Time-trend Analysis of the Impact of Universal Rotavirus Vaccination in Brazil

Source Citation: Costa I, Linhares AC, Cunha MH, Tuboi S, Argüello DF, Justino MC, *et al*. Sustained decrease in gastroenteritis-related deaths and hospitalizations in children less than 5 years of age after the introduction of rotavirus vaccination: A time-trend analysis in Brazil (2001-2010). Pediatr Infect Dis J. 2016;35:e180-90.

***Section Editor*:** ABHIJEET SAHA

SUMMARY

To estimate population level vaccine effect, the authors conducted a time–trend analysis on all-cause gastroenteritis (GE)-related death certificate-reported deaths (DCRDs), hospital deaths (HDs) and hospitalizations trends in <5-year-olds before (2001–2005) and after (2007–2010) rotavirus vaccine introduction. During the post vaccine introduction period, there was an overall age-independent GE-related DCRDs reduction (20.9%, *P*=0.04) observed in children <5 years of age; a reduction was also seen in infants (20.8%, *P*=0.003). Age-independent GE-related HDs and hospitalizations reductions (57.1%, *P*<0.0001 and 26.6%, *P*<0.0001, respectively) were observed in <5-year-olds; HDs reductions were also observed for each age group (<1-year-olds: 55.0%, *P*<0.0001 and 1- to <5-year-olds: 59.5%, *P*<0.0001). Observed annual frequencies of GE-related DCRDs, HDs and hospitalizations were lower than the predicted value in each age group in all years after 2006. The authors conclude that GE-related DCRDs, HDs and hospitalizations were significantly reduced in <1 and in 1- to <5-year-old Brazilian children after rotavirus vaccine introduction, which provides additional evidence of the direct and indirect population-level effect of rotavirus vaccination on GE-related mortality and morbidity in children.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: The discovery of rotavirus as the major pathogen for acute childhood gastroenteritis in developed countries stimulated the development of safe and efficacious vaccines. The two currently available formulations (introduced in 2006), include a monovalent human rotavirus vaccine and a pentavalent bovine-human reassortant vaccine. The overall efficacy of both preparations is similar in developed countries (>95%), whereas it is much lower in African and Asian countries [1]. In South America, efficacy ranges around 80-85% [2]. In Latin American and Caribbean countries, 8000 annual under-five deaths attributed to rotavirus [3], prompted universal infant vaccination in six countries including Brazil, as early as 2006 itself. Within the next few years, another 8 nations initiated vaccination programs.

This study [4] was a retrospective analysis of Brazilian national databases recording mortality and disease-specific hospital admission rates. The databases were examined to obtain (*i*) annual gastroenteritis related mortality (irrespective of etiology) among under-five children during 2001-2009; (*ii*) in-hospital gastroenteritis mortality among under-five during 2001-2010; and (*iii*) hospital admission rates for gastroenteritis in the same population during the same period. The investigators also explored trends of these three outcomes prior to introduction of rotavirus vaccination, to estimate expected values if vaccination had not been introduced.

The analysis showed a steady decline in overall gastroenteritis-related mortality, in-hospital mortality, and hospital admission rates. The respective reductions between the beginning and end of the analysis period were 61%, 84% and 31%. The authors also reported that the post-vaccination reductions were out of proportion to the expected/predicted decline that was recorded in pre-vaccination years, suggesting that vaccination was responsible. In general, these impressive reductions were recorded for all three outcomes among infants, as well as among children <5 year old overall, although some of the differences did not achieve statistical significance. There were regional variations within the country, with the northern and north-eastern regions (traditionally regarded as socio-economically weaker) showing highest vaccination impact, despite lowest vaccination coverage.

