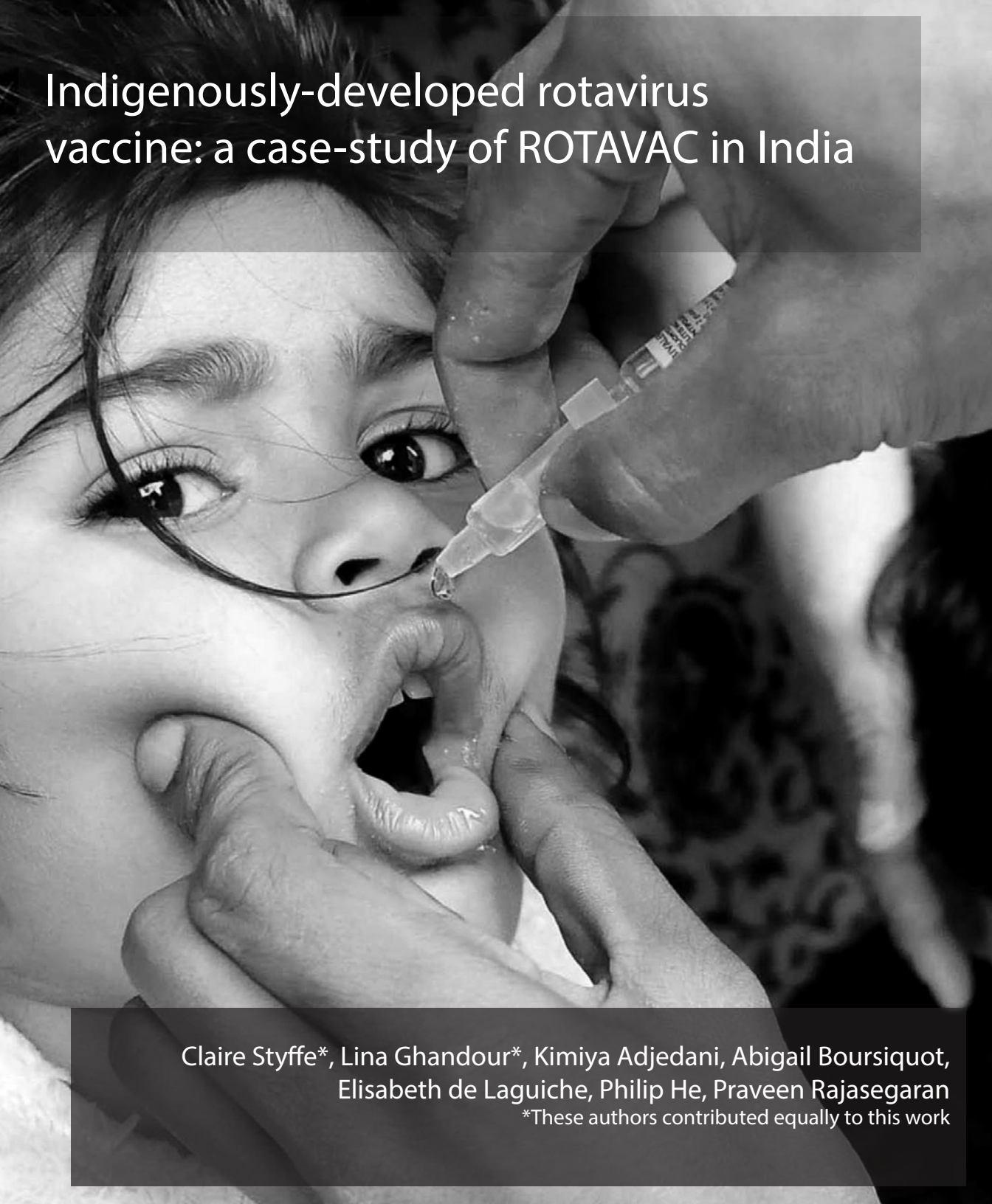
Indigenously-developed rotavirus vaccine: a case-study of ROTAVAC in India



