Rotavirus vaccine trials in icddr,b and future use of the vaccine in Bangladesh

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Abstract

Safe and effective rotavirus vaccines (RV) are needed to reduce the enormous public health burden of rotavirus illness in developing countries. Vaccination is critical for effective control of rotavirus infection since it cannot be prevented with improvements in water and sanitation. The International Centre for Diarrhoeal Disease Research, Bangladesh (icddr.b) has completed several ground-breaking RV trials (phase I-Phase IV). The safety, immunogenicity, efficacy and effectiveness of different RVs were evaluated among both urban and rural population. Herein, we present the results, policy implications, lessons-learned for successful implementation of these trials as well as future directions for rotavirus vaccination in Bangladesh.

Key words: Rotavirus vaccine; Bangladesh, efficacy study
Introduction

Nearly all infants experience at least one rotavirus infection without vaccination by two years of age, and eventually, 118,000 children under five years of age died globally due to rotavirus in 2019 [1]. Most deaths occur in low- and middle-income countries (LMICs) especially in Africa and Asia [2]. Many of the deaths can be prevented if children had access to safe and effective rotavirus vaccines where urgent care for severe rotavirus illness is often limited or even inaccessible. For decades the icddr,b played a significant role in evaluating rotavirus vaccine safety, immunogenicity, efficacy and effectiveness in high-mortality, low-income settings in Bangladesh. These vaccine studies led by the icddr,b made an important contribution to the growing body of evidence that demonstrated the safety, efficacy, and potential lifesaving impact of rotavirus vaccines and accelerated the availability of rotavirus vaccine through the recommendation of the World Health Organization since June 2009. Currently, 110 countries have already introduced the rotavirus vaccine in their national immunization programs [3]. However, the battle against one of the leading childhood killers is yet to be over as more significant than 40 percent of the world’s children still do not have access to the rotavirus vaccine. Many children with no access to the rotavirus vaccine live in low-income settings of Asia and Africa, delaying introducing the vaccine in routine immunization programs. Also due to the high price of the rotavirus vaccines (approximately 19–24 USD per dose) and lack of adequate cold chain facilities, many countries could not introduce the vaccine in routine immunisation program. Further, low-income, or slum-dwelling people cannot afford it who need it most. There are 3 million infants in the annual birth cohort without access to rotavirus vaccines in Bangladesh where one diarrheal disease hospitalization can cost more than 20% of the average monthly household income for an extremely poor family [3,4]. Bangladesh can save an estimated US$ 66.8 million annually (J
Hossain, personal communication) by introducing the rotavirus vaccine in routine immunization programs, which will prevent approximately 135,000 hospitalizations per year.

**The icddr,b Model**

icddr,b is the world’s largest diarrheal hospital treating more than 200,000 patients a year. For the last 50 years, its research continues to evaluate low-cost, scalable vaccines against rotavirus, cholera, other enteric and respiratory diseases, and different non-interventional public health approaches. Notably, its development of Oral Rehydration Solution (ORS) has saved tens of millions of lives and created a profound impact on global health crises. With the support of highly knowledgeable and skilled scientists, clinicians, researchers, nurses, health workers, and auxiliary staff with unparalleled experience, icddr,b can undertake various investigations on emerging infectious diseases and new interventions to reduce maternal and neonatal mortality.

The icddr,b has conducted several rotavirus vaccine (RV) trials ranging from phase I to III and post marketing evaluation of the vaccines (phase IV). Three US FDA licensed rotavirus vaccines were tested and evaluated in the icddr,b trials including: Tetravalent rhesus rotavirus vaccine (RRV-TV, RotaShield, Wyeth Lederle), Pentavalent rotavirus vaccine (PRV, RotaTeq®, Merck & Co.) and monovalent rotavirus vaccine (Rotarix®, GlaxoSmithKline) [2,5,6,7]. We also studied the co-administration of rotavirus vaccines with oral polio vaccine (OPV) provided through routine immunization programs [6]. These trials were conducted in both urban and rural areas and the trial sample sizes ranged from a few hundred to several thousand. The safety, immunogenicity, efficacy and effectiveness of the vaccines were evaluated (Table 1).
Trial Outcomes

