Prospective Study of the Burden of Acute Gastroenteritis and Rotavirus Gastroenteritis in Children Less Than 5 Years of Age, in Padova, Italy

C. Giaquinto, S. Callegaro, B. Andreola, M. Bernuzzi, L. Cantarutti, R. D'Elia, S. Drago, A. De Marchi, P. Falconi, M. Felice, G. Giancola, C. Lista, C. Manni, M. Perin, F. Pisetta, A. Scamarcia, M. P. Sidran, L. Da Dalt

Abstract

Background: Data on the burden of rotavirus gastroenteritis in Europe are needed to help understand the potential impact of introducing new rotavirus vaccines.

Materials and Methods: As part of prospective observational study (Rotavirus gastroenteritis Epidemiology and Viral types in Europe Accounting for Losses in Public Health and Society Study, REVEAL) conducted in 2004–2005 in seven European countries, we studied, the characteristics of acute gastroenteritis and rotavirus gastroenteritis in children less than 5 years in primary care, emergency room and hospital settings (Padova, Italy).

Results: A total of 757 children with acute gastroenteritis were included and enzyme-linked immunoabsorbent assay (ELISA) results were available for 725 cases. The overall estimated annual incidence for rotavirus gastroenteritis was 4.7%. Overall, rotavirus gastroenteritis was estimated to account for 43.6% of acute gastroenteritis cases. Among children with acute gastroenteritis (AGE) aged 6–23 months, 61.2% were rotavirus positive. Rotavirus gastroenteritis (RVGE) was responsible for 68.8% of hospitalizations, 61% of emergency consultations, and 33% of primary care consultations. The most prevalent serotype was G9 (84.4%) followed by G1 (11.8%). The relative risk for rotavirus gastroenteritis of being referred to hospital after an initial consultation in primary care was 3.37 (95% CI: 1.77–6.43) and 3.38 (95% CI: 2.28–5.01) for emergency room referral. Children with rotavirus gastroenteritis generally had more severe disease than children with rotavirus-negative gastroenteritis.

Conclusion: Rotavirus accounts for a significant proportion of acute gastroenteritis cases in children less than 5 years in Italy, many of whom require frequent primary care consultations, or care in emergency room or hospital settings.

Infection 2008; 36: 351–357
DOI 10.1007/s15010-008-7200-6

Introduction

Rotavirus (RV) is the leading cause of severe, acute gastroenteritis (AGE) in young children worldwide [1–3] affecting nearly all children by the age of five. Rotavirus gastroenteritis (RVGE) is a significant cause of death among young children accounting for an estimated 39% of all deaths worldwide due to diarrhea in children less than 5 years old [4]. In industrialized countries, the mortality rate for RVGE is low, but rotavirus is a significant cause of disease and hospitalizations [2]. Every year, it is estimated that RVGE accounts for 231 deaths, > 87,000 hospitalizations and almost 700,000 outpatients' visits in Europe [5].

The direct and indirect costs of RVGE, together with the impact of children's illness on their families, including transmission, stress and loss of work days for parents, contribute to a substantial burden of disease associated with rotavirus [6–11].

Given the prevalence of RVGE and the associated morbidity and mortality, rotavirus is an obvious target for vaccination. Two new vaccines (a pentavalent human–bovine [WC3 strain] reassortant rotavirus vaccine containing G1, G2, G3, G4 and P[8] human serotypes [Rotateq; Merck & Co., distributed in Europe by Sanofi Pasteur MSD] [12] and a live attenuated G1P[8] monovalent human rotavirus vaccine [Rotarix, Glaxo Smith Kline, biologicals, Rixensart] [13]) have been shown to be safe and effective in protecting infants and children against RVGE and have been recently licenced in Europe.