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Abstract

India has a high burden of rotavirus, a disease that causes gastroenteritis. ROTAVAC is an indigenously-developed rotavirus vaccine that was researched and manufactured in India by Bharat Biotech. It was introduced in India's Universal Immunization Program in four states in 2016 and expanded to five more in 2017. While its efficacy rate is similar to that of other rotavirus vaccines, it is far cheaper, making its introduction in the Indian health care system cost-efficient. Bharat Biotech were able to market ROTAVAC at only USD 1 per dose due to savings incurred by manufacturing locally, and the innovative team science approach used in the vaccine development. Challenges in implementing ROTAVAC remain, including lack of funding, vaccine coverage disparities and a lack of medical consensus on the vaccine's importance. The absence of data on project funding, vaccine uptake and rotavirus incidence rates renders a conclusive analysis difficult, and stresses the importance of strong surveillance systems and data transparency. Despite such challenges, ROTAVAC remains an encouraging example of a low-income country researching and developing a successful vaccine, a process usually reserved for high-income countries. Its development and WHO pre-qualification have immense potential to reduce the rotavirus burden in India and other developing nations.

Introduction

Diarrheal disease is the most common cause of hospitalization and death in children globally and accounts for roughly one in six deaths among children under five years of age.1 Approximately 15% of India's child mortality is attributable to diarrheal diseases.2 Rotavirus is a viral infection that predominantly affects children; it can cause gastroenteritis, an inflammation of the stomach and intestines, which results in severe diarrhea and dehydration.3 Rotavirus is the leading cause of severe diarrheal disease-associated morbidity and mortality among children in developed and developing countries, accounting for 37% of diarrheal-related deaths worldwide.4,5 Notably, over 22% of all rotavirus deaths are estimated to have occurred in India, approximately 50% of which occurred in the first year of life and affected girls disproportionately (Figure 1).6,

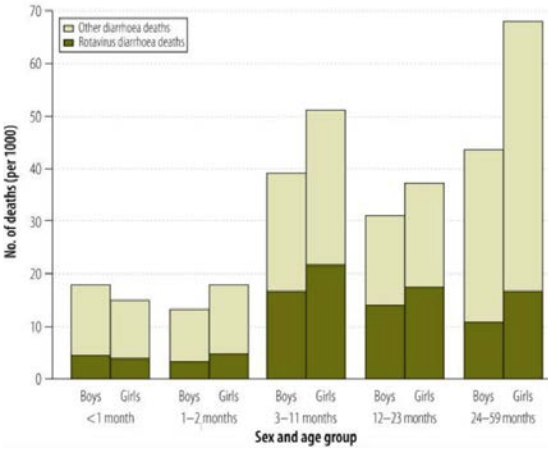

Figure 1. Estimated overall number of diarrheal deaths and rotavirus-attributable diarrheal deaths among Indian children younger than 5 years, by age and sex, during 2005.

Currently, there is no treatment for rotavirus infection; however, immunizing infants against rotavirus has shown to protect them from acquiring the infection and decreases the risk of infant death due to diarrhea.7 Several licensed vaccines have been shown to be safe and effec-

tive against rotavirus, including Rotarix and RotaTeq.7 India has recently manufactured ROTAVAC, an indigenously researched and developed vaccine. This paper explores the progress, ongoing challenges and potential future implications of the ROTAVAC vaccine for children under 5 in India.

