Distribution of Rotavirus Genotypes in Europe, 2004–2005: The REVEAL Study

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Background. Rotavirus gastroenteritis (RVGE) constitutes a significant burden of pediatric disease. Knowledge of currently cocirculating rotavirus genotypes is required to help guide immunization strategies.

Methods. During the 2004–2005 RVGE season, a prospective, multicenter, observational study of RVGE was conducted in children <5 years of age seeking health care in primary care, emergency department, and hospital settings in selected areas of Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom. Rotavirus was identified by enzyme-linked immunosorbent assay (ELISA), and genotypes were determined by reverse-transcription polymerase chain reaction (RT-PCR) analysis of stool samples for which ELISA results were positive.

Results. ELISA results were available for 2712 of the 2846 children with acute gastroenteritis who were recruited for the study; of these 2712 children, 1102 (40.6%) were rotavirus positive. RT-PCR results were available for 1031 children with ELISA-positive samples. G1–G4 and G9 were the most prevalent genotypes identified: G1 was identified in Spain, Sweden, and the United Kingdom; G9 in Italy, France, and Belgium; and G4 in Germany. Only the G4 and G9 genotypes were identified in all study areas. Rotavirus infections showed seasonal variation, with different patterns noted among the genotypes.

Conclusions. Rotavirus genotypes G1–G4 and G9 are associated with the majority of RVGE infections in the areas studied, with geographic and seasonal variation in the distributions of rotavirus strains. Rotavirus vaccines should, therefore, provide protection against all major genotypes to decrease effectively the RVGE disease burden in Europe.

Rotavirus gastroenteritis (RVGE) constitutes a significant disease burden in children <5 years of age worldwide. It is an important contributor to childhood morbidity and mortality in developing countries [1], but it also causes considerable morbidity in industrialized countries. A recent estimate suggested that RVGE accounts for 231 deaths, >87,000 hospitalizations, and almost 700,000 outpatient visits annually within the European Union [2].

Rotavirus is a member of the *Reoviridae* family. It has a nonenveloped particle, with a double capsid, a core containing the viral genome, and 2 surface proteins, VP4 and VP7. Rotaviruses are classified into 7 serogroups (A–G) on the basis of the antigenic properties of shared epitopes on the major structural protein, VP6 [3]. Groups A–C are human pathogens, with group A viruses being most commonly associated with childhood infections [4]. Within these groups, viruses are classified into serotypes on the basis of antigenic differences in VP4 and VP7 in the outer capsid. To

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The Journal of Infectious Diseases 2007;195:S17–25

0022-1899/2007/19509S1-0003$15.00
DOI: 10.1086/516715

Potential conflicts of interest: 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. C.G. has an educational grant from and a consultation agreement with Sanofi Pasteur MSD, GlaxoSmithKline, Abbott, Roche, Tibotec, and Boehringer Ingelheim. All other authors report no potential conflicts.

Presented in part: XXIV Annual Meeting of the European Society of Pediatric Infectious Diseases, Basel, Switzerland, 3–5 May 2006 (abstract 36); 7th Annual 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 P.V.D., C.G., M.M., P.T., and M.V.d.W.). The REVEAL Study is supported by Sanofi Pasteur MSD (study number X03-ROT-510). Supplement sponsorship is detailed in the Acknowledgments.

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

date, 15 group A VP7 antigens (known as "G types"), and 14 VP4 antigens (known as "P types") have been identified in humans [5]. For G types, the serotypes and genotypes are generally concordant [5, 6], so G types are usually referred to only by their serotype (e.g., G1). In contrast, discordant nomenclature exits for P genotypes and serotypes; because of technical challenges, more P genotypes than P serotypes have been described. P types are generally referred to by their genotype number, which is denoted in brackets (e.g., P[8]) [5].

Among group A rotaviruses, 5 G serotypes (G1–G4 and G9) constitute >90% of G serotypes detected globally [5], with infections due to G9 becoming more prevalent in recent years [3, 7, 8]. Rotavirus strains of the G1, G3, G4, and G9 serotypes are preferentially associated with the P[8] genotype, whereas G2 serotype strains are most frequently associated with the P[4] genotype [5]. It has been impossible to predict which rotavirus type will infect children in any season or country, because the seasonal and geographic distributions of rotavirus serotypes have been unpredictable [6, 8].

