



STUDY PROTOCOL

Impact of rotavirus vaccines on rotavirus-associated hospitalizations in the Valencia Region, Spain

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RESEARCH TEAM

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INTRODUCTION

Two oral live-attenuated rotavirus vaccines, indicated for infants ages 6-12 up to 24 or 32 weeks of age, are currently globally licensed: a monovalent human vaccine, Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium), administered in a two-dose series (RV1), and a pentavalent bovine-human reassortant vaccine, RotaTeq® (Merck & Co., Inc., West Point, PA, USA), with a three-dose schedule (RV5). RV1 and RV5 have been available in Spain since August 2006 and January 2007, respectively. Although institutions such as the World Health Organization, the Centers for Disease Control and Prevention, and the Pediatric Spanish Society, recommend the inclusion of rotavirus vaccination in national immunization programmes, the Spanish National Health System (NHS) does not fund rotavirus vaccines. Due to the incidental finding of circovirus DNA contamination in both vaccines, the Spanish Medicines Agency suspended RV5 distribution during June-November 2010, and RV1 distribution since March 2010. As of November 2014, RV1 distribution remains suspended in Spain. ¹ Both vaccines have shown relevant benefits in terms of protective association against acute gastroenteritis. ^{2,3} Recently, an additional benefit of these vaccines has been shown: a protective association against childhood seizures. ^{4,5} Our aim is to assess the impact of rotavirus vaccines on serious rotavirus-associated health care events, including gastroenteritis and seizures, and their impact on healthcare utilization, in a setting with low/moderate rotavirus vaccine coverage.

OBJECTIVES

Primary objectives

To assess the impact of rotavirus vaccines on hospitalized acute rotavirus gastroenteritis among Valencia Region's population aged less than 5 years

Secondary objectives

To assess the impact of rotavirus vaccines on hospitalized acute gastroenteritis among Valencia Region's population aged less than 5 years

To assess the impact of rotavirus vaccines on hospitalized childhood seizures among Valencia Region's population aged less than 5 years

To assess the change in hospitalizations, and their costs, for rotavirus acute gastroenteritis, acute gastroenteritis, and seizures following rotavirus vaccines introduction among Valencia Region's population aged less than 5 years

METHODS

A retrospective, population-based, ecological study will be performed using the region's health care databases from 1st January 2002 until date of data extraction.

Study population

The population of interest will be Valencia Region's children born from 1st January 2002 through 31st December 2014 aged less than 5 years during the study period.

Study setting and data sources

The Valencia Region, one of the 17 Autonomous Regions of Spain, has a population of approximately 5,000,000 inhabitants, and an annual birth cohort of 48,000 infants. Approximately 98.3% of the population is covered by the public health system. The regional health system is divided into 24 Departments. It includes 32 public hospitals, 24 of them attending acute paediatric patients.

Population-based administrative database

The regional population-based administrative database, SIP, collects and updates identification data, geographic location, assignment of health services, and access to public health services for both residents of the Valencia Community and non-residents with access to public health services. It includes APSI characteristic which is an identification code defined for each person at any time including: inhabitant's registration status, nationality (Spanish or not), sex, year of birth, health department assigned, health care

insurance, residence status, migrations, work activity, geopolitical group, and social exclusion. Since 2005, SIP can be linked with the hospital discharge database.

Hospital Discharge Database

The Spanish hospital discharge database, CMBD, collects diagnosis and procedures as an assessment of medical activity. The coding system used is ICD-9-CM. The main discharge diagnosis is coded in first position, and diagnosis relevance decreases as the position number increases. Using CMBD is compulsory for all public hospitals, and over 95% of all discharges are included. According to the Spanish Ministry of Health, data are considered reliable since 2002.

Vaccine Registry

All patient data can be linked to a vaccine registry (Registro de Vacunas Nominal, RVN), which is part of the population-based online registry (Sistema de Información Vacunal, SIV) put in place in 2000 that captures the immunization history of each individual. Data are registered from public and some private health centres. Available data includes vaccine by type, manufacturer, batch number, number of dose, place and administration date, and, if applicable, risk group. Data are considered reliable since 2005.

IMS Health

Manufacturers, pharmaceutical wholesalers, and distributors report IMS Health the shipment of vaccine doses to every distribution channel including hospitals, clinics, retail and pharmacies.

Outcomes

Acute gastroenteritis-associated hospitalizations will be identified from CMBD through a search of the following ICD-9-CM codes: 001-009 (intestinal infectious diseases), 558.9 (other and unspecified non-infectious gastroenteritis and colitis), and 787.91 (diarrhoea not otherwise specified).

