ROTAVIRUS GENOTYPES IN EUROPE 2004–2005: THE REVEAL* STUDY

* **R**otavirus Gastroenteritis **E**pidemiology and **V**iral Types in **E**urope **A**ccounting for **L**osses in Public Health and Society

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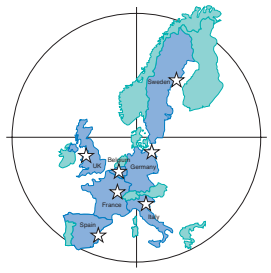
INTRODUCTION

- Rotavirus gastroenteritis (RVGE) constitutes a significant disease burden in children <5 years old worldwide. Almost all children are infected by 5 years of age.[1] It was recently estimated that RVGE accounts for 231 deaths, >87,000 hospitalisations and ~700,000 outpatient visits annually in the European Union.[2]
- Rotaviruses comprise 7 serogroups (A–G), based on the antigenic properties of shared epitopes on the major structural protein, VP6. Group A viruses are the most common in childhood. Serogroups are further classified into serotypes on the basis of antigenic differences in the VP4 and VP7 outer-capsid proteins. Fifteen group A VP7 antigens (G types) and 14 VP4 antigens (P types) have been identified in humans.
- RVGE is now a vaccine-preventable disease, as effective rotavirus vaccines are available. Immunisation strategies should be based on the incidence of RVGE by age, the causative serotypes and total disease burden. However, comprehensive Europe-wide data have been lacking until now.
- The **R**otavirus Gastroenteritis **E**pidemiology and **V**iral Types in **E**urope **A**ccounting for **L**osses in Public Health and Society (REVEAL) Study has assessed the annual incidence rates of acute gastroenteritis (AGE) and RVGE in children <5 years old seeking medical attention in primary care, emergency care, and hospital settings in 7 European countries. A secondary objective was to describe the distribution of rotavirus genotypes associated with RVGE. The study findings have been reported recently.[3–6]

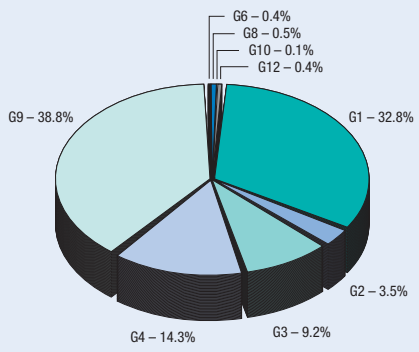
METHODS

- This was a prospective, 1-year observational study conducted in the 2004–2005 season using a common protocol in Belgium, France, Germany, Italy, Spain, Sweden and the UK.



- In each country, a study area was selected (population ~ 255,000), in which all hospitals and emergency rooms that might see children with AGE, and a sample of primary care physicians (general practitioners/paediatricians), were included.
- All children <5 years old presenting with AGE during the study period (1 October 2004 to 30 September 2005) were eligible. AGE was defined as an episode of at least 3 loose stools, or at least 3 watery stools, or forceful vomiting associated with gastroenteritis, in a 24-hour period in the 7 days before the medical visit; the episode must have been preceded by a 14-day symptom-free period.
- If a child visited >1 healthcare setting during the AGE episode, they were included in the study at the highest level of care, in increasing order: primary care, emergency room, hospital. Children presenting more than once were considered as separate cases.
- At central laboratories, rotavirus was identified by ELISA on stool samples obtained within 14 days of symptom onset. In ELISA-positive samples, G genotypes were determined by reverse transcriptase-PCR (RT-PCR).
- For each study area, the distribution of rotavirus genotypes was estimated by extrapolating data from the included children to children who were eligible but not included, and adjusting for participation rates and the primary care sampling fraction.

Figure 1. Distribution of circulating genotypes among rotavirus-positive children (corrected for participation rates and sampling fraction).

