Clinical Consequences of Rotavirus Acute Gastroenteritis in Europe, 2004–2005: The REVEAL Study

Carlo Giaquinto,[1] Pierre Van Damme,[2] Frédéric Huet,[3] Leif Gothefors,[4] Melanie Maxwell,[5] Peter Todd,[6] and Liviana da Dalt,[1] on behalf of the REVEAL Study Group[a]

[1]Department of Pediatrics, University of Padua, Padua, Italy; [2]Faculty of Medicine, Centre for the Evaluation of Vaccination, World Health Organization Collaborating Centre for the Control and Prevention of Viral Hepatitis, University of Antwerp, Antwerp, Belgium; [3]Service de Pédiatrie 1, Hôpital d'Enfants, Centre Hospitalier Universitaire Dijon, Dijon, France; [4]Department of Clinical Sciences/Pediatrics, Umeå University, Umeå, Sweden; [5]Clinical Practice Research Unit, [6]Wirral Hospital National Health Service Trust, Wirral, Merseyside, United Kingdom

Background. The availability of comprehensive, up-to-date epidemiologic data would improve the understanding of the disease burden and clinical consequences of rotavirus gastroenteritis (RVGE) in Europe.

Methods. During the 2004–2005 season, a prospective, multicenter, observational study was conducted in children <5 years of age in primary care, emergency department, and hospital settings in selected areas of Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom. The clinical consequences of acute gastroenteritis (AGE) and RVGE were estimated.

Results. The estimated percentage of children with rotavirus-positive AGE admitted to a hospital was 10.4%–36.0%, compared with 2.1%–23.5% of children with rotavirus-negative AGE. In France, Germany, Italy, Spain, and the United Kingdom, the relative risk of hospitalization was statistically significantly higher for children with rotavirus-positive AGE than for those with rotavirus-negative AGE. Children with rotavirus-positive AGE were more likely to have lethargy, fever, vomiting, and dehydration, and, therefore, more severe disease than were children with rotavirus-negative AGE. Dehydration was up to 5.5 times more likely in children with rotavirus-positive AGE than in those with rotavirus-negative AGE.

Conclusions. Rotavirus-positive AGE is more severe, causes more dehydration, and results in more emergency department consultations and hospitalizations than does rotavirus-negative AGE. Variations in the management of RVGE seen across study areas could be explained by differences in health care systems. Routine rotavirus vaccination of infants could significantly reduce the substantial burden of RVGE and would have major benefits for potential patients, their families, and health care providers.

Diarrhea is one of the most common illnesses of children worldwide [1], and, in developing countries, it is the third most common cause of childhood deaths [2]. Worldwide, rotavirus is the leading cause of acute gastroenteritis (AGE) [3], and it is the most frequent cause of severe diarrhea in children <5 years of age. Rotavirus infections affect virtually all children worldwide by the age of 5 years [4]. Every year, ~600,000 children die of rotavirus disease, mainly in developing countries [5]. In industrialized countries, where there is generally good access to health care, mortality due to rotavirus gastroenteritis (RVGE) is very low. Rotavirus infection is, however, a major reason for hospitalization among children with AGE [6–8], which has a significant impact

Potential conflicts of interest: C.G. has an educational grant from and a consultation agreement with Sanofi Pasteur MSD, GlaxoSmithKline, Abbott, Roche, Tibotec, and Boehringer Ingelheim. P.V.D. has been principal investigator of vaccine trials for Merck, Sanofi Pasteur MSD, and GlaxoSmithKline Biologicals, for which the University of Antwerp receives research grants. L.G. has been principal investigator of vaccine trials for GlaxoSmithKline, Merck, Sanofi Pasteur MSD, Wyeth, and MedImmune. All other authors report no potential conflicts.

Reprints or correspondence: Dr. Carlo Giaquinto, Dipartimento di Pediatria, Via Giustiniani 3, 35128 Padova, Italy (carlog@pediatria.unipd.it).

The Journal of Infectious Diseases 2007; 195:S26–35

0022-1899/2007/19509S1-0004$15.00
DOI: 10.1086/516717

Presented in part: XXIV Annual Meeting of the European Society of Pediatric Infectious Diseases, Basel, Switzerland, 3–5 May 2006 (abstract 36); 7th International Rotavirus Symposium, Lisbon, Portugal, 12–13 June 2006; European Academy of Paediatrics Congress, Barcelona, Spain, 7–10 October 2006.

Financial support: Sanofi Pasteur MSD (unrestricted educational grants to C.G., P.V.D., F.H., M.M., P.T., and L.d.D.). The REVEAL Study is supported by Sanofi Pasteur MSD (study number X03-ROT-510). L.G. was principal investigator of vaccine trials that received financial support from GlaxoSmithKline, Merck, Sanofi Pasteur MSD, Wyeth, and MedImmune. Supplement sponsorship is detailed in the Acknowledgments.

[a] Further details of the REVEAL Study Group are provided after the text.

on utilization of health care resources and costs. The direct and indirect costs of RVGE, together with the impact of children's illness on their families, including disease transmission, stress, and loss of workdays for parents, contribute to a substantial burden of disease associated with rotavirus [9]. The magnitude of this problem is underestimated, because many children with RVGE may not present for medical treatment, and many who do present are not asked to provide a stool specimen for rotavirus testing, especially in primary care [10].

Rotavirus is transmitted primarily by the fecal-oral route [11, 12], although transmission via airborne droplets has also been rarely reported [13, 14]. Rotavirus is highly contagious; only a small infectious dose (<100 virus particles) is required to infect another person. Once a person is infected, high numbers ($>10^{12}$ particles/g) of viral particles are shed in stool [13, 14].

RVGE is characterized by profuse watery diarrhea—as many as 20 episodes of diarrhea or vomiting per day in severe cases [15]—with loss of fluid and electrolytes that can last for 2–7 days, potentially leading to severe or fatal dehydration. The exact pathophysiologic mechanisms of RVGE are unclear, but the disease is thought to result from several processes acting simultaneously rather than from any single process [16, 17].

