REVIEW ARTICLE

Epidemiology and Prospects for Prevention of Rotavirus Disease in India

***G KAHN, *S FITZWATER, #J TATE, †G KANG, $N GANGULY, **G NAIR, ##D STEELE, ††R ARORA, $$M CHAWLA-SARKAR, #U PARASHAR AND ***M SANTOSHAM**

*From *Department of International Health, Johns Hopkins University, Baltimore, USA; #Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, USA; †Department of Gastrointestinal Sciences, Christian Medical College, Vellore, India; $Translational Health Science and Technology Institute, New Delhi, India; **National Institute of Cholera and Enteric Diseases, Kolkata, India; ##Rotavirus Vaccine Program, PATH, Seattle, USA; ††Division of Epidemiology and Communicable Diseases, Indian Council of Medical Research, New Delhi, India; $$National Institute of Cholera and Enteric Diseases, Kolkata, India; and *** Department of International Health, Johns Hopkins University, Baltimore, USA.*

Correspondence to: Dr M Santosham, Department of International Health, Johns Hopkins University, Baltimore, USA. msantosh@jhsph.edu

Context: With rotavirus vaccines now available globally, it will be useful to assemble the available evidence on the epidemiology and burden of rotavirus gastroenteritis in India, in order to weigh the urgency of introducing a vaccine to help control rotavirus disease.

Evidence Acquisition: We reviewed published studies on rotavirus infection and genotype distribution in India, as well as safety and immunogenicity studies of currently available vaccines. PubMed was searched for papers published after 1990, and several authors who are experts in the field recommended papers of known significance.

Results: Rotavirus accounts for close to 40% of hospitalizations for diarrhea in India, with more recent studies showing an increased proportion compared with older studies. There is substantial serotype diversity in India, although there is less intra-country variation than previously thought. Two genotypes, G1P[8] and G2P[4], account for roughly 50% of symptomatic infections in non-neonates. Currently licensed vaccines are safe, and although the efficacy appears lower in developing countries, given the extremely high incidence of diarrhea these could still be cost-effective interventions.

Conclusions: The epidemiology and burden of rotavirus diarrhea is fairly well characterized in India. Introducing rotavirus vaccine into the UIP, along with adequate surveillance, should be an important part of efforts to reduce diarrhea mortality, the third leading cause of death among Indian children, and achieve the country's MDG goals.

Key words: *Epidemiology, Serotype distribution, Rotavirus, Vaccine*.

Diarrhea, the third leading killer of children in India today, is responsible for 13% of all deaths in children <5 years of age and kills an estimated 300,000 children in India each year [1]. Rotavirus is the leading cause of severe diarrhea in Indian children under 5, and has been projected to cause 457,000 to 884,000 hospitalizations, 2,000,000 outpatient visits, and 122,000-153,000 deaths annually [2]. The objectives of this paper are to review the epidemiology of rotavirus in India, describe currently available and candidate rotavirus vaccines, and examine the potential impact and cost-effectiveness of a national rotavirus vaccination program.

EPIDEMIOLOGY

Burden of Rotavirus Diarrhea

Nationally representative data on the incidence of severe rotavirus disease in India are lacking. However, a recent prospective birth cohort study in Vellore rigorously characterized the burden of rotavirus infection among children under 3 years of age [3]. The incidence of rotavirus diarrhea was 0.25 (95% CI 0.22, 0.29) per child-year in children under 3 and 0.49 (0.42, 0.58) per child-year in children under 1. 48% of children experienced at least one episode of rotaviral diarrhea by age 3. In another cohort study in an urban slum population in New Delhi [4], the overall annual incidence of rotavirus hospitalizations in children <5 years of age was 337/100,000; incidence for 1-year-olds was 1,270/100,000 with low incidence in the first 3 months of life; incidence for 2-year-olds was 534/100,000; and incidence for 3-5 year olds was 12/100,000. This study highlights the importance of young age in severe rotavirus infections, but because the study looked at incidence of hospitalization and not disease, these numbers do not represent the true incidence of rotavirus disease in India.

The contribution of rotavirus to diarrhea mortality is typically inferred from diarrhea hospitalizations, which are reasonably assumed to represent severe cases. The proportion of all diarrhea hospitalizations caused by rotavirus has been evaluated in numerous studies in India. On average, 34% (inter study variation (ISV): 19-50%) of all diarrhea hospitalizations are the result of rotavirus infections [4-16] (***Table* I**). The proportion of severe diarrhea attributable to rotavirus has increased from an average of 25% (ISV: 21-28%) in studies which were completed prior to 2000 to over 38% (ISV: 19-50%) in studies that were completed after 2005. A similar increase has been seen globally. It is postulated that improvements in sanitation and use of antimicrobials have had a greater impact on preventing bacterial and parasitic gastroenteritis (GE) than rotavirus [17]. The reasons for this discrepancy are discussed later in the article.

