

COMMENTARY



Prospects for rotavirus vaccine introduction in the Philippines: Bridging the available evidence into immunization policy

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ABSTRACT

Rotavirus (RV) diarrhea is one of the most common cause of childhood morbidity and mortality in the world. The World Health Organization has recommended RV vaccines' use in national immunization programs since 2009. However, access to vaccines remain limited, particularly for most low- and middle-income countries where the burden of the disease is high. The Philippines is a lower-middle income country in Asia where RV vaccination remains limited. Recent studies in the Philippines indicate an estimated vaccine effectiveness of 60% against RV hospitalization, and a 50–60% reduction of all cause diarrhea among children aged under 5 within the population. Furthermore, we estimate that 225 rotavirus cases can be prevented per 1000 children vaccinated against RV. This information will be crucial as policymakers decide on expanding RV vaccination nationwide.

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Introduction

Globally, diarrhea is the fifth leading cause of mortality, responsible for 446,000 deaths among children under 5 years of age in 2016.¹ Diarrhea is also a leading cause of morbidity and results in long term adverse health outcomes.² The most common cause of diarrhea in childhood is rotavirus.³

Rotavirus vaccine was recommended by the World Health Organization (WHO) in 2009 for use in all national immunization programs and must be prioritized in countries where deaths due to rotavirus diarrhea are substantial.⁴ At that time, two available rotavirus vaccines were licensed internationally and available at reduced prices for Gavi-eligible countries. However, introduction of RV vaccines in middle- and lower-middle income countries, particularly in Asia have been slow. As of 2016, the WHO Southeast Asia and Western Pacific Regions had the fewest countries that introduced RV vaccines.⁵ We present the experience in the Philippines, a lower-middle income country in Asia, where RV vaccine introduction remains limited to selected regions.

Rotavirus in the Philippines

Diarrhea was the second leading cause of death in children 1–4 years of age and the 6th leading cause of death in infants in 2014 in the Philippines.⁶ Since the 1980s, rotavirus has been described as one of the leading cause of hospitalized and outpatient diarrhea for children.^{7–16} Studies from the 1980s to early 2000s have estimated that RV was the cause of 20–40% of all diarrhea cases, which varies in different settings (i.e., hospitalization vs. outpatient consults). The most recent study, performed

in an urban area from 2005 to 2006, estimated the burden of RV at 31% among diarrheal hospitalizations, 30% among emergency consults for diarrhea, and 15% among diarrheal outpatient consults in children <5 years old.¹⁷

Considering the significant burden of diarrhea, the Philippines was the first country in Asia to introduce the monovalent RV (RV1) (Rotarix[®], GSK) vaccine in 2012 in its routine immunization program. At that time of initial roll-out, RV vaccination was limited to the families who belonged to the lowest economic quintile and were receiving conditional cash transfer (CCT) from the government. However, implementation proved to be difficult. First, families in the program were not evenly distributed throughout the country, hence delivery of RV vaccines was complicated and required knowledge of the geographic distribution of the targeted families. Second, not all families in the program have children who were aged 6 to 15 weeks, which was the recommended age group to receive the first dose of the vaccine at that time of introduction. The difficulties encountered in targeting resulted in low vaccination coverage. At the same time, some sectors felt that funding may be better allocated to other priorities instead of an expensive vaccine for diarrheal diseases. It was argued that improving the implementation of other preventive measures such as exclusive breastfeeding, improvements in nutrition, hygiene, and water quality; and the implementation of the Integrated Management of Childhood Illness (IMCI), Oral Rehydration Therapy (ORT) and Zinc Supplementation will improve outcomes for diarrhea. At that time, information from clinical trials reported varying vaccine efficacy depending on the region where the study was conducted ranging from 81% in Latin America to

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42.7% in Bangladesh.¹⁸ Hence, policymakers requested the Expanded Programme on Immunization (EPI) of the Department of Health (DOH) to collate more information on the burden of rotavirus and assess the effectiveness of the RV vaccine in the Philippines.

In 2012, the rotavirus sentinel surveillance was established in the Philippines in a phased manner in seven hospitals distributed across the different regions in the country (Figure 1). Children under five years of age who underwent treatment with intravenous rehydration for acute diarrhea in

a surveillance hospital are included in the surveillance. Diarrhea is defined using the standard WHO case definition as the passage of 3 or more stools within a 24 hour period for ≤ 14 days as a child years of age.¹⁹ Specimens are collected and sent to the Research Institute for Tropical Medicine (RITM), where ELISA Immunoassay for RV confirmation of suspected cases was performed. In 2012, the CARAGA Region had the highest number of reported cases of diarrhea. Since this was also the region with one of the highest poverty rates in the country,²⁰ the sentinel hospital in CARAGA, the D.O. Plaza



Figure 1. Rotavirus sentinel surveillance sites in the Philippines.

Hospital (DOPH) was chosen as the site for the RV vaccine effectiveness assessment.

Rotavirus vaccine effect in the Philippines

In 2014, using the platform of the rotavirus surveillance in DOPH, an effectiveness assessment was initiated. Only children eligible to participate in the surveillance and eligible to have received the RV vaccine were included. RV1 vaccine was given at 6 and 10 weeks of age together with oral polio vaccine. Vaccination status was verified in the clinic records. Results show that at least one dose of RV1 vaccine, was found to have a vaccine effectiveness (VE) of 60% (24–79%) against RV hospitalization and 64% (11–85%) against severe RV diarrhea.²¹ Using information from the study, we calculated the number of RV cases that can be prevented per 1,000 vaccinated with the following formula:

$$RV \text{ prevented} = \frac{\text{Cases in unvaccinated}}{\text{Number unvaccinated}} - \frac{\text{Cases in vaccinated}}{\text{Number vaccinated}} \times 1000$$

Among children older than 8 months, we found that approximately 225 cases of RV can be prevented per 1,000 children vaccinated.

