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Rotavirus vaccine implementation: evidence to fill the gap?

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In the maelstrom of COVID-19, it is easy to forget the importance of non-COVID health interventions and the processes that policy makers use to choose where to allocate limited resources. Rotavirus vaccines have consistently been shown to save lives in low-income settings and to be cost-effective in most low-income and middle-income countries (LMICs) when compared with no vaccination, with multiple instances where rotavirus vaccination was found to be highly cost-effective or even cost-saving.[1] Of the 110 countries that have introduced rotavirus vaccines into their national immunisation programmes, 53 have accessed support from Gavi, the Vaccine Alliance. Currently, 65 countries have no expressed plans to introduce rotavirus vaccines, including 57 not eligible for Gavi support.

The challenge of implementing preventive vaccines against diseases perceived as non-fatal requires investment of resources against competing priorities. In *The Lancet Global Health*, Frédéric Debellut and colleagues evaluated the cost-effectiveness of available rotavirus vaccines in middle-income countries (MICs) that are above the income threshold for Gavi support to purchase vaccines.[2] The authors estimated the number of rotavirus gastroenteritis cases, clinic visits, hospitalisations, and deaths averted by vaccination in children younger than 5 years over a 10-year period in 63 MICs not eligible for Gavi support. They calculated cost-effectiveness ratios and benefit–risk ratios and evaluated three alternative vaccines available globally (Rotarix, Rotavac, and Rotasiil), using information from vaccine manufacturers regarding anticipated vaccine prices.

Debellut and colleagues estimated that, over the period 2020–29 in the 63 countries assessed, rotavirus vaccines could avert 77 million (95% uncertainty interval 51–103) cases of rotavirus gastroenteritis and 21 million (12–36) clinic visits, 3 million (1·4–5·6) hospitalisations, and 37 900 (25 900–55 900) deaths due to rotavirus gastroenteritis. The benefit–risk ratio for hospitalisations prevented versus those potentially caused by vaccination exceeded 250:1 in all countries. Unsurprisingly, even using recent stringent cost-effectiveness thresholds based on cost per disability adjusted life-years (DALYs), rotavirus vaccination appeared to be cost-effective in more than three quarters of these MICs (48 [77%] of 62).[2,3] Of the 63 countries considered in this analysis, only 30 have introduced rotavirus vaccines to date.

As more countries introduce rotavirus vaccines into their national immunisation programmes—including many low-income, high-burden countries in Africa, as well as MICs in Europe, South America, and Asia—a comprehensive understanding of the effect of rotavirus vaccination on disease burden and child mortality has emerged. In almost every instance, vaccination has substantially reduced hospitalisations due to rotavirus diarrhoea and diarrhoea-related deaths in all regions of the world, across all wealth strata.[4]

Debellut and colleagues' study illustrates not only the cost-effectiveness of rotavirus vaccines in these settings, but also underscores the importance of emerging vaccine manufacturers in ensuring equitable global access to affordable vaccines. Of the two vaccines used widely in high-income settings, Rotateq (Merck and Co, Kenilworth, NJ, USA) and Rotarix (GlaxoSmithKline, Rixensart, Belgium), only Rotarix was included in the analysis because of Rotateq supply constraints and probable use in settings with far higher prices per dose. However, the two different Indian-manufactured vaccines were estimated to be substantially more cost-effective in all evaluated countries than Rotarix, despite requiring three-dose regimens compared with Rotarix' two doses.[2]

Societal costs, adding the family impact of caring for a sick child and lost productivity from parental paid employment, were included as secondary analyses. This is appropriate, as governmental decisions for health technology assessments typically exclude societal costs, and lost productivity from short absences from parental work, such as might occur with rotavirus gastroenteritis, remains difficult to quantify.[5] Crucially, these analyses endeavoured to use conservative inputs into the model, to not overstate vaccine cost-effectiveness. The only exception to this might be the use of country-specific coverage rates for infant diphtheria-tetanus-pertussis vaccine doses, which are higher in some high-income and low-income settings than rotavirus coverage.[6,7] Although this might marginally overestimate benefits (and risks), it is unlikely to materially affect these findings.

