

Clinical Characteristics, Health Care Resource Utilization and Direct Medical Costs of Rotavirus Hospitalizations in Spain (2013-2018)

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Abstract

Background: Rotavirus (RV) is the most common cause of severe gastroenteritis (GE) in infants and young children worldwide and is associated with a significant clinical and economic burden. The objective of this study was to analyze the characteristics, healthcare resource utilization and the direct medical costs related to RVGE hospitalizations.

Methods: An observational, multicenter, cross-sectional study was conducted from June 2013 to May 2018 at the pediatric departments of 12 hospitals from different Spanish regions. Children under 5 years of age admitted to the hospital with a confirmed diagnosis of RVGE were selected. Data on clinical characteristics, healthcare resource use and costs were collected from patient records and hospital databases.

Results: Most children hospitalized for RVGE did not have any previous medical condition or chronic disease. Forty-seven percent had previously visited the ER, 27% had visited a primary care pediatrician, and 15% had received pharmacological treatment prior to hospital admission due to an RVGE episode. The average length of a hospital stay for RVGE was 5.6 days, and the mean medical costs of RVGE hospitalizations per episode ranged from 3,940€ to 4,100€. The highest direct medical cost was due to the hospital stay.

Conclusion: This study shows a high burden of health resource utilization and costs related to the management of cases of RVGE requiring hospitalization. RV vaccination with high coverage rates should be considered to minimize the clinical and economic impacts of this disease on the health care system.

Background

Rotavirus (RV) remains one of the leading causes of severe diarrhea requiring hospitalization in children worldwide [1]. In Western Europe, RV is the cause of 25.3–63.5% of all acute gastroenteritis (AGE) in children < 5 years of age, and nosocomial RV-related acute gastroenteritis (RVGE) accounted for 47–69% of all hospital-acquired AGE leading to a prolongation of hospital stays [2, 3]. Hospitalizations due to RVGE have been associated with frequent and high utilization of healthcare resources [3, 4] and, as a consequence, substantial direct medical and societal costs [4, 5].

Two rotavirus vaccines have been available in Spain since 2006: RotaTeq®, (MSD) [10] and Rotarix®, (GSK) [11], but not included in the National Immunization Program. They are use under pediatricians' recommendations and fully paid by parents, reaching an intermediate vaccination coverage rate with significant differences between regions. RV vaccines have demonstrated to be highly effective, achieving 60–90% reductions in outpatient visits, emergency room (ER) visits, and hospitalizations due to severe AGE in children in many Western European and, indirectly, days missed from work of parents [6–9, 12].

To assess the actual burden of RVGE, both an accurate number of RVGE-related hospitalizations and their associated use of resources and related medical costs should be estimated. The use of hospital administrative databases have been found to underestimate the actual hospital admission incidence, likely due to the selected hospital discharge codification [13–15]. Furthermore, estimation of the use of medical resources and related costs might be hampered by the limited data available in those databases [13, 15, 16]. Therefore, obtaining precise information on the use of medical resources and the estimated direct medical costs related to RVGE

hospitalizations from hospital medical records of confirmed RV patients allows for a more comprehensive evaluation of the burden of disease.

The objectives of our study were to describe the clinical characteristics and healthcare resource utilization of children under 5 years of age hospitalized due to RVGE in Spain during a 5-year period and to estimate the related direct medical costs.

Methods

Study design

This was an observational, multicenter, cross-sectional study conducted at the pediatric departments of Spanish hospitals from different regions.

Twelve hospitals from 11 different provinces that systematically tests for RV in children hospitalized due to AGE and have electronic records in the Microbiology and Pediatric Departments were selected. The analyzed data corresponded to a 5-year period (from June 2013 to May 2018).

This study was designed, conducted and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology [17]. This study was reviewed and approved by the Euskadi Independent Ethics Committee for Research with Medicines (CEIC-E).

Study population and data collection

All children under 5 years of age admitted to the participating hospitals with a microbiologically confirmed diagnosis of RVGE during the 5-year period and with available patients' medical charts including the necessary data for study objectives analyses (clinical, diagnostic and treatment-related data) were identified as study population.

Information on the RVGE diagnosis among hospitalized children due to AGE was collected from the Microbiology Department databases. The type of test used for microbiological determination by each hospital during the study period was also collected. Hospital medical records of children included in the analysis were reviewed to collect information on their clinical characteristics and use of health care resources.

