STUDY PROTOCOL

Impact of Rotavirus Vaccination on Acute Gastroenteritis outpatient and emergency department visits using “Real World Data” from the Valencia Region, Spain

RESEARCH TEAM

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INTRODUCTION

Acute gastroenteritis (AGE) is a frequent disease, with rotavirus (RV) being the main cause in children under 5 years of age. Every year, RV accounted for 231 deaths, more than 87,000 hospitalisations, and nearly 700,000 outpatient visits in Europe (1). In addition to the clinical impact, these rotavirus-associated events result in increased medical expenses, lost productivity, and other costs to society and families (2-7).

In Spain, rotavirus vaccines have been available since 2006 (RV1) and 2007 (RV5). In spite of WHO and ACIP recommend the inclusion of rotavirus vaccination in national immunization programmes (8, 9), they are neither funded nor reimbursed by the National Health System and their coverage rate is, therefore, moderate, around 40-50% (10, 11). Benefits of rotavirus vaccines have been widely studied. These kind of studies in Spain have separately, and for varied populations and time periods, analysed vaccines impact on RVAGE-hospitalizations (up to 71% reduction in infants) (11), all-cause AGE hospitalizations (up to 39% reduction in infants) (11) and effectiveness (over 85% effective against rotavirus hospitalization among young children) (12).

While the effect of vaccination on childhood hospitalizations for rotavirus has been well described, the effects of rotavirus vaccine on ED and outpatients visits are less well documented. An analysis in the USA showed reductions in ED visits for gastroenteritis up to 31% in the first five years following rotavirus vaccine introduction from 2007–2011, and up to 20% in outpatient (non-ED) visits for gastroenteritis in the same time period (13). In the same line, a recent study published in UK showed that the incidence of gastrointestinal disease decreased by 23% and 13% for ED and GP, respectively, after post-vaccine introduction compared to pre-vaccination era (14).

However, rotavirus vaccine impact on gastrointestinal disease outcomes across these levels of health care system (outpatients and ED) in Spain has not yet been estimated. The only approximation has been the estimation of the hypothetic impact of the introduction of a universal rotavirus vaccination programme with RotaTeq (90% coverage rate) by using mathematical models (15). This would lead to the prevention of 34,287 ED visits (-82%) and 35,187 outpatient-consultations (-73%) of RVGE annually in Spain, respectively.

This study aims to provide for the first time a comprehensive evaluation of the impact of rotavirus vaccines on ED and outpatient utilization among children <5 years of age of the Valencia Region, for acute gastroenteritis. This approach will provide estimates of the economic impact of rotavirus vaccines on outpatients and ED visits and the national health system associated costs.

The Valencia Region accounts with a network of health care databases linked together, which allow the linkage of ED and outpatients registries with the vaccine status at individual level. This powerful tool allows us to estimate the real impact of rotavirus vaccines in the

prevention of ED and outpatients visits.

OBJECTIVES

Primary objectives

- To estimate the impact of rotavirus vaccination on all-cause acute gastroenteritis outpatient (AGE-O) and Emergency Department (AGE-ED) consultations among children aged less than 5 years from the Valencia Region.

Secondary objectives

- To estimate the risk of AGE-O and AGE-ED consultations between vaccinated and non-vaccinated children aged less than 5 years from the Valencia Region.

- To estimate the economic impact of rotavirus vaccines on AGE-O and AGE-ED visits and the national health system associated costs among children aged less than 5 years from the Valencia Region.

Hypotheses

Following the introduction of rotavirus vaccination, incidence of gastrointestinal disease could be reduced across the health-care system. As demonstrated for hospitalizations, an important decline in both AGE-O and AGE-ED rates could be observed. This reduction will represent a savings for the national health system.

METHODS

Study Design

An observational retrospective, population-based study will be performed using real world data from the region's health care databases from 1st January 2009 until date of data extraction.

Study population

The population of interest will be Valencia Region's children less than 5 years during the study period.

Exclusion criteria

Subjects with less than 6 months of registration to the Public Health System (PHS) or with vaccination registry mistakes will be excluded.

