Investigator Studies Program (MISP) Protocol Template

Requirements for Submitting a Full Proposal

Section #1 - MISP Protocol Identification

Study Title:	Spatio-temporal impact of Rotavirus vaccine coverage on Rotavirus Hospitalizations in the Valencia Region, Spain	
Request Date:	Version 2 date 25 October 2017	
Institution Name	*FISABIO-Public Health*	
Investigator Contact Information: – Full address – Phone No. – Fax No. – e-mail address	Principal investigator	Dr. Javier Díez-Domingo[1], Pediatrician, MD, PhD
	Co-investigators	Mónica López-Lacort[1], Mathematician, MSc Dr. Miguel Ángel Martínez-Beneito[2], Mathematician, PhD Dr. Cintia Muñoz-Quiles[1], Biologist, PhD Dr. Alejandro Orrico-Sánchez[1], PharmD, PhD
	[1]Vaccine Research Unit. FISABIO-Public Health *[2] Health Inequalities Unit. FISABIO-Public Health* Avda Cataluña, 21 46020 Valencia, Spain Telephone: +34 961 925 968 lopez_monlac@gva.es	

Section #2- Core Protocol	
2.1 Objectives & Hypotheses	## 2.1 Objectives ### Primary objectives • To estimate spatio-temporal impact of rotavirus vaccine coverage on rotavirus acute gastroenteritis hospitalizations among Valencia Region´s population aged less than 3 years. • To assess space-time variation in hospitalized acute rotavirus gastroenteritis risk among Valencia Region´s population aged less than 3 years. • To assess space-time variation in rotavirus vaccine coverage among Valencia Region´s population aged less than 3 years. ### Secondary objectives • To estimate spatio-temporal impact of rotavirus vaccine coverage in acute gastroenteritis hospitalizations among Valencia Region´s population aged less than 3 years. • To assess space-time variation in hospitalized acute gastroenteritis risk among Valencia Region´s population aged less than 3 years. ### 2.1.1 Hypotheses As rotavirus vaccines are not funded by the Spanish National Health System, strong geographical and temporal pattern will be probably observed due to different standard of living, pediatricians recommendations, etc. Thus, we hypothesized a spatial and temporal association between vaccination coverage and the rate of hospitalizations for rotavirus / gastroenteritis.

2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data

2.2 Background

Rotavirus (RV) is the most common cause of gastroenteritis in children worldwide [1]. An estimated 75,000 children aged <5 years are hospitalized for rotavirus acute gastroenteritis (RVAGE) each year in European countries, leading to high demands on health care systems [2]. In the Valencia Region the 84% of rotavirus hospitalizations occurred in children <2 years of age [3].

Two rotavirus vaccines (RV1; Rotarix®, GSK and RV5; RotaTeq®, Merck), have been licensed in Spain since 2006 and 2007, respectively. However from 2010 to 2017 only RotaTeq® was available. Although institutions such as WHO and CDC recommend the inclusion of rotavirus vaccination in national immunization programmes, the Spanish National Health System (NHS) does not fund rotavirus vaccines.

Several studies in our country have shown the effectiveness and impact of RV vaccines in RVAGE and all-cause AGE-hospitalizations [4-8]. In The Valencia Region, despite the low-medium vaccine coverage, the introduction of rotavirus vaccines had a specific coverage-related response impact in the hospitalizations for RVAGE and AGE in children <5 years and their use substantially reduced hospital related costs. However, the results showed large variations in both vaccination coverage and hospitalization rates (figures 1-3) and high variability among health departments [3].

Bayesian spatio-temporal models allow to asses variations across health care areas and regions. This well known disease mapping methodology has been validated to explain geographical hospital risk variations [9;10] and, therefore, could be used to show the geographical distribution of the impact of vaccination. There are no spatio-temporal studies of the impact of rotavirus vaccination on RVAGE-related hospitalizations in Spain and few worldwide. These analyses allow scientists to detect geographical-time patterns in underinmunization.

Our aim is to assess the spatio-temporal impact of rotavirus vaccines on RVAGE-associated hospitalizations among children under 3 years of age of the Region of Valencia.

