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Rotavirus genotypes in children in the Basque Country (northern Spain) over a 13-year period (July 1996–June 2009)

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Abstract To describe the circulation dynamics of human rotavirus genotypes in a region of southern Europe over a 13-year period. The G- and P-types of rotavirus isolates of patients aged less than 5 years were analyzed using multiplex, reverse transcription polymerase-chain reaction. Of 1,538 isolates investigated, a combination of individual G- and P-types was obtained in 1,368. The most prevalent combination was G1[P8] (57.5% of the genotyped strains), which circulated in all seasons and predominated in nine out of 13 seasons. The strains G2[P4] (14.4%), G3[P8] (8.3%), G4[P8] (5.5%) and G9[P8] (13.4%) circulated intermittently. G4[P8] strains were frequently detected in the 1990s but only sporadically after 2000. G9[P8] strains emerged from 1997–1998 and became dominant in the winters of 2005–2007. G2[P4] strains were predominant in 2003–2004, before the rotavirus vaccines were commercialized. Unusual combinations of common G- and P-types and the presence of unusual G- and/or P-types (G6[P14], G8[P8], G8[P14] and G12[P8]) were rarely observed (<1%). We found no differences in hospitalization due to distinct genotypes. G-types G1–G4 and G9 represented >99% of circulating rotaviruses over a 13-year period. Therefore, vaccine efficacy in this region can be expected to be high.

Introduction

Human group A rotavirus is the main cause of severe acute gastroenteritis (AGE) among children worldwide. Approximately half a million children are estimated to die each year from rotavirus AGE, mostly in developing countries [1]. In developed countries, this disease also has a substantial impact due to the high number of hospitalizations, outpatient and emergency department visits, and family costs it provokes [2–4]. Two oral vaccines, Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) and RotaTeq® (Merck and Company, Whitehouse Station, NJ, USA), have shown good efficacy in preventing rotavirus disease [5, 6]. These vaccines have recently been introduced into the immunization schedules of some countries [5, 7] and are being considered for inclusion by many others. Rotarix contains an attenuated strain of a human rotavirus genotype G1[P8], while RotaTeq includes strains from five human-bovine reassortant rotaviruses, expressing the human G-types G1–G4 and the human P-type P[8], respectively [5].

Rotavirus contains two structural proteins, VP4 and VP7, which induce the synthesis of neutralizing antibodies, codified in two genetic segments that can segregate independently and which form the basis of the classification system, based on G (VP7) and P (VP4) types [8]. Given the variety of existing rotavirus genotypes, the frequency with which they undergo genetic reassortment and the occasional transmission of animal rotaviruses to humans [9, 10], circulating genotypes must be monitored to detect the emergence of new or unusual strains that could spread geographically and compromise the effectiveness of vaccination programs [5, 9]. This article presents the results of rotavirus G- and P-typing over a 13-year period in children in the Basque Country (Spain).

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Materials and methods

Study population

This prospective study was performed in the regions of San Sebastián, Tolosa and Urola-Costa (Basque Country, northern Spain), with 405,745 inhabitants, of which 19,738 were aged less than 5 years, according to the municipal censuses for 2006 (Basque Institute of Statistics), representing 20.6% of the pediatric population of the Basque Country. The study included all patients aged less than 5 years who sought medical care for AGE in our region and for whom stool cultures were requested, both from the hospital and from the outpatient clinics in the study area, between July 1996 and June 2009. Duplicate episodes occurring in the same semester were not included. Among hospitalized children, infections in which the stool samples were obtained 5 days or more after hospital admission were considered to be nosocomial. Rotarix was commercialized in Spain in July 2006 and in RotaTeq in February 2007. Neither of these two vaccines (which are not subsidized) have been included in the Basque Health System vaccination calendar, and the mean coverage for both vaccines in the last 2 years of the study was estimated to be less than 30%.