Rotavirus Vaccines

Development of the ROTAVAC Vaccine

The road to developing of ROTAVAC was a long one, beginning in 1985 when a pediatrician at the All India Institute of Medical Sciences remarked that several infants were becoming infected with rotavirus in the hospital, but were not showing symptoms.8 Infection with the neonatal 116(E) strain protected these babies from reinfection, thus highlighting its potential to be used in a vaccine.9 From there, Indian and American scientists collaborated through the Indo-American Vaccine Action Program to characterize the strain and develop it into a vaccine candidate.9 In 1998, the Indo-American Vaccine Action Program held a meeting in India to identify potential manufacturers; Bharat Biotech International, a young Hyderabad-based company without any licenced products at the time was selected to manufacture the vaccine.9

A number of different partners collaborated to ensure that the vaccine moved through development and manufacturing efficiently; Bharat Biotech International, the Center for Disease Control and Prevention, the National Institutes of Health, the All India Institute of Medical Sciences, Stanford University and the Indian Institute of Science were supported by the Bill and Melinda Gates Foundation-funded Children's Vaccine program to move the candidates through production, testing and surveillance.8 Thus, public-private partnerships were created and the Indian government played a key role in supporting the intervention.8 While Bharat Biotech reportedly invested USD 20 million into the manufacturing process, little information exists regarding how much funding other partners contributed to the development effort.10 Greater transparency with regards to funding is necessary to fully evaluate the expenses incurred by the Indian government and the cost-effectiveness of the intervention.

Clinical trials began in India in 2005 under the supervision of researchers at the Society for Applied Studies, the KEM Hospital and Research Center and the Christian Medical College. This represents a remarkable divergence from the traditional development pathway in India; usually well-known vaccines from the West are manufactured in Indian government labs and then distributed through the public and private health sector.11 ROTAVAC is not only based on a strain of rotavirus found in India, but was also researched with Indian partners, manufactured by an Indian pharmaceutical company and underwent clinical trials in India, making it a rare example of a health technology that was developed and tested primarily in India; it can therefore be considered an indigenous vaccine.9

A randomised double-blind, placebo-controlled, multicentre trial was conducted, whereby infants were randomly assigned to receive either placebo or three doses of the 116E vac-

cine at ages six to seven weeks, ten weeks and fourteen weeks.12 Results indicate a 56% efficacy rate for the first year, with a slight decrease to 49% in the second year.12 In addition, results also revealed that the vaccine entails lower risks of intussusception compared to first generation rotavirus vaccine.13 In fact, clinical trial on ROTAVAC showed no association with intussusception, and post-marketing surveillance of ROTAVAC is in place to monitor alterations of intussusception risk of the vaccine.13 Following Phase I and II clinical trials in infants, toddlers and adults, ROTAVAC has also been found to be safe and immunogenic.13 The demonstrated efficacy and safety of the ROTAVAC vaccine led to its licensing in India in 2014, and the obtainment of the World Health Organization (WHO) prequalification in 2018.14,15

ROTAVAC is now being implemented in the Universal Immunization Program in India.16 The vaccine has been integrated to the routine immunization programs of 9 states, following a phased introduction model.17 The initial stage in 2014 targeted 4 states: Andhra Pradesh, Himalchal Pradesh, Haryana and Orissa.18 Diarrheal disease burden, routine immunization coverage, system preparedness and state willingness to introduce the vaccine were taken into consideration to identify suitable states for the initiation of the vaccine introduction (Figure 2).17 Five additional states were added in 2017: Assam, Chhattisgarh, Madhya Pradesh, Rajasthan and Tamil Nadu.17 The Rota Council reports that up to this day, close to 35 million doses of ROTAVAC have been administered in India.18

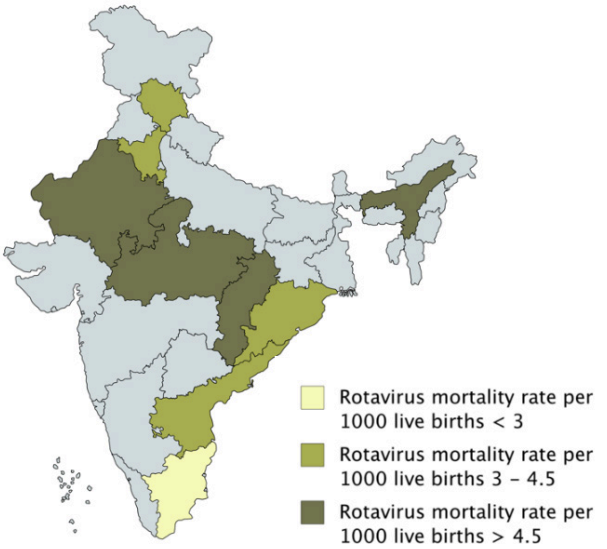

Figure 2. Estimated rotavirus-attributable diarrheal mortality rates among children under 5 years of age in 9 states in India prior to introduction of ROTAVAC, in 2005.

