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Impact of rotavirus vaccination on childhood hospitalizations for seizures: Heterologous or unforeseen direct vaccine effects?

A. Salas [a,b,1], J. Pardo-Seco [a,b,1], M. Cebey-López [a], J.M. Martinón-Martínez [a], J. Gómez-Rial [a], M.J. Currás-Tuala [a], S. Pischedda [a,b], R. Barral-Arca [a,b], A. Justicia-Grande [a], I. Rivero-Calle [a], J. Vilar [c], F. Martinón-Torres [a,*]

[a] Grupo de Investigación en Genética, Vacunas, Infecciones y Pediatría (GENVIP), Hospital Clínico Universitario and Universidade de Santiago de Compostela (SERGAS), Galicia, Spain
[b] Unidade de Xenética, Instituto de Ciencias Forenses, Facultade de Medicina, Universidade de Santiago de Compostela, and GenPoB Research Group, Instituto de Investigaciones Sanitarias (IDIS), Hospital Clínico Universitario de Santiago (SERGAS), Galicia, Spain
[c] Department of Mathematics, Universidade da Coruña, Campus de Elviña SN, 15071 La Coruña, Spain

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ABSTRACT

There is a growing interest in the possible relationship between rotavirus (RV) vaccine and hospitalizations due to childhood seizures. We explored variation in hospitalization rates after 9 years of vaccination against pre-vaccination period for children <5 years of age from Galicia (Northwest Spain) before and after the introduction of the RV vaccines. Hospitalization rates for childhood seizures in Galician children were compared before and after RV vaccine introduction (in 2007) using different statistical approaches, including time series analyses. Our study cohort totaled 7,712 children <5 years of age admitted to hospital between 2002 and 2015 for "all kind of childhood seizures". Hospitalization rates decreases steadily with reductions ranging from 22.3% (95% CI: 15.0–29.1) in 2008, to 50.9% (95% CI: 45.5–55.7) in 2014, and significant results were also observed for <1, 1, and 2-year-old children in comparison with pre-vaccination period hospitalization rate. Regression models indicate a negative association between RV vaccination and hospitalizations for all kind of seizures. In addition, time series analyses are consistent with this finding and predict that vaccination coverage will affect hospitalization rates for "all kind of seizures" after 9 months. The results strongly support that RV vaccination has significantly reduced hospitalization rates due to childhood seizures.

1. Introduction

Rotavirus (RV) is one of the main causes of acute gastroenteritis in the paediatric population [1,2] and is a major cause of mortality in low-income countries and a significant cause of morbidity in developed countries [1]. Two vaccines against RV have been approved for use in Spain in the last decade: a monovalent RV vaccine (RV1; Rotarix®, GlaxoSmithKline Biologicals) and a pentavalent RV vaccine (RV5; RotaTeq®, Merck & Co., Inc.). Rotarix® was the first oral vaccine against RV licensed in Spain in August 2006; it consists in two oral doses that should preferably be given before 16 weeks of age. RotaTeq®, was licensed in January 2007, and posology consists in a three oral doses vaccine, and is intended for infants aged between six and 32 weeks, with at least 4 weeks between different administrations. None of these vaccines are included as part of routine vaccination schedule in Spain and they are not reimbursed. After the detection of porcine circovirus DNA in both vaccines, the 'Agencia Española Medicamentos y Productos Sanitarios' (AEMPS; www.aemps.gob.es) did not authorize the release of new batches of vaccines to the Spanish market in March and July 2010, respectively. Months later, after verifying that these finding did not generate safety or efficacy problems, the distribution of RotaTeq® was again authorized in November 2010, while the release of the batches of Rotarix® was done in June 2016. The vaccination coverage in population <5 years old in 2015 was 35.3% (73.1% of them being fully-vaccinated).

The introduction of the RV vaccine resulted in a high effectiveness and significant impact on acute gastroenteritis (AGE) admissions, and specifically AGE caused by RV [3–10]. However, the relationship between RV and non-intestinal diseases has only just begun to be investigated [11–14]. One of the most studied manifestations of RV infection is childhood seizure by different mechanisms, with RV infection being a known cause of neurological illness [11–14]. In recent years, a few studies have focused on

* Corresponding author.
E-mail address: federico.martinon.torres@sergas.es (F. Martinón-Torres).
[1] Equal contribution.

