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Rotavirus gastroenteritis in Latin America: A hospital-based study in children under 3 years of age

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ABSTRACT

Rotavirus is the leading cause of severe diarrheal disease and dehydration in infants in both developed and developing countries. Vaccines have recently been developed, but detailed epidemiological information, which is needed for decisions about how and where to introduce vaccination, was lacking for many Latin American countries. The primary objective of this study was to measure the incidence and disease burden of rotavirus in young children presenting to Latin American hospitals with gastroenteritis. In addition it allowed to setting up the methodology to further conduct a large phase III trial with a rotavirus vaccine in the region. This was a prospective, multi-center surveillance study of gastroenteritis in children <3 years old presenting to hospitals in 11 Latin American countries. Questionnaires and stool samples were collected from 6521 of 8031 enrolled cases (73% inpatients). Among these, 3122 (49%) were rotavirus positive. Of the rotavirus-positive cases, 12% were <6 months, 48% <1 year and 87% <2 years old; 23% received antibiotics before diagnosis. Median hospital stay was 2 days, 78% received intravenous rehydration. Overall strain distribution was G1 (59%), G2 (1%), G3 (12%), G4 (20%), G9 (6%), G12 (1%), untypable (7%) with large local variations. The direct economic impact on families was considerable: 48% of caregivers lost time from paid work and 69% of families were financially affected by their child's illness. This study confirms the high disease burden of rotavirus gastroenteritis among children in Latin America, which might be reduced by the use of effective vaccines.

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1. Introduction

Rotavirus causes a considerable disease burden worldwide. Each year, rotavirus is estimated to be responsible for over 130 million cases of diarrhea, requiring 25 million clinic visits and 2 million hospitalizations [1] and causing nearly 600,000 deaths in children under 5 years of age [2]. Although the incidence of rotavirus appears similar throughout the world, a disproportionate number of deaths occur in developing countries. Parashar et al. [1,2] have estimated that 82% of rotavirus deaths occur in children in the poorest countries.

The World Health Organization (WHO) has identified rotavirus as 'the leading cause of severe diarrheal disease and dehydration of infants in both developed and developing countries [3].

Detailed, prospective information on the burden of disease caused by rotavirus infection was lacking for many Latin American countries [1]. However, such information is essential to take decisions about whether and how to introduce vaccination [4]. In accordance with WHO recommendations [3], this study was conducted to describe the epidemiology and disease burden of rotavirus in children under 3 years of age in various countries throughout Latin America. In addition to this, it was an opportunity of setting up the field and laboratory methodologies to subsequently conduct a large phase III trial with the human rotavirus vaccine in Latin America.

2. Material and methods

This was a multi-country, multi-center, prospective, hospital-based study which took place in 75 centers spread over 11 Latin American countries: Argentina, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, and Venezuela. Centers were selected by their capacity to perform surveillance for acute gastroenteritis and their potential to further participate in a large safety and efficacy trial of RIX4414 vaccine (*Rotarix*TM, GlaxoSmithKline [GSK] Biologicals, Rixensart, Belgium). The surveillance ran from November 2002 to September 2003, until the start of the trial, and was regarded as an opportunity to establish all logistic and laboratory methodologies required to conduct a subsequent large phase III trial with the RIX4414 vaccine. We aimed to enroll all children less than 3 years of age treated at participating hospitals for an episode of acute gastroenteritis. Acute gastroenteritis was defined as diarrhea (three or more looser stools within a day), with or without vomiting. Severe gastroenteritis was defined as hospitalization (at least over one night) with rehydration therapy (oral or intravenous (IV), equivalent to WHO plan B or C) at a medical facility for gastroenteritis.

After giving informed consent, parents, or guardians were asked or assisted to complete a questionnaire about the current episode of gastroenteritis, such as whether the child received oral or intravenous rehydration or antibiotics, and about the length of hospitalization. Additional treatment details were obtained from medical charts.

A questionnaire was used to collect details about socioeconomic impact for caregivers including: taking time off work; distance traveled to the hospital; cost of reaching the hospital; cost of medication, clinical tests and other medical fees; and the overall financial impact of the illness. The questionnaire was distributed to the parents of 50 consecutive inpatients and 50 consecutive outpatients per country at centers selected to give a representative sample across the study population.

Stool samples were collected for each episode, tested for rotavirus antigen, and, if found positive, genotyped. Initial testing was performed at local centers. Rota-Strip (Coris BioConcept, Gembloux, Belgium) or ELISA (Premier Rotaclone, Medidian Diagnostics

Inc., USA) was used to detect rotavirus antigen. Genotyping was performed using reverse transcriptase polymerase chain reaction (RT-PCR) techniques [5]. Further genotyping on samples that could not be characterized by local centers was performed at GSK Biologicals, Rixensart, Belgium.