In view of the current lack of knowledge of the epidemiologic profile of RVGE in Europe, we performed a prospective study in 7 countries. The primary objective of the Rotavirus Gastroenteritis Epidemiology and Viral Types in Europe Accounting for Losses in Public Health and Society (REVEAL) Study was to assess the annual incidence rates for AGE and RVGE among children <5 years of age in 3 different health care settings—hospital, emergency department, and primary care—in a specific study area in each country [8]. The secondary objectives of the study were to describe the distribution of rotavirus serotypes associated with RVGE [18], to evaluate the medical and societal costs of RVGE [9], and, as presented in the current article, to describe the clinical impact of RVGE.

MATERIALS AND METHODS

The REVEAL Study was a prospective, multicenter, observational study of AGE in children <5 years of age, performed over a 12-month period (1 October 2004–30 September 2005) in selected areas of 7 countries: Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom. The study was conducted in accordance with the 2004 revision of the Declaration of Helsinki, the guidelines for Good Epidemiological Practice [19], and local regulatory requirements. The protocol was approved by the local ethics committees.

Full details of the study design and sampling procedures are described elsewhere in this supplement [8]. In brief, a selected region within each country, which included both urban and rural populations, was identified. The study areas were as follows: Antwerp, Belgium; Dijon, France; Rostock, Germany; Padua, Italy; Gandia and Denia (Valencia), Spain; Västerbotten County, Sweden; and the Wirral, United Kingdom. Within each study area, all hospitals and emergency departments and a convenience sample of primary care physicians (general practitioners and/or pediatricians) participated in the study. All children <5 years of age presenting with AGE during the study period were eligible for inclusion. The numbers of children <5 years of age in each area were as follows: 14,193 in Belgium, 13,108 in France, 15,844 in Germany, 16,000 in Italy, 14,856 in Spain, 12,763 in Sweden, and 17,488 in the United Kingdom [8]. Children who had participated in a trial of a rotavirus vaccine or who had a nosocomial AGE were excluded.

AGE was defined as an episode of at least 3 loose stools, 3 watery stools, or forceful vomiting associated with gastroenteritis occurring within a 24-h period during the 7 days before the medical visit; the episode must have been preceded by a symptom-free period of 14 days, in the absence of a previously diagnosed chronic gastrointestinal tract disease with symptoms compatible with the definition of AGE (e.g., celiac disease or Hirschsprung disease). Rotavirus-positive AGE was defined as AGE (corresponding to the clinical definition) with rotavirus detection by ELISA. The serotyping and genotyping methods used are described elsewhere [8, 18].

Data relating to the nature and duration of symptoms were collected via a series of questionnaires completed by the parents and physician, as well as by the nurse responsible for hospitalized children. The physician completed a baseline questionnaire with details of inclusion criteria, environmental factors (e.g., breast-feeding and previous episodes of gastroenteritis in the past 12 months), health care utilization related to the AGE episode before the inclusion visit, medication prescribed, and laboratory investigations requested during the inclusion visit and the results of those investigations for the detection of rotavirus. Parents completed a baseline questionnaire relating to sociodemographic and environmental factors (e.g., education and employment status of parents, number of children and adults in the household, and care of the child during the day). For children who were hospitalized, a follow-up questionnaire was completed by the treating nurse with or without the parents, relating to the nature and duration of symptoms of AGE, laboratory tests, and rehydration therapy (intravenous [iv] fluids and oral rehydration solutions). For all children, the parents completed a follow-up questionnaire at the end of the episode, relating to the nature and duration of symptoms, additional health care utilization for AGE since the inclusion visit (e.g., additional primary care or emergency department visits or hospitalization), and other parameters associated with the cost of RVGE (e.g., medication at home and number of workdays lost by parents).

If a child visited >1 health care setting during the AGE episode, he or she was included in the study at the highest level

of care, in increasing order: primary care, emergency department, hospital. For example, a child who consulted a primary care physician and also required hospitalization was included in the hospital setting. In the German study area, there were no inclusions for the emergency department setting, because all eligible children consulting at emergency departments were referred to a hospital and were therefore included in the hospital setting. Children who satisfied the eligibility criteria but 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 not included in the study.

For each study area, the overall incidence rates for AGE and RVGE were estimated by extrapolating data from the included children to children who were eligible but not included, while adjusting for response rates and sampling fraction [8]. It was assumed that the characteristics and outcomes among children who were eligible but not included were similar to those of children who were included. All statistical analyses were performed using SAS software (version 8.2; SAS Institute). All data were summarized in frequency tables.

RESULTS

Across the 7 study areas, 12 hospitals, 18 emergency departments, and 139 primary care physicians participated in the study [8]. Overall, 8301 children were assessed for eligibility. Of these, 7082 (85.3%) children were eligible for inclusion in the study, of whom 2846 (40.2%) were included. The age category and date of consultation for the remaining 4236 eligible children who were not included were recorded on a screening list, along with their age category and date of consultation. These data were used in the calculation of rotavirus incidence estimates. The most common reasons for noninclusion of the remaining 4236 children were parental consent not obtained (58%–97%) and inability to speak the native language (3%–42%).

The majority of children were <2 years of age, and the male: female ratio was ~55:45 for all areas except Sweden, where slightly more girls than boys were included. The number of participants per setting and country, the estimated incidence by country and age group, and the estimated seasonal distribution of AGE and RVGE occurrence are described elsewhere in this supplement [8].

The overall estimated percentages of children with RVGE among all children with AGE were 44.7% in Belgium, 33.5% in France, 27.8% in Germany, 43.6% in Italy, 31.2% in Spain, 52.0% in Sweden, and 35.9% in the United Kingdom. The percentage of estimated AGE cases due to rotavirus varied between settings. Rotavirus infection accounted for up to 69%, 64%, and 41% of children with AGE in the hospital, emergency department, and primary care settings, respectively, in individual study areas (table 1). In general, RVGE was more frequent among children who were hospitalized or seen in emergency departments than among those seen only in primary care.

