Report

STUDY	**Spatio-temporal impact of Rotavirus vaccine coverage on Rotavirus Hospitalizations in the Valencia Region, Spain**
PROTOCOL	JDD-ROT-2017-01
VERSION	**FV**
DATE	04/12/2018
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1. Objectives

1.1. 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.

1.2. 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. Results

The study included 721,471 children < 3 years old, 189,247 of them were rotavirus vaccinated. There were a total of 17,482 AGE hospitalizations, 28% (4,871) of these were codified as RVAGE. AGE and RVAGE hospitalizations represented 8.4% and 2.4% of the total hospitalizations for any cause (207,014 hospitalizations for all causes). 2,248 AGE and 200 RVAGE admissions corresponding to rotavirus vaccinated children.

2.1. Spatio-temporal rotavirus vaccine impact

2.1.1. The model

A Bayesian spatio-temporal model for each outcome was constructed to analyze RVAGE and AGE hospitalization rates (number of hospitalizations divided into population at risk) and to estimate the vaccination impact on these hospitalizations.

The model assumed the number of hospitalizations (RVAGE or AGE) in the different observation units (counts aggregated by vaccination status, sex, age, health department, biennial periods and health care district), $Y = \{y_1, \dots, y_n\}$, followed a binomial distribution:

$$y_i \sim Bin(\theta_i, N_i), \quad i = 1, \dots, n$$

Where, θ_i, is the hospitalization rate and N_i the population for each observation unit. θ_i was modeled considering the link *logit* as follows:

$$\log\left(\frac{\theta_i}{1-\theta_i}\right) = \log\left(\frac{\delta_i}{1-\delta_i}\right) + \beta_0 + \sum_{j=1}^{3} \beta_j X_j + \alpha_d + u_t + v_{tm}$$

We assumed the subscripts, $d_i = d$, $t_i = t$ and $m_i = m$.

$$d = 1, \dots, 24 \qquad t = 1, \dots, 6 \qquad m = 1, \dots, 241$$

$\log\left(\frac{\delta_i}{1-\delta_i}\right)$ acts as an offset term to control the hospital attraction (people who live near the hospital hospitalized more frequently than other who live furthest), where δ is the hospitalization rate for all causes measured in each health care district *(supplemental 1),* this rate was estimated by the spatial Besag-York-Mollié model. β_0 is the intercept term and β_j are the parameters associated with the fix effects, X_j: vaccination status, sex and age. The health department random effect denotes, α_d, where it is distributed as

$$\alpha_d \sim N(0, \sigma^2)$$

The period effect, u_t, was modeled considering correlation between adjacent periods by a conditional autoregressive (CAR) prior distribution. The spatio-temporal effect, v_{tm}, takes into account an order one autoregressive temporal dependence. The spatio-temporal effect for the first period was formulated as

$$v_{1m} = (1-\rho^2)^{-1/2} W_{1m}$$

and for the following periods,

$$v_{tm} = \rho v_{t-1\,m} + W_{tm} \qquad t = 2, \dots, 6$$

being ρ the correlation coefficient distributed as a uniform ranged between -1 and 1. The spatial effect for each time period, W_{tm}, assumed a neighbourhood relationship between adjacent geographical zones following the Besag-York-Mollié model, which also includes the heterogeneity among health care districts. Non-informative flat priors distributions were considered for β_j $(j = 0, .., 3)$ parameteres. The priors distributions for the standard deviations of unstructured and spatially (or temporally) structured random effects were defined considering non-informative uniforms distributions ranged between 0 - 5.

We estimated the number of rotavirus hospitalizations averted to assess the impact of rotavirus vaccination by health care district and time period. The number of averted cases by vaccination was calculated as the difference between the predicted hospitalizations by the adjusted model without the vaccine effect and the predicted hospitalizations by the model explained above.

In order to calibrate the simulation process, a burn-in of 2,000 initial iterations was ignored. After that, 10,000 iterations were run and only 1 in every 10 of them was saved. Simulations convergence was assessed by visual inspection of posterior distributions history plots, by the scale reduction factor and by the effective sample size implemented in the package R2WinBUGS of the statistical software R.

R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) and WinBUGS program was used to perform the analysis using MCMC methods, specifically using the simulation Gibbs Sampling technique.

2.1.2. Model results

Table 1: **Model coefficients, Odds Ratio (OR) and 95% Credibility Intervals (CI).**

	RVAGE		**AGE**	
	Coefficient, posterior mean (95% CI)	**OR (95% CI)**	**Coefficient, posterior mean (95% CI)**	**OR (95% CI)**
Intercept	-4.88 (-5.01,-4.76)		-3.78 (-3.88,-3.67)	
Vaccination Status				
Unvaccinated	0	1	0	1
Vaccinated	-1.96 (-2.11,-1.81)	0.14 (0.12,0.16)	-0.64 (-0.68,-0.59)	0.53 (0.5,0.55)
Age				
0 years	0	1	0	1
1 year	-0.24 (-0.3,-0.18)	0.79 (0.74,0.84)	-0.16 (-0.19,-0.13)	0.85 (0.82,0.88)
2 years	-1.28 (-1.36,-1.2)	0.28 (0.26,0.3)	-0.87 (-0.91,-0.83)	0.42 (0.4,0.44)
Sex				
Males	0	1	0	1
Females	-0.21 (-0.27,-0.16)	0.81 (0.77,0.85)	-0.16 (-0.2,-0.13)	0.85 (0.82,0.88)
Heterogeneity (random effect)				
Health department (unstructured)	0.28 (0.18,0.43)		0.22 (0.15,0.32)	
Health care district (unstructured)	0.08 (0,0.18)		0.05 (0,0.11)	
Health care district (structured)	0.38 (0.3,0.47)		0.32 (0.27,0.37)	
Period (structured)	0.19 (0.08,0.46)		0.17 (0.08,0.39)	
ρ	0.39 (0.15,0.6)		0.36 (0.21,0.5)	