Virological studies

The presence of group A rotavirus antigen in stool was investigated with a commercial enzyme immunoassay (EIA) kit, following the manufacturer's instructions (IDEIA™ Rotavirus, Dako Diagnostics Ltd., Ely, Cams, UK). Samples with remaining material in which EIA provided the highest optical density (>2000) were suspended in phosphate buffered saline or B199 medium (Sigma-Aldrich, St Louis MO, USA), frozen at -80°C and subsequently analyzed for G- and P-type through multiplex, reverse transcription (RT)-polymerase chain reaction (PCR) methods [10] from 2006 onwards. Viral RNA was obtained with an automatic BioRobot® M48 extractor (Qiagen GmbH, Hilden, Germany) using the MagAttact® Virus Mini M48 kit or the NucliSENS® Easy-Mag platform (bio-Mérieux SA, Marcy l'Etoile, France). Transcription of RNA to cDNA was performed with M-MuLV reverse transcriptase (USB Corp., Cleveland, OH, USA), using random hexamers. Each PCR run included a negative control (water control), which was treated identically to the clinical samples throughout the experiment. Samples in which no amplicon was obtained with this genotyping method were reassayed with the same primers but using the Qiagen Multiplex PCR Kit (Qiagen, GmbH, Hilden, Germany) ($n=135$). All procedures were performed with routine precautions to avoid contamination. In selected

cases, i.e. unusual G-types, the amplicons obtained were sequenced, using an AbiPrism 3100 Genetic Analyser (Applied Biosystems, Foster City, CA, USA).

Nucleotide sequence accession numbers

VP7 and VP4 partial sequences of some unusual strains (G6[P14], G8[P14] and G12[P8]) found in this study were deposited in the GenBank database under accession numbers GU563713–GU563720.

Statistical analysis

The chi-square test was used to compare the proportions of rotavirus-positive children. Analysis of variance was used to compare the ages of children infected with distinct rotavirus genotypes. Significance was set at $\alpha=5\%$.

Results

Characterization of rotavirus infection episodes

During the study period, 50,115 stool samples from children aged less than 5 years with AGE were obtained. Rotavirus was detected in 5,131 (10.2%), corresponding to 4,870 AGE episodes occurring in 4,816 children (2,688 boys and 2,128 girls). The seasonal distribution of rotavirus AGE episodes for each year of the study can be seen in Fig. 1. A total of 546 episodes occurred in infants aged less than 6 months (11.2%), 1,438 (29.5%) in infants aged 6 to <12 months and 1,920 (39.4%) in children aged 12 to <24 months. Among community-acquired rotavirus AGE episodes ($n=4,752$), 437 required hospitalization (9.2%). A further 118 (2.4%) episodes of rotavirus infection occurred in children hospitalized for other reasons.

Genotypes

G- and P-types were investigated in the samples of 1,538 rotavirus AGE episodes. Both types were obtained in 1,368 samples (88.9%, 91.9% including mixed infections) and the G-type was obtained in 1,438 (93.5%) (Table 1). Co-circulation of more than one G-type was a constant finding throughout the study, although one or two predominated in each season. The combination of G- and P-types most frequently detected in the 13 years of the study was rotavirus G1[P8] (57.5%, 786/1368), dominating in nine seasons and circulating in all (Table 2). To better illustrate circulation of rotavirus genotypes in the Basque Country, Fig. 2 shows data on the G-type (G1–G4) obtained through serotyping in this region between 1989 and 1995 [11]. Rotavirus G9[P8] (13.4%) was detected sporadically from

