

Editorial

Prospects for Routine Childhood Vaccination against Rotavirus in India

Rotavirus is the leading cause of severe acute gastroenteritis (AGE) in children under 5 years of age worldwide. In both developing and industrialized countries, about one-third of AGE hospitalizations in children under 5 are attributable to rotavirus infection.¹ While rotavirus AGE is ubiquitous, more than 90% of the estimated 453 000 annual rotavirus deaths occur in developing countries,¹ primarily because access to appropriate medical care is suboptimal in these settings and the healthcare costs involved. Because rotavirus is a 'democratic' pathogen that infects all children worldwide, rich or poor, in the first five years of life, interventions to improve environmental hygiene, water quality and health behaviour are considered unlikely to have a significant impact on reducing disease transmission. These factors, together with early epidemiological observations that infants naturally infected with rotavirus are at reduced risk for subsequent rotavirus infection and disease, led to efforts to develop vaccines for effective prevention of rotavirus AGE. We review the biological features of rotavirus that are relevant for vaccination, the experience with rotavirus vaccination programmes globally, and the prospects for routine vaccination of Indian children against rotavirus.

Biology of rotavirus

The rotavirus genome consists of 11 segments of double-stranded RNA surrounded by a triple-layered viral capsid. The outer capsid proteins, VP7, the glycoprotein (G-protein) and VP4, the protease-cleaved (P-protein), determine the serotype specificity and form the basis of the binary classification (G and P type) of rotavirus. Five common rotavirus strains (P[8]G1; P[4]G2; P[8]G3; P[8]G4; and P[8]G9) predominate globally; however, the distribution of strains can vary substantially across different time periods and geographic regions.²

Two aspects of rotavirus biology are particularly relevant for vaccine development. First, the segmented genome of rotavirus readily reassorts during coinfection with multiple rotavirus strains, a feature that has been utilized in the development of reassortant vaccines by inserting gene segments coding human G and P proteins into an animal rotavirus strain backbone. The reassortant virus thus developed retains the natural avirulence of animal rotavirus strains for humans, but is capable of eliciting antibodies to the human surface protein antigens and provides protection against subsequent illness. Second, while the first rotavirus infection leads to a primarily homotypic serum antibody response against the G serotype of the infecting rotavirus strain, repeat rotavirus infections elicit both a homotypic and heterotypic (against strains with different G serotypes) antibody response. Similarly, immunization with multiple doses of rotavirus vaccine is anticipated to elicit a broad immune response with cross-protection against non-vaccine strains.

Experience with rotavirus vaccination programmes worldwide

Two live, oral rotavirus vaccines—RotaTeq (Merck and Co.) and Rotarix (GSK Biologicals)—are currently licensed in over 100 countries worldwide. RotaTeq is a pentavalent vaccine with five bovine-human reassortant rotavirus strains expressing

G1-4 and P[8] human antigens; it is administered as a three-dose series concomitantly with the first three DPT vaccine doses.³ Rotarix is a monovalent vaccine consisting of a single human rotavirus strain of P[8]G1 specificity; it is administered as a two-dose series concomitantly with the first two DTP vaccine doses.⁴

While RotaTeq and Rotarix differ in composition and schedule, both vaccines were found to be highly efficacious (85%–98%) against severe rotavirus AGE in pivotal pre-licensure trials conducted in the USA, Latin America and Europe, and both vaccines protected well against a range of circulating rotavirus strains. Because live oral vaccines have a history of performing less well in developing countries, both RotaTeq and Rotarix were specifically tested in low-income countries in Africa and Asia. As expected, vaccine efficacy was modest in these trials, ranging from 51% to 64% against severe rotavirus AGE in the first year of life.^{5–7} Despite lower efficacy, the absolute number of rotavirus AGE cases prevented by vaccination of a given number of children was greater in low-income countries because of the substantially greater baseline rotavirus burden in these settings, leading to a WHO recommendation for global use of rotavirus in 2009.⁸

More than 30 countries—primarily high- and middle-income countries in the Americas, Europe and Australia—have implemented national rotavirus vaccination programmes that had a rapid and notable impact on reducing the burden of diarrhoea in these countries. Declines of 17%–55% in all-cause gastroenteritis hospitalization and of 49%–89% in rotavirus hospitalizations among children under 5 years of age have been observed.⁹ In some countries, declines in severe diarrhoea have been observed in children above 5 years of age and even in adult populations, suggesting indirect benefits (i.e. herd immunity) from vaccination of young children.⁹ Of note, the first evidence of the impact of rotavirus vaccination in reducing deaths from childhood diarrhoea, a key outcome that was not evaluated in clinical trials, has been shown post-introduction in two large countries of Latin America. In Mexico, a sustained 3-year decline of 35%–40% in diarrhoea mortality in children under 5 was seen from 2008 to 2010 following implementation of rotavirus vaccination in 2006.^{10,11} Similarly, in Brazil, a decline of 22%–41% in diarrhoea mortality among children under 5 was seen with 2–3 years of vaccine implementation in 2006.^{12,13}

