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Severity of rotavirus gastroenteritis in Indian children requiring hospitalization

Thuppal V. Sowmyanarayanan[a,1], Sasirekha Ramani[a,1], Rajiv Sarkar[a], Rajesh Arumugam[a], Jubal P. Warier[a], Prabhakar D. Moses[b], Anna Simon[b], Indira Agarwal[b], Anuradha Bose[c], Rashmi Arora[d], Gagandeep Kang[a,*]

[a] Department of Gastrointestinal Sciences, Christian Medical College, Vellore, India
[b] Department of Child Health, Christian Medical College, Vellore, India
[c] Department of Community Health, Christian Medical College, Vellore, India
[d] Indian Council of Medical Research, New Delhi, India

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ABSTRACT

Introduction: The burden of rotavirus gastroenteritis is greatest in India and other developing countries. With the availability of two licensed vaccines and a number of additional vaccines in various stages of development and trial, analysis of detailed clinical information is essential for the development of a uniform method of severity assessment.
Methods: Diarrhoeal stool samples from 1001 children <5 years of age hospitalized with gastroenteritis were screened for rotavirus using a commercial enzyme immunoassay. Positive samples were confirmed by genotyping using hemi nested multiplex RT-PCR. Detailed clinical data was collected for gastroenteritis assessment for 934 children and extraintestinal presentations were analyzed in 470 children. Severity scoring was carried out for all children using the Vesikari score and in a subset by Clark's scoring system.
Results: Rotavirus was detected in 35.4% of samples tested between December 2005 and November 2008. Clark's and Vesikari scores showed moderate correlation but varied greatly in the categorization of severe disease. Using Clark's scoring, only 1.6% were categorized as presenting with severe disease in comparison to 66.1% by the Vesikari score. Association of extraintestinal symptoms with rotavirus gastroenteritis was not documented in this study.
Conclusion: The assessment of disease severity using two common severity scoring systems highlights the difference in the categorization of "severe" disease. This underscores the need for a robust scoring system which is needed for vaccine trial and in post-licensure surveillance, because vaccine efficacy is estimated for protection against severe rotavirus gastroenteritis.

1. Introduction

Group A rotavirus causes over half a million deaths in infants and young children worldwide [1]. The recognition of the worldwide disease burden and the potential for prevention of morbidity and mortality through vaccines led to the establishment of a number of national and regional rotavirus surveillance networks [2]. Since 2002, data on rotavirus surveillance has been generated from at least 196 sites in 59 countries [3]. These studies reiterate the role of rotavirus as the predominant cause of gastroenteritis in children less than 5 years of age.

The majority of deaths due to rotavirus occur in the developing countries of Asia and Africa, with India contributing to nearly one fourth of the global deaths [1]. To establish the need for a rotavirus vaccine as well as provide timely and geographically representative information on the disease burden and prevalence of rotavirus strains, the multi-centre Indian Rotavirus Strain Surveillance Network (IRSN) was established in December 2005. Data collected from over 4000 children hospitalized with diarrhoea over a 2 year period highlighted the immense disease burden as well as the complex epidemiology of rotavirus in India and provided important data to inform public health policies [4].

While epidemiological data on rotavirus strains has thus been strengthened, there is limited detailed clinical description of disease and particularly of severity, reduction of which is a key outcome measure for vaccines. The two most commonly used scoring systems for the assessment of rotavirus severity are the 20-point Vesikari scoring key [5] and the 24-point Clark's scoring system [6], which have been employed in the large scale clinical trials for the evaluation of vaccine efficacy [7,8]. There are however very few head-to-head comparisons of the two scoring systems and their definitions of "severe" disease [9]. More recently, comprehensive case definitions and guidelines for the collection of data during

* Corresponding author. Tel.: +91 416 2282052; fax: +91 416 2232035.
E-mail address: gkang@cmcvellore.ac.in (G. Kang).
[1] TVS and SR contributed equally to this work.

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Table 1
Clark and Vesikari assessment of clinical severity.

