Ready to Measure Impact? The Introduction of Rotavirus Vaccine in India

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In the past few years, two live attenuated, orally-administered rotavirus vaccines were available for Indian children immunized by pediatricians in private practice – a monovalent human rotavirus vaccine [RV1; Rotarix (GSK Biologicals, Rixensart, Belgium)] and a pentavalent bovine-human reassortant vaccine [RV5; RotaTeq (Merck and Co, Inc, Pennsylvania)] [1,2]. Initially, in 2006, these vaccines were recommended by the World Health Organization (WHO) for countries in regions where clinical trial data were available, but in 2009 – following additional clinical trials in low income countries – the WHO extended its recommendation to include rotavirus vaccines in the routine immunization programs in all countries, and particularly in those with high child mortality due to diarrhea [3]. However, the cost of the vaccines was high, and with a birth cohort of 27 million, it seemed challenging to consider the introduction of a rotavirus vaccine for routine use in India. Yet today, a vaccination program has begun, initially for four states, but with plans to cover the entire country rapidly.

How did we get here? The amazing story of the Rotavac vaccine – developed from an Indian strain by an Indian scientist, supported by an international science community, to make and test a vaccine in India – should serve as a paradigm for future research and development efforts in India [4,5]. However, the policy decision to introduce a rotavirus vaccine, also came from several other novel features. In 2001, the Indian Council for Medical Research (ICMR) and the Centers for Disease Control and Prevention (CDC) in Atlanta, USA, began planning a network for surveillance for rotavirus in different parts of India. It was a slow process, but high quality data collection began in 2005, and has been sustained for over a decade generating information using a uniform protocol for recruitment, data collection and testing for children hospitalized for gastroenteritis [6,7]. In over 25,000 specimens that have been collected and tested over the past ten years, rotavirus positivity in children admitted to hospitals with diarrhea is between 35% to 40%, indicating a very large burden of severe disease. Additional studies also showed the devastating economic impact of rotavirus gastroenteritis among poor families resulting in hospitalization and catastrophic expenses [8].

At the time when these studies and the efficacy trials of the Rotavac vaccine were being done, the two internationally licensed vaccines became available in India following immunogenicity bridging studies. The Indian Academy of Pediatrics reviewed the performance of the vaccines and included them in their immunization schedule. With this inclusion, the vaccine began to be offered and widely used for children of parents who could use private immunization services, but the vaccines were not available to poorer children, because each course of vaccines cost several thousand rupees. In 2013, the results from the phase 3 clinical trials of Rotavac became available and demonstrated its safety and efficacy [9]. These data, along with the very comprehensive disease burden data available through the ICMR's National Rotavirus Surveillance Network were presented to the National Technical Advisory Group on Immunization [6,7,10], which made a recommendation in 2014 for introduction of the vaccine into the national immunization program. The Ministry of Health and Family Welfare accepted this recommendation, procured vaccine, conducted training and begun a early phase introduction in the states of Odisha, Andhra Pradesh, Haryana and Himachal Pradesh, with other states to follow when feasible.

Now that India has its own rotavirus vaccine in use, issues including performance and impact under conditions of routine use, effectiveness against currently circulating strains, safety, and cost-effectiveness will need to be examined. The international experience with the two currently available oral rotavirus vaccines in immunization programs does provide insight into the likely performance and impact of the Rotavac vaccine in India. Since 2006, rotavirus vaccines have been introduced in 80 countries, including several countries in Latin America and Africa. Rotavirus vaccines have had a large impact on mortality, hospitalizations and outpatient visits in countries that have introduced the vaccine into