3. Results

The surveillance period lasted from November 2002 to September 2003. Study duration at each center varied between 2 and 8 months, depending on when surveillance started (Table 1).

3.1. Subjects and stool samples

A total of 8031 children with acute gastroenteritis were enrolled, of whom 73% (5867) were considered inpatients and 27% (2157) outpatients (hospitalization status was missing in 7 cases). The number of subjects enrolled by country is summarized in Table 1. The male:female ratio was 1.4:1. The median age of the subjects was 1 year. Stool samples were collected from 81% of patients. Sampling frequency varied by country, ranging from 48% in Brazil and 59% in Chile, to almost 100% in all other countries. Of the 6361 stool samples tested for rotavirus, 49% (3122) tested positive. The proportion of rotavirus-positive samples showed seasonal variation, with country-specific values ranging from 4% to 79% of cases each month. Of the rotavirus-positive cases, 12% (379) were under 6 months old, 35% (1107) were between 6 and 11 months old, 40% (1239) were between 12 and 23 months old, and 13% (397) were between 24 and 35 months old. The age distribution varied between countries. In Venezuela, for example, a higher proportion of rotavirus infections occurred in very young children (11% of cases were less than 3 months of age compared with 1.5% or less in other countries in this study). The proportion of children aged less than 7 months was highest in Venezuela and the Dominican Republic (30% and 28%, respectively compared with 6–18% in other countries). In Colombia, children were only enrolled from 6 months of age. Fig. 1 shows the proportion of cases at different ages by country and overall.

3.2. Genotypes

Genotype data were available from 1236 samples. Overall, 59 (5%) had mixed genotypes, with relatively high rates in Mexico (15%) and Nicaragua (21%). A total of 7% of samples were untypable. Table 2 shows strain distribution by country. The most common strain was G1 (59% overall) except in Chile, where G4 predominated, and in Costa Rica and Nicaragua where G3 predominated. G9 was as high as 22% of cases in Brazil and 14% in Mexico. G12 was found occasionally in Brazil, Mexico, and the Dominican Republic. A total of 15 strains (11%) from the Dominican Republic were of non-human origin.

3.3. Treatments and outcomes

Before coming to the hospital, 5% of children (390) received IV rehydration, 46% (3657) received oral rehydration, and 23% (1815) received antibiotics. At the hospital, 78% (6263) received IV rehydration, 63% (5028) received oral rehydration, and 30% (2415) received antibiotics. The proportions receiving these treatments were similar for rotavirus-positive and rotavirus-negative cases. Median duration of hospitalization was 2 days for both rotavirus-positive and negative cases. However, national medians ranged from 0 (in the Dominican Republic) to 4 days (in Brazil). Two fatalities occurred among the 2290 children with RV for whom the outcome was known.

Table 1
Study duration, enrollment and range of monthly percentages of rotavirus-positive stool samples by country.

	Study start	Study end	Study duration (days)	Children enrolled	N (samples tested)	% Rotavirus positive stool samples		
						Overall	Maximum monthly	Minimum monthly
Argentina	March 2003	July 2003	150	639	580	50	55	43
Brazil	March 2003	September 2003	194	1475	680	46	58	38
Chile	January 2003	June 2003	158	886	525	51	60	35
Colombia	May 2003	June 2003	50	55	46	17	24	14
Costa Rica	December 2002	June 2003	190	795	635	53	63	11
Dominican Rep.	January 2003	June 2003	153	400	395	62	80	35
Honduras	January 2003	June 2003	151	405	394	37	52	9
Mexico	January 2003	June 2003	179	1306	1154	59	79	10
Nicaragua	March 2003	June 2003	114	229	219	61	70	51
Panama	January 2003	June 2003	161	1491	1432	41	67	4
Venezuela	November 2002	June 2003	220	350	301	40	78	8
Overall	November 2002	September 2003	315	8031	6361	49	55	27

3.4. Economic impact of rotavirus infection on families

The cost questionnaire was completed by 675 caregivers (96% of whom were the child's parents) looking after children with rotavirus-positive disease. The median distance to bring the child to hospital was 8 km (but ranged from 0.1 to 148 km); 71% of relatives had to pay for this transport and 58% had to pay for transport to visit their child. The median number of trips to the hospital to visit their child was three (ranging from 1 to 24). The most common modes of transport were buses or trains (used for 33% of all journeys), then taxis (28%) or cars (25%).