There was a risk reduction on RVAGE and AGE-hospitalizations with rotavirus vaccination, the hospitalization rates were 86% (95%CI: 84-88) and 47% (95%CI: 45-50) lower in vaccinees for RVAGE and AGE. Risk of RVAGE and AGE-hospitalization decreased with increasing age, reducing to 72% (95%CI: 70-74) and 58% (95%CI: 56-60) respectively in children two years old compared to children aged less than one year. Girls had 19% (95%CI: 15-23) and 15% (95%CI: 12-18) less RVAGE and AGE-hospitalization risk than boys. A strong variability in both RVAGE and AGE hospitalization rates was found among health departments *(figure 1)*. AGE-hospitalization risk showed a downward trend over the studied years, RVAGE rate only declined between 2005 and 2010. RVAGE peaked in 2013-2014, with 8% (95%CI:

6-14) higher rate than the average for the whole study period *(figure 2)*. For both outcomes we found structured (non-random) spatio-temporal patterns. The spatio-temporal effect maps *(figure 3)* evidenced spatial clusters after adjusting by confounders.

Figure 1: variability between health departments.

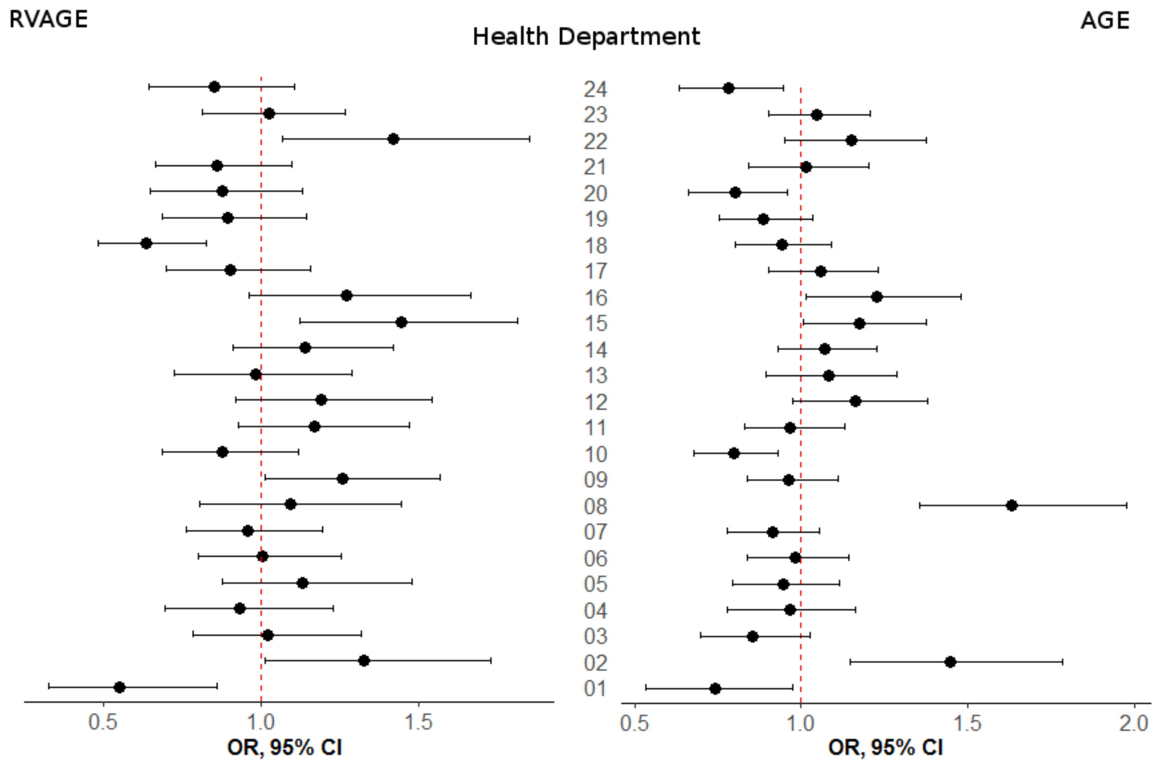


Figure 2: Variability between time periods.