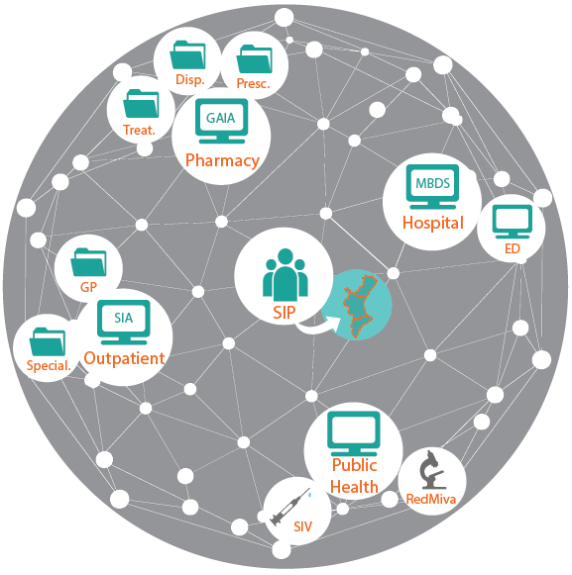
Follow-up period

Date of inclusion in the study will be defined as 1st January 2009 if the subject was continuously registered in PHS for at least 6 months before this date and was aged less than 5 years old, or first date after 1st January 2009 when the subject was continuously registered for at least 6 months before this date and was under 5 years old. Follow up ended when they left Valencia (data of deletion from SIP) or their death or at the end of the study, whichever occurred first.

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.

Figure: Some databases of the Valencia Region



SIP

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.

ED database

The ED database has been launched in 2008 and collects diagnosis and procedures as an assessment of medical activity. The coding system used is ICD-CM. The main discharge diagnosis is coded in first position, and diagnosis relevance decreases as the position number increases. Description of the diagnoses is available for all visits; therefore, data can be extracted using free text algorithms.

Outpatient

SIA is a primary care database used across the entire Valencia healthcare system. It was set up in 2006 and the percentage of the population included increased from 73.1% in 2007 to 88.8% in 2008 and to 95.7% in 2009. Currently, it is used in all Valencia´s Health Care System. This database contains primary care and Specialty care Centers diagnoses and procedures (physician coded using the International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM)) and the recorded text about each episode and patient by the pediatrician, other physician, and by the nurse responsible.

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 centers. 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.

Data from these databases can be linked through a unique personal identification number.
Case definition

Outcomes

We will consider for the analysis 3 different outcomes:

1- AGE-O: all-cause acute gastroenteritis outpatients visits.
2- AGE-ED: all-cause acute gastroenteritis emergency department visits.
3- AGE-O or AGE-ED: all-cause acute gastroenteritis outpatient and emergency

department visits.

These definitions will be extracted from ED and SIA databases through a systematic search of the following ICD-MC codes:

- ICD-9-MC codes: 001-009 (intestinal infectious diseases), 558.9 (other and unspecified non-infectious gastroenteritis and colitis), and 787.91 (diarrhoea not otherwise specified).
- ICD-10-MC codes: A00 – A09, K52.XX, R19.7.

A limited 45% of all ED visits during 2008-2013 include the main diagnosis codified. From 2013, codification in ED increased up to around 73% in 2017. Approximately 50% of the health departments have maintained a codification percentage between 80-100% during the study period.

As there is high under-codification variability between years and health departments, for the case definitions involving ED, we will estimate the vaccine impact (VI) only considering those data from the eligible 50% of health departments that have maintained high codification among time. Nevertheless, we will also estimate the VI for all health departments as sensitivity analysis.

Vaccination Status (Exposure)

Vaccination status will be assessed as a time-varying exposure. Eligible children were considered as vaccinated with a dose of rotavirus vaccine when at least 14 days had elapsed since each dose administration. The following categories will be considered:

- Fully vaccinated (three doses of RV5 or two doses of RV1);
- Partially vaccinated two doses (one dose of RV5 or RV1, two doses of RV5);
- Unvaccinated (absence of record for rotavirus vaccination in SIV);

Explanatory variables

Variables that are relevant to the diseases will be considered for the analysis: gender, age, year, month, urban/rural residence, social exclusion risk, health department, municipality and health care district.

Data collection

Data privacy will be protected by using anonymised data. The following variables will be requested to the different databases for the period from 1 January 2009 until the date of data extraction for all children aged less than 5 years:

Data to be extracted from SIP:

- Identification block including SIP number (anonymised), sex, date of birth and other geographical of birth, place and date of registration (except variables allowing subjects identification such as name, surname, phone number, DNI, etc).

- Regular location block that includes complete address, health map information as health department and census information among others (excluding postal data that allows identifying subjects address).
- Cessation block including cessation cause and description, cessation date and date of death (when applicable).

