Commentary

New paradigms for indigenous vaccines

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Vaccines are widely recognized as one of medicine’s greatest achievements. Without vaccinations, millions of children and adults would contract a range of serious diseases that are now prevented by vaccines, and many would have long-lasting effects, like the polio affected children most older Indians grew up with, or even die. Vaccination is one of the most important tools in public health, protecting individuals and communities from disease, and the range of diseases that can be prevented by vaccines is expanding across and beyond infectious diseases. Research has shown there are powerful links between population health and economic well-being. Childhood vaccination in particular is a valuable investment because it not only reduces morbidity and mortality in a country but also promotes national economic growth and poverty reduction [1].

Until a few decades ago, new vaccines were developed and made in the first world, by large companies, who focused on the markets from which they could derive maximal return on investment. This led to a situation where the bulk of disease lay in poorer countries while the vaccine supply, limited in amount and by price, was mainly in countries with low disease burden and high purchasing power. The significant lag in getting vaccines to children who most needed them was addressed by governments and international agencies such as UNICEF and the WHO Expanded Programme of Immunization, who sought to widen the reach of vaccines to children everywhere, with some but limited success. With the launch of the GAVI Alliance in 2000, vaccine uptake improved and has continued to improve in developing countries. Vaccination rates against the six key diseases have increased from around 20% in 1980 to approximately 80% in 2009, and the burden of vaccine-preventable diseases has dropped dramatically [2].

However, beyond the six diseases targeted initially, are a range of infectious diseases that continue to cause high levels of morbidity and mortality in several parts of the world for which vaccines exist or can be developed, if resources are available. Particularly for countries like India, where respiratory infection and diarrhoea each contribute >10% to the mortality burden in young children [3], there is a need for safe, effective and affordable vaccines for use in the public health system. Investments in vaccine development require an appetite for risk taking and long term investment, given that failures are to be expected in translating academic success to marketable products.

An outstanding example of the new world paradigm in affordable, safe and effective vaccine development is the Rotavac vaccine. As with most vaccine candidates, the story began with an academic institution, the All India Institute of Medical Sciences (AIIMS), where in the 1980s, M.K. Bhan noticed that a strain of rotavirus produced asymptomatic infections in neonates in the nursery and protected them from subsequent disease. He started an informal joint research program with Roger Glass, who worked initially in Bangladesh and later at the Centers for Disease Control and Prevention (CDC) in Atlanta and at the National Institutes of Health (NIH). In 1989–1990, they attracted research support from the Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India and NIH, under the joint Indo-US Vaccine Action Program (VAP), and went to work on further characterization of this unusual neonatal strain, now known as 116E. The 116E strain was identified to be a human bovine reassortant, with a bovine derived surface protein. Almost in parallel, another bovine-human reassortant infecting neonates, I321, was described from Bangalore, by Durga Rao of the Indian Institute of Science (IISc) working with Harry Greenberg from Stanford University [4].

The NIH contracted with DynCorp to produce clinical–grade pilot lots of the vaccines in 1997 and evaluate those lots in American adults and children prior to shipping them to India. In 1998, the Indo-US VAP solicited commercial partners in India for the next stage of development and identified Bharat Biotech International Ltd. (BBIL), a Hyderabad-based vaccine manufacturing company, to develop both vaccine candidates. In 2000, a consortium of academic, public and private partners including BBIL, 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, with PATH joining the collaborative effort through the Bill and Melinda Gates Foundation-funded Children’s Vaccine Program.

This was a unique group, bringing together an unusual combination of domestic and international partners, committed to social innovation with a clear goal of developing a safe and effective vaccine that would reach the populations that most needed it at an affordable price. In 2003, BBIL Bharat convened the various partners to discuss the clinical development plan for the 116E and I321 vaccine lots. Trials conducted in 2005 showed that while both of them were safe, 116E provided significantly better immune response.

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to the vaccine [5]. The development was then taken forward to late phase II and then phase III with the 116E candidate, under the leadership of Nita Bhandari at the Society for Applied Studies, a non-governmental organization formed of researchers formerly at AIIMS, committed to child health research. The partners then expanded to include researchers at the KEM hospital and Research Centre, Pune and the Christian Medical College, Vellore to carry out the phase III clinical trial for efficacy that required recruitment of 6800 infants and their follow up for a period of two years, and the Translational Health Science and Technology Institute, Delhi to analyze all the clinical samples. The clinical trial was carried out to the highest international standards, with remarkably low loss to follow up, a critical determinant of trial quality. In addition, the intensive monitoring and follow up of participants and provision of access to medical care and referrals resulted in lower than expected numbers of deaths at all three sites, pointing to the attention paid to participant safety in the trial. Despite the early treatment and referrals, the data indicate that 116E based vaccine (now known as Rotavac) provided a level of protection (56% during the first year) comparable to other licensed rotavirus vaccines in developing countries [6] which did not drop significantly in the second year of life [7].

The sharing of the costs of development between several partners played a crucial role in the ability to limit the price of the vaccine to just $1 per dose. BBIL invested in a highly efficient manufacturing process and innovative product development efforts, which also contribute to keeping the costs low.

This joint, very collaborative, effort has been a new paradigm for innovation in strategy and process and has resulted in the availability of safe and effective product for Indian and other developing country markets. The deployment of this product now requires further partnerships—in consideration of the introduction of the vaccine into the public health system and in continued safety surveillance. No vaccine is 100% safe, and with other licensed, available rotavirus vaccines, a small (1 in 20,000–100,000) risk of intussusception has been seen in post-marketing surveillance and additional safety studies carried out by a number of agencies, including the CDC and the immunization programs of several countries. For countries such as India, continued engagement from governmental agencies is necessary to generate and to effectively use evidence for public health decision-making.

The Rotavac development effort is one that can and should be emulated for other vaccines and by other vaccine manufacturers. The government support and endorsement, national partnerships, international collaboration and trust, all brought value that should not be underestimated in this effort to develop a vaccine for India and the world.

References