Special Article

Epidemiology of Rotavirus in India

Vivek Jain,[1†] Umesh D. Parashar[1] Roger I. Glass[1] and Maharaj K. Bhan[2]

[1]Viral Gastroenteritis Section, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia
[2]Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India
†Stanford University School of Medicine, Stanford, California. USA.

Abstract. Rotavirus is the leading cause of childhood diarrhea worldwide, causing an estimated 600,000 deaths each year. To assess the potential benefits of a national rotavirus immunization program in India, we analyzed 40 published studies of rotavirus that were conducted between 1976 and 1997 and included a total of approximately 13,000 Indian pediatric inpatients. Pediatric studies featuring 100 or more patients and lasting at least 12 months in duration and all neonatal studies were analyzed. Rotavirus was detected in a median of 18% of pediatric patients and 28% of neonates surveyed. Fifty percent of all children hospitalized with rotavirus by age 5 were hospitalized by the age of 6 months, 75% by the age of 9 months, and almost 100% by the age of 2 years. Rotavirus was most prevalent (31%) in children between 7 and 12 months of age, followed by children between 1 and 2 years of age (20%), and children <7 months of age (13%). VP7 genotypes G1 and G2 were most commonly isolated although significant heterogeneity of serotypes was observed. P[11], G9 strains were most frequently isolated among neonates. In 1998; approximately 98,000 childhood deaths were caused by rotavirus. These data underscore the urgent need for safe and effective interventions against rotavirus such as vaccines. The significant diversity of rotavirus strains and young age of hospitalization pose unique challenges to the formulation of a rotavirus immunization program in India, but raise the possibility of utilizing a neonatal vaccine to provide effective coverage.
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Severe dehydrating diarrhea is a major cause of childhood morbidity and mortality throughout the developing world.[1] Rotavirus is the leading cause of severe diarrhea in children under five years of age, causing approximately 600,000 deaths each year.[2] Because the incidence of rotavirus infection is similar among children in industrialized and developing countries, improvements in hygiene and access to safe water and food may not significantly reduce the prevalence of rotavirus. Immunization offers one of the most promising and direct routes to reducing the prevalence of rotavirus disease, but significant challenges to instituting national rotavirus immunization programs exist. This review of the epidemiology of rotavirus in India examines several important issues facing by policymakers and others aiming to introduce rotavirus vaccines in India. In order to assess the potential benefits of a national rotavirus immunization program, an updated estimate of the disease burden of rotavirus in India is provided. The age distribution of children with severe rotavirus disease is examined to help establish an appropriate timetable for vaccination. Furthermore, characteristics of neonatal rotavirus disease in India are also examined. Lastly, in order to document the overall level of strain diversity in the environment, studies are reviewed to determine the most common circulating genotypes of rotavirus.

Reprint requests : Prof. M.K. Bhan, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029, India. Fax : 091-11-6862663.
E-mail : mkbhan@medinst.ernet.in

METHODS

Papers were included in this study based on a MEDLINE search of entries dating from 1973 using the keywords "rotavirus" and "India". Additional references were obtained from citations in these papers and through discussions with experts in the field. Studies that focused on patients hospitalized for rotavirus disease were selected and categorized as either pediatric or neonatal studies, based on the age of the population studied. Among papers focused on pediatric inpatients, we limited our analysis to those lasting at least 12 months in duration and featuring at least 100 children. We excluded studies that did not use a recognized diagnostic technique as the basis for rotavirus detection. Because of the limited number of studies on neonatal rotavirus, we did not exclude any neonatal studies based on these criteria.

Studies were then grouped by geographic region as well as by city, and the prevalence of rotavirus infection was analyzed in each group. Using pooled data from a subset of the pediatric inpatient studies that provided this information, we examined the cumulative frequency and median prevalence of rotavirus infection in children of different age groups.

To examine the characteristics of circulating rotaviruses in India, we analyzed studies that assessed the G- and P-genotypes (VP7 and VP4 genotypes) of strains isolated from pediatric or neonatal inpatient, and determined the most commonly isolated strain or strains.

Using data from published studies of childhood diarrhea and statistics compiled by the UNICEF and WHO, in conjunction with the results from our own review of pediatric inpatient studies, we estimated the total burden of rotavirus-associated deaths in India.

