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PRIMARY CARE-BASED SURVEILLANCE TO ESTIMATE THE BURDEN OF ROTAVIRUS GASTROENTERITIS IN CHILDREN AGED <5 YEARS IN EUROPE

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BACKGROUND

- Rotavirus (RV) is the leading cause of acute gastroenteritis (AGE) in infants and young children worldwide.[1]
- Recent hospital-based surveillance shows RVGE to place high demands on European healthcare systems, accounting for 56.2% of hospitalizations and 32.8% of ER visits due to community-acquired AGE in children aged <5 years.[2]
- **S**urveillance for **P**rimary Care Centers for **R**otavirus **I**nfections in **K**ids (**SPRIK**) was undertaken to estimate the burden of RVGE leading to a general practitioner (GP)/ pediatrician visit among European children aged <5 years and to assess family transmission patterns of RV.
- Data generated by the study will be useful for policy makers in determining the need for implementation of RV vaccination in their countries.

METHODS

- This was a prospective study involving 88 GP/pediatrician practices covering well-defined populations in 6 European countries (Czech Republic, Germany, Italy, Poland, Spain and the UK).
- The **primary study objective** was to estimate the incidence of RVGE leading to a GP/pediatrician visit among children <5 years of age in a well-defined population.
- **Secondary study objectives** were to:
  - determine age, disease severity, and seasonal distribution of RVGE among children <5 years of age
  - identify prevalent RV genotypes among children <5 years of age
  - assess transmission patterns of RVGE among household children <5 years of age.
- Practices were selected at convenience based on existing medical practice networks. In each country, a GP/pediatrician network was selected which covered a surveillance population of 5,000–10,000 children <5 years of age in towns/municipalities with well-established boundaries.
- All children aged <5 years from the defined population presenting with AGE were screened for recruitment and their parents/carers asked for written informed consent for stool sample collection and testing.
- AGE was defined as diarrhea (≥3 loose stools/24 hours) for less than 14 days.
- Stool samples were screened in the physician's office for the presence of RV using a rapid stool diagnostic test (Rota-Strip, Coris Bioconcept, Belgium).
- If a stool sample was not available for testing at the time of the initial visit, parents/carers were asked to provide a stool sample within 4 days.
- All RV+ samples were confirmed and characterized in the same reference laboratory using a RT-PCR based method to determine RV G and P types.
- RV+ children were enrolled for study participation and parental interview. Parents were contacted by phone 14 days after the study visit to obtain follow-up information on disease outcome.
- Parents of enrolled children who had other children aged <5 years in the household and who gave their written consent were asked to contact the GP/pediatrician if any of these other children developed AGE within 14 days of enrolment of the study subject. A study nurse was dispatched to the household or parents visited the GP/pediatrician and a stool sample was collected from the sick child.

RESULTS

Study population and proportion of PCR+ cases

- From October 2005–May 2007, 5009 children aged <5 years presenting with AGE were screened for study participation. Of these, 4093 were tested with Rota-Strip, 590 of whom were RV+ (14.4%).
- The number of cases varied considerably between countries, being highest in Spain and lowest in the UK.
- A total of 518/5009 children (10.3%) were RV+ by PCR. This proportion varied between countries, ranging from 1.7% in the UK to 18.8% in Germany (Table 1).

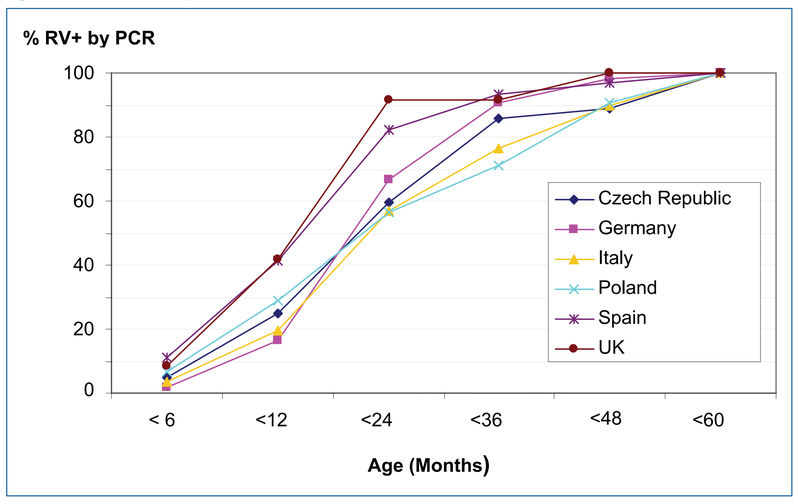
Table 1. Proportion of cases who were RV+ by PCR

