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Original Article

Impact of the rotavirus vaccine in Valladolid, Spain: An interrupted time series analysis

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ABSTRACT

Rotavirus vaccines (RV) have decreased the infant morbidity and mortality in countries that included RV in their national schedule. Rotavirus vaccination is recommended by the Spanish Society of Pediatrics; however, Spain, as most countries in Europe, has authorized commercialization but not included RV in its national vaccination program. We assessed the impact of RV on the rotavirus hospitalization rate through an interrupted time series analysis. There was a 46.8% (95% CI: 29.3–60.2) decrease on the rotavirus hospitalizations rate in the study region after RV commercialization in 2006. Currently there is limited evidence about the impact of RV in Europe, especially among countries not offering systematic vaccination in their national schedule. Documentation of RV coverage, effectiveness and impact is urgently needed in these countries.

1. Introduction

Two rotavirus vaccines, Rotarix (GlaxoSmithKline, Rixensart, Belgium) and RotaTeq (Merck and Co, Sanofi Pasteur MSD, Lyon, France), are licensed since 2006 [1]. Several countries have included rotavirus vaccines in their routine vaccination programs, and high impact has been documented worldwide [2–6].

In Europe, 12 countries have introduced the rotavirus in their national immunization programs [7]. The rest of the European countries have commercialized rotavirus vaccines, but vaccines have not been integrated in the routine schedules. This is the case for Spain, where the vaccine is recommended by the Spanish Association of Paediatrics but not included in the national immunization program [8], therefore vaccine needs to be purchased by caregivers. Since 2010, only RotaTeq is available in the Spanish market.

Estimates of the impact of the rotavirus vaccine are mainly coming from countries including rotavirus as part of the national vaccination program [9]. Here, we present an interrupted time series analysis to describe the impact of the rotavirus vaccine commercialization in an area of Spain that has maintained stable surveillance of rotavirus diseases since 2000 [10].

2. Methods

2.1. Study design and participants

We carried out an observational retrospective study. The study period comprised 14 years from 2000 to 2013. The target population was children under 5 years of age admitted in the Valladolid Clinical University Hospital (CUH). The CUH is the main tertiary hospital of Castilla y Leon region (~2.5 million population) and serves a population around 250,000 inhabitants from Valladolid Province, including 5% of children under five.

2.2. Variables and sources of information

The main variable of interest was the number of admissions due to rotavirus gastroenteritis (code IDC10-CM: 008.61). Secondary variables of interest included the number of admissions due to diarrhea (codes IDC10-CM: 001-009 and 558), the median age of infection and the median duration of the hospitalization. These four outcomes were obtained from the admission register of the

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CUH. In addition, the total number of deaths in Valladolid Province was obtained from the National Institute of Statistics.

2.3. Statistical analysis

The primary outcome was the weekly rotavirus hospitalization rate. Two periods were considered in the analysis: the pre-vaccine commercialization period (January 2000–June 2006) and the post-vaccine commercialization period (July 2006–December 2013).

First, a generalized linear model with robust Poisson distribution including trend, seasonality and epidemic weeks was fitted to weekly counts of rotavirus cases in the pre-vaccine commercialization period to forecast the number of cases in the post-vaccine commercialization period. Epidemic weeks were defined by the Farrington algorithm [11]. The population was included as a log-offset. The relative reduction in the number of cases was estimated by: (expected number of cases – observed number of cases)/expected number of cases per cent.

Second, an interrupted time series analysis (segmented generalized linear model with robust Poisson distribution) was used to analyze changes in the trend of rotavirus hospitalizations after vaccine commercialization. The population was included as a log-offset. This model was adjusted by the pre-vaccine commercialization secular trend, seasonality and epidemic weeks. Stata 11.2 (StataCorp, College Station TX) was used to perform the analysis.

As secondary outcomes, we described the median age of infection, the median duration of the stay and the crude mortality rate in the two above mentioned periods.