RESULTS

Pediatric Inpatient Studies

A total of 30 studies that met the criteria for inclusion were analyzed (Table 1). Geographically, these studies represented in variety of regions within India : 13 were from North Indian states, 6 from eastern states, 3 from western states and 8 from southern states. The studies were conducted between 1976 and 1997 and included a total patient population of 12,164 children. Ten of the studies lasted 12 months; the longest spanned 84 months. All but two of the studies employed an enzyme linked immunosorbent assay (ELISA) as the primary or sole method of detection of rotavirus in the stool, while others used polyacrylamide gel electrophoresis (PAGE), a latex agglutination test or reverse-transcription PCR (RT-PCR) as well. A majority of the studies screened hospitalized children less than 5 years of age, while a small number focused on children under 3. Rotavirus was detected in a median 18% (inter quartile range [IQR], 15-23%) of patients hospitalized for severe diarrhea.

Age of Children Hospitalized Due to Severe Rotavirus Infection

Nine studies that contained detailed information on age were used to compile a cumulative frequency plot of the age distribution of children hospitalized with rotavirus (Fig. 1). Fifty percent of all children hospitalized with rotavirus by five years of age were hospitalized by the age of 6 months, 75% by the age of 9 months, and almost 100% by the age of 12 years.

Elelven studies that provided age-specific rates of rotavirus infection were used to estimate the median prevalence of rotavirus in children of different ages (Fig. 2). Rotavirus was most prevalent (31%) in children between 7 and 12 months of age, followed by children between the ages of 1 to 2 years (20%), and children <7months of age (13%).

Neonatal Studies

We reviewed 6 studies from three geographic regions that examined neonatal rotavirus infections (Table 2). These studies were conducted between 1978 and 1993 and included a total of 878 neonates from 10 hospitals in 4 cities. A majority of the studies investigated neonates less than 2 weeks of age. Most of these studies, as with the pediatric studies, used an ELISA as the primary diagnostic method for the detection of rotavirus. Rotavirus was identified in the stools of a median 28% of neonates.

Rotavirus Genotypes

A total of 7 pediatric and 3 neonatal papers contained

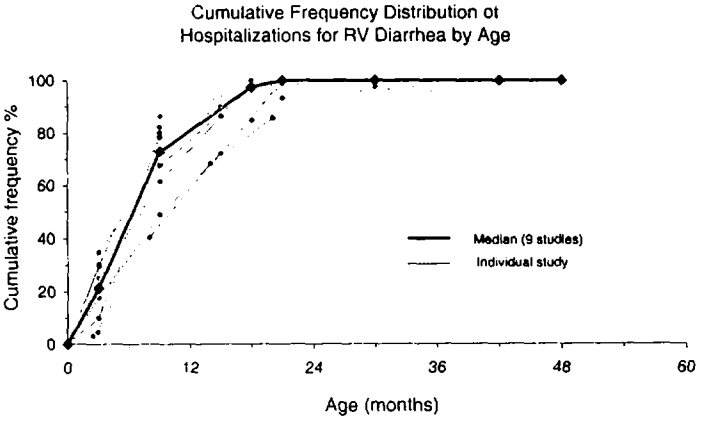

Fig. 1. Cumulative Frequency Distribution of Hospitalizatios for Rotavirus Diarrhea by Age.

Age Group (mo.)	0-6	7-12	13-24	25-36	37-48	49-60	5-12y
Min.	2.7	6.2	6.8	0	0	0	4.1
Max	23.8	57.5	36.7	21.4	12.5	8.6	4.1
Median	13.4	30.8	20	5.1	3.2	0	4.1

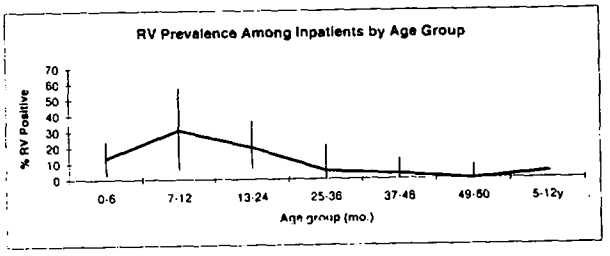

Fig. 2. Rotavirus prevalence among inpatients by age group. Median rate of rotavirus infection in various age groups. Bars represent minimum and maximum of studies surveyed.

detailed data about the genotypes of rotavirus strains isolated from patients in the study (Table 3). The most commonly reported VP7 genotypes were G1 and G2 while the most common VP4 genotype was P[4]. There was great orerall diversity in the rotavirus strains as well as a significant proportion of children with mixed rotavirus infections. Genotype G9, P[11] was the most common strain detected in each of the 3 neonatal studies surveyed.