The first rotavirus vaccine trial conducted by icddr,b was a phase II randomized, double-blinded, placebo-controlled trial to test the safety and immunogenicity of RRV-TV during the period of 1998-1999 in rural Bangladesh. The study showed that RRV-TV was comparably immunogenically (87% seroresponse rate) and safe to other trials conducted in the developing world [5]. The study data reassured rural children with common malnutrition can have immunologic responses to vaccination like those in developed countries and supported future trials of rotavirus vaccines in developing countries [5]. We conducted a phase I study with human monovalent vaccine (Rotarix®) among 90 toddlers in 2002 to determine the safety of the vaccine in urban slum area (unpublished). Another phase II randomized, placebo-controlled immunogenicity study was conducted during the period of 2005-2006 among 300 healthy infants living in an urban slum to test the safety and immunogenicity of two doses of the human monovalent vaccine (Rotarix®) when co-administered with OPV, which is routinely administered at 6, 10 and 14 weeks of age. The study findings strongly suggested that Rotarix® can be concomitantly given with OPV in routine immunization without interference in immunogenicity and facilitated the decision on rapid and effective integration of rotavirus vaccine into the routine EPI program in many countries [6].

The icddr,b conducted a phase III clinical study among 2036 infants to assess the safety, immunogenicity, and efficacy of the three-dose RotaTeq® vaccine administered at 6, 10, and 14 weeks of age along with Vietnam and scientists from other institutions simultaneously conducted trials in three sites in Africa (Kenya, Ghana and Mali). The study showed a significant reduction of severe rotavirus disease by 51% in the first year of life, when children are at the greatest risk of diarrhea-related illness and death, supporting expansion of WHO recommendations to promote the global use of Rotavirus vaccine [7]. Our study was the first
clinical efficacy trial of an already licensed rotavirus vaccine in developing countries in Asia that showed even with lower efficacy than the data reported in trials of RotaTeq® in developed countries; rotavirus vaccine can significantly reduce the burden of severe disease [7]. We conducted the first effectiveness study in a cluster-randomized design of a rotavirus vaccination program using Rotarix® in rural Bangladesh, where rotavirus diarrhea rates were compared between clusters with and without Rotarix®, allowing the first examination of overall, direct and indirect protection by a rotavirus vaccine. The study showed that 2 doses of Rotarix® vaccine works well under programmatic conditions and is 41% effective against severe acute rotavirus diarrhea, although indirect protection of non-vaccinees was not demonstrable [2]. This was the first study to provide real-world efficacy data on the WHO-recommended two-dose rotavirus vaccine schedule in a low-resource setting in Asia. The study provided valuable insight on research to understand programmatic means to address waning effectiveness after vaccination and the need for booster doses to improve and extend protection [2]. We also compared a new heat-stable formulation of lyophilized live attenuated pentavalent rotavirus vaccine (HSRV) manufactured by MSD Wellcome Trust Hilleman Laboratories, New Delhi, India with RotaTeq® in a randomized Phase I/II among infants living in urban slum which was the first trial of its kind. HSRV was found safe and immunogenic (88% seroresponse rate) [8]. Such a heat-stable rotavirus vaccine that can sustain at 45°C for 7 months is important for resource-limited settings where most of the rotavirus burden exists and maintaining a cold chain is challenging. Our study generates new data on newer rotavirus vaccine formulations that can partially or entirely eliminate cold chain dependence and reduce associated costs [8].
Future Directions

Our experience with rotavirus vaccine trials indicates that all phases of clinical trials with GCP standard can be conducted maintaining high quality and coverage in urban slums and in rural populations of Bangladesh. For all the trials, we accomplished enrollment of a large number of study participants within the timeline and high compliance of study related activities. We conducted these studies in vulnerable slum and rural populations by maintaining a community relationship which benefitted the study population to a large extent. The rotavirus-effectiveness study provided experience with the vaccine in a ‘real-world’ setting, and valuable lessons were learnt on routine vaccine delivery in Bangladesh.

