Rotavirus Vaccines at the Threshold of Implementation in India

Rotavirus, the leading cause of severe acute gastroenteritis in young children, persists as a major contributor to mortality and severe morbidity in Indian children.1,2 Recent data confirm that rotavirus continues to have a high disease and economic burden in India and that rotavirus strains circulating in the population are diverse.2,3 An indigenously produced rotavirus vaccine (ROTAVAC, Bharat Biotech International Limited of India) has been shown to prevent severe gastroenteritis due to rotavirus in Indian children.4 The Government of India has announced that rotavirus vaccine will be introduced into the universal immunization programme.5 In anticipation of the introduction of rotavirus vaccine in India, we review the newly available data on the disease and economic burden caused by rotavirus, its circulating strains, data from clinical trials of the first indigenously produced rotavirus vaccine, and examine issues for monitoring vaccine impact and safety following introduction.

Robust, local estimates of rotavirus disease burden are available in India. Sentinel hospital-based surveillance conducted as part of the Indian Rotavirus Surveillance Network has consistently shown that rotavirus is responsible for approximately 40% of diarrhoea hospitalizations among children <5 years of age in various regions of India.3,6 The majority of rotavirus hospitalizations occur among children <2 years of age and younger children often have more severe disease.7–10 Seasonal peaks in rotavirus hospitalizations occur during the cool months in northern India but rotavirus hospitalizations occur year-round in southern India.7,10,11 The virus also causes a substantial burden in outpatient settings, and as with rotavirus hospitalizations, the majority of cases in outpatient settings occur in children <2 years of age.12,13 In a birth cohort study in southern India, 95% of children had been infected with rotavirus by their third birthday including 18% of children who were infected as neonates.14,15 Children may have multiple infections throughout childhood but the interval between infections lengthens with subsequent infections.14 By their fifth birthday, an estimated 1 of every 344 Indian children will die from rotavirus, 1 of every 23–46 children will be hospitalized for rotavirus diarrhoea, and 1 in every 6–12 children will have had an outpatient visit for rotavirus diarrhoea.2 These estimates for India translate into 78 500 deaths, 872 000 hospitalizations, over 3.2 million outpatient visits, and 11.4 million episodes of diarrhoea due to rotavirus each year in children <5 years of age.2

Rotavirus disease also creates a substantial economic burden in India. Each year, rotavirus hospitalizations and outpatient visits among children <5 years of age results in costs of ₹4.9 billion and due to rotavirus result in an additional ₹5.4 billion, respectively.2 As a result of the high rotavirus disease and economic burden, a national rotavirus vaccination programme is likely to be cost-effective in India.16,17 At a cost of less than 1 US$ per dose (the publicly stated cost of the Indian manufactured Rotavac vaccine), a national rotavirus vaccination programme in India would cost ₹4.47 billion per year, which is less than the current estimated treatment costs for rotavirus diarrhoea.2 Given the heterogeneity of rotavirus disease burden across geographic and socioeconomic subgroups in India, poorer states with higher mortality will have the greatest reduction in mortality due to diarrhoea whereas richer states with lower mortality will have the greatest costs averted (Fig. 1).16,17

The most commonly detected strains of rotavirus in India are G1P[8], G2P[4] and G9P[8], which are also some of the most common strains circulating globally, though some secular and regional variations occur.7,8,10–12,18 In recent years, detection of G12 has
increased both in India and worldwide. High frequency of untypeable strains has also been identified in some studies in India; however, this frequency was lower when alternate extraction and sequencing methods were used. In a birth cohort study, G10P[11] was frequently detected among neonates with asymptomatic infections in southern India. It is unknown whether this strain circulates among neonates in other regions.

