

RESEARCH PAPER

Impact of vaccination uptake on hospitalizations due to rotavirus acute gastroenteritis in 2 different socioeconomic areas of Spain

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ABSTRACT

Rotavirus is the leading cause of hospitalization due to acute gastroenteritis (AGE) in infants and toddlers. However, rotavirus vaccination has been associated with a decline in hospitalization rates due to rotavirus AGE.

A descriptive retrospective study was conducted to analyze the impact of rotavirus vaccination on the rate of hospitalizations due to AGE among children ≤ 2 years old in 2 areas of the province of Almería, Spain. After eight years of rotavirus vaccination, rates of hospitalizations due to rotavirus AGE are diminished. This decline is closely related to vaccine coverage in the studied areas.

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Introduction

Rotavirus is the most frequent cause of severe diarrhea in children < 5 years, causing a high number of hospitalizations due to acute gastroenteritis (AGE).^{1–4} In high income countries, 65% of first episodes of rotavirus occur among infants < 1 y old.⁵

Rotavirus AGE accounted for a large public health burden in the European Union before vaccination era. It has been estimated that rotavirus caused 3.6 million episodes, 231 deaths and more than 87,000 hospitalizations among 23.6 million children < 5 y in Europe.⁶ In Spain, rotavirus AGE represents 14% to 30% of all cases of AGE and requires hospitalization in 25% of cases.⁷

As of January, 2015, 13 countries in the WHO European Region (Armenia, Austria, Belgium, Estonia, Finland, Georgia, Germany, Israel, Luxembourg, Moldova, Norway, United Kingdom, and Uzbekistan) had already included rotavirus vaccines into their national immunization programs.⁸ Reductions in hospitalizations due to rotavirus AGE have been reported in many countries in Europe^{9–16} and mathematical models have calculated a huge impact on the burden of rotavirus disease.¹⁷ In the United States, where the rotavirus vaccine is recommended for routine immunization of infants, the rate of hospitalizations due to rotavirus AGE is also reduced.^{18,19}

Currently licensed rotavirus vaccines include a pentavalent rotavirus vaccine (RotaTeq[®], Sanofi Pasteur MSD) and a monovalent rotavirus vaccine (Rotarix[®], GlaxoSmithKline). Since 2013, the World Health organization (WHO) states that all national immunization programs should include rotavirus vaccines.^{20,21}

Rotavirus vaccines were licensed in Spain in late 2006. Since 2008, the Advisory Board of Vaccines of Spanish Association of Pediatrics is recommending vaccination against rotavirus in all infants.²² However, rotavirus vaccine is not included in the national vaccination schedule and it is not financed by the public health system. As a result of this health policy, there are large differences in vaccine coverage in Spain.

In 2010 the Spanish Drugs and Health Products Agency (AEMPS) suspended temporarily the release of both vaccines due to the detection of DNA fragments of porcine circovirus. Although in September 2010 the European Medicines Agency (EMA) confirmed a positive risk-benefit balance,²³ AEMPS kept the suspension of monovalent vaccine. Only pentavalent vaccine is currently available in Spain. However, the suspension of both vaccines for 5 months was associated with an increase in hospitalizations due to rotavirus AGE in Spain,²⁴ showing the first reverse evidence of effectiveness of rotavirus vaccines.

From an epidemiological point of view, it is important to know the impact of vaccination on general population. Rotavirus vaccination may have indirect benefits by herd immunity in unvaccinated population, including older children and adults.^{25–27}

This is a descriptive retrospective study to analyze the impact of rotavirus vaccination on the rate of hospitalizations due to AGE among children < 2 y old in 2 areas of the province of Almería, Spain, that could help to guide rotavirus vaccine policies from a public health point of view