The proportion of diarrhea cases attributable to rotavirus is notably lower in outpatient studies and community studies. A previous review found that rotavirus accounts a median of 15% of community diarrheal cases in India and 16% of diarrheal outpatients [18]. Two additional studies, conducted in Pune and Vellore, found a mean proportion of 12% (ISV: 7-16) [6, 10]. The higher prevalence of rotavirus among hospitalized persons suggests that rotavirus gastroenteritis is generally more severe than that of other etiologies, an observation corroborated by the Vellore cohort, where the proportion of diarrhea cases due to rotavirus increased with increasing disease severity, from 11.5% in the least severe cases to 67.4% in the most [3].

TABLE I PROPORTION OF DIARRHEA CASES DUE TO ROTAVIRUS

Study Location	Proportion RV+	Total Diarrhea Cases	Age	Year
Hospital Studies				
Pune[5]	28.2%	945	<5	1992-1996
Pune[6]	28.3%	628	<5	1993-1996
Chennai[7]	22.5%	745	<3	1995-1999
Vellore[8]	21.0%	602	<5	1995-1999
Kolkata[9]	34.7%	266	<4	1998-2000
Delhi[4]	23.5%	584	<5	2000-2001
Vellore[10]	27.4%	343	<5	2002-2003
Kolkata and Berhampur [11]	36.3%	545	<4	2003-2005
Lucknow[12]	19.2%	412	<3	2004-2008
Kolkata[13]	37.3%	668	<4	2005-2006
Delhi[14]	36.9%	862	<2	2005-2007
Nationwide[15]	39.2%	4243	<5	2005-2007
Manipur[16]	49.9%	489	<5	2005-2008
Summary	33.6%	11,332		
Community Studies				
Pune[6]	15.5%	489	<5	1993-1996
Vellore[10]	7.1%	351	<2	2002-2003
Summary	12.0%	840		

RV+: Rotavirus positive; Before 2000: 26.1 %; between 2000-2005: 29.1 %; after 2005: 38.3%.

Neonatal infections

The prevalence of rotavirus in neonates is high in India, ranging from 22% to 73% [19-23]. Neonatal infections are commonly asymptomatic, with 69-95% not showing overt signs of GE [21-24]. However, rotavirus infection has been detected significantly more in neonates with diarrhea than in those without (55.5% *vs* 44.4%, $P<0.001$) suggesting that neonates are not entirely immune to rotavirus GE [22]. Viral shedding can begin as early as 2 days of age, generally peaks around 3-6 days and resolves by 2 weeks of age; the likelihood of acquiring an infection is related to length of stay in the hospital after birth [19, 21,24]. Neonatal infections may be protective against future rotavirus diarrhea, although results are conflicting. This phenomena was first observed in a cohort of infants in Australia, where neonatal infection was not protective against subsequent reinfection but was protective against severe symptoms when reinfection occurred [25]. In a cohort in New Delhi, infants with neonatal infections suffered 46% fewer episodes of rotavirus diarrhea and 22% fewer episodes of all-cause diarrhea in the first year of life [21]. Similarly, in a cohort of Bangalore children followed for 2 years, 2% of neonatally infected children had rotavirus-associated diarrhea, while 39% of those not neonatally infected had symptomatic rotavirus infections ($P<0.001$).[20] However, a larger study in Vellore did not find any association between neonatal infection and either incidence or severity of future rotavirus or all-cause GE [23]. The Bangalore and Vellore studies limited their analyses to children infected with particular RV types, strain I321 in Bangalore and G10P [11] in Vellore, making it difficult to compare the two results. The role that neonatal rotavirus infections play in disease epidemiology remains unclear, although given the high burden of rotavirus disease observed in India any protective effect seems likely to be minimal.

Age distribution

Most rotavirus disease in India occurs in the first two years of life. In hospital-based studies, 87% (ISV: 58-

95%) of all rotavirus cases in children under 5 yr occurred by 18 months of age [4-8, 10, 12, 15, 26]. Additionally, rotavirus GE is uncommon in the youngest children; only 13% (ISV: 10-25%) of rotavirus cases in hospital studies were in children younger than 6 months old. However, outpatient and community studies found a higher proportion of cases (30%) in children under 6 months [6, 10]. The difference in age distribution between settings is likely largely a function of severity: in young children, infection with rotavirus may be attenuated by the persistence of maternal antibodies and thus, severe disease is less common.

Seasonality

While some studies in India have found no association between rotavirus infection and time of year [10,16], most have observed an increase in rotavirus-associated diarrhea during the winter months, October to February, throughout the country [4,5,7,12,15,27,28]. The observed proportion of rotavirus cases occurring in the cooler season has ranged from 59% to 72%, with a median of 64%. The northern, more temperate regions may exhibit stronger seasonality [15]. Nevertheless, studies in Kolkata [29], Pune [5], and Chennai [7] have observed seasonal effects despite their tropical climates, so the degree to which seasonality varies by geography remains unresolved.