Prevention of RVGE could have important medical, economic and societal consequences also in industrialized countries. The availability of these vaccines requires the development of an immunization strategy that takes into account the incidence by age, the serotypes causing the

C. Giaquinto *(corresponding author)*, **S. Callegaro, B. Andreola, R. D'Elia, M. Perin, L. Da Dalt**
Dept. of Pediatrics, University of Padova, Via Giustiniani 3, 35128, Padova, Italy; Phone: (+39/049) -8213585, Fax: -8753865,
e-mail: carlog@pediatria.unipd.it
M. Bernuzzi, L. Cantarutti, S. Drago, A. De Marchi, P. Falconi, M. Felice, G. Giancola, C. Lista, C. Manni, F. Pisetta, A. Scamarcia, M.P. Sidran
Family Pediatricians - Pedianet Rotavirus Study Group

Received: May 8, 2007 · Revision accepted: January 8, 2008
Published online: July 16, 2008

disease, and the total burden of RVGE disease in each European country.

The REVEAL study (Rotavirus gastroenteritis Epidemiology and Viral types in Europe Accounting for Losses in Public Health and Society Study) was a prospective, multi-center, observational study of AGE in children less than 5 years old in selected areas of seven European countries: Belgium, France, Germany, Italy, Spain, Sweden, and UK. The primary objective was to assess the annual incidences of acute gastroenteritis (AGE) and RVGE in children less than 5 years old in primary care, emergency care, and hospital settings. The secondary objectives of the study were to describe the distribution of rotavirus serotypes associated with RVGE, to describe the clinical impact of RVGE, and to compare the clinical and management characteristics of RVGE with those of all other causes of AGE. In this paper, we describe the results evaluated in Padova Italy.

Methods

Study Design

We performed a prospective, observational study of AGE and RVGE in children less than 5 years old in Padova and the surrounding area.

The study was conducted for a 12-month period and was designed to determine the annual incidences of AGE and RVGE in children less than 5 years old in primary care, emergency room, and hospital settings in this study area.

The study was conducted in accordance with the guidelines for Good Epidemiological Practice [14], and was approved by the Ethics Committees of Azienda Ospedaliera di Padova and ASL 16.

Study Area Selection

In order to compare similar settings in different countries about 300,000 inhabitants were required to live in each REVEAL study area.

The selected area in Italy had 392,827 inhabitants [15] among which 4.1% (16,000) were children less than 5 years of age. All hospitals and emergency rooms that might see children with AGE were included in the study along with a sample of family pediatricians (N = 11) sufficient to ensure the monitoring of a population of at least 5,000 children aged < 5 years.

Inclusion and Exclusion Criteria

All children less than 5 years old who were living in Padova during the study period and who required medical intervention (primary care, emergency room, hospital) for AGE were eligible for inclusion in the study. AGE was defined as an episode within 24 h of at least three loose stools, or at least three watery stools, or forceful vomiting associated with diarrhea, in the 7 days before the medical visit; the episode must have been preceded by a symptom-free period of 14 days. We excluded children who presented only with vomiting since this alone is a very common sign in the first years of life often associated with other, non-gastrointestinal disease. Children were not eligible if they had a previously diagnosed chronic (i.e., celiac disease, Hirschprung, malabsorption) or surgical (i.e., intususseption,, occlusions) gastrointestinal tract disease, immunodeficiency, recent abdominal surgery, cystic fibrosis or food allergy with symptoms compatible with the definition of AGE, or had a nosocomial AGE. Eligible children whose parents did not give written informed consent, whose parents did not speak the native language of the country, or had no access to a telephone were classified as ''not included eligible children''. These children were recorded on a ''screening list'', which contained details of their age group and consultation date, which was used to estimate incidences from observed data.

If a child visited more than one healthcare facility during the AGE episode, the data relating to the highest level of care were included in the study. A child that consulted a primary care physician and also required hospitalization was considered as entering the study in the hospital setting. Children presenting more than once during the study period were considered as separate cases, provided they had been symptom-free for at least 14 days.

Data Collection

Data for each child were collected via a series of questionnaires. At baseline (before performing the enzyme-linked immunoabsorbent assay [ELISA], see below) the pediatrician completed a questionnaire with details of inclusion criteria, environmental factors, healthcare utilization related to the AGE episode before the inclusion visit, medication prescribed, and laboratory tests. Parents also completed a baseline questionnaire to provide to socio-demographic and environmental data.

For hospitalized children, a follow-up questionnaire was completed by the treating physician and parents to provide information on the nature, duration and management of AGE. Parents completed a follow-up questionnaire at the end of the episode, to provide information on the nature and duration of symptoms and additional healthcare utilization.