Local intestinal immunity appears to confer some protection against subsequent rotavirus infections [5]. Although the first rotavirus infection can be asymptomatic if it occurs while maternal protection persists, the first episode of RVGE typically is the most severe, and additional infections are less severe or asymptomatic [9, 10]. Although complete protection against reinfection with other rotavirus strains is not achieved, it has been reported that 3 infections reduce the risk of serious rotavirus-associated diarrhea by almost 100% [11].

Rotavirus infections have been identified as an important target for vaccination. The first licensed vaccine was withdrawn after it was shown to be associated with a risk of intussusception in vaccinated infants [4]. Recently, a naturally attenuated pentavalent (G1–G4 and P[8]) human-bovine (WC3 strain) reassortant rotavirus vaccine [12] and an attenuated monovalent (G1P[8]) human rotavirus vaccine [13] have been granted market authorization in the European Union, because no signal of increased risk of intussusception was seen in large clinical trials of either vaccine, and because both effectively protect against RVGE. An effective vaccination program requires protection against major prevalent rotavirus serotypes/genotypes [11]; however, no Europe-wide data are available on the epidemiologic profile of rotavirus. To date, with rare exceptions [14], only national studies have been performed, and these have used different methodologies.

To address this need, we performed a prospective study of the epidemiologic profile of rotavirus in 7 European 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 of acute gastroenteritis (AGE) and RVGE in children <5 years of age seeking health care in primary care, emergency department, and hospital settings in a specific study area in each country [15]. The secondary objectives of the study were to describe the distribution of rotavirus genotypes associated with RVGE (the subject of the present article), to describe the clinical influence of RVGE [16], and to evaluate the medical and societal costs of RVGE [17].

MATERIALS AND METHODS

A prospective, multicenter, observational study of AGE in children <5 years of age seeking health care was 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 [18], and local regulatory requirements. The protocol was approved by the local ethics committee in each study area.

Full details of the study design and sampling procedures are described elsewhere [15]. In brief, within each country, a selected region was identified that included both urban and rural populations. 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) were included in the study. All children <5 years of age who presented with AGE during the study period were eligible for inclusion. 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, at least 3 watery stools, or forceful vomiting associated with gastroenteritis occurring during a 24-h period in 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).

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. The levels of care, from the lowest to the highest level, were as follows: primary care, emergency department, and 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 the hospital, and they were, therefore, included in the hospital setting.

Not included in the study were those children who satisfied

Table 1. Observed and estimated numbers of rotavirus (RV) gastroenteritis cases and available reverse-transcription polymerase chain reaction (RT-PCR) results, by setting and by study area.

Study area, finding	Hospital		Emergency department		Primary care setting		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[b]	39 (58.2)	140 (58.1)	2 (40.0)	112 (39.9)	16 (41.0)	227 (41.3)	479 (44.7)
RT-PCR results available	36	109	2	112	16	205	426
France (n = 281)							
Total	63	205	120	770	98	969	1944
ELISA results available	54		111		97		
RV positive, no. (%) of samples[b]	30 (55.6)	114 (55.6)	50 (45.0)	347 (45.1)	19 (19.6)	190 (19.6)	651 (33.5)
RT-PCR results available	28	91	47	301	19	185	577
Germany (n = 499)							
Total	85	121	0[c]	0	414	2544	2665
ELISA results available	81		NA		403		
RV positive, no. (%) of samples[b]	53 (65.4)	80 (66.1)	NA	NA	105 (26.1)	662 (26.0)	742 (27.8)
RT-PCR results available	51	73	NA	NA	98	603	676
Italy (n = 757)							
Total	83	122	266	494	408	1108	1724
ELISA results available	80		241		404		
RV positive, no. (%) of samples[b]	55 (68.8)	84 (68.9)	148 (61.4)	303 (61.3)	133 (32.9)	364 (32.9)	751 (43.6)
RT-PCR results available	53	77	137	254	127	345	676
Spain (n = 801)							
Total	101	181	299	797	401	1277	2255
ELISA results available	98		286		388		
RV positive, no. (%) of samples[b]	52 (53.1)	96 (53.0)	101 (35.3)	282 (35.4)	99 (25.5)	325 (25.5)	703 (31.2)
RT-PCR results available	48	86	93	249	87	275	610
Sweden (n = 221)							
Total	115	159	92	275	14[d]	104[d]	538
ELISA results available	111		85		14		
RV positive, no. (%) of samples[b]	69 (62.2)	98 (61.6)	54 (63.5)	174 (63.3)	1 (7.1)	8 (7.7)	280 (52.0)
RT-PCR results available	65	90	52	156	1	8	254
United Kingdom (n = 160)							
Total	68	84	37	55	55	871	1010
ELISA results available	64		37		47		
RV positive, no. (%) of samples[b]	39 (60.9)	51 (60.7)	22 (59.5)	33 (60.0)	15 (31.9)	279 (32.0)	363 (35.9)
RT-PCR results available	36	45	22	32	13	203	280