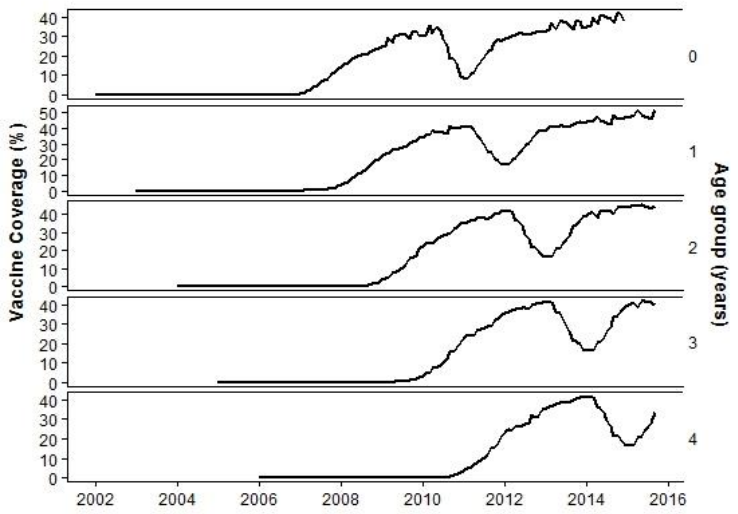

Figure 1: Rotavirus vaccine coverage by age groups.

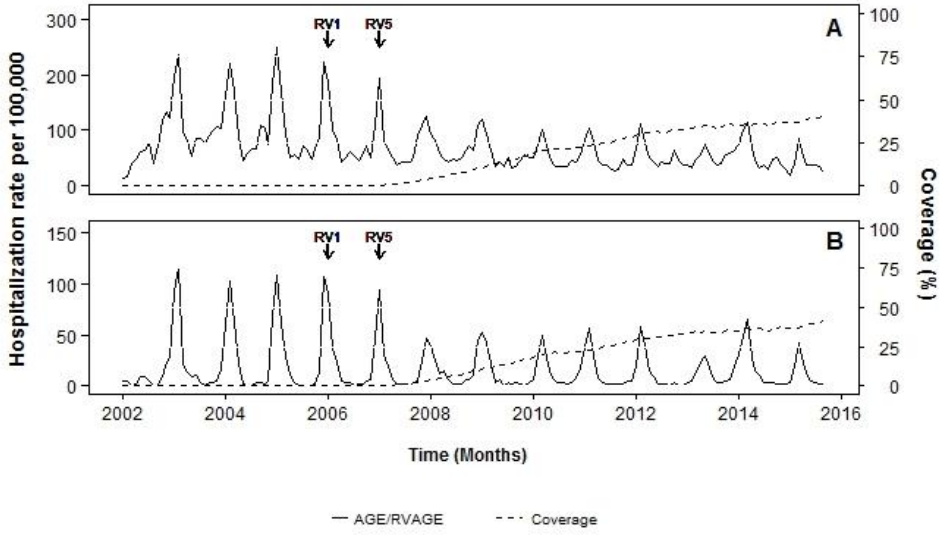

Figure 2: Monthly rate of **A** rotavirus acute gastroenteritis-associated hospitalizations, **B** acute gastroenteritis -associated hospitalizations and coverage in children < 5 years-old

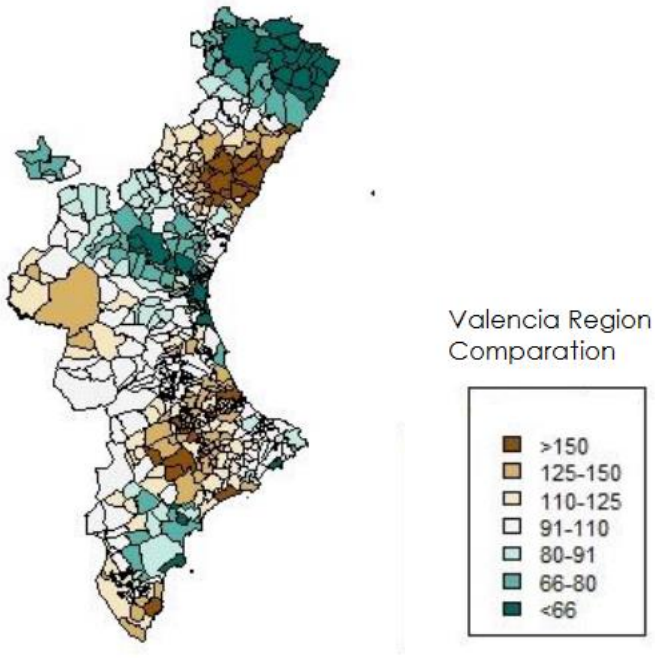

Figure 3: Standardized rotavirus hospitalization ratio, children aged less than 3 years-old

2.3 Study Design

2.3 Study Design

An observational retrospective, population-based study will be performed using the region's health care databases from 1st January 2003 until date of data extraction.