Comparative analysis of Rotarix, RotaTeq and ROTAVAC

Along with ROTAVAC, there are currently two other licensed rotavirus vaccines: RotaTeq and Rotarix. While ROTAVAC's 56% efficacy rate is comparable to that of RotaTeq and Rotarix, it differs in terms of origin and price. Rotarix and RotaTeq are both designed and manufactured by large Western pharmaceutical companies in high-income countries and cost USD 20 and USD 15 per dose, respectively.19-21 In contrast, ROTAVAC is designed and manufactured in India and is marketed at only USD 1 per dose.20,21 Rotarix and RotaTeq were deemed too expensive for the Indian market, and much of the impetus for ROTAVAC's fabrication lied

in creating an effective vaccine that could address the high rates of Rotavirus in India at an affordable price.11 For a more detailed comparison of Rotarix, RotaTeq and ROTAVAC, see Table 1. As data regarding uptake and incidence rates following ROTAVAC immunization in India is lacking, it remains difficult to fully evaluate the effectiveness of ROTAVAC introduction in India and compare its effect with other vaccines.

Cost-effectiveness Analysis

The prevalence of rotavirus episodes in India translates into significant financial strains on the national healthcare system.24 The introduction of ROTAVAC on a national level therefore represents the potential to greatly reduce the prevalence of rotavirus and thus its associated costs. The initial approach to evaluate the impact of the ROTAVAC vaccine relied on a comparison of rotavirus incidence rates prior to and post ROTAVAC introduction. However, this data was unavailable, which called for a shift towards an economic impact analysis, looking at the cost effectiveness of the introduction of ROTAVAC.

Various studies examine the potential savings that the ROTAVAC vaccine could generate, comparing the forecasted cost of the vaccination programme with the current costs incurred by the medical treatment of rotavirus.24-27 ROTAVAC vaccine is not yet available in all states in India; thus, all analyses presented rely on projected figures and numbers. This highlights the need for national surveillance to obtain accurate data to monitor and project the impact of introducing ROTAVAC vaccine on a national scale.

The existing literature measuring the financial impact of ROTAVAC provides an overview of the number of deaths, hospitalizations and outpatient visits that are caused by rotavirus. While authors tend to provide similar estimates for the numbers of deaths and hospitalizations, the numbers of outpatient visits vary. For clarity purposes, this review is therefore based on the numbers given by John et al. who provide a recent and targeted cost benefit analysis for the introduction of ROTAVAC in India.25

Attribute	Rotarix	RotaTeq	ROTAVAC
Manufacturer	GlaxoSmithKline[20]	Merck[19]	Bharat Biotech[20]
Country of Origin	United Kingdom[20]	United States[19]	India[20]
Year of Issue	2008 [28]	2006 [29]	2014[14]
Development Stage	Phase IV WHO pre-qualified[20]	Phase IV WHO pre-qualified[20]	Phase IV WHO pre-qualified[20]
Strain	G1, P[8][23]	G1, G2, G3, G4, P1A[8][19]	116E[22]
Type of Vaccine	Attenuated human[22]	Bovine reassortants[19]	Natural bovine neonatal[22]
Efficacy in LMICs	71.7% in Latin America[20] 61.7% in Africa[20]	51% in South East Asia [20] 64.2% in Africa[29] 48.1% in India[21]	56% in India[20]
Efficacy in HICs	92.4% in Finland[20] >96% in Southeast Asia[20]	98% in Europe/US[20]	n.a.
Vaccination schedule	2 doses (2 and 4 months of age)[21]	3 doses (2, 4 and 6 months of age)[21]	3 doses (6, 10, and 14 weeks of age)[21]
Scale	Latin America, Europe, Southeast Asia, Africa[20]	United States, Europe, Southeast Asia, Africa[20]	Nine States in India[17]
Cost in India	USD 20 per dose[21]	USD 15 per dose[21]	USD 1 per dose[21]
Cost-effectiveness analysis	In India, incremental cost-effectiveness ratio is USD 21.4 to USD 24 per DALYs[21]	n.a.	Cost-effectiveness is superior to Rotarix[21]