Scoring key	Score		
	1	2	3
Clark			
Diarrhoea			
No. of stools/day	2–4	5–7	>7
No. of days	1–4	5–7	>7
Vomiting			
No. of emesis/day	1–3	4–6	>6
No. of days	2	3–5	>5
Rectal temperature			
Degree (C)	38.1–38.2	38.3–38.7	≥38.8
No. of days	1–2	3–4	≥5
Behavioural symptoms			
Description	Irritable/less playful	Lethargy/listless	Seizure
No. of days	1–2	3–4	≥5
Vesikari			
Duration of diarrhoea	1–4	5	6
Max. no. of diarrhoeal stools in 24 h	1–3	4–5	>6
Duration of vomiting	1	2	>3
Max. no. of vomiting episodes in 24 h	1	2–4	≥5
Degree of fever (C)	37.1–38.4	38.5–38.9	≥39
Level of dehydration		5%*	>5%**
Treatment	Rehydration	Hospitalization	

Definition of dehydration as per IMNCI – (*) At least 2 of 3 features – restlessness, sunken eyes or slow return on skin pinch, must be present.
Definition of dehydration as per IMNCI – (**) At least 2 of 4 features – lethargy, sunken eyes, very slow return on skin pinch or poor feeding, must be present.

rotavirus vaccine trials have been published by the Brighton Collaboration Diarrhoea Working Group [10]. While a composite severity scoring scale was not provided by the group, variables that could be useful in describing the severity of diarrhoea were listed making reference to the Vesikari score. Collection of data on other clinical characteristics and history such as seizures and sepsis were also recommended.

The need for uniform case definitions and data collections is valuable in the context of several additional rotavirus vaccines in various stages of clinical trials in India and other developing countries. With the possibility of large amounts of data generated from these clinical studies in the near future, an important comparison group will be cases of hospitalization with rotavirus diarrhoea. This objective of this study is to provide detailed clinical data on hospitalization with rotavirus gastroenteritis in Indian children, including a breakdown of components of Vesikari severity assessment, dehydration as well as other clinical manifestations seen with gastroenteritis in children. Importantly, this study also provides a comparison of the two severity scores in a subset of children that underscores the need for a uniform description of severe disease.

2. Materials and methods

2.1. Study site

The study was carried out at the Christian Medical College (CMC), Vellore, one of the primary sites for the IRSN involved in the collection of clinical data and specimens, testing for rotavirus, training participating investigators as well as a quality control. The study hospital is a 2500 bed tertiary care hospital in southern India with approximately 400 paediatric admissions each month including about 40 cases presenting with diarrhoea requiring hospitalization for rehydration.

2.2. Study design

The study design for the IRSN has been described previously [4]. Briefly, all children under 5 years of age presenting to the hospital with acute gastroenteritis and requiring hospitalization for rehydration for at least 6 h were enrolled in the study after written consent was obtained from the parent or guardian. Standardized protocols were followed for the enrolment and diagnostic evaluation of children in this study. One stool sample was collected within 24–48 h of hospitalization. Demographic data and clinical information on duration and frequency of diarrhoea and vomiting, degree of fever and dehydration were recorded on a standard case report form for all children at admission by a study clinician. Additional clinical data on extraintestinal manifestations and outcomes were recorded where available, by review of the inpatient chart post-discharge. The study was approved by the Institutional Review Board of CMC, Vellore.

2.3. Assessment of severity

The severity of diarrhoea was assessed for all children using the 20-point Vesikari scoring system based on the duration and peak frequency of diarrhoea and vomiting, degree of fever, severity of dehydration and treatment provided [5] using data collected at admission. The level of dehydration was assessed using the Integrated Management of Neonatal and Childhood Illnesses (IMNCI) criteria (Table 1). An episode was considered mild for scores 0–5, moderate for 6–10 and severe for score ≥11. The data were collected for Vesikari scoring throughout the IRSN surveillance, but additional information on duration of fever, dehydration, presence and duration of seizures were collected for assessment of severity using the 24-point Clark scoring scale [6] on all children for the last 9 months. Axillary or oral temperature measurements were used instead of rectal temperatures. According to Clark's scoring key, a episode was considered mild for a score of 0–8, moderate to severe for scores 9–16 and severe for scores 17–24 [9]. (Table 1)