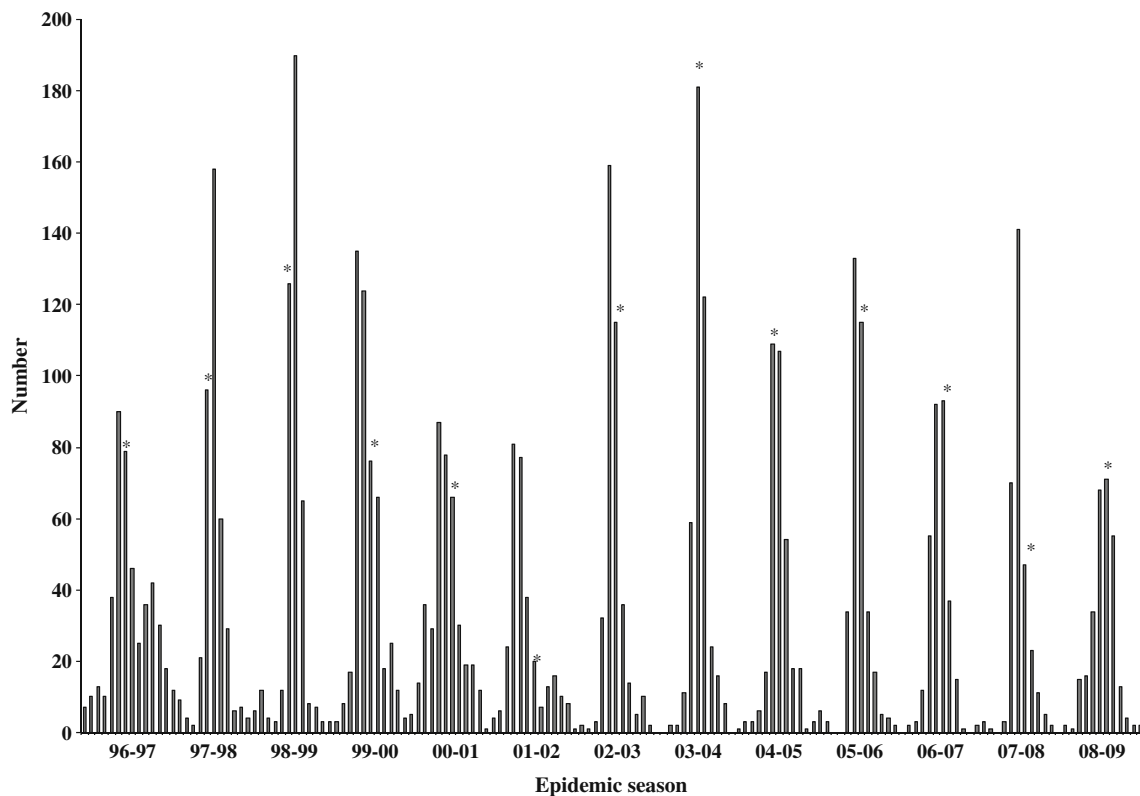


Fig. 1 Monthly distribution of acute gastroenteritis episodes due to rotavirus in children aged less than 5 years obtained in the regions of San Sebastián, Tolosa and Urola-Costa (Basque Country, Spain)

between July 1996 and June 2009. The *asterisk* denotes the month of January of each year

April 1998, in a total of nine seasons, and was codominant with G1[P8] in the 2005–2006 season and dominant for the first time from 2006–2007. Rotavirus strains G2[P4] and G3[P8] showed intense circulation in some seasons, and G2 [P4] became dominant in the 2003–2004 season. G4[P8] rotaviruses circulated widely in the first triennium of the study (27.8%, 65/234) and were predominant in the 1997–1998 epidemic, but represented only 0.9% (10/1134) of the strains genotyped after July 1999. Unusual G-types (G6, G8, G12) were detected in seven episodes (0.5%, six confirmed by sequencing, one G12 not sequenced) and unusual combinations of common G- and P-types, especially G1[P4] and G2[P8], were observed in eight episodes (0.6%). Mixed infections with more than one G-type were uncommon ($n=45$, 2.9%). A total of 150 rotavirus AGE episodes in which G- and P-types were studied occurred in children hospitalized for AGE due to rotavirus. We found no differences in hospitalization due to distinct genotypes, or in the age at which the infection occurred (Table 2).

Discussion

This study shows the dynamics of rotavirus G- and P-types circulation over 13 consecutive epidemics in children in the

Basque Country (Spain). The data from this study, together with those from a previous study [11], provide information on 20 years of monitoring of rotavirus G-types (July 1989–June 2009, 2802 strains studied) (Fig. 2). The burden of rotavirus disease on the health care system was substantial during the study period, despite a remarkable decrease in the incidence of rotavirus AGE observed in the first decade of this century [12]. In line with the results of previous studies performed in developed countries in recent years, we observed predominant circulation of G1[P8] strains, the emergence of G9[P8] strains, and scarce detection of G-type strains other than G1–G4 and G9 [2, 9, 13–15]. In 14 of the 20 seasons after 1989, the main G-type was G1, a percentage similar to that also observed over a 20-year period (1985–2004) in Palermo, Italy [16]. G1 caused more than half of the infections genotyped and showed significant circulation in all epidemics. In contrast, circulation of the remaining genotypes, especially G2, G3 and G4, was intermittent and was undetectable for varying periods (1–3 years). The predominance of G1 strains could be due to the wide genetic and antigenic heterogeneity of the population of strains of this genotype [16].