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

[a] Estimated values take into account the participation rate and patients for whom ELISA results were missing. It was assumed that patients for whom ELISA results were missing would have the same proportion of RV-positive samples as would patients for whom results were available. However, missing RT-PCR results were not adjusted in this way, because no assumptions could be made as to which specific rotavirus serotypes might be missing.

[b] Percentage of samples that were RV-positive among patients for whom an ELISA result was available.

[c] 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.

[d] 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 a higher level of care or were treated at home.

the eligibility criteria but whose parents did not provide written, informed consent, whose parents did not speak the native language of the country (the parents could have had difficulties completing the study forms), or whose parents did not have access to a telephone. Data relating to the nature and duration of symptoms were collected in a series of questionnaires completed by the parents and physician in all settings and by a nurse in the hospital setting.

For identification and genotyping of rotavirus, one stool sample from each child was obtained during the consultation,

Table 2. Estimated genotype distribution for children aged ≤24 months and >24 months, by study area.

Study area, age group	Children, by genotype, no. (%)							
	All	G1	G2	G3	G4	G6	G8	G9
Belgium								
≤24 months	326	63 (19.3)	35 (10.7)	47 (14.4)	90 (27.6)	0 (0)	0 (0)	91 (27.9)
>24 months	100	59 (59.0)	6 (6)	0 (0)	13 (13.0)	0 (0)	0 (0)	22 (22.0)
France								
≤24 months	491	0 (0)	46 (9.4)	176 (35.8)	6 (1.2)	0 (0)	10 (2.0)	253 (51.5)
>24 months	92	0 (0)	0 (0)	20 (21.7)	0 (0)	6 (6.5)	0 (0)	66 (71.7)
Germany								
≤24 months	519	136 (26.2)	0 (0)	40 (7.7)	300 (57.8)	0 (0)	0 (0)	43 (8.3)
>24 months	155	58 (37.4)	0 (0)	0 (0)	79 (51.0)	0 (0)	6 (3.9)	12 (7.7)
Italy								
≤24 months	429	58 (13.5)	10 (2.3)	2 (0.5)	3 (0.7)	3 (0.7)	0 (0)	353 (82.3)
>24 months	243	21 (8.6)	5 (2.1)	0 (0)	0 (0)	0 (0)	3 (1.2)	214 (88.1)
Spain								
≤24 months	465	290 (62.4)	14 (3.0)	27 (5.8)	3 (0.6)	6 (1.3)	0 (0)	125 (26.9)
>24 months	144	82 (56.9)	2 (1.4)	11 (7.6)	0 (0)	0 (0)	0 (0)	49 (34.0)
Sweden								
≤24 months	140	76 (54.3)	4 (2.9)	0 (0)	3 (2.1)	0 (0)	0 (0)	57 (40.7)
>24 months	106	68 (64.1)	0 (0)	0 (0)	1 (0.9)	0 (0)	0 (0)	37 (34.9)
United Kingdom								
≤24 months	223	185 (83.0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	37 (16.6)
>24 months	58	54 (93.1)	0 (0)	1 (1.7)	1 (1.7)	0 (0)	0 (0)	2 (3.4)