2.4. Laboratory procedures

A 10% faecal suspension was screened for rotavirus using a commercial enzyme immunoassay (EIA) for detection of VP6 antigen (Rota IDEIA, Dako Ltd, Ely, United Kingdom) according to the manufacturer's instructions. Viral RNA was extracted from 30% EIA positive faecal suspensions using *Trizol* reagent (Invitrogen, Paisley, United Kingdom). Complementary DNA (cDNA) was generated

by reverse transcription using 400 U of Moloney murine leukemia virus reverse transcriptase (M-MLV) reverse transcriptase (Invitrogen, Paisley, United Kingdom) in the presence of random primers (hexamers; Pd(N)6, Pharmacia Biotech, Little Chalfont, United Kingdom). The cDNA was used as the template for genotyping in hemi-nested multiplex PCRs for VP7 (G type) and VP4 (P type) genes using published oligonucleotide primers and protocols [11–14]. Samples that were positive by EIA but negative on genotyping were tested by PCR for the VP6 gene to confirm rotavirus positivity.

2.5. Statistical analysis

The data were analyzed using Stata 10.0 (STATA Corp. College Station, TX, USA). Descriptive analysis was performed for all variables. Demographic and clinical characteristics were compared between rotavirus positive and negative children using two-tailed *t*-test or Mann–Whitney '*U*' test for continuous variables depending on the distribution of data. Two categorical variables were compared using chi-square test or Fisher's exact test, as applicable. Pearson's correlation coefficient test was used to calculate the correlation between the Vesikari and Clark severity scores.

3. Results

3.1. Burden of rotavirus gastroenteritis

A total of 1184 children hospitalized with diarrhoea between December 2005 and November 2008 were enrolled in the study. Stool samples were collected from 1001 children. Rotavirus was detected by EIA in 390 samples of which 354 were confirmed by PCR, thus accounting for 35.4% of all diarrhoeal admissions. The mean (SD) duration of hospitalization was 3 (2.1) days. Overall, children with rotavirus gastroenteritis were hospitalized for a shorter duration [Mean (SD) = 2.7 (1.6) days] in comparison to children with non-rotavirus gastroenteritis [Mean (SD) = 3.1 (2.3) days, $p = 0.001$]. Rotavirus infections were seen throughout the year with no distinct seasonality. Of the 354 confirmed cases of rotavirus gastroenteritis, G and P types were identified in 341 (96.3%) and 296 (83.6%) of cases respectively. The most common genotypes were G2P [4] (30.8%), G1P [8] (17.8%) and G9P [8] (15.8%) The distribution of rotavirus genotypes is shown in Supplemental Figure I.

The median age (IQR) of children hospitalized with diarrhoea was 9 (5–15) months. Children with rotavirus gastroenteritis were significantly older [median age (IQR) = 10 (7–15) months] than children without rotavirus diarrhoea [median age (IQR) = 8 (3–15) months, $p < 0.001$]. The distribution of rotavirus positivity rates by age revealed significantly fewer cases of rotavirus diarrhoea in children less than 6 months of age ($p < 0.001$) and greater than 36 months of age ($p = 0.015$). Significantly higher positivity rates were seen in the 7–12 months and 13–18 months age groups ($p < 0.001$ and 0.005 respectively) (Supplemental Figure II).

3.2. Clinical data and severity scores

Clinical information for the Vesikari score could be collected for 934 children, including 335 with rotavirus detected in stool. Table 2 provides a description of rotavirus gastroenteritis using the components of the Vesikari score and a comparison for the same parameters among children with non-rotavirus gastroenteritis. Components used for the assessment of dehydration are also described. Interestingly, although rotavirus infection resulted in significantly more cases of dehydration ($p = 0.012$), comparison of the indicators of dehydration such as decreased urine output, irritability, lethargy, feeding, sunken eyes and skin pinch showed no significant differences between the two groups.