Rotavirus infections with G9[P8] strains were detected in April 1998 and subsequently in almost all epidemic seasons, although in small proportions until the 2005–2007

Table 1 Distribution of rotavirus genotypes causing episodes of acute gastroenteritis in children aged less than 5 years in the regions of San Sebastian, Tolosa and Urola-Costa (Basque Country, Spain) between July 1996 and June 2009

Genotypes	Yearly seasons (values given in %)													Total	
	96–97	97–98	98–99	99–00	00–01	01–02	02–03	03–04	04–05	05–06	06–07	07–08	08–09	<i>n</i>	(%)
G1[P8]	61.3	13.5	52.5	89.5	42.4	84.9	90.0	22.4	50.3	42.7	23.8	54.8	87.3	786	(51.1)
G2[P4]	3.2	19.5	15.8	0	28.8	1.4	0	55.2	0	0.5	0.7	35.0	1.8	197	(12.8)
G3[P8]	0	0.8	0	0	3.4	0	1.0	5.6	32.7	6.0	28.6	0	0	114	(7.4)
G4[P8]	21.0	32.3	8.9	1.2	0	1.4	2.0	0	2.0	0	0	0	2.7	75	(4.9)
G9[P8]	0	2.3	5.9	3.5	1.7	0	2.0	0	2.0	42.7	45.6	2.8	0	183	(11.9)
Unusual G- and P-types ^a	0	3.0	2.0	0	1.7	0	0	1.6	1.4	0	0	0.6	0.9	13	(0.8)
Subtotal G- and P-typed	85.5	71.4	85.1	94.2	78.0	87.7	95.0	84.8	88.4	91.7	98.6	93.2	92.7	1368	(88.9)
G1[N]	1.6	0.8	2.0	1.2	3.4	1.4	0	0	0.7	0.9	0	0	0	11	(0.7)
G2[N]	1.6	0.8	0	0	0	0	0	0	0	0	0	0	0.9	3	(0.2)
G3[N]	0	0	1.0	0	0	0	0	0	0	1.8	0	0	0	5	(0.3)
G4[N]	0	0.8	0	0	0	0	0	0.8	0	0	0	0	0	2	(0.1)
G9[N]	0	0.8	0	0	0	0	0	0	0.7	0	0	0	0	2	(0.1)
G12[N]	0	0	0	0	0	0	0	0	0.7	0.5	0	0	0	2	(0.1)
Subtotal G-typed P[N]	3.2	3.0	3.0	1.2	3.4	1.4	0	0.8	2.0	3.2	0	0	0.9	25	(1.6)
Mixed G-types ^b	4.8	7.5	5.9	0	0	1.4	1.0	0	1.4	2.8	0.7	5.1	5.5	45	(2.9)
Subtotal G-typed	93.5	82.0	94.1	95.3	81.4	90.4	96.0	85.6	91.8	97.7	99.3	98.3	99.1	1438	(93.5)
G-negative ^c	6.5	18.0	5.9	4.7	18.6	9.6	4.0	14.4	8.2	2.3	0.7	1.7	0.9	100	(6.5)
Total number of strains	62	133	101	86	59	73	100	125	147	218	147	177	110	1538	

^a 3 G1[P4] (1 in 1997–98; 1 in 1998–99; 1 in 2003–04); 5 G2[P8] (2 in 1997–98, 1 in 1998–99; 1 in 2000–01; 1 in 2003–04); 2 G12[P8] in 2004–05; 1 G6 [P14] in 2007–08; 1 G8[P8] in 1997–98; 1 G8P[14] in 2008–09