DALYs: Disability-adjusted life years; LMICs: Low and middle income countries; HICs: High income countries

Table 1. Comparative analysis of Rotarix, RotaTeq, and ROTAVAC vaccines

Based on the 2011 Indian birth cohort comprising of 27,098,000 children, John et al. found that 42.0% (n= 11,373,098) had an episode of rotavirus, 28.8% (n= 3,271,187) received outpatient

care, 7.67% (n= 872,315) were hospitalized, and 0.69% (n= 78,583) of children died from the infection (Figure 3).25 The cost of hospitalization added up to INR 4.7 billion (~USD 65 million) annually, while outpatient visits cost 5.5 billion (~USD 75 million)* annually.25

The total cost of a ROTAVAC vaccination campaign in India for the 2011 cohort is estimated to amount to INR 4.47 billion (~USD 62 million)*.25 This estimation is contingent on ROTAVAC's price, which was kept at USD 1 per dose.21 In comparison, Rotarix and RotaTeq cost USD 20 and USD 15 per dose respectively.21 The total cost of a vaccination campaign using one or the other of these two vaccines would be incrementally higher. More data would, however, be needed to make a more precise analysis comparing the total cost of a vaccination campaign using either one of these three vaccines, given the detail of the elements accounted for in the total estimated cost provided by John et al.

Complementing John et al.'s cost benefit analysis, Rose et al. forecast the introduction of the vaccine to result in a 13% nation-wide reduction in symptomatic rotavirus infection, and a 34.6% drop in rotavirus mortality.27

According to John et al.'s analysis, the hospitalization and outpatient care costs tied to rotavirus in India exceed INR 10.4 billion (~USD 143 million)*.25 The introduction of the vaccine would however cost INR 4.5 billion (~USD 62 million)*, and is projected to result in a 13% reduction in the nation-wide rotavirus infection as well as a 34% drop in mortality.27 While these impacts substantiate the necessity to scale up the vaccination program, further data regarding the prevalence and the savings would be required to have a reliable estimation of the benefits of the ROTAVAC vaccine scale up in India.

Figure 3. Estimates of the burden of rotavirus in India based on the 2011 birth cohort of 27,098,000 children.

Discussion

Downstream outcomes of ROTAVAC scale-up in India

Much of the success of ROTAVAC lies in its efficacy; with a 56% efficacy rate, it is comparable to the other leading vaccines Rotarix and RotaTeq, making it a valid alternative.24,12 Its reduced cost is also a key factor in its success; with a price of USD 1 per dose, it is far cheaper than Rotarix and RotaTeq which cost around USD 15 per dose.30 This reduction in price makes the distribution of ROTAVAC highly cost effective, and would be cheaper than the current expenditure on rotavirus hospitalizations.31

The indigenous nature of the vaccine develop-

ment and production is not only a victory for the Indian pharmaceutical company Bharat Biotech International, but is also an important contributor to the vaccine's potential success. Production of the vaccine in India allowed stakeholders to mitigate costs and taxes associated with importing the vaccine, rendering it even more cost-beneficial. India maintains very high basic customs duties, in some cases exceeding 20 percent, on drug formulations, including life-saving drugs and finished medicines.32 These high tariffs contribute to the higher costs associated with each dose of the two licensed and imported vaccines, RotaTeq and Rotarix.32 By manufacturing and distributing the ROTAVAC vaccines in India, these costs could be averted and the vaccine was made available at a lower cost.

