

Epidemiological Profile of Rotaviral Infection in India: Challenges for the 21st Century

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Background. Rotaviruses cause acute viral gastroenteritis worldwide. It has been estimated that, each year, 440,000 deaths that occur among children are attributed to rotavirus infection, mainly in developing countries. In India, the diversity of rotaviruses reported during the 1980s and 1990s emphasizes the need for surveillance of cocirculating strains, to follow the rapid changes in circulation and to detect novel strains.

Methods. We analyzed data from published epidemiological studies, to collate available information on serotyping and genotyping of rotaviruses before the initiation of a national rotavirus surveillance program. The studies included 18 Indian cities and were performed during 1996–2001.

Results. Rotaviruses were detected in 23.4% of patients with diarrhea who presented to the hospital. There were marked geographic differences in virus circulation, with G1 being the single most common G type identified in all parts of India, except for western India. Group B rotaviruses were reported from Kolkata and Pune. Human infections with strains G6, G8, G10, and G9P[19], which may occur as a result of zoonotic transmission of bovine and porcine rotaviruses, were reported from western, southern, and eastern India.

Conclusions. The remarkable diversity of rotaviruses circulating in India highlights the need for uniform, widespread surveillance for rotaviruses before the initiation and during the implementation of immunization programs.

Rotaviruses are the major cause of acute viral gastroenteritis in humans and animals worldwide. A recent review of the burden of rotavirus disease—associated morbidity and mortality estimated that 440,000 deaths occurring among children could be attributed to rotavirus infection and that 82% of all such deaths occurred in developing countries [1]. Because of this disease burden, several vaccines against rotavirus have been developed or are in development, and they are expected to be introduced within the next few years [2]. Before the introduction of a vaccine, it is important to document both the disease burden and strain circulation, to establish a baseline against which the effect of the introduction of a vaccine can be measured. This is of particular impor-

ance in countries, such as India, that are most likely to benefit from the introduction of vaccines and in which mortality is high and the reassortment that results in the development of unusual strains is known to occur.

Rotaviruses are classified into 7 different serogroups (A–G), on the basis of the antigenic specificity of the capsid proteins in the virus, as well as on the basis of the pattern of the electrophoretic mobility of the 11 RNA segments of the viral genome. Of the 7 rotavirus serogroups, only groups A–C are known to infect humans, and group A rotaviruses are viruses that cause severe, life-threatening disease in children worldwide. The inner capsid protein VP6 comprises the greatest mass of the particle, and it bears the subgroup (SG) specificities that allow antigenic classification of group A viruses into SG I, SG II, SG I and II, or neither SG, on the basis of their reactivity with SG-specific monoclonal antibodies (MAbs) 255/60 and 631/9. For group A viruses, further typing schemes were introduced on the basis of antigenic epitopes on the proteins that form the inner capsid (for VP6, SGs I and II) and on proteins of the outer capsid—that is, the glycoprotein VP7 (G

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serotypes)—and the spike protein VP4 (P serotypes). VP7 and VP4 elicit neutralizing antibodies. Neutralizing mouse MABs for typing VP7 are easily derived and have been used extensively in epidemiological surveys [3]. Neutralizing MABs and hyper-immune serum samples have been used to type VP4, but they had problems of sensitivity and cross-reactivity. In recent years, reverse-transcription polymerase chain reaction (RT-PCR) has been used in molecular epidemiological studies. All known G serotypes have been correlated with genotypes; however, more P genotypes than serotypes have been identified, which has led to the development of a serotype/genotype dual nomenclature for P types [4]. The incidence and distribution of group A rotavirus serotypes and genotypes vary between geographical areas during a rotavirus infection season, as well as from one such season to the next. Globally, G1–G4 and P1A[8] and P1B[4] are the most common G and P types that cause disease in humans [1]. Nevertheless, other G types have been found to be prevalent in different areas of the world; of note, G9 strains were reported in India before they spread to other geographic regions [5].