Critical appraisal: This analysis [4] had several strengths. First, the investigators used five years of pre-vaccination data, and three to four years post-

vaccination data. Three separate outcomes were examined that together provide an overall picture of gastroenteritis mortality and morbidity among children in Brazil. Further, they undertook subgroup analysis by age group, and region. The investigators also studied additional databases on population census, as well as vaccination coverage. Robust statistical methods were used to present and/or compare data. This analysis also accounted for the pre-vaccination decline in diarrhea mortality and morbidity (likely associated with better hygiene, sanitation, oral rehydration therapy, *etc*) to estimate whether vaccination had additional benefit. Such methodological refinements increase confidence in the data presented.

The authors also acknowledged methodological limitations with their analysis. These include difficulties in calculating the effect of non-vaccination strategies, failure of databases to distinguish rotavirus (*versus* other causes) of gastroenteritis, the risk of databases not capturing all potentially available data, and failure to distinguish between single and repeat episodes of diarrhea.

It should be recognized that this analysis [4] is not the first evaluation of rotavirus vaccine impact in Brazil, although it is the most recent, has the longest time-frame and included multiple outcomes. A recent systematic review [5] of studies among children <5-y-old residing in 16 Latin American and Caribbean countries, calculated pooled effectiveness of 63.5% to 72.2% against rotavirus hospitalization with the monovalent vaccine. The estimates of effectiveness were higher for infants <1-y-old than children under-five overall. Similarly, the Pan American Health Organization (PAHO) [6] compared mortality in 2009, among the five countries initiating vaccination in 2006 (Brazil, El Salvador, Mexico, Nicaragua, and Panama) *versus* four countries without vaccination programs (Argentina, Chile, Costa Rica, and Paraguay). Four of the five countries with vaccination (exception being Panama) recorded significant decline in mortality rates during 2006 to 2009, whereas no decline was seen in the four non-vaccination countries. Further, all-cause diarrhea mortality declined in infants <1 year of age, as well as children <5 years of age, post-vaccination in four of the five countries (exception Nicaragua).

Pre- and post-vaccine introduction hospital-based surveillance systems at the institutional, state, regional or national level in Brazil also recorded significant reductions in diarrhea mortality [7-11], proportion of diarrhea cases due to rotavirus [12], hospitalization with rotavirus diarrhea [13,14], and hospitalization with diarrhea (irrespective of cause) [7-10,13,15,16]. These declines occurred among infants <1-y-old as well as among under-five children, although the greatest decline was noted in infants [9,10,13,14]. The samples sizes in these studies ranged from a few hundred to a few thousand. As in this study [4], previous analyses also suggested highest impact in least developed populations [14].

Although rotavirus vaccine was designed to protect against severe rotavirus diarrhea, this may not always happen. In a small prospective study [17] in northern Brazil, investigators identified 1023 rotavirus diarrhea episodes among children. Very severe gastroenteritis was reported in 16.7%, 17.9% and 13.5% of unvaccinated, partially vaccinated and fully vaccinated children, respectively. Although it is well recognized that fully vaccinated children are not necessarily protected from rotavirus diarrhea [18,19], the risk factors and/or determinants of this susceptibility are unclear.

What impact did rotavirus vaccination have on child survival in Brazil? The authors highlighted 88% decline in under-five mortality related to gastroenteritis between 1990 and 2009 [4]. However, there is no explanation why 1990 was chosen as the baseline year, considering that all outcomes in the study were measured from 2000 onwards. Detailed analysis of Brazil's under-five mortality rate (U5MR) and infant mortality rate (IMR) is presented in ***Table* I** [20-30]. This shows a dramatic decline in U5MR and IMR in the year 2006 that progressed over the subsequent years. Since rotavirus vaccination was

TABLE I CHILDHOOD MORTALITY RATE, ACCESS TO SAFE WATER AND ADEQUATE SANITATION IN BRAZIL

Year	*U5MR*	*IMR*	*Access to safe water*	*Adequate sanitation*
2002	36	30	89%	75%
2003	35	33	NA	NA
2004	34	32	90%	75%
2005	33	31	90%	NA
2006	20	19	91%	77%
2007	22	20	NA	NA
2008	NA	NA	97%	80%
2009	21	17	NA	NA
2010	19	17	98%	79%
2011	16	14	97%	81%
2012	14	13	98%	81%
2013	14	12	NA	NA

IMR: infant mortality rate/1000 live births; NA: not available; U5MR: under-five mortality rate/1000 live births
Data from references 20 to 30.

initiated in 2006 and vaccine coverage was less than 40% that year, this decline cannot be attributed to vaccination. Further, it appears that gastroenteritis contributes a negligible fraction to overall childhood mortality in Brazil. Based on these data, it appears that rotavirus vaccination contributed little to the reduction in childhood mortality. ***Table* I** also highlights other achievements in Brazil that could positively impact burden of gastroenteritis.