There were a few challenges faced in the trials, such as maintaining proper temperature of vaccines in very hot weather and carrying vaccine cold boxes during rainy season with difficult transportation system, but it was managed successfully because of very careful forward planning. There were no unacceptable temperature deviations recorded during vaccine and sample storage or transportation, nor any record of vaccine vial damage. Retention of study participants in a mobile population, particularly in urban areas with migration rates of about 25% per year, was hard to achieve. The study clinic provided outpatient services for the study population 7 days a week from 8:30 to 5 PM and remained open for 24 hours for any emergency services. After office hours, mothers could easily communicate with study medical officers and respective field staff over the phone to ensure necessary treatment of their infants. Standard medical care was provided free of cost, and we referred patients to the nearby hospitals when inpatient services were needed. All these initiatives highly encouraged the community in both the urban slums and rural Bangladesh to take part in our studies over many years.
In 2016, Bangladesh applied to GAVI for rotavirus vaccination and anticipated to introduce Rotarix® in routine immunization in 2018 [9]. GAVI support funds cover the cost of rotavirus vaccine procurement and a one-time grant to cover introduction costs in eligible countries. This allowed countries in Africa and Asia, where most rotavirus deaths occur, to introduce the vaccine. But the introduction in Bangladesh was delayed due to lack of infrastructure, the need to expand and upgrade the cold chain facilities to support the planned EPI expansion in the whole country [10]. There was also an escalation in the target population for all vaccinees from 3.25 million to 3.76 million during the proposed timeframe. While the focus was first on the peripheral cold storage expansion and was mostly complete, central storage facility timelines dropped back significantly. Furthermore, there was limited time, resources, and funding for rotavirus vaccine introduction due to competing priorities with measles-rubella vaccination campaign planned in late 2019 [11] to overcome the burden of measles in the country that began to surge around the time GAVI approved Bangladesh’s application for Rotavirus vaccination. Overall, insufficient readiness of Bangladesh EPI and lack of planning to guide a realistic introduction timeline contributed to the substantial delay for the rotavirus vaccine introduction in Bangladesh, and introduction has not begun at the time of this writing.

We are optimistic that Bangladesh will hasten the process to introduce the rotavirus vaccine initially approved in principle. We need strong political commitment and approval from different national immunisation committees (scientific and technical sub-committees) to ensure that appropriate attention and energy is focused on implementing the country’s rotavirus vaccination plans. Further, the decision of introduction of any new vaccine also depends on the different studies conducted by research organizations particularly on disease burden and cost effectiveness analysis. Coordination between EPI officials, global and national rotavirus experts, vaccine developers, and concerned people is crucial to explaining
the intervention to the policymakers to convince them to step ahead and take the necessary action. Even after the introduction of the rotavirus vaccine, there can be a shortage of supply, hence there must be a backup plan for possible alternative products for uninterrupted vaccine supply. A coalition with neighbouring India which contains the developers of two recent WHO prequalified rotavirus vaccines (ROTAVAC by Bharat Biotech and ROTASIIL by Serum Institute of India) can make the transition easier. After vaccine introduction, post-vaccination surveillance is important to identify, manage post-vaccination risk (e.g., intussusception) for understanding the impact of vaccination and undertaking post-vaccination control measures [12]. The routine introduction of rotavirus vaccine will ultimately save lives and bring hope for a brighter future.
Notes

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Conflict of Interest

No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.
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| Vaccine candidate                          | Study Year   | Study type and Design                                      | Vaccine schedule | Age of admin | Study groups | No. of Participants | Results         |
|-------------------------------------------|--------------|------------------------------------------------------------|------------------|--------------|--------------|---------------------|------------------|
| Rhesus rotavirus tetravalent vaccine (RRV-TV) [5] | 1998-1999    | Phase II, Randomized, double blinded, Placebo Controlled trial | 3 doses           | 6,10 and 14 weeks | RRV-TV       | 55                  | 87% Immunogenic  |
|                                           |              |                                                            |                  |              | Placebo      | 54                  | 32% Immunogenic  |
| Human monovalent vaccine (Rotarix®) [6] (NCT00139334) | 2005-2006    | Phase II, Randomized, double blinded, Placebo Controlled trial | 2 doses           | 12 and 16 weeks | Rotarix +OPV   | 100                 | 57% Immunogenic  |
|                                           |              |                                                            |                  |              | Rotarix      | 100                 | 67% Immunogenic  |
|                                           |              |                                                            |                  |              | Placebo      | 100                 | 19% Immunogenic  |
| RotaTeq [7] (NCT00362648)                 | 2007-2009    | Phase III, Randomized, double blinded, Placebo Controlled trial | 3 doses           | 6,10 and 14 weeks | RotaTeq     | 1018                | 48% Efficacious  |
|                                           |              |                                                            |                  |              | Placebo      | 1018                |                  |
| Human monovalent vaccine (Rotarix®)[2] (NCT 00737503) | 2008-2011    | Phase IV, Open-label, Cluster-Randomized Trial             | 2 doses           | 6 and 10 weeks | Rotarix      | 6527                | 41% Effective    |
|                                           |              |                                                            |                  |              | OPV          | 5791                |                  |
| Heat Stable Rotavirus vaccine (by Hilleman) and RotaTeq [8] (NCT02728869) | 2016-2017    | Phase I/II, Randomized controlled Trial                    | 3 doses           | 6,10 and 14 weeks | Heat Stable Rotavirus vaccine | 25 | 88% Immunogenic |
|                                           |              |                                                            |                  |              | RotaTeq      | 25                  | 84% Immunogenic  |