NOTE. The total estimated nos. of children, by genotype, are different between the tables, because of rounding performed during the calculations. Data are not shown for genotype G10, which was detected only in Spain (in 3 [2.1%] of children >24 months of age), or for genotype G12, which was detected only in Italy (in 6 [1.4%] of children ≤24 months of age) and Sweden (in 6 [4.3%] of children ≤24 months of age and in 1 [0.9%] of children >24 months age).

if possible, by the physician/health care worker. When this was not possible, the parent/guardian collected the sample in a container provided to them; the sample was then refrigerated. The stool sample was collected within 14 days of the onset of symptoms (ideally, within the first 3 days of the onset of symptoms). Subsequently, the samples were stored at −20°C in a centralized freezer in each study area. At 2–4-month intervals, the samples were packed in dry ice and were sent by courier to the laboratory of Dr. Richard L. Ward at Cincinnati Children's Hospital Medical Center (Cincinnati, Ohio) for rotavirus detection performed using ELISA [19]. The samples then were forwarded to Merck Research Laboratories (West Point, PA), where samples that were found to be positive for rotavirus by means of ELISA underwent reverse-transcription polymerase chain reaction (RT-PCR), followed by sequencing for identification of G genotypes [20].

For each study area, the overall incidence rates for AGE, RVGE, and rotavirus genotypes were estimated by extrapolating data from the children included in the study to children who were eligible for but were not included in the study and then by adjusting for response rates (see [15]). It was assumed that the characteristics of and outcomes for children who were eligible for inclusion but were not included in the study were similar to those for children who were included in the study.

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, 2846 children with AGE were recruited from 12 hospitals, 18 emergency departments, and 139 primary care physicians. The majority of children were 6–24 months of age, and there were slightly more boys than girls included in all study areas (51.8%–60.7% of children were boys).

Rotavirus ELISA results were available for 2712 of the 2846 children included (samples were not available for 125 children, and 9 results were inconclusive). The ELISA results were positive for 1102 children (40.6%). The percentage of children with AGE who were found to be rotavirus positive ranged from 53.1% to 68.8% for hospitalized children, from 35.3% to 63.5% for those seen in emergency departments, and from 7.1% to 41% for those seen in primary care settings (table 1).

Taking into account the participation rate and sampling fraction (i.e., the number of children seen by primary care physicians participating in the study divided by the total number of children living in the study area) [15], the estimated total number of rotavirus-positive children in each study area ranged