Does rotavirus vaccination affect circulating genotypes of the virus? This is a difficult issue to resolve. Extensive data from Brazil suggests that immediately after vaccine introduction, the predominant circulating genotype G1P[8] rapidly declined and G2 genotypes abounded [8,12,13,31-34]. However it is still unclear whether these changes reflect selection pressure induced by vaccination or merely natural variations noted with rotavirus A genotypes [31,35]. Although there is data suggesting that the monovalent vaccine (one as well as two doses) has considerable efficacy and/or effectiveness against G2P[4] genotype also [33], this distinction could have bearing on vaccine impact in subsequent years if genotypes not protected by current vaccine(s) emerge. For example, a recent three-year study [36] during 2012 to 2014 of over 3400 specimens showed G3P[8] in 35-40% sample sin 2012 and 2013, but rarely in 2014. G12P[8] genotype was present in a quarter of the samples in 2012, almost absent in 2013, but noted in over 85% samples in 2014, suggesting an outbreak with this genotype. Genotype analysis of about 6200 samples from 2007 to 2011 [37] showed that G2P[4] dominated during 2007-2010, followed by G9P[8] in 2011, and then G12P[8] in 2012. Mixed infections and unusual combinations were also noted. It is difficult to establish whether this could be a direct or indirect consequence of vaccination.

It is important to note that 7 of the 9 authors of this study [4] are present or past employees of the monovalent vaccine manufacturer. Although this is unlikely to bias the data presented, it raises the question whether there could be selective data reporting. For example, one assumes that the national databases would contain robust information on intussusception, although this aspect has not been touched upon at all. This issue is important because a group of independent researchers from CDC (USA) [38] identified higher risk of intussusception within 7 days of receiving the first dose of monovalent rotavirus vaccine in Mexico but not Brazil; whereas infants in Brazil had a higher risk within seven days after receiving the second dose. The investigators could attribute an annual increase of 96 cases in the two countries and 5 deaths to monovalent rotavirus vaccine.

Cost-effectiveness analyses (CEA) in Brazil prior to introduction of rotavirus vaccination (*i.e* based on mathematical modeling of hypothetical cohorts) suggested that national rotavirus vaccination could decrease over three quarters of rotavirus related health-care burden. Even at vaccine price of roughly 8 USD per dose, a reasonable cost-effectiveness ratio could be achieved [39]. Another similar analysis [40] suggested that although the vaccination program could cost more than the direct and indirect savings, vaccination would be a cost-effective exercise. In contrast, after the introduction of the vaccine, actual cost calculations suggested that despite impressive reductions in disease burden and mortality, the overall financial burden of the health-care system increased after introducing vaccination [41]. This disparity is important to recognize as it can affect planning and decision-making in countries considering rotavirus vaccination programs.

Extendibility: Brazil and India share many similarities. Both countries are of continental proportions in terms of geographic size, population density, ethnic backgrounds, regional differences and diversities among people with respect to socio-economic status, education, access to health-care *etc.* Whereas some of the distinctions in Brazil are regional, in India stark differences exist within the same state, district, city or community. Therefore for public health issues, it is challenging to think of India as a single epidemiological unit. There are also vast differences in the health-care scenario of the two countries. A clear contrast is the universal immunization coverage of almost 99% for BCG, DPT and measles vaccines in Brazil over the past 15 years. Even the recently introduced rotavirus vaccination achieved over 80% coverage for two doses within 3-4 years of introduction [20-30,42]. Further, it appears that under-five mortality rate and infant mortality rate have been declining rapidly over the past two decades, through large-scale national efforts (***Table* I**). Early introduction of rotavirus vaccination itself is probably a consequence of these efforts.