Study population

The population of interest will be Valencia Region's children less than 3 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

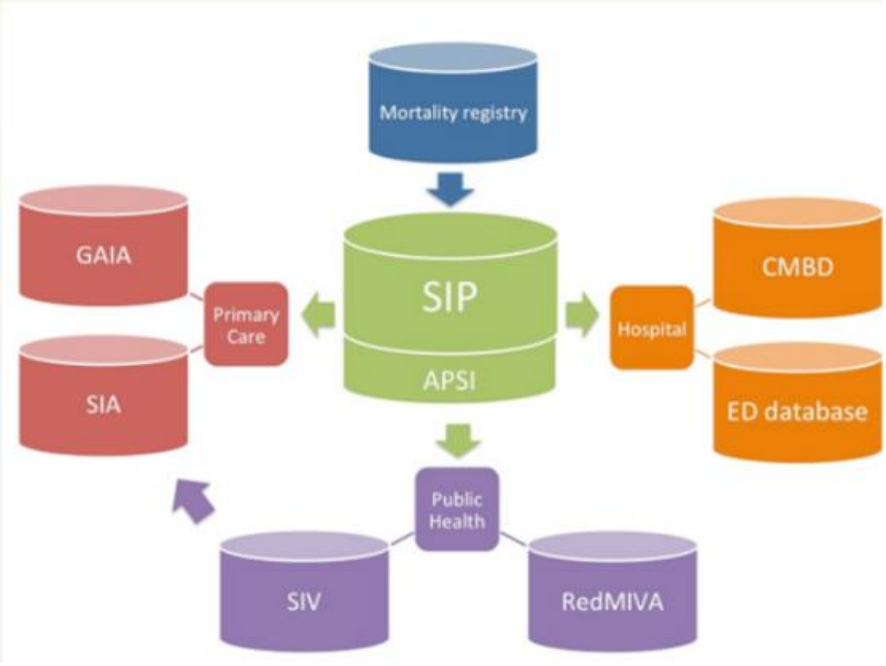

Figure 4: Some databases of the Valencia Region

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, MBDS (minimum basic data set), 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 MBDS 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.

All these databases can be linked by a unique personal identification number.

Outcomes

Acute gastroenteritis-associated hospitalizations will be identified from MBDS 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

Vaccine coverage

Rotavirus vaccination coverage, obtained from SIV, will be defined as the vaccinated proportion of the study population and we will consider two categories for the analysis:

(1) Fully vaccinated (three doses of RV5, two doses of RV1 or three doses of unknown brand), (2) Vaccinated with at least one dose (at least one dose of RV5, RV1 or unknown brand), with no distinction between vaccine brands.

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

Explanatory Variables

For the study the following variables (among others) will be considered:

Gender (Male/Female)

Health department: The regional health system is currently divided into 24 Departments, which includes 24 paediatric hospitals. However, the distribution of departments has changed over the years. Thus, we will consider for the analysis the structure of 2002 consisting of 20 departments, one of which has no paediatric section at the hospital and children were derived to the closest department.

Municipality

Health care district

Year (2003- until date of data extraction)

Age in years (0,1,2)

Vaccine coverage or Number of children vaccinated (%/ N)

Hospitalization rate *and* ***number of hospitalizations*** *for all causes except acute gastroenteritis:*

When the economic crisis started in Spain, changes in admission policies took place to save resources and therefore not all the hospitalizations changes could be attributable to the vaccine. Also, this data will be requested in order to describe the burden of the outcomes of interest among the total of hospitalizations. The hospitalizations for all causes will be recoded, these will be used to control the hospital attraction (People who live near the hospital hospitalized more frequently than other who live furthest).

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 2003 until the date of data extraction for children aged less than 3 years:

Data to be extracted from SIP:

- Identification block including SIP number, sex, date of birth and other geographical of birth, place and date of registration.
- Regular location block that includes complete address, health map information as health department and census information among others.
- Cessation block including cessation cause and description, cessation date and date of death (when applicable).

Data to be extracted from MBDS:

- Anonymized Personal Identification Number (SIP)
- Birth date
- Sex
- Municipality of residence
- Postal code
- Health department
- Health care district
- Date of hospital admission
- Date of hospital discharge
- Diagnoses at discharge (main and secondary diagnoses)
- Procedures during the hospitalization

- Discharge destination (destination on discharge)

For any ICD-9-CM code (001-999) in any diagnosis position.