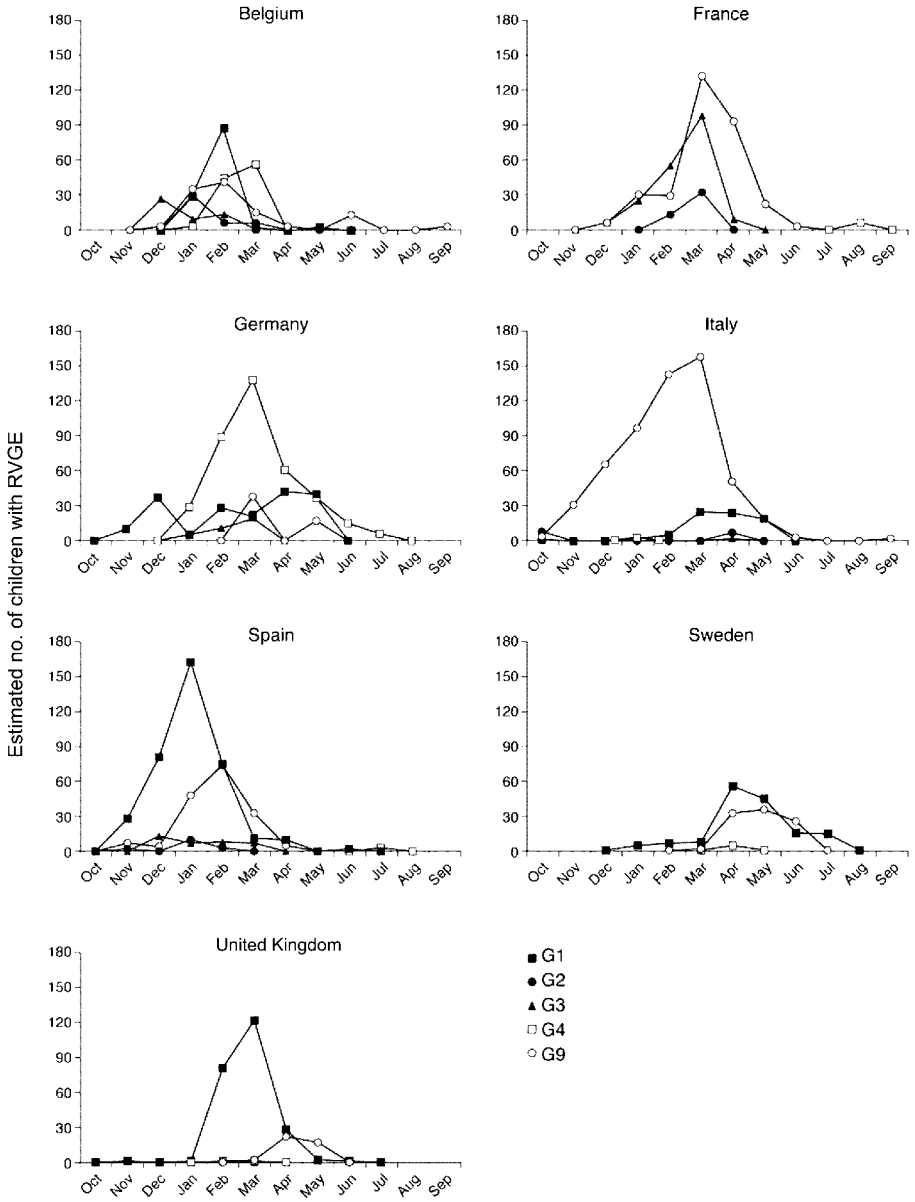

Figure 1. Estimated seasonal distribution of genotypes (G1–G4 and G9) in each study area. RVGE, rotavirus gastroenteritis.

from 280 in Sweden to 751 in Italy (table 1). The overall estimated percentage of children with rotavirus-positive AGE was 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 (table 1).

Of the 1102 samples that were found to be positive for rotavirus by ELISA, 1031 had available RT-PCR results (71 samples contained RNA in an insufficient amount for RT-PCR to be performed). On the basis of the estimated incidence of RVGE in each country and the proportions of patients drawn from hospitalized, emergency department, and primary care populations, the distribution of rotavirus genotypes was estimated for each country. Overall, the most prevalent genotypes were G1–G4 and G9, with distributions differing between the areas. G1 was the most prevalent genotype in the United Kingdom (85.4%), Spain (61%), Sweden (57.1%), and Belgium (28.4%). G9 was predominant in Italy (83.9%) and France (54.8%). In Germany, the predominant G genotype was G4 (56.1%). Only G4 and G9 were identified in all study areas, and only G9 was present in a substantial percentage of children in each area. Although G2 and G3 were not predominant in any study area, G2 was present in 9.6% of samples in Belgium and G3 was present in 33.6% of samples in France. G10 was detected only in Spain, and G12 was detected only in Italy and Sweden.

In general, no particular genotype occurred more commonly in younger children ($\leq$24 months of age) than in older children

Table 3. Estimated no. (percentage) of hospitalized and nonhospitalized children, by genotype.