One stool sample was obtained for rotavirus testing from each child within 14 days of symptoms onset. ELISA was used to identify rotavirus [16]. Children with a positive ELISA result were classified as having RVGE and their stool sample was analyzed using reverse transcriptase polymerase chain reaction (RT-PCR) followed by sequencing for identification of G serotypes [17].

Calculation of Estimated Incidences

The estimated incidences for AGE and RVGE were calculated by extrapolating data from those children included in the study, taking into account the response rates and, for primary care setting, the sampling fraction (the number of children seen by participating primary care physicians divided by the total number of children living in the study area). These estimates were then used as numerators in the calculation of the estimated incidences for AGE and RVGE [18]. In the results section, data are presented as observed (subjects included) and estimated (observed cases extrapolated to sampling fraction and participation rate to the study).

Statistical Analyzes

Discrete data (e.g., gender) were presented in frequency tables, and continuous data (e.g., age and duration of symptoms) were presented with descriptive statistics (frequency, mean, standard deviation, median, and range). All statistical analyzes were performed using SAS® software (SAS Institute, Cary, NC, USA).

Results

Study Populations

In Padova area, one hospital, one emergency room and 11 family pediatricians participated in the study.

Table 1
Observed distribution of age and sex of children with acute gastroenteritis in Padova, Italy.

Age (months)	N	%
< 3	10	1.3
3–5	31	4.1
6–11	130	17.2
12–23	276	36.5
24–35	150	19.8
36–47	98	12.9
48–59	61	8.1
Gender		
Male	441	58.3
Female	316	41.7
Total	757	

In overall, 1,193 children were screened. Of these, 1,076 children (90.1%) were eligible for inclusion in the study and 757 were included as follows: 408 in primary care practice, 266 in emergency rooms and 83 in the hospital. The reasons for non-inclusion were parental consent not obtained (57.7%), inability to speak Italian language (41.7%) and no phone access (0.6%) The demographic characteristics of the studied population are summarized in Table 1.

ELISA Results

Out of a total of 757 children, ELISA results were not available for 32 children; for 29 of them because no sample was taken and for 3 because the test result was not interpretable. Of the 725 available ELISA results, 336 (46.3%) were positive for rotavirus.

Observed and Estimated Percentage of AGE due to Rotavirus

The observed percentage of rotavirus among AGE children varied between the different settings: 32.9% in primary care settings (n = 133), 61.4% in emergency room (n = 148) and 68.8% in the hospital (n = 55) (Table 2). Taking into account the setting specific response rates, sampling fraction for primary care and missing ELISA results, the overall estimated percentage of AGE due to RV was 43.6%.

Respectively, 58.9% and 63.6% of AGE and RVGE occurred children less than 2 years. Few children above 3 years of age were affected.

Estimated Annual Incidences of AGE and RVGE

Assuming that the incidence of AGE is the same for the whole population in the study area (about 16,000 children under 5 years of age), we estimated that a total of 1,724 children would have AGE (16,000 × 10.78/100) and 751 of these (16,000 × 4.7/100) would have RVGE (Table 3). The estimated global cumulative annual incidence of

Table 2
Observed and estimated number of children per setting.

	Hospital		Emergency room		Primary care		Total	
	Observed	Estimated[a]	Observed	Estimated[a]	Observed	Estimated[a]	…	Estimated[a]
Total	83	122	266	494	408	1,108		1,724
ELISA results available	80		241		404			
RV+ (%)	55 (68.8)	84 (68.9)	148 (61.4)	303 (61.3)	133 (32.9)	364 (32.9)		751 (43.6)
RV– (%)	25 (31.3)	38 (31.1)	93 (38.6)	191 (38.7)	271 (67.1)	744 (67.1)		973 (56.4)

RV+: rotavirus-positive samples, RV–: rotavirus-negative samples, ELISA: enzyme-linked immunosorbent assay; [a] estimated values take into account participation rate, sampling fraction, and missing ELISA results. It was assumed that missing ELISA results would have the same proportion of RV-positive samples as those samples for which results were available

Table 3
Estimated incidence (×100 children) of acute gastroenteritis (AGE) and rotavirus-positive AGE (RVGE) by age group and overall in Padova, Italy (2004–2005).