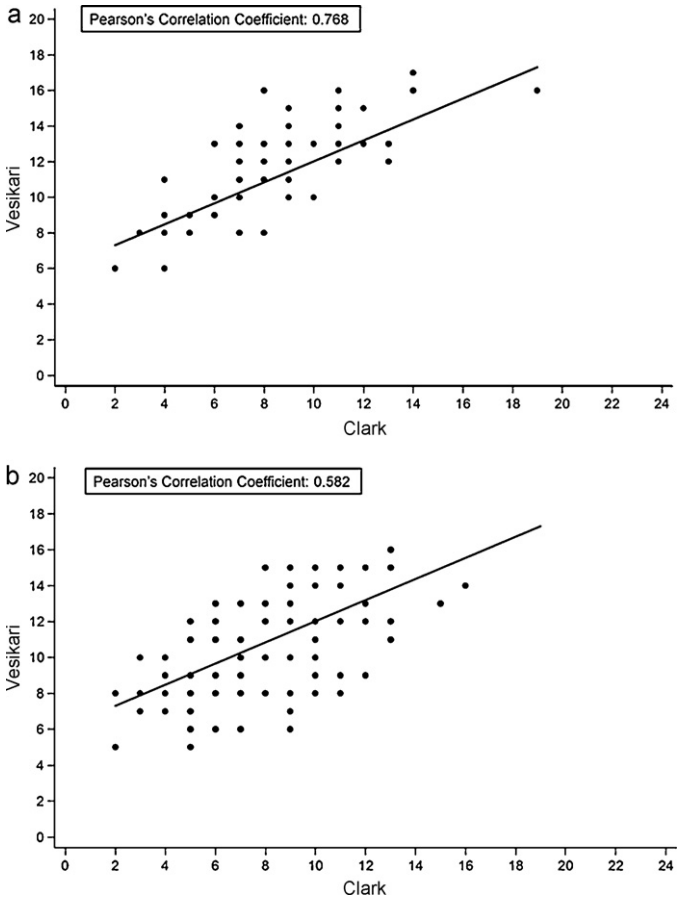

Fig. 1. Correlation of Vesikari and Clark's scores for disease severity for (a) children hospitalized with rotavirus diarrhoea ($n = 59$) and (b) children hospitalized with diarrhoea and no rotavirus detected in stool ($n = 97$).

Children with rotavirus diarrhoea presented with higher Vesikari scores [Mean (SD) = 11.7 (2.7)] than children hospitalized with non-rotaviral gastroenteritis [Mean (SD) Vesikari score = 10.8 (2.9), $p < 0.001$] (Table 2). It was seen that 71% of children hospitalized with rotavirus diarrhoea presented with severe disease and 28% with moderate disease.

In addition to Vesikari scores, severity assessment using the Clark score was carried for a subset of 156 children during the latter part of the surveillance. Seizure is a component of the Clark's scoring system that is not evaluated in the Vesikari scoring key. Overall, moderate correlation was seen between scoring systems (Pearson's correlation co-efficient, $r = 0.652$) with higher correlation for cases with rotavirus gastroenteritis ($r = 0.768$) than non-rotavirus gastroenteritis ($r = 0.582$) (Fig. 1). Despite the correlation, there was great variability in the clinical description of severity by both methods. Using Clark's scoring, 52.6% of children were categorized as presenting with mild disease while only 0.6% had severe illness. By contrast in this same sub population, the Vesikari scores defined only 1.3% of children as presenting with mild disease (Table 3).

Since genotyping and severity data were available in this study, the effect of genotype on severity was explored. It was interesting to note that although the Vesikari scores were not significantly different across genotypes ($p = 0.452$), the severity score for common genotypes G1P [8], G2P [4] and G9P [8] [Mean (SD) = 11.9 (2.3)] was higher than infection with multiple strains, unusual genotypes and untypable strains [Mean (SD) score = 11.2 (3.1), $p = 0.031$].