Data on rotavirus disease and strain characterization are available from India, but the studies from which these data were obtained were performed at different times and used a variety of methodologies. Despite these limitations, a review done in 2001 highlighted the significant diversity of viruses in India at the time [5]. Subsequent publications, produced by laboratories in India that have been performing studies of the genotyping and characterization of strains in different geographic and health care locations, have added to the documentation of a marked diversity of the rotavirus strains in circulation, as well as a high prevalence of unusual types and unusual strains not found in developed countries. Studies published during the 5-year period of 1999–2004 are reviewed here to collate recent data on the diversity of circulating genotypes.

METHODS

The present review is based on (1) a search of MEDLINE entries from 1990 to the present, by use of the keywords “rotavirus,” “India,” and “epidemiology,” (2) a search of the citations presented in these MEDLINE articles, and (3) discussions with experts from laboratories at 5 sites in India. Studies that were categorized as neonatal studies, on the basis of the age of the population studied, were excluded from the review. Studies that had been included in a previous review [5] were not individually analyzed, although, for purposes of comparison, the data from the previous review are included in table 1 for comparison. The present review included data and studies that were not analyzed in the previous review. The studies selected for review were performed between 1993 and 2001, and the articles that reported the findings of these studies were published from 2001 to 2004. If a publication more recent than the previous review

[5] was included, then data that had been analyzed in the previous review were excluded, although new data were included. Studies that reported subsets of samples that were subsequently included in other publications were excluded, and the study that included the most complete data set was included, to ensure that the same samples were not included more than once in the present analysis. We selected studies that, by use of either serotyping or RT-PCR, characterized rotavirus strains associated with infections in humans. Studies that did not characterize strains by use of either technique were excluded. Most studies did not analyze samples separately on the basis of the year of isolation of the strains, and, hence, the data were pooled. Data from both inpatient and outpatient studies were included, although not all studies stated whether the patients had been admitted to the hospital. Data from studies in which strains detected in children underwent either genotyping or serotyping were pooled to estimate the relative frequency of the VP7 (G) and VP4 (P) types in different geographic regions of India. The present study was approved by the research committee of the Christian Medical College (Vellore, India).

RESULTS

G- and P-Typing

Data from G- and P-typing are presented in table 1. All studies reviewed here were performed using samples obtained from children who presented to a health care facility with diarrhea. The range of the rates of rotavirus detection in these studies was 16.2%–35.4% (median, 23.4%) [6–14]. The studies included in the analysis used different methods for the identification and typing of strains, which may account for the marked differences in the percentage of nontypeable strains noted at different sites. Sites where serotyping with antibodies was the sole typing technique used reported many cross-reactive strains, as well as a higher proportion of nontypeable strains. On the basis of these data, the increased use of molecular methods for the characterization of rotavirus strains provides not only increased sensitivity for typing but, also, allows accurate and more-complete characterization of strains, as well as identification of putative reassortant strains, which are widespread in India.

Geographic Differences in G Types

The data from different geographic areas were analyzed for G types alone, because P-typing was not performed in all studies. The studies were performed during the 5 years from 1996 to 2001, and the data pertained to samples collected from children in 18 cities in India (figure 1). There were significant differences in the distribution of G types. Overall, G1 strains were the most common strains noted, except in western India. Eastern India had the highest percentage of G1 strains (41% of strains). G2 strains were also seen in all parts of the country, and G2 was the single G type most often identified in northern India (29%

Table 1. Results of G- and P-typing of rotavirus strains identified as the cause of diarrhea in children in India, as compiled from studies published in 1999–2004.

Site in India, year(s)	Reference	No. of strains that underwent G-typing	G type identified							No. of strains that underwent P-typing	P type identified					
			G1	G2	G3	G4	G9	Mixed G types	Nontypeable		P[4]	P[8]	P[6]	P[11]	Mixed P types	Nontypeable
Multiple																
1983–1997	[4] ^a	748	110	158	94	61	36	55	234	213	50	47	59	3	14	40
1996–1998	[5]	287	51	99	2	32	50	31	22	287	63	69	88	10	33	24
2001	[6]	126	62	17	...	6	...	26	15	126	19	61	19	27
1998–2000	[7]	159	61	38	...	20	...	11	29	138	35	51	8	...	26	19
1998–1999	[8]	82	33	7	9	12	7	...	14	82	19	31	2	30
Chennai, 1997–1999	[9]	48	7	33	1	7	...	ND
Hyderabad, 1998–1999	[10]	46	16	8	...	5	17	ND
Kolkata, 1999–2000	[11]	150	49	27	...	30	...	18	16	ND
Pune, 1993–1996	[12]	254	16	47	12	2	...	61	115	ND
Vellore, 1995–1999	[13]	126	50	24	1	30	5	10	25	126	32	38	7	48

NOTE. ND, not done.