Health care resources collected comprised the utilized resources prior to hospital admission (primary care and ER visits and treatments) and the resources used during hospitalization. In the case of nosocomial RV infections only resource consumption related to the management of the RVGE were collected.

To assess direct medical costs related to health care resource utilization, the unit costs were obtained from the cost accounting of each hospital or from the Oblikue-e.Salud database, when the required information was not available from the hospital databases. Oblikue database collects Spanish unit costs obtained from more than 300 data sources retrieved from published articles, official health services tariffs of the Autonomous Communities, and discharge records from the National Health System hospitals. [18]

All study data were reviewed and recorded in an electronic case report form by the investigators.

Statistical analysis

For the description of the clinical characteristics and use of health care recourses of the RVGE hospitalizations, a sample size of 969 patients was estimated to allow the detection of a patient profile with the characteristics present in 8% of the studied population with a precision of $\pm 1.8\%$ percentage units and a two-sided alpha risk with $p = 0.05$ (type I error). Based on the Orrico-Sánchez et al. [19] study, the proportion of RVGE cases among all hospitalizations in children < 5 years of age during the postvaccine introduction period was 1.9%. The study was performed in 20 hospitals from the Autonomous Community of Valencia over a 7-year period, representing approximately 20 RVGE hospitalizations per hospital and year. Therefore, by selecting a convenience sample of 12 hospitals would provide a total of 1,200 hospitalizations due to RVGE during the 5-year period with a precision of 0.79% and a level of confidence of 95%. A randomized selection was performed among the total sample of children hospitalized due to RVGE in the participating hospitals.

For the clinical characteristics and resource consumption descriptive analysis, absolute and relative frequency distributions for the qualitative variables and the mean and standard deviation (SD) for quantitative variables are presented.

To calculate the cost per episode of RVGE hospitalization, the following costs were considered: ICU hospital stay, inpatient hospital stay, microbiological and other diagnostic tests, pharmacologic treatments, and hygienic-dietary measures. Hospital length of stay for community-acquired RVGE episodes was calculated as follows: hospital discharge date minus the date hospital admission plus 1; and, in cases of nosocomial RVGE episodes as: date of hospital discharge minus the date of microbiological diagnosis of RVGE plus 1.

The unit costs related to the use of resources were calculated as the average unit costs obtained from the cost accounting of each hospital, or, if not available (for example, hygienic-dietary measures), it was obtained from the Oblikue-e.Salud database. Unit costs of pharmacologic treatments were obtained from the database of the General Council of the official Colleges of Pharmacists (BotPlus: <https://botplusweb.portalfarma.com/>). Tests/treatment for which no available unit cost was identified or for which the duration was not recorded were not included in the cost analysis.

The direct medical costs of hospitalization for RVGE were calculated as the sum of the costs of the hospital stay, diagnostic tests, pharmacological treatment and hygienic-dietary measures. Additionally, the total medical costs per RVGE episode, defined as the direct medical cost of hospitalization for RVGE and the cost derived from ER visits, out-of-hospital visits, treatment prior to hospitalizations and the length of readmissions, all related to the RVGE episode, were calculated.

The costs were estimated for each case and year during the study period. The costs were quantified by multiplying the registered natural units of the use of health care resources by the unit costs obtained for each resource. All costs were expressed in euros and corrected according to the consumer index price for 2019.

All statistical analyses were performed using the statistical program Statistical Package SAS version 9.4. A level of statistical significance of 0.05 was applied to all statistical tests.

Results

From June 2013 to May 2018, 1,731 RVGE hospitalizations in children < 5 years were collected. We randomly selected 1,089 RVGE episodes from those recorded in the hospital databases of the study hospitals, 1,002 of

which met the selection criteria and were included for the evaluation of the clinical characteristics. Data for the health resources and direct medical costs analyses was available for 994 hospitalized children (Supplementary Fig. 1).

The mean age (SD) of cases was 13.70 (11.71) months, and 59.1% were boys. Most children (90,1%) and parents (75,9%) had Spanish nationality and 70.7% of RVGE hospitalizations occurred between January and April, with a peak in March.

Among all RVGE hospitalizations, prematurity and low birth weight was reported in 13.4% and 10.1% of cases, respectively, and in 19.3% of patients, a chronic disease was informed (Table 1). Sixty percent of patients were nursing children, 26,1% of whom were breastfed (Table 1). Among other epidemiological characteristics of interest, 27.0% of patients were attending a daycare center or school at the time of admission, and 21.3% were confirmed to have household contacts with similar symptomatology, with an average of 1.34 (SD 0.74) contacts affected (Table 1).

