Spatio-temporal impact of self-financed rotavirus vaccination on rotavirus and acute gastroenteritis hospitalisations in the valencia region, spain.

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Research article

Keywords: Rotavirus, vaccine impact, spatio-temporal, real-world data, Bayesian model

Posted Date: August 27th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-15736/v4

Version of Record: A version of this preprint was published on September 7th, 2020. See the published version at https://doi.org/10.1186/s12879-020-05373-0.

SPATIO-TEMPORAL IMPACT OF SELF-FINANCED ROTAVIRUS VACCINATION ON ROTAVIRUS AND ACUTE GASTROENTERITIS HOSPITALISATIONS IN THE VALENCIA REGION, SPAIN.

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Abstract

Background:

Several studies have shown a substantial impact of Rotavirus (RV) vaccination on the burden of RV and all-cause acute gastroenteritis (AGE). However, the results of most impact studies could be confused by a dynamic and complex space-time

process. Therefore, there is a need to analyse the impact of RV vaccination on RV and AGE hospitalisations in a space-time framework to detect geographical-time patterns while avoiding the potential confusion caused by population inequalities in the impact estimations.

Methods:

A retrospective population-based study using real-world data from the Valencia Region was performed among children aged less than 3 years old in the period 2005-2016. A Bayesian spatio-temporal model was constructed to analyse RV and AGE hospitalisations and to estimate the vaccination impact measured in averted hospitalisations.

Results: We found important spatio-temporal patterns in RV and AGE hospitalisations, RV vaccination coverage and in their associated adverted hospitalisations. Overall, ~1866 hospital admissions for RV were averted by RV vaccination during 2007–2016. Despite the low-medium vaccine coverage (~50%) in 2015-2016, relevant 36% and 20% reductions were estimated in RV and AGE hospitalisations respectively.

Conclusions: The introduction of the RV vaccines has substantially reduced the number of RV hospitalisations, averting ~1866 admissions during 2007-2016 which

38 were space and time dependent. This study improves the methodologies commonly
39 used to estimate the RV vaccine impact and their interpretation.

40 *Keywords: Rotavirus, vaccine impact, spatio-temporal, real-world data, Bayesian*
41 *model*

42 Background

43 Rotavirus (RV) is the leading cause of gastroenteritis in children <5 years of age
44 worldwide (1). Prior to the license of the two live-attenuated rotavirus vaccines (RV1;
45 Rotarix®, GSK and RV5; RotaTeq®, MSD) in 2006 and 2007, respectively, RV infection
46 caused approximately 138 million episodes of acute gastroenteritis (AGE) per year
47 (~2 million hospitalisations), of which ~3.6 million (~87,000 hospitalisations)
48 occurred in Europe.(2)
49 The World Health Organization (WHO) recommended including RV vaccination
50 worldwide. The recommended schedule is two (RV1) or three (RV5) oral doses and
51 should be completed between 6-32 weeks of age. Currently, 98 countries have
52 introduced RV vaccines into their national immunisation programs.(3) This measure
53 has had a major impact on the burden of AGE, decreasing RV outpatient visits and
54 hospitalisations by 60%-90% in Europe (4) (5) (6) (7),
55 Although in Spain RV vaccines are recommended by the Spanish Paediatric
56 Association but not funded by the National Health System (NHS), several post-

57 authorization studies have also shown their effectiveness and impact on AGE and
58 RV-AGE hospitalisations (8) (9) (10) (11) (12). The Valencia Region of Spain could
59 show a specific coverage-related impact of RV vaccines on AGE and RV-AGE
60 hospitalisations and costs, despite the low-medium vaccine coverage (40%-50%).(8)
61 Following WHO recommendations, most post-authorization studies usually estimate
62 impact of the RV vaccine by comparing trends of RV or AGE hospitalisations in pre-
63 and post- vaccination periods (7) (13) (14). However, this ecological design is highly
64 prone to bias and confounding (15) (16) (17).
65 In fact, a number of key studies have shown that the spread of infectious diseases
66 are heterogeneously distributed in space because places differ in their environmental
67 and population characteristics (18) (19). Consequently, epidemiological studies are
68 often confounded by complex and dynamic spatio-temporal processes (20), (18). RV
69 vaccine uptake and hospitalisations could, therefore, vary from time to time and
70 between places for different reasons, including complex interaction of population
71 demographics, socioeconomic inequalities, environmental factors, circulation of RV
72 strains and their interactions across space and time (21). Spatial variation in RV
73 vaccination coverage (22) and in RV hospitalisations has been previously shown in
74 the USA, Germany, Brazil, New Zealand (23) (24) (25).
75 A previous study in Spain showed strong variability in both vaccination coverage and