Table 2
Clinical description of rotavirus gastroenteritis using components of the Vesikari numerical scoring system.

Clinical characteristic	Rotavirus positive	Rotavirus negative	*p*-value
	(*n* = 335)	(*n* = 599)	
Mean Vesikari score (SD)	11.7 (2.7)	10.8 (2.9)	<0.001
Severity of disease using Vesikari score			
Mild	4 (1.2%)	18 (3.0%)	0.08
Moderate	94 (28.1%)	255 (42.6%)	<0.001
Severe	236 (70.7%)	326 (54.4%)	<0.001
Median (IQR) duration of diarrhoea in days	2 (1–3)	2 (1–3)	0.96
1–4	299 (89.3%)	488 (81.5%)	0.002
5	11 (3.3%)	30 (5.0%)	0.22
≥6	25 (7.5%)	80 (13.4%)	0.006
Median frequency (IQR) of diarrhoea in 24 h	8 (5–12)	7 (5–10)	0.485
1–3	39 (11.6%)	43 (7.2%)	0.02
4–5	67 (20.0%)	149 (24.9%)	0.09
≥6	229 (68.4%)	406 (67.8%)	0.85
Presence of vomiting	278 (83.0%)	382 (63.8%)	<0.001
Median (IQR) duration of vomiting in days	2 (1–3)	1 (0–2)	<0.001
1	103 (30.7%)	172 (28.7%)	0.51
2	90 (26.9%)	102 (17.0%)	<0.001
≥3	85 (25.4%)	108 (18.0%)	0.008
Median frequency (IQR) of vomiting in 24 h	4 (2–6)	2 (0–5)	<0.001
1	17 (5.1%)	34 (5.7%)	0.69
2–4	130 (38.8%)	197 (32.9%)	0.07
≥5	130 (38.8%)	151 (25.2%)	<0.001
Temperature >37 °C	156 (46.6%)	333 (55.6%)	0.008
<37	179 (53.4%)	266 (44.4%)	0.008
37.1–38.4	136 (40.6%)	297 (49.6%)	0.008
38.5–38.9	13 (3.9%)	27 (4.5%)	0.65
≥39	7 (2.1%)	9 (1.5%)	0.5
Levels of dehydration			
None	64 (19.1%)	161 (26.9%)	0.019
1–5%	222 (66.3%)	347 (57.9%)	
≥6%	49 (14.6%)	91 (15.2%)	
Indices of dehydration			
Decreased urine output	39 (11.6%)	67 (11.2%)	0.833
Lethargy	185 (55.2%)	352 (58.7%)	0.294
Irritability	130 (38.8%)	217 (36.2%)	0.434
Feeding well	196 (58.5%)	358 (59.8%)	0.707
Sunken eyes	130 (38.8%)	208 (34.7%)	0.213
Normal return of skin pinch	121 (36.1%)	225 (37.6%)	0.9
Slow return of skin pinch	184 (54.9%)	320 (53.4%)	
Very slow return of skin pinch	30 (9.0%)	54 (9.0%)	
IV Rehydration	315 (94%)	551 (92%)	0.249

3.3. Other clinical presentations

The charts of all 1001 children in the study were reviewed for collection of additional clinical information. However, data on other clinical presentations apart from symptoms of gastroenteritis were available only for 470 children. There were no significant differences in rates of detection of extraintestinal manifestations such as upper and lower respiratory tract infections, urinary tract infections and seizures between children with and without rotavirus detected in stool (Table 4). One case of intussusception occurred in a child with non-rotavirus gastroenteritis. A two-month old child presenting with necrotizing enterocolitis stage I tested positive for rotavirus. Laboratory results showed significantly more hypernatremia in children with rotavirus gastroenteritis (5.1%) than non-rotaviral gastroenteritis (1.8%, $p = 0.047$).