^a Review of data published up to the year 2000.

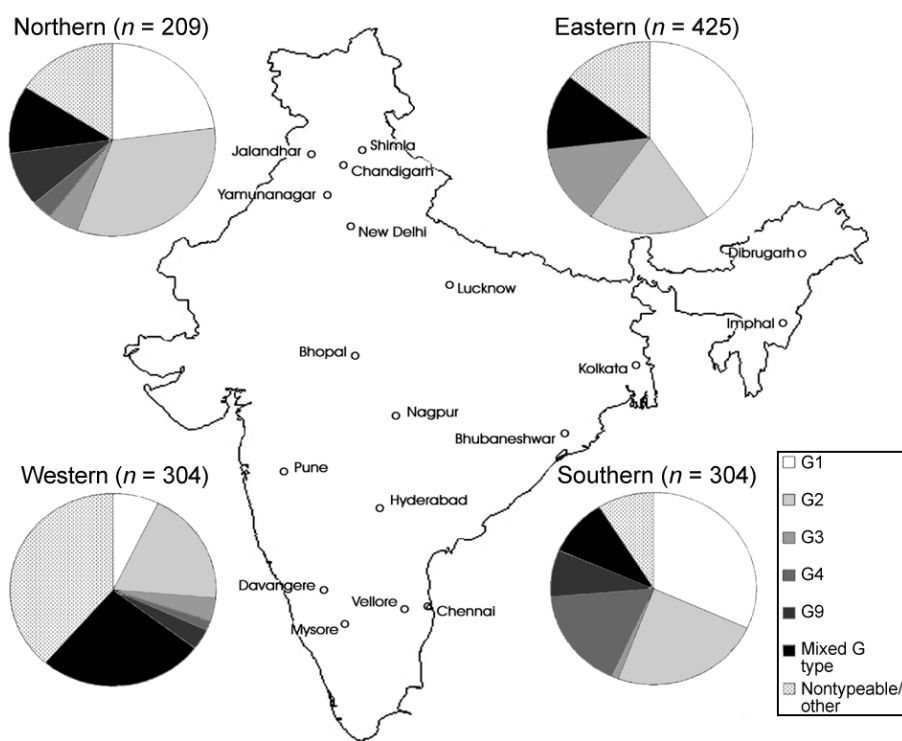


Figure 1. Relative distribution of G types in different geographic regions in northern (New Delhi, Lucknow, Chandigarh, Shimla, Jalandhar, Yamunanagar, and Bhopal), eastern (Kolkata, Dibrugarh, Bhubaneshwar, and Imphal), southern (Mysore, Vellore, Chennai, Hyderabad, and Davangere), and western (Pune and Nagpur) India.

of strains). G3 strains were not reported at all in 4 studies, and, overall, the prevalence of G3 strains noted during the review period (1.9%) was much lower than the prevalence that had been reported in a previous review (12.5%) [5]. G4 strains were also reported from all parts of the country, and, in some studies [8, 13], G4 was the second most common G type identified. A peculiar feature of infections with G9 rotavirus strains was noted in eastern India: the G9 strains were seen exclusively in mixed infections in 2 separate studies [7, 8]. Sequencing of a full-length VP7 gene obtained from a subset of these strains showed that, at the nucleotide level, these strains had 97%–99% homology to G9 strains isolated in Brazil, Malawi, Thailand, and the United States [8].