Estimates of Rotavirus-associated Mortality in India

To estimate the annual mortality from rotavirus in Indian children, we used data from the UNICEF State of the World's Children 2000 report (http://www.unicef.org/sowc00) and WHO. Based on India's 1998 birth cohort of

TABLE 1. Rotavirus Detection Rates from 30 Inpatient Studies of Pediatric Gastroenteritis

Inclusion Criteria:

1. Medline search for "rotavirus" and "India", plus studies referenced within these papers.
2. Sample size >100 children.
3. Study duration 12 mo. or longer.

	Geographic Information		Reference (will be reduced to No.)			Study Characteristics			Patient Characteristics	
Region	India State	India City	Ref.	Authors	Years	Duration	Detection	No. in study	Ages	%RV
North India										
Delhi										
	Delhi	-	3	Bhan *et al.*	1985	12	ELISA	136	<5	24
	Delhi	Rural center (Balabgarh)	3	Bhan *et al.*	1985	12	ELISA	142	<5	31
	Delhi	-	4	Agarwal *et al.*	1985	12	ELISA	256	<5	7
	Delhi	-	5	Agarwal *et al.*	1986-87	12	ELISA	385	<5	21
	Delhi	-	6	Chakravarti *et al.*	1987-88	12	ELISA	288	<5	15
	Delhi	-	7	Chakravarti *et al.*	1987-89	30	ELISA, PAGE	978	<5	18
	Delhi	-	8	Patwari *et al.*	1989-90	12	ELISA	400	<3	6
	Delhi	-	9	Husain *et al.*	1990-91	24	ELISA, PAGE RT-PCR	450	<5	14
	Delhi	-	10	Husain *et al.*	NS	NS	RT-PCR, ELISA, PAGE	450	<5	15
Other										
	Haryana	Chandigarh	11	Broor *et al.*	1982-83	12	ELISA	242	<5	18
	Haryana	Chandigarh	12	Singh *et al.*	1982-85	45	ELISA, PAGE	694	<5	16
	Haryana	Chandigarh	13	Sharma *et al.*	NS	NS	ELISA	176	NS	19
	U.P.	Aligarh	14	Malik *et al.*	1982-83	12	ELISA	216	<5	19
East India	W. Bengal	Kolkata	15	Saha *et al.*	1979-81	24	ELISA	245	<12	22
	W. Bengal	Kolkata	16	Sen *et al.*	1979-81	28	ELISA	356	<12	12
	W. Bengal	Kolkata	17[2]	Sen *et al.*	1982-83	16	ELISA	198	<5	14
	W. Bengal	Kolkata	18	Ghosh & Naik	1985-87	23	PAGE, ELISA	220	NS	21
	W. Bengal	Kolkata	19	Ghosh *et al.*	1986-88	24	ELISA	218	<6 mo.	5
	Manipur	Imphal	20	Krishnan *et al.*	1989-92	28	PAGE, ELISA RT-PCR	535	NS	41

TABLE 1. Contd.....

Region	India State	India City	Ref.	Authors	Years	Duration (mo.)	Detection Assaya	No. in study	Ages (yrs.)	% RV Positive
West India										
	Maharashtra	Pune	21	Singh *et al.*	1982-83	24	ELISA, EM	204	<4	30
	Maharashtra	Mumbai	22	Desai & Banker	1984-86	24	EM, ELISA, Latex	273	<5	23
	Maharashtra	Pune	23	Kelkar, SD	1990-93	28	ELISA	772	NS	26
South India										
	Kerala	Calicut	24	Paniker *et al.*	1976-78	16	EM	365	<5	71
	Karnataka	Bangalore	25	Bhat *et al.*	1983	12	ELISA	379	< 5	16
	Tamil Nadu	Vellore	26	Huilan *et al.*	1983-84	24	EM, ELISA	916	< 3	18
	Tamil Nadu	Vellore	27	Brown *et al.*	1983-85	24	EM, ELISA PAGE	916	<3	18
	Karnataka	Manipal	28	Ballal *et al.*	1987-88	12	Latex	268	< 5	15
	Karnataka	Bangalore	29	Aijaz *et al.*	1988-94	84	PAGE, ELISA	694	NS	22
	Karnataka	Mysore	29	Aijaz *et al.*	1993-94	24	PAGE, ELISA	447	NS	11
	Tamil Nadu	Chennai	30	Ananathan *et al.*	1996-97	21	ELISA	345	<2	26
Total	9 States	13 Cities			23 Years: 1976-1997		12164 Tested		Median % RV : 18 (Range, 5-71)	

Notes :

NS : Not Stated

Detection assays: most papers seemed to obtain the % RV positive figure from ELISA typing, but many performed additional diagnostic tests as well.

