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Incidence, seasonality and serotypes of rotavirus in Gipuzkoa (Basque Country), Spain. A 14-year study

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SUMMARY

Over a 14-year period (1984–97) the presence of rotavirus in stool samples from children under 15 years with acute gastroenteritis was studied by enzymoimmunoanalysis. Serotyping (G1–G4) was performed using monoclonal antibodies. A total of 17348 children under 15 were investigated. Rotavirus was detected in 3637 (21·0%) specimens, 74·6% of which were from children younger than 2 years old. G1 and G4 were the most frequent serotypes. In 1991–7, the minimum incidence of rotavirus gastroenteritis in children under 4 years of age was 21·7 cases/1000 children/year. By the age of 5 years, at least 1 out of 11·3 children and probably 1 out of every 5–6 children in this area had experienced an episode of rotavirus gastroenteritis that required medical care. In the 1984–90 period a clear seasonality was not observed but in the second period of the study (1991–7), seasonality was marked, with peak activity in winter.

INTRODUCTION

Rotavirus is the main cause of gastroenteritis in childhood in the world. Every year, rotavirus gastroenteritis kills more than 800000 children in developing countries [1, 2]. In industrialized countries, the infection usually is more benign, but it claims a large amount of expensive health-care resources [1–5]. By the age of 5, almost all children have been infected. The incidence of hospitalization for rotavirus gastroenteritis has been studied in various countries [2, 3, 6–9]. In contrast, there are few studies of outpatients because the necessary virological studies are not routinely performed for these patients. However, such studies are essential for understanding the global impact of this infection.

In recent years, various prototype rotavirus vaccines have been studied. In clinical trials it has been documented that some of the vaccines provide a good level of protection against diarrhoea caused by this virus [10, 11], particularly against the most severe forms. As a result of this situation, it has become necessary to collect objective information on the impact of this infection on health in different populations in order to develop a vaccination policy. The present study collected information on cases of confirmed rotavirus gastroenteritis in inpatients and outpatients in the province of Gipuzkoa (Basque Country, Spain) during 14 years (1984–97).

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METHODS

The province of Gipuzkoa is located in the north-eastern part of the Autonomic Community of Basque Country (Spain), which is bounded to the north by the Cantabrian Sea and France. It has an area of 1997 km^2

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with 682883 inhabitants. The climate is temperate, with high levels of regular rainfall. Nuestra Señora de Aránzazu Hospital (96 paediatric beds) provides care for 400480 inhabitants of Donostialdea and Tolosaldea, most of whom live in urban areas; 52577 are younger than 15. This figure accounts for 58% of the children in the province of Gipuzkoa and 19% of the children of the Autonomic Community of Basque Country, respectively [12]. In the 1980s Basque Country experienced a major reduction in birth rate.

Patients

This study included all patients under 15 who sought medical care for acute gastroenteritis and for whom stool cultures were requested between January 1984 and December 1997. In this time period, rotavirus analysis was carried out systematically on all stool samples sent to the microbiology laboratory. Seventy percent of patients studied were children seen at the hospital paediatric emergency service, and the remainder were children seen in the hospital outpatient clinics. The children who acquired rotavirus infection during their hospital stay comprised less than 7% of the sample. Patients, not just stool samples, were evaluated. Cases of repeat infections within a 6-month time interval were eliminated, in order to avoid duplicated patients with a prolonged period of rotavirus excretion. If the same patient had a new infection after 6 months, the case was considered a new case.

Laboratory methods

Group A rotavirus antigen in stool was detected with commercial enzymoimmunoanalysis kits following manufacturers' instructions: until 1989: Enzygnost Rotavirus Antigen, polyclonal (Behringwerke AG, Marburg, Germany); 1990–3: Enzygnost Rotavirus Antigen, monoclonal, and since 1994, IDEIA™ Rotavirus (Dako Diagnostics Ltd., Ely, Cams, UK). In children, the sensitivity and specificity of the ELISA methods used exceeds 80% [13, 14].

Positive specimens collected after March 1989 were stored at −40 °C for further study. Serotyping was carried out with the technique of B. S. Coulson [15] using monoclonal antibodies for serotypes G1–G4 (Sylenus Laboratories, Hawthorn, Australia). Only samples obtained between April 1989 and December 1995 with an optical density of >1000 in the rotavirus antigen test were processed for serotyping.

Data analysis

Incidences were calculated using the official 1986 and 1996 population figures (municipal censuses) of the Basque Institute of Statistics [12, 16]. χ^2 test was used to compare the proportions of rotavirus-positive children. The level of significance chosen was $\alpha = 5\%$.