RV/AGE hospitalisation rates over time and between health departments. (8) Thus, it would be important to evaluate variations in the RV/AGE hospitalisation risk and the impact of RV vaccination in a space-time framework to detect geographical-time patterns while avoiding the potential confusion caused by population inequalities in the impact estimates (8) (26) (18) (12) (7) (24).

Our aim is to assess the spatio-temporal impact of RV vaccines on RV and AGE-associated hospitalisations in children under 3 years of age in the Valencia Region using real-world data. In this study, real space-time rotavirus vaccination impact is predicted in terms of number of averted hospitalisations.

Methods

Setting and study population

This is a retrospective, population-based study using real-world data from the Valencia Region, including all children less than 3 years old living in the Region between 2005 and 2016.

The Valencia Region of Spain has approximately 4 900 000 inhabitants. Of them, around 3% (~150 000 children) are younger than 3 years old. The regional health system is divided into 34 public hospitals (24 of them with paediatric emergency rooms) and 241 health care districts structured into 24 health departments. As RV

94 vaccines are administered to infants from six weeks of age, children with the first
95 dose of RV vaccine recorded before six weeks of age were excluded from the study.

96 Data sources

97 The Valencia Region has a set of multiple electronic databases collecting health and
98 sociodemographic data from 98% of the population (27). The population information
99 system (SIP) was used to determine the population and their socio-demographics
100 characteristics (sex, date of birth, health department, and health care district).
101 Health care district and department are assigned by place of residence.
102 Hospitalisations were collected from the minimum basic data set (MBDS). The
103 vaccine information system (SIV) was used to obtain the vaccinated population; this
104 source captures the immunisation history of each individual. Population,
105 hospitalisation, and vaccination data were linked at individual level through a unique
106 personal identification number. (28)

107 Outcomes and exposure

108 Our outcomes were identified from MBDS through a search of the following ICD-
109 codes: (a) RV hospitalisations: hospitalisations with a discharge diagnosis of
110 enteritis due to rotavirus (ICD-9-CM code 008.61, ICD-10 A08.0) in any diagnosis
111 position. (b) AGE hospitalisations: hospitalisation with a discharge diagnosis of

gastroenteritis-associated episode (ICD-9-CM codes 001-009, 558.9, 787.91; ICD-10 codes A00 – A09, K52.XX, R19.7) in any diagnosis position.

Vaccination status was assessed as a time-varying variable. Children were considered vaccinated from the date of the first dose of RV5 or RV1 and unvaccinated before that date. Children with no recorded rotavirus vaccination in SIV were considered as unvaccinated.

Vaccination coverage was calculated as the proportion of the children <3 years old vaccinated with at least one dose of RV1 or RV5.

Spatio-temporal analyses

The database for the analysis gathered population and hospitalisations aggregated by vaccination status, sex, age, health department, biennial periods (two-years period), and health care district.

A Bayesian spatio-temporal ecological model was constructed to analyse RV and AGE hospitalisation rates and to estimate the impact of vaccination on hospitalisations.

The model assumed that the number of hospitalisations (for RV or AGE) in the different observation units, $Y = \{y_1, \dots, y_{vsadtm}, \dots, y_n\}$, followed a binomial distribution, where “v” indexes the two vaccination status, “s” the two sexes, “a” the 3 age groups (0, 1 and 2 years old), “d” the 24 health departments, “t” the 6 (biennial)

periods, and “m” the 241 health districts. From now on, we will index y by y_i instead of y_{vsadtm} where i spans all the values of the sub-indexes v, s, a, d, t and m to make the notation shorter. Thus, the model assumed proceeds as follows:

$$y_i \sim Bin(\theta_i, N_i), \quad i = 1, \dots, 15{,}718$$

Where θ_i is the hospitalisation rate and N_i the population for each observation unit. θ_i was modelled considering the logit link as follows:

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

where $\log\left(\frac{\delta_m}{1-\delta_m}\right)$ acts as an offset term to control for the hospital attraction (people who live near the hospital are more frequently admitted to it than those who live far from hospital, (see additional file 1)), where δ_m is the estimated hospitalisation rate for all causes measured in each health care district. This rate was estimated using the spatial Besag-York-Mollié model (29) on hospital admissions for any cause. This offset makes that if no other term in the linear predictor had an effect, the corresponding risk, θ_i, would be that corresponding to general hospital admissions for that health care district. β_0 is the intercept term and β_j are the parameters associated with the categories of the covariates, X_j: vaccination status, sex and age. The health department random effect, α_d, was considered to fit the differences in admission policies between hospitals. α_d was considered to have the following distribution

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

where σ is also estimated within the model. No spatial dependence was considered for this term because it is expected to fit the admission policies of each hospital, which should not follow any spatial pattern. The biennial period effect, u_t, was introduced to control the expected temporal variability in RV and AGE incidence. It was modelled as a random effect considering correlation between adjacent periods by a first order random walk modelled as an intrinsic conditional autoregressive (ICAR) prior distribution. Besides the temporal and spatial (health department) terms already mentioned, it was considered appropriate to include a spatio-temporal term that could jointly vary in time and space. The random effect v_{tm} reproduces this effect. This term is assumed to follow a spatio-temporal autoregressive model. (30) Thus, 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

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

where W_{tm} follows a spatial Besag, York and Mollié model (29) for each time period t inducing spatial dependence on $v_{t\,m}$. On the other hand, ρ controls the temporal dependence in $v_{t\,m}$. This parameter is assumed to follow a uniform prior distribution

between -1 and 1. Non-informative flat prior distributions were considered for β_j ($j = 0,..,3$) parameters. Uniform prior distributions between 0 and 5 were considered for the standard deviations of all the random effects in the model.

Predictive distributions were used to estimate the number of rotavirus hospitalisations averted in order to assess the impact of rotavirus vaccination by health care district and time period. The number of cases averted by vaccination was calculated as the difference between the hospitalisations predicted by the adjusted model without the vaccine effect and the hospitalisations predicted by the model explained above.

R (Foundation for Statistical Computing, Vienna, Austria) and WinBUGS (Cambridge Biostatistics Unit and the Imperial College School of Medicine, London) software were used to perform the analysis using MCMC methods. A total of 2000 initial iterations were used as burn-in period of the MCMC. Subsequently, 10 000 iterations were run and only 1 in every 10 of them was saved. Three chains were simulated in total. MCMC convergence was assessed by visual inspection of history plots of posterior samples, the Brooks-Gelman-Rubin scale reduction factor, and the effective sample size implemented in the R2WinBUGS package of R. All statistical analyses conducted for this study are completely reproducible, and the data and the

186 R code used for statistical analysis can be found as supplemental digital content to
187 the paper.

188 ## Results

189 The study included 721 471 children < 3 years old. Of these, 189 247 were vaccinated
190 against RV. There were a total of 17,482 AGE hospitalisations, of which 28% (4871)
191 were codified as RV. AGE and RV hospitalisations accounted for 8.4% and 2.4%
192 respectively of all hospitalisations (207 014 hospitalisations for any cause).
193 Vaccinated children accounted for 2248 AGE and 200 RV admissions.

194 Spatio-temporal hospitalisation rate and relative risk

195 Risk of RV and AGE hospitalisations decreased with RV vaccination (Table 1). RV
196 and AGE hospitalisation rates were 86% (95% CI: 84-88) and 47% (95% CI: 45-50)
197 lower in vaccinees, respectively. Risk of RV and AGE hospitalisation also decreased
198 with increasing age, by 72% (95% CI: 70-74) and 58% (95% CI: 56-60) respectively in
199 two-year-old children as compared to those aged less than one year old. Risk of RV
200 and AGE-hospitalisation was respectively 19% (95% CI: 15-23) and 15% (95% CI: 12-
201 18) lower in girls as compared to boys. A strong variability in both RV and AGE
202 hospitalisation rates was found between health departments (additional file 2). Risk
203 of AGE hospitalisation showed a downward trend during the study (additional file 2),
204 while the RV rate only declined between 2005 and 2010. Once controlled the vaccine

205 effect, RV peaked in 2013-2014, with an 8% (95% CI: 6-14) higher rate than the
206 average risk for the whole study period (additional file 2). Additional structured
207 spatio-temporal interaction was found for both outcomes. The spatio-temporal effect
208 maps (additional file 2) showed spatial clusters after adjusting for confounders.