Country	No. of children aged <5 years with AGE	No. of cases RV+ by PCR	% RV+ by PCR	95% CI
Czech Republic	550	64	11.6	9.1, 14.6
Germany	320	60	18.8	14.6, 23.5
Italy	661	110	16.6	13.9, 19.7
Poland	662	76	11.5	9.2, 14.2
Spain	2088	196	9.4	8.2, 10.7
UK	728	12	1.7	0.9, 2.9
Overall	5009	518	10.3	9.5, 11.2

CI, confidence interval

- A total of 509 PCR+ subjects were eligible for inclusion in the per protocol analysis. Mean (±SD) age was 20.1±13.3 months and 48.9% were female.
- In all, 69.1% of PCR+ RVGE occurred in children aged <2 years, 30.1% in those aged <1 year and 6.9% in infants aged <6 months (Fig. 1).

Figure 1. Cumulative distribution of the percentage of AGE cases due to RV (PCR+) by age for each country



Incidence rate of PCR+ RVGE

- The incidence rate of PCR+ RVGE among all children aged <5 years varied between countries, from 26.9 per 1000 person-years in Spain to 9.5 per 1000 person-years in Poland (Table 2).

Table 2. Population-based incidence of PCR+ RVGE among all children aged <5 years

Country*	Estimated RVGE cases	Total no. of children-years <5 years old	Incidence per 1000 person-years	95% CI
Czech Republic	68	5178.5	13.1	10.2, 16.6
Italy	105	5829.45	18.1	14.8, 21.9
Poland	80	8431.9	9.5	7.5, 11.8
Spain	247	9188.5	26.9	23.6, 30.4

**Incidence could not be calculated for Germany due to lack of information for the denominator i.e. total number of children-years <5 years old; incidence was not calculated for the UK as the number of recruited children was much lower than expected*

- In the three countries where incidence could be calculated by age, the highest incidence of PCR+ RVGE was seen in children aged 12 to <24 months and/or in children aged 0 to <12 months (Table 3).

Table 3. Population-based incidence of PCR+ RVGE by age range

Country*	Age range (months)	Estimated RVGE cases	Total no. of children-years <5 years old	Incidence per 1000 person-years	95% CI
Italy	0–<12	20	1069.7	18.9	11.6, 29.2
	12–<24	41	1185	**34.7**	24.9, 47.0
	24–<36	20	1165.9	16.9	10.3, 26.2
	36–<48	14	1189.8	11.8	6.4, 19.7
	48–<60	10	1218.9	8.4	4.1, 15.3
Poland	0–<12	22	1562.6	**14.1**	8.9, 21.4
	12–<24	21	1629	12.8	7.9, 19.6
	24–<36	13	1668.6	7.5	3.9, 13.0
	36–<48	14	1686	8.4	4.6, 14.1
	48–<60	9	1598.7	5.4	2.4, 10.3
Spain	0–<12	95	1797.6	52.6	43.5, 64.3
	12–<24	100	1884.9	**53**	43.1, 64.5
	24–<36	31	1886.9	16.3	11.1, 23.2
	36–<48	9	1832.9	4.7	2.1, 9.1
	48–<60	9	1786.2	5.1	2.3, 9.6