Because a previous rhesus–human reassortant rotavirus vaccine (Rotashield, Wyeth) was withdrawn from the US market in 1999 after it was associated with intussusception,¹⁴ this potential adverse event has been closely monitored with current rotavirus vaccines. In large pre-licensure clinical trials of 60 000–70 000 infants each, no increased risk of intussusception was found with either RotaTeq or Rotarix.^{3,4} However, post-licensure evaluations have found a low-level risk of intussusception with both current vaccines in some populations. The level of risk seen with current rotavirus vaccine (~1–2 excess intussusception cases per 100 000 vaccinated infants) is about five- to ten-fold lower than the risk of 1 intussusception per 10 000 infants vaccinated with Rotashield.¹⁵ Furthermore, the well documented health benefits of rotavirus vaccination substantially exceed the low risk of intussusception. Based on these considerations, national and international policy groups have continued to support recommendations for routine use of rotavirus vaccines.

Prospects for rotavirus vaccination in India

The potential benefits of rotavirus vaccination in India are evident from the tremendous health burden of rotavirus disease in Indian children. India suffers the greatest mortality burden of rotavirus among all countries, alone accounting for approximately one-fifth (~100 000) of the estimated global deaths from rotavirus.¹ The morbidity burden of rotavirus is evident from data from the Indian Rotavirus Surveillance Network, which reported that over a 2-year period from 2005–07, rotavirus was found in approximately 39% of 4243 children under 5 years of age admitted to 10 hospitals located in seven cities across India.¹⁶ Based on these and other data, rotavirus has been estimated to cause approximately 457 000–884 000 hospitalizations and 2 million outpatient clinic visits each year in Indian children, incurring healthcare costs of ₹2.0–3.4 billion (US\$ 41–72 million).¹⁷

Both RotaTeq and Rotarix are licensed in India and are available in the private market at a price of ₹2200–2700 for a full vaccine series, respectively. In addition, vaccine manufacturers in India are currently developing several candidate rotavirus vaccines. The most advanced candidate is a monovalent vaccine based on the rotavirus strain 116E, a natural reassortant of the human rotavirus G9P[11] strain with the VP4 protein from a bovine rotavirus strain that was isolated from an asymptotically infected neonate from the nursery of the All India Institute of Medical Sciences in New Delhi. This vaccine showed promising results in an immunogenicity trial, and a phase 3 multicentre clinical trial is currently ongoing at sites in Delhi, Pune and Vellore, with results anticipated within the next 1–2 years. In addition, multivalent bovine–human reassortant rotavirus vaccines developed by two other Indian manufacturers are in earlier stages of clinical development, and thus potentially several indigenously manufactured rotavirus vaccines may be available for use in India within the next 5 years.

The well-documented health and economic burden of rotavirus diarrhoea and the availability of several rotavirus vaccines, including the potential availability in 2–3 years of indigenously manufactured vaccines, provide the evidence base for decisions to implement these vaccines in the Indian national immunization programme. Although the efficacy of neither the international nor the indigenously manufactured vaccines in Indian children is yet known, it is expected to be moderate, similar to that seen in other low-income settings. However, even a moderately effective vaccine is likely to have substantial public health impact because of the tremendous burden of rotavirus AGE in India. Factors such as vaccine supply, affordability and other programmatic factors will also need to be considered in decisions to implement vaccination. The potential availability of indigenously manufactured rotavirus vaccines is particularly promising in this regard, both in terms of ensuring adequate supply and a competitive, affordable vaccine price.

Implementation of routine rotavirus vaccination of Indian children will provide an opportunity to assess key aspects of vaccine performance post-licensure through epidemiological studies. Such studies can examine efficacy in high-risk groups, such as malnourished children, and also examine efficacy against a range of rotavirus strains in circulation. While rotavirus vaccines appear to provide good homotypic and heterotypic protection, evaluation of vaccine effectiveness against a range of circulating strains may be relevant in countries such as India with great diversity of circulating rotavirus strains.¹⁶ In addition, indirect benefits (i.e. herd immunity) of rotavirus vaccination have been observed in several high- and middle-income countries that have implemented routine rotavirus vaccination, and post-licensure evaluations will also allow assessment of potential indirect benefits in Indian children. If found, such indirect benefits could substantially amplify the total health benefits of vaccination for the entire population. Also, given the low-level risk of intussusception identified with rotavirus vaccination in some countries, implementation of efforts to monitor for this adverse event would be prudent. While the large anticipated health benefits of vaccination are likely to substantially exceed a low risk of intussusception, even if it exists, availability of post-licensure data on both the benefits and risks of vaccination will allow policy-makers to make sound, evidence-based decisions.