Study area, genotype	Hospitalized children[a]	Children not hospitalized[a]
Belgium		
G1	15 (12.3)	107 (87.7)
G2	15 (36.6)	26 (63.4)
G3	9 (19.1)	38 (80.9)
G4	21 (20.4)	82 (79.6)
G9	49 (43.4)	64 (56.6)
France		
G2	3 (6.5)	43 (93.5)
G3	26 (13.3)	170 (86.7)
G4	0 (0.0)	6 (100.0)
G6	0 (0.0)	6 (100.0)
G8	0 (0.0)	10 (100.0)
G9	63 (19.7)	256 (80.3)
Germany		
G1	23 (11.9)	171 (88.1)
G3	3 (7.5)	37 (92.5)
G4	45 (11.9)	334 (88.1)
G8	0 (0.0)	6 (100.0)
G9	1 (1.8)	54 (98.2)
Italy		
G1	6 (7.6)	73 (92.4)
G2	1 (6.7)	14 (93.3)
G3	0 (0.0)	2 (100.0)
G4	0 (0.0)	3 (100.0)
G6	0 (0.0)	3 (100.0)
G8	0 (0.0)	3 (100.0)
G9	69 (12.2)	498 (87.8)
G12	1 (16.7)	5 (83.3)
Spain		
G1	50 (13.4)	322 (86.6)
G2	2 (12.5)	14 (87.5)
G3	4 (10.5)	34 (89.5)
G4	0 (0.0)	3 (100.0)
G6	0 (0.0)	6 (100.0)
G9	30 (17.2)	144 (82.8)
G10	0 (0.0)	3 (100.0)
Sweden		
G1	53 (36.8)	91 (63.2)
G2	1 (25.0)	3 (75.0)
G4	4 (100.0)	0 (0.0)
G9	28 (29.8)	66 (70.2)
G12	4 (57.1)	3 (42.9)
United Kingdom		
G1	40 (16.7)	199 (83.3)
G3	1 (100.0)	0 (0.0)
G4	0 (0.0)	2 (100.0)
G9	3 (7.7)	36 (92.3)

[a] The total estimated nos. of children, by genotype, are different between the tables, because of rounding performed during the calculations.

(>24 months of age) (table 2). Although in some countries, such as Belgium and Germany, G3 was absent in older children but was detected in 15.0% and 7.7%, respectively, of children ⩽24 months of age, this finding was not seen in the other countries.

The season for RVGE extended from December through April, with the peak incidence occurring between January and March [15]. The distribution of rotavirus genotypes varied during the study period; the peak for G1 generally occurred earlier (January through March), whereas, for G4 and G9, the peak incidences generally occurred later (February through May) (figure 1).

The association between rotavirus genotype and severity of RVGE was assessed for the most prevalent genotypes in each country, by determining the percentage of children hospitalized by genotype. The data do not suggest that any genotype was more prevalent among hospitalized children than among nonhospitalized children, although the numbers of children were generally small (table 3). For specific clinical variables, such as dehydration, the number of cases per genotype was too small to draw conclusions regarding any association with genotype.

DISCUSSION

The REVEAL Study investigated the distribution of rotavirus genotypes in well-defined areas of 7 European countries from October 2004 through September 2005, by use of a common protocol in 3 settings (primary care, emergency department, and hospital settings). Five genotypes (G1–G4 and G9) were found to be circulating within the study areas, and, together, they accounted for 98% of RVGE cases in the study areas. The remaining 2% of RVGE cases were due to the G6, G8, G10, and G12 genotypes; however, genotype distribution varied between study areas, and there was no evidence of any associations between genotype and either the age of the affected children or the need for hospitalization, albeit in relatively small samples.

To our knowledge, the REVEAL Study is the first study to investigate systematically AGE and RVGE in >2800 children <5 years of age during an entire season, by use of a common protocol in 3 health care settings (hospital, emergency department, and primary care settings) in 7 areas in Europe. Furthermore, the rotavirus ELISAs and RT-PCR analyses were performed in single, central laboratories.

When our results are interpreted, consideration should be given to the potential study limitations [15]. For example, only children seeking health care could be included in the study. In addition, it was assumed that the percentage of positive ELISA results was the same for children for whom ELISA results were not available as for children for whom such results were available. Furthermore, mixed infections with >1 rotavirus genotype were not identified. Samples that were found to have negative ELISA results did not undergo RT-PCR, which is known to be more sensitive than ELISA, and, therefore, this could have led

to underestimation of the number of rotavirus-positive infections [21, 22]. Also, although PCR results were not available for 71 samples, because of insufficient RNA, the samples were assumed to have positive ELISA results; in the study, the case definition included a positive ELISA result.

An additional potential limitation is that the rotavirus P-type results from our study are not yet available. Nevertheless, it is known that the P[8] genotype is preferentially associated with G1, G3, G4, and G9, and that G1P1[8] is associated with >70% of rotavirus infections in North America, Europe, and Australia [5, 6]. We can, therefore, assume that it is likely that P[8] will be found in most of the study samples.