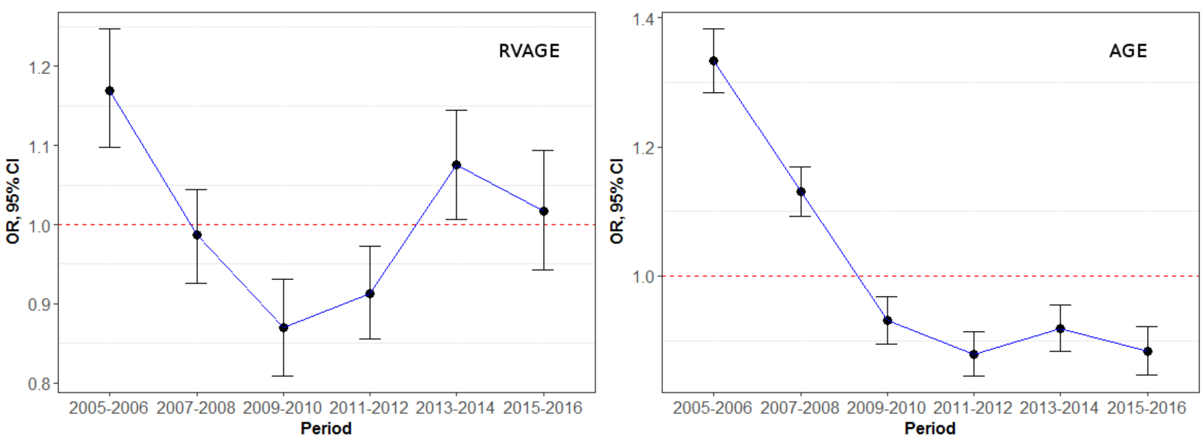
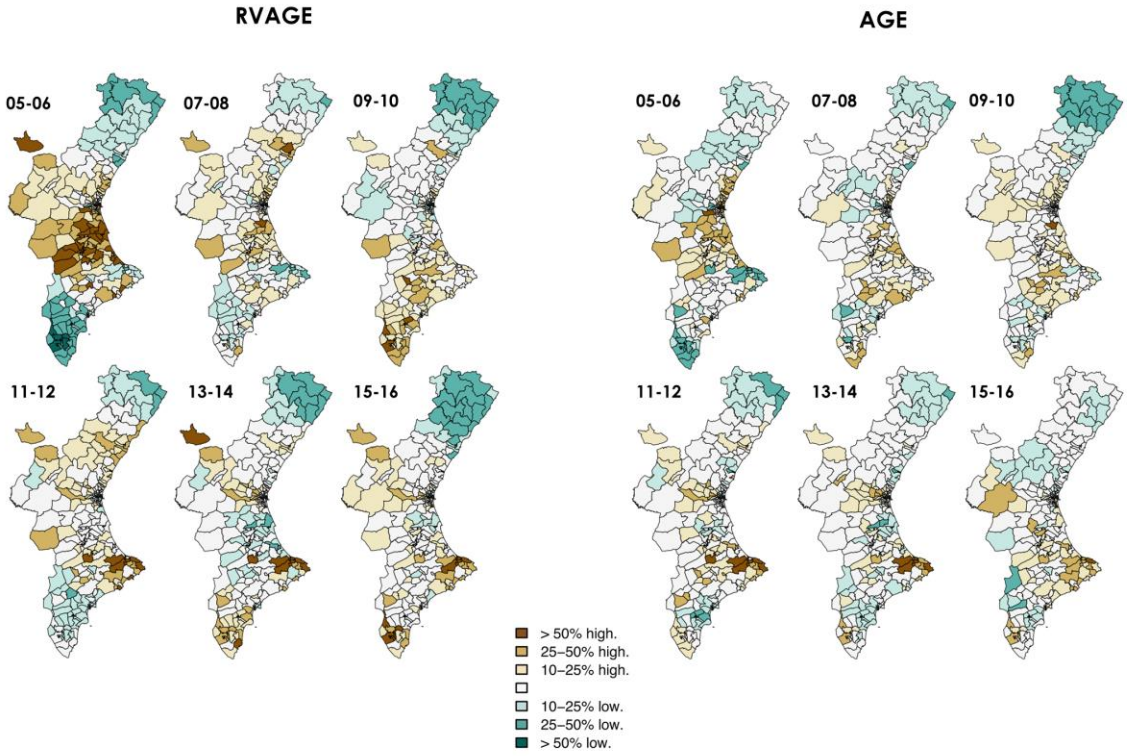


Figure 3: **Spatio-temporal effect, OR posterior mean.**



Rotavirus vaccination impact

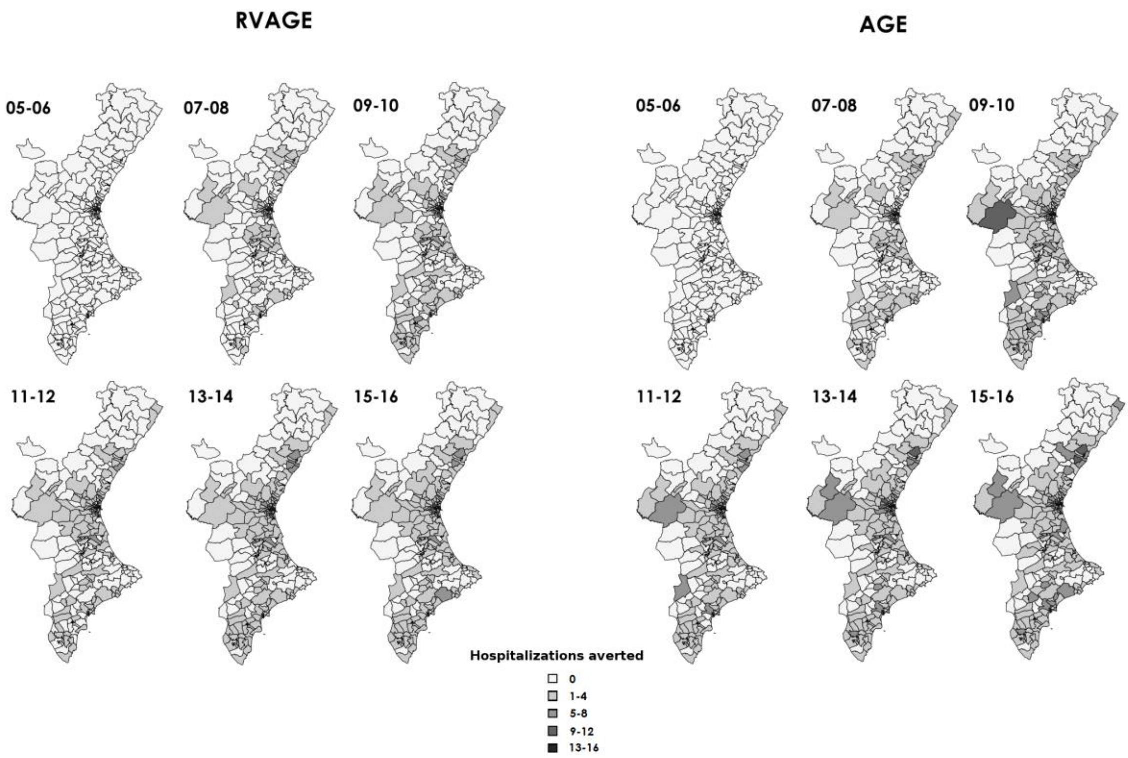
Table 2: **Impact of rotavirus vaccination on RVAGE and AGE hospitalizations by period. Hospitalizations percentage reduction and number of hospitalizations averted estimated by the model.**