Although most mortality from rotavirus gastroenteritis occurs in low-income settings, the MICs included in this analysis account for more than one in every five rotavirus deaths. Vaccine implementation could prevent up to 4·5 million gastroenteritis admissions over 10 years, with the excess risk of 6700 additional intussusception admissions over the same period, assuming no age restriction upon dosing. Unlike in 1999, with the withdrawal of Rotashield vaccine (Wyeth, Chadds Ford Township, PA, USA) due to association with intussusception in the USA, subsequent implementation of other rotavirus vaccines with weaker and less consistent associations with intussusception than those of Rotashield do not appear to have affected vaccine implementation in more than 105 countries to date.[8]

Since 2018, the availability of WHO prequalified Rotasiil (Serum Institute of India, Pune, India) and Rotavac (Bharat Biotech, Hyderabad, India) has substantially improved the cost-effectiveness of rotavirus vaccines. Practically, the Rotasiil new liquid prequalified product and the five-dose Rotavac open-vial use preparation might improve programmatic use, decrease cold-chain storage and transport space requirements, and help reduce costs.[9,10] The availability of these vaccines has increased the number of MICs able to implement rotavirus vaccination programmes. Of the 62 countries with gross domestic product data available, Rotarix, with its two-dose schedule, had a 90% chance of being cost-effective in nine countries, whereas the addition of Rotasiil and Rotavac increased this to 41 countries, despite their three-dose schedules. The welcome entry of vaccine manufacturers from LMICs has boosted potential access for millions of infants to life-saving vaccines.

Debellut and colleagues' work underlines the opportunity for many MICs to implement rotavirus vaccination as a cost-effective intervention, with several large MICs yet to introduce the vaccine. Cooperative regional purchasing might also further decrease costs and increase access for additional MICs. However, although the cost-per-DALY threshold used by Debellut and colleagues is likely to be accepted internationally, other local factors might contribute to national decision making, including societal costs and safety concerns, and would need to be addressed.

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1 Pecenka C, Debellut F, Bar-Zeev N, Anwari P, Nonvignon J, Clark A. Cost-effectiveness analysis for rotavirus vaccine decision-making: how can we best inform evolving and complex choices in vaccine product selection? *Vaccine* 2020; **38:** 1277–79.

2 Debellut F, Clark A, Pecenka C, et al. Evaluating the potential economic and health impact of rotavirus vaccination in 63 middle-income countries not eligible for Gavi funding: a modelling study. *Lancet Glob Health* 2021; **9:** e942–56.

3 Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. *Value Health* 2016; **19:** 929–35.

4 ROTA Council. Rotavirus: common, severe, devastating, preventable. Baltimore, MA: Rotavirus Organization of Technical Allies, 2016.

5 Yuasa A, Yonemoto N, LoPresti M, Ikeda S. Use of productivity loss/gain in cost-effectiveness analyses for drugs: a systematic review. *Pharmacoeconomics* 2021; **39:** 81–97.

6 Peck M, Gacic-Dobo M, Diallo MS, Nedelec Y, Sodha SV, Wallace AS. Global routine vaccination coverage, 2018. *MMWR Morb Mortal Wkly Rep* 2019; **68:** 937–42.

7 Aliabadi N, Wikswo ME, Tate JE, et al. Factors associated with rotavirus vaccine coverage. *Pediatrics* 2019; **143:** e20181824.

8 Reddy SN, Nair NP, Tate JE, et al. Intussusception after rotavirus vaccine introduction in India. *N Engl J Med* 2020; **383:** 1932–40.

9 van Hoek AJ, Ngama M, Ismail A, et al. A cost effectiveness and capacity analysis for the introduction of universal rotavirus vaccination in Kenya: comparison between Rotarix and RotaTeq vaccines. *PLoS One* 2012; **7:** e47511.

10 Madsen LB, Ustrup M, Hansen KS, Nyasulu PS, Bygbjerg IC, Konradsen F. Estimating the costs of implementing the rotavirus vaccine in the national immunisation programme: the case of Malawi. *Trop Med Int Health* 2014; **19:** 177–85.