Estimated hospitalization rates among children with rotavirus-positive or rotavirus-negative AGE. In all study areas, the estimated percentage of children with rotavirus-positive AGE who were hospitalized was higher than the estimated percentage of children with rotavirus-negative AGE who were hospitalized. These percentages ranged from 10.4% in Germany to 36.0% in Sweden, for rotavirus-positive AGE, and from 2.1% in Germany to 23.5% in Sweden, for rotavirus-negative AGE (figure 1).

Duration of hospitalization for children with rotavirus-positive or rotavirus-negative AGE. The mean duration of hospitalization among children with rotavirus-positive AGE ranged from 2.5 days in Sweden to 5.0 days in Germany. A similar finding was observed for children with rotavirus-negative AGE, for whom the mean duration of hospitalization ranged from 2.4 days in the United Kingdom to 5.2 days in Germany (data not shown).

Referral for additional health care. A substantial percentage of patients visited >1 health care setting (data not shown). Of children who first consulted in the primary care setting, 33%–68% subsequently required medical care in another clinical setting. In primary care settings in all study areas, the percentages of children with rotavirus-positive disease who were referred to either an emergency department (6.1%–45.3%) or a hospital (13.0%–57.1%) were greater than the corresponding percentages of children with rotavirus-negative disease (0%–18.1% and 3.8%–28.1%, respectively) (table 2). The relative risk (RR) of being referred to an emergency department after an initial consultation in primary care was higher for children with rotavirus-positive AGE than for those with rotavirus-negative AGE, and this difference reached statistical significance in France and Italy. The RR for hospitalization after an initial consultation in primary care was also higher for children with rotavirus-positive AGE than for those with rotavirus-negative AGE, and this difference reached statistical significance in France, Germany, Italy, Spain, and the United Kingdom.

Estimated frequency of clinical symptoms among children with rotavirus-positive or rotavirus-negative AGE. In all study areas, the estimated frequency of symptoms of AGE, such as dehydration, vomiting, lethargy, and fever, was generally higher among children with rotavirus-positive AGE than among those with rotavirus-negative AGE.

Across study areas, the estimated percentage of children with rotavirus-positive AGE who were dehydrated ranged from 11.1% to 71.4% (figure 2). In 5 of the 7 study areas, dehydration was 1.8–5.5 times more likely in children with rotavirus-positive AGE than in those with rotavirus-negative AGE; in the remaining 2 countries, there was no increased likelihood of dehydration. Vomiting was also more common in children with

Table 1. Observed and estimated numbers of children in each setting, by study area.

Study area, finding	Hospital		Emergency department		Primary care		Total estimated[a]
	Observed	Estimated[a]	Observed	Estimated[a]	Observed	Estimated[a]	
Belgium (n = 127)							
Total	79	241	5	281	43	550	1072
ELISA results available	67		5		39		
RV positive, no. (%) of samples	39 (58.2)	140 (58.1)	2 (40.0)	112 (39.9)	16 (41.0)	227 (41.3)	479 (44.7)
RV negative, no. (%) of samples	28 (41.8)	101 (41.9)	3 (60.0)	169 (60.1)	23 (59.0)	323 (58.7)	593 (55.3)
France (n = 281)							
Total	63	205	120	770	98	969	1944
ELISA results available	54		111		97		
RV positive, no. (%) of samples	30 (55.6)	114 (55.6)	50 (45.0)	347 (45.1)	19 (19.6)	190 (19.6)	651 (33.5)
RV negative, no. (%) of samples	24 (44.4)	91 (44.4)	61 (55.0)	423 (54.9)	78 (80.4)	779 (80.4)	1293 (66.5)
Germany (n = 499)							
Total	85	121	0[b]	0	414	2544	2665
ELISA results available	81		NA		403		
RV positive, no. (%) of samples	53 (65.4)	80 (66.1)	NA	NA	105 (26.1)	662 (26.0)	742 (27.8)
RV negative, no. (%) of samples	28 (34.6)	41 (33.9)	NA	NA	298 (73.9)	1882 (74.0)	1923 (72.2)
Italy (n = 757)							
Total	83	122	266	494	408	1108	1724
ELISA results available	80		241		404		
RV positive, no. (%) of samples	55 (68.8)	84 (68.9)	148 (61.4)	303 (61.3)	133 (32.9)	364 (32.9)	751 (43.6)
RV negative, no. (%) of samples	25 (31.3)	38 (31.1)	93 (38.6)	191 (38.7)	271 (67.1)	744 (67.1)	973 (56.4)
Spain (n = 801)							
Total	101	181	299	797	401	1277	2255
ELISA results available	98		286		388		
RV positive, no. (%) of samples	52 (53.1)	96 (53.0)	101 (35.3)	282 (35.4)	99 (25.5)	325 (25.5)	703 (31.2)
RV negative, no. (%) of samples	46 (46.9)	85 (47.0)	185 (64.7)	515 (64.6)	289 (74.5)	952 (74.5)	1552 (68.8)
Sweden (n = 221)							
Total	115	159	92	275	14[c]	104[c]	538
ELISA results available	111		85		14		
RV positive, no. (%) of samples	69 (62.2)	98 (61.6)	54 (63.5)	174 (63.3)	1 (7.1)	8 (7.7)	280 (52.0)
RV negative, no. (%) of samples	42 (37.8)	61 (38.4)	31 (36.5)	101 (36.7)	13 (92.9)	96 (92.3)	258 (48.0)
United Kingdom (n = 160)							
Total	68	84	37	55	55	871	1010
ELISA results available	64		37		47		
RV positive, no. (%) of samples	39 (60.9)	51 (60.7)	22 (59.5)	33 (60.0)	15 (31.9)	279 (32.0)	363 (35.9)
RV negative, no. (%) of samples	25 (39.1)	33 (39.3)	15 (40.5)	22 (40.0)	32 (68.1)	592 (68.0)	647 (64.1)

NOTE. Data are no. of children, unless otherwise indicated. NA, not applicable; RV, rotavirus.