209 Spatio-temporal RV vaccination coverage

210 Rotavirus vaccination coverage varied considerably across the Valencia Region
211 during the study period, with pockets of undervaccination (lower coverages) in many
212 health care districts. Vaccination rates increased over the years in the districts. In
213 2016, 50% of the health care districts had a coverage higher than 53% (IQR: 35%-
214 64%) (Figure1). The overall RV vaccination coverage increased from 0% to 49% during
215 the study period.

216 Spatio-temporal RV vaccination impact

217 The number of hospitalisations averted by vaccination was coverage-dependent
218 (Table 2), with impact of vaccination increasing as the number of vaccinees
219 increased. With 189 247 children vaccinated, 1142 (95% CI: 1069-1222) RV and 1866
220 (95% CI: 1736-1992) AGE hospitalisations were averted. This represented overall
221 reductions of 19.9 % (95% CI: 19.7-20.2) in RV hospitalisations and 10.2% (95% CI:
222 9.7-10.5) in AGE hospitalisations for the whole period. The number of
223 hospitalisations averted increased over time with increasing coverage. In 2015-2016,

224 with a vaccination coverage of approximately 50%, there were reductions of 35.6%
225 (95% CI: 35.2-36.1) and 19.7 % (95% CI: 19.0-20.3) in RV and AGE hospitalisations
226 respectively (Table 2). Maps in Figure 2 show the distribution of RV and AGE
227 hospitalisations averted by health care district over time. The impact on RV and AGE
228 hospitalisations was greater in health care districts with higher coverage. Assuming
229 100% RV vaccine coverage, RV hospitalisations would be expected to be reduced by
230 85.8% (95% CI: 84.8-86.5) or 4,920 (95% CI: 4602-5221) hospitalisations in the case
231 of RV, and AGE hospitalisations by 46.9% (95% CI: 45.1-48.4) or 8,606 (95% CI: 8056-
232 9148) hospitalisations as compared to admissions if no child had been vaccinated
233 during the study period.

234 ## Discussion

235 This is the first study estimating the spatio-temporal impact of RV vaccination on RV
236 and AGE hospitalisations. The number of averted hospitalisations by RV vaccination
237 was increasing in space and time in the Valencia Region during the study period in
238 children <3 years. Overall, ~1866 hospital admissions for AGE (potentially
239 attributable to RV) were averted during 2007–2016. Despite the low-medium vaccine
240 coverage (~50%) in 2015-2016, relevant 36% and 20% reductions were estimated in
241 RV and AGE hospitalisations respectively. It should be noted that ~8606
242 hospitalisations would have possibly been averted during the whole study period if

243 all children had been vaccinated. Direct benefits of vaccination were observed in the
244 reduction of hospitalisation rates for RV (86%) and GEA (47%) in vaccinated children.
245 These results are in accordance with the vaccine effectiveness estimated in the
246 Valencia Region previously (9). Regarding the spatio-temporal results, substantial
247 variability was seen in RV vaccine coverage and hospitalisation risk for RV and AGE
248 among health departments and health care districts. Spatio-temporal clusters were
249 clearly distinguished. These patterns could be explained by climatic, environmental,
250 sociodemographic, or economic differences, or by the different admission policies of
251 health departments.
252 Although other impact studies reported relevant reductions in both RV and AGE
253 hospitalisations in children <5 years following RV vaccination (4), (6), (6) (31), (32),
254 (7), (13) , (14), (33), only two of them showed a coverage-dependent response (8),
255 (34). Moreover, many of them were time-trend ecological studies comparing
256 hospitalisation data in pre and post-vaccine populations and a historical pre-vaccine
257 group (7), (13) , (14), (33). Even though this is the most commonly used method, it
258 has been associated with potential confusion bias (15), (16). The reported impact
259 of the vaccination could be due to other secular trends caused by, changes in
260 reporting, in medical practices, in health seeking behaviour, etc (35). Besides,
261 vaccine impact based on hospitalisation data is prone to confounding, because