Even without an exploration of rotavirus epidemiology in India, in terms of disease burden, contribution to childhood mortality, prevalent genotypes, variations in vaccine effectiveness, *etc*; it is easy to recognize that the conclusions of this study [4] cannot be directly extrapolated to the Indian setting.

Conclusion: This retrospective analysis confirms that universal rotavirus vaccination in Brazil resulted in significant decline in overall gastroenteritis-related morality, in-hospital gastroenteritis deaths, and hospital admission rate among under-five children. However, the implications of changing serotypes, financial burden,

potential increase in intussusception, *etc* have not been explored. Caution should be exercised in extrapolating these data for evidence-based decisions in India

Funding: None; *Competing interest*: None stated.

JOSEPH L MATHEW
Department of Pediatrics, PGIMER, Chandigarh, India.
dr.joseph.l.mathew@gmail.com

REFERENCES

1. Vesikari T. Rotavirus vaccination: a concise review. Clin Microbiol Infect 2012;18:57-63.
2. Linhares AC, Justino MC. Rotavirus vaccination in Brazil: effectiveness and health impact seven years post-introduction. Expert Rev Vaccines. 2014; 13:43-57.
3. Centers for Disease Control and Prevention (CDC). Progress in the introduction of rotavirus vaccine—Latin America and the Caribbean, 2006-2010. MMWR. 2011;60:1611-4.
4. Costa I, Linhares AC, Cunha MH, Tuboi S, Argüello DF, Justino MC, *et al*. Sustained decrease in gastroenteritis-related deaths and hospitalizations in children less than 5 years of age after the introduction of rotavirus vaccination: a time-trend analysis in Brazil (2001-2010). Pediatr Infect Dis J. 2016; 35:e180-90.
5. de Oliveira LH, Camacho LA, Coutinho ES, Ruiz-Matus C, Leite JP. Rotavirus vaccine effectiveness in Latin American and Caribbean countries: A systematic review and meta-analysis. Vaccine. 2015;33(Suppl 1):A248-54.
6. Paternina-Caicedo A, Parashar UD, Alvis-Guzmán N, De Oliveira LH, Castaño-Zuluaga A, Cotes-Cantillo K, *et al*. Effect of rotavirus vaccine on childhood diarrhea mortality in five Latin American countries. Vaccine. 2015; 33:3923-8.
7. Teles E, Moscovici L, Monteiro RA, Alves D, Laprega MR, Bellissimo-Rodrigues F. The effectiveness of a rotavirus vaccine in preventing hospitalizations and deaths presumably due to acute infectious diarrhea in Brazilian children: a quasi-experimental study. Rev Soc Bras Med Trop. 2015; 48:129-35.
8. Gurgel RQ, Alvarez Ade J, Rodrigues A, Ribeiro RR, Dolabella SS, Da Mota NL, *et al.* Incidence of rotavirus and circulating genotypes in Northeast Brazil during 7 years of national rotavirus vaccination. PLoS One. 2014; 9:e110217.
9. Gurgel RQ, Ilozue C, Correia JB, Centenari C, Oliveira SM, Cuevas LE. Impact of rotavirus vaccination on diarrhoea mortality and hospital admissions in Brazil. Trop Med Int Health. 2011;16:1180-4.
10. do Carmo GM, Yen C, Cortes J, Siqueira AA, de Oliveira WK, Cortez-Escalante JJ, *et al.* Decline in diarrhea mortality and admissions after routine childhood rotavirus immunization in Brazil: a time-series analysis. PLoS Med. 2011;8:e1001024.