1. 12 month duration inferred from description of seasonality data.
2. Data from two hospitals combined : one hospital studied only <5 y kids, the other studied all kids. >5 y data from second hospital excluded.

Table 2. Rotavirus Detection Rates from Clinical Studies of Neonates

Geographic Information			Patient Characteristics			Study Characteristics			Comments
City	Reference	Hospital (s)	No. in study	Rotavirus Infection (%)	Age	Detection Assays	Years	Duration (mo.)	
Pondicherry	31	A	79	22	< 4 w	ELISA	1983	2	
Kolkata	32	A	82	5	2-9 d	ELISA	1982-83	12	
		B	49	2					
Delhi	33	A	204	73	<2 w	ELISA, PAGE	1986-88	24	% RV+ greater with longer hosp. stays overall, 88% <1w, so less age distortion, infants discharged after one day
Delhi	34	A	25	16	<2 w	ELISA, RT-PCR	1992-93	2	
		B	32	16					
		C	23	0					
		D	38	42					
		E	26	19					
		F	25	32					
Delhi	35	A	274	36	<3 d	ELISA, PAGE	1985-86	8	1. only 20% were diarrheal 2. some infants kept longer in the hospitals, these had higher overall rates of RV
Vellore	36	A	21	67	<10 d	counterimmuno-electrophoresis	1978	1	
Totals									
4 Cities		10 Hospitals	878 Neonates	Mean = 20.5 Median = 27.5			1978-1993		

Notes : Neonatal RV infection is very common in India. Nosocomial transmission is a common mode of disease spread.
3/4 cities, and 7/10 hospitals surveyed had significant rates (>15%) of RV infection among neonates.
General trend observed among studies: longer hospital stays resulted in higher neonatal infection rates. Some of the papers break down the rates among neonates who had differing hospital stays.
Cases detailed in these studies were often asymptomatic (not diarrheal).

24,671,000 infants and the 1998 under-5 mortality rate of 105 per 1000, a total of 2,590,000 deaths in children under 5 is estimated to have occurred in 1998. According to World Health Organization estimation approximately 21% of under-5 deaths in India are attributable to severe diarrhea, leading to an estimate of 544,000 diarrhea-associated deaths in children under 5. Based on our finding that rotavirus was detected in a median of 18% of children hospitalized with diarrhea and assuming that this proportion is similar to the percentage of diarrhea-associated deaths attributable to rotavirus, we estimate that in 1998, rotavirus caused approximately 98,000 deaths in India.

DISCUSSION

The findings of this review clearly demonstrate the tremendous morbidity and mortality associated with severe rotavirus disease in Indian children. Rotavirus was detected in a median of 18% of Indian children hospitalized with severe diarrhea. Based on our estimate of close to 100,000 annual deaths caused by rotavirus, 1 in every 250 chidlren born in India will die from rotavirus by the age of 5 years, and India accounts for approximately 17% of the world's estimated rotavirus-associated deaths.

While this assessed disease burden of rotavirus is great, for several reasons it is likely underestimated the true magnitude of the problem. First, it does not include the burden of moderate to severe rotavirus diarrhea that often requires hydration therapy either in the hospital or on outpatient basis. Second, it does not include the adverse consequences of malnutrition and underweight that often result from rotavirus diarrhea in a young child. Finally, the indirect and intangible burdens of the loss of caretaker productivity and the physical and emotional suffering caused by a severe illness in a young child are not assessed. The true magnitude of the burden of rotavirus is probably substantially greater than what we have assessed, underscoring the need for interventions against this pathogen.

Oral rehydration therapy (ORT) is one of the most effective interventions against dehydrating diarrhea and is believed to have been a major cause of the decline in the global burden of this disease over the past two decades.[1] In India, according to the recent National Family Health Survey, only about 30% of children have adequate access to ORT and coverage rates have not improved significantly in recent years. Given that a majority of Indian children live in rural areas where increasing access to ORT is particularly difficult because of economic and social constraints, interventions that can adequately reach this population are particularly needed. Immunization is one such intervention that has been shown to reach a large segment of the rural population in India, and a rotavirus vaccine that reaches the poorest Indian children could offer an effective measure to reduce the burden of rotavirus diarrhea.