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the possible effects of RV vaccines on the prevention of hospitalization due to seizures of different origins, showing contradicting results [15–21]. Payne et al. [15] observed that full RV vaccination reduced significantly the risk of childhood seizures at least during the year following vaccination, with an 18–21% decrease in risk of seizures requiring emergency care attendance or hospitalization, as compared with unvaccinated children. Sheridan et al. [16] also found that RV vaccine was 35.8% and 38.0% effective to prevent emergency department presentation and subsequent hospitalization, respectively, for febrile seizures among children up to two years following vaccination. In line with these findings, Pardo-Seco et al. [17] obtained corroborative results from a Galician cohort (Northwest Spain). Most recently, Pringle et al. [18] indicated a lower relative risk (RR) of seizure-associated hospitalizations among vaccinated children <5 years old in the United States (RR: 0.95; 95% CI: 0.94–0.95); while Burke et al. [19] showed a reduction of seizure hospitalization risk by 24% and 14% among fully and partially RV-vaccinated children, respectively.

In contrast, the recent article by Orrico-Sánchez et al. [20] indicated a lack of impact of RV vaccines on hospitalizations in children <5 years old in a cohort from Region of Valencia (Southeast Spain). However, when examining their results, a trend towards a lower RR of seizure-related hospitalizations is observed at different RV vaccine coverage ranges [20], even though the values were not statistically significant. Noteworthy, a few statistical issues have been raised [22–24] in regards to the Orrico-Sánchez et al. [20] article (see more below). Most recently, Biggart et al. [21] could not detect any evidence supporting the potential heterologous effect of the RV vaccine (see some concerns discussed below).

In the present study, we further explore the potential effect of RV vaccination on hospitalization rates by seizures in children <5 years old in Galicia (Northwest Spain).

2. Material and methods

We compared global hospitalization rates for the pre-vaccination period (2002–2006) with those for each year of vaccination period (2008–2015). Vaccination coverage was compared between <5 years old admitted patients against general population of the same age range. Negative binomial regression and time series analysis were undertaken in order to shed further light on the potential effects of RV vaccination on hospitalization rates due to seizures before and after the introduction of vaccines in Galicia.

2.1. Data source

The present study represents a hospital-based surveillance study; therefore, no sampling of patients was required. We obtained clinical data from the database known as '*Conjunto Mínimo Básico de Datos de Hospitalización de Agudos*' (CMBD-HA, Minimum Data Set of Acute Hospitalizations). This represents the official surveillance system of hospitalizations in Galicia (a Spanish region located in the Northwest of the Iberian Peninsula). The hospital network of Galician Health Service (*Servicio Gallego de Salud*, SERGAS) is constituted by fourteen hospitals. The database contains personal, administrative and medical data for all patients admitted to any hospital in the Galician region, with diagnoses codified according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

All patients admitted for the following diagnostics were considered: (a) "all kind of seizures" (780.3* [convulsions] + 779.0* [convulsions in newborns] + 333.2* [myoclonus] + 345.* [epilepsy]; ICD-9-CM codes), (b) convulsions (780.3*), and (c) epilepsy (345.*). These ICD-9-CM code combinations have shown a positive predictive value for seizures [25] and they have been considered in several previous studies [15,17,18,20]. The diagnosis, date of birth, sex, and date of admission were collected for each case identified. Data from general population (including age, sex, and year) were obtained from the *Instituto Galego de Estadística* (www.ige.eu). The annual and monthly hospitalization rates were calculated both for the whole study population (children <5 years of age), and by age groups (<1, 1, 2, 3, and 4 years) in the period from 2002 to 2015.

In Spain, vaccination status for each individual must be disclosed and stored in official Public Health records. A database was obtained from these records and matched with hospitalization records in order to assess if there is any difference between vaccination coverage in patients admitted to hospital for seizures compared to general population <5 years old.

The study protocol was reviewed and approved by the Clinical Research Ethics Committee of Galicia (Comité Ético de Investigación Clínica de Galicia; reference code 2017/256).

2.2. Statistical procedures

Comparison of global hospitalization rates for pre-vaccination and vaccination period was made with Fisher's exact test. The results are presented as preventive fraction (PF), which can be calculated as 1–OR (if there is a decrease in hospitalization rates, the PF will be positive). In this particular analysis we excluded 2007 because this is the year when the RV vaccine was introduced.

Negative binomial regression for counted data was employed to model the monthly number of hospitalizations by "all kind of seizures" and convulsions in order to check if vaccination coverage is significantly related with hospitalization rates. For this purpose, we considered other variables to avoid confounding effect: sex, age, RV vaccination coverage for population < 5 years old (categorized in "0%", "1–14%", "15–29%", and "≥30%"), month of admission, and population size <5 years old. We did not introduce time since vaccine licensure as a variable in the model (see Gómez-Rial et al. [22,23] for a criticism of Orrico-Sánchez et al. [20]), because this variable is expected to be highly correlated with vaccination coverage; the introduction of both variables in the model could result in over-fitting and multicollinearity, affecting individual predictors.