[a] Estimated values take into account the participation rate 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.

[b] In the German study area, all eligible children who presented to the emergency department with acute gastroenteritis during the study were referred to the hospital, so there were no inclusions for the emergency department setting.

[c] In the primary care setting in the Swedish study area, parents generally called a nurse advice service located in the same medical center as the primary care physicians. Therefore, on the basis of the nurses' advice, most children with acute gastroenteritis were referred to higher care or treated at home.

rotavirus infection; it was estimated to occur in 76.7%–99.5% of such children, compared with 56.1%–82.9% of children with rotavirus-negative disease, and it was more likely to be the first sign of AGE in children who were rotavirus positive than in those who were rotavirus negative (data not shown). Across study areas, the estimated percentages of the other common symptoms of AGE among children with rotavirus-positive AGE were as follows: diarrhea, 91.0%–99.2%; fever, 58.4%–90.1%; irritability, 59.2%–89.1%; and lethargy, 52.8%–95.0%. Among children with rotavirus-negative AGE, the corresponding estimated percentages were as follows: dehydration, 3.2%–35.7%; diarrhea, 83.2%–99.2%; fever, 38.2%–60.7%; irritability, 71.8%–91.5%; and lethargy, 41.9%–82.4%.

Treatment and laboratory investigations for children with rotavirus-positive or rotavirus-negative AGE. In the primary care setting across 6 of the 7 study areas, 36.8%–61.5% of

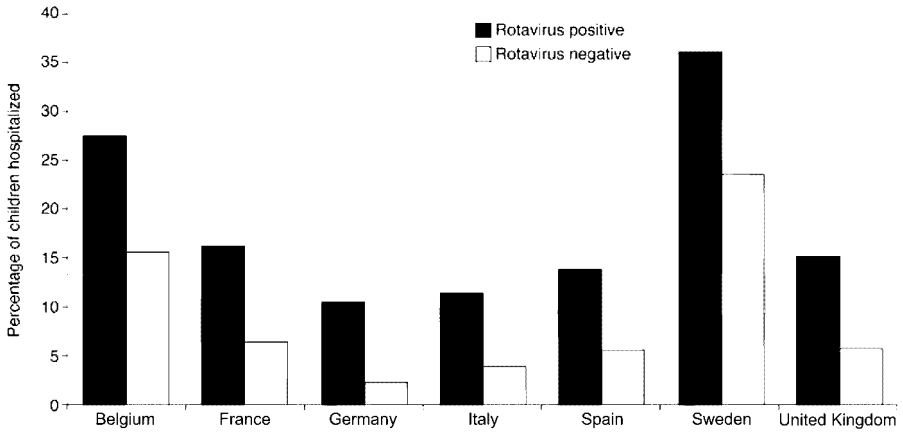

Figure 1. Estimated percentages of children with rotavirus-positive acute gastroenteritis (AGE) *(black bars)* or rotavirus-negative AGE *(white bars)* who were hospitalized, by study area.

children with rotavirus-positive AGE were prescribed medication, such as antidiarrheal, anti-infective, or analgesic agents, compared with 26.1%–79.5% of children with rotavirus-negative AGE. In Sweden, only 1 child had confirmed rotavirus-positive AGE, so Sweden was excluded from this analysis. In the emergency department setting in France, Italy, Spain, and the United Kingdom, up to 64.0% of children with rotavirus-positive AGE and up to 55.7% of children with rotavirus-negative AGE received prescribed medication. In Sweden, the majority of the children received either no medication or over-the-counter medication (80% and 90% of children with rotavirus-positive and rotavirus-negative AGE, respectively). In Germany, no children were included in the emergency department setting, and, in Belgium, only 5 children were included. Among hospitalized children, 21.2%–69.2% of those with rotavirus-positive AGE and 12.5%–90.9% of those with rotavirus-negative AGE were given prescribed medication exclusively. Up to 57.9% of children with rotavirus-positive AGE seen in primary care received both prescribed and over-the-counter medication; in emergency department and hospital settings, the percentages were 26.0% and 28.9%, respectively. Few patients in any health care setting received only over-the-counter medication.

There was considerable variation in the percentage of children hospitalized with AGE who received iv rehydration therapy and/or oral rehydration solutions. In the Italian study area, for example, 91.5% of children with rotavirus-positive AGE and 71.4% of children with rotavirus-negative AGE received iv fluids, whereas, in the United Kingdom, children received either oral rehydration solutions or both oral and iv rehydration therapy; none received only iv rehydration therapy. A minority of children in Belgium, France, Italy, Spain, and Sweden received no rehydration therapy (data not shown). Across the study areas, substantial variation occurred in the percentage of children who had laboratory investigations performed, such as stool or blood sample analysis, or ultrasound examination performed during the initial evaluation in the hospital setting. Among children with rotavirus-positive AGE, 6.5%–94.3% had laboratory investigations performed, whereas 24.1%–96.4% of children with rotavirus-negative AGE had laboratory investigations performed. The percentages were lower in the emergency department and primary care settings, with 0%–61.5% and 0%–21.0%, respectively, of children with rotavirus-positive AGE and 11.5%–66.7% and 6.4%–30.8%, respectively, of children with rotavirus-negative AGE having laboratory investigations performed.