Acute gastroenteritis events will be classified as:

- Rotavirus acute gastroenteritis hospitalization: hospitalization with a discharge diagnosis of enteritis due to rotavirus (ICD-9-CM code 008.61) in any diagnosis position
- Acute gastroenteritis hospitalization: hospitalization with a discharge diagnosis of gastroenteritis-associated episode (ICD-9-CM codes 001-009, 558.9, 787.91) in any diagnosis position

Seizure events will be identified from CMBD and ED database through a search of the following ICD-9-CM codes in first discharge diagnosis position: 780.3 (convulsions), 779.0 (convulsions in newborn), 333.2 (myoclonus), or 345 (epilepsy)

- Seizure hospitalization: hospitalization with a discharge diagnosis of seizures (ICD-9-CM code 780.3, 779.0, 333.2, or 345) in first diagnosis position

Exposure

Rotavirus vaccination coverage will be assessed as follows:

Rotavirus vaccine status will be assessed according to the following categories: (1) Fully vaccinated (three doses of RV5 or two doses of RV1), (2) Vaccinated with at least one dose (at least one dose of RV5 or RV1)

Because rotavirus vaccines are not included in the official immunization schedule, there is a possibility of underreporting of rotavirus vaccination by providers, although almost all (86%) rotavirus vaccine doses distributed in Valencia during the 2009–2012 period were registered in SIV as administered in children aged less than one year.⁶ However, we cannot rule-out the possibility that some doses could have been missed or administered in private vaccination centres not using SIV, or outside the health care setting. Therefore, rotavirus vaccination will be assessed using two data sources, the regional vaccine registry in which administered vaccines are recorded and data from IMS Health, which will provide data on number of doses distributed. In addition, we will estimate a range of the vaccine coverage for rotavirus vaccine based on the lower and higher results found.

- (a) Using data from SIV

If one or more of the vaccine doses registered as administered do not

indicate vaccine brand, the brand assumed for all doses will be the one specifically mentioned for the remaining doses. All vaccine doses administered from November 2010 until the end of the study period with missing data on vaccine brand will be assumed to be RV5 since, from this date onwards, this was the only rotavirus vaccine available in the Spanish market.

Children who do not have a record for rotavirus vaccination in SIV will be considered as unvaccinated.

- (b) Using data on number of rotavirus doses distributed obtained from IMS Health
- (c) Using jointly data obtained from IMS Health and SIV

Pneumococcal vaccination coverage will be assessed according to the following categories: (1) Vaccinated with at least one dose (at least one dose of PCV7, PCV10 or PCV13)

- (a) Using data on number of pneumococcal vaccine doses distributed obtained from IMS Health
- (b) Using jointly data obtained from IMS Health and SIV

Pneumococcal vaccination coverage will not be assessed using only data obtained from SIV since those data is not reliable until 2005-2006.

Data collection

Data to be extracted from SIP: number of Valencia Region's children born from 1st January 2002 through 31st December 2014 and aged less than 5 years during the study period (2002-until date of data extraction) by gender and health department

	Age in months							
	0-2	3-5	6-11	12-23	24-35	36-47	48-59	<60

Jan 2002								
Feb 2002								
Mar 2002								
...								

Data to be extracted from CMBD: Number of rotavirus acute gastroenteritis hospitalizations, acute gastroenteritis hospitalizations, seizures hospitalizations, and hospitalizations for any reason among Valencia Region's population born from 1st January through 31st December 2014 and aged less than 5 years during the study period (2002-until date of data extraction) by gender and health department. In addition, days of hospital stay will be also requested.

- (a) For each one of the following ICD-9-CM codes in any discharge diagnosis position: 001-009 (intestinal infectious diseases), 008.61 (rotavirus), 558.9 (other unspecified non-infectious gastroenteritis and colitis), 787.91 (diarrhea)
- (b) For each one of the following ICD-9-CM codes in first discharge diagnosis position: 780.3 (convulsions), 779.0 (convulsions in newborn), 333.2 (myoclonus) and 345 (epilepsy and recurrent seizures)
- (c) For any ICD-9-CM code (001-999) in any diagnosis position (this data will be requested in order to describe the burden of the outcomes of interest among the total of hospitalizations)

	Age in months							
	0-2	3-5	6-11	12-23	24-35	36-47	48-59	<60
Jan 2002								

Feb 2002								
Mar 2002								
...								

