

BMJ Open Burden of rotavirus gastroenteritis in children <5 years of age in Greece: hospital-based prospective surveillance (2008–2010)

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ABSTRACT

Objectives: This study describes the epidemiology of rotavirus (RV) gastroenteritis (GE) disease following the introduction of RV vaccination in Greece in 2006.

Design: A prospective hospital-based surveillance.

Setting: A multicentre study was conducted at six hospitals in Greece between July 2008 and March 2010. The hospitals selected served 70% of the paediatric population in Greece.

Participants: Children aged <5 years who visited the emergency rooms (ERs) or hospitalised with acute GE or acquired acute GE 48 h after hospitalisation and with a confirmed RV-positive stool test were enrolled.

Primary and secondary outcome measures: The occurrence of RVGE among all acute GE ER visits and hospitalisations and the occurrence of nosocomial RVGE are reported with 95% exact CI. Age-specific proportions of RVGE, seasonality and prevalence of RV genotypes were estimated. Incidence rates of nosocomial acute GE and RVGE are expressed in terms of 1000 children-years with 95% exact Poisson CI. Median duration of hospitalisation and prolongation of hospitalisation due to nosocomial RVGE were reported.

Results: RVGE proportions were 10.7% (95% CI 5.5% to 18.3%) and 23.8% (95% CI 20.0% to 28.0%) of acute GE ER visits and hospitalisations, respectively; and 21.6% (95% CI 9.8% to 38.2%) of nosocomial acute GE cases. The majority of RVGE cases occurred in children aged <24 months (53%). RV infection peaked between December and May (31.4%). The most common RV genotypes were G4 (59.6%) and P [8] (75.2%). The median duration of RVGE hospitalisation was 4 days (range 1–10 days). Incidence of nosocomial RVGE was 0.3 (95% CI 0.2 to 0.7)/1000 children-years. The median prolongation of hospitalisation due to nosocomial RVGE was 5 days (range 4–7 days).

Conclusions: Our analysis report low proportions of RVGE among acute GE cases in Greece which may be attributable to available RV vaccination in Greece. Future impact/effectiveness studies are necessary to confirm this finding.

Clinical Trial Registration: NCT00751686.

Strengths and limitations of this study

- The prospective design allowed us to collect robust demographical and clinical data on children with rotavirus gastroenteritis (RVGE) disease as well as to confirm RVGE cases by stool testing.
- Low numbers of patients who were enrolled, which resulted in RVGE proportions that may not be fully representative of the paediatric population in Greece.
- In addition, we did not have data for the same settings prior to vaccine introduction to assess any decline in the burden of RVGE disease after implementation of RV vaccines in Greece.

INTRODUCTION

Rotavirus (RV) is the most common cause of acute gastroenteritis (GE) in children aged <5 years worldwide.^{1 2} In the European Union (EU), RVGE is the most frequent vaccine-preventable illness in children aged <5 years and is associated with significant morbidity.^{3–5} Few observational studies describe the epidemiology of RVGE in Greece.^{6–10} RVGE proportions depending on the season have been reported in the range 20–50% of acute GE cases.^{6–10} Two live, oral RV vaccines—*Rotarix* (GlaxoSmithKline Vaccines, Belgium) and *RotaTeq* (Merck and Co, Inc, Whitehouse Station, New Jersey, USA), have been introduced worldwide and widely used since 2006.¹¹ Many countries in the EU have implemented vaccination of healthy infants against RV following the recommendation of the WHO.^{11 12}

Although, RV vaccination in Greece was included in the national immunisation programme in December 2011,¹³ the vaccine coverage attained until today is low, which is due in part attributed to the cost of the

vaccine with partial reimbursement (75%).¹² Moreover, RV vaccination in Greece is an optional vaccine and is recommended only for high-risk groups,¹³ which has led to the perception that RVGE is not a serious disease.¹² Some recent observational studies demonstrate a decline in the burden of RVGE disease in Greece^{9–10} since vaccine introduction in 2007; however, further investigation is warranted to assess whether this decline was due to vaccine uptake or not. This prospective, hospital-based observational study aimed to provide data on the epidemiology of RVGE disease 1 year after RV vaccines became available in Greece.