^b Mixture of G-types (number): G1+G2 (13); G1+G3 (1); G1+G4 (6); G1+G9 (12); G2+G3 (2); G2+G4 (1); G2+G9 (2); G3 + G4 (3); G3 + G9 (3); G4 + G9 (2)

^c 29 were P[8] and 17 [P4]

seasons. In Europe, sporadic detection of G9 strains was reported in Italy in the first half of the 1990s [17]. However, after the emergence of the new lineage 3 in the United States in 1993–1994, G9 strains spread throughout the world and became a common genotype globally [9]. In

Europe, the new strains were initially detected in the United Kingdom (1995–1996) combined with P-type 6, which was replaced by P-type 8 in the next few years [18], becoming dominant in several seasons from 2000 onwards: Belgium 2000–2001 and 2002–2003 [19], Ireland 2001–2002 [20],

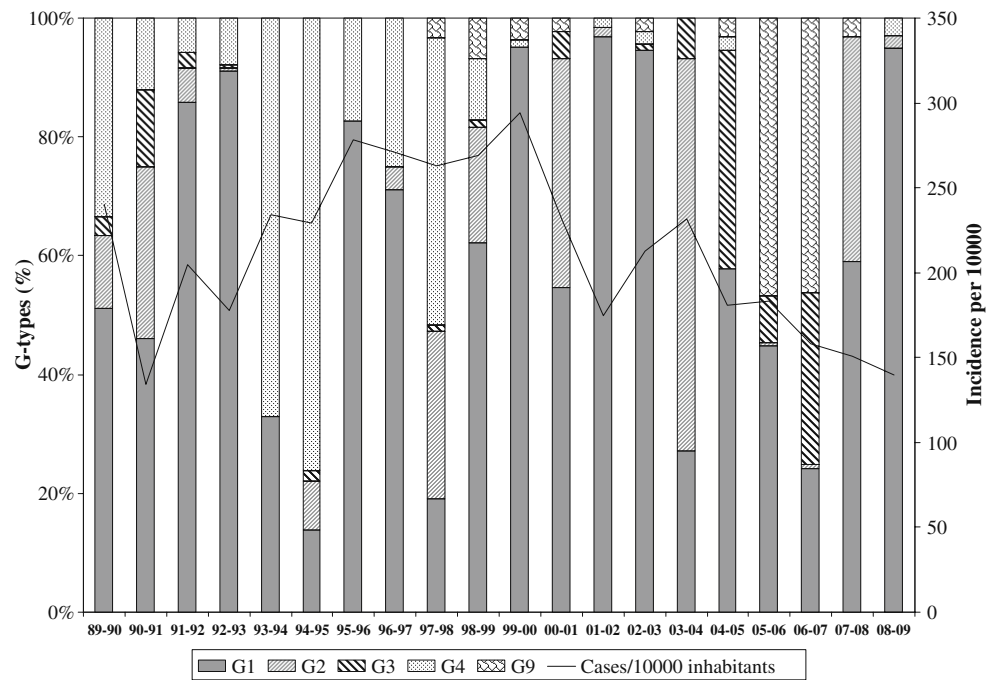
Table 2 Rotavirus genotypes in relation to hospitalization. Children hospitalized for community-acquired rotavirus gastroenteritis between July 1996 and June 2009

Genotype	Number	Hospitalized children		Age (months) mean ± standard deviation ^b
		N ^o	(%) ^a	
G1[P8]	786	81	(10.3)	15.4±9.9
G2[P4]	197	18	(9.1)	16.9±10.2
G3[P8]	114	14	(12.3)	15.3±9.9
G4[P8]	75	4	(5.3)	16.9±10.7
G9[P8]	183	19	(10.4)	16.1±10.4
Other (unusual strains and mixed G-types)	58	5	(8.6)	
G-negative	100	9	(9.0)	
Total genotyped	1538	150	(9.8)	

^a Chi squared test with 4 degrees of freedom (G1–G9)=2.74, $p=0.60$ (non-significant)

^b Analysis of variance (G1–G9), $F=0.96$; $p=0.43$ (non-significant)