			%, N (95% CI)	
Period	Children Vaccinated (N)	RV Vaccine coverage (%)	RVAGE Hospitalizations averted	AGE Hospitalizations averted
2005-2006	149	0.1	0%, 0(0, 0)	0%, 1(1, 1)
2007-2008	28,202	11.0	9%, 92(84, 100)	5%, 169(157, 180)
2009-2010	61,577	23.7	23%, 211(193, 230)	13%, 390(361, 420)
2011-2012	86,630	34.7	24%, 213(193, 232)	13%, 359(330, 387)
2013-2014	86,141	37.3	30%, 303(274, 332)	16%, 446(412, 482)
2015-2016	106,331	48.6	36%, 323(295, 356)	20%, 502(463, 543)

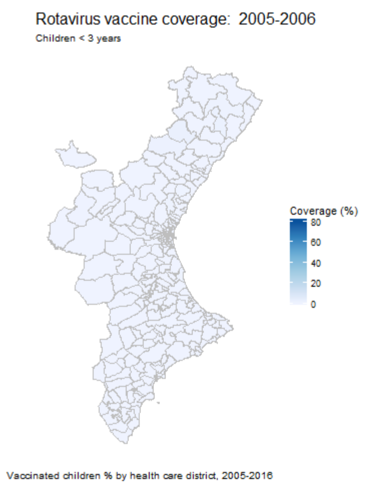
The number of hospitalizations averted by vaccination was coverage-dependent, the vaccination impact increased with higher number of vaccinees. The coverage rose from 0% to 49% during the study period. With 189,247 children vaccinated 1,142 (95%CI: 1,069-1,222) RVAGE and 1,866 (95%CI: 1,736-1,992) AGE-hospitalizations were averted. This supposed a global reduction of 19.9 % (95%CI: 19.7-20.2) in RVAGE hospitalizations and 10.2% (95% CI: 9.7-10.5) AGE-hospitalizations for the whole period. The number of hospitalizations averted increased with time as coverage incremented. In 2015-2016 the vaccination of approximately 50% of children supposed a reduction of 35.6% (95% CI: 35.2-36.1) and 19.7 % (95% CI: 19.0-20.3)

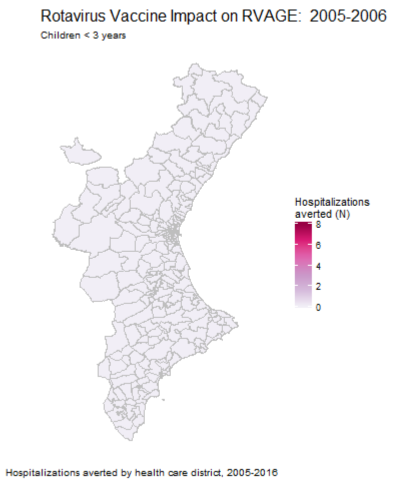
RVAGE and AGE hospitalizations respectively (table 2). The maps in the figure 3 show the distribution of RVAGE and AGE hospitalizations averted by health care district over the years. Health care districts with higher coverage had more impact on RVAGE and AGE hospitalizations (supplemental 5). If we assume a 100% RV vaccine coverage, we would expect to reduce the RVAGE-hospitalizations by 85.8% (95% CI: 84.8-86.5) [corresponding to 4,920 (95% CI: 4,602-5,221) hospitalizations] in the case of RVAGE and the AGE-hospitalizations by 46.9% (95% CI: 45.1-48.4) [corresponding to 8,606 (95% CI: 8,056-9,148) hospitalizations].

Figure 3: **Spatio-temporal rotavirus vaccine impact, average of hospitalizations averted.**



Rotavirus vaccination impact on RVAGE-Hospitalizations





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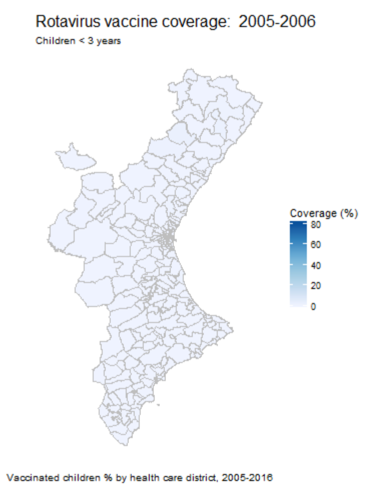
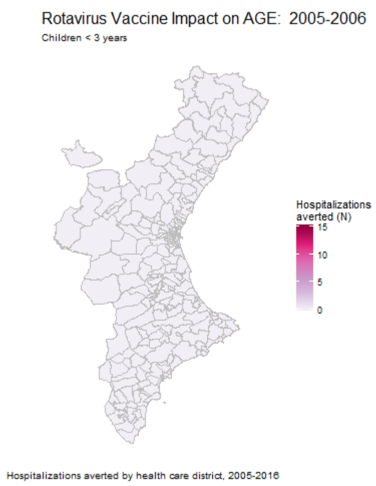
Rotavirus vaccination impact on AGE-Hospitalizations