Data to be requested from SIA (including primary care, consultations and comorbidities):

- Patient identifier within the health system (codified)
- Date of diagnosis activation (diagnosis of interest)
- Date of diagnosis deactivation (diagnosis of interest)
- Diagnosis description (diagnosis of interest)
- Number of visits between date of diagnosis activation (diagnosis of interest) and the end of the follow-up
- Date of the visits (dd/mm/yyyy)
- Date of diagnosis deactivation (active diagnoses between 365 days prior to the date of diagnosis activation (diagnosis of interest) and the end of the follow-up
- Professional attendance (GP/Specialist)
- Procedure code
- Procedure description
- Approved service code
- Contact type
- Professional type

For any diagnosis code ICD-9-CM or ICD-10-CM related to AGE-O (ICD-9-CM codes 001-009, 558.9, 787.91; ICD-10 codes A00 – A09, K52.XX, R19.7).

Data to be extracted from ED:

- Anonymized Personal Identification Number (SIP)
- Date of birth
- Gender
- Municipality
- Postal code
- Hospital assigned
- Hospital attended
- Health department assigned
- Health department attended
- Health care district
- Date of ED admission (dd/mm/yyyy)
- Date of ED discharge (dd/mm/yyyy)
- Discharge cause (main and following)
- Diagnoses at discharge (main and secondary diagnoses)
- Procedures during the hospitalization
- Discharge destination (destination after discharge)

For any diagnosis code ICD-9-CM or ICD-10-CM related to AGE-ED (ICD-9-CM codes 001-009, 558.9, 787.91; ICD-10 codes A00 – A09, K52.XX, R19.7) in any diagnosis position.

Data to be extracted from SIV:
- Anonymized Personal Identification Number (SIP)
- Date of birth (dd/mm/yyyy)
- Vaccine brand
- Number of doses
- Administration date (dd/mm/yyyy)
- Vaccination in a private or no private centre

For all rotavirus vaccines (RV1 and RV5)
Subjects who received at least one vaccine in a private centre will be also requested.

Statistical analysis

Estimation of sample size

Currently, approximately 4,900,000 inhabitants of Valencia Region are covered by the public health system. Since the study is restricted to subjects aged less than 5 years and approximately 4.7% of the Region's population is younger than this age (data from Statistics National Institute, INE), we might expect approx. 230000/year children.

Descriptive analysis

A descriptive analysis will be developed, yearly outpatients and ED rates will be calculated as the number of AGE-O or AGE-ED visits divided by the total population by gender, age, health department and in general.

Primary and secondary objectives analysis:

To estimate impact of rotavirus vaccination on AGE-O and AGE-ED visits, we will develop a Bayesian negative binomial (or Poisson) model. Gender, age, calendar year, health department, health care district, municipality and their interactions will be considered for the confounding adjustment.
The impact of rotavirus vaccines on AGE-O and AGE-ED will be estimated by the number of visits averted due to the rotavirus vaccines protection through the adjusted model predictive distributions.

The risk of AGE-O and AGE-ED consultations between vaccinated and non-vaccinated children will be estimated using the abovementioned model.

Descriptive analyses on cost-related AGE-O and AGE-ED consultations avoided due to vaccination protection will be calculated.

Analyses will be carried out using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) and WinBUGS.

Limitations

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.

A limited 45% of all ED visits during 2008-2013 include the main diagnosis codified. From 2013, codification in ED increased up to around 73% in 2017. Approximately 50% of the health departments have maintained a codification percentage between 80-100% during the study period.

An infraestimation of the AGE disease burden might occur due to home care episodes not recorded.

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.
The study will be approved by the Independent Review Board (Ethics Research Committee).
The study will be sent to the Spanish Medicine Agency (AEMPS) for 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].

TIMELINES

TIMELINES	MONTHS																								
Activities	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Study design and protocol																									
IBR and AEMPS submission																									
Data collection SIA, SIV, ED and SIP																									
Data management and analysis																									
Primary Objective																									
Secondary Objectives																									
Provisional Report Review and discusion																									
Secondary Objectives																									
Results interpretation and discusion																									
Final Report																									
Manuscript Preparation and Submission																									

* 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	3.000,00 €
Statistical analysis plan design	1.000,00 €
Ethical and regulatory processes: IRB submission, IRB dispenses, Spanish Medicines Agency classification	1.000,00 €
Study coordination	3.000,00 €
Data management	32.000,00 €
Data request, data extraction (4 databases), data cleaning, data merging and tabulation, data quality review.	
Data analysis and study results: statistical analysis plan implementation, preparation and presentation of study results.	3.000,00 €
Manuscript and final report Preparation and submission	5.000,00 €
SUBTOTAL	48.000,00 €
OVERHEAD 25%	12.000,00 €
TOTAL BUDGET	60.000,00 €

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