Fig. 2 Percent distribution of the main rotavirus G-types (G1–G4 and G9) in children aged less than 5 years with acute gastroenteritis due to rotavirus in the regions of San Sebastián, Tolosa and Urola-Costa (Basque Country, Spain) in 20 consecutive seasons. The distribution from July 1989–June 1996 was studied by serotyping (G1–G4 types, see reference 11) and between July 1996 and June 2009 by genotyping (G1–G4 and G9 types, present study). The percentage of strains that could not be G-typed was 22% with serotyping and 6.5% with genotyping. The continuous line (referring to the secondary axis) represents the incidence of rotavirus infection (antigen-positive cases) in children aged less than 5 years



France 2004–2005 [14], Hungary 2004–2006 [21]. Our study, as well as one other study [22], demonstrates that epidemic circulation of the G9[P8] strains in Spain was delayed until the 2005–2006 season. The predominance of G2 strains in Brazil after the introduction of the G1P[8] monovalent vaccine could be due to selection of strains against which the vaccine is less effective [23]. Interestingly, G2 strains circulated widely in the Basque Country in eight seasons between 1989 and 2009 (Fig. 2) and were dominant in the 2003–2004 epidemic, before the vaccines were commercialized. These results show that substantial fluctuations occur naturally in the circulation of this genotype and that only prolonged surveillance is useful to analyze the effect of substitution after vaccination. A well-documented finding in this survey was the marked decrease in the current decade in the circulation of the G4 genotype. This genotype circulated widely in our environment in the 1990s but only sporadically after 1999, in line with prior reports in Spain [22] but in contrast with reports from other European regions [2, 22, 24–26].

We detected few infections with unusual combinations of G- and P-types, notable combinations being the G1[P4] and G2[P8] genotypes, which represented 0.6% of the genotyped episodes. These genotypes were probably secondary to reassortment among co-circulating human genotypes [18, 27] and were also the most frequent unusual combinations found in other regions [9, 15, 18, 26]. The origin of these recombinant viruses probably lies in mixed infections, which were also infrequent in our study (2.9%). Three strains belonging to G-types 6 (G6[P14]) and 8 (G8[P8]) and G8 [P14]) were detected. G6 and G8 strains are frequently found

in bovine cattle [9] and are rarely detected in human infections in Europe [14, 15, 18, 21, 25, 26]. Human [P14] rotavirus strains have been reported exceptionally across the globe and probably represent occasional interspecies transmission from ruminants [28]. Likewise, we detected G-type 12 strains, which have recently spread throughout the world and are increasingly identified in Europe [14, 25, 29]. Of the 1,538 rotavirus strains investigated, 6.5% could not be G- and P-typed, a percentage that could be expected from the results of other studies [9, 12].

The percentage of strains from hospitalized patients was similar for the distinct G-types; consequently, differences in their aggressivity seems unlikely [2, 25]. Greater pathogenicity has been associated with some genotypes [30, 31], which is currently a cause of controversy. This greater pathogenicity could be related to the introduction of new strains against which the population lacks immunity [31] and could therefore be transitory. The pattern of circulating genotypes shows continental and subcontinental variations, which could be important when predicting the potential impact of vaccination [9, 13, 15]. In the Basque Country, a G-type and/or a P-type was included in the monovalent and pentavalent vaccines for 85.4% and 99.8% of the genotyped strains, respectively; when the simultaneous presence of the G- and P-types contained in the vaccines was considered, these percentages were 57.5% and 71.6%.

In conclusion, G1–G4 and G9 represented >99% of the circulating rotaviruses in the Basque Country between 1996 and 2009. G-type 1 strains predominated (57.5%), circulating significantly in all epidemics. Co-circulation of more

than one genotype was normal, one of which occasionally became dominant for one or two seasons, in fluctuations that are currently unpredictable. Other G-types, such as G6, G8 and G12, as well as reassortment of common G- and P-types, were detected occasionally. In view of the circulating genotypes in this region and the changes produced over time, vaccine efficacy can be expected to be high. However, after the introduction of vaccination, rotavirus surveillance should be maintained due to the high genetic variability of this virus.

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