A parallel impact assessment was also conducted by comparing diarrheal admissions and outpatient consults in an area where RV1 was introduced and an area where RV was yet to be introduced.²² In this study, the declines in the total number of hospitalizations from all-cause diarrhea was observed at 28%, 56%, 63%, and 59%, across the 4 years post-routine RV1 immunization, consecutively. In contrast, no similar reductions were seen in the area where no vaccination occurred.

We also investigated other factors that may affect all-cause diarrhea cases such as breastfeeding rates, changes in access to clean water and improved sanitation in the area where vaccination occurred. We found no changes in any of these factors during the years reviewed. The reduction in the hospitalized cases was not limited to the targeted population but was also seen in children older than 1 year, which may suggest herd effects. The extension of the vaccine's effect to the unvaccinated population (older children), and non-vaccine targets (immunocompromised patients, pregnant women, elderly), dramatically expands the vaccine's potential benefit in the community.

Prioritizing rotavirus vaccines

RV vaccines were shown to perform differently in various settings, with higher efficacy²³ and effectiveness^{24,25} seen in higher income countries and those with low mortality. The VE of 60% of any dose of RV1 vaccine against RV hospitalization is comparable to the results of other middle-income countries (VE- 57%, 95% CI 47–66%, $p < 0.001$) in the recent meta-analysis.²⁵

The first two internationally available RV vaccines: RV1 (Rotarix®, GSK) and RV5 (Rotateq®, Merck), were WHO pre-qualified in 2009 and 2008, respectively. WHO

prequalification allows United Nation agencies to procure certain products including vaccines. Despite the availability of these two vaccines, RV vaccine demand was slower than anticipated. As of 2016, 110 countries representing 69% of the global birth cohort still have not adopted RV vaccine into their national immunization programs.⁵ Each country may have different reasons for the delay in RV vaccine adoption, some of these may include programmatic challenges, lack of cold chain capacity, concerns over long-term vaccine pricing particularly for non-Gavi eligible countries, and sustainable supply availability.²⁶ In the Philippines, cold chain capacity was increased in 2014, paving the way for introduction of new vaccines. The Philippines has never been Gavi-eligible and was only one of two middle-income countries to procure RV1 vaccines through UNICEF from 2014 to 2016, with the cost of ~US\$15 per 2-dose course.²⁶ The cost of procurement of RV1 in 2012 was more than the costs of procurement for all traditional EPI vaccines (BCG, DPT-HepB-Hib, measles, OPV). Costs of vaccine and budget allocation are important considerations particularly in lower-middle income countries where limited resources require prioritization of different interventions. Although one study has shown that the RV1 vaccine is cost-effective when the full course costs ~US\$20.6,²⁷ another study using a dynamic transmission model and a full course vaccine cost of US\$19.7 showed otherwise.²⁸

In some Asian countries, including the Philippines, a private market for vaccines exist.²⁹ Previously, new vaccines are only available in the private clinics and the costs for RV vaccines in the market in 2018 ranged from US\$34 to \$44 per dose.³⁰ The Philippines' EPI estimates that approximately 10% of the targeted population obtain their immunizations from private clinics of pediatricians or general practitioners. In 2010, as new vaccines become available, specific line items for vaccine financing were included in the national budget allowing earlier adoption of vaccines into the national immunization programs.

In March and September 2018, two new RV vaccines, the monovalent 116E strain (Rotavac®, Bharat Biotech International, India) and the pentavalent G1, G2, G3, G4, and G9 (Rotasiil®, Serum Institute of India, India), respectively achieved WHO prequalification. Rotavac® has a vaccine efficacy of 53.6% for severe RV diarrhea in India³¹ while Rotasiil® has efficacies of 60.5% to 66.7% in India³² and Niger,³³ respectively. These vaccines cost less, with Rotavac's price in India at US\$2.85 for a full course³⁴ and Rotasiil® is estimated to cost less than US\$6 for a full course.³⁵ Furthermore, Rotasiil® has the distinct advantage over the other vaccines as being more heat stable³³ and can be used outside the cold chain. Since 2016, phased introduction of RV vaccines began in India, which has the highest burden of RV disease globally.

Lower middle-income countries receive minimal support from Gavi and other funding agencies for upscaling of their immunization programs. Most low-income countries supported by Gavi, meanwhile, are facing issues on the sustainability of the program once the support is withdrawn. With the background of limited resources and competing priorities, economic analysis is crucial for most countries on new vaccine introduction in the immunization program. Newer vaccines released in the market

may change the cost-benefit ratio to favor the use of vaccines in most of Gavi-countries, and low- and middle-income countries without Gavi support. Newer vaccines also have distinct properties that may change how the vaccines work in real-life settings.

In the Philippines, the policymakers sought for additional evidence to assist in the decision-making for the introduction of RV vaccines in the routine immunization. Equitable access to life-saving vaccines is important for all countries to achieve the sustainable development goals (SDGs). The status of RV vaccine introduction in the Philippines reflects the decision of most of lower middle income countries in Asia in the slow adoption of the vaccine in the immunization program. In this paper, we present the information requested by policymakers to inform their decisions for possible expansion of RV vaccine nationwide.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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