Table 1
Epidemiological characteristics of RVGE episodes hospitalized in children < 5 years of age
(N = 1,002)

Epidemiological Characteristics	N subjects/Total sample	Percentage
Previous conditions		
Prematurity	131/981	13.4%
≤ 32 weeks	46/131	35.4%
≤ 37 weeks	84/131	64.6%
Low birth weight,	98/970	10.1%
≤ 2,500 g	66/98	68.0%
≤ 1,500 g	31/98	32.0%
Malabsorption syndrome	12/994	1.2%
Gastroesophageal Reflux Disease	18/992	1.8%
Chronic disease		
Pneumopathy	41/193	21.2%
Gastrointestinal disorders	36/193	18.7%
Cardiopathy	32/193	16.6%
Encephalopathy	28/193	14.5%
Nephropathy	25/193	13.0%
Failure to thrive	16/193	8.3%
Type of feeding at hospital admission time		
Nursing children	456/750	60.8%
Breastfeeding	119/456	26.1%
Formula	253/456	55.5%
Mixed	84/456	22.8%
Day care or school attendance		
	147/544	27.0%
Household contacts with similar symptoms		
	153/719	21.3%

The most commonly reported symptoms of RVGE were diarrhea (94.4%), vomiting (64.6%), and fever (55.8%), with mean (SD) durations of 2.97 (1.63), 2.16 (1.12), and 2.11 (2.25) days, respectively. The mean (SD) number of episodes per day was 7.1 (4.26) for diarrhea and 5.4 (4.48) for vomiting. Abdominal pain was reported in 11.5%, and other symptoms in 21.1% of cases.

Dehydration was the most frequent complication registered (48.5%). The severity of dehydration is described in Fig. 2, and almost all children with dehydration (98,8%) received intravenous rehydration at admission. The frequencies of other complications are summarized in Fig. 2. The mean number of episodes (SD) in patients presenting seizures was 2.48 (2.59).

Among the total RVGE episodes, 16.5% were identified as nosocomial infections. Regarding hospitalization outcome, 999 patients (99,7%) were discharged, and 3 died. Two of the deaths were reported as unrelated to the RVGE episode, and 1 was possibly related. Finally, 9 children (0.9%) had to be readmitted following discharge due to a cause related to their previous RVGE episode.

Use of resources prior to hospital admission

Forty-six point seven percent of the children (462/990) attended the ER before the hospitalizations with a mean (SD) of 1.48 (0.75) visits, and 27.4% (211/770) attended primary care pediatric office with a mean (SD) of 1.24 (0.61) visits due to the RVGE episode. In addition, 15.4% (150/973) of patients were prescribed a pharmacological treatment before their hospitalization. The frequencies of the medications and their respective treatment durations are displayed in Table 2.

Table 2

Pharmacological and therapeutic interventions for the RVGE episodes before and during hospitalization.

Pharmacological treatments	N subjects (%)	Mean Duration (Days) (SD)
Prior to hospitalization (N = 150)		
Analgesics	3 (2.0%)	2.00 (1.00)
Antipyretics	49 (32.7%)	2.44 (1.54)
Antidiarrheal/antisecretory agents	2 (1.3%)	—
Antiemetics	24 (16.0%)	1.68 (0.75)
Antibiotics	23 (15.3%)	2.87 (2.03)
Oral rehydration solutions	71 (47.3%)	2.42 (1.19)
Probiotics	6 (4.0%)	4.60 (5.86)
Other	27 (18.0%)	46.13 (103.10)
During hospitalization (N = 534)*		

N in brackets: number of total evaluable subjects.; * n = 306 RVGE episodes with a total n = 534 pharmacologic treatments
 ACE inhibitors = angiotensin-converting enzyme inhibitors; IV = intravenous; h = hours; d = days.