The proportion of patients with at least one dose of RV vaccine was computed for the whole population, and for hospitalized children. Moreover, 95% CI for vaccination rates were calculated for each year analyzed. Differences between yearly proportions were evaluated with Chi-square test.

Time series ARMA (Auto-Regressive Moving-Average) [26] models were obtained for hospitalization rates for "all kind of seizures" (and convulsions) taking into account the pre-vaccination period data (2002–2006), and temporal structure of the data. A stationary time series X_t is an ARMA(p,q) model if it satisfies:

$$X_t = \phi_0 + \sum_{i=1}^{p} \phi_i X_{t-i} + \sum_{j=1}^{q} \theta_j \varepsilon_{t-j} + \varepsilon_t;$$

where ε_t is a white noise series. Therefore, this model has an autoregressive part of order p and a moving average part of order q. This model was subsequently used to predict hospitalization rates during the post-vaccination period.

In addition, dynamic regression models among monthly hospitalization rates (for "all kind of seizures" and convulsions) and vaccination coverage were additionally explored as follows:

$$X_t = \beta_0 + \beta_1 VC_{t-k} + \varepsilon_t;$$

where X_t is the hospitalization rate for "all kind of seizures" (convulsions) in the instant t, VC_{t-k} is the time series of monthly

vaccination coverage in the time *t-k*, ε_t is the model error in instant *t*, and, β_0 and β_1 are the regression coefficients.

The statistical analysis and graphical plots were generated with software R [27]. The time series analyses were performed using the *TSA* package [28]. The nominal significance level considered was 0.05; and Bonferroni adjustment was used to account for multiple testing when necessary.

3. Results

3.1. Comparison hospitalization rates between pre- and vaccination periods

RV vaccines were introduced in Spain between late 2006 and early 2007, reaching moderate coverage in the Galicia region for <1 year-old population (ranging 22.3% to 49.3%). A total of 7,712 admissions for "all kind of seizures" in children <5 years old were recorded in the study period (2002–2015), distributed as follows: 5,328 admitted for convulsions, 1,920 admitted for epilepsy, 374 hospitalized for neonatal convulsions, and 90 admitted for myoclonus.

Comparing with the average hospitalization rate in pre-vaccination period (2002–2006), significant and sustained reductions in hospitalization rates were found for "all kind of seizures" codes for children <5 years old for all years of the vaccination period, with sustained reductions ranging from 22.3% (95% CI: 15.0–29.1) in year 2008, to 50.9% (95% CI: 45.5–55.7) in year 2014 (Fig. 1A, Table S1). Considering age groups, significant results were also observed for all years and vaccination period children <1 year old (ranging from 21.1% [95% CI: 6.1–34.2] in 2011 to 49.8% [95% CI: 38.1–59.7] in 2014), 1 year (ranging from 32.0% [95% CI: 20.6–42.1] in 2008 to 63.9% [95% CI: 56.1–70.5] in 2014), and 2 years old (ranging from 20.8% [95% CI: 3.3–35.6] in 2008 to 56.3% [95% CI: 44.5–66.0] in 2015). For 3 year-old children there were significant results in the late years (2011, 2014, and 2015), which may indicate that the reduction in admission for seizures is maintained through the years (Fig. 1A, Table S1).

Analyzing specifically the convulsions codes, significant reductions in hospitalization rates were also found for children < 5 years old for all years of the vaccination period with reductions ranging from 29.2% (95% CI: 21.1–36.6) in year 2008 to 60.6% (95% CI: 55.0–65.6) in year 2014 (Fig. 1B, Table S1). Considering age groups, significant results were also observed for children <1 (ranging from 36.7% [95% CI: 19.0–51.1] in 2011 to 59.4% [95% CI: 45.4–70.4] in 2014), 1 year (ranging from 30.7% [95% CI: 18.1–41.6] in 2008 to 66.8% [95% CI: 58.7–73.6] in 2014), and 2 years old (ranging from 27.8% [95% CI: 9.1–43.2] in 2008 to 67.5% [95% CI: 56.0–76.5] in 2015). In this case, for the 3 year-old group reductions appear over a longer period in comparison with the "all kind of seizures" category diagnostics (2010, 2011, 2013, 2014, 2015) (Fig. 1B, Table S1). There are no significant and sustained results for epilepsy codes (Fig. 1C, Table S1); therefore, epilepsy was not considered in the followed-up analyses. Calculations for myoclonus and convulsions in newborns were not performed due the low number of cases.