their national immunization program, including some evidence suggesting that rotavirus vaccines may offer indirect protection to older, unvaccinated age groups. The effect of rotavirus vaccination in reducing deaths from childhood diarrhea in some countries in Latin America has been remarkable, with Mexico's introduction of vaccination in 2007 followed by an all-cause diarrhea mortality rate decline by two-thirds compared with the pre-vaccine baseline [11]. In other interesting findings, researchers have seen indirect effects of rotavirus vaccines among older children and adults, with sharp reductions in rotavirus gastroenteritis hospitalizations in groups who did not receive vaccine [12], indicating that young children may be the major transmitters of rotaviruses in the community. In post-licensure efficacy studies in Africa (South Africa and Malawi), the Rotarix vaccine at 10 and 14 weeks of age had 59% efficacy against severe rotavirus diarrhea during the first year of life and three doses at 6, 10, and 14 weeks of age had 64% efficacy [13]. In Malawi, efficacy was 50% for two and three dose recipients during the first year of life, but in the second year of life, efficacy was 3% in two dose recipients and 33% among three dose recipients. Malawi has recently reported post-introduction effectiveness of 64% in the first year following vaccination [14]. With Rotateq given at 6, 10, and 14 weeks of age in Africa (Ghana, Kenya, and Mali), the efficacy was 64%; and in Asia (Bangladesh and Vietnam), the efficacy was 51% against severe rotavirus disease during the first year of life [15,16]. Effectiveness data from Rwanda demonstrated 61-70% reduction in rotavirus hospitalizations [17]. These post-licensure studies also demonstrated sustained protection against a range of strains not included in the vaccines [14,17].

An additional issue to consider is safety. Large trials of 60,000-70,000 infants failed to detect increased risk of intussusception following rotavirus vaccination within a month of any dose of the two internationally licensed vaccines. However, post-marketing surveillance has detected a small increased risk of intussusception (1-2 excess cases per 100,000 infants vaccinated) in the first week following the first dose of vaccine in most populations where the vaccines have been given to several hundred-thousands of infants with monitoring [18]. Although with the severity of rotavirus disease and the need for management of the acute condition prevented by the vaccine, assessments have found favorable benefit-risk ratios for vaccination [19]; intussusception is a serious condition requiring urgent care for which clear referral pathways must be available.

Overall, it appears likely that due to the high rotavirus burden, the introduction of a vaccine in India will have a significant impact on disease, protect against a wide variety of circulating strains, and result in a decrease in the economic burden of rotavirus in India. Studies to examine rotavirus vaccine impact and safety using proven study designs should be conducted to help answer many of these questions and provide support for sustained use of rotavirus vaccine in India, and the ICMR has begun its efforts to provide the end-to-end data for evaluation of the performance of the vaccine in the national immunization program.

Funding: None; *Competing interest*: None stated.

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Healthcare Interventions and Vaccines

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Rotavirus infections are ubiquitous. Where vaccines have been widely introduced, there has been an extraordinary positive impact on mortality and morbidity. There is much yet to be done in India to ensure full introduction of rotavirus vaccination in the national immunization program. There are many challenges in implementation of a new vaccine for a large birth cohort and new challenges will surely emerge, as with any effort on this scale. Our collective experience will deal with existing and emerging issues, and full deployment of the vaccine will save hundreds of thousands of lives and will greatly improve the health of children. On the science and technology front, the development and deployment of an indigenous vaccine is exemplary, and raises confidence that more such efforts will follow. The Indian vaccine industry, indeed all of India, should take great pride in what it did in the manufacture of vaccines in general and against rotavirus in particular. Two big cheers are due to India.

Yet, this is a time for introspection and self-criticism. We need to ask ourselves if we could have gone ahead faster and implemented faster. We also need to learn from the rotavirus experience what we need to do for immunization programs in general, and for specific vaccines as needed. While our vaccine and vaccination challenges are complex, our programs can be broken down into components in a pipeline. Each component can be analyzed and we can chart out where and how we can do better. Reality is far more complex, dynamic and unpredictable but such an approach and a constant self-appraisal can help in strategic development and implementation.

We can divide the components in the pipeline into research, the 'valley of death' that needs to be crossed to take vaccine development into trials, manufacture, implementation and monitoring. While a detailed analysis is needed, I outline aspects that need attention, and try and point to realistic routes to address these problems. In each of these components, we can analyze our strengths, weaknesses and, very important, the efforts needed to address the problem. These components and the current situation are broadly and qualitatively summarized in ***Table* I**. A constant and critical mapping of each cell in the table, for each vaccine candidate, is needed. As a research funder, not directly involved in deep-downstream implementation (a responsibility of central and state health ministries), this dynamic mapping could be anchored by a partnership of the Department of Biotechnology (DBT) and the Indian Council of Medical Research (ICMR). Such a 'landscaping' unit, organically connected with our reality is an effort which the DBT will put in place. Indeed, some such structures are already in place; learning from their successes and weaknesses, and