METHODS

Study design and subjects

This prospective, hospital-based, multicentre, study was conducted at six hospitals in Greece between July 2008 and March 2010. The study hospitals were selected based on an established paediatric clinic network which included metropolitan general hospitals with tertiary paediatric clinics which were used as reference sites for paediatric diseases including GE. The hospitals covered approximately 70% of the paediatric population in Greece. Surveillance was conducted for a time period of 12 months at each hospital.

The study included a main study visit and a follow-up visit or phone call 14 days after the main study visit. Children aged <5 years who visited the emergency room (ER) or hospitalised with acute GE (defined as the occurrence of diarrhoea for <14 days) or developed acute GE at least 48 h after hospitalisation, and with an RV-positive stool sample were enrolled in the study. Children with acute GE always visited the ER first and were discharged if the case of acute GE was diagnosed as mild. The acute GE cases were hospitalised if the acute GE episode was considered to be severe. In addition, patients who developed acute GE at least 48 h after hospitalisation for any other cause were also included for stool testing. If the stool samples were not tested at the time of the visit, then the parent/guardian was requested to provide a sample within 4 days of the study visit. A child became ineligible to participate in the study on the day of his/her fifth birthday. If a child who was previously enrolled visited any of the study centres included in this study with a new episode of GE and with a minimum of 14 symptom-free days since the previous episode, then the child was enrolled in the study as a new case of acute GE. Any patient who developed acute GE at least 48 h after hospitalisation (for any other cause) was listed as a case of nosocomial infection.

Parents of enrolled children were interviewed to obtain demographic information such as date of birth and gender, medical history, information about the general symptoms of the GE episode (fever, diarrhoea, vomiting, weight loss and behavioural symptoms) and treatment of the current acute GE episode. If the child was hospitalised, the date of discharge and follow-up

information after discharge were recorded. A follow-up phone call to the parent/guardian of the enrolled child or, where feasible, an additional visit 14 days after the most recent episode of RVGE to ascertain the clinical outcome of the episode marked the completion of procedures for the case.

Estimation of sample size

The population for target enrolment considered was all children <5 years of age seen at the selected hospital ER departments and hospitalisations for acute GE or with nosocomial RV infection, and with an RV-positive test during the surveillance period. Across all the study sites selected in Greece, the target enrolment was based on the assumption that 30% (95% CI 23.6% to 36.4%) of acute GE cases were due to RV and the incidence of nosocomial RVGE was 2.5/1000 child-days (95% CI 1.4 to 4.4) of hospitalisation.^{1–7}

Ethical approvals

Written informed consent was obtained from the parents/guardians prior to the conduct of any study procedures and before enrolment of the children into the study. The study was conducted according to the principles of Good Clinical Practice, the Declaration of Helsinki, 1996 and local regulations of the country.

Laboratory assays

Stool samples were screened for the presence of RV antigen using an immunochromatographic qualitative test kit, *RotaStrip* (C-1001; Coris BioConcept, Gembloux, Belgium).¹⁴ RV-positive stool samples were genotyped at the Laboratory of Diagnostic Cytology, University Hospital, ATTIKON, Athens, Greece using a two-step reverse transcriptase-PCR. Multiplexed PCR was performed using a real-time PCR machine with type-specific primers and *TaqMan* probes.¹⁵

Endpoints and statistical analysis

Categorical data (gender, seasonal distribution and disease severity) are presented as proportions with one decimal. The occurrence of RVGE among all acute GE ER visits and hospitalisations and the occurrence of nosocomial RVGE are reported with 95% exact CI. The incidence rates of nosocomial acute GE and RVGE are expressed in terms of 1000 children-years with 95% exact Poisson CI.¹⁶ Incidence rate was calculated by dividing the number of nosocomial RVGE cases by the number of hospitalised children (for any cause) which was identified as the group at a risk of acquiring RV infection. The severity of GE episodes was scored on the basis of 20-point Vesikari Scale.¹⁷ A score of ≥ 11 on the Vesikari Scale indicated severe GE. All statistical analyses were performed using Statistical Analysis System (SAS) V.9.2.