Age group	Hospital		Emergency room		Primary care		Global	
	AGE	RVGE	AGE	RVGE	AGE	RVGE	AGE	RVGE
1–5	0.99	0.31	0.92	0.25	3.69	0.49	5.60	1.05
6–11	0.99	0.62	5.36	3.08	12.07	4.86	18.41	8.56
12–23	1.53	1.28	5.41	3.13	12.72	4.94	19.66	9.34
24–35	0.69	0.41	3.39	2.04	6.56	1.54	10.65	3.99
36–47	0.22	0.19	2.59	1.36	4.20	1.29	7.01	2.84
48–59	0.38	0.13	0.88	0.41	3.22	0.84	4.47	1.38
1–59	0.76	0.53	3.09	1.89	6.93	2.27	10.78	4.69

Table 4
Overall estimated distribution of clinical signs and symptoms of children with rotavirus-positive (RV+) and rotavirus-negative (RV–) acute gastroenteritis.

	RV+		RV–		p
	N	%	N	%	
Symptoms					
Dehydration	258	36.29	104	11.06	<0.0001
Diarrhea	681	98.55	881	97.78	0.2612
Vomiting	642	93.18	556	61.44	<0.0001
Fever	559	81.01	400	44.20	<0.0001
Irritable or less playful	382	59.22	515	71.83	<0.0001
Lethargic or listless	584	90.68	451	62.99	<0.0001
Seizure	17	2.65	16	2.23	0.6157

AGE for this population was 10.78%, ranging from 4.47% to 19.66 % in different age groups. The overall annual incidence for RVGE was 4.69 per 100 children (Table 3). For both AGE and RVGE, the estimated global cumulative annual incidence was highest in the children aged 6–23 months.

Signs and Symptoms

The estimated frequency of symptoms of AGE, such as dehydration, vomiting, lethargy, and fever were generally significantly higher among children with rotavirus-positive AGE than among those with rotavirus-negative AGE (Table 4).

The estimated percentage of children with RVGE who were dehydrated was 36.3% and dehydration was three times more likely in children with RVGE than in those with rotavirus-negative AGE (11.0%).

According to Clark scoring scheme [2] (based on clinical symptoms: diarrhea, vomiting, rectal temperature and behavioral symptoms), 76.3% of RVGE and 43.7% of RV negative AGE were considered as moderate or severe.

Estimated Distribution of Rotavirus by Serotype

The most prevalent serotypes were G1 (11.9%), G2 (2.2%), G3 (0.3%), G4 (0.4%), and G9 (83.6%). Our results do not suggest any association between serotype, age or disease severity (data not shown). The association between RV serotype and severity of RVGE was assessed by evaluating the proportions of infected children who had mild, moderate or severe disease. No evidence of any association with severe RVGE was observed for any serotype, however, the numbers are too small to draw any definitive conclusion.

Estimated Seasonal Distribution of AGE and RVGE Occurrence

AGE occurred most frequently between October and May, with a peak incidence between January and March. The monthly distribution of RVGE showed a peak of rotavirus cases in March 2005, when rotavirus-positive cases represented more than 90% of AGE (Figure 1). Data on the seasonal distribution of specific serotypes shows that G1 appeared towards the end of the epidemic (Feb –May) and later than G9 [19].