262 hospitalisations rates are closely related to changes in the quality, access and use of
263 the health care system which often occur simultaneously with introduction of new
264 vaccines (17).
265 On the other hand, few spatial and spatio-temporal models have studied RV and AGE
266 dynamics and none of them included the vaccination status of the population. Spatial
267 variation in RV hospitalisations explained by sociodemographic characteristics of the
268 population has previously been shown in studies conducted in Germany and New
269 Zealand (23), (24). Other studies in the USA and Brazil found that spatio-temporal
270 variation in birth rate can lead to secular changes in the RV pattern (21), (25). Finally,
271 a study conducted in Bhutan showed that rainfall and temperature explain much of
272 the spatio-temporal dynamics of diarrhoea (possibly due to RV infection in
273 approximately 23% of cases) (31). The studies developed in Germany and New
274 Zealand were based in aggregated data over time, however, caution should be taken
275 when interpreting this analysis because the area-specific risk may be overestimated
276 or underestimated. Furthermore, none of these standard models considered spatio-
277 temporal dependence; however, what occurs in a health care district is intimately
278 related to what occurs in the adjacent one and is also related to what happened
279 previously (36).

The present study analysed the impact of RV vaccination on RV and AGE hospitalisations from a different point of view. We developed a sophisticated spatio-temporal model that allowed us to estimate the RV vaccination impact in terms of adverted hospitalisations according to the number of children vaccinated. The spatio-temporal approach improves the commonly used methodologies to estimate the RV vaccine impact and its interpretation as follows. First of all, this analysis showed the evolution of the impact of RV vaccination and the risk of hospitalisation for RV/AGE in the Valencia Region at the health care district level over time. Second, adjusting by spatial variables such us health care district and health department in the analysis, several potentially attributable biases can be controlled. Those biases could have been caused by economic inequalities, environmental factors, socio-demographic differences or even possible changes in hospitalisations-admission policies (37) (38) (21) (39). Moreover, the hospitalisation rate for any cause of each health care district was included to adjust the confusion caused by hospital attraction or other secular trends (17). Finally, the Bayesian approach used allowed us to adequately capture dependencies among health areas and the potential relationship of data over time that cannot be easily modelled in classical statistics (40) (41).

298 Nevertheless, some limitations of our study should be highlighted. First of all, RV
299 vaccines are not included in the official immunisation schedule, which may suggest
300 differences between rotavirus vaccinees and non-vaccinees in terms of
301 socioeconomic conditions and health-seeking behaviour. Therefore, socioeconomic
302 factors might be an important confounder of our results and admissions at private
303 hospitals should also be considered in future studies.
304 Secondly, although the positive predictive value of the rotavirus ICD-9-CM code
305 identifying acute gastroenteritis attributable to rotavirus using MBDS resulted in 90%
306 (9), different immunochromatographic methods with different sensitivities and
307 specificities could have been used in the different hospitals during the study period
308 (42). In fact, based on the difference found in the number of hospitalisations
309 prevented for AGE and RV (1866 vs. 1142), ~40% of underdiagnosis in RV
310 hospitalisations was detected in the present study. Thirdly, health care district and
311 health department could have varied over time; but only the last updated information
312 was available. Fourthly, children who were unable to receive RV vaccines according
313 to manufacturer recommendations (i.e. immunocompromised children) were not
314 excluded from the analysis due to the lack of information.
315

316 Finally, it should be noted that both vaccines (RV1 and RV5) were used concurrently
317 until 2010. But, RV5 was the only rotavirus vaccine available in Spain between 2010
318 and 2016. Therefore, results will have a limited value for estimating the impact of
319 RV1.

320 ## Conclusions

321 In summary, the introduction of the RV vaccines has substantially reduced the
322 number of RV hospitalisations. The sophisticated spatio-temporal analysis allows us
323 to show the impact of different vaccine coverage rates in terms of avoided
324 hospitalisations in a geographical-time framework. Interestingly, our study predicted
325 that ~8606 RV hospitalisations could have been adverted with all children
326 vaccinated. This study improves the methodologies commonly used to estimate the
327 RV vaccine impact and its interpretation. The spatio-temporal model avoided the
328 potential confusion caused by population inequalities in the impact estimations. It
329 also detects spatial clusters of the RV and AGE-hospitalisation risk attributable to
330 common environmental, demographical, or cultural effects shared by neighboring
331 regions.