3. Results

3.1. Incidence of rotavirus gastroenteritis

A total of 1652 hospitalization with gastroenteritis as a primary diagnosis were registered during the study period in children under the age of five. The incidence rate of gastroenteritis hospitalizations was 11.0 per 1000 children-year during the study period.

A total of 592 rotavirus gastroenteritis hospitalizations were registered during the study period in children under the age of five. The incidence rate during the pre-vaccination period was 5.9 cases per 1000 children-year and 2.7 during the post-vaccination period (Table 1). The highest incidence rate was observed in children under 12 months of age both in the pre and post-vaccination periods (16.6 and 7.5 per 1000-children respectively).

3.2. Interrupted time series analysis

We assessed the impact of RV on the number of rotavirus hospitalizations through an interrupted time series analysis (Fig. 1). We estimated a 46.8% (95% CI: 29.3–60.2) reduction in the number of rotavirus cases comparing the expected with the observed number of cases for the post-vaccine commercialization period. In the multivariate interrupted time series analysis, the change in the trend was statistically significant after vaccine commercialization (Table 2). Most of the reduction in the number of rotavirus cases occurred since 2010 as a result of the decreasing trend and the absence of epidemic season (Fig. 1).

3.3. Secondary outcomes: median age of infection, duration of the hospitalization and mortality rates

The median age of infection was slightly higher in the post-vaccine commercialization period ($p = 0.02$) (Table 1). The increase occurred mainly in the 2010–2013 period (median age at hospitalization = 12.5 months). The median duration of the stay decreased since 2004; this trend did not change significantly after vaccine commercialization ($p = 0.704$).

The mortality rate in children under five was 1.1 per 1000 children-year in the pre-vaccine period and 0.7 in the post-vaccine period. The variation was not significant after adjustment by the pre-existing trend ($p = 0.175$).

4. Discussion

The results presented here show a moderate impact of the rotavirus commercialization in Spain on the number of admissions due to rotavirus in the study region. The mortality rate in children under five has remained stable after vaccine commercialization. The reduction documented in our study is the result of the decreasing trend in the post vaccine introduction period and a lower number of epidemic years. The decreasing trend was not affected by the interruption of Rotatix commercialization in Spain in 2010. The decrease in the hospitalization rate is lower than in other countries that have introduced rotavirus vaccine in their national vaccination program [2–6,9]. Rotavirus vaccination is recommended by the Spanish Society of Pediatrics but it has to be purchased by the caregivers, thus a key factor that can explain these differences is low and heterogeneous distribution of the vaccine coverage in the study region.

The main limitation of this study is that our results are only representative of the study area and they should not be extrapolated to other regions in Spain; although, similar findings have been documented in other areas of the country [12,13]. Nonetheless, the relatively low geographical scale of our study represents some advantages. First, the data collection system and study population has remained stable over time without major variations in the socio-economic composition and health seeking behavior, factors that can influence hospitalization rates. Second, hospitalization

Table 1
Rotavirus gastroenteritis (RV-GE) hospitalization rate, gastroenteritis (GE) hospitalization rate, crude mortality rate, median age of infection and the median duration of the stay and the in the pre and post-vaccine commercialization periods. Valladolid University Hospital, Spain. 2000–2013.

Indicators	Pre-vaccine period (2000–June 2006)			Post-vaccine period (July 2006–2013)		
	n	Persons-year	Estimate[a]	*n*	Persons-year	Estimate[a]
GE hospitalization rate	1095	60,050	18.2	557	89,840	6.2
RV-GE hospitalization rate	352	60,050	5.9	240	89,840	2.7[a]
<12 months	189	11,362	16.6	129	17,289	7.5
12–23 months	121	11,905	10.2	78	18,305	4.3
24–59 months	42	36,783	1.1	33	54,246	0.6
Mortality rate[b]	129	120,100	1.1	122	179,680	0.7
Median age of RV-GE hospitalization	352		11.1	240		11.5
Median stay of RV-GE hospitalization	352		6.0	240		4.0

[a] Rates are expressed in cases/deaths per 1000 per year, median age is express in months, and median stay is expressed in days.
[b] Mortality rates are provided for the entire Valladolid province as desegregated counts of death were not available for the catchment area of the Valladolid University Hospital.