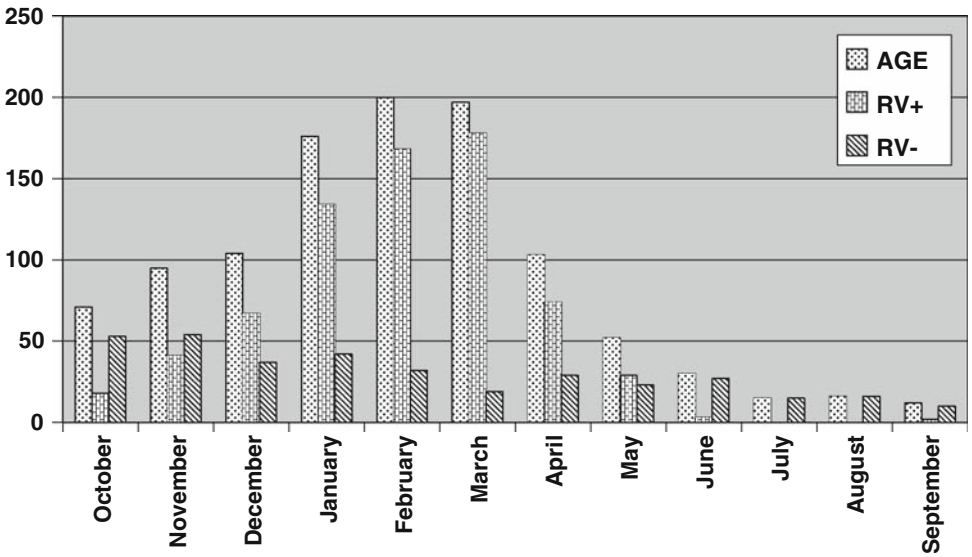

Figure 1. Estimated seasonal distribution of rotavirus-positive (RV+) and rotavirus-negative (RV–) acute gastroenteritis (AGE).

Hospitalization and Referral to Additional Health Care

The estimated percentage of hospitalized children with RVGE was higher than that of children with rotavirus-negative AGE (11.2% vs 3.9%). The average length of stay among children with RVGE was 3.7 ± 1.56 days which was similar to that observed for rotavirus-negative AGE (3.67 ± 1.98 days, p = 0.9).

More than 50% of children had visited at least one healthcare setting before their inclusion visit: 61.8% and 52.7% of hospitalized and emergency RVGE cases, respectively.

Of children included in primary care, 11.1% subsequently required medical care, which was more frequent in RVGE cases (16.8%) than in rotavirus-negative AGE (8.5%).

The relative risk for RVGE of being referred to another clinical setting after an initial consultation in primary care was 3.38 (95% CI: 2.28–5.01) for emergency and 3.37 (95% CI: 1.77–6.43) for hospital referrals.

Treatment and Laboratory Investigations for Children with RVGE or Rotavirus-Negative AGE

In the primary care setting, 72.9% of children with RVGE were prescribed medication, such as anti-diarrheal (probiotic), drugs for functional gastrointestinal disorders, or analgesic agents, compared with 66.8% of children with rotavirus-negative AGE. In the emergency room setting, 50.7% of children with RVGE and 47.3% of children with rotavirus-negative AGE received prescribed medication. Among hospitalized children, 100% of those with RVGE and 76.2% of those with rotavirus-negative AGE were given IV rehydration.

Discussion

This study is a part of REVEAL study, the first large-scale epidemiologic study to investigate RVGE across Europe using a common protocol [18]. Our results suggest that in the Padova area RVGE accounts for more than 40% of AGE cases in children less than 5 years old, being responsible for 68% of hospitalizations, 61% of emergency room and 33% of primary care consultation for AGE The estimated annual incidence for AGE was 10.8 per 100 children, while those for RVGE was 4.7 per 100 children.

In the interpretation and extrapolation of our findings some strengths and limitations should be pointed out. The strengths of the study consist in the inclusion of a high number of children, the prospective data collection over a 12-month period for all children under 5 years seen in three different health care settings and the use of a central laboratory for RV ELISA and RT-PCR testing [18].

Potential limitations of this study are that only children seeking healthcare were included and that the incidence calculations relied on extrapolation of data from an observed population to that of the entire population of children presenting with AGE to the health care structures participating in the study, based on the assumption that the non-included children with AGE/RVGE would have similar characteristics. Although the response rate in Italy was particularly good as compared with other countries participating in the REVEAL study [18], we cannot exclude the possibility that non-participation or non-inclusion may be confounding factors especially for children seen at emergency care level where the workload may have affected the recruitment rate (54%). Moreover, the use of the highest level of care for each child and the exclusion of children with nosocomial RVGE may have led to underestimation of the incidences and, therefore, of the burden of disease.