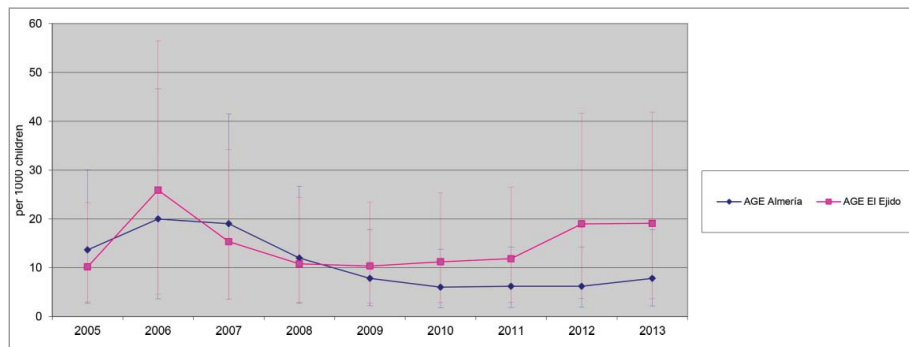


Figure 1. Rate of all causes AGE hospitalizations 2005–2013 (95% CI) Hospitalizations due to AGE (cases per 1,000 in children <2 y old population) in Hospital Torrecárdenas, Almería city and Hospital Poniente (El Ejido city) between 2005 and 2013. AGE, acute gastroenteritis. Annual rate of hospitalization was estimated using as denominator the number of newborns in birth cohorts during the present year and the previous year, and the obtained figure was divided by 2 CI: Confidence Interval.

Results

Between 2005 and 2013, there were 1,298 hospitalizations due to AGE (634 in Almería Hospital and 664 in El Ejido hospital) in children <2 y. Among them, 197 cases (31 %) were caused by rotavirus infection, in the Hospital Torrecárdenas (located in Almería city, the provincial capital) and 204 (30.5%) in El Ejido. A decline in hospitalizations due to rotavirus AGE, with an accompanying decline in hospitalizations due to all-cause of AGE, were observed since 2007 in both areas (Figs. 1 and 2). However, the reduction of both all-cause AGE and Rotavirus AGE was lower in El Ejido Hospital than in the hospital in Almería city (Table 1 and Fig. 2). Furthermore, an increase in the incidence rates of rotavirus hospitalizations was observed in El Ejido coinciding with a decrease in rotavirus vaccine coverage (Table 1).

Use of rotavirus vaccine significantly reduced the rates per 1000 children < 2 y of hospitalizations due to AGE between the 2005–2006 and 2007–2013 periods (before and after the introduction of Rotavirus Vaccines), with a decline of 30.4% of all-causes AGE ($p < 0.0001$) and 23% of Rotavirus AGE ($p < 0.0001$) studying combined data from both hospitals (Poisson regression). In addition, the reduction of Rotavirus hospitalizations rates was higher in Almería hospital (RR= 1.67, 1.24–2.25 CI 95% shift) than in El Ejido hospital (RR= 1.29, 0.89–1.71 CI 95% shift) (Table 2).

Uptake of rotavirus vaccines reached its peak in 2007 in Almería (77.1%) and in 2009 in El Ejido (44.8%). In 2010, both areas had the lowest coverage (32.6% and 23.3% respectively) and since then they never have raised above 50% (Table 2). Since 2010, an increase in the rate of rotavirus hospitalizations was observed in El Ejido hospital. However, in the Almería hospital those rates remained stable the following years.

Discussion

Introduction of rotavirus vaccines was associated with a reduced rate of hospitalizations due to rotavirus AGE in both hospitals. However, higher vaccine coverage in the hospital of Almería was associated with a lower rate of hospitalizations due to rotavirus AGE compared to the hospital in El Ejido.

The differences in coverage between the 2 hospitals could be influenced by the different social and economic situation of both areas with a higher level of immigration in El Ejido area.

Limited and variable coverage has also been found in other studies in Spain, including differences in coverage between Spanish and foreigner children.²⁸ It has been estimated that the implementation of universal rotavirus vaccination in Spain could reduce hospitalizations due to rotavirus AGE by 76% to 95%.⁷ Martínón-Torres *et al.* aimed to determine the effectiveness of rotavirus vaccines in Spain. From October 2008 to June 2009, among 467 consecutive children <2 y with AGE included in a pediatric research network (ReGALIP, www.regalip.org),