RESULTS

Study population

During the study period, 29 504 ER visits and 22 963 hospitalisations for any cause were reported in children aged <5 years at the study hospitals. Of these, 7.9% (2333; 95% CI 7.6% to 8.2%) and 5.7% (1311; 95% CI 5.4% to 6.0%) of the children visited the ER and were hospitalised for acute GE, respectively. Stool samples were collected from 4.4% (103/2333) of children who visited the ER for acute GE, 34.9% (458/1311) of children hospitalised with acute GE and 72.5% (37/51) of children diagnosed as nosocomial acute GE.

Occurrence of RVGE

The proportions of RVGE cases were 10.7% (11/103; 95% CI 5.5% to 18.3%) of acute GE ER visits, 23.8% (109/458; 95% CI 20.0% to 28.0%) of acute GE hospitalisations and 21.6% (8/37; 95% CI 9.8% to 38.2%) of nosocomial acute GE cases. Therefore, a total of 128 RVGE cases were enrolled in the study (figure 1). The median age of the children enrolled in the study was 19.5 months (range 0.0–58 months); 53.9% children were male. The demographic characteristics of children with confirmed RVGE are summarised in table 1. Among the RVGE cases, 53% of the cases were observed in children <24 months of age. The highest number of RVGE cases was reported in infants aged 6–12 months (22/128; 17.2%), followed by infants aged <6 months (17/128; 13.3%) and children aged 12–18 months (17/128; 13.3%). The age distributions of RVGE cases by patient groups, that is, ER visits, hospitalisations and nosocomial RVGE are shown in figure 2.

Nosocomial RVGE

The demographic characteristics of children confirmed with nosocomial RVGE are summarised in table 1. The median age of children with nosocomial RVGE was 9 months (range 1–44 months). RVGE proportion among nosocomial acute GE was 21.6% (8/37; 95% CI

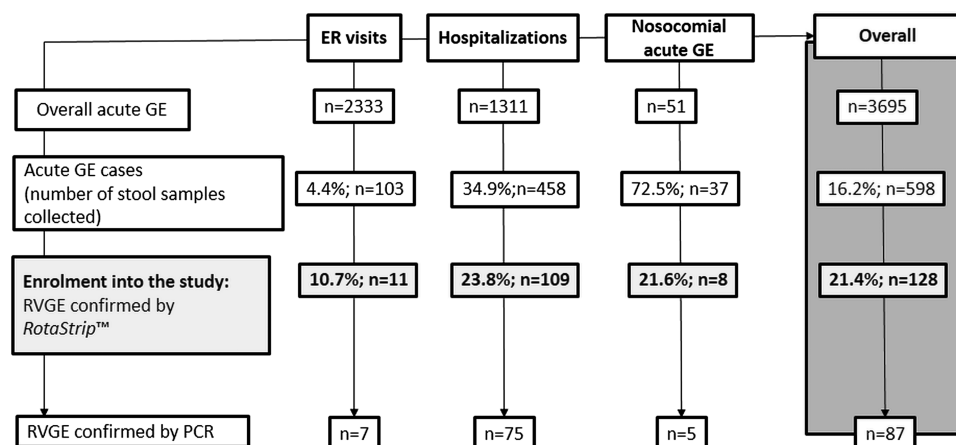
9.8% to 38.2%). The median additional hospitalisation duration due to nosocomial RV infection was 5 days (range 4–7 days). The incidence rates of nosocomial acute GE and nosocomial RVGE in children aged <5 years were 2.2/1000 children-years (95% CI 1.7 to 2.9) and 0.3/1000 children-years (95% CI 0.2 to 0.7), respectively.