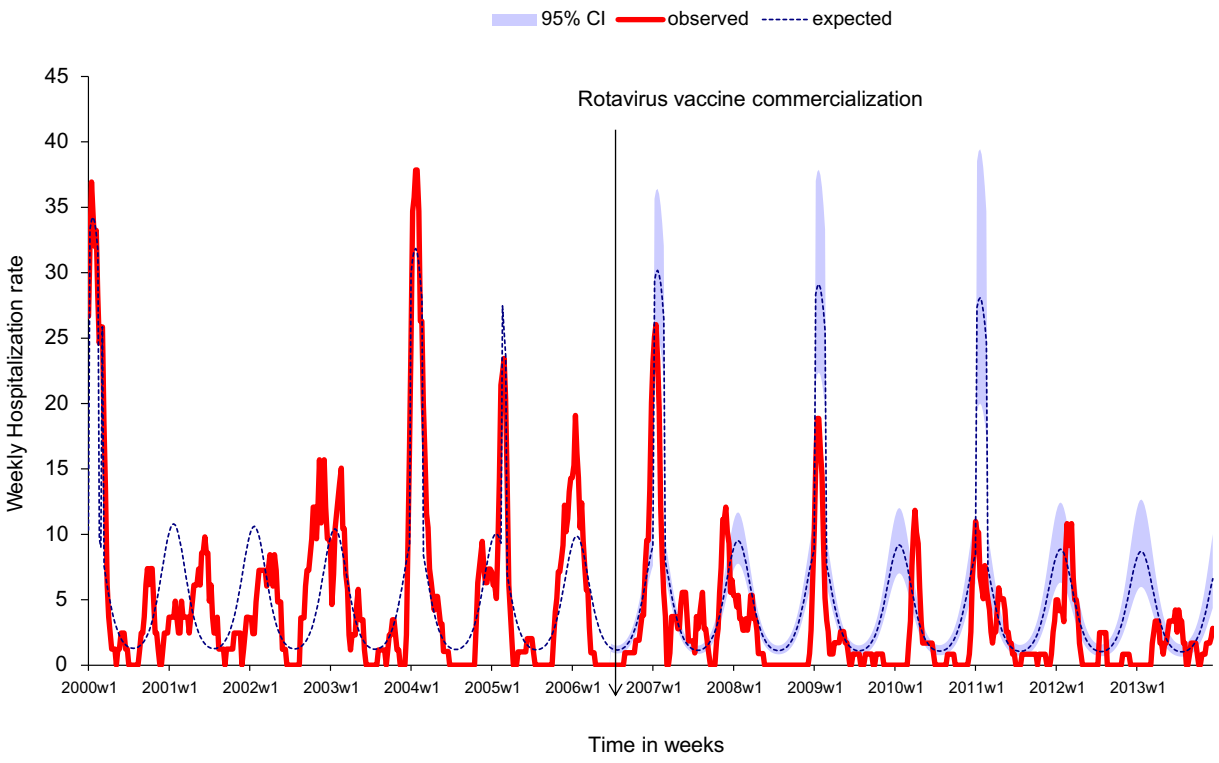

Fig. 1. Observed rotavirus hospitalization (IDC-9-CM-code: 008.61) rates per 10,000 children (under five)-year and expected hospitalization rates in the post-vaccine commercialization period (August 2006–2013) including 95% confidence intervals (CI), Valladolid University Hospital, Spain. *The expected values were estimated using a robust Poisson regression model that included a baseline trend and an annual cycle and epidemic years. We assume the proportion of epidemic years and the same percentage of epidemic week in the post vaccine introduction period than in the pre vaccine introduction period in order to calculate the expected number of rotavirus cases.

Table 2
Segmented generalized linear model with robust Poisson distribution.