Pharmacological treatments	N subjects (%)	Mean Duration (Days) (SD)
Antibiotics	133 (24.9%)	5.31 (3.29)
Antipyretics	117 (21.9%)	1.90 (1.28)
Oral rehydration solutions	89 (16.7%)	1.98 (1.34)
Antiemetics	46 (8.6%)	3.03 (7.55)
Analgesics	27 (5.1%)	2.44 (1.46)
Gastric protectors	18 (3.4%)	9.91 (12.53)
Vitamins and iron supplements	18 (3.4%)	16.78 (15.78)
Respiratory drugs	16 (3.0%)	5.42 (3.70)
Corticosteroids	14 (2.6%)	6.89 (3.76)
Anticonvulsants	7 (1.3%)	2.00 (1.73)
Benzodiazepines	6 (1.1%)	1.00 (0.00)
Probiotics	5 (0.9%)	4.67 (3.06)
Diuretics	4 (0.7%)	20.00 (.)
ACE inhibitors	4 (0.7%)	—
Antihypertensive agents	3 (0.6%)	—
Amino acids and derivatives	3 (0.6%)	19.00 (.)
Antidiarrheal/antisecretory agents	2 (0.4%)	10.00(.)
Other	22 (4.1%)	8.42 (9.45)
Dietary and hygiene measures during hospitalization	N subjects (%)	Mean Duration (SD)
IV rehydration serum (N = 988)	785 (79.5%)	33.31 (34.67) h
IV bicarbonate (N = 997)	40 (4.0%)	0.59 (7.02) h
Special diets (N = 996)	56 (5.6%)	0.03 (0.42) d
Lactose-free milk	25 (44.6%)	0.06 (0.61) d
Casein hydrolysate	16 (28.6%)	0.01 (0.11) d
Whey protein hydrolysate	4 (7.1%)	0.00 (0.10) d
Hydrolyzed other	4 (7.1%)	0.03 (0.39) d
Parenteral nutrition	9 (16.1%)	0.06 (0.98) d
Nasogastric tube feeding (N = 994)	22 (2.2%)	
<p>N in brackets: number of total evaluable subjects.; *n = 306 RVGE episodes with a total n = 534 pharmacologic treatments ACE inhibitors = angiotensin-converting enzyme inhibitors; IV = intravenous; h = hours; d = days.</p>		

Use of resources during the hospitalization

The mean (SD) length of hospital stay due to RVGE was 5.59 (7.61) days, with a split of 5.54 (7.56) days for hospital inpatient stay and 0.05 (0.37) days in the ICU.

Immunochromatography was the most widely used test for the microbiological determination of RVGE during hospital admission (Table 3). In 94% of the recorded RVGE episodes, other tests were performed to determine other pathogens (Table 3). Globally, 66 RVGE hospital cases tested positive for coinfection, the most frequent pathogen being adenovirus and bacteria (stool culture).

In 90.2% of the recorded RVGE episodes, other diagnostic tests were performed during hospital admission (accounting for a total of 2,138 diagnostic tests). The most frequently performed tests are summarized in Table 3.

Table 3

Diagnostic test performed for RVGE confirmation at admission and other tests during hospitalization

MICROBIOLOGICAL DIAGNOSTIC TEST	N subjects (%)	N of tests Mean (SD)
Test performed for microbiological diagnosis of RVGE (N = 1,002)		
Immunochromatography	930 (92.8%)	0.95 (0.45)
ELISA	1 (0.1%)	0.00 (0.03)
Stool culture	284 (28.3%)	0.30 (0.52)
PCR	82 (8.2%)	0.09 (0.31)
Other	8 (0.8%)	0.01 (0.0)
Tests for detection of coinfection with other pathogens (N = 935)		
Adenovirus	858 (91.8%)	—
Positive	28 (3.3%)	—
Norovirus	131 (14.0%)	—
Positive	2 (1.5%)	—
Sapovirus	54 (5.8%)	—
Positive	2 (3.7%)	—
Coronavirus	2 (0.2%)	—
Positive	0 (0.0%)	—
Bocavirus	3 (0.3%)	—
Positive	0 (0.0%)	—
Bacteriae (stool culture)	670 (71.7%)	—
Positive	20 (3.0%)	—
Others	332 (35.5%)	—
Positive	14 (4.2%)	—
Other diagnostic tests (N = 2,138)*		
Blood tests	844 (39.5%)	—
Complete blood count	752 (89,1%)	1.22 (1.43)
Biochemistry	790 (93,6%)	1.61 (2.33)
N in brackets: number of diagnostic tests performed		
SD = Standard deviation; ELISA = Enzyme-linked immunoassay; PCR = Polymerase Chain Reaction; CT scan = Computerized tomography scan; MIR = Magnetic Resonance Imaging; ECG = Electrocardiogram; EEG = Electroencephalogram.		
*A total of n = 2138 diagnostic tests performed in 901 recorded RVGE episodes		