Serotype diversity

Rotavirus isolates from India are genetically heterogeneous [4, 8-16, 30-35] (***Web Table* I**). Such genetic diversity is characteristic of Asia as a whole [36, 37], and phylogenetic analyses of the VP7 (G) and VP4 (P) genes from India show >95% homology with Asian reference strains for most isolates [16,27,35], suggesting that rotavirus strains circulating in India are part of a larger Asian transmission pool. The distribution of serotypes is similar in northern and southern areas of the country and a few genotypes, namely G1P[8] and G2P[4], often predominate in studies of non-neonates. (***Figs*. 1, 2**)

Neonates are infected with a more limited spectrum of viruses. In each study, one strain seems to predominate over other strains, although the particular strain varies from study to study, with G9P [11] [19, 21], G10P [11] [20, 38], and G12P[6] [27] having been observed. Interestingly, several of these isolates have genetic homology with non-human rotavirus, suggesting human and animal reassortant viruses play a large role in neonatal infections [20,21,38].

Approximately 9% of all isolates are mixed infections. The components of the mixed infections had a similar distribution to the single-type infection distribution. Additionally, roughly 13% of G types and 15% of P types were classified as untypable. However, recent studies employing direct sequencing have illuminated the importance of point mutations at the primer binding sites in causing failures of PCR detection and genotyping [14, 33]. Sequencing the genome of 16 previously untypable rotavirus isolates found that the strains were a mixture of common genotypes, including G1, G8, G9 and G12 and P[4] and P[8], with point mutations at the primer binding sites [33].

Treatment and Prevention

No specific treatment exists for rotavirus gastroenteritis, and repeat infections are common in children [3]. Sanitation and hygiene improvements have had a tremendous impact on diarrheal disease due to bacteria and parasites but less of an impact on rotavirus disease. This is evinced by the persistence of rotavirus in high income settings and the previously noted increase in the proportion of GE cases due to rotavirus, and is thought to be due to transmission through person-to-person contact, which persists even as fecal-oral transmission diminishes [39]. Reduced osmolality oral rehydration solution (ORS) effectively prevents and treats dehydration, and also reduces diarrheal output [39], but the 2005 National Family Health Survey found that nationally only 26% of children with diarrhea receive ORS [40]. Unlike many other diarrheal pathogens, the proportion of diarrhea

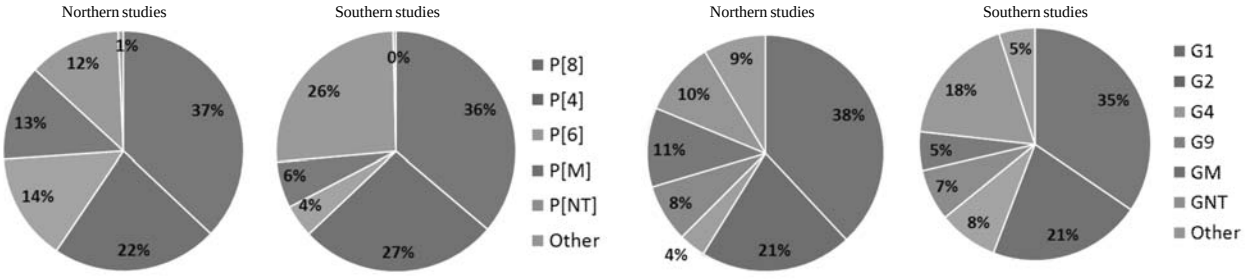

FIG. 1 *Rotavirus P serotype diversity in Northern and Southern India.*

caused by rotavirus does not vary widely between developed and developing countries [41]. To date, the only specific prevention strategy is immunization with rotavirus vaccines.

ROTAVIRUS VACCINES

Currently, two rotavirus vaccines are available on the international market (Box) Rotarix (GlaxoSmithKline, Rixensart, Belgium) is a monovalent rotavirus vaccine (RV1) created by attenuating a highly antigenic strain of human G1P[8] rotavirus [42]. RotaTeq (Merck and Co., Whitehouse Station, USA) is a pentavalent vaccine (RV5) created by reassorting G and P antigens from human rotavirus, G1, G2, G3, G4 and P[1] with a bovine rotavirus strain [43]. While efficacy data from India are not yet available, both vaccines have been tested extensively in a number of high and low income settings which can be used predict the efficacy likely to be seen in India (***Table* II**) [39,44-46]. These vaccines are less effective against medically attended rotavirus GE in lower income settings, varying in low and lower middle income countries from 74% to 49%, with lower efficacy seen in the lowest income countries [47]. Efficacies against severe all-cause GE have ranged from 56% to 25%, with a less clear cut impact between high and middle and low income countries (***Table* II**) [42, 47-50]. The efficacy of existing rotavirus vaccines in India are likely to fall into the range for other low and middle income countries. These vaccines appear to be cross protective against non-vaccine strains [51], with similar efficacy against vaccine and non-vaccine strains [47]. Vaccine efficacy, therefore, should be comparable between countries with different serotype profiles, and be minimally affected in serotype diverse countries such as India.