DISCUSSION

The REVEAL Study is, to our knowledge, the first large-scale prospective epidemiologic study of pediatric RVGE in Europe in 3 health care settings: hospital, emergency department, and primary care. The results from the REVEAL Study show that, in all 7 study areas, rotavirus is responsible for a high percentage of AGE among children <5 years of age and that RVGE is more frequent among children 6–23 months of age than among those in other age groups [8]. The REVEAL Study data presented in this article show that rotavirus-positive AGE is more severe than rotavirus-negative AGE. Symptoms such as dehydration, vomiting, lethargy, and fever were more frequently observed among children with rotavirus-positive AGE than among those with rotavirus-negative AGE. Among children who first consulted in primary care, the greater severity of rotavirus-positive AGE was also reflected by the higher risk of emergency department or hospital admission for children with rotavirus-positive AGE than for those with rotavirus-negative AGE. In addition, in all areas studied, rotavirus infection was the underlying cause of illness in the majority of children hospitalized with AGE.

A major strength of the REVEAL Study is that >2800 children

Table 2. Observed percentages of children with rotavirus (RV)–positive or RV-negative acute gastroenteritis (AGE) first seen in the primary care setting who were referred to an emergency department or hospital.

Study area	First seen in primary care, no.	Emergency department		Hospital	
		Referrals, no. (%)	RR (95% CI)	Referrals, no. (%)	RR (95% CI)
Belgium					
Total	72				
RV positive	33	2 (6.1)	NA[a]	15 (45.5)	1.62 (0.83–3.15)
RV negative	32	0 (0)	NA	9 (28.1)	1.00
ELISA result not available[b]	7				
France					
Total	179				
RV positive	64	29 (45.3)	2.80 (1.68–4.67)	16 (25.0)	2.63 (1.27–5.43)
RV negative	105	17 (16.2)	1.00	10 (9.5)	1.00
ELISA result not available[b]	10				
Germany					
Total	452				
RV positive	121	0[c] (0[c])	NA	16 (13.2)	2.21 (1.17–4.15)
RV negative	317	0[c] (0[c])	NA	19 (6.0)	1.00
ELISA result not available[b]	14				
Italy					
Total	568				
RV positive	239	75 (31.4)	3.38 (2.28–5.01)	31 (13.0)	3.37 (1.77–6.43)
RV negative	312	29 (9.3)	1.00	12 (3.9)	1.00
ELISA result not available[b]	17				
Spain					
Total	546				
RV positive	159	38 (23.9)	1.32 (0.93–1.88)	22 (13.8)	3.66 (1.92–6.96)
RV negative	370	67 (18.1)	1.00	14 (3.8)	1.00
ELISA result not available[b]	17				
Sweden					
Total	37				
RV positive	14	5 (35.7)	2.62 (0.74–9.28)	8 (57.1)	2.10 (0.92–4.75)
RV negative	22	3 (13.6)	1.00	6 (27.3)	1.00
ELISA result not available[b]	1				
United Kingdom					
Total	106				
RV positive	42	8 (19.1)	1.41 (0.56–3.58)	19 (45.2)	1.81 (1.02–3.22)
RV negative	52	7 (13.5)	1.00	13 (25.0)	1.00
ELISA result not available[b]	12				

NOTE. The reference group for RR calculations is RV-negative patients, for whom risk is equal to 1.0. CI, confidence interval; NA, not applicable; RR, relative risk.

[a] RR calculation was not possible, because there were no referrals in the RV-negative group.

[b] ELISA results were not available, either because there were insufficient samples or the test results were not interpretable.

[c] In the German study area, all eligible children who presented to the emergency department with AGE during the study were referred to the hospital, so there were no inclusions for the emergency department setting.

were included from hospital, emergency department, and primary care settings in selected study areas in 7 countries. Additionally, the same protocol was used in all study areas, and the study covered an entire season of RVGE. Furthermore, a central laboratory performed the rotavirus ELISAs. A potential limitation of this study, however, is that the incidence rate calculations relied on extrapolation of data from an observed population to the whole population of each study area, on the basis of the assumption that the nonincluded children with AGE/RVGE would have similar characteristics (see [8]). Other potential limitations, which may result in underestimation of the incidence of RVGE, were that only children seeking health care could be included in the study and that only samples that were found to be positive by ELISA were analyzed using reverse-transcription polymerase chain reaction, a more sensitive assay than ELISA [20, 21]. In this study, we did not look for other

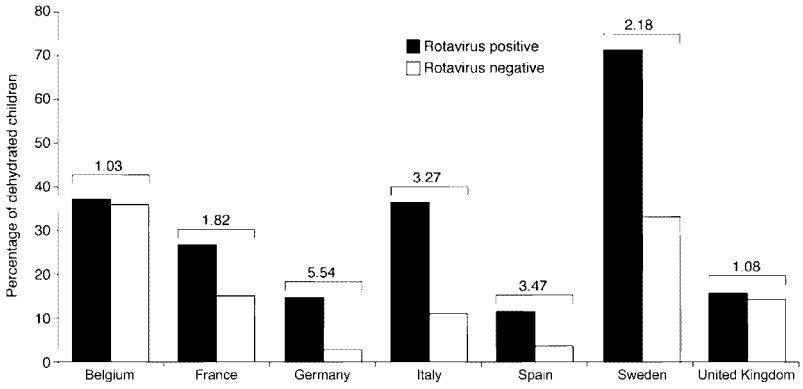

Figure 2. Estimated percentages of children with dehydration among those with rotavirus-positive acute gastroenteritis (AGE) *(black bars)* or rotavirus-negative AGE *(white bars),* by study area. The prevalence ratio for dehydration, calculated as the estimated percentage of children with dehydration among those with rotavirus-positive AGE divided by the percentage of children with dehydration among those with rotavirus-negative AGE, is indicated for each study area above the bars.

possible pathogens that could have been responsible for AGE, and it is important to remember that, because there is a wide variety of infectious agents that could cause rotavirus-negative AGE, this group is likely to encompass a heterogeneous population, particularly in comparison with the rotavirus-positive AGE population. Another potential limitation is that not all primary care physicians participating in the study had computerized records to provide reliable data on the number of children <5 years of age in the study area (the denominator). In practices using paper records, therefore, denominators were calculated from the list of patients attending the physician's office during the study period [8], but this denominator might not include all children <5 years of age and so could have led to overestimation of the rates of AGE and RVGE in the primary care setting.