Our findings highlight several distinctive features of the epidemiology of rotavirus in India. The age distribution of children hospitalized with rotavirus indicates that severe rotavirus disease occurs at an early age in Indian children and neonatal rotavirus infections, although often asymptomatic, are common. While infants less than one year of age account for only 50% of all rotavirus hospitalizations in the United States,[1] approximately 80% of all rotavirus hospitalizations occur in infants. The diversity of rotavirus strains in India appears to be markedly greater than that observed elsewhere. Compared to the U.S., for example, where the four main genotypes G1-4 account for the large majority of circulating strains a significant proportion of rotavirus infections in India were caused by serotype G9, mixed serotypes, or non-typeable serotypes. Furthermore, significant diversity of strains even within a single community was observed and some studies documented the presence of unusual rotavirus strains that appear to be natural reassortants of human and bovine rotaviruses. While the reasons for this unusual diversity of strains are unknown, it may be related to the year round circulation of high titers of rotavirus and the consequent evoluation of strains through natural reassortment.[4-8]

The distinctive epidemiology of rotavirus in India raises important considerations for planning strategies for rotavirus immunization in India. The young age of children with severe rotavirus disease suggests the need for an accelerated immunization schedule, perhaps featuring vaccination of infants in the earliest months of life. A strategy based on an accelerated immunization raises additional questions, however, about the immunogenicity and efficacy of vaccines in very young infants. Especially given that neonatal infections appear to be common in Inda, care must be taken while testing vaccines to take into account the effect of the presence of pre-existing immunity from a neonatal rotavirus infection. The presence of maternal rotavirus antibody in early infancy might also diminish the immune response to vaccination. Clearly, this area demands a greater focus, especially in light of the fact that immunization in the neonatal period or early infancy may offer an effective and appropriate intervention in this setting. The great diversity of rotavirus strains indicates that to be effective in India, vaccines would have to be formulated to provide protection against a broad range of strains. Towards this end, some have proposed the use of neonatal rotavirus strains as the basis for a rotavirus vaccine in India.

In 1998, the first rotavirus vaccine, a tetravalent preparation containing rotavirus serotypes G1-G4, was licensed for immunization of infants in the United States. Subsequently, in 1999, this vaccine was withdrawn following reports of intussusception among vaccine recipients. Several other rotavirus vaccines, including those based on neonatal rotavirus strains, are currently under development and may be available for use within the next few years.[3,5,7] Some of these candidate vaccines

TABLE 3. Summary of Pediatric and Neonatal Rotavirus G- and P-serotypes in India

City	Ref.	Study Characteristics			G-type							P-type						Predominant Strain
		Years	No. Tested	Detection Method	G1	G2	G3	G4	G9	G-M	G-NT	P[4]	P[6]	P[8]	P[11]	P[M]	P[NT]	
Pediatric Studies																		
Vellore	27	1983-85	46	EM, ELISA, PAGE	15	3	2	12	-	-	14	-	-	-	-	-	-	G1
Bangalore & Mysore	29	1988-94	200	PAGE, ELISA	38	21	65	7	-	-	69	-	-	-	-	-	-	G3
Chennai	30	1996-97	85	ELISA	10	34	5	16	-	5	20		-	-	-	-	-	G2
Pune	23	1990-93	107	ELISA	15	49	1	9	-	33	98	-	-	-	-	-	-	G2
				ELISA														G1, P[8];
Delhi	9	1990-91	51/57[a]	PAGE, RT-PCR	17	13	5	4	-	5	7	14	4	23	-	2	14	G2, P[4]
Multicenter	37	1993	63	RT-PCR HYB	7	14	7	6	15	7	7	13	27	8	1	7	7	G9, P[6]
Multicenter	38	1994-95	93	RT-PCR, HYB	8	24	9	7	21	5	19	23	28	16	2	5	19	G2, P[4]
Neonatal Studies																		
Delhi	BKD	1986-88	21	RT-PCR, HYB	-	1	2	-	18	-	-	1	-	-	20	-	-	G9, P[11]
Delhi	"	1992-93	54	RT-PCR, HYB	-	-	-	-	44	8	2	-	10	-	36	8	-	G9, P[11]
Delhi	34	1992-93	48	ELISA, RT-PCR	-	-	-	-	43	2	3	-	5	-	35	8	-	G9, P[11]

a: 51 tested for G-type; 57 for P-type

are being indigenously developed in India. Clearly, the safety and efficacy of these vaccines will have to be carefully evaluated before they are implemented. In countries like India, where the disease burden of rotavirus is great, the potential risks from any rotavirus vaccine will have to be weighed against the potential benefits from prevention of severe rotavirus disease. In addition, a rotavirus vaccine for India will have to be affordable to the health system and address the distinctive epidemiological features of rotavirus. Appropriate implementation of a safe and effective rotavirus vaccine could lead to a major reduction in the tremendous disease bruden of rotavirus in Indian children.

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