed by the DCGI.

A unique social innovation model

ROTA VAC[®]'s development journey is a true model of successful partnership between the United States and India, involving renowned experts from a range of agencies and sectors across the two countries. With the costs of the development shared by several partners, Bharat Biotech was able to commit to a price of US \$1.00/dose (or approximately INR 54/dose) for *ROTA VAC*[®]. This affordable innovation program built on the early-stage research contributions made through the Indo-US Vaccine Action Programme for development of the neonatal rotavirus strain 116E by DBT, NIH, AIIMS, CDC, and Stanford University, and eventually included numerous other experts and agencies from both countries. This partnership-based endeavour has been a truly innovative approach to vaccine development and resulted in the production of a safe and efficacious oral rotavirus vaccine, *ROTA VAC*[®].

ROTA VAC[®] is also unique in that it is truly an Indian vaccine—it involves a virus strain, a company, and clinical trial sites from India, as well as the support and participation of the Government of India. As such, Bharat Biotech plans to register the vaccine for use in India first. However, they will also seek to have *ROTA VAC*[®] approved (“prequalified”) by the World Health Organization, so it may be

procured for subsidized use in the developing world, giving it the potential to have an enormous impact on global public health by reducing rotavirus-related illness and deaths worldwide.

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This document is available online in English, Hindi, Tamil, Telugu, and Marathi:
<http://www.defeatdd.org/rotavac-clinical-trial-results>

DBT website: <http://dbtindia.nic.in>

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