Despite the potential limitations, our findings are consistent with those from other studies that have shown a greater severity of rotavirus-positive AGE compared with rotavirus-negative AGE, with a higher frequency of dehydration, vomiting, and fever [22–25]. However, it is not possible to diagnose rotavirus infection on the basis of the clinical symptoms alone, because these are neither specific nor distinguishable from AGE due to other common causes [26]. From a clinical perspective, this is not a major concern, because there are no specific treatments available for rotavirus infection, and physicians cannot reliably predict whether any given child will develop severe disease [27].

Some investigators have noted an association between a higher hospitalization rate associated with rotavirus-positive AGE, compared with rotavirus-negative AGE [28, 29], suggesting a more severe course for rotavirus-positive AGE. This has been confirmed by our study, in which the estimated hospitalization rates were higher for children with rotavirus-positive AGE in all study areas, ranging from 10.4% (Germany) to 36% (Sweden), compared with 2.1% (Germany) to 23.5% (Sweden) for children with rotavirus-negative AGE. This is consistent with the observation that rotavirus-positive AGE is >3 times more likely to result in hospitalization than is gastroenteritis from other causes [28].

Variability in hospitalization and treatment rates found in different study areas more likely reflects different models of care for children with AGE than differences in strain or serotype virulence or in host population susceptibility. In Sweden, for example, most children are cared for at home or, if dehydrated, in a hospital. In Italy, however, children with AGE and mild dehydration often receive care, including oral rehydration solutions, at home, provided by visiting primary care pediatricians; only patients with more severe disease are referred to a hospital. This is reflected by the infrequent use of oral rehydration solutions and the frequent use of iv rehydration therapy in hospitalized children in Italy, compared with other countries. The mean duration of hospitalization that we observed was similar for children with rotavirus-positive AGE and those with rotavirus-negative AGE in our study. This may be explained by the fact that children are usually hospitalized when they are dehydrated or at risk of dehydration, regardless of the etiology of AGE.

The criteria for assessing dehydration in the study were the same in all countries. We did not provide any specific training, because we wanted the study to be as pragmatic as possible. We observed wide variation in the estimated percentage of rotavirus-positive children who were dehydrated (11%–71.4%), but the data collected do not enable us to explain this variation. For example, in Spain, it was estimated that 11.1% of children with RVGE were dehydrated, whereas, in hospitals, 88.9% of the children with RVGE were given iv rehydration therapy. However, in Belgium and Sweden, where the estimated percentages of rotavirus-positive children who were dehydrated were the highest (36.8% and 71.4%, respectively), the majority

of the children were included in the hospital setting (62.2% and 52.0%, respectively) and, therefore, were more likely to have more severe disease.

A previous epidemiologic study estimated that rotavirus accounts for >230 deaths annually among children <5 years of age in the European Union [30], most of them due to dehydration and delay in hospitalization. As would be predicted from the expected incidence of RVGE and the high level of health care provided in the study areas, no deaths were observed during this investigation.

We observed that the RR for emergency department care and hospital referrals among children who first consulted in the primary care setting was higher for children with rotavirus-positive AGE in both settings. This was statistically significant in France and Italy for emergency department referral and in France, Germany, Italy, Spain, and the United Kingdom for hospital referral. This important finding suggests that prevention of RVGE could greatly reduce the hospitalization rate for children with AGE. In addition, many children received care in multiple clinical settings, indicating that there can be considerable burden for patients, parents, and health care resources across multiple clinical settings.

Across the study, the percentage of children who were prescribed medication, such as an antidiarrheal agent, varied, and comparable percentages of children with rotavirus-positive AGE or rotavirus-negative AGE received prescribed medication in any study area. Similarly, there was considerable variation in the percentage of children hospitalized with AGE who received iv and/or oral rehydration therapies, reflecting different clinical practice in different study areas. Despite the established role of rehydration therapy in the management of children with AGE, some hospitalized children in the study were reported as not having received any rehydration therapy.

Our study showed that the incidence of RVGE is high in Europe, and most children <5 years of age are at risk [8]. Rotavirus-positive AGE is more severe than rotavirus-negative AGE, with higher frequencies of dehydration, vomiting, fever, and signs of lethargy and a greater risk of hospitalization. Compared with children with rotavirus-negative AGE, children with rotavirus-positive AGE more often present to multiple health care settings, providing evidence for the greater clinical impact of rotavirus AGE compared with that of nonrotavirus AGE. Reductions in the incidence and severity of RVGE would, therefore, have major benefits for potential patients, families, and health care providers. A decrease in hospital admissions due to community-acquired RVGE would be accompanied by a reduction in nosocomial rotavirus infections, which account for a large proportion of hospitalized children with RVGE [7, 31, 32]. The REVEAL Study has provided essential data on the clinical impact of RVGE and underlines the importance and likely benefits of early childhood vaccination.

THE REVEAL STUDY GROUP

Principal Investigators

Pierre Van Damme and Marie Van der Wielen (University of Antwerp, Antwerp, Belgium); Frédéric Huet, Mondher Chouchane, Pierre Pothier, and Raphaelle Maudinas (University Hospital, Dijon, France); Christel Hülße and Martina Littman (Health Authorities of Mecklenburg Western Pomerania, Rostock, Germany); Carlo Giaquinto (University of Padua, Padua, Italy); Jose Mª Paricio Talayero (Hospital G.U. Marina Alta, Denia, Spain); Miguel Tomás Vila (Hospital Francesc de Borja, Gandia, Spain); Leif Gothefors and Margareta Baeckman (Umeå University Hospital, Umeå, Sweden); Peter Todd and Claire Allan (Arrowe Park Hospital, Wirral, Merseyside, United Kingdom); and Melanie Maxwell (Clinical Practice Research Unit, Wirral Hospital NHS Trust, Wirral, Merseyside, United Kingdom).