3.2. Negative binomial regression for patients admitted for seizures

This model shows significant values for variable age, showing the 1 year-old age group as the one with the highest risk (Table 1). The sex variable is also significant, showing an OR lower than 1 for the female population. The model suggests the existence of seasonality in the number of admissions for "all kind of seizures", with significant ORs lower than 1 for the summer months in comparison with January; this is consistent with RV seasonality noted in a previous study in Galicia [29]. The vaccination coverage shows significant results for all categories, obtaining lower ORs when higher coverages are considered (0.89 [95% CI : 0.81, 0.98] for 1%–14% coverage; 0.83 [95% CI: 0.74, 0.93] for 15–30% coverage; and 0.70 [0.64, 0.78] for coverage $\geq$ 30%), which strongly supports the association between admissions for "all kind of seizures" and RV vaccination.

The results of the negative binomial regression model for convulsion agree with the results for "all kind of seizures", obtaining more significant and strong results for higher vaccination coverage (0.84 [95% CI: 0.75–0.93] for 1%–14% coverage; 0.74 [95% CI: 0.65–0.85] for 15–30% coverage; and 0.57 [95% CI: 0.51–0.64] for coverage $\geq$ 30%) (Table 1). According to age, the results show that the ages of maximum risk are 1 and 2 years old.

3.3. Vaccination coverage in admitted patients versus general population

The vaccination coverage (with at least one dose) was computed for the general population (<5 years old) and for patients admitted for "all kind of seizures" and "convulsions" (Table 2, Fig. 2). The results show significantly lower coverages for admitted children in comparison with the general population for every year considered – except for children admitted for "all kind of seizures" in 2007 – with *P*-values surpassing Bonferroni correction threshold in the majority of cases.

3.4. Time series analysis

Monthly hospitalization rates for "all kind of seizures" and convulsions in the period 2002–2006 for children < 5 years old fit an

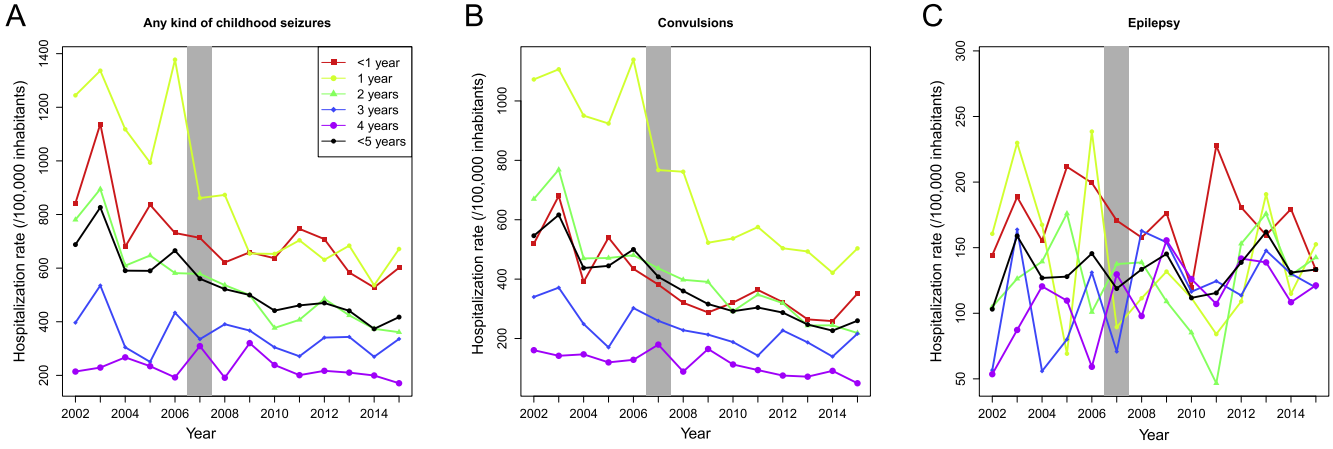

Fig. 1. Yearly hospitalization rates for children younger than 5 years in the study period admitted for (A) "all kind of seizures", (B) convulsions and (C) epilepsy.

Table 1
Negative binomial regression model for number of admissions by "all kind of seizures" and convulsions. Age, sex, month of admission, population number (×1000), and vaccination coverage were considered as independent variables.