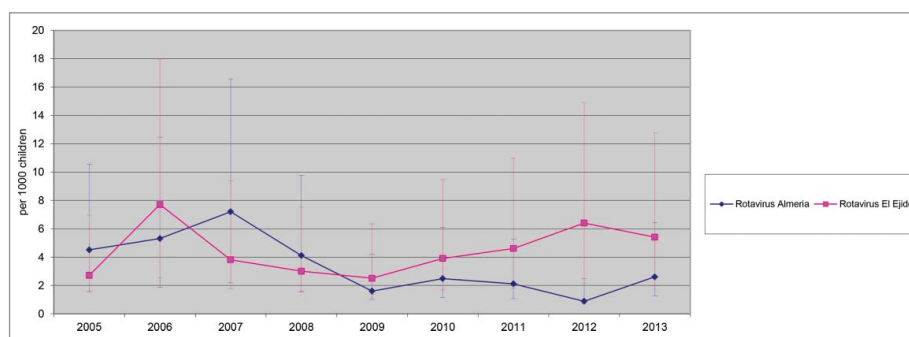


Figure 2. Rate of Rotavirus hospitalizations 2005–2013 (95% CI) Hospitalizations due to Rotavirus (cases per 1,000 in children <2 y old population) in Hospital Torrecárdenas, Almería city and Hospital Poniente (El Ejido city) between 2005 and 2013. AGE, acute gastroenteritis. Annual rate of hospitalization was estimated using as denominator the number of newborns in birth cohorts during the present year and the previous year, and the obtained figure was divided by 2 CI: Confidence Interval.

Table 1. Changes in hospitalizations due to rotavirus AGE (2005–2013) and Coverage of rotavirus vaccine***

Year	Hospital in Almería city					Hospital in El Ejido				
	AGE (n)	Rotavirus (n)	Incidence rate per 1,000 population*	Change** (%)	Coverage of rotavirus vaccine (%)	AGE (n)	Rotavirus (n)	Incidence rate per 1,000 population*	Change** (%)	Coverage of rotavirus vaccine (%)
2005	97	32	4.50	—	—	45	12	2.71	—	—
2006	120	31	5.30	—	—	120	36	7.70	—	—
2007	114	42	7.20	↑ 35.80	77.1	71	18	3.80	↓ 40.80	23.7
2008	72	26	4.10	↓ 22.60	69.9	53	15	3.00	↓ 55.80	36.9
2009	50	10	1.60	↓ 69.80	66.1	53	13	2.50	↓ 55.80	44.8
2010	44	18	2.48	↓ 53.20	32.6	58	21	3.90	↓ 51.60	23.3
2011	44	15	2.11	↓ 60.20	50.5	63	25	4.60	↓ 47.50	25.3
2012	42	6	0.88	↓ 83.40	49.1	100	34	6.40	↓ 16.60	29.5
2013	51	17	2.60	↓ 50.90	48.2	101	29	5.40	↓ 15.80	42.6

Notes. AGE, acute gastroenteritis.

*Population of children <2 y old.

**Compared to year 2006.

*** % of patients with complete rotavirus vaccination (3 doses of RotaTeq® or 2 doses of Rotarix®)

32.3% were rotavirus positive and 35.0% had received at least one dose of vaccine. The effectiveness of rotavirus vaccines to prevent hospitalization due to rotavirus AGE was 95.6% (85.6–98.6%).²⁹

In both areas, the uptakes for rotavirus vaccines reached their lowest level in 2010 related to the temporary suspension of both vaccines. The coverage increased after the suspension in 2010, but it has never achieved the levels found previously. This fact was related to an increase in the rates of AGE and rotavirus hospitalization in El Ejido hospital, where the coverage of rotavirus vaccine has never been above 30% until 2013. However, in Almería, where the coverage was around 50%, AGE and rotavirus hospitalizations rates has remained low, and even diminished in 2012.

This study only assessed rotavirus AGE cases, but not cases of AGE of different etiology or AGE due to unspecified viral infections. As Gil-Prieto *et al.*¹⁷ pointed out, rotavirus AGE is not a reportable disease in Spain and many pediatricians do not ask for specific tests because the treatment does not significantly change. These authors found a 24% of rotavirus-coded hospitalizations in children <5 years, but also a 15% of undetermined etiology diarrhea, and they suggested that part of diarrhea cases coded as non-rotavirus AGE could be non-diagnosed rotavirus AGE.