MICROBIOLOGICAL DIAGNOSTIC TEST	N subjects (%)	N of tests Mean (SD)
Coagulation	47 (5,6%)	0.08 (0.52)
Other	99 (11,7%)	0.25 (0.64)
Blood gases	673 (31.5%)	1.31 (1.78)
Abdominal ultrasound scan	41 (1.9%)	0.05 (0.24)
Abdominal/plain X-rays	49 (2.3%)	0.09 (0.73)
Ultrasound	26 (1.2%)	0.03 (0.23)
CT scan	8 (0.4%)	0.01 (0.09)
MRI	2 (0.1%)	0.00 (0.04)
Urinalysis	99 (4.6%)	0.12 (0.39)
Culture	344 (16.1%)	0.38 (0.84)
ECG and EEG	28 (1.3%)	0.03 (0.17)
ECG	10 (35.7%)	
EEG	18 (64.3%)	
Other tests	24 (1.1%)	0.02 (0.19)
N in brackets: number of diagnostic tests performed		
SD = Standard deviation; ELISA = Enzyme-linked immunoassay; PCR = Polymerase Chain Reaction; CT scan = Computerized tomography scan; MIR = Magnetic Resonance Imaging; ECG = Electrocardiogram; EEG = Electroencephalogram.		
*A total of n = 2138 diagnostic tests performed in 901 recorded RVGE episodes		

A total of 309 (30.9%) children hospitalized due to RVGE received at least one pharmacological treatment during hospitalization (Table 2), mainly, antibiotics (24.9%), antipyretics (21.9%) and oral rehydration solutions (16.7%). Their respective mean (SD) treatment durations were 5.31 (3.29), 1.90 (1.28), and 1.98 (1.34) days. Additionally, among the dietary and hygiene interventions during hospital admission, intravenous rehydration was administered in 785 (79.5%) of the RVGE episodes, with an average duration of 33.31 (34.67) hours (Table 2).

Direct medical costs of hospitalization for RVGE

The average direct medical cost related to the RVGE hospitalization during the study period was €3,940.38 (€5,248.85). The total associated cost for RVGE episodes, including the costs of medical resources reported before, during hospitalization and related to readmissions, was of €4,100.11 (€5,283.63) (Table 4). Among the direct medical costs, the highest was due to hospital stay on a ward with a cost of €3676.63 (€5,013), followed by hygienic dietary measures (€97.24; €645.81). Prior to hospitalization, ER visits represented the highest cost (Table 4). No differences were observed in the direct medical costs across the study period. Direct medical costs in each of the participating sites ranged from €3,163.47 (€3,083.06) to €5,843.24 (€8,716.44) (Supplementary Table 1).

Table 4
Direct Medical Costs (€) related to the RVGE episodes

Direct Medical Costs	Global	2013–2014	2014–2015	2015–2016	2016–2017	2017–2018	p-value ¹
During hospitalization							
Hospital stay (Ward)	3,676.63	3,949.32	3,753.12	3,602.46	3,883.43	3,098.48	0.7977
Mean (SD)	(5,013.00)	(5,920.96)	(5,341.70)	(5,365.19)	(5,036.95)	(2,550.77)	
Hospital stay (ICU)	62.11	27.27	126.08	41.12	73.34	26.09	0.4929
Mean (SD)	(498.74)	(271.36)	(793.99)	(315.16)	(527.09)	(250.77)	
Microbiological diagnostic test	26.01	24.81	30.78	23.68	24.82	24.99	0.6793
Mean (SD)	(45.17)	(10.71)	(92.58)	(11.05)	(11.93)	(9.71)	
Other diagnostic tests	76.74	68.68	80.18	77.46	73.54	84.51	0.3027
Mean (SD)	(100.23)	(82.76)	(102.76)	(79.43)	(78.85)	(144.99)	
Pharmacologic treatments	1.65	1.29	2.07	2.68	1.02	1.35	0.4272
Mean (SD)	(9.58)	(4.19)	(6.80)	(20.51)	(3.65)	(5.31)	
Hygienic-dietary measures	97.24	36.69	153.64	121.99	112.04	52.93	0.6960
Mean (SD)	(645.81)	(238.63)	(827.24)	(965.49)	(586.08)	(316.76)	
Total direct hospitalization	3,940.38	4,108.07	4,145.86	3,869.38	4,168.19	3,288.36	0.8794
Mean (SD)	(5,248.85)	(5,955.87)	(5,921.35)	(5,556.53)	(5,181.77)	(2,723.54)	
Prior to hospitalization							
ER visits	103.34	103.70	102.21	97.07	103.67	110.85	0.9114
Mean (SD)	(137.66)	(140.91)	(140.19)	(129.77)	(137.17)	(139.59)	
Outpatient visits	25.98	25.53	27.99	18.23	21.95	35.90	0.0089
Mean (SD)	(58.93)	(60.29)	(64.31)	(47.15)	(55.39)	(63.18)	

SD: Standard deviation; ER: Emergency room.