	All kind of seizures		Convulsions	
Variables	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age				
<1 year of age	1	–	1	–
1 year of age	1.28 (1.19, 1.39)	<0.0001	2.03 (1.85, 2.22)	<0.0001
2 years of age	0.79 (0.73, 0.87)	<0.0001	1.15 (1.04, 1.27)	0.0085
3 years of age	0.52 (0.48, 0.58)	<0.0001	0.66 (0.58, 0.73)	<0.0001
4 years of age	0.35 (0.31, 0.38)	<0.0001	0.33 (0.29, 0.38)	<0.0001
Sex				
Male	1	–	1	–
Female	0.81 (0.76, 0.86)	<0.0001	0.78 (0.73, 0.85)	<0.0001
Month				
January	1	–	1	–
February	1.13 (1.00, 1.27)	0.0526	1.08 (0.95, 1.24)	0.2550
March	1.11 (0.98, 1.25)	0.0969	1.03 (0.90, 1.18)	0.6238
April	0.95 (0.83, 1.07)	0.3745	0.85 (0.74, 0.98)	0.0251
May	0.97 (0.86, 1.10)	0.6565	0.83 (0.72, 0.95)	0.0078
June	0.81 (0.71, 0.92)	0.0012	0.71 (0.62, 0.83)	<0.0001
July	0.82 (0.72, 0.93)	0.0019	0.68 (0.59, 0.79)	<0.0001
August	0.76 (0.67, 0.87)	<0.0001	0.65 (0.56, 0.76)	<0.0001
September	0.74 (0.65, 0.84)	<0.0001	0.62 (0.53, 0.72)	<0.0001
October	1.02 (0.90, 1.16)	0.7288	0.89 (0.77, 1.02)	0.3036
November	1.04 (0.92, 1.17)	0.5426	0.90 (0.79, 1.04)	0.3982
December	1.02 (0.90, 1.15)	0.8093	0.95 (0.83, 1.09)	0.9998
Population (×1000)	1.00 (0.94, 1.06)	0.9639	0.96 (0.90, 1.03)	0.2455
Vaccination coverage				
0%	1	–	1	–
1%–14%	0.89 (0.81, 0.98)	0.0195	0.84 (0.75, 0.93)	0.0018
15%–29%	0.83 (0.74, 0.93)	0.0015	0.74 (0.65, 0.85)	0.0002
≥30%	0.70 (0.64, 0.78)	<0.0001	0.57 (0.51, 0.64)	<0.0001

Table 2
Population RV-vaccine coverage rates for children younger than 5 years for general population, patients admitted for "all kind of seizures" and patients admitted for convulsions. *P*-values to test the differences with global coverage were computed using Chi-square test. *P-values surpassing Bonferroni correction threshold.

		All kind of seizures		Convulsions	
Year	**Population coverage**	**Coverage (95% CI)**	***P*-value**	**Coverage (95% CI)**	***P*-value**
2007	4.0%	2.9% (1.8, 4.7)	0.2022	1.8% (0.9, 3.6)	0.0248
2008	10.8%	6.3% (4.6, 8.8)	0.0010*	5.8% (3.8, 8.8)	0.0023*
2009	18.1%	10.7% (8.3, 13.6)	<0.0001*	13.6% (10.3, 17.8)	0.0360
2010	21.5%	11.3% (8.7, 14.6)	<0.0001*	13.2% (9.8, 17.5)	0.0005*
2011	26.4%	14.3% (11.5, 17.8)	<0.0001*	16.9% (13.2, 21.4)	0.0001*
2012	29.8%	15.1% (12.2, 18.5)	<0.0001*	18.6% (14.6, 23.4)	<0.0001*
2013	30.3%	14.6% (11.6, 18.2)	<0.0001*	18.3% (14.0, 23.5)	<0.0001*
2014	30.5%	19.5% (15.8, 23.8)	<0.0001*	22.7% (17.8, 28.6)	0.0106
2015	35.4%	17.9% (14.5, 22.0)	<0.0001*	19.4% (15.0, 24.7)	<0.0001*

ARMA(0,2) model (Fig. 3). This model depends on two moving-average coefficients that are estimated from the residuals obtained in previous times; that is, the forecasting on time $t + k$ will depend on noise series on time $t + k$–1 and time $t + k$–2, which are estimated by their mean, which is zero if $k > 2$. Therefore, from the point $t + 2$ onward the forecasting is constant (flat observed values depicted in blue in Fig. 3A and B). Moreover, the ARMA(0,2) model improves its performance (under an Akaike and Bayesian Information Criteria) when adding an additive coefficient to correct for an outlier data point in December 2003.