In Italy and Spain, 27% [23] and 31% [24], respectively, of children who were hospitalized for AGE were found to have rotavirus infections. The percentage was reported to be 41% in Germany [25], 43% in England and Wales [26], and 31%–51% in France [27, 28]. Although direct comparisons are difficult because of the different methods used, including the case definition, these percentages are clearly lower than those estimated in the current study. However, it is possible that our results might simply reflect the epidemiologic profile of rotavirus for this particular study period.

We found that the prevalence of the G9 genotype was high in some areas studied, accounting for 54.8% and 83.9% of rotavirus infections, respectively, in France and Italy, and for only 8.1% and 12.9% in Germany and the United Kingdom, respectively. Recent years have seen a growth in the importance of the G9 genotype in many countries worldwide, including the United States, Australia, Japan, France, and Ireland [8, 29, 30]. In particular, an increased prevalence of the G9 genotype in Italy has been noted [31, 32]. Rahman et al. [33] have also reported a high prevalence of the G9 genotype in Belgium, although the distribution varied by year.

Currently, there are few data regarding the association between rotavirus serotypes and the age of the infected children, and, between studies, there is considerable variation in the age groups that have been investigated. Although it has been suggested that G9 is associated with neonatal outbreaks of RVGE [34], studies in Belgium, France, and Hungary found no difference in the distribution of the G9 genotype by age, compared with that of rotavirus strains of other genotypes [33, 35, 36]. We found no evidence of any consistent difference in the distribution of genotypes between age groups.

Some investigators have used hospitalization as a proxy for RVGE severity, and one study, performed in the United Kingdom, that compared children requiring hospitalization with children managed in the primary care setting, found that the proportions of children infected with G1P[8], G3P[8], and G4P[8] were not significantly different in the 2 settings [37]. Although results from 2 studies performed in the United Kingdom suggest that infection with the G9 serotype is associated with more severe disease [29, 37], studies in Italy and the United States have found no association between G9 and disease severity [38, 39]. Similarly, in the REVEAL Study, we found no evidence that any genotype, including G9, was more prevalent among hospitalized children than among children who were not hospitalized. This finding is in agreement with the findings of most previously reported European studies [35, 40, 41], although one study reported that the G2P[4] type was associated with more severe gastroenteritis than was the G1P[8] or G4P[8] type [36]. One possible explanation for the apparently greater severity of disease associated with newly emergent serotypes may be the absence of immunity within the population [42].

The unpredictable seasonal and geographic variations in the prevalence of the various rotavirus genotypes have been reported elsewhere [6, 8]. The present results confirm that the circulation of the various genotypes and the timing of their peak incidence are highly variable between the study areas. This variability in the distribution of rotavirus genotypes between countries and seasons supports the need for a vaccine that can provide effective protection against all of the common rotavirus types circulating in Europe. It has been suggested that infection with non-G2P[4] viruses will not induce substantial long-lasting protection against the G2P[4] viruses, and, therefore, polyvalent vaccines may be more effective against this virus, compared with monovalent vaccines [5].

In conclusion, we have shown that rotavirus genotypes G1–G4 and G9 are associated with the majority of rotavirus infections in the areas studied. Consistent with the literature, there was considerable geographic and seasonal variation in the distributions of the rotavirus genotypes, reflecting the unpredictable nature of rotavirus infections. The results of the present study highlight the necessity for a rotavirus vaccine to provide effective protection against all the major genotypes, to decrease the important disease burden of pediatric RVGE in Europe. In addition, the REVEAL Study has provided useful data for assessing the need for introducing rotavirus vaccines into national immunization calendars. After the introduction of routine immunization programs, ongoing surveillance of rotavirus types circulating in Europe will be necessary to monitor for the emergence of genotypes other than those included in the vaccine, as well as for the potential vaccine-induced emergence of antibody escape mutants. The REVEAL Study provides an initial basis for such surveillance and will complement larger, long-term surveillance programs (such as the ongoing European Rotavirus Network [43]), thereby adding to our understanding of the diversity of rotavirus strains cocirculating in Europe.

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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 (Epi-Concept, 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.

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