In summary, given the well-documented health burden of severe rotavirus AGE in Indian children and the availability of several licensed rotavirus vaccines, the stage is set for evidence-based policy decisions around implementation of these vaccines for routine immunization of Indian children. The introduction of the vaccine should have a notable impact in reducing the large health and economic burden of rotavirus diarrhoea in Indian children, and should ideally be accompanied by post-licensure evaluation of vaccine effectiveness and safety to generate key evidence to show the value of, and sustain use of, rotavirus vaccines in India.

REFERENCES

- 1 Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD; WHO-coordinated Global Rotavirus Surveillance Network. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years

- before the introduction of universal rotavirus vaccination programmes: A systematic review and meta-analysis. *Lancet Infect Dis* 2012;**12**:136–41.
- 2 Bányai K, László B, Duque J, Steele AD, Nelson EA, Gentsch JR, *et al.* Systematic review of regional and temporal trends in global rotavirus strain diversity in the pre rotavirus vaccine era: Insights for understanding the impact of rotavirus vaccination programs. *Vaccine* 2012;**30** (Suppl 1):A122–A130.
 - 3 Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, *et al.*; Rotavirus Efficacy and Safety Trial (REST) Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;**354**:23–33.
 - 4 Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SC, *et al.*; Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;**354**:11–22.
 - 5 Zaman K, Dang DA, Victor JC, Shin S, Yunus M, Dallas MJ, *et al.* Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: A randomised, double-blind, placebo-controlled trial. *Lancet* 2010;**376**:615–23.
 - 6 Armah GE, Sow SO, Breiman RF, Dallas MJ, Tapia MD, Feikin DR, *et al.* Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: A randomised, double-blind, placebo-controlled trial. *Lancet* 2010;**376**:606–14.
 - 7 Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, Louw C, *et al.* Effect of human rotavirus vaccine on severe diarrhea in African infants. *N Engl J Med* 2010;**362**:289–98.
 - 8 World Health Organization. Rotavirus vaccines: An update. *Wkly Epidemiol Rec* 2009;**84**:533–40.
 - 9 Patel MM, Steele D, Gentsch JR, Wecker J, Glass RI, Parashar UD. Real-world impact of rotavirus vaccination. *Pediatr Infect Dis J* 2011;**30** (1 Suppl):S1–S5.
 - 10 Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, Esparza-Aguilar M, Johnson B, Gomez-Altamirano CM, *et al.* Effect of rotavirus vaccination on death from childhood diarrhoea in Mexico. *N Engl J Med* 2010;**362**:299–305.
 - 11 Richardson V, Parashar U, Patel M. Childhood diarrhoea deaths after rotavirus vaccination in Mexico. *N Engl J Med* 2011;**365**:772–3.
 - 12 do Carmo GM, Yen C, Cortes J, Siqueira AA, de Oliveira WK, Cortez-Escalante JJ, *et al.* Decline in diarrhoea mortality and admissions after routine childhood rotavirus immunization in Brazil: A time-series analysis. *PLoS Med* 2011;**8**:e1001024.
 - 13 Lanzieri TM, Linhares AC, Costa I, Kolhe DA, Cunha MH, Ortega-Barria E, *et al.* Impact of rotavirus vaccination on childhood deaths from diarrhoea in Brazil. *Int J Infect Dis* 2011;**15**:e206–e210.
 - 14 Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, *et al.* Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med* 2001;**344**:564–72.
 - 15 Patel MM, Lopez-Collada VR, Bulhoes MM, De Oliveira LH, Bautista Márquez A, Flannery B, *et al.* Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *N Engl J Med* 2011;**364**:2283–92.
 - 16 Kang G, Arora R, Chitambar SD, Deshpande J, Gupte MD, Kulkarni M, *et al.* Multicenter, hospital-based surveillance of rotavirus disease and strains among Indian children aged <5 years. *J Infect Dis* 2009;**200** (Suppl 1):S147–S153.
 - 17 Tate JE, Chitambar S, Esposito DH, Sarkar R, Gladstone B, Ramani S, *et al.* Disease and economic burden of rotavirus diarrhoea in India. *Vaccine* 2009;**27** (Suppl 5):F18–F24.

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