In high and middle income countries, recent introductions of RV1 and RV5 have had remarkable impact on rotavirus disease despite limited uptake and have provided both direct and indirect protection in the under 5 population [51]. In the USA, a 42%-50% decrease in GE hospital admissions was seen in children aged 3 to 23 months during 2008 rotavirus season, two years after RV5 introduction, while only one-third of children <2 years had received one or more doses of RV5 [52]. Additionally, a 28%-45% reduction in GE hospitalizations was demonstrated during the rotavirus season in children age-ineligible to receive RV5, suggesting significant indirect protection [52]. In El Salvador, the introduction of RV1 was followed by a 76% decrease in the number of hospitalizations due to rotavirus GE and a 32% reduction in all-cause GE hospitalization within two years [46, 53]. Australia, which introduced both RV1 and RV5, saw a 74% decrease in the same timeframe [54].

Two post-marketing studies have examined the impact of vaccination against mortality from diarrhea. After RV1 introduction, Mexico saw a 35% (95% CI: 29-39)

TABLE II EFFICACY OF RV1 OR RV5 AGAINST ROTAVIRUS MANIFESTATIONS

Severe rotavirus gastroenteritis		
Income level [a]	Efficacy range	Citations
High	96-84%	[39, 44]
Upper middle	90-77%	[39]
Lower middle	74-55%	[39, 45, 46]
Lower	64-49%	[39]
Hospitalization due to all cause gastroenteritis		
Income status [a]	Efficacy range	Citations
High	56-30%	[48-50]
Middle or lower	44-25%	[42, 47]

[a] *World Bank 2008 classification; RV1: monovalent and RV5: pentavalent rotavirus vaccines.*

BOX: ROTAVIRUS VACCINES CURRENTLY AVAILABLE OR UNDER DEVELOPMENT

Type	*Company*	*Schedule*	*Status*
Live pentavalent human-bovine reassortant (RV5)	Merck: Whitehouse Station, USA (Rotateq®)	Three doses given with DTP	International use
Live attenuated human rotavirus (RV1)	GlaxoSmithKline: Genval, Belgium (Rotarix®)	Two doses, given with 1st and 2nd DTP	International use
Live attenuated lamb rotavirus (LLV)	Lanzhou Institute of Biological Products: Lanzhou, China	First dose given from 2 to 36 months, yearly booster	Licensed for use in China
Serially passaged human neonatal rotavirus strain	Bharat Biotech International Limited: Hyderabad, India	Under development	Strains characterized. No phase 3 clinical trial data available
Bovine human reassortant rotavirus vaccine	Serum Institute of India and Shantha Biotechnics	Under development	No clinical trial data available

reduction in the rate of diarrheal deaths predominantly during the usual rotavirus season among children age-appropriate for the vaccine [55]. After RV1 introduction in Brazil in 2006, 30% (95% CI: 19-41) and 39% (95% CI: 29-49) decreases in gastroenteritis mortality were noted in 2007 and 2008, respectively, when compared to the mortality rates in 2004-2005 [56]. While suggestive of substantial benefit, both studies were observational and the results should be interpreted with caution.

Due to the association between intussusception and a previously licensed live reassortant human-simian vaccine, both RV1 and RV5 were under increased scrutiny for adverse events following vaccination. During RV1 and RV5 development, >50,000 infants were followed in clinical trials of each vaccine to determine if there is an increased risk of intussusception, but none was found [57]. Emerging data from post-marketing surveillance in Australia and Mexico suggest a low level increased risk of intussusception (about 1-2 cases per 100,000 vaccinated) in the first week following vaccination [58]. While more data are needed to fully understand intussusception risk across a range of settings, at the level of risk observed, the benefits of vaccination appear to greatly exceed the risks. At the rate observed in Mexico, vaccination would result in an additional 20-40 cases of intussusception, while preventing an estimated 700 deaths and 12,000 hospitalizations from diarrhea [58]. Additionally, no increased rate of serious adverse events such as fever, vomiting, or diarrhea was noted for either vaccine [57]. Vaccine-associated disease has been noted in children with severe combined immunodeficiency [59]. However, no increase in adverse effects or mortality has been shown in HIV-positive children in South Africa [57].

Based on the experiences of other developing countries, a rotavirus vaccine introduced in India would be expected to exhibit lower efficacy against rotavirus GE than seen in high income countries, but still prevent a significant proportion of all-cause GE mortality and hospitalizations. A small increased risk of intussusception would be far outweighed by the number of diarrhea deaths prevented.