¹Kruskal-Wallis test

Direct Medical Costs	Global	2013–2014	2014–2015	2015–2016	2016–2017	2017–2018	p-value¹
Prior pharmacologic treatments	0.41 (1.64)	0.51 (1.85)	0.40 (1.57)	0.56 (1.92)	0.34 (1.60)	0.29 (1.20)	0.2794
Mean (SD)							
After hospitalization							
Rehospitalization length of stay	30.00 (727.54)	9.99 (140.92)	123.15 (1,518.95)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.1269
Mean (SD)							
Total costs related with the RVGE episode	4,100.11 (5,283.63)	4,247.80 (5,932.51)	4,399.61 (6,100.49)	3,985.23 (5,536.02)	4,293.15 (5,171.30)	3,435.39 (2,708.19)	0.8323
Mean (SD)							
SD: Standard deviation; ER: Emergency room.							
¹ Kruskal-Wallis test							

Discussion

Our study showed a high burden of RVGE hospitalizations leading to significant health resource utilization and costs related to the management of these severe cases of RVGE.

Most of the hospitalized children with RVGE included in our study did not report previous medical conditions or chronic diseases [20, 21]. Moreover, among children hospitalized due to RVGE, similar to what has been observed for RVGE cases managed at primary care, attendance to daycare or school centers is not predominant [22, 23].

As described in other studies, dehydration is highly frequent among RVGE cases due to the occurrence and intensity of symptoms [24], with a not negligible proportion of cases suffering severe dehydration. However, our study was not designed to evaluate the rate of dehydration in RVGE, and the high rates of this complication could be biased, as dehydration was likely the cause of admission in many of the children. Seizures have been previously described as a complication related to RVGE. The frequency reported in our study (5%) is within the range of what has been observed in other studies [25–27]. Although RV-related seizures are usually benign and self-limited, they may lead to ER visits and hospitalizations and considerable stress for parents [28].

Regarding the use of health care resources, we found that almost half of the patients who were hospitalized due to an RVGE episode had previously attended the ER, and approximately 30% had visited a primary care pediatrician on more than one occasion before hospital admission. Moreover, approximately 15% of all RVGE cases were hospitalized despite having received pharmacological treatment, mainly oral rehydration solutions, prior to their hospital admission. Altogether, this suggests the significant impact of RVGE episodes on the disease burden at different health care levels.

It is important to highlight the long average length of the hospital stay (5.6 days) observed. This figure was somewhat higher than what has been reported in previous studies, ranging from 2.5 to 5 days [3, 4], but similar to those in others [19, 24]. The results from the study performed in the Autonomous Community of Valencia including a long period of time (2002–2015), showed the relationship of the average length of hospital stay with age, with children < 2 years having an approximately 50% longer average length of stay than the older groups, therefore, the age distributions in the different studies may explain these differences. Our study also took into consideration nosocomial infections, for whom length of hospital stay is difficult to estimate. We used the date of the microbiological diagnosis as a reference for its calculation, which may overestimate the prolongation of the stay related to RV infection in those cases. Other factors that may have contributed to longer hospital stays include the high percentage (almost 80%) of patients in our study who needed intravenous hydration. This figure is within the upper limit of the range of many European countries [3, 4].

Apart from the consequent high use of medical resources, we assume that this hospital stay must have had an important impact on the number of workdays lost by parents and caregivers, as well as other indirect costs, although the latter were not the objective of our study. In fact, it has been estimated that RVGE hospitalizations of children cause work absenteeism in nearly 70% of parents, with a mean number of days off from work of 4, negatively impacting their quality of life [12].

Regarding pharmacological treatment and other therapeutic interventions administered during hospitalization, surprisingly, antibiotic use was reported in ~ 25% of the RVGE cases in our study, despite the low frequency of detected bacterial coinfection. In line with this result, a study performed in 8 European countries including Spain, assessing the appropriateness of antibiotic prescription in febrile children, showed that one-third of all antibiotic prescriptions in ED were of inappropriate or inconclusive indication [29]. This suggests that certain vaccinations, including that against RV, may contribute to an improvement in rational use of antimicrobial and to the implementation of antimicrobial stewardship guidelines.