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2.2. RotApp

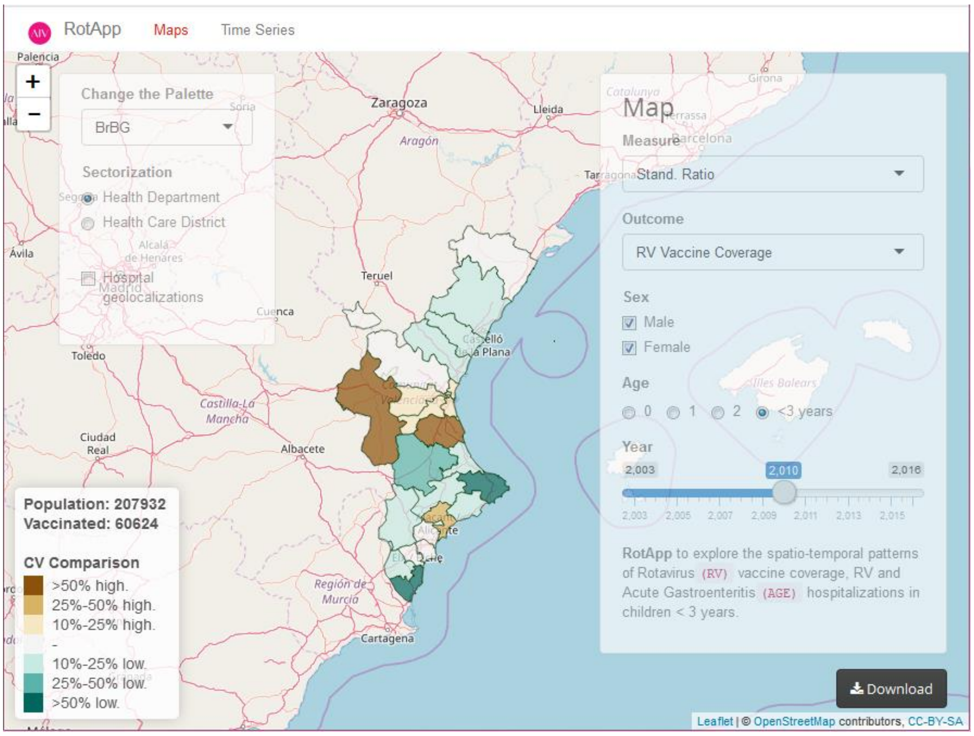
To explore the spatio-temporal patterns of rotavirus vaccine coverage, RVAGE and AGE hospitalizations in children < 3 years we developed a shiny web application. This app allows users interact with the data and the analysis. We can found the RotApp in the following link:

https://rotapp.shinyapps.io/app_-_vf3/

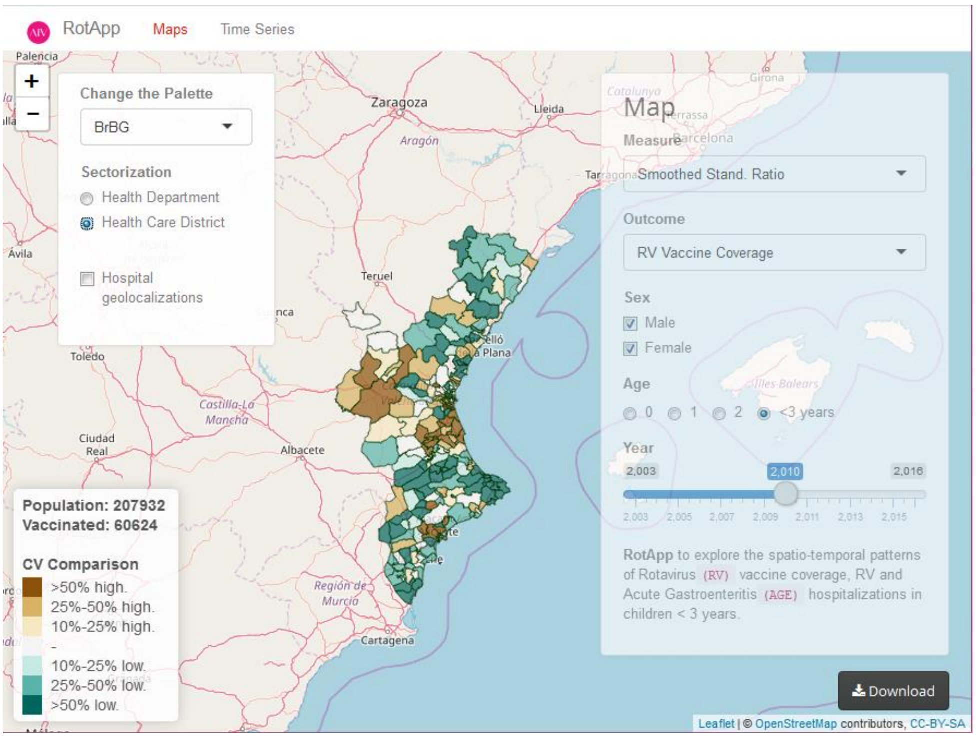
With this app we can visualize dynamic maps and temporal trends for the different outcomes. There are two ways for geographic stratification:

- Health Department
- Health Care District

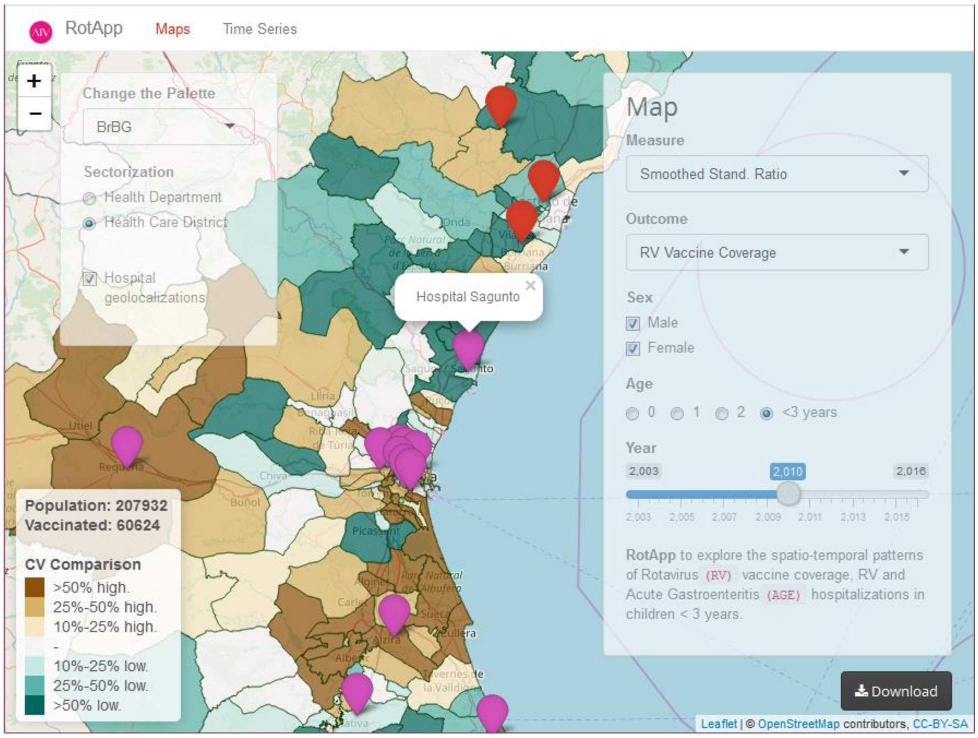
Health Department Map



Health Care District Map

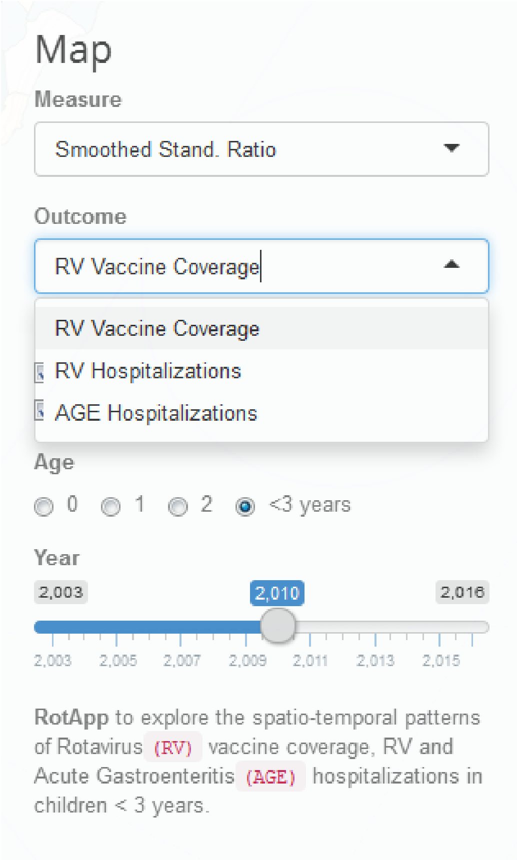


In the left panel we can change the color palette, selecting the map and plotting the hospital localization markers. Zoom into the geographical areas can be obtained from these maps.



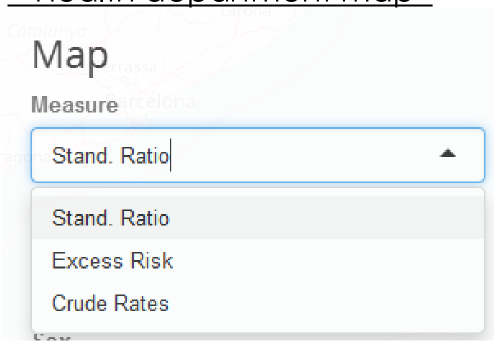
In the right panel we can choose the outcomes and measures to explore each year, furthermore we can plot maps for specific ages and sex.

Outcomes

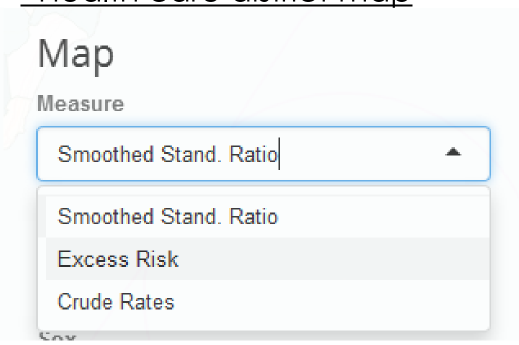


To explore spatial patterns we estimated the standardized ratios (observed/expected cases) for the different outcomes. Sometimes, neighboring small areas show opposite risks, without reflecting the risk of the disease; they are reflecting the distribution of the population. To solve this problem in health care district maps, we estimated the smoothed risks by the Besag-York-Mollié model. In the case of health department maps the model only contemplated unstructured random effects.