The descriptive and retrospective design of this study means some limitations. Data on vaccination state of individuals were not available. With a better knowledge of rotavirus epidemiology and the introduction of new rotavirus vaccines, test for

Rotavirus have become a routine test in the last years, so presumably number of rotavirus detected has increased which could be influence negatively the decrease of hospitalizations. Uptakes were computed using data from sales of rotavirus vaccines and the cohorts of newborns in the areas that might have some bias. On the other hand, hospitalizations rates were calculated using numbers of hospitalizations and newborns in the area. However, the data analyzed showed a strong relation between the rotavirus vaccines uptakes and the rates of hospitalization due to rotavirus.

Conclusion

After eight years of rotavirus vaccination in Spain, hospitalizations due to rotavirus AGE are diminished. This decline is closely related to vaccine coverage in the studied areas.

Patients and methods

Study design

A retrospective chart review was performed looking for hospitalizations due to AGE in patients <2 y old between January 2006 and December 2013 in 2 hospitals in Almería province in Spain (Hospital Torrecárdenas in Almería covering around 300.000 inhabitants and Hospital Poniente in El Ejido covering around 225.000 inhabitants). Records of patients hospitalized due to AGE were reviewed. Diagnosis codes for Acute

Table 2. Incidence Rate per 1000 in children < 2 y old population comparing pre-vaccine period (2005–2006) and After introduction period (2007–2013) in both Hospitals.

Year	Rotavirus Almería (n)	Incidence rate per 1,000 population Almería	Rate Ratio	CI 95% shift	
				Lower	Upper
2005–2006	63	4.86	1.67	1.24	2.25
2007–2013	134	2.90			
Year	Rotavirus El Ejido (n)	Incidence rate per 1,000 population El Ejido	Rate Ratio	CI 95% shift	
2005–2006	48	5.27	1.23	0.89	1.71
2007–2013	155	4.25			

Confidence Interval

Gastroenteritis or Enteritis were selected. Rotavirus diagnosis was made using immunochromatography test in stools. A positive test was classified as rotavirus AGE. Most AGE patients had a stool test performed. Few cases without Rotavirus test were due to difficulties to obtain the specimen within the hospitalization stay. Time periods compared were 2005–2006 (before introduction of rotavirus vaccines) and 2007–2013 (after introduction of rotavirus vaccines).

Statistical analysis

Descriptive statistical analyses were performed. To find out whether the decline in hospitalizations due to rotavirus was statistically significant over time, an overdispersion Poisson regression model was used to estimate a time trend. Number of hospitalizations and time were used as dependent and independent variables, respectively. Significance level was set at 0.05.

To estimate the annual rate of hospitalization due to rotavirus AGE per 1,000 children ≤ 2 years, the number of newborns in birth cohorts during the present year and the previous year were added, and the obtained figure was divided by 2. To estimate the annual vaccine coverage, the number of vaccine doses sold in the area was divided by the birth cohort, and the obtained figure was divided by 3 for RotaTeq[®] and by 2 for Rotarix[®]. Data on birth cohorts were from Statistical Institute of Andalucía (<http://www.juntadeandalucia.es/institutodeestadisticaycartografia/>) and data on sold vaccines were obtained from IMS Health España (<http://www.imshealth.com>).

All statistical analysis was performed by using IBM SPSS Statistics 22.0.

Abbreviations

AGE	acute gastroenteritis
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
DNA	deoxyribonucleic acid
EMA	European Medicines Agency
WHO	World Health Organization

Disclosure of potential conflicts of interest

None of the authors has received honoraria related to this manuscript. FGS has received honoraria as consultant or conferences from Pfizer, GSK, Novartis and Sanofi Pasteur MSD in the past

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Authors' contributions

Study design: Francisco Gimenez-Sanchez. Data collection: all authors. Analysis and interpretation of data: all authors. Drafting of the manuscript: Francisco Gimenez-Sanchez. Revision of the manuscript: all authors. Final manuscript was reviewed and approved by all authors before submission.

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