Nearly half the caregivers (46%) paid for medication, 14% paid for clinical tests, 34% for consultation, and 45% for other fees. The proportion of families paying for each aspect varied considerably by country. Of those completing the questionnaire, 48% (320) had lost time from paid work, with a median of 12 h (range 1–108) lost. Most families (69%) stated that they had been financially affected by their child's illness. Families paid for medical expenses by borrowing in 52% of cases, while 31% said they had to cut other expenses, 29% used savings, 11% asked for donations, and 3% sold assets.

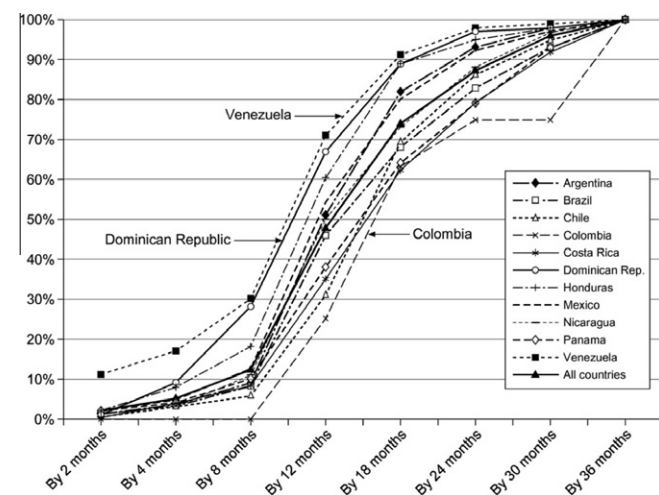


Fig. 1. Cumulative age distribution (%) of rotavirus-positive subjects by country and over all countries. This figure shows the proportion of cases at different ages by country and overall.

4. Discussion

This multi-country, prospective, hospital-based study of 8031 children represents the largest epidemiological study of rotavirus gastroenteritis in Latin America to date. It confirms the considerable disease burden associated with rotavirus infection in children less than 3 years of age.

Rotavirus was identified from almost half the children (49%) who received treatment at a hospital for acute gastroenteritis. This finding is similar to that reported previously [6], where rotavirus was found in 47% of children under 36 months hospitalized with diarrhea during a period of 2 years in Chile, 38% in Venezuela, and 71% in Argentina. In a 5-year study in Venezuela, rotavirus was observed in 43% of inpatient cases [7]. In another 5-year Venezuelan study, rotavirus accounted for 31% of gastroenteritis hospitalizations [8]. A review of 18 studies across Latin America reported a median rate of rotavirus of 31% in both inpatients and outpatients [4].

Although rotavirus infection shows a seasonal pattern, it has been shown to occur all year round [7,9]. Kane et al. [4] noted that 'in most countries, rotavirus was detected throughout the year' and found only two locations in Brazil where rotavirus was not detected for two consecutive months. Velázquez et al. [10] showed a peak in mortality in childhood diarrhea during the fall-winter season in Mexico which coincided with a higher proportion of rotavirus-positive cases. In our study, rotavirus accounted for about 10% of cases of gastroenteritis in the months when it was least prevalent and up to 80% in the high season.

The majority of cases of rotavirus gastroenteritis (87%) occurred in children under 2 years of age. About half of the cases (48%) occurred under 1 year of age, ranging from 31% in Chile to 71% in Venezuela. This matches findings from earlier studies in the region. Kane et al. [4] found that between 40% and 50% of cases occur before the age of 1 year in Argentina, Brazil and Paraguay. Similarly to our findings, one Venezuelan study in Caracas found a high proportion (85%) of patients with rotavirus gastroenteritis presenting to a hospital to be under 1 year of age [7]. A study from Valencia in Venezuela also found that children aged 3–11 months had the highest frequency of rotavirus infection and more serious disease than those aged 2–5 years [8]. In this study, the proportion of children under 12 months was lower in Valencia than Caracas (61% vs. 85%). In some countries, rotavirus infection occurs at a particularly early age, possibly due to factors such as heavier exposition owing to high population density, broad strain diversity, and the year-

Table 2
Rotavirus strain distribution: % of subjects with strains of each type.