11. Lanzieri TM, Linhares AC, Costa I, Kolhe DA, Cunha MH, Ortega-Barria E, *et al.* Impact of rotavirus vaccination on childhood deaths from diarrhea in Brazil. Int J Infect Dis. 2011;15:e206-10.
12. Carvalho-Costa FA, Volotão Ede M, de Assis RM, Fialho AM, de Andrade Jda S, Rocha LN, *et al*. Laboratory-based rotavirus surveillance during the introduction of a vaccination program, Brazil, 2005-2009. Pediatr Infect Dis J. 2011;30:S35-41.
13. Sáfadi MA, Berezin EN, Munford V, Almeida FJ, de Moraes JC, Pinheiro CF, *et al*. Hospital-based surveillance to evaluate the impact of rotavirus vaccination in São Paulo, Brazil. Pediatr Infect Dis J. 2010;29:1019-22.
14. Fernandes EG, Sato HK, Leshem E, Flannery B, Konstantyner TC, Veras MA, *et al*. Impact of rotavirus vaccination on diarrhea-related hospitalizations in São Paulo State, Brazil. Vaccine. 2014;32:3402-8.
15. Masukawa Mde L, Moriwaki AM, Uchimura NS, Souza EM, Uchimura TT. Intervention analysis of introduction of rotavirus vaccine on hospital admissions rates due to acute diarrhea. Cad Saude Publica. 2014;30:2101-11.
16. Lanzieri TM, Costa I, Shafi FA, Cunha MH, Ortega-Barria E, Linhares AC, *et al*. Trends in hospitalizations from all-cause gastroenteritis in children younger than 5 years of age in Brazil before and after human rotavirus vaccine introduction, 1998-2007. Pediatr Infect Dis J. 2010;29:673-5.
17. Justino MC, Brasil P, Abreu E, Miranda Y, Mascarenhas JD, Guerra SF, *et al*. Clinical severity and rotavirus vaccination among children hospitalized for acute gastroenteritis in Belém, Northern Brazil. J Trop Pediatr. 2016. pii: fmv098. [Epub ahead of print].
18. Sandra CA, Estevam GK, Penati M, Soares LA, Ferreira RG, Orlandi PP, *et al*. Detection of rotavirus in children with acute gastroenteritis in Porto Velho, Rondonia, Brazil. Arch Virol. 2014;159:1139-42.
19. Borges AM, Dias e Souza M, Fiaccadori FS, Cardoso DD. Monitoring the circulation of rotavirus among children after the introduction of the Rotarix vaccine in Goiânia, Brazil. Mem Inst Oswaldo Cruz. 2011;106:499-501.
20. UNICEF. State of the World's Children. 2015 Report. Available from: *http://www.unicef.org/publications/files/SOWC_2015_Summary_and_Tables.pdf*. Accessed June 15, 2016.
21. UNICEF. State of the World's Children. 2014 Report. Available: from: *http://www.unicef.org/sowc2014/numbers/documents/english/SOWC2014_In%20Numbers_28%20Jan.pdf*. Accessed June 15, 2016.
22. UNICEF. State of the World's Children. 2013 Report. Available from: *http://www.unicef.org/sowc2013/files/SWCR2013_ENG_Lo_res_24_Apr_2020.pdf*. Accessed June 15, 2016
23. UNICEF. State of the World's Children. 2012 Report. Available from: *http://www.unicef.org/sowc2012/pdfs/SOWC%202012-Main%20Report_EN_13Mar2012.pdf*. Accessed June 15, 2016.
24. UNICEF. State of the World's Children. 2011 Report. Available from: *http://www.unicef.org/sowc2011/pdfs/SOWC-2011-Main-Report_EN_02092011.pdf*. Accessed June 15, 2016.
25. UNICEF. State of the World's Children. 2011 Report. Available from: *http://www.unicef.org/sowc2011/pdfs/SOWC-2011-Main-Report_EN_02092011.pdf*. Accessed June 15, 2016.