RVGE disease characteristics

Higher numbers of RVGE cases (figure 3) were reported between December and May with an overall RVGE proportion of 31.4% (114/363) among those tested, when compared with the rest of the year. During December and May, the proportion of RVGE among acute GE hospitalisations was 34.3% (95/277) among those tested. The highest number of RVGE cases was reported in April 2009 (41.3%; n=26). The highest number of RVGE cases in hospitalised acute GE cases was recorded in January 2009 (17.4%; 19/109) whereas among acute GE ER visits the highest number of RVGE cases was recorded in April 2009 (45.5%; 5/11). The distributions of acute GE and RVGE cases each month of the year are shown in figure 3.

Among the RVGE cases, 85.2% (109/128) of the samples were genotyped. Of these, 81.8% (9/11), 84.4% (92/109) and all (100%; 8/8) samples from the different patient groups, that is, ER visits, hospitalisations and nosocomial RVGE were genotyped. The most commonly detected RV genotypes were G4 (59.6%; 65/109) and P [8] (75.2%; 82/109). The RV genotype distributions by patient groups are summarised in table 1.

Data on severity, symptoms, treatment and outcome of the acute GE episode, RVGE hospitalisation duration and follow-up are shown in table 1. Before and during the visit, 52.3% (67/128) and 41.4% (53/128) of RVGE cases, respectively, were reported as severe. Before and during the visit, diarrhoea was reported in 84.2% (101/128) and 92.1% (117/128) of RVGE cases, respectively. Fever and vomiting were reported in 61.7% (74/128) and 71.7%



Time period: July 2008 – March 2010

Figure 1 Study design.

Table 1 Study population and RVGE disease characteristics

Study population and RVGE disease characteristics								
Parameters/patient group		Hospitalisations (N=109)		ER visits (N=11)		Nosocomial (N=8)		RV+ (N=128)
Age (months)								
Median		21.0		21.0		9.0		19.5
Range		0.0–58.0		3.0–58.0		1.0–44.0		0–58
Gender (%)								
Male		49.5		72.7		87.5		53.9
Female		50.5		27.3		12.5		46.1
Hospitalisation duration (days) median (range)		4.0 (1.0–10.0)		–		5.0 (4.0–7.0)		4.0 (1.0–10.0)
Overall age groups (months)								
<6		5.0 (3.0–10.0)				5.0 (5.0–5.0)		5.0 (3.0–10.0)
6–12		5.0 (3.0–10.0)				5.0 (5.0–7.0)		5.0 (3.0–10.0)
12–24		4.5 (3.0–8.0)				5.5 (5.0–6.0)		5.0 (3.0–8.0)
24–<60		4.0 (1.0–8.0)				5.5 (4.0–7.0)		4.0 (1.0–8.0)
N (%)								
Time point	Before	During	Before	During	Before	During	Before	During
Severity								
Mild (<7)	17 (15.6)	18 (16.5)	3 (27.3)	8 (72.7)	8 (100.0)	1 (12.5)	28 (21.9)	27 (21.1)
Moderate (7–10)	28 (25.7)	43 (39.4)	5 (45.5)	2 (18.2)	–	3 (37.5)	33 (25.8)	48 (37.5)
Severe (≥11)	64 (58.7)	48 (44.0)	3 (27.3)	1 (9.1)	–	4 (50.0)	67 (52.3)	53 (41.4)
Symptoms								
Vomiting	78 (71.6)	62 (56.9)	8 (72.7)	3 (30.0)	–	6 (75.0)	86 (71.7)	71 (55.9)
Fever	66 (60.6)	71 (65.1)	8 (72.7)	5 (50.0)		2 (25.0)	74 (61.7)	78 (61.4)
Diarrhoea	90 (82.6)	102 (93.6)	11 (100.0)	7 (70.0)		8 (100.0)	101 (84.2)	117 (92.1)
Treatment received								
Oral rehydration	37 (33.9)	64 (58.7)	2 (18.2)	2 (20.0)	–	5 (62.5)	39 (32.5)	71 (55.9)
Intravenous rehydration	4 (3.7)	99 (90.8)	–	1 (10.0)		7 (87.5)	4 (3.3)	107 (84.3)
Outcome at discharge								
Recovered	109 (100.0)		11 (100.0)		8 (100.0)		128 (100.0)	
Follow-up 14 days after discharge								
Diarrhoea	8 (8.2)		3 (27.3)		0 (0)		11 (9.6)	
RV genotype distribution								
G1 (% of total RV+)	16 (17.4)		3 (33.3)		1 (12.5)		20 (18.3)	
G2	6 (6.5)		–		1 (12.5)		7 (6.4)	
G3	4 (4.3)		–		–		4 (3.7)	
G4	56 (60.9)		5 (55.6)		4 (50.0)		65 (59.6)	
P4	6 (6.5)		–		1 (12.5)		7 (6.4)	
P8	71 (77.2)		7 (77.8)		4 (50.0)		82 (75.2)	
ER, emergency room; RV, rotavirus; RVGE, RV gastroenteritis.								