Data to be extracted from SIV: Number of rotavirus vaccinees among Valencia Region's population born from 1st January through 31st December 2014 and aged less than 5 years during the study period (Aug 2006-until date of data extraction) by gender and health department

	RV1		RV5	
	≥1 dose	2 doses	≥1 dose	3 doses
Aug 2006				
Sep 2006				
Oct 2006				
...				

Number of pneumococcal vaccinees among Valencia Region's population born from 1st January through 31st December 2014 and aged less than 5 years during the study period (Oct 2002-until date of data extraction) by gender and health department

	PCV7	PCV10	PCV13
Oct 2002			
Nov 2002			
Dec 2002			
...			

Data on number of distributed doses of rotavirus vaccines to be requested from IMS Health by health department:

	RV1	RV5
Aug 2006		
Sep 2006		
Oct 2006		
...		

Data on number of distributed doses of pneumococcal conjugate vaccines to be requested from IMS Health by health department:

	PCV7	PCV10	PCV13
Oct 2002			
Nov 2002			
Dec 2002			
...			

Statistical analysis

Monthly and yearly incidence rates will be calculated as the number of hospitalizations for the outcomes of interest divided by the total population at risk during each month/year of the study period.

We will evaluate the impact of vaccination by using data from CMBD, which provide robust pre-vaccination period data, in order to assess trends in hospitalizations due to acute rotavirus gastroenteritis, acute gastroenteritis, and seizures during the period prior to rotavirus vaccines licensure and utilization in Spain. Years 2002 to 2006 will be considered pre-vaccination period, years 2007 onwards will be considered the post-vaccination period.

The impact of rotavirus vaccines to prevent the outcomes of interest will be described by assessing the changes in hospitalization rates during the post-

vaccination period (per year) compared to the pre-vaccination period. To account for secular trends, expected annual hospitalization rates for the post-vaccination period will be generated, by using Poisson regression analysis of the 2002-2006 annual rates.⁷ These expected rates will be compared with the annual observed rates from 2007 onwards.

Poisson regression will be used for assessing the correlation between the hospitalization rates and rotavirus vaccines coverage. Age group, calendar year, pneumococcal conjugate vaccine coverage (only in the analysis on seizures), health department, and percent differences between expected and observed hospitalization rates (as a secular trends proxy) will be considered as covariates.

The changes in hospitalizations will be calculated by comparing the difference between number of hospitalizations and related costs in the post-vaccination period (per year) compared to the pre-vaccination period. To account for secular trends, expected annual hospitalizations will be compared with the annual observed hospitalization from 2007 onwards.

Analyses will be carried out using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) or Stata/SE 13.1 (StataCorp LP Texas, USA). All tests will be two-sided with a significance level of 0.05.

Limitations

This is an impact (ecological) study and, therefore, there is no direct link between exposures in a given child and the outcomes observed. Thus, causality cannot be attributed to the exposure. In addition, ecological studies present a lack of control for confounding: rotavirus vaccines are not included in the official immunization schedule and this may suggest differences between rotavirus vaccinees and non-vaccinees with respect to socio-economic conditions and health seeking behaviour.

Because the years prior to vaccine introduction are compared to years subsequent to vaccine introduction, secular trends unrelated to vaccination could affect the outcome's incidence. For these reasons, adjustments for secular trends will be included.

The PPV of the rotavirus ICD-9-CM code identifying acute gastroenteritis attributable to rotavirus has been assessed as $\approx 90\%$ within CMBD.⁸ The PPV of the ICD-9-CM codes identifying seizures has not been assessed within the CMBD database.

RV1 and RV5 were used concurrently until 2010. Nonetheless, since 2010-2011, the only rotavirus vaccine available in Spain is RV5. Therefore, results will have limited value to estimate the impact of RV1. Thus, the study assumes that most of the impact is due to RV5. Nonetheless, our expectation is that the vaccine utilization data will provide confirmation that most rotavirus vaccine doses distributed in Valencia during the study period are RV5.

Most vaccines can cause febrile seizures, which are usually limited in duration and severity. These seizures could sometimes be difficult to distinguish from other types of seizures. Pneumococcal vaccination may be a confounder since pneumococcal conjugate vaccines could cause febrile seizures, and they were also not included in the immunization schedule during the study period. Therefore, adjustments for pneumococcal conjugate vaccine coverage will be included.