26. UNICEF. State of the World's Children. 2011 Report. Available from: *http://www.unicef.org/sowc2011/pdfs/SOWC-2011-Main-Report_EN_02092011.pdf*. Accessed June 15, 2016.
27. UNICEF. State of the World's Children. 2011 Report. Available from: *http://www.unicef.org/sowc2011/pdfs/SOWC-2011-Main-Report_EN_02092011.pdf*. Accessed June 15, 2016.
28. UNICEF. State of the World's Children. 2006 Report. Available from: *http://www.unicef.org/sowc06/pdfs/sowc06_fullreport.pdf*. Accessed June 15, 2016.
29. UNICEF. State of the World's Children. 2005 Report. Available from: *http://www.unicef.org/sowc05/english/sowc05.pdf*. Accessed June 15, 2016.
30. UNICEF. State of the World's Children. 2004 Report. Available from: *http://www.unicef.org/sowc04/files/SOWC_O4_eng.pdf*. Accessed June 15, 2016.
31. Guerra SF, Linhares AC, Mascarenhas JD, Oliveira A, Justino MC, Soares LS, *et al*. Rotavirus strain surveillance for three years following the introduction of rotavirus vaccine into Belém, Brazil. J Med Virol. 2015;87:1303-10.
32. Ichihara MY, Rodrigues LC, Teles Santos CA, Teixeira Mda G, De Jesus SR, Alvim De Matos SM, *et al*. Effectiveness of rotavirus vaccine against hospitalized rotavirus diarrhea: A case-control study. Vaccine. 2014;32:2740-7.
33. Montenegro FM, Falbo AR, Germano EM, Correia NB, Souza Eda S, Nakagomi O, *et al*. Reduction in rotavirus disease and sustained predominance of G2P[4] rotavirus strain following introduction of rotavirus vaccine in Recife, Brazil. J Trop Pediatr. 2015;61:206-9.
34. Assis AS, Valle DA, Antunes GR, Tibiriça SH, Assis RM, Leite JP, *et al*. Rotavirus epidemiology before and after vaccine introduction. J Pediatr (Rio J). 2013;89:470-6.
35. Almeida TN, Fiaccadori FS, Souza M, Borges AM, Cardoso DD. Molecular characterization of group A rotavirus before and after the introduction of vaccines in Brazil. Rev Soc Bras Med Trop. 2015;48:599-602.
36. Luchs A, Cilli A, Morillo SG, Gregório Dde S, de Souza KA, Vieira HR, *et al*. Detection of the emerging rotavirus G12P[8] genotype at high frequency in brazil in 2014: Successive replacement of predominant strains after vaccine introduction. Acta Trop. 2016;156:87-94.
37. Luchs A, Cilli A, Morillo SG, Carmona Rde C, Timenetsky Mdo C. Rotavirus genotypes circulating in Brazil, 2007-2012: Implications for the vaccine program. Rev Inst Med Trop Sao Paulo. 2015;57:305-13.
38. Patel MM, López-Collada VR, Bulhões 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.
39. Constenla DO, Linhares AC, Rheingans RD, Antil LR, Waldman EA, da Silva LJ. Economic impact of a rotavirus vaccine in Brazil. J Health Popul Nutr. 2008;26:388-96.
40. de Soárez PC, Valentim J, Sartori AM, Novaes HM. Cost-effectiveness analysis of routine rotavirus vaccination in Brazil. Rev Panam Salud Publica. 2008;23:221-30.
41. Centenari C, Gurgel RQ, Bohland AK, Oliveira DM, Faragher B, Cuevas LE. Rotavirus vaccination in northeast Brazil: a laudable intervention, but can it lead to cost-savings? Vaccine. 2010;28:4162-8.
42. Flannery B, Samad S, de Moraes JC, Tate JE, Danovaro-Holliday MC, de Oliveira LH, *et al*. Uptake of oral rotavirus vaccine and timeliness of routine immunization in Brazil's National Immunization Program. Vaccine. 2013; 31:1523-8.