ER, emergency room; RV, rotavirus; RVGE, RV gastroenteritis.

(86/128) of RVGE cases before the visit, respectively. During the visit, 61.4% (78/128) and 55.9% (71/128) of RVGE cases reported fever and vomiting, respectively. After 14 days of patient discharge from the hospital, telephone follow-up revealed that 9.6% (11/128) of RVGE cases still reported the episodes of diarrhoea. The median duration of RVGE hospitalisation was 4 days (range 1–10 days), with the longest durations in children aged <1 year (table 1). Regarding the treatment of GE, oral rehydration therapy (55.9%; 71/128) was the preferred mode of treatment administered prior to the hospital visit. During the hospital visit, the preferred mode of treatment administered was intravenous rehydration therapy which was given to 84.3% (107/128) of RVGE cases (table 1).

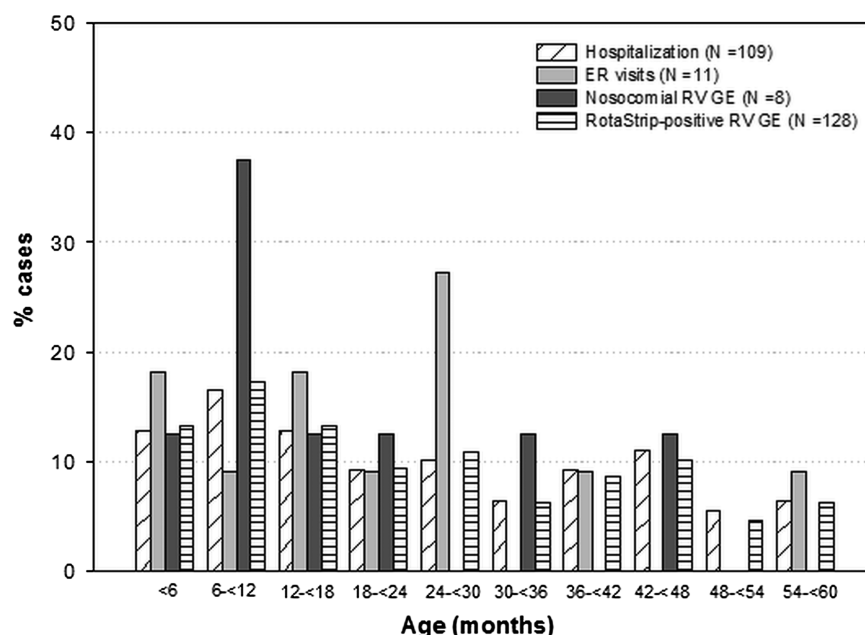
Overall, 3.9% (5/128) and 0.8% (1/128) of RVGE cases had a history of pulmonary or cardiac disease,

respectively. In addition, 7% (9/128) of RVGE cases had a history of acute GE. All enrolled children had recovered at the time of discharge from the hospital.

DISCUSSION

The findings from the present study add to the existing epidemiological data on RVGE disease following the introduction of RV vaccination in Greece in 2007. Our data indicate that 10.7% of acute GE ER visits and 23.8% of acute GE hospitalisations were caused by RV. Since introduction of RV vaccines in Greece in 2007, lower proportions of acute GE due to RV have been recorded.^{9 10} In Greece, during 2008–2009, RV was responsible for 24.7% of acute GE hospitalisations.⁹ Trimis *et al*¹⁰ reported a slight reduction in annual

Figure 2 Age distribution of children aged <5 years.