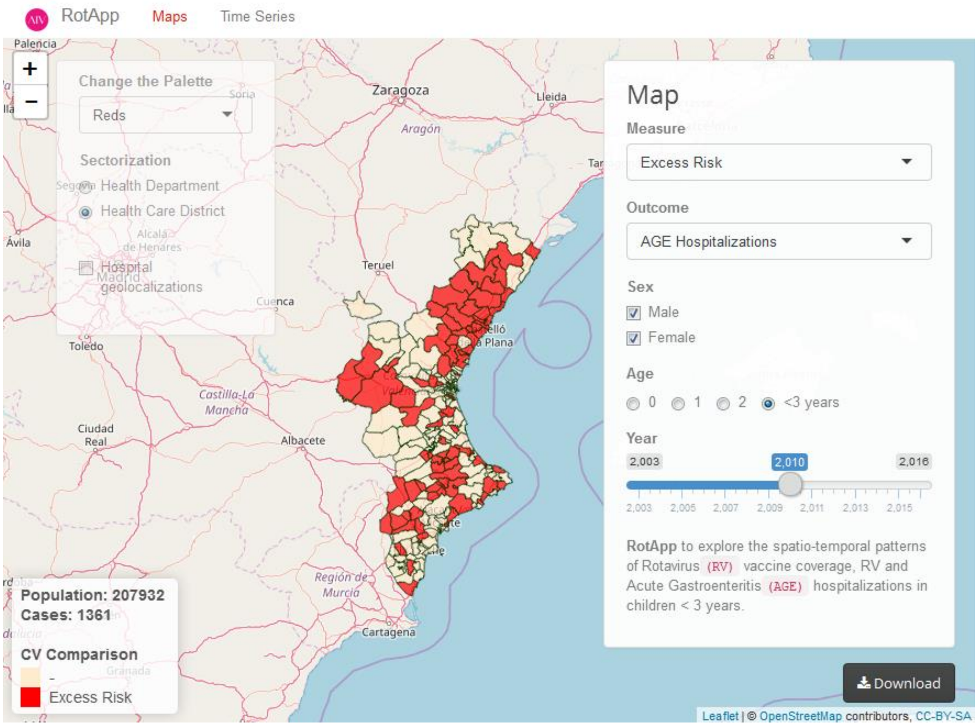
Health department map



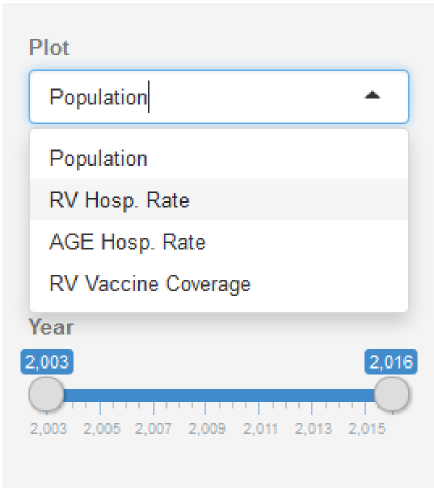
Health care district map



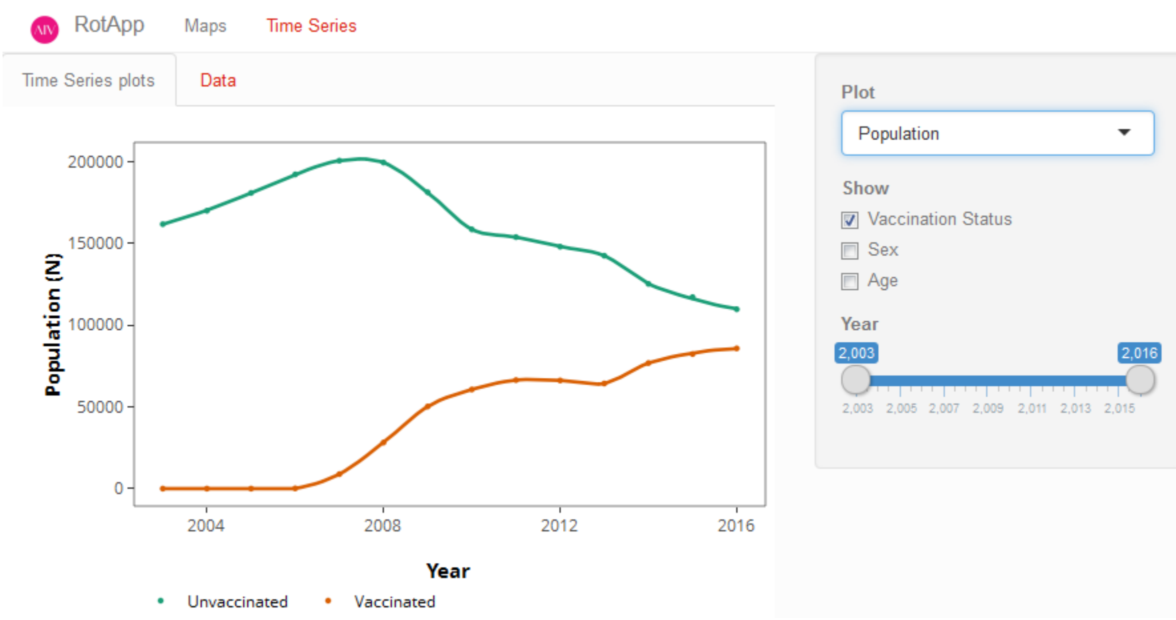
We stratified the standardized ratios by excess risk or no excess risk, this measure provides a bicolor map where only the risk zones are colored.