RESULTS

Between 1984 and 1997, 28860 stool samples from 17348 patients under 15 (62·5% under 2) with acute gastroenteritis were received for microbiological study. Rotavirus antigen was detected in 3637 patients (21·0%): 1947 males (53·5% and 1668 females (45·9%) (male/female ratio 1:2:1). In 22 newborn patients (0·6%), sex was not noted. The annual number of detected patients with rotavirus in 1984–97 was 367, 382, 152, 222, 86, 249, 101, 283, 217, 158, 325, 398, 402 and 295, respectively. The percentage of rotavirus infections detected in patients with gastroenteritis who were included in the study was similar in the two study periods: 21·1% (1559/7399) in the 1984–90 period and 20·9% (2078/9949) in the 1991–7 period.

Incidence by age

Seventy-five percent (74·6%) (2713/3637) of the patients with rotavirus gastroenteritis were under 2 years old. Table 1 shows the annual incidence (number of children with rotavirus gastroenteritis/1000 children/year) in relation to age in the 1984–90 and 1991–7 periods. A higher incidence of rotavirus infection was observed in 1991–7. The mean annual incidence per 1000 inhabitants under 15 years was 2·6 cases in 1984–90 and 5·6 cases in 1991–7. The highest incidence was observed in children 6–11 months-old, reaching 56·6 cases/1000 children/year in the 1991–7 period.

Seasonality

Rotavirus was detected throughout the study period and in every month of the 168-month study, except two non-consecutive months. The seasonal distri-

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Table 1. *Distribution and annual incidence by age of the patients with rotavirus gastroenteritis detected in Donostialdea and Tolosaldea (Gipuzkoa, Basque Country, Spain) in 1984–90 and 1991–7*

	1984–90			1991–7				
Age	No. of rotavirus cases	Population*	Incidence†	No. of rotavirus cases	Population*	Incidence†	χ^2	*P*
0–5 months	343	1821	26·9	282	1595	25·3	0·76	0·38
6–11 months	405	1821	31·8	632	1595	56·6	121·53	< 0·001
12–23 months	347	3666	13·5	704	3091	32·5	226·20	< 0·001
24–35 months	117	3991	4·2	218	3116	10·0	64·36	< 0·001
36–47 months	42	4395	1·4	68	3143	3·1	18·59	< 0·001
4–7 years	102	21183	0·7	73	12586	0·8	1·49	0·22
8–14 years	61	49571	0·2	43	27451	0·2	1·48	0·22
Unknown	142			58				
Total	1559	86448	2·6	2078	52577	5·6	592·6	< 0·001

* Population at risk every year.
† Mean annual incidence per 1000 children of the corresponding age.