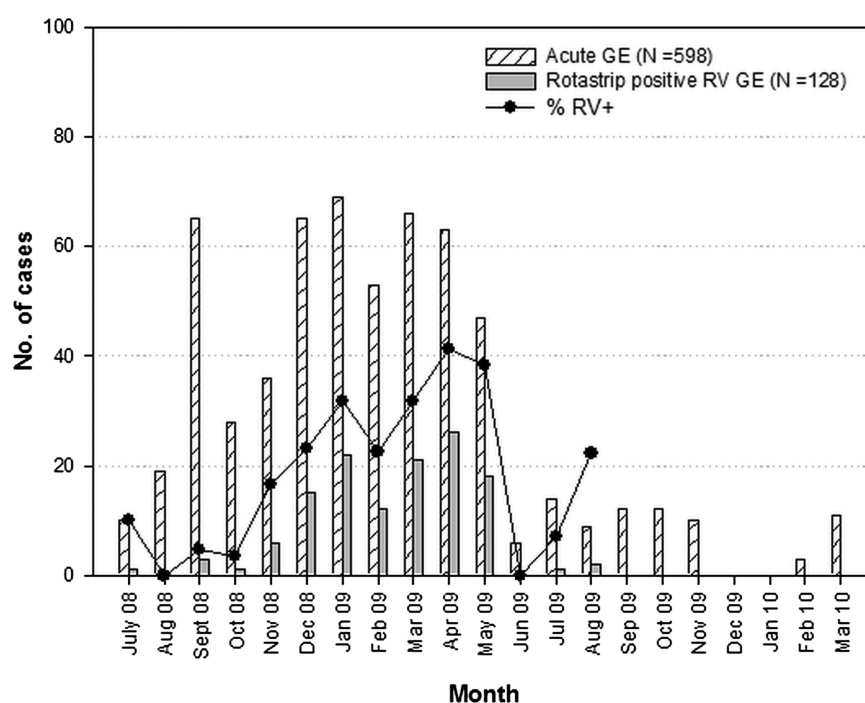


RVGE rates between 2006 and 2010, although the proportions during the RV season were consistent with the previous studies.^{7 8} Trimis *et al*¹⁰ also reported that the likelihood of RV infection among children hospitalised for acute GE between 2008 and 2010 in Greece was significantly reduced when compared with children hospitalised for acute GE between 2006 and 2008 (OR=0.64; 95% CI 0.49 to 0.84, $p<0.001$). The present study reports lower proportions of RVGE disease in Greece than reported prior to RV vaccine introduction; however, comparable proportions of RVGE were estimated to those reported after vaccine introduction in Greece. We assume that these findings may be the result of

protection conferred directly by vaccination in young children although our study did not have data on RVGE burden prior to vaccine introduction. Prospective monitoring is warranted to confirm any decline in the RVGE disease burden due to vaccine uptake in Greece.

In our study, the peak in RV infection was reported between December and May and RV was responsible for 31.4% and 34.3% of all acute GE and hospitalised acute GE, respectively. In Greece, during the RV season in 2006, RV was responsible for 49.1% and 45.7% of acute GE ER visits and hospitalisations, respectively.⁷ Similar proportions were reported between January 2007 and June 2008 in Greece where RV was responsible for

Figure 3 Seasonal distribution of acute gastroenteritis (GE) and rotavirus GE cases in children aged <5 years.