Candidate Rotavirus Vaccines in India

Several candidate rotavirus vaccines are under development in India. One candidate is based on a neonatal rotavirus strain, 116E. This strain is a natural reassortant between a human rotavirus virus G9P[11] strain with the VP4 protein from a bovine rotavirus strain and was originally isolated from a neonate with an asymptomatic rotavirus infection [60]. A recent randomized double blinded placebo controlled trial for this strain has demonstrated that the vaccine elicits a strong immune response in Indian children and was not associated with an increase in adverse events [61]. Phase 3 trials of the 116E vaccine in India are in progress and will provide data regarding rotavirus vaccine efficacy in India. If successful, this vaccine provides the possibility of a locally developed and tested rotavirus vaccine for the Indian and international markets.

Other vaccine candidates under development are various constructs of the UK bovine strain-based reassortant vaccine developed by the US NIH [62]. The reassortant parent strains for the vaccine have been licensed out to various manufacturers in India, Brazil, and China. Indian-manufactured UK reassortant vaccines are currently in phase 1 or 2 clinical trials.

Challenges to rotavirus vaccine performance in developing countries such as India

Live oral vaccines have had an inconsistent performance in India and other developing countries. For example, oral polio vaccine (OPV) is less immunogenic and requires more doses to protect children in India compared with children in the developed world [63]. Similarly, the effectiveness of currently available rotavirus vaccines (RV1 and RV5) is also inversely correlated (***Table* II**) to the childhood mortality levels in the countries where the clinical trials were performed [64].

Reasons that live oral rotavirus vaccines are less efficacious in developing countries are not fully understood. In developing countries, higher levels of maternal rotavirus antibodies are passively transferred to babies during gestation and persist in infancy and some studies suggest that rotavirus vaccine neutralizing activity in breast milk is higher in developing countries and may reduce vaccine titer and adversely affect vaccine take[65], although breastfeeding has not been shown to decrease the efficacy of RV5 [66]. Furthermore, co-administration of OPV and rotavirus vaccines results in a small decrease in the antibody response against rotavirus for both RV1 and RV5, although the decrease is not significant in several studies after the full course of both vaccines [39]. Neither of the currently available rotavirus vaccines appears to interfere with polio immunity, as anti-polio antibodies were similar regardless of if rotavirus vaccine was given. Other reasons for poor vaccine performance could be a higher prevalence of distinct medical conditions such as tuberculosis, intestinal infections with other microorganisms, and malnutrition.

Potential impact and cost-effectiveness of rotavirus vaccines in India

Estimates derived from available Indian child mortality data suggest that, at current immunization levels, a

national rotavirus vaccination program in India would prevent 27,000 to 44,000 deaths in children <5 years of age annually [39, 67]. Rotavirus vaccine would prevent 1 case of severe gastroenteritis disease for every 11 children immunized, and prevent one death for every 470 children immunized [68]. The potential impact of rotavirus vaccines in India is partially hindered by a relatively low proportion of children who receive routine immunizations, which in 2006 was 52% for the third dose of the diphtheria, tetanus, pertussis vaccine [40]. If full immunization with rotavirus vaccine were reached, an additional 14,000 rotavirus deaths each year could be prevented [39]. Improving the overall performance of the immunization system is critical to the success of any vaccine introduction.

The cost-effectiveness of a national rotavirus vaccination program in India has been evaluated in two separate studies, which reached similar conclusions [67, 68]. At a vaccine price of US $1.00 per dose, the price set by Bharat Biotech [69], these models estimated an incremental cost effectiveness ratio of $21.41 to $34 per disability adjusted life year, which satisfies the WHO criterion for a cost effective intervention. Even at the current UNICEF prices, rotavirus vaccination is considered highly cost effective under WHO criteria [67].

Summary

Rotavirus diarrhea causes substantial mortality and morbidity in young children in India with the greatest burden among children <2 years of age. Two rotavirus vaccines are currently available on the international market. Additionally, at least two candidate vaccines are under development by Indian manufacturers and may be nationally licensed within 3-4 years. Despite the tremendous diversity of rotavirus strains in India, rotavirus vaccines provide cross-protection and have been shown to be effective against both vaccine and non-vaccine strains. At current coverage levels of routine childhood immunizations, the introduction of rotavirus vaccine in India could prevent up to one third of rotavirus-related deaths [67]. Introduction of rotavirus vaccine into the national immunization program of India at an affordable price would be a cost effective way to reduce the tremendous morbidity and mortality due to rotavirus disease in Indian children.

Note : The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC).

Contributors: MS and UP conceived and designed the review, and revised the manuscript. MS will act as guarantor of the study. G Kahn, SF, and JT were responsible for initial review of published studies and manuscript writing. G Kang, NG, GN, DS, RA, and MC-S contributed substantially to manuscript revisions, including providing expert opinion and additional studies for inclusion, and interpreting results. The final manuscript was approved by all authors.