Despite these potential limitations our data support the major role played by rotavirus in pediatric AGE and altogether a significantly high annual incidence of RVGE in children under 5 years of age. Several previous studies have reported incidence and hospitalization rates for RVGE in Europe. However, direct comparison is difficult or impossible because of differences in the definitions of disease, selected study populations, and diversity in methods used. In Italy, studies in the primary care setting have reported annual AGE incidences of 7.6 per 100 children [20], but without any indication of the RV etiology. Results from hospital based studies showed that rotavirus is the most common cause of severe gastroenteritis in Italian children (25%) [21] and is strongly associated with disease severity [22].

Our finding that the majority of RVGE occurred in children aged 6–23 months is consistent with previous observations of the epidemiology of rotavirus infection [2, 6, 23].This can be explained by the protective effect of maternal antibodies in infants < 6 months old, and the development of natural immunity after repeated infections in children above 2 years old [24, 25]. In Italy there are no data on the incidence of RVGE relative to age, however, in one study, the incidence of AGE was shown to be higher between 6 and 24 months and during the winter period [20], suggesting indirectly that RV can be a major cause of AGE in this population.

Our results show that the greatest burden of AGE was between October and May, and are consistent with previous reports [5, 23, 26]. The high hospitalization rate due to RVGE over a short period may have an important impact on healthcare services, as this coincides with peaks for other winter diseases (e.g., RSV bronchiolitis), thus placing a considerable burden on hospital services [27].

Keeping in mind that rotavirus serotypes change unpredictably every year and that the results of this study are limited to a 12-month study period, it is nevertheless interesting to point out the very high observed prevalence of G9, accounting for more than 80% of RV infections. The increased prevalence of G9 in Italy was already observed by others [28] and seen also in some other European countries (Belgium, France and Sweden)

participating in the REVEAL study [18]. Currently there are few data regarding the relationship between RV serotypes and the age of infected children. Although it has been suggested that G9 is associated with neonatal outbreaks of RVGE [29], studies in France, Hungary and Belgium found no difference in the age distribution of G9 compared with other RV strains [30–32]. In the present study, we found no differences in the distribution of serotypes between age groups. Although two studies in the UK have suggested that infection with G9 is associated with more severe disease [33, 34], in concordance with other studies in Italy [28] and US [35], our study found no correlation between G9 and severity of disease.

Higher hospitalization rates for RVGE than for rotavirus-negative AGE, suggesting a more severe course for RVGE, have been previously described [21, 36]. We did not observe any significant difference of mean duration of hospitalization between RVGE and rotavirus-negative AGE. However, this may be explained by the fact that children are hospitalized based on the degree of dehydration regardless of the etiology of AGE. Once they are admitted for rehydration, the inpatient treatment course is quite standardized.

The prospective design of our study and the very low drop out rate in children who first consulted in primary care setting allowed us to calculate the relative risk of hospital and emergency care referral. Children with RVGE had a significant risk of referral which was over three times higher than that of children with RV negative AGE. This important finding suggests that prevention of RVGE could greatly reduce the hospitalization rate for children with AGE.

Symptoms such as dehydration, vomiting, lethargy, and fever were more frequently observed among children with RVGE than among those with rotavirus-negative AGE. Although rotavirus-negative AGE likely represent a heterogeneous population, since a wide range of infectious agents can cause AGE, our findings are consistent with those from other studies that have shown a greater severity of RVGE compared with rotavirus-negative AGE [37–41].

Padova province is a very rich area in the north-east of Italy and study findings could probably be extrapolated to most of the central and northern regions of Italy where the socio-economic and health care systems are very similar. However, it would be more difficult to extrapolate these results to the southern regions of Italy due to important differences in the healthcare systems and the socio-economic structures. In addition we cannot be certain that the incidence of RVGE and the distribution of serotypes observed in the study region reflect those in other regions, and therefore, it is difficult to extrapolate the results.

Our findings show that RVGE represent a major cause of morbidity in children living in the North East Region of Italy which could be substantially reduced by routine rotavirus vaccination of infants. As RVGE appears to occur more frequently from 6 to 23 months of age vaccination should be recommended to be completed by 6 months of age.

Acknowledgment

Research fundings for the REVEAL study were provided by Sanofi Pasteur MSD.

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