Group B Rotaviruses

In 1997 and 1998, group B rotaviruses were identified as the cause of sporadic cases of diarrheal disease in adults in Kolkata, India, representing the first description of cases of human group B rotavirus disease outside China [15]. Genetic analysis revealed that the CAL-1 strain was genetically more similar to the Chinese ADRV strain than to animal group B rotaviruses [16]. During 2000 and 2001, group B rotaviruses were detected in Bangladesh, India, in both adults and children with diarrhea. Genetic analysis of the VP7, VP4, VP6, VP2, and nonstructural protein (NSP) 1–5 genes showed high sequence homology to

CAL-1 (>97.6%); this finding suggests that, although CAL-1 and ADRV may have evolved from a common ancestral strain, the Indian and Bangladeshi group B rotavirus strains are a separate lineage [17]. However, the same investigators have sequenced the VP7 and NSP5 genes of 3 bovine group B rotavirus strains and have shown that these strains have $\leq 60\%$ identity to CAL-1 and ADRV and may represent a genotype that is different from the genotype that infects humans in the same geographic region [18]. A recent report from Pune, India, also described 3 strains, obtained from adults with diarrhea in 1993 and 1998, for which RNA migration patterns resembled those of group B rotavirus and for which the nucleotide sequence of gene 8 showed a high level of homology to CAL-1, indicating that human group B rotavirus is likely present in many regions of India [19].

Unusual Group A Rotaviruses that Cause Diarrhea in Children

A number of studies reported identifying unusual strains of rotaviruses that caused infections in humans during 1996–2001. In addition to providing published data on the typing of rotaviruses from epidemiological studies, which are reported below, more-intensive characterization of nontypeable strains has resulted in the identification of G6 strains with partial VP7 nucleotide sequences resembling RF, a bovine rotavirus strain reported from France [20]. Table 2 provides details regarding

Table 2. Potential animal-human reassortant rotavirus strains reported from India, as compiled from data in studies published in 1999–2004.

City in India, reference	Type	% Amino acid homology to strain	Potential origin
Vellore [14]	G8	VP7: 97% to A5	Bovine
Mysore [21]	G8	VP7: 96% to A5	Bovine
Manipur [22]	G9P[19]	VP7: 97.5% to Mc323 and other G9 strains VP4: 98.7% to Mc345 and 95.6% to 4F VP6: 98.7% to 4F, A131, and A253 NSP4: 98.3% to A34	Human Human, porcine Porcine Porcine
Vellore [23]	G10P[11]	VP7: 98% to I321, >90% to B75 and B69 VP4: >90% to I321 and D14367 VP6: >95% to I321 and 22R NSP4: >95% to I321 and CBNU-1	Human, bovine Human, bovine Human, bovine Human, bovine

NOTE. NSP4, nonstructural protein 4.

potential animal-human reassortant strains that were reported from India during the period of the review. The G9P[11] strain and G9 other viruses, which were reported to be potential bovine-human reassortants that had adapted and had spread among humans in the late 1980s and 1990s, appear to continue to circulate in different parts of the country (table 1).

G8 strains. G8 strains that cause diarrhea in children have been reported from Vellore and Mysore, India [14, 19]. The single G8 strain (99-19774) recovered from a child with diarrhea in Vellore was 96% identical, at the nucleotide level, and 97% identical, at the amino acid level, to bovine strain A5 [14, 24]. This strain appeared to be more closely related to strain A5 than to strain MP409 (the G8 strain from Mysore, which was also isolated from a child with diarrhea), to which it had 90% similarity at the nucleotide level and 96% similarity at the amino acid level [21, 24] (table 2).

G9P[19] strains. Molecular characterization of a rotavirus strain that was identified from an outbreak of infantile gastroenteritis and that had a long electropherotype with SG I specificity, revealed that the VP6, VP4, and NSP1-5 genes of strain RMC321 were closely related to those of porcine rotaviruses, whereas the VP7 gene showed 98.5% identity to G9 rotaviruses from India [22] (table 2). In Manipur, India, where the virus strain was obtained, rearing of pigs is a common occupation, and people live in close proximity to their livestock, often in poor sanitary conditions. This and other studies again demonstrate the potential for zoonotic transmission of rotavirus in India, although collection of porcine stool samples during a 4-year period in Manipur did not identify porcine rotavirus [22].