42.3% and 47.8% of acute GE ER visits and hospitalisations, respectively, in children <5 years of age, with the number of RVGE cases peaking between January and April.^{7,8} Published data from Greece suggests late winter seasonality for RVGE disease (January to April).⁶⁻⁹ However, in countries in the EU where RV vaccination has been implemented through the national programmes the RV seasonal peaks were delayed and attenuated postvaccination¹⁸⁻²⁰ when compared with the RV seasonal peaks observed in Greece. Our analysis revealed that the majority of RVGE cases were reported in young children aged <24 months, which has also been observed in the European countries previously.²¹ Notably, the peak of RV infection coincides with the peak of other severe infectious diseases in young children, thereby adding to the already existing pressure on healthcare services. Our data report that G4 and G1 were the most common G types whereas P8 and P4 were the most common P types that were detected in the majority of stool samples collected in this analysis. These reports are in line with the published genotype data in Greece^{8,10} and from the European countries.²² The median duration of hospitalisation for RVGE cases was 4 days; this was within the range reported for countries in Western Europe (2.5–5 days).²² This median duration of hospitalisation was, however, significantly lower than the mean duration of RVGE hospitalisation (5.14±3.18 days) reported for Greece previously.⁷

The incidence rate of nosocomial RVGE in children aged <5 years was 0.3/1000 children-years and the median additional hospitalisation duration due to nosocomial RV infection was 5 days. The burden of nosocomial RVGE in the present study was lower than that reported for countries in Europe and with a lower median additional hospitalisation duration (5 days (range 4–7 days)) than that reported for Europe (range 6.3–15 days).²³ Data from our study indicate that the proportions of severe acute GE episodes among RVGE cases were high; severe episodes of acute GE are associated with long durations of hospitalisation. In addition, the proportions of children reporting vomiting and fever along with severe episodes of diarrhoea were high. Consequently, all these factors result in an additional consumption of medical resources which may increase the economic burden associated with RVGE in Greece.

In line with the recommendation from the WHO, vaccination against RV is now recommended in the European guidelines.²⁴ Several countries in the EU (Belgium,¹⁸ Germany,¹⁹ France,²⁵ Austria²⁰ and Spain²⁶) have reported a positive impact following the introduction of RV vaccination in their national immunisation programmes. Although RV vaccination in Greece is available through the national immunisation programme¹³ it is still an optional vaccine and is recommended only for the high-risk groups. We expect that awareness about RVGE disease in addition to widespread implementation of RV vaccines may help further reduce the burden of RVGE disease in Greece.

The present analysis has several strengths and limitations. The prospective design allowed us to collect robust demographical and clinical data on children with RVGE disease as well as to confirm RVGE cases by stool testing. The main limitation of our study was that low numbers of patients were enrolled, which resulted in RVGE proportions that may not be fully representative of the paediatric population in Greece: indeed 4.4% of acute GE ER visits and 34.9% of acute GE hospitalisations were tested for RV in the present study. This proportion was relatively higher for nosocomial acute GE cases (72.5%). In addition, we did not have data for the same settings prior to vaccine introduction to assess any decline in the burden of RVGE disease after implementation of RV vaccines in Greece. Given these limitations, we did, however, perform an exhaustive review of the published literature on RVGE epidemiology in Greece, which allowed for comparison by hospital sites, common testing methodology and time period.

In conclusion, data from the present study provide evidence of low proportions of RVGE among acute GE which may be attributable to available RV vaccination in Greece. However, appropriate impact/effectiveness studies are necessary to confirm this finding.

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Competing interests AK received employment (private practice) fees outside of this present publication. AT received a grant from GlaxoSmithKline group of companies for the study, whereas VP's institution received a grant for the present study. Outside the present publication, VP has also received fees for the Viral Hepatitis Prevention Board (VHPB) and WAVE board membership, talks at national and international meetings, lectures on varicella vaccine and travel/accommodation/meeting expenses for the European Society for Paediatric Infectious Diseases (ESPID) conference. IK has received honoraria from GSK for scientific presentations on vaccines at national congresses and

travel/accommodation/meeting expenses for national and international congresses. KG and KH are employees of GlaxoSmithKline group of companies.

Patient consent Obtained.

Ethics approval The study protocol and the informed consent were reviewed and approved by the Institutional Review Boards and the Greek National Drug Organisation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Researchers can request access to anonymised patient-level data from GSK clinical studies to conduct further research through the GSK website at the following URL address: <https://clinicalstudydata.gsk.com>

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