REGULATORY AND ETHICAL CONSIDERATIONS

The study will be conducted in accordance with all applicable regulatory requirements, including all applicable subject privacy requirements, the guiding principles of the Declaration of Helsinki, and Ethical Guidelines for Epidemiological Investigations.

Since all data will be requested as aggregated, there is no need for Ethics approval. Nevertheless, the study will be informed to the Ethics Research Committee of the Dirección General de Salud Pública/Centro Superior de Investigación en Salud Pública (CEIC DGSP/CSISP).

The study will be informed to the Spanish Medicine Agency (AEMPS) in order to request its classification (as 'Estudio post-autorización otros diseños, EPA-OD') according to the existing legislation (Orden SAS/3470/2009). The study will be also informed to the Pharmacy Agency of the Valencian Government according to the existing legislation [Resolución de 16 de junio de 2009, de la Conselleria de Sanitat].



PHARMACOVIGILANCE

In accordance with the Guideline on Good pharmacovigilance practices (Directive 2001/83/EC as amended 2010/84/EU and regulation 726/2004) and Orden SAS/3470/2009 about observational post-licensure studies, as the study design is based on secondary use of data, suspected adverse reactions associated with a Sanofi Pasteur MSD product (or susceptible to be) must not be individually reported to competent Health Authority on an individual basis. Suspected adverse events, if any, will be summarised in the study report.

TIMELINES

TASKS	MONTHS					
	1	2	3	4	5	6
Spanish Medicines Agency classification						
Contract signature						
Acquisition of data*						
Analysis*						
Discussion of results*						
Manuscript + report*						

* These activities would start once the contract has been signed

DISSEMINATION STRATEGY

The dissemination actions will comprise at least:

- Publication of a scientific paper in an indexed scientific journal
- Participation in one national and in one international scientific meeting/congress

BUDGET

ACTIVITIES	COST
Study design and statistical analysis plan	3,000 €
Data collection and data management Data request, data extraction, data cleaning, data tabulation, data quality review	9,000 €
Data analysis and results presentation Statistical analysis plan implementation, presentation and discussion of results	3,000 €
Manuscript and final report Preparation and submission	2,000 €
SUBTOTAL	17,000 €
OVERHEAD 25%	4,250 €
TOTAL BUDGET	21,250 €

The funding entity will pay expenses derived from the participation in one national and in one international scientific meeting/congress, as well as manuscript publication expenses and data requested from IMS Health.

REFERENCES

1. Perez-Vilar S, Díez-Domingo J, Lopez-Lacort M, Martínez-Ubeda S, Martínez-Beneito MA. Effectiveness of rotavirus vaccines, licensed but not funded, against rotavirus hospitalizations in the Valencia Region, Spain. *BMC infectious diseases* 2015;15:92.
2. Rha B, Tate JE, Payne DC, et al. Effectiveness and impact of rotavirus vaccines in the United States - 2006-2012. *Expert review of vaccines* 2014;13:365-76.
3. Karafillakis E, Hassounah S, Atchison C. Effectiveness and impact of rotavirus vaccines in Europe, 2006-2014. *Vaccine* 2015;33:2097-107.
4. Payne DC, Baggs J, Zerr DM, et al. Protective association between rotavirus vaccination and childhood seizures in the year following vaccination in US children. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014;58:173-7.
5. Pardo-Seco J, Cebey-Lopez M, Martinon-Torres N, et al. Impact of Rotavirus Vaccination on Childhood Hospitalization for Seizures. *The Pediatric infectious disease journal* 2015.
6. Pastor-Villalba E, Martín-Ivorra R, Alguacil-Ramos AM, Portero-Alonso A, Lluch Rodrigo J. [Exhaustividad en la declaración en el sistema de información vacunal (SIV) de vacunas no incluidas en el calendario sistemático infantil de la Comunidad Valenciana. Años 2009 a 2012]. P04. 7th Congress of the Spanish Association of Vaccinology. Cáceres (Spain) 2013.
7. Desai R, Haberling D, Holman RC, et al. Impact of rotavirus vaccine on diarrhea-associated disease burden among American Indian and Alaska Native children. *Pediatrics* 2012;129:e907-13.
8. López-Lacort M, Pérez-Vilar S, Martínez-Beneito MA, Pérez-Breva L, Sastre-Cantón M, Díez-Domingo J. Estimating positive predictive value of the rotavirus ICD-9-CM discharge code: what to do with cases without laboratory result? 32nd Annual Meeting of the European Society for Paediatric Infectious Diseases. Dublin (Ireland) 2014.