Data to be extracted from SIV:

- Anonymized Personal Identification Number (SIP)
- Birth date
- Vaccine brand
- Number of doses
- Administration date
- Vaccination in a private or no private centre

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.

The PPV of the rotavirus ICD-9-CM code identifying acute gastroenteritis attributable to rotavirus has been assessed as ≅90% within MBDS [13].

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.

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) of the Dirección General de SaludPública/Centro Superior de Investigación en SaludPública (CEIC DGSP/CSISP).

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].

2.4 Study Flowchart

The following table shows the timelines of the study:

TASK	PARTICIPANTS	MONTHS											
		1	2	3	4	5	6	7	8	9	10	11	12
Develop study protocol	JDD, MLL,MMB, CMQ,AOS,	■											
Legal and Ethical requirements	MLL, AOS, CMQ		■										
Statistical analysis plan design	MLL, MMB, AOS, JDD,			■									
Data request	MLL		■	■	■	■	■						
Medical record review	MLL, JDD						■						
Data cleaning, merging and tabulation	MLL				■	■	■	■	■	■			
Data analysis	JDD, MLL,MMB, CMQ,AOS,						■	■	■	■			
Discussion and presentation of results	JDD, MLL,MMB, CMQ,AOS,										■		
Preparation and submission of manuscript	JDD, MLL,MMB, CMQ,AOS,											■	
Preparation and submission of final study report	JDD, MLL,MMB, CMQ,AOS,												■

* These activities would start once the contract has been signed

2.5 Study Procedures

See study design, section 2.3

2.6 Study Duration

See study flowchart, section 2.4

2.7 Statistical Analysis and Sample Size Justification

2.7 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 3 years and approximately 4.5% of the Spanish population is younger than this age (data from Statistics National Institute, INE), we might expect approx. 220500 children.

Descriptive analysis

A descriptive analysis will be developed, yearly hospitalization rates will be calculated as the number of hospitalizations for the outcomes of interest divided by the total population (other rates will be calculated considering the total number of hospitalizations as denominator) by gender, age, health department and in general.

Primary and secondary objectives analysis

- *To estimate spatio-temporal impact of rotavirus vaccine coverage on rotavirus acute gastroenteritis hospitalizations among Valencia Region´s population aged less than 3 years.* ***(Primary Objective)***

- *To estimate spatio-temporal impact of rotavirus vaccine coverage in acute gastroenteritis hospitalizations among Valencia Region´s population aged less than 3 years.* ***(Secondary Objective)***

We will evaluate the spatio-temporal impact of vaccination on rotavirus hospitalization rates (response variable) by a Bayesian spatio-temporal logistic regression contemplating gender, age, health department, bi-annual periods and municipality, we will use *the methodology developed by Martinez-Beneito et al.* [10] that allows to incorporate all these sources of dependence among rates in a single model [11; 12].

- *To assess space-time variation in hospitalized acute rotavirus gastroenteritis risk among Valencia Region´s population aged less than 3 years.* ***(Primary Objective)***

- *To assess space-time variation in rotavirus vaccine coverage among Valencia Region´s population aged less than 3 years.* ***(Primary Objective)***

- *To assess space-time variation in hospitalized acute gastroenteritis risk among Valencia Region´s population aged less than 3 years.* ***(Secondary Objective)***

To evaluate the space-time behavior of rotavirus/ hospitalization rates and vaccine coverage, we will model by the Besag-York-Mollié model the following smoothed risk estimates: the standardized hospitalization ratio and