	N samples serotyped	G1	G2	G3	G4	G9	G12	Mixed	Untypable
Argentina	95	96	0	0	0	0	0	0	4
Brazil	272	68	1	0.4	2	22	2	2	7
Chile	265	23	1	0	73	0	0	6	9
Colombia	8	88	0	0	0	0	0	0	13
Costa Rica	81	30	0	68	2	0	0	0	0
Dominican Rep.	131	57	2	21	0	0	2	2	19 ^a
Honduras	83	100	0	0	0	0	0	0	0
Mexico	78	79	4	6	14	14	1	15	4
Nicaragua	94	45	3	49	24	0	0	21	4
Panama	100	89	4	7	0	0	0	0	0
Venezuela	29	45	0	14	21	0	0	7	28
Overall	1236	59	1	12	20	6	1	5	7

Note: % across strains can be >100% due to mixed infections.

^a Including 11% of non-human origin.

round occurrence of the disease. In Brazil for example, 35% of all rotavirus infections occur by 6 months of age [11].

Detailed information about the age distribution is crucial for designing a vaccine and planning an effective vaccination program. To be effective for Latin America, a rotavirus vaccine must offer protection before the age of 4 months and last until at least 2 years of age when the period of highest risk for severe disease and mortality has passed. Encouraging data on the efficacy of a new human attenuated rotavirus vaccine have recently been published [9]. As of May 2010, 13 Latin American countries have introduced *Rotarix*TM (GlaxoSmithKline, Rixensart, Belgium), into the national expanded program for immunization. In addition, *RotaTeq*TM (Merck Vaccines, Whitehouse Station, New Jersey, USA) has been integrated into the National Immunization Programs of two countries.

In line with the global distribution of genotypes [10,12,13], and with an earlier study in Mexico [14], G1 was the most common strain overall. However, the emergence of G9 as an important genotype in Brazil and Mexico is significant. This suggestion of an increasing importance of G9 in Latin America matches the finding that the G9 type is emerging in other regions as well [13,15–20].

The proportion of the G2 genotype in our study was low (1%) [21,22]. This strain had a higher prevalence in the past and accounted for outbreaks a decade ago [13,23,24]. Rodriguez et al. [14] found the G2 serotype to represent, on average, 16% among samples collected from 8 Mexican centers between 1994 and 1997. However, a low prevalence of G2 was also found in a recent study in Colombia which found serotypes G1, G3 and G9 representing 57.9%, 21.1% and 15.8% of all typed samples, but G2 comprised only 5.3% (20). Finally, the preponderance of G3 in Nicaragua and Costa Rica, as well as G4 in Chile, suggest the presence of local epidemics. Equally, G4 has also been described in epidemics in Italy and Spain [25–27]. Overall, our findings are suggestive that genotype distribution varies largely according to location, even when data are collected during the same season.

This study also illustrates the substantial economic burden of rotavirus infection. Most cases presenting to the study centers were hospitalized (with a median stay of 2 days) and most required IV rehydration. About one in four children also received antibiotics, which in most cases were not warranted. The current study also examined the direct economic effects on affected families and showed considerable time taken from work and a marked financial impact on families, about half of whom reported borrowing money to pay medical expenses.

The current study had some limitations. Because, in most of the countries, surveillance occurred mainly during the expected rotavirus season, the proportion of cases caused by rotavirus (49%) may be an overestimate that would mainly reflect the disease

burden during the rotavirus season. However, our findings are similar to those of earlier studies [6,7], suggesting that they may provide a reasonably accurate picture. As the study did not run for an entire year, we did not estimate the annual incidence of acute gastroenteritis in our study population. Two epidemiological studies to estimate the incidence of rotavirus-associated hospitalizations have just been concluded in Argentina and the Dominican Republic. Those studies lasted for 1 and 2 years respectively and will therefore provide additional reliable incidence information.

This study exemplifies the considerable disease burden associated with rotavirus infection in Latin America. It confirms the observation that children between 6 months and 2 years of age are most commonly affected. As expected, G1 was the most common serotype responsible for rotavirus infections, although G3, G4 and especially G9 were also found to be important, varying by location. Our findings also indicate that rotavirus infection poses a considerable socio-economic burden for the families affected. Given the prevalence and disease burden of rotavirus infection in Latin America, a safe and effective vaccine could provide important public health benefits.

Trademarks

Rotarix is a trademark of GlaxoSmithKline group of companies.

RotaTeq is a trademark of Merck and Co., Inc. group of companies.

Conflict of interests

All investigators were funded through their institutions by GlaxoSmithKline Biologicals.

Yolanda Cervantes, Ricardo Rüttiman, Eduardo Ortega-Barria, Pilar Rubio and Thomas B. Breuer were employed by GlaxoSmithKline Biologicals at the time of this study.

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