



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.

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