<table>
<tr><td></td><td>the standardized vaccination rate, considering bi-annual periods and municipality.</td></tr>
<tr><td>2.8 Specific Drug Supply Requirements</td><td>Not applicable for this study</td></tr>
<tr><td>2.9 Adverse Experience Reporting</td><td><h2>2.9 PHARMACOVIGILANCE</h2>
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 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.</td></tr>
<tr><td>2.10 Itemized Study Budget</td><td><h2>2.10 Budget</h2>
<table>
<tr><th>ACTIVITIES</th><th>COST</th></tr>
<tr><td>Study design and statistical analysis plan</td><td>6486.96 €</td></tr>
<tr><td>Presentation to the IRB and Spanish Medicine Agency</td><td>1000 €</td></tr>
<tr><td>Data collection and data management
Data request, data extraction, data cleaning, data tabulation, data quality review</td><td>9000 €</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Data analysis and results presentation
Statistical analysis plan implementation, statistical analysis, presentation and discussion of results</td><td>15000 €</td></tr>
<tr><td>Advice on statistical issues</td><td>5000 €</td></tr>
<tr><td>Manuscript and final report
Preparation and submission of the publication</td><td>4500 €</td></tr>
<tr><td>Open Access (Vaccine)</td><td>2600 €</td></tr>
<tr><td>SUBTOTAL</td><td>43586.96 €</td></tr>
<tr><td>OVERHEAD 25%</td><td>6538.044 €</td></tr>
<tr><td>TOTAL BUDGET</td><td>50125 €</td></tr>
</table></td></tr>
</table>

2.11 References	## 2.11 References 1. Tate JE, Parashar UD. 2014. Rotavirus vaccines in routine use. Clin Infect Dis. 59(9):1291-1301. 2. Impact of rotavirus vaccination – generic study protocol [accessed]. http://ecdc.europa.eu/en/publications/Publications/Rotavirus-impact-vaccination-April-2013.pdf. 3. Orrico-Sanchez A, López-Lacort M, Pérez-Vilar S, Díez-Domingo J. 2017. Long-term impact of self-financed rotavirus vaccines on rotavirus-associated hospitalizations and costs in the valencia region, spain. BMC Infect Dis. 17(1):267. 4. Orrico-Sanchez A, Lopez-Lacort M, Perez-Vilar S, Diez-Domingo J. 2017. Long-term impact of self-financed rotavirus vaccines on rotavirus-associated hospitalizations and costs in the valencia region, spain. Bmc Infectious Diseases. 17. 5. Perez-Vilar S, Diez-Domingo J, Lopez-Lacort M, Martinez-Ubeda S, Martinez-Beneito MA. 2015. Effectiveness of rotavirus vaccines, licensed but not funded, against rotavirus hospitalizations in the valencia region, spain. Bmc Infectious Diseases. 15. 6. Gil-Prieto R, Gonzalez-Escalada A, Alvaro-Meca A, Garcia-Garcia L, San-Martin M, Gonzalez-Lopez A, Gil-de-Miguel A. 2013. Impact of non-routine rotavirus vaccination on hospitalizations for diarrhoea and rotavirus infections in spain. Vaccine. 31(43):5000-5004. 7. Martinón-Torres F, Aramburo A, Martinón-Torres N, Cebey M, Seoane-Pillado MT, Redondo-Collazo L, Martinón-Sánchez JM. 2013. A reverse evidence of rotavirus vaccines impact. Hum Vaccin Immunother. 9(6):1289-1291. 8. Redondo O, Cano R, Simon L. 2015. Decline in rotavirus hospitalizations following the first three years of vaccination in castile-la mancha, spain (vol 11, pg 769. Human Vaccines & Immunotherapeutics. 11(12):2931-2932. 9. Librero J, Ibanez B, Martinez-Lizaga N, Peiro S, Bernal-Delgado E, Spanish Atlas Med Practice V. 2017. Applying spatio-temporal models to assess variations across health care areas and regions: Lessons from the decentralized spanish national health system. Plos One. 12(2). 10. Martinez-Beneito MA, Lopez-Quilez A, Botella-Rocamora P. 2008. An autoregressive approach to spatio-temporal disease mapping. Statistics in Medicine. 27(15):2874-2889. 11. Knorr-Held L. 2000. Bayesian modelling of inseparable space-time variation in disease risk. Statistics in Medicine. 19(17-18):2555-2567. 12. Botella-Rocamora P, Martinez-Beneito MA, Banerjee S. 2015. A unifying modeling framework for highly multivariate disease mapping. Statistics in Medicine. 34(9):1548-1559.

	13. 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.
2.12 Publication Plan	The dissemination actions will comprise at least: - Publication of a scientific paper in an indexed scientific journal (preferably Vaccine or Human Vaccines) - Participation in one national and in one international scientific meeting/congress: ESPID 2018 (international), Meeting of the Spanish Pediatric association 2018 (National)
2.13 Curriculum Vitae	Investigator should provide curriculum vitae in English and a listing of references to MSD.
2.13 Protocol Submission for Investigator-Initiated Studies	U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiisp.com Non U.S. protocols should be submitted to the MSD office by the investigators.