Immunization Expert's Viewpoint

This is a well-planned study in which a pre-existing declining secular trend is taken in to consideration while measuring the 'net' impact of national-level introduction of a human monovalent rotavirus vaccine (Rotarix) on all-cause gastroenteritis-related deaths and hospitali-zations in children in Brazil [1]. The vaccine demonstrated not only significant reductions in the hospital deaths and admissions related to all-cause gastroenteritis (GE) among the targeted age group, but in the older age groups of 1-5 years also. Hence, rotavirus vaccine has demonstrated an indirect effect of the vaccine (herd effect) on population. There were 'net' reductions in both observed mortality and morbidity figures up to 5 years after the introduction of vaccine into the Brazilian national immunization program (NIP) than predicted values after accounting for the baseline pre-existing trend of the disease [1].

One of the key findings of the study is that quite paradoxically, the rotavirus vaccine had greatest impact in the more populous, under-developed and more impoverished Northern and North-Eastern regions, despite these regions having lower vaccine coverage in comparison to other regions [1]. This finding is particularly encouraging to India since the country has also recently introduced rotavirus vaccine in few states. Though demographically and economically India and Brazil are different, these two particular regions have relatively similar prevailing conditions as in India. This phenomenon has also been observed in South Africa and Malawi trial of Rotarix [2] where the number of severe rotavirus GE episodes averted per every 100 vaccine doses were far greater in Malawi than in South Africa despite having lower estimates of vaccine efficacy in latter. This was mainly because of significantly higher disease burden of rotavirus disease in Malawi than in South Africa. So, this study has got some implications for India too. India has also registered a declining secular trend of the rotavirus-related disease in last few years [3], though not as pronounced as in Brazil. As stated above, India has introduced Rotavac, an indigenously developed RV vaccine, in its national immunization program (NIP). This vaccine has got a moderate efficacy of 56.3% in first year and 48.9% in second year of life [4]. However, the

efficacy trials are not a direct proxy for the population-level impact of a vaccine as efficacy trials are conducted under more ideal conditions with strict monitoring of subjects and dosage administration. It would be of paramount significance to measure overall real-world impact and effectiveness of these new generations rotavirus vaccines in a large developing country of Asia. As of today, 81 countries have introduced rotavirus vaccines in their NIPs [5], and the population impact of these has been demonstrated in many developing countries of Latin America, Africa and Eastern Europe [6]. But the evidence of their utility by the country-level effectiveness study from any developing country of the Asia is still lacking. Considering the vastness of the country coupled with prevailing poor sanitary conditions and weak healthcare system, the data generated by rotavirus vaccine impact studies from India would probably be the most convincing, incontrovertible evidence of the utility of the current generation of vaccines from one of the most challenging regions of the world.

Funding: None; *Competing interest*: None stated.

VIPIN M VASHISHTHA
Consultant Pediatrician,
Mangla Hospital & Research Center,
Bijnor, UP, India.
vipinipsita@gmail.com

REFERENCES

1. Costa I, Linhares AC, Cunha MH, Tuboi S, Argüello DF, Justino MC, *et al.* Sustained decrease in gastroenteritis-related deaths and hospitalizations in children less than 5 years of age after the introduction of rotavirus vaccination: A time-trend analysis in Brazil (2001-2010). Pediatr Infect Dis J. 2016;35:e180-90.
2. 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.
3. John J, Sarkar R, Muliyil J, Bhandari N, Bhan MK, Kang G. Rotavirus gastroenteritis in India, 2011-2013: Revised estimates of disease burden and potential impact of vaccines. Vaccine. 2014;32:A5-9.
4. Bhandari N, Rongsen-Chandola T, Bavdekar A, John J, Antony K, Taneja S, *et al.* Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian children in the second year of life. Vaccine. 2014;32:A110-6.
5. Rotavirus vaccines access and delivery – Country introductions of rotavirus vaccines. Available from: *http://sites.path.org/rotavirusvaccine/country-introduction-maps-and-spreadsheet/* Accessed June 16, 2016.
6. Parashar UD, Johnson H, Steele AD, Tate JE. Health impact of rotavirus vaccination in developing countries: Progress and way forward. Clin Infect Dis. 2016; 62:S91-5.