


Rotavirus vaccination as a public health strategy to reduce the burden of hospitalization: The field experience of Italy (2008–2018)

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Abstract

Rotavirus (RV) infection is a leading cause of severe diarrhea among children younger than 5 years old and a considerable cause of RV gastroenteritis (RVGE) hospitalization. This study aimed to evaluate the impact of vaccination in Italy in the reduction of the burden of RV-related disease, estimating the relation between vaccination coverage and hospitalization rates. RVGE-related hospitalizations that occurred in Italy from 2008 to 2018 among children aged 0–35 months were assessed by consulting the Hospital Discharge Record database and including records whose ICD-9-CM diagnosis code was 008.61 in the first or in any diagnosis position. In the 2008–2018 period, a total of 17 535 791 at-risk person-years were considered and 74 211 (423.2 cases \times 100 000 per year) RVGE hospitalizations were observed. Higher hospitalization rates occurred in males (456.6 vs. 387.9 \times 100 000 per year) and in children aged 1 year (507.8 \times 100 000 per year). Poisson regression analysis showed a decrease of -1.25% in hospitalization rates (-1.19% to -1.31% , $p < 0.001$) per unit increase in vaccination coverage. This is the first study that correlates hospitalization rate reduction with a percentage increase in vaccination coverage. Our findings strongly support RV vaccination as an effective public health strategy for reducing RVGE-related hospitalizations.

KEYWORDS

cohort study, hospitalization risk, rotavirus, vaccine

1 | INTRODUCTION

Since 1973, rotavirus (RV) infection has been identified as a major cause of acute gastroenteritis in newborns and young children.^{1,2} Although its burden has reduced over the past decade, it continues to be the leading global cause of severe diarrhea in children under 5 years of age and a significant cause of admission to hospital.^{3–5}

In fact, according to the Global Burden of Disease 2019 Study the mortality rate attributable to RV infection dropped from 659 053 in 1990 to 235 331 in 2019.⁶ In high-income countries, morbidity and health costs associated with RV infections are still considerable⁷; however, in low- and middle-income countries, RV gastroenteritis (RVGE) is a public health emergency.^{5,8} In Southeast Asia, for example, RVGE persists to account for a significant portion of total

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diarrhea mortality, especially in low-income countries with worse living standards and hygienic conditions.⁹ Unfortunately, the scientific literature on the incidence of RV-related hospitalizations is scant, limiting the availability of up-to-date global health and economic impact estimates.

In 2003, Parashar et al. published for the first time a global estimate of hospitalizations attributable to RV infections, estimating that about two million hospitalizations per year occurred among children younger than 5 years old.¹⁰ These findings were consistent with those recently reported by a number of study groups from other countries, who also accounted for the role of RV vaccination.^{11,12}

Medical treatments employing oral rehydration solution, sanitation, and water purification have been the only effective strategies to reduce diarrhea-associated mortality over the past two decades¹³; such interventions, however, were not cost-effective toward RV infection and its complications; consequently, in 2007, the World Health Organization advised countries to include RV vaccination in their national immunization programs as it should be considered a the most effective and cost-effective strategy to prevent RV-related morbidity and mortality.^{14,15} To date, 116 countries have incorporated RV vaccination into their national immunization programs,^{16,17} and numerous European nations have embraced a universal vaccination program as part of their childhood immunization schedules. Vaccine effectiveness against RVGE hospitalizations and outpatient visits has been demonstrated to be strong, particularly in regions with high vaccination coverage,^{6,18-22} although it should be noted that the RV vaccines effectiveness differs across countries.^{6,9,21,22}

RV vaccines are recommended for newborns beginning in the sixth week of life, and the vaccination regimen should be completed by 24 or 32 weeks of life for RV1²³ and RV5,²⁴ respectively. These vaccines have demonstrated high and durable efficacy against severe RV gastroenteritis in highly developed countries, but lower and less durable efficacy in sub-Saharan Africa and South Asia.²⁵⁻²⁷ RV1, for instance, was more effective in Europe (90.4% of severe RV infections were prevented) than in Africa (61.2%). Similarly, RV5 revealed effectiveness rates ranging from 83% to 100% in high-income countries such as the United States and Finland, but rates of 30%–74% in Nicaragua, a low-income country.⁶

With vaccination, the burden of RV dropped considerably, as shown by the decline in hospitalizations and emergency room visits.²⁸

Sicily was the first Italian region to offer universal RV vaccination in 2013. After 1 year, 25% of children aged 0–11 months in Sicily were vaccinated against RV, resulting in a 35% decrease in RVGE hospitalizations.²⁹⁻³¹ However, published estimates of the number of RV-related hospitalizations worldwide are limited, as are research evaluating the association between hospitalizations and vaccine coverage.

The purpose of this study was to examine the impact of vaccine coverage achieved in Italy on the decrease of the burden of RV-related disease by investigating the association between vaccination coverage among children less than 36 months and hospitalization rates.

2 | MATERIALS AND METHODS

RVGE-related hospitalizations among children aged 0–35 months were examined by consulting the Hospital Discharge Record (HDRs) database collected annually by the Italian Ministry of Health, which is the primary source for collecting information on every patient discharged from public and private hospitals in Italy.