G10 strains. A high incidence of asymptomatic rotavirus infection in neonates has been reported in various studies from India, with infections due to G9P[11] strains reported in northern India and with G10P[11] strains reported in southern India [25–27]. A recent report of infection with G10P[11] strains in India differed from previous reports (1) in the association of these strains with disease in >50% of the neonatal cases analyzed

and, also, (2) in the identification of G10P[11] rotavirus strains that cause sporadic infection in older children and result in disease severe enough to require hospitalization [23]. Therefore, these findings indicate that, in Vellore, at least, G10P[11] strains are not exclusive to neonatal or asymptomatic infections.

Sequence alignment and phylogenetic analysis of a subset of these strains showed that the gene encoding the VP7 of the G10 strains was very closely related to that of the neonatal asymptomatic strain I321 (homology at the nucleotide level, >98%) [23]. The sequences of the G10 strains found in this study were also more closely related to the sequences derived from bovine strains isolated in India than to other G10 human strains previously found in Japan and the United Kingdom [23, 27]. The P[11] sequences derived from the strains reported in this study were highly conserved and were >90% homologous, at the nucleotide level, to strain I321 and to a bovine rotavirus isolate from Japan [23] (table 2).

G12 strains. The VP7 genes of rotaviruses for which the first round of a nested multiplex RT-PCR yielded a product but for which the second round failed to determine type, were sequenced by workers in Kolkata, India. Three rotaviruses identified in children <8 months of age were identified as G12 strains. These rotaviruses had high (i.e., 97%–99%) sequence homology to strains identified in the United States (strain Se585) and Thailand (strain T152) and had 90% sequence homology to strain L26, the G12 prototype [28].

DISCUSSION

The present review highlights the increasing diversity of rotaviruses in India. Rotaviruses diversify and evolve mainly through 2 mechanisms. The first mechanism is the accumulation of point mutations, which generates genetic lineages and leads to the emergence of antibody escape mutants. The second mechanism is genetic shift, in which exchange of genetic material through gene reassortment occurs during dual infection of a

single cell [29]. Also, zoonotic transmission and gene reassortment between human and animal rotaviruses contribute to the generation of diversity among rotaviruses that infect humans [29]. With the range of bovine strains reported from India [30–32], it appears likely that unique animal-human mixing patterns in India contribute to the potential interspecies spread of rotaviruses. Although direct evidence of zoonotic transmission has not been obtained by characterization of human and animal strains that are linked by sequence similarity, time, and place, it appears likely that this form of transmission and the subsequent adaptation of strains do occur.

In articles published during a 5-year period, 4 VP7 types (G6, G8, G10, and G12) and 1 VP4 type (P[19]) have been newly identified as causes of diarrhea in children and adults. Of the G types, G6, G8, and G10 have been reported in the limited data on animal rotaviruses in India [30–32]. Although G15 viruses have been reported in dairy cattle in India, the G15 type has not been found in humans; however, this may be the result of a lack of testing. In general, the use of molecular methods for characterization of rotavirus strains provides increased sensitivity for typing, and the use of RT-PCR for the detection of VP7 and VP4 allows the types of the 2 rotavirus neutralization target proteins to be characterized accurately. This has led to the realization that the diversity of cocirculating rotaviruses is much greater than previously was thought, and it has revealed that reassortment and the introduction of novel rotavirus types into the human population through zoonotic transmission are likely to be relatively common events in India, as is likely with regard to the G8, G10, and P[19] strains (table 2). It is also interesting to note that, other than G5 strains, all G types that have been reported in association with infections in humans are now found in India.

Although the correlates of protection are not yet fully understood, it is thought that protection from infection and severe disease may be type specific. Therefore, monitoring of both the rotavirus types cocirculating at any one time and the emergence of novel rotaviruses is crucial for determining the efficacy of any rotavirus vaccine and for monitoring during the implementation of any vaccination program.

The complex epidemiological profile of rotaviruses in India highlights the need for a unified protocol for surveillance of circulating strains by Indian laboratories, and a national rotavirus surveillance program is being developed with support from the Indian Council of Medical Research and the India Rotavirus Vaccine Project at the Program for Appropriate Technology in Health. With the rapid evolution of rotaviruses by the accumulation of point mutations and the generation of reassortant in multiple infections, both the application of existing methods and the frequent monitoring and updating of genotyping methods will be required on a national scale.

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