We did not observe any seasonal component, i.e. a cyclical behavior of the data (e.g. by year). Similarly, predicted values for monthly hospitalization rates for convulsion in 2007–2015 period were again higher than the observed ones in the majority of cases (Fig. 3C, D). The cross-correlation between the differentiated series was calculated, obtaining a significant retard of $k = 9$, which means that the vaccination coverage in a certain moment will affect to hospitalization rate for "all kind of seizures" after 9 months.

Using ordinary least square methods, we obtained an estimated value of $\beta_1 = -4.782$ (P-value = 5.9×10^{-5}), which strongly supports the relation existing between "all kind of seizures" hospitalization rates and vaccination coverage. An analogous analysis was performed for monthly hospitalization rates for convulsions, again obtaining a significant retard of $k = 9$, and an estimated value of $\beta_1 = -4.648$ (P-value = 5.2×10^{-6}).

3.5. Limitations of the present study

The present study cannot be considered to be totally independent evidence from our findings in Pardo-Seco et al. [17]. Thus, in our previous article, we used estimated RV vaccination rates for all the inferences, whereas here we have accessed actual data on vaccinated children population, allowing a deeper analysis of the real impact of vaccination coverage (including time series analysis) on hospitalization rates and covering a larger observation

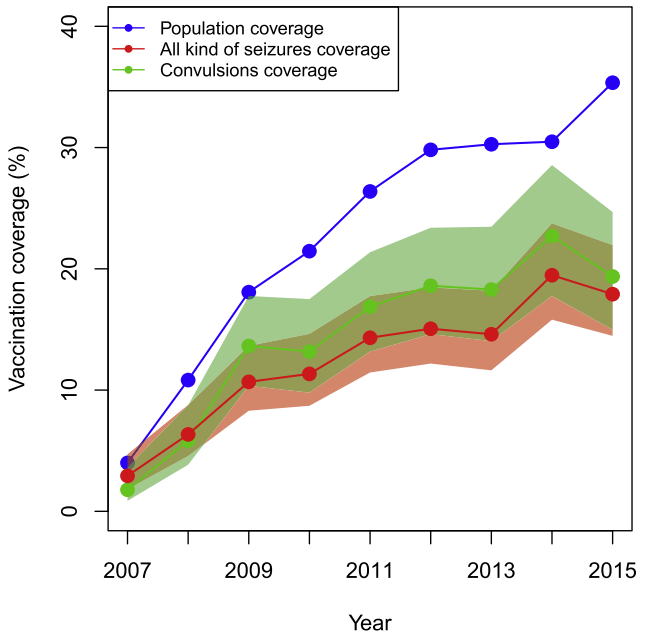

Fig. 2. RV vaccination coverage (at least one dose) for children younger than 5 years in whole population, children admitted for "all kind of seizures", and convulsions. The colored polygons represent the 95% CIs.

period (14 years). The results of the present study are fully consistent with those obtained previously [17].

On the other hand, we observed an underrepresentation of vaccinated children in those hospitalized (Fig. 2). We interpret that the RV vaccine confers protection to children, preventing them from hospitalization; however, there is not demographic/clinical data available that allow to evaluate the impact of other possible missing variable that differentiate vaccinated from non-vaccinated cohorts.

Finally, our approach is strictly statistical, and therefore, it is not possible to investigate, with the data available, if the effect of vaccination is due to e.g. herd immunity or other unknown epidemiological mechanism.

4. Discussion

Rotavirus infection has been linked to several systemic and extra intestinal manifestations, mainly seizures and autoimmune disorders [22,30]. Unexpected positive impact of RV vaccine has been previously observed in celiac disease [31] and type-1-diabetes [32], beside seizures [15–19].