4. Discussion

The epidemiology of rotavirus gastroenteritis has been extensively studied over the last several decades. Recent multi-country surveillance studies using standardized and comparable techniques have strengthened epidemiological data and provided region specific targets for vaccine development [15]. However, with the licensure of two rotavirus vaccines and number of others in different stages of development and testing, a clear description of clinical characteristics and definition of severity is of immense importance both for comparison with data from clinical trials and in post licensure surveillance studies. Case definitions such as those provided by the Brighton Collaboration Diarrhoea Working Group are an important step in this direction [10].

Data collected from recent rotavirus surveillance studies in India were used for detailed clinical analysis in this study. All components

Table 3
Comparison of Clark and Vesikari categorization of disease severity for children with and without rotavirus gastroenteritis.

Severity characteristic	Rotavirus gastroenteritis (*n* = 59)		Non-rotavirus gastroenteritis (*n* = 97)	
	Clark score	Vesikari score	Clark score	Vesikari score
Mean severity score (SD)	8.4 (3.2)	11.6 (2.7)	8.1 (3.0)	10.6 (2.7)
Proportion (%) of children with mild disease	31 (52.5%)	0 (0%)	51 (52.6%)	2 (2.1%)
Proportion (%) of children with moderate disease	27 (45.8%)	20 (33.9%)	46 (47.4%)	46 (47.4%)
Proportion (%) of children with severe disease	1 (1.7%)	39 (66.1%)	0 (0%)	49 (50.5%)

Table 4
Extraintestinal presentations and other clinical symptoms among children hospitalized with gastroenteritis.

Additional clinical data	Number of rotavirus positive children ($n = 137$)	Number of rotavirus negative children ($n = 333$)	p-value
	n (%)	n (%)	
Extraintestinal manifestation			
Lower respiratory tract infection	23 (16.8%)	74 (22.2%)	0.186
Upper respiratory tract infection	12 (8.8%)	22 (6.6%)	0.413
Urinary tract infection	10 (7.3%)	20 (6.0%)	0.602
Seizures	10 (7.3%)	32 (9.6%)	0.425
Sepsis	12 (8.8%)	41 (12.3%)	0.268
Viral exanthem	4 (2.9%)	8 (2.4%)	0.747
CNS infection	8 (5.8%)	19 (5.7%)	0.955
Shock	7 (5.1%)	16 (4.8%)	0.889
Metabolic acidosis	3 (2.2%)	14 (4.2%)	0.288
Other clinical data			
Anaemia	14 (10.2%)	21 (6.3%)	0.142
Faulty feeding	35 (25.6%)	63 (18.9%)	0.108
Protein energy malnutrition	16 (11.7%)	38 (11.4%)	0.934
Hypernatremia	7 (5.1%)	6 (1.8%)	0.047
Hypokalemia	2 (1.5%)	15 (4.5%)	0.108
Failure to thrive	3 (2.2%)	13 (3.9%)	0.352
Lactose intolerance	9 (2.5%)	17 (2.6%)	0.935

of the Vesikari scoring key were assessed among 934 children with and without rotavirus gastroenteritis. Given the lack of published data on other presentations, additional clinical findings on seizures, respiratory illness, sepsis, etc. as well as factors that may affect evaluation of diarrhoea such as protein energy malnutrition and lactose intolerance were assessed in a subset of 470 children where data were available from hospital records. The Brighton Working Group suggested about 19 variables for describing diarrhoeal episodes. It was recognized that some parameters such as nausea, tenesmus and cramping may be difficult to determine in very small children. Other features such as visual consistency of stool and presence of blood or mucus were not ascertained in this study.