Variables	IRR[a]	(95% CI)	*p*-Value
Secular trend	1.000	(0.999–1.000)	0.468
Annual cycle (sine curve)	1.746	(1.581–1.928)	0.000
Annual cycle (cosine curve)	2.129	(1.912–2.371)	0.000
Epidemic weeks	3.377	(2.987–3.818)	0.000
Change in level after vaccine commercialization	0.883	(0.723–1.077)	0.219
Change in the trend after vaccine commercialization	0.998	(0.997–0.999)	0.000

[a] IRR: weekly incidence risk ratio.

rates were well characterized before vaccination introduction [10,14,15], which allows better understanding in the season-to-season variation and the influence of the epidemic years. This has been mentioned as one of the major limitations in before-after studies including short periods of time [9]. This is relevant for impact studies as season-to-season variation can have a large influence on the estimates considering that unexpected large decreases in the hospitalization rates have described during specific years in countries were vaccine has not been used [16]. Third, the long follow-up period after vaccine introduction, allows characterizing how rates are reduced. Our study clearly shows how relevant is the reduction of epidemic years in decreasing diseases burden, especially in the last 4 years of the study period. Long pre and post vaccine introduction period allow to eliminate confounding related with season-to-season variation or modifications in the seasonal patterns associated with changes in the percentage of children susceptible in the study population [17].

In relation with the modification of the percentage of children susceptible, it is interesting to mention that the median age of rotavirus hospitalization slightly increase after vaccine commercialization in our time series. An effective vaccination in children between 6 and 14 weeks is expected to increase the age of infection as a result of the decreasing number of children susceptible at early ages, as observed in other studies [5,6]. The slightly increase in the age of infection is coherent with a moderate reduction in the proportion of children under five susceptible to rotavirus infection, and is likely related with the low amplitude of the rotavirus season in the last years of our time series.

The duration of the rotavirus hospitalizations has decreased in the last years in the study area. This decreasing trend started before the vaccine introduction and it is probably not linked with the vaccination itself, but with the implementation of stricter criteria for discharge. Stricter criteria for discharge reduce the duration of the stay and thus decrease the direct cost of rotavirus infections. However, they could increase the indirect cost for the parents. Cost-benefit estimates have been crucial in the decision making process for rotavirus vaccine introduction [9,10]. Thus, accurate and updated estimates of the key parameter for economic evaluations are needed in order to better inform decision makers [18].

Rotavirus vaccines can be purchased in European countries that have not introduced the vaccine in the national programs. The

European Society for Paediatric Gastroenterology, Hepatology and Nutrition, the European Society for Paediatric Infectious Diseases and the Spanish Society of Paediatrics recommend the use of rotavirus vaccines [8]. Nonetheless, the little information available in countries with rotavirus vaccine not included in the immunization schedules has shown low vaccine coverage [19], as it is estimated in the study area (~40%) [Supplementary Appendix]. The low coverage could explain the moderate impact described here. The high cost of the current vaccines might discourage both caregivers to purchase the vaccine and decision makers to include the vaccine in the immunization schedules [8,20], especially since 2007 considering the current economic crisis. On the other hand, the reduction of the rotavirus hospitalization rates and absence large epidemic peaks, have likely had a positive indirect effect for those requiring medical attention at a time of the year where other seasonal pathogens, like influenza, cause high attendance to emergency services. The decrease in the number of hospitalization due to rotavirus could reduce as well the risk for nosocomial outbreaks in winter periods [21].

In conclusion, we documented a decrease on the rotavirus hospitalizations rate in the study region after the vaccine commercialization in 2006 despite the fact that rotavirus vaccine is not part of the national immunization program in Spain. A better understanding of the direct and indirect benefits of vaccine is required in Spain and in other countries without national rotavirus immunization programs. Vaccine coverage estimates and reason for not vaccination are urgently needed to identify population that might be suffering the highest burden of disease and could serve to reconsider vaccination policies in Europe.

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Authors contributions

Conceived and designed the study: All authors. Performed the study: FJL APR JME. Analyzed the data: FJL JME. Wrote the first draft of the manuscript: FJL JME. Contributed to the writing of the manuscript: all authors. Agree with manuscript results and conclusions: all authors.

Conflict of interest

Authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.trivac.2016.04.005.

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