Rotavirus vaccination seems to protect children against hospital admission due to seizures. Several studies had previously analyzed the possible relation existing between RV vaccination and childhood seizures reduction rates [15–21] with most of them showing a significant risk reduction for convulsions [15–19]. In our study

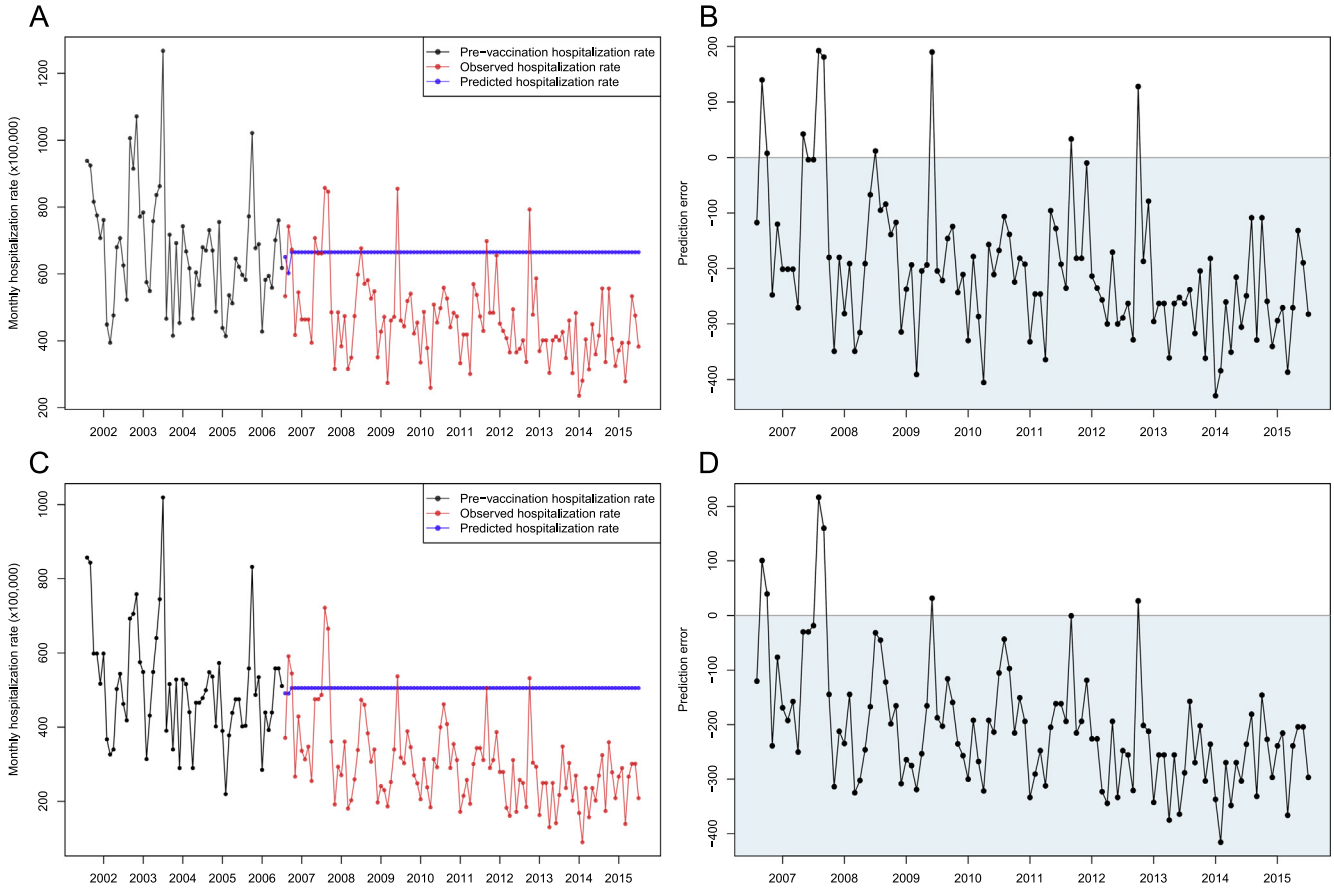

Fig. 3. Time series models for monthly hospitalization rates for (A) "all kind of seizures", and (C) for convulsions; using data from the pre-vaccination period (2002–2006) and estimates for the vaccination period (2007–2015) compared to the observed values. (B) Deviations of the observed monthly hospitalization rates from estimated values according to the ARMA(0,2) model for "all kind of seizures", and (D) for convulsions.

we have confirmed, using different complementary approaches, the protective role of RV vaccination related to hospitalization admission for seizures, focusing specifically on the effect of vaccination coverage in population younger than 5 years of age. Although a proper *meta*-analysis of the literature is not possible due to the different methodologies and epidemiological strategies followed by different authors, the overall previous findings converge in the same direction as ours [15–19].