Comparison of the Clark and Vesikari scores showed moderate correlation between absolute scores, but the two systems greatly differed in their description of mild and severe disease. The two methods did not differ greatly in the assessment of diarrhoea, but varied for vomiting. The Clark system also includes duration of fever and behavioural symptoms, such as lethargy or irritability, which are not included in the Vesikari score. The lack of clinical data on the duration of the behavioural symptoms prevented the assessment of severity using the Clark's scoring key in a larger subset of children. However, in the 156 cases assessed, it was noted that the Clark's scoring system resulted in an under estimate of cases that appeared clinically severe and required intravenous rehydration. Although the disparity in the numerical score appears to be largely due to the range used for each category, a previous study modified the range, without a marked difference in severity assessment [9]. The Vesikari scoring key has been more extensively used in hospital based studies on rotavirus diarrhoea and in clinical trials of vaccines, but a protocol for assessment of severity needs to define where, how and when data will be collected. Active and passive surveillance studies, frequency, timing and method of assessment in active studies, sources of information on duration and treatment will all influence the data from which a score is calculated. For example, accurate temperature measurements are possible in hospital but may not always be possible in all field studies. In a community based birth cohort study in Vellore, the scoring system was modified to a 19-point scale and temperatures were recorded as normal, low-grade fever, and high-grade fever as reported by the caregivers [16]. These data underscore the need for the use of a standardized scoring system to make data comparable between different study populations and is particularly relevant in the context of determining vaccine efficacy against "severe" rotavirus diarrhoea. Ease of use and the lack of inclusion of behavioural characteristics which can be variably reported make the Vesikari score more deployable in the field, but it is important to define protocol driven use to ensure comparability across studies.

Overall, children with rotavirus gastroenteritis had more severe, longer disease associated with vomiting than children with non-rotavirus gastroenteritis [17,18], but required shorter hospitalization [19]. A shorter duration of admission but greater severity at admission and the higher rates of hypernatremia indicate an illness where dehydration is rapid, but recovery with appropriate rehydration is also rapid. The decision to hospitalize the child is based mainly on the requirement for supervised oral or intravenous rehydration as determined by the consulting physician. Though economic considerations can also influence decisions on hospitalizations, the study hospital has a policy of providing free treatment to deserving patients with acute illness, and hence socio-economic status is unlikely to have played a role. Distance from healthcare influences access, but would not result in unnecessary hospitalization.

The high number of children requiring intravenous rehydration for both rotavirus and non-rotavirus gastroenteritis was due to the study design and enrolment criteria where a child was included only if he/she presented with diarrhoea requiring hospitalization for at least 6 h for supervised oral rehydration or any duration of intravenous rehydration. In this setting, most cases presenting with mild dehydration requiring only oral rehydration solution were treated in the emergency rooms and discharged within 6 h. Fever, lethargy and extra-intestinal symptoms associated with rotavirus in some studies were not seen [17,20]. Although antigenemia and viremia have been reported in children with rotavirus gastroenteritis, their clinical consequence remains unclear [21]. Testing for antigenemia was carried out for a subset of this population in another study and the lack of an association with extraintestinal symptoms was reported [22]. Extra-intestinal symptoms in rotavirus disease have been tracked for several years, and relatively high rates of extraintestinal symptoms associated with gastroenteritis have been noted, as in this report. In part, these may be due to a selection bias, since a referral hospital is more likely to receive and admit children with complications. However, the data presented here and additional data do not indicate an association with rotaviral etiology.

An interesting epidemiological observation in this study was the correlation between genotype and severity of disease. While G1P [8], G2P [4] and G9P [8] accounted for 64.4% of strains, a number of unusual strains including uncommon G and P combinations such as

G1P [4], G2P [8] and bovine-human reassortant strains such as G10P [11] were also identified. G3 and G4 rotaviruses were not seen in this population. The common genotypes caused more severe disease than rare or reassortant strains. Higher disease severity has been shown to correspond with greater virus replication by stool viral load [23]. It would be interesting to quantify the rotavirus shed in stools of children infected with these genotypes and determine if viral load is greater in common genotypes, indicating a replicative advantage possibly resulting in more severe disease. However, it is important to note that the hospital based study design is biased towards severe cases and a better assessment of severity and genotype can be obtained through a combination of hospital and community based studies.

In summary, the study provides an in-depth clinical description of rotavirus gastroenteritis and underscores the need for a uniform measure of severity assessment and clinical data collection in vaccine studies.

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Conflict of interest: None to declare

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2011.07.145.

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