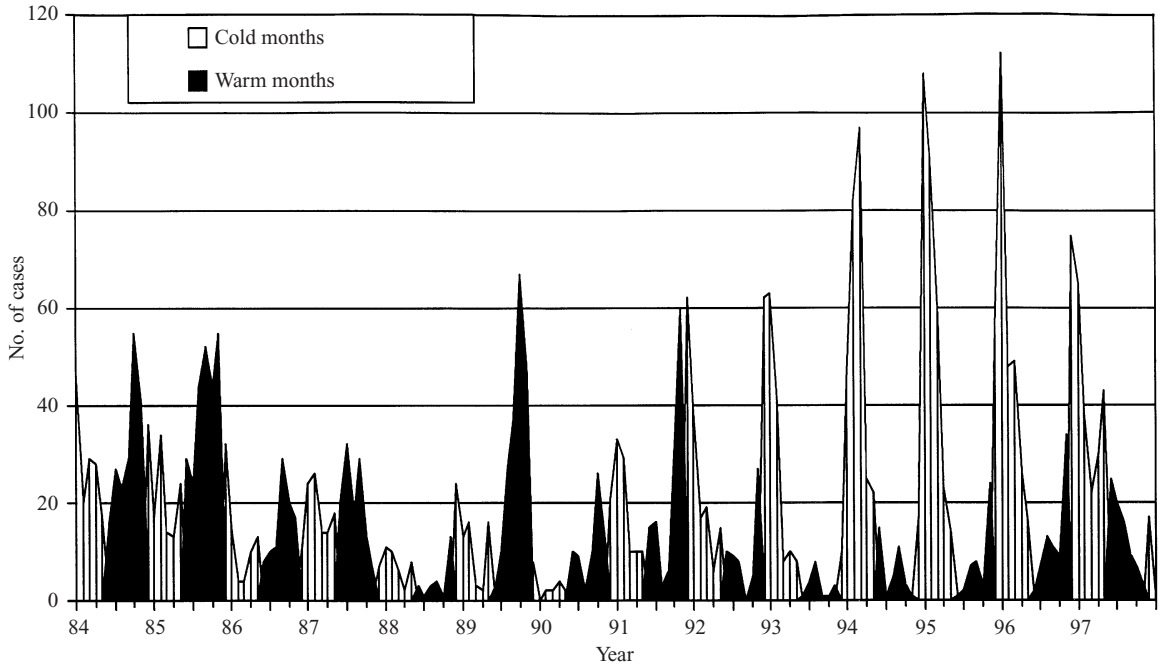

Fig. 1. Seasonal distribution of cases of rotavirus gastroenteritis detected in children under 15 in Donostialdea and Tolosaldea (Gipuzkoa, Basque Country, Spain) in 1984–97 ($n = 3637$). Cases occurring in cold months (December–May) are shown in white and cases occurring in warm months (June–November) are shown in black.

bution can be seen in Figure 1. From the situation of high-grade endemism with irregular rotavirus circulation and moderate seasonal variations that characterized the first period (1984–91), the pattern of infection became typically seasonal with large winter outbreaks after 1991. The monthly distribution of rotavirus infections and the percentages of rotavirus gastroenteritis relative to the total number of episodes of diarrhoea are shown in Table 2. In the 1984–90 period, these percentages varied little from month to month (range 15·3–26·3%). However, in the 1991–7 period the variations were more marked, with rotavirus being detected in 50·3% of the diarrhoea cases seen in January but in only 5·1% of the diarrhoea cases seen in September. In 1984–90, rotavirus activity occurred mainly from September to February, whereas in 1991–7 the peak activity was from December to March.

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Table 2. *Monthly distribution of children with gastroenteritis (overall and rotavirus) in the two time periods studied (1984–90 and 1991–7)*

	1984–90			1991–7				
	Gastro-enteritis cases	Rotavirus positive		Gastro-enteritis cases	Rotavirus positive			
Month	(*n*)	*n*	(%)	(*n*)	*n*	(%)	χ^2	*P*
Jan.	480	126	26·3	926	466	50·3	75·16	< 0·001
Feb.	434	112	25·8	828	346	41·8	31·45	< 0·001
Mar.	395	72	18·2	684	264	38·6	48·45	< 0·001
Apr.	426	73	17·1	605	130	21·5	2·99	0·08
May	498	98	19·7	675	128	19·0	0·09	0·76
June	557	89	16·0	741	69	9·3	3·22	< 0·001
July	737	113	15·3	763	59	7·7	21·33	< 0·001
Aug.	799	128	16·0	923	60	6·5	34·90	< 0·001
Sept.	888	190	21·4	910	46	5·1	105·25	< 0·001
Oct.	917	226	24·7	1019	57	5·6	140·37	< 0·001
Nov.	709	193	27·2	904	152	16·8	25·60	< 0·001
Dec.	559	139	24·9	971	301	31·0	6·51	0·011
Total	7399	1559	21·1	9949	2078	20·9	0·09	0·76

Serotype distribution

The rotavirus serotype was determined in 1264 patients of 1731 diagnosed between April 1989 and December 1995. The rotaviruses of 991 patients (78·4%) were typable as serotypes G1–G4. G1 was the most frequent serotype, being detected in 562 (56·7%) of the serotypable cases. This serotype predominated until 1993. It was followed by serotype G4 in 321 (32·4%), G2 in 84 (8·5%), and G3 in 24 (2·4%). Serotypes G1 and G4 were detected every year in the 7 years in which serotyping was performed; the annual number of isolates in 1989–95 was 76, 43, 132, 118, 88, 47 and 58 for serotype G1 and 55, 3, 21, 4, 20, 90 and 128 for serotype G4, respectively. Serotypes G2 and G3 were detected sporadically or as small clusters of cases.

DISCUSSION

Over a 14-year period, the present study collected information on cases of rotavirus infection diagnosed and their epidemiological features in a specific geographic area (Gipuzkoa, Basque Country, Spain) and well-defined population, children under 15. Since the presence of rotavirus antigen was investigated in all stool samples using homogeneous methods throughout the study period, we assume that the variations found reflect the dynamics of viral circulation in our region. The cases studied do not represent every case of rotavirus gastroenteritis occurring in the study area. In fact, we estimate that the incidence reported here represents only 50% or less of the infections that lead to clinical manifestations of gastroenteritis, reflecting severe or moderately severe cases. In 1991–7 the minimum incidence of rotavirus gastroenteritis in children under 15 years was 5·6 cases/1000 children/year. In this period, by the age of 5, at least one out of every 11·3 children and probably 1 out of every 5–6 children in the geographic study area had gastroenteritis due to rotavirus that required medical attention. This 50% figure was based on the diarrhoeal episodes reported to the Health Department and the proportion of these that had a stool sample analysed in the Department of Microbiology [17]. These findings slightly exceed the estimates of the effects of rotavirus infection on children reported in the US [5, 6]. Glass and colleagues [6] estimated that by the age of 5 years, one out of every 8 children required medical care for a rotavirus gastroenteritis. Tucker and colleagues [5] estimated that by the age of 5 one out of every 9·5 children required medical attention and one out of every 24 children required urgent medical care for rotavirus gastroenteritis. In another study carried out in our region, we investigated the incidence of hospitalization for rotavirus infection in the same population and found that one