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

REFERENCES

1. Bassani DG, Kumar R, Awasthi S, Morris SK, Paul VK, Shet A, *et al*. Causes of neonatal and child mortality in India: a nationally representative mortality survey. Lancet. 2010;376:1853-60.
2. 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:F18-24.
3. Gladstone BP, Ramani S, Mukhopadhya I, Muliyil J, Sarkar R, Rehman AM, *et al*. Protective effect of natural rotavirus infection in an Indian birth cohort. N Engl J Med. 2011;365:337-46.
4. Bahl R, Ray P, Subodh S, Shambharkar P, Saxena M, Parashar U, *et al*. Incidence of severe rotavirus diarrhea in New Delhi, India, and G and P types of the infecting rotavirus strains. J Infect Dis. 2005;192:S114-9.
5. Kelkar SD, Purohit SG, Simha KV. Prevalence of rotavirus diarrhoea among hospitalized children in Pune, India. Indian J Med Res. 1999;109:131-5.
6. Kelkar SD, Purohit SG, Boralkar AN, Verma SP. Prevalence of rotavirus diarrhea among outpatients and hospitalized patients: a comparison. Southeast Asian J Trop Med Public Health. 2001;32:494-9.
7. Saravanan P, Ananthan S, Ananthasubramanian M. Rotavirus infection among infants and young children in Chennai, South India. Indian J Med Microbiol. 2004;22:212-21.
8. Kang G, Green J, Gallimore CI, Brown DW. Molecular epidemiology of rotaviral infection in South Indian children with acute diarrhea from 1995-1996 to 1998-1999. J Med Virol. 2002;67:101-5.
9. Das S, Sen A, Uma G, Varghese V, Chaudhuri S, Bhattacharya SK, *et al*. Genomic diversity of group A rotavirus strains infecting humans in eastern India. J Clin Microbiol. 2002;40:146-9.
10. Banerjee I, Ramani S, Primrose B, Moses P, Iturriza-Gomara M, Gray JJ, *et al*. Comparative study of the epidemiology of rotavirus in children from a community-based birth cohort and a hospital in South India. J Clin Microbiol. 2006;44:2468-74.
11. Samajdar S, Varghese V, Barman P, Ghosh S, Mitra U, Dutta P, *et al*. Changing pattern of human group A rotaviruses: emergence of G12 as an important pathogen among children in eastern India. J Clin Virol. 2006;36:183-8.
12. Mishra V, Awasthi S, Nag VL, Tandon R. Genomic diversity of group A rotavirus strains in patients aged 1-36 months admitted for acute watery diarrhoea in northern India: a hospital-based study. Clin Microbiol Infect. 2010;16:45-50.
13. Samajdar S, Ghosh S, Chawla-Sarkar M, Mitra U, Dutta P, Kobayashi N, *et al*. Increase in prevalence of human group A rotavirus G9 strains as an important VP7 genotype among children in eastern India. J Clin Virol. 2008;43:334-9.