**Rotavirus vaccines in India**

The first indigenously produced rotavirus vaccine licensed in India, Rotavac, is a live oral attenuated vaccine based on a natural human–bovine reassortant strain, G9P[11], which causes asymptomatic infection in neonates. The vaccine is administered in a three-dose schedule with doses given at 6, 10 and 14 weeks of age. In a multicentre, phase 3 clinical trial conducted in three geographically dispersed and culturally diverse cities in India, the vaccine had a 56% efficacy (95% CI 37%–70%) against severe rotavirus gastroenteritis during the first year of life, despite the use of extensive healthcare provisions in the trial which may have reduced the severity of disease. The efficacy of this vaccine was comparable to that of the two currently available, internationally licensed rotavirus vaccines in low-income settings (51%–64%). However, unlike the internationally licensed rotavirus vaccines, whose protective efficacy appears to wane in the second year of life, Rotavac had sustained efficacy in the second year of life (49%, 95% CI 17%–68%). The vaccine also provided protection against a wide variety of vaccine mismatch strains, including G1P[8], G2P[4] and G12P[6], which were the most common circulating strains during the time period when the clinical trial was conducted. This cross-protection is reassuring given the diversity of circulating strains seen in India.

Additional oral rotavirus vaccines are also being developed by Indian manufacturers. An oral bovine rotavirus pentavalent vaccine (BRV-PV) containing bovine–human reassortant strains of serotype G1, G2, G3, G4 and G9 developed by the Serum Institute of India in collaboration with the National Institutes of Health (NIH), USA has been found to be safe and immunogenic in phase 1 and 2 clinical trials, and its efficacy against severe rotavirus gastroenteritis is being assessed in phase 3 trials. Another bovine–human reassortant vaccine based on the NIH bovine–human reassortant strains is under development by Shantha Biotechnics Limited, and has recently entered a phase 3 efficacy trial. This oral bovine reassortant tetravalent vaccine (BRV-TV) contains serotypes G1, G2, G3 and G4.

**Monitoring implementation of rotavirus vaccines in India**

As inclusion of rotavirus vaccine into the universal immunization programme becomes a near-term reality for India, plans are being developed for monitoring the impact and safety
of rotavirus vaccine in routine use. The Indian Rotavirus Surveillance Network coordinated by the Indian Council of Medical Research was initiated in 2005 and uses standardized protocols for enrolment and diagnostic evaluation to generate timely and geographically representative information on clinical, epidemiological and virological features of severe rotavirus disease in Indian children and could play a key role in measuring the impact of the vaccine. This network is currently operational in 28 sentinel hospital sites located all over India for recruitment of clinical cases with seven regional laboratories and four referral laboratories for testing by enzyme-linked immunosorbent assay (ELISA) and genotyping by polymerase chain reaction (PCR). Rotavirus vaccine is likely to be introduced in a phased manner by states as the manufacturer scales up the production of the vaccine. Strengthening or expanding surveillance for rotavirus gastroenteritis in early vaccine-introducing states will provide data on trends in rotavirus and all-cause diarrhoea hospitalizations that can be monitored before and after the introduction of rotavirus vaccine. Additionally, in the early phases for vaccine rollout, the surveillance sites can serve as the basis for evaluation of effectiveness of a vaccine using a case–control design.

Post-marketing surveillance studies for the two internationally licensed rotavirus vaccines have identified a safety signal with 1–5 excess cases of intussusception per 100,000 immunized infants in several countries.26–32 While the risk–benefit ratio of rotavirus vaccines remains overwhelmingly in favour of the vaccine, concern around this highly publicised, albeit rare, adverse event creates an express need to generate valid data on the occurrence of intussusception when a new rotavirus vaccine is introduced into the universal immunization programme. Once rotavirus vaccine is introduced, interpreting post-introduction surveillance data on adverse events requires careful planning and an understanding of the underlying event rates. Currently, no systematic data are available on the baseline rate of intussusception in India. However, establishing a monitoring process at healthcare facilities to recognize and manage cases of intussusception among children will be available for India.

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Summary

India is poised to introduce rotavirus vaccines into its routine childhood immunization programme. Substantial data are available on disease and economic burden of rotavirus gastroenteritis and on circulating strains in India, which highlight the public health need for a rotavirus vaccine. A locally manufactured oral rotavirus vaccine has been licensed in India and it has shown to be effective against severe rotavirus gastroenteritis in Indian children. The Government of India has announced that the vaccine will be included in the universal immunization programme. Careful planning and preparation for post-licensure impact and safety evaluations will ensure that additional high quality benefit–risk data will be available for India.

REFERENCES