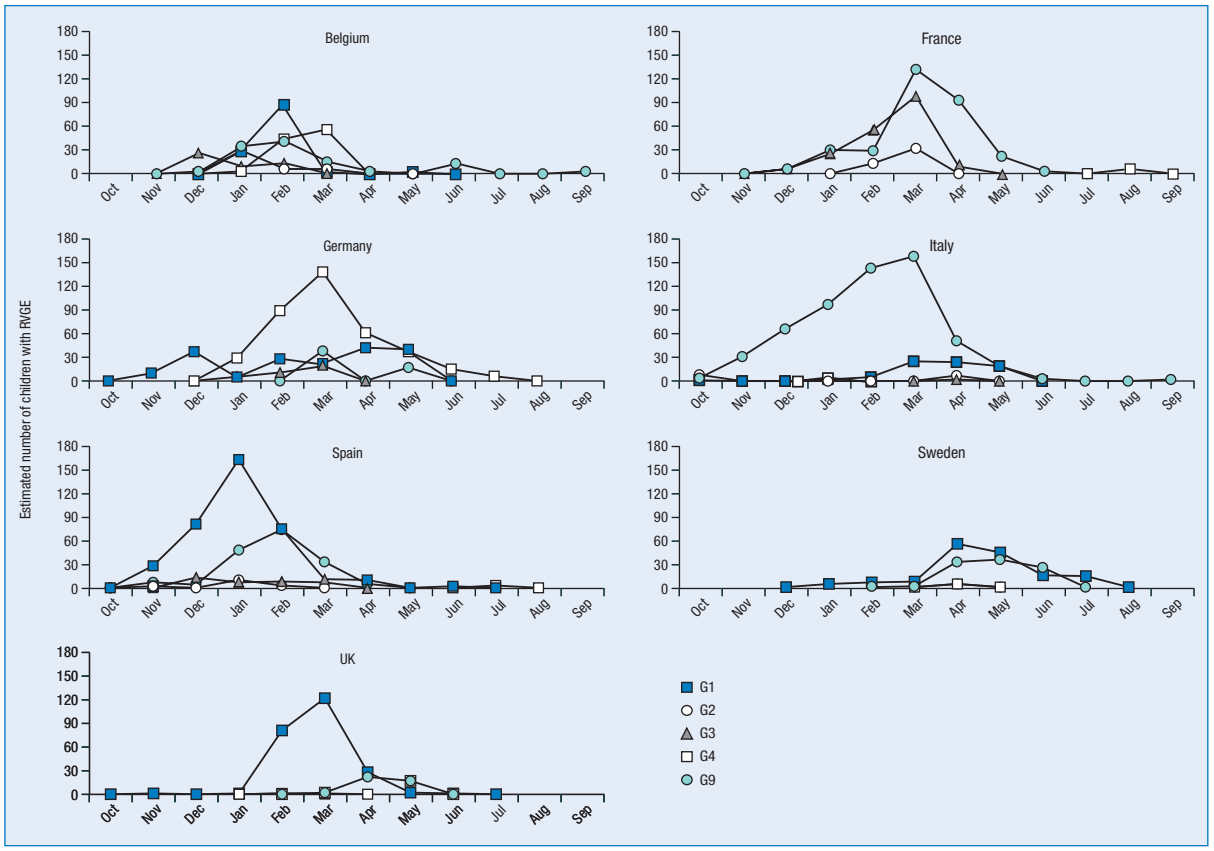


Over 98% of rotavirus cases were caused by G1, G2, G3, G4 and G9

Table 1. Estimated rotavirus genotype distribution by study area (highest percentage per study area highlighted).