To the best of our knowledge, the article by Orrico-Sánchez et al. [20] is the only one claiming a lack of effect for the RV vaccine on seizure hospitalization rates in a different Spanish cohort (children <5 years old in the Valencia region). A few points of this study merit further attention. First, these authors reported adjusted RR values below 1 for different RV vaccine coverages, even though their 95% CI upper limits slightly surpassed 1. Secondly, the authors made a nonspecific used of the terms convulsion and seizure. Third, the Poisson regression model used by Orrico-Sánchez et al. [20] was adjusted (among other variables) by time in post-vaccination period, total hospitalization rate except convulsions, and time of study, among others. These variables are likely to be highly correlated (e.g. vaccination coverage will increase with time). In fact, results (see their Table 2) show a significant correlation between vaccination coverage and hospitalization rates for any cause except RV-AGE and seizures. From this, it can be deduced that there is correlation between vaccination coverage and total hospitalization rates except by convulsions (included in the Poisson regression model). Overall, there is evidence indicating that the regression model exposed by Orrico-Sánchez el al. [20] could be affected by strong collinearity among the variables, and the use of statistical variables is unfortunately confused. Overall, it is not possible to anticipate from the data available in this publication [20] if the decisions taken in regard to the use of variables could have introduced statistical noise affecting the regression model, which could lead to wrong predictors estimates and/or a lack of statistical power [22–24].

Recently, Biggart et al. [21] did not find significant differences in hospitalization rates for seizures. This study reported results somehow contradictory to the trend observed in the literature. These authors used interrupted time series analysis to study the heterologous effect of RV vaccine. This kind of time series analysis needs the use of independent data what led the authors to consider yearly hospitalization rates instead of e.g. monthly hospitalization rates (as done in the present study). Unfortunately, this implied the used of an extremely low number of data values to estimate the model (at most, four years of vaccination for their youngest age group; see their Figs. 1 and 2), which necessarily leads to a low statistical power. This fact may explain their inability to obtain significant findings.

In our previous study [17], we found significant reductions in median hospitalization rates comparing the pre-vaccination to the vaccination period, with decrease rates ranging from 16.2% (95% CI: 8.3, 23.5) to 34.0% (95% CI: 27.3, 40.1%) in the 2007–2012 period for "all kind of seizures". In the present study we present additional strong evidence supporting a protective effect for RV vaccination against hospitalization admissions for seizures. Different methodologies were used for this purpose (e.g. regression models and time series analysis) obtaining significant results in each case.

Whether this unexpected benefit exerted by RV vaccines is mainly due to the prevention of RV infections in infants otherwise susceptible to the neurological tropism of RV, and/or a true heterologous effect of the vaccine, remains unknown [30]. The role of RV infection as the cause of seizures is well established in the scientific literature [14]. A hypothesis has been proposed that argues a key role for the viral nonstructural protein 4 (NSP4) through a disruption of Ca^{2+} homeostasis that may result in neurotoxicity and neurotransmitter dysregulation [11]. Another possible explanation for RV-induced seizures is through direct central nervous system infection action [33]. This hypothesis is supported by several studies demonstrating RV detection in spinal fluid [34].

Convulsions are a relatively common condition, which according to The Epilepsy Foundation (www.epilepsy.com), is the fourth most common neurological disorder, affecting an estimated 3 million Americans. Although a great variety of factors influence the incidence and prevalence of seizures, between 0.5 and 1% of the child population will have at least one seizure during their lifetime. If our results are extrapolated to the global population, and considering that as of August 2018, 98 countries have introduced RV vaccines in their national immunization programs (i.e., public sector), the implications of RV vaccination, would be outstanding, since it might also act as a preventive epileptic drug with success rates as high as some of the first line drugs, for free and with greater security profiles.

Finally, while we detected an association between RV vaccine and "all kind of seizures" and "convulsions", we did not observe a specific association with epilepsy. This is not necessarily a contradictory result, namely, it mights just reflect a different meaning and sensitivity of the code selected. It is important to note that epilepsy code is much more restrictive, designates a chronic condition for the diagnosed child and before the establishment of epilepsy diagnosis, children can be admitted to the hospital due to convulsions or seizures episodes of unspecified origin more than one time. These differences could explain the statistical associations observed in the present study.

5. Conclusion

RV vaccines seem to provide a protective effect against hospitalization due to seizures in childhood. These results agree with the trend observed in the majority of previously published studies and confirm the expanded benefit of RV vaccines, either through true heterologous effects or unforeseen direct effects. The precise mechanism underlying these effects remains to be elucidated and deserves further exploration. In the meantime, this positive effect should be probably considered when evaluating the efficiency of vaccination against RV.

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FMT received honoraria from GSK, Pfizer, Sanofi Pasteur, MSD, and Janssen for taking part in advisory boards, expert meetings

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.04.086.

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