Participating Pediatricians, General Practitioners, and Hospital Staff

Belgium. A. Vertruyen, P. Vanoverschelde, and the pediatric staff of Sint-Vincentius Hospital, Antwerp; G. Veereman and the pediatric staff of Queen Paola Children's Hospital, Antwerp; and the following general practitioners: E. Boydens, M. Cramm, J. De Rooze, P. De Smedt, P. Hannes, H. Hofkens, K. Maus, H. Nuyts, K. Peeters, H. Sahbaz, H. Stoop, H. Straetemans, F. Van Godtsenhoven, J. Van Herck, and M. Verhulst.

France. Hospital pediatricians from Clinique Ste-Marthe: M. Dauvergne, F. Funes de la Vega, H. Planson, D. Tenenbaum, and Abdel Zouaidia (clinical research associate).

General practitioners: J.-N. Beis, D. Bompy, P. Bugnon, F. Chaillot, P. Chapuis, F. Danjean-Meyer, E. Debost, A. Gebrael, D. Girard, P. Hedoin, C. Huber, T. Jean, P. Jemelen, M.-P. Lambert, B. Megraoua, G. Morel, F. Morlon, J.-Y. Servant, P. Sondey, Y. Sturm, and T. Vannier.

Primary care pediatricians: R. Baruteau and B. Virey.

Emergency staff from SOS 21: F. Arcos, C. Chapuis, R. Gauyacq, O. Joly, R. Khong, T. Lavagna, and V. Mathelin.

Germany. General practitioners and family pediatricians: U. Baum, W.-D. Bohm, R. Greupner, H. Harder-Walter, K. Held, A. Hendel, A. Lange, A. Martin, M. Nahlik, M. Paul, U. Pfennig, M. Richter, E.-D. Ruickoldt, T. Schremmer, S. Sengbusch, B. Stein, R. Tinz, K. Warncke, C. Wendt, and C. Will.

Italy. Hospital pediatricians: L. da Dalt, S. Callegaro, B. Andreola, and M. Perin.

Primary care pediatricians: M. Bernuzzi, L. Cantarutti, S. Drago, A. De Marchi, P. Falconi, M. Felice, G. Giancola, C. Lista, C. Manni, F. Pisetta, and M. P. Sidran.

Spain. J.-M. Alentado Femenia, M.-T. Asensi Monzo, M.-J. Benlloch Muncharaz, A. Bernal Ferrer, B. Beseler Soto, G. Castellanos Gomez, J.-I. Collar del Castillo, P. Garcia Tamarit, D. Gómez Sánchez, M. Grieco Burucua, I. Izquierdo Fos, L.

Landa Rivera, J. Lledo Bernabeu, T. Llobat Estelles, M.-L. Lucas Abad, M.-A. Martín Sobrino, E. Olaya Lopez, M. Oltra Benavent, O. Peñalver Giner, R. Perello Castellano, J. Pérez Verdú, P. Puig Aracil, J. Raheb Azahar, M. Ramos Garcia, F. Ribes Lopez, F. Sanantonio Valdearcos, M. Sánchez Palomares, B. Santa Pau, L. Santos Serrano, J.-M. Sequi Canet, G. Serer Alminana, M. Soriano Carreras, and A. Uribelarrea Sierra.

Sweden. M. Alvin, M. Holmberg, K. Josefsson, K. Kristensen, M. Lindberg, B. Ögren, S. Persson, T. Rahm, and P. Wall, from the Health Care Center and their associated Child Health Centers.

United Kingdom. Hospital pediatricians: P. Bundred and the staff of Ward 11 from Arrowe Park Hospital, Wirral, Merseyside.

Private pediatricians: K. Allaudin, E. Cameron, T. D. Henessy, A. Hussain, V. K. Joshi, M. Lodh, M. Martin-Hiero, S. Murty, Y. Patwala, J. Renwick, R. Smye, P. Tandon, and S. William.

Sanofi Pasteur MSD Participants

F. Belghiti, C. Cohen Sabas, M. Ginson, M. Haugh, L. Hessel, M. Kulig, N. Largeron, L. Marcelon, M. H. Metzger, J. Naysmith, L. Nicolas, C. Serrand, M. Trichard, O. van der Hel, and M. Watson.

Sanofi Pasteur MSD affiliates: M. Maître (Lyon, France), P. Dhont (Brussels, Belgium), N. Kitchin (Maidenhead, United Kingdom), I. Oyagüez (Madrid, Spain), H. Diehm (Leimen, Germany), S. Jow (Leimen, Germany), R. Di Marzo (Rome, Italy), and C. Young (Stockholm, Sweden).

Acknowledgments

We thank the following people whose collaboration contributed to the success of the REVEAL Study: F.-A. Allaert and N. Vernet (Cenbiotech, Dijon, France); D. J. DiStefano, G. Kulnis, M. Maliga, and L. Mallette (Merck Research Laboratory, Wayne, Pennsylvania); T. Busse, D. Knowlton, A. Morris, J. Mount, D. Sander, G. Vorholt, and R. Ward (Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio); V. Iyer and N. McKendrick (Communigen, Oxford, United Kingdom); A. Moren (EpiConcept, Paris, France); B. Pedalino (Sanofi Pasteur MSD [Europe], Lyon, France); Quintiles Strategic Research Services (Levallois-Perret, France); Quintiles Data Management & Statistics (Tanneries, France); B&C International S.A. (Mechelen, Belgium); AREMIS (Neuilly-sur-Seine, France); and Aegisnet France, Germany, Italy, Spain, Sweden, and United Kingdom. We also thank A. Charlett (Health Protection Agency, London, United Kingdom), D. Gendrel (Hôpital St. Vincent de Paul, Paris, France), M. Koopmans (Infectious Diseases and Perinatal Screening, Bilthoven, The Netherlands), and A. Krämer (Universität Bielefeld, Bielefeld, Germany) for taking part in 2 expert panel meetings held in October 2005 and April 2006 to discuss the results of the REVEAL Study. Last, but not least, we thank all the children and their parents who participated.