332 ## Abbreviations

333 AGE All-cause acute gastroenteritis

CMBD Spanish hospital discharge database

CrI Credible intervals

NHS National Health System

OR Odds Ratio

RV Rotavirus

RV1 Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium)

RV5 RotaTeq® (Merck & Co., Inc., West Point, PA, USA)

SIP Valencia's administrative population-based database

SIV Valencia's Vaccine Information System

WHO World Health Organization

Declarations

Funding

This study was funded by SPMSD. The company had no role in the analysis or discussion of the results.

Availability of data and materials

Additional analysis and results are available in RotApp AIV (rotapp.shinyapps.io/aiv2019).

All statistical analyses conducted for this study are completely reproducible, and the data and the R code used for statistical analysis can be found in the following repository, https://drive.google.com/drive/folders/1UaZskXYjy7yYFSW7vpycTI_r4kcf6RwG?usp=sharing.

Authors' contributions

MLL, AOS, CMQ, MAMB and JDD contributed to the study design. MLL managed and analysed the data. All authors participated in the results interpretation and discussion. MLL drafted the manuscript. All authors were involved in the critical revision of drafts and approved the final manuscript version.

Competing interests

MLL, AOS, CMQ and JDD ever received travel grants to attend meetings sponsored by pharmaceutical companies. MAMB has no conflicts of interests. JDD has been principal investigator in clinical trials sponsored by SPMSD, MSD, GSK and Pfizer. JDD acted as Advisor for GSK and SPMSD.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Dirección General de Salud Pública/Centro Superior de Investigación en Salud Pública.

Acknowledgements

Not applicable.

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Figures

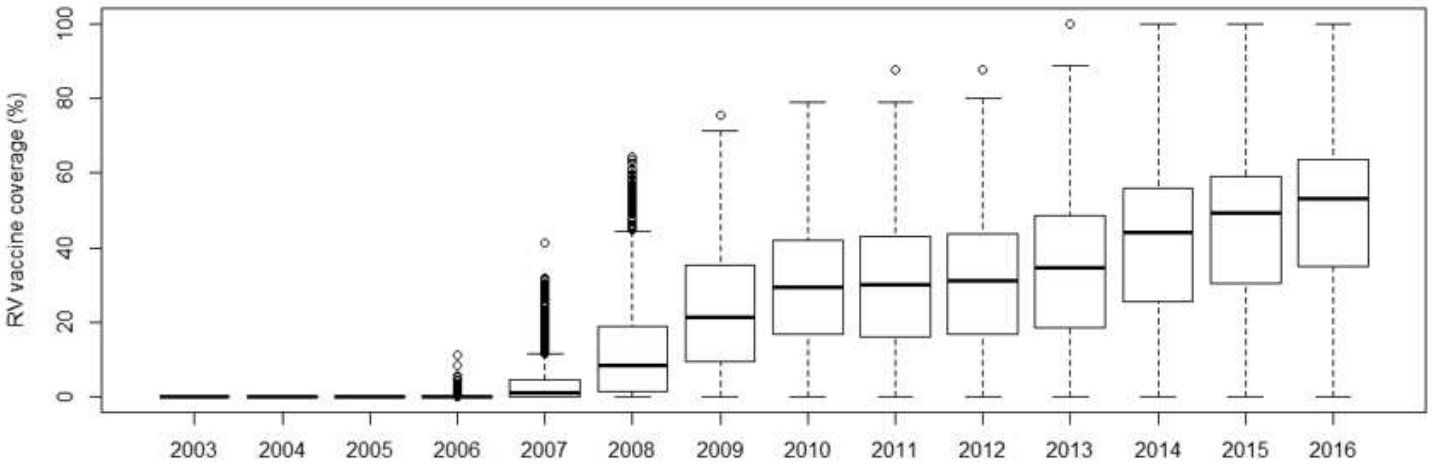

Figure 1

Description of RV vaccine coverage (%) by health care district and year.