Particularly important to consider is the manner in which the vaccine was developed; an innovative, 'team science' strategy was employed, along with funding from both public and private stakeholders, facilitating the production of the vaccination.8 The efforts of clinical and translational investigators from thirteen different institutions, including the US Center for Disease Control and Prevention, the Indian Institute of Science, Stanford University and the National Institute of Allergy and Infectious Diseases aided in technical challenges, while funding from the Indian government, Bharat Biotech International and PATH helped enable local manufacturing.8 Sharing costs between such a variety of partners was paramount to keeping the price to only USD 1 per dose, and Bharat Biotech International used highly efficient manufacturing procedures and inventive production techniques to further limit costs.25

Implementation Challenges

Despite the success in developing a cheap and effective vaccination, there still remain challenges in ensuring that the vaccine is distributed equitably and reduces the incidence of rotavirus. There lacks a strong political will in India to invest heavily in health; currently, only 2.2% of the 2018-2019 annual GDP is spent on health, less than half of the WHO recommended 5%.33,34 Of that 2.2%, 9.9% is allocated to routine immunizations.33 It is important to note, however, that this is a substantial increase from the 3% of the health budget that was previously allocated to vaccination.35 This lack of financial commitment echoes the lack of political will, which further trickles down to a lack of supply as there are only two domestic manufacturers of the vaccine in India, despite the considerable demand.36

As India is a large, diverse country with a population of over 1.34 billion people, significant implementation challenges exist. Vaccinations are provided free of charge under the Universal Immunization Program, yet disparities in coverage pose a challenge to widespread implementation. Factors such as gender, birth order, area of residence, parental education, religion, caste and community literacy levels influence vaccine uptake rates.31 Boys generally have higher vaccination coverage as compared to girls and urban areas tend to have increased vaccination coverage as compared to rural areas. Furthermore, those living in slum housing have lower rates of coverage compared to other urban dwellers, as

do migrants compared to the resident population.31 Both urban and rural poor populations have lower vaccination coverage as compared to wealthier ones.31

While an efficacy rate of 56% is comparable to that of other rotavirus vaccinations and is often cited as an indication of the vaccine's success, there are arguments that such an efficacy rate is not high enough to justify implementing ROTAVAC as a standard vaccination. As Dr. Jacob Puliyel, head of the Department of Pediatrics at the St. Stephen's Hospital in Delhi, notes: "Do you know another vaccine with 50% efficacy that is used for public health programs? It is a toss up [Sic] if the vaccine will work for you. If 100% [of the] population is vaccinated it will reduce 50 [of the] rotavirus deaths. What are the numbers needed to treat [to prevent one death]?".30 Others argue that the ROTAVAC vaccine trial enrolled only 6800 participants, a small sample necessary to establish safety for rare events.12 In comparison, over 70,000 and 17,500 subjects were enrolled in the clinical trials for RotaTeq and Rotarix respectively.19, 37

Further challenges include a varying degree of medical confidence in the vaccine. Studies found that the vaccine was more favourably accepted among paediatricians, 70-88% of whom would recommend it, while only 46-55% of family physicians were willing to recommend it with a smaller proportion seeing a need for rotavirus vaccination relative to paediatricians.16 Family physicians serve as patients' first point of entry into the medical system, while paediatricians work at a more specialized level and often work in hospitals. Furthermore, family physicians provide quality and cost-effective healthcare relative to the ever increasing costs of tertiary care facilities and hospital-based settings where most pediatricians work.38 As such, the average Indian citizen is more likely to interact with a family physician than a paediatrician and is thus less likely to receive a recommendation to become immunized against rotavirus.