		Children by genotype, n (%)								
Study area	Total N	G1	G2	G3	G4	G6	G8	G9	G10	G12
Belgium	426	122 **(28.6)**	41 (9.6)	47 (11.0)	103 (24.2)	0 (0)	0 (0)	113 (26.5)	0 (0)	0 (0)
France	583	0 (0)	46 (7.9)	196 (33.6)	6 (1.0)	6 (1.0)	10 (1.7)	319 **(54.7)**	0 (0)	0 (0)
Germany	674	194 (28.8)	0 (0)	40 (5.9)	379 **(56.2)**	0 (0)	6 (0.9)	55 (8.2)	0 (0)	0 (0)
Italy	678	79 (11.7)	15 (2.2)	2 (0.3)	3 (0.4)	3 (0.4)	3 (0.4)	567 **(83.6)**	0 (0)	6 (0.9)
Spain	612	372 **(60.8)**	16 (2.6)	38 (6.2)	3 (0.5)	6 (1.0)	0 (0)	174 (28.4)	3 (0.5)	0 (0)
Sweden	253	144 **(56.9)**	4 (1.6)	0 (0)	4 (1.6)	0 (0)	0 (0)	94 (37.2)	0 (0)	7 (2.8)
UK	281	239 **(85.1)**	0 (0)	1 (0.4)	2 (0.7)	0 (0)	0 (0)	39 (13.9)	0 (0)	0 (0)

Figure 2. Estimated seasonal distribution of rotavirus genotypes in each study area.



RESULTS

- 2846 children were included in the study. ELISA results were available for 2712 children, and 1102 (40.6%) were rotavirus positive. RT-PCR results were available for 1031 rotavirus-positive ELISA samples (71 samples contained insufficient RNA for RT-PCR).
- G1, G2, G3, G4, and G9 were the most prevalent genotypes (**Figure 1; Table 1**):
  - G1 was predominant in Belgium, Spain, Sweden and the UK
  - G9 was predominant in France and Italy
  - G4 was predominant in Germany
  - Only G4 and G9 were identified in all study areas
  - Only G9 was present in a substantial percentage of children in each area
  - G2 and G3 were not predominant in any study area, but G2 was present in 9.6% of samples in Belgium and G3 in 33.6% of samples in France.
- No particular genotype occurred more commonly in younger children (≤24 months old) compared with older children.
- The distribution of rotavirus genotypes varied seasonally (**Figure 2**):
  - G1 generally peaked earlier (January to April)
  - G4 and G9 generally peaked later (February to May).
- Hospitalisation is sometimes used as an indicator of RVGE severity. In this study, no genotype appeared to be more prevalent among hospitalised children compared with those not hospitalised, although numbers were generally small.

CONCLUSIONS

- The REVEAL Study was the first large, prospective, international study to investigate systematically the burden of paediatric AGE and RVGE, and the distribution of rotavirus genotypes, across Europe in 3 clinical settings using a common protocol.
- Rotavirus genotypes G1, G2, G3, G4 and G9 were associated with the majority of RVGE infections, accounting for 98% of RVGE cases.
- There was considerable geographic and seasonal variation in the distributions of genotypes. Rotavirus vaccines should, therefore, provide effective protection against all major genotypes to decrease substantially the burden of paediatric RVGE in Europe.
- Following the introduction of immunisation programmes, a rotavirus surveillance system will be needed to evaluate the evolution of rotavirus genotypes circulating in Europe. The REVEAL Study provides an initial basis for such surveillance.

REFERENCES

1. Velázquez FR et al. N Engl J Med 1996;335:1022–8.
2. Soriano-Gabarró M et al. Pediatr Infect Dis J 2006;25 (suppl 1):S7–S11.
3. Van Damme P et al. J Infect Dis 2007;195 (suppl 1):S4–S16.
4. Van Damme P et al. J Infect Dis 2007;195 (suppl 1):S17–S25.
5. Giaquinto C et al. J Infect Dis 2007;195 (suppl 1):S26–S35.
6. Giaquinto C et al. J Infect Dis 2007;195 (suppl 1):S36–S44.

The REVEAL Study is published as a supplement to The Journal of Infectious Diseases, which is available at the Sanofi Pasteur MSD stand.