The mean medical cost of RVGE hospitalizations per episode was 3,940€, increasing to 4,100€ when out-of-hospital costs related to the episode were considered. It is important to note that these last costs may be underestimated due to the retrospective nature of our study, using the hospital medical records of patients in which not all medical visits and treatments occurring before hospitalization may be recorded. Our study only considered the most severe presentation of disease, representing the management of cases requiring hospitalizations. Although these costs represent a significant proportion of the economic burden of disease, the clinical burden of RV disease is much higher in primary care, and the indirect costs assumed by families are not negligible. The study by Bouzón-Alejandro et al. [30] prospectively assessed indirect costs related to RVGE in Spain, showing a mean cost per case of 192.7€ (SD 219.8€). Therefore, additional research contributing to the global economic impact of disease estimation is warranted.

More than 95% of the average total medical cost associated with hospital admission due to an RVGE episode was attributable to the hospital stay. This was expected, as there is no specific pharmacological treatment for RV infection, and case management is focused on fluid replacement and symptom mitigation [1].

Our estimated average cost per episode is higher than that reported in other studies performed previously in Spain [14, 15, 31]. Different factors may explain these differences. First, the increase in costs over time, as there were many years of differences between the periods analyzed in those previous studies and ours. Second, the cost in those studies was mainly estimated by using the Diagnosis Related Groups for Disease (DRG). According

to the DRG reimbursement system, patients belong to a group of diagnostically homogeneous cases; therefore, patients within the same category are similar clinically and are expected to use the same level of hospital resources. There is no specific DRG for RV, and a DRG including AGE and other miscellaneous digestive disorders in age < 18 years was mainly used. RV is known to cause more severe AGE than other pathogens, probably leading to longer hospital stays [7]. Therefore, the lack of a specific GRD for RVGE may be responsible for an underestimation of RVGE hospitalization costs when using the DRG cost assignment. In our study, the use of different health resources related to hospitalization and unit costs calculated from hospital accounting information may have led to more precise estimations of the actual costs of RVGE-related hospitalizations. Finally, hospital length in our study seems to be longer than that obtained in other studies, as previously reported, with the cost per day of hospitalization being the major contributor to the total cost of episode management.

However, there is an important variability in the cost per RVGE hospitalization from one participating hospital to another, ranging from €3,000 to €5,800, probably due to differences in patient management protocols. Therefore, comparisons should be performed with caution.

This study has several strengths. This is the first nationwide study conducted in the post-licensure RV vaccine era evaluating the healthcare resources consumption and the direct medical costs associated to RV hospitalizations. Additionally, we included a large sample size from different hospitals and different regions and used hospital medical records as source of information, allowing us to obtain more detailed information on health care resource use and costs, unlike the use of administrative databases, which may have underestimated the actual burden of RVGE disease management at the hospital level [13, 16, 31, 32]. Furthermore, complementary information was retrieved from the microbiology department databases at each hospital.

Some study limitations must however be acknowledged. Due to its retrospective design, data availability was sometimes limited by the recorded information from study sources. A proportion of episodes in our sample were nosocomial and/or reported having previous medical conditions. It is known that RV infection may complicate the course of patients with previous conditions especially immunocompromising diseases [33]. This may have an impact on the severity and resource consumption analysis (including antibiotic use). While we cannot exclude the possibility of nosocomial transmission complicating the course of disease and resulting in cost overestimation due to RVGE, we have tried to minimize this bias by only including costs related to the treatment of RVGE in the estimations for nosocomial cases. Another limitation is the absence of an analysis of indirect costs, such as the absenteeism of parents and its economic consequences. Nonetheless, it has been confirmed that the greatest contribution to the disease burden comes from direct health care costs [3, 12].

Conclusion

Health care resource utilization associated with RVGE hospitalization and the derived direct costs in Spanish hospitals are high, representing a substantial economic burden of RV severe cases requiring hospital management. This fact reinforces the importance of RV vaccination with high vaccination coverage rates for the minimization of the clinical and economic impact of disease in the health care system. Other studies that may help to estimate the global economic burden of disease related to RV infections in Spain and the potential pharmacoeconomic impact of preventive measures are granted.

Abbreviations

AGE, acute gastroenteritis

CI, confidence interval

DRG, Diagnosis Related Groups for Disease

ER, emergency room

ICG, Immunochromatography

ICU, intensive care unit

RVs, Rotaviruses

GE, gastroenteritis

RVGE,

SD, standard deviation

Declarations

Ethics approval and consent to participate

The study was designed, conducted and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology, with the ethical principles of the Declaration of Helsinki, and with the current Spanish legislation related to observational studies (Ministerial Order SAS/3470/2009).