Supplement sponsorship. This article was published as part of a supplement entitled "The REVEAL Study: Epidemiology and Economic Impact of Pediatric Rotavirus Gastroenteritis in Europe," sponsored by Sanofi Pasteur MSD.

References

1. Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. Bull World Health Organ **2003**; 81:197–204.
2. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? Lancet **2003**; 361:2226–34.
3. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis **2003**; 9:565–72.
4. Velázquez FR, Matson DO, Calva JJ, et al. Rotavirus infections in infants as protection against subsequent infections. N Engl J Med **1996**; 335: 1022–8.
5. Parashar UD, Gibson CJ, Bresse JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis **2006**; 12:304–6.
6. Koopmans M, Brown D. Seasonality and diversity of Group A rotaviruses in Europe. Acta Paediatr Suppl **1999**; 88:14–9.
7. Pediatric Rotavirus European Committee (PROTECT). The paediatric burden of rotavirus disease in Europe. Epidemiol Infect **2006**; 134: 908–16.
8. Van Damme P, Giaquinto C, Huet F, et al., on behalf of the REVEAL Study Group. Multicenter prospective study of the burden of rotavirus acute gastroenteritis in Europe, 2004–2005: the REVEAL Study. J Infect Dis **2007**; 195(Suppl 1):S4–16 (in this supplement).
9. Giaquinto C, Van Damme P, Huet F, Gothefors L, Van der Wielen M, on behalf of the REVEAL Study Group. Costs of community-acquired pediatric rotavirus gastroenteritis in 7 European countries: the REVEAL Study. J Infect Dis **2007**; 195(Suppl 1):S36–44 (in this supplement).
10. Crowley DS, Ryan MJ, Wall PG. Gastroenteritis in children under 5 years of age in England and Wales. Commun Dis Rep CDR Rev **1997**;7: R82–6.
11. Dennehy PH. Transmission of rotavirus and other enteric pathogens in the home. Pediatr Infect Dis J **2000**; 19:S103–5.
12. Leung AK, Kellner JD, Davies HD. Rotavirus gastroenteritis. Adv Ther **2005**; 22:476–87.
13. Cook SM, Glass RI, LeBaron CW, Ho MS. Global seasonality of rotavirus infections. Bull World Health Organ **1990**; 68:171–7.
14. Glass RI, Parashar UD, Bresee JS, et al. Rotavirus vaccines: current prospects and future challenges. Lancet **2006**; 368:323–32.
15. Matson DO. Rotaviruses. In: Long SS, Pickering LK, Prober CG, eds. Principles and practice of pediatric infectious diseases. 2nd ed. New York: Churchill Livingstone, **2003**:1105–8.
16. Anderson EJ, Weber SG. Rotavirus infection in adults. Lancet Infect Dis **2004**; 4:91–9.
17. Clark B, McKendrick M. A review of viral gastroenteritis. Curr Opin Infect Dis **2004**; 17:461–9.
18. Van Damme P, Giaquinto C, Maxwell M, Todd P, Van der Wielen M, on behalf of the REVEAL Study Group. Distribution of rotavirus genotypes in Europe, 2004–2005: the REVEAL Study. J Infect Dis **2007**; 195(Suppl 1):S17–25 (in this supplement).
19. International Epidemiological Association European Federation. Good epidemiological practice (GEP): proper conduct in epidemiologic research. June **2004**. Available at: http://www.IEAWeb.org/GoodPract.htm. Accessed 14 November 2006.
20. Gunson RN, Miller J, Leonard A, Carman WF. Importance of PCR in the diagnosis and understanding of rotavirus illness in the community. Commun Dis Public Health **2003**; 6:63–5.
21. Simpson R, Aliyu S, Iturriza-Gómara M, Desselberger U, Gray J. Infantile viral gastroenteritis: on the way to closing the diagnostic gap. J Med Virol **2003**; 70:258–62.
22. Rodriguez WJ, Kim HW, Arrobio JO, et al. Clinical features of acute gastroenteritis associated with human reovirus-like agent in infants and young children. J Pediatr **1977**; 91:188–93.
23. Maki M. A prospective clinical study of rotavirus diarrhea in young children. Acta Paediatr Scand **1981**; 70:107–13.
24. Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of

numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis **1990**; 22:259–67.
25. Kurugol Z, Geylani S, Karaca Y, et al. Rotavirus gastroenteritis among children under five years of age in Izmir, Turkey. Turk J Pediatr **2003**;45: 290–4.
26. Clark HF, Offit PA. Vaccines for rotavirus gastroenteritis universally needed for infants. Pediatr Ann **2004**; 33:536–43.
27. Raebel MA, Ou BS. Rotavirus disease and its prevention in infants and children. Pharmacotherapy **1999**; 19:1279–95.
28. Ehlken B, Laubereau B, Karmaus W, Petersen G, Rohwedder A, Forster J. Prospective population-based study on rotavirus disease in Germany. Acta Paediatr **2002**; 91:769–75.
29. Colomba C, De Grazia S, Giammanco GM, et al. Viral gastroenteritis in children hospitalised in Sicily, Italy. Eur J Clin Microbiol Infect Dis **2006**; 25:570–5.
30. Soriano-Gabarró M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. Pediatr Infect Dis J **2006**; 25:S7–11.
31. Fischer TK, Bresee JS, Glass RI. Rotavirus vaccines and the prevention of hospital-acquired diarrhea in children. Vaccine **2004**; 22(Suppl 1): S49–54.
32. Gleizes O, Desselberger U, Tatochenko V, et al. Nosocomial rotavirus infection in European countries: a review of the epidemiology, severity and economic burden of hospital-acquired rotavirus disease. Pediatr Infect Dis J **2006**; 25:S12–21.