14. Chakravarti A, Chauhan MS, Sharma A, Verma V. Distribution of human rotavirus G and P genotypes in a hospital setting from Northern India. Southeast Asian J Trop Med Public Health. 2010;41:1145-52.
15. 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:S147-53.
16. Mukherjee A, Chattopadhyay S, Bagchi P, Dutta D, Singh NB, Arora R, *et al*. Surveillance and molecular characterization of rotavirus strains circulating in Manipur, north-eastern India: increasing prevalence of emerging G12 strains. Infect Genet Evol. 2010;10:311-20.
17. Parashar UD, Gibson CJ, Bresse JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis. 2006;12:304-6.
18. Ramani S, Kang G. Burden of disease & molecular epidemiology of group A rotavirus infections in India. Indian J Med Res. 2007;125:619-32.
19. Cicirello HG, Das BK, Gupta A, Bhan MK, Gentsch JR, Kumar R, *et al*. High prevalence of rotavirus infection among neonates born at hospitals in Delhi, India: predisposition of newborns for infection with unusual rotavirus. Pediatr Infect Dis J. 1994;13:720-4.
20. Vethanayagam RR, Ananda Babu M, Nagalaxmi KS, Maiya PP, Venkatesh HA, Purohit S, *et al*. Possible role of neonatal infection with the asymptomatic reassortant rotavirus (RV) strain I321 in the decrease in hospital admissions for RV diarrhea, Bangalore, India, 1988-1999. J Infect Dis. 2004;189:2282-9.
21. Bhan MK, Lew JF, Sazawal S, Das BK, Gentsch JR, Glass RI. Protection conferred by neonatal rotavirus infection against subsequent rotavirus diarrhea. J Infect Dis. 1993;168:282-7.
22. Ramani S, Sowmyanarayanan TV, Gladstone BP, Bhowmick K, Asirvatham JR, Jana AK, *et al*. Rotavirus infection in the neonatal nurseries of a tertiary care hospital in India. Pediatr Infect Dis J. 2008;27:719-23.
23. Banerjee I, Gladstone BP, Le Fevre AM, Ramani S, Iturriza-Gomara M, Gray JJ, *et al*. Neonatal infection with G10P[11] rotavirus did not confer protection against subsequent rotavirus infection in a community cohort in Vellore, South India. J Infect Dis. 2007;195:625-32.
24. Broor S, Ghosh D, Mathur P. Molecular epidemiology of rotaviruses in India. Indian J Med Res. 2003;118:59-67.
25. Bishop RF, Barnes GL, Cipriani E, Lund JS. Clinical immunity after neonatal rotavirus infection. A prospective longitudinal study in young children. N Engl J Med. 1983;309:72-6.
26. Chitambar SD, Tatte VS, Dhongde R, Kalrao V. High frequency of rotavirus viremia in children with acute gastroenteritis: discordance of strains detected in stool and sera. J Med Virol. 2008;80:2169-76.
27. Ray P, Sharma S, Agarwal RK, Longmei K, Gentsch JR, Paul VK, *et al*. First detection of G12 rotaviruses in newborns with neonatal rotavirus infection at all India Institute of Medical Sciences, New Delhi, India. J Clin Microbiol. 2007;45:3824-7.
28. Phukan AC, Patgiri DK, Mahanta J. Rotavirus associated acute diarrhoea in hospitalized children in Dibrugarh, north-east India. Indian J Pathol Microbiol. 2003;46: 274-8.
29. Nair GB, Ramamurthy T, Bhattacharya MK, Krishnan T, Ganguly S, Saha DR, *et al*. Emerging trends in the etiology of enteric pathogens as evidenced from an active surveillance of hospitalized diarrhoeal patients in Kolkata, India. Gut Pathog. 2010;2:4.
30. Das S, Varghese V, Chaudhuri S, Barman P, Kojima K, Dutta P, *et al*. Genetic variability of human rotavirus strains isolated from Eastern and Northern India. J Med Virol. 2004;72:156-61.
31. Jain V, Das BK, Bhan MK, Glass RI, Gentsch JR. Great diversity of group A rotavirus strains and high prevalence of mixed rotavirus infections in India. J Clin Microbiol. 2001;39:3524-9.
32. Sharma S, Ray P, Gentsch JR, Glass RI, Kalra V, Bhan MK. Emergence of G12 rotavirus strains in Delhi, India, in 2000 to 2007. J Clin Microbiol. 2008;46:1343-8.
33. Sharma S, Paul VK, Bhan MK, Ray P. Genomic characterization of nontypeable rotaviruses and detection of a rare G8 strain in Delhi, India. J Clin Microbiol. 2009;47:3998-4005.
34. Tatte VS, Gentsch JR, Chitambar SD. Characterization of group A rotavirus infections in adolescents and adults from Pune, India: 1993-1996 and 2004-2007. J Med Virol. 2010;82:519-27.
35. Zade JK, Chhabra P, Chitambar SD. Characterization of VP7 and VP4 genes of rotavirus strains: 1990-1994 and 2000-2002. Epidemiol Infect. 2009;137:936-42.
36. Santos N, Hoshino Y. Global distribution of rotavirus serotypes/genotypes and its implication for the development and implementation of an effective rotavirus vaccine. Rev Med Virol. 2005;15:29-56.
37. Nelson EA, Bresee JS, Parashar UD, Widdowson MA, Glass RI. Rotavirus epidemiology: the Asian Rotavirus Surveillance Network. Vaccine. 2008;26:3192-6.
38. Iturriza Gomara M, Kang G, Mammen A, Jana AK, Abraham M, Desselberger U, *et al*. Characterization of G10P[11] rotaviruses causing acute gastroenteritis in neonates and infants in Vellore, India. J Clin Microbiol. 2004;42:2541-7.
39. Chandran A, Fitzwater S, Zhen A, Santosham M. Prevention of rotavirus gastroenteritis in infants and children: rotavirus vaccine safety, efficacy, and potential impact of vaccines. Biologics. 2010;4:213-29.
40. National Family Health Survey (NFHS-3), 2005–06: India: Volume I. Mumbai: IIPS; 2007.
41. Parashar UD, Burton A, Lanata C, Boschi-Pinto C, Shibuya K, Steele D, *et al*. Global mortality associated with rotavirus disease among children in 2004. J Infect Dis. 2009;200:S9-S15.
42. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, *et al*. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006;354:11-22.
43. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, *et al*. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus

vaccine. N Engl J Med. 2006;354:23-33.
44. Field EJ, Vally H, Grimwood K, Lambert SB. Pentavalent rotavirus vaccine and prevention of gastroenteritis hospitalizations in Australia. Pediatrics. 2010;126: e506-12.
45. Yen C, Armero Guardado JA, Alberto P, Rodriguez Araujo DS, Mena C, Cuellar E, *et al*. Decline in Rotavirus Hospitalizations and Health Care Visits for Childhood Diarrhea Following Rotavirus Vaccination in El Salvador. Pediatr Infect Dis J. 2010 Nov 2.
46. de Palma O, Cruz L, Ramos H, de Baires A, Villatoro N, Pastor D, *et al*. Effectiveness of rotavirus vaccination against childhood diarrhoea in El Salvador: case-control study. BMJ. 2010;340:c2825.
47. 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.
48. Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R, *et al*. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet. 2007;370:1757-63.
49. Phua KB, Lim FS, Lau YL, Nelson EA, Huang LM, Quak SH, *et al*. Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: randomised, double-blind, controlled study. Vaccine. 2009;27:5936-41.
50. Muhsen K, Chodick G, Goren S, Shalev V, Cohen D. The uptake of rotavirus vaccine and its effectiveness in preventing acute gastroenteritis in the community. Vaccine. 2010;29:91-4.
51. Patel MM, Steele D, Gentsch JR, Wecker J, Glass RI, Parashar UD. Real-world impact of rotavirus vaccination. Pediatr Infect Dis J. 2011;30:S1-5.
52. Curns AT, Steiner CA, Barrett M, Hunter K, Wilson E, Parashar UD. Reduction in acute gastroenteritis hospitalizations among US children after introduction of rotavirus vaccine: analysis of hospital discharge data from 18 US states. J Infect Dis. 2010;201:1617-24.
53. Yen C, Armero Guardado JA, Alberto P, Rodriguez Araujo DS, Mena C, Cuellar E, *et al*. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in EI salvador. Pediatr Infect Dis J. 2011;30:S6-S10.
54. Paulke-Korinek M, Rendi-Wagner P, Kundi M, Kronik R, Kollaritsch H. Universal mass vaccination against rotavirus gastroenteritis: impact on hospitalization rates in austrian children. Pediatr Infect Dis J. 2010;29:319-23.
55. 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 diarrhea in Mexico. N Engl J Med. 2010;362:299-305.
56. 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.
57. Soares-Weiser K, Maclehose H, Ben-Aharon I, Goldberg E, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2010:CD008521.
58. WHO. Rotavirus vaccine and intussusception. Weekly epidemiological record. 2011;86:38-40.
59. Patel NC, Hertel PM, Estes MK, de la Morena M, Petru AM, Noroski LM, *et al*. Vaccine-acquired rotavirus in infants with severe combined immunodeficiency. N Engl J Med. 2010;362:314-9.
60. Bhandari N, Sharma P, Glass RI, Ray P, Greenberg H, Taneja S, *et al*. Safety and immunogenicity of two live attenuated human rotavirus vaccine candidates, 116E and I321, in infants: results of a randomised controlled trial. Vaccine. 2006;24:5817-23.
61. Bhandari N, Sharma P, Taneja S, Kumar T, Rongsen-Chandola T, Appaiahgari MB, *et al*. A dose-escalation safety and immunogenicity study of live attenuated oral rotavirus vaccine 116E in infants: a randomized, double-blind, placebo-controlled trial. J Infect Dis. 2009;200:421-9.
62. Clements-Mann ML, Dudas R, Hoshino Y, Nehring P, Sperber E, Wagner M, *et al*. Safety and immunogenicity of live attenuated quadrivalent human-bovine (UK) reassortant rotavirus vaccine administered with childhood vaccines to infants. Vaccine. 2001;19:4676-84.
63. Patriarca PA, Wright PF, John TJ. Factors affecting the immunogenicity of oral poliovirus vaccine in developing countries: review. Rev Infect Dis. 1991;13:926-39.
64. Tate JE, Patel MM, Steele AD, Gentsch JR, Payne DC, Cortese MM, *et al*. Global impact of rotavirus vaccines. Expert Rev Vaccines. 2010;9:395-407.
65. Moon KB. Differential rotavirus antibody profiles in breast milk specimens from mothers with infants in developed and developing countries. American Society for Virology Conference Vancouver, BC, Canada. 2009 Oct.
66. Goveia MG, DiNubile MJ, Dallas MJ, Heaton PM, Kuter BJ. Efficacy of pentavalent human-bovine (WC3) reassortant rotavirus vaccine based on breastfeeding frequency. Pediatr Infect Dis J. 2008;27:656-8.
67. Esposito DH, Tate JE, Kang G, Parashar UD. Projected impact and cost-effectiveness of a rotavirus vaccination program in India, 2008. Clin Infect Dis. 2011;52:171-7.
68. Rose J, Hawthorn RL, Watts B, Singer ME. Public health impact and cost effectiveness of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in India: model based analysis. BMJ. 2009;339:b3653.
69. Press Release - Bharat Biotech announces the price of Rotavac. Bharat Biotech. June 6, 2011. http://www.bharatbiotech.com/BBIL-GAVI-ROTAVAC-Press%20Release-06June2011-F.pdf.