**Only Italy, Poland and Spain provided information for the denominator by age group*

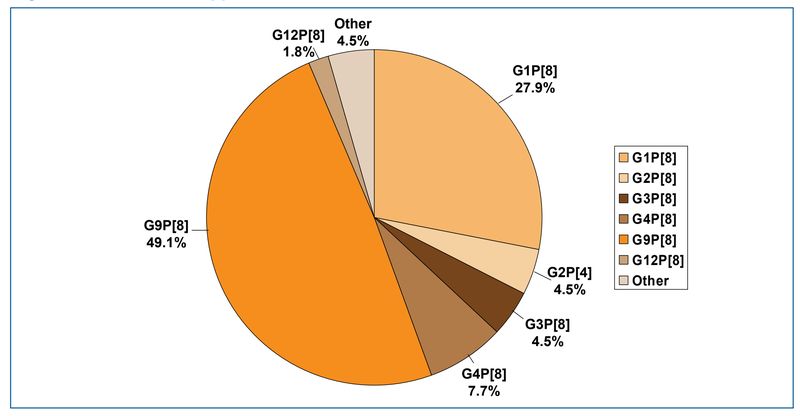
Seasonality

- 93.1% of all PCR+ RVGE cases occurred between the months of December and May.
- This seasonal distribution of RVGE was seen in all participating countries and across all age groups.

RV G and P types

- 509 RVGE PCR+ stool samples were available for genotyping in the reference laboratory.
- Predominant RV types were G9P[8] and G1P[8], accounting for 49.1% and 27.9% of cases, respectively (Fig. 2). G2P4 represented less than 5% of total strains.
- RV type distribution varied between countries:
  - G9P[8] was the most common type in Poland (54/76 [87.5%]) and Spain (171/196 [87.2%]).
  - G1P[8] was predominant in the Czech Republic (56/64 [87.5%]), Italy (45/107 [42.1%]) and the UK (9/12 [75%])
  - G4P[8] and G1P[8] both prevailed in Germany (17/54 [31.5%] and 13/54 [24.1%], respectively).

Figure 2. Overall RV type distribution (N=509)



RVGE disease characteristics

- A shown in Table 4, most children with RVGE (83.8%) presented with moderate or severe disease (assessed on the Vesikari scale) and with mild/moderate or no dehydration.[3]
- The proportion of severe cases varied between countries, ranging from 21.1% in Poland to 48.1% in Germany.

Table 4. Disease characteristics of PCR+ RVGE

Characteristic	PCR+ RVGE (N=509)
Severity (Vesikari scale)[6], %	
Mild (1–6)	16.2
Moderate (7–10)	46.1
Severe (≥11)	37.7
Symptoms, %	
Vomiting	79.2
Fever	66.8
Change in behavior	86.1
Degree of dehydration, %	
No dehydration	63.5
Mild or moderate	35.5
Severe	0.8
Unknown	2.2
Treatment received, %	
Oral rehydration	75.5
IV rehydration therapy	2.6

Household transmission of RVGE

- Overall, 19.7% (24/122) of other children aged <5 years resident in the same household developed RVGE in the 14 days after their sibling visited the GP/pediatrician because of RVGE.
- The percentage of primary RVGE leading to secondary disease among household children aged <5 years varied between countries and was as high as 38.5% in the Czech Republic.

CONCLUSIONS

- This is the largest European study to assess the burden of RVGE in outpatient settings and household transmission patterns to date, with a high participation rate.
- Results show the burden of RVGE to be high among children aged <5 years visiting primary care centers for AGE, with RV accounting for 10.3% (1.7–18.8%) of all AGE cases.
- As in other recent European surveillance studies,[2,4] disease burden appears greatest among the youngest children with 69.1% of all RVGE occurring among children aged <2 years and 30.1% in those aged <1 year.
- RV G and P types identified were similar to other recent studies in Europe.[5,6] RV type distribution varied considerably between countries as previously reported.
- Almost all (93.1%) RVGE occurred between the months of December and May, which is the RV season in Europe.
- Analysis of household transmission rates show that RVGE can be easily transmitted to other children aged <5 years resident in the same household, with up to 38.5% of primary RVGE leading to secondary disease among household children <5 years of age.
- These findings provide evidence that RVGE disease burden is considerable among outpatients and supports the concept that early RV vaccination may have a major impact in reducing RVGE morbidity in Europe, as well as providing a useful baseline indicator of RV burden for assessment of vaccine impact.

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