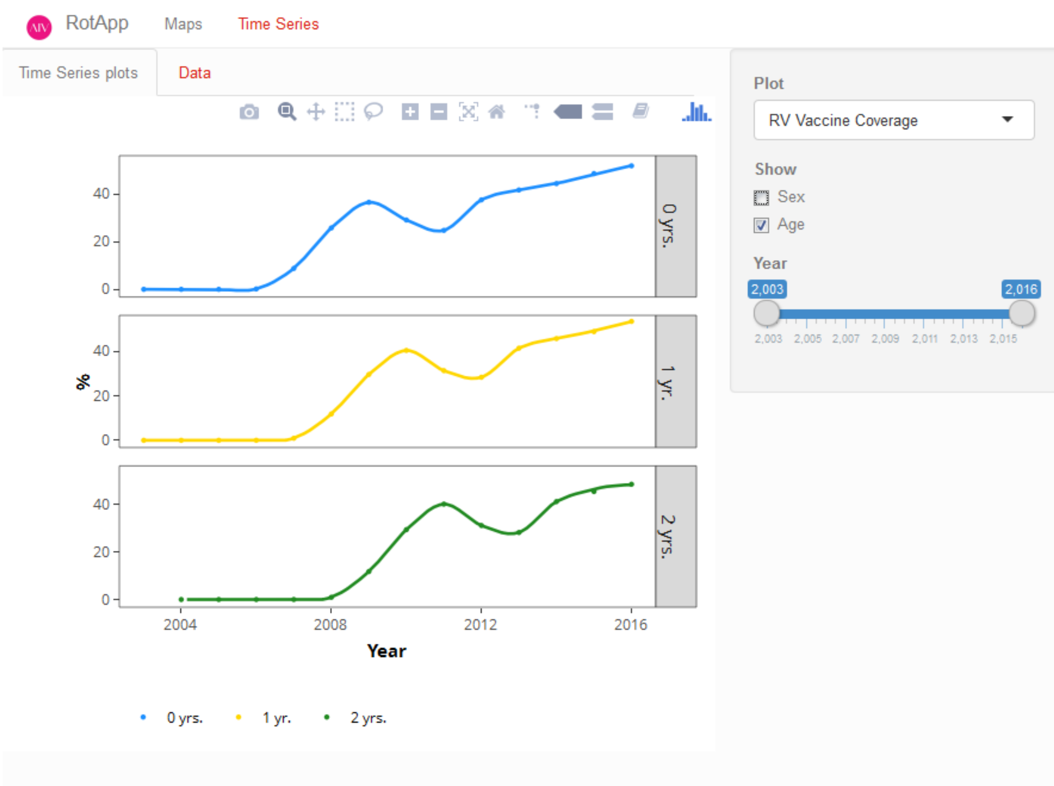


In the time series tab panel we can describe temporal trends form population, rotavirus vaccine coverage, and RVAGE and AGE hospitalizations rates.

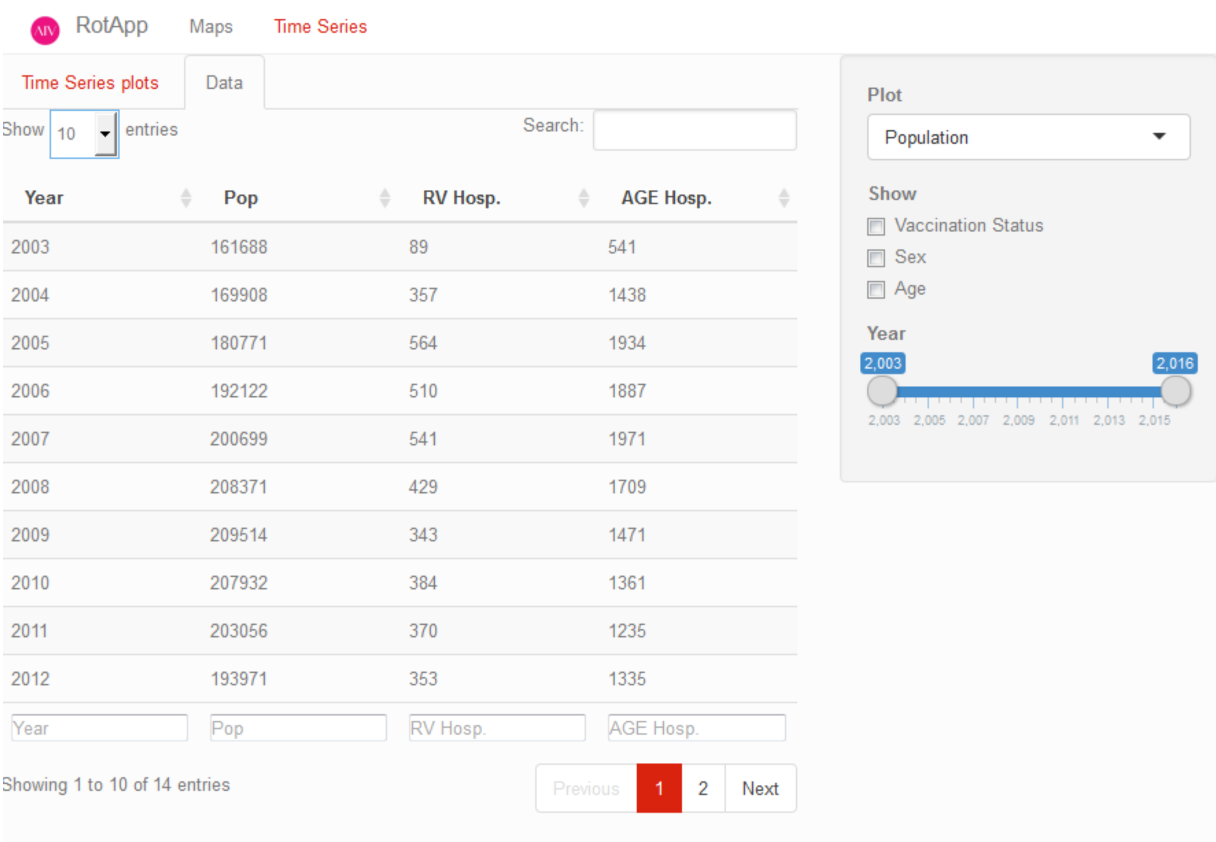


In the right panel we have the option for stratify time series by sex, age and vaccination status.





Data tab open a data table where the available variables are: the calendar year, vaccination status, sex, age, population, number of RVAGE and AGE hospitalizations. When vaccine coverage is selected population vaccinated will be shown.


RotApp Maps Time Series

Time Series plots | Data

Show 10 entries Search:

Year	Pop	RV Hosp.	AGE Hosp.
2003	161688	89	541
2004	169908	357	1438
2005	180771	564	1934
2006	192122	510	1887
2007	200699	541	1971
2008	208371	429	1709
2009	209514	343	1471
2010	207932	384	1361
2011	203056	370	1235
2012	193971	353	1335
Year	Pop	RV Hosp.	AGE Hosp.

Showing 1 to 10 of 14 entries

Previous 1 2 Next

Plot

Population

Show

Vaccination Status

Sex

Age

Year

2,003 2,016

2,003 2,005 2,007 2,009 2,011 2,013 2,015