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out of every 77 inhabitants under 15 years of age in the study area had been hospitalized for rotavirus gastroenteritis [18].

As has been observed in other temperate regions of the world [7, 8, 19–21], rotavirus infection was present throughout the year, but was more frequent in cold months. However, over the 14-year study period, important changes were observed in the seasonal pattern. In the 1980s, seasonality was not very marked and there were peaks of activity in summer and autumn. Later, in the 1990s, seasonality was intense and peak activity occurred in winter. In most studies, seasonality did not vary much over long time periods [21], although variations in the timing of peak activity were reported [19–23]. The typical pattern of regular epidemics that appear in cold months in industrialized countries is similar to that observed in our region in the 1991–7 period of this study. However, the seasonal pattern observed in the 1980s recalls the pattern reported in less-developed countries with a tropical climate in which the seasonality of rotavirus infection is unclear or non-existent [2, 19]. Improvements in hygiene, health and social conditions of the local populace in recent times probably have contributed to the change in seasonal pattern. In fact, a decrease in the prevalence of other infections with faeco-oral transmission has been noted it in our region in recent years [24, 25]. One of the local improvements has involved drinking water. Although more than 99% of inhabitants had running water at home, drinking water was disinfected with gaseous chlorine until the end of the 1980s. At the end of 1989 a new water supply treatment plant was inaugurated which provided coagulation, flocculation, sedimentation, filtration and chlorination treatment [26]. This treatment plant supplies most of the people living in the study area. Before this water supply plant was inaugurated, rotavirus was detected in water samples of the network following a gastroenteritis outbreak [26]. In other countries, gastroenteritis outbreaks originating from water supplies have been attributed to rotavirus [27–29]. Likewise, it has been suggested that the transmission of rotavirus by water favours an endemic status and absence of seasonality of this infection [27]. We think that water could have been a frequent transmission route of rotavirus during the 1980s, specially in the warmer months, but not after the new water supply plant was established. However, this hypothesis remains speculative in the absence of supporting evidence.

The rapid decline in birth rate that has recently taken place in Basque Country also could have contributed to the appearance of epidemic forms, rather than a more constant viral circulation, by decreasing familial transmission. In contrast with the total period fertility rate in 1975–6 of 2·67 children per woman, by 1990–1 it was only 0·97 [30]. However, the changes in the epidemiological pattern of rotavirus gastroenteritis that are consistent with improved hygiene and health and a lower birth rate cannot explain the increased incidence observed in the 1991–7 period of the study. This apparent contradiction could be explained in part by social factors such as the growth in the use of the Public Health System and day-care centres and changes in the way in which the Public Health System is used by the population. In fact, the number of patients seen for gastroenteritis and for rotavirus gastroenteritis both increased by about 25% (data not showed). The seasonal pattern observed in the 1984–90 period indicates a level of rotavirus transmission that is more sustained than in the later period and consistent with an earlier and more efficient viral transmission. It is possible that acquisition of the infection at later ages, as in the 1991–7 part of the study, may make diarrhoeal symptoms more likely contributing to the increased incidence observed. In fact, rotavirus infections are more frequently asymptomatic in newborns than in older children [2, 31].

The overall pattern of serotypes was similar to those described in other countries of continental Europe [32, 33]. As in most other studies, the G1 serotype was predominant [1, 2, 32–37]. The second most frequent serotype was G4, which predominated in two consecutive epidemic periods (1993–4 and 1994–5). Every year, a single serotype was responsible for the outbreak, except in 1989 and 1993–4 during which both the G1 and G4 serotypes co-circulated at high levels.

In Spain, the epidemiology and impact of rotavirus infections are little known. Rotavirus infections are not subject to specific surveillance. The main indicator for this type of infection is the information derived from the Microbiological Information System, which consists of a series of laboratories that voluntarily report cases [38]. However, only limited information can be obtained from this source and from the few published studies available [39, 40]. Still this information in conjunction with the results of this study suggests that the epidemiology of rotavirus infection in Spain is similar to that observed in other industrialized countries.

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