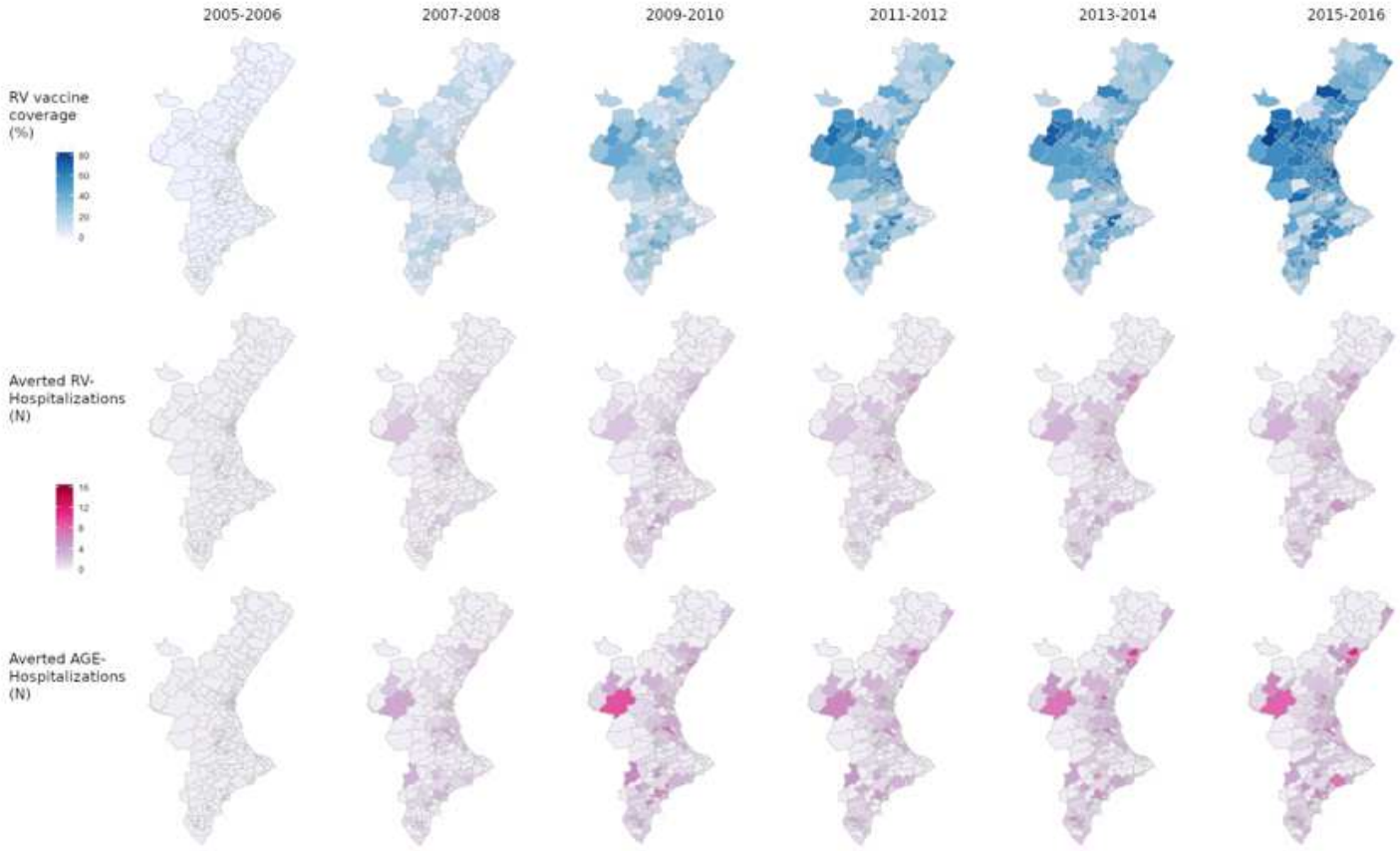

Figure 2

Spatio-temporal impact of RV vaccination on RV and AGE hospitalisations. RV vaccine coverage (%) and number of averted hospitalisations by health care district and period estimated in the spatio-temporal model.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalFiles.zip
- additionalfile2.docx
- additionalfile1.html