This study was reviewed and approved by the Euskadi Independent Ethics Committee for Research with Medicines (CEIC-E).

According to the Guidelines for Good Pharmacoepidemiology Practices and the Spanish regulation for non-interventional observational studies, when using secondary data sources in which a procedure for de-identification of data is implemented, there is no need for subject informed consent collection. In the present study, only already existing data from databases and clinical records was collected, there was no interview with subjects, and all data was securely and adequately dissociated. The Euskadi Independent Ethics Committee for Research with Medicines (CEIC-E) approved this informed consent waiver.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

MC and MSM are employees of MSD Spain. All other authors do not have any competing interest.

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Authors' Contribution

JA, MMH, JTRA, JRC, and MSM contributed to the study design. JA, MMH, JTRA, JRC, MC and MSM participate in the analysis of data and drafted the manuscript. JA, SAM, BCG, EG, LDM, MM, ED, BFL, MUM, MIR, BCS, FCM, JRS and JRC contributed to the acquisition of data. All authors were involved in the critical review and revising of the final manuscript.

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Figures



Figure 1

Geographical distribution of study hospitals

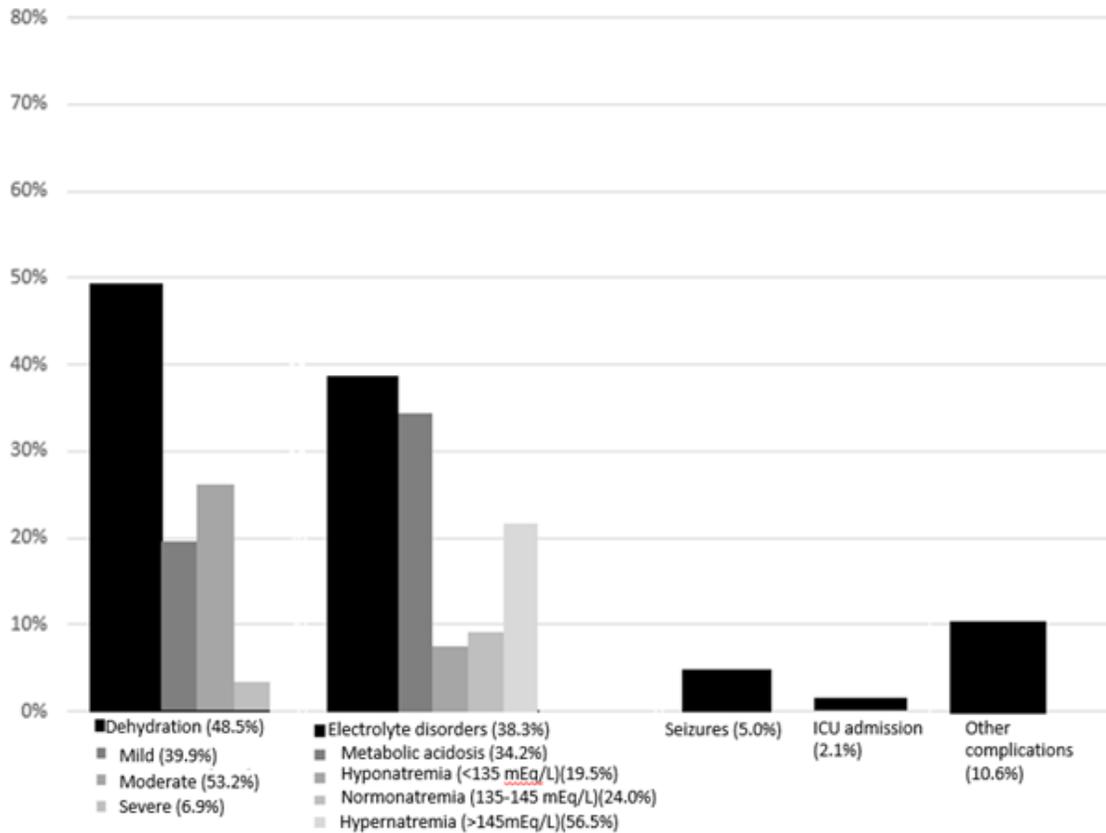


Figure 2

Frequency of complications reported in RVGE hospitalization episodes in children < 5 years of age.

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