Lessons Learned

ROTAVAC challenges the notion that only high income countries (HICs) are capable of researching and manufacturing technological innovations such as vaccines. Vaccine development is usually undertaken by large pharmaceutical companies in high-income countries which can lead to high vaccine prices, making such lifesaving innovations expensive and inaccessible to low and middle-income countries (LMICs).39 The successful production of ROTAVAC demonstrates that LMICs are in fact capable of developing technologies usually reserved for HICs and that such an endeavour can lead to decreases in costs, making these innovations more affordable to those who need them most.

The reduced price of ROTAVAC allows for greater access in India, and has profound implications for reducing rates of rotavirus and associated mortality in Indian children.25 The affordability of ROTAVAC compared to RotaTeq and Rotarix however, is not only a positive development for India, but also for those in other LMICs. ROTAVAC achieved WHO prequalification in January 2018, meaning that United

Nations Agencies and the Global Alliance for Vaccines and Immunisation (GAVI) can now include it as part of their programmes to equitably distribute vaccinations, though GAVI does not currently include ROTAVAC on its distribution list.15,40 By being available for procurement by GAVI and other agencies, the low cost benefits of ROTAVAC may be distributed to other heavily burdened countries and may play an essential role in reducing rotavirus in a number of low-income settings. India has previously faced concern over cheap and low-quality vaccines, but the recent WHO pre-qualification of ROTAVAC is an indication of a high quality and may improve global perceptions on Indian vaccine production. 41

The successful development of ROTAVAC owes much to its innovative, 'team science' structure, which incorporated a multidisciplinary research and development team with a variety of public and private funders.9 Further, using public-private partnerships and team science has created structures and relationships in India and abroad that may now be used again in the future development of other health technologies.42 Such approach is an inventive model that has profound implications for the future development of other health technologies and stresses the potential of public-private partnerships. By adopting such a strategy, other LMICs may be able to develop their own affordable health tools that have so far been reserved for HICs and multinational corporations. This is consequently not only an encouraging example for other LMICs but also a pioneering endeavour that has laid the framework for successive locally produced innovations.

Limited surveillance data on the uptake of ROTAVAC vaccine has made it difficult to evaluate its impact in India. The WHO Global Vaccine Action Plan outlines the importance of improving the quality of immunization data, strengthening disease surveillance systems and promoting the use of technologies for comprehensive collection and analysis of immunization data.43 While there is abundant information on the burden of rotavirus in India and projected cost-benefit analysis, there is little to indicate how the introduction of ROTAVAC to nine states has proceeded, what the coverage has been or what impact it has had on rotavirus incidence. Thus, while there exists plenty of data suggesting how promising this novel vaccine is, there is little to confirm its predicted impact. This stresses the importance of strong immunization surveillance systems and the dissemination of transparent data. ROTAVAC remains a new vaccine and it is possible that data is currently being collected; however, while other countries may look toward ROTAVAC as a successful example of how to develop an indigenous health technology, they should consider the importance of accompanying the distribution of such an intervention with a robust surveillance system, to ensure that the innovation is meeting predicted targets and functioning adequately.

Conclusion

The introduction of the indigenous rotavirus vaccine, ROTAVAC, presents a useful case-study to understand the value in promoting

sustainable research and development pathways in developing countries like India. ROTAVAC's main strengths lie in its reduced price and potential to prevent rotavirus associated morbidity and mortality. It remains an encouraging example that LMICs can in fact locally develop high quality, efficacious vaccines to improve access to preventive health tools. There continues to be a number of challenges in the distribution of ROTAVAC, including a lack of political will and funding, implementation difficulties associated with a large and diverse country and a lack of medical consensus on the benefit of administering the vaccine. This is not uncommon and demonstrates that despite the immense potential that an indigenously researched and manufactured vaccine can have, there are also obstacles associated with the rollout and scale up of such an intervention. In spite of all the challenges and logistical difficulties, inclusion of the indigenously developed rotavirus vaccine in national immunization schedules should remain one of India's major commitments against vaccine preventable diseases.

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