Each HDR contains demographic data (birthplace, residence, gender, and date of birth), admission and discharge dates, discharge status (“discharged/transferred” or “expired”), and up to six discharge diagnoses (one principal and five secondary diagnoses) coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).³²

All HDRs recorded in the national database from January 1, 2008 to December 31, 2018 with the ICD-9-CM code 008.61 in the first or any other diagnosis position, leading to a diagnosis of “rotavirus gastroenteritis” in children aged 0–35 months, were examined.

The total number of children under the age of 3 in Italy from 2008 to 2018 was acquired by consulting the database of the Italian National Institute of Statistics, the country's leading producer of official government statistics.³³

Official Ministry of Health data were used to obtain vaccination coverage at 24 months by Italian region for cohorts born between 2014 and 2018.³⁴

2.1 | Statistical analysis

Qualitative data were summarized as absolute frequencies and rates (cases × 100 000 at risk subjects per year). Hospitalization rates per 100 000 were calculated using the census population for children aged 0–35 months from 2008 to 2018.

Vaccination coverage was reported as relative frequency (%). A Joinpoint regression analysis was used to evaluate the time trends of hospitalization rates and the average annual percent change through the entire considered period. This analytical approach was selected because it is a well-established methodology for modeling trends over time using connected linear segments and accurately identifying years of the trends in which rates significantly change.³⁵

The association between vaccination coverage and hospitalization rates, both measured on an annual and regional basis, was evaluated by a multivariable Poisson regression analysis. Regression coefficients, adjusted for year of study, was used for modeling the percentage reduction of hospitalization rates per percentage unit increase in vaccination coverage.

A $p < 0.05$ was considered as statistically significant.

Analyses were performed using R Software analysis (version 4.0.5; R Foundation for Statistical Computing) and, as for the Joinpoint analysis, the packages “Segmented” and “Strucchange” were used.³⁶

TABLE 1 General characteristics of the RVGE hospitalized cases reported from 2008 to 2018.

	N	RGVE hospitalization rates (cases × 100 000)
Total	74 211	423.2
Sex		
M	41 140	456.6
F	33 071	387.9
Age (months)		
0–11	27 133	475.1
12–23	29 774	507.8
24–35	17 304	290.2
Year		
2008	9016	536.1
2009	7119	417.9
2010	9456	554.1
2011	6957	409.1
2012	7657	469.5
2013	5033	312.2
2014	6958	437.0
2015	9440	611.3
2016	3454	231.5
2017	5603	385.1
2018	3518	248.3
Deaths	8	0.045

Abbreviation: RVGE, rotavirus gastroenteritis.

3 | RESULTS

During the study period, a total of 17 535 791 at-risk children aged 0–35 months were observed (9 010 282 males and 8 525 509 females), with an annual mean of 1 594 162 children.

As shown in Table 1, a total of 74 211 RVGE hospitalizations were reported (423.2 cases × 100 000 per year). Males (456.6 vs. 387.9 × 100 000 per year) and children aged 12–23 months old had higher hospitalization rates (507.8 × 100 000 per year). The average yearly percentage decrease in hospitalization rates was –7.32% each year ($p \leq 0.001$), indicating a consistent decline over time.

The RV vaccine coverage, stratified by Italian region and birth cohort, is reported in Table 2. RV vaccine coverage by region was very heterogeneous, ranging from 0.14% (Molise, 2016) to 75.55% (Calabria, 2016). Some regions (e.g., Sicily, Campania, and Puglia) embraced universal mass RV vaccination earlier and more efficiently than others (i.e., Lombardy, Molise, and Umbria) in their immunization schedules. In 16 regions, the 2016 birth cohort's immunization coverage persisted to be below 20% (and for 1 region data was not available).

TABLE 2 Rotavirus vaccination coverage at 24 months by birth cohort and region.

Region	Coverage at 24 months (%)				
	2014	2015	2016	2017	2018
Piedmont	6.39	8.5	11.47	18.68	75.81
Valle d'Aosta	0	0.21	0.94	1.13	23.71
Lombardy	ND	ND	ND	8.99	74.21
Aut. Prov. Bolzano	0.91	1.03	2.72	23.63	41.69
Aut. Prov. Trento	0	0.73	0.94	2.6	72.89
Veneto	2.53	6.26	11.23	25.99	80.95
Friuli-Venezia Giulia	2.01	4.09	9.47	22.3	66.57
Liguria	16.76	20.07	19.67	39.68	58.08
Emilia-Romagna	3.76	6.22	9.69	26.34	73.45
Tuscany	8.14	8.27	10.16	23.25	43.95
Umbria	0	0	0.25	1.04	27.62
Marche	0.53	1.51	2.69	9.77	58.99
Lazio	7.01	7.44	18.69	38.43	43.73
Abruzzo	0.52	1.02	1	13.44	44.46
Molise	0	0.09	0.14	1.2	73.97
Campania	0.33	0.76	1.56	4	39.89
Puglia	21.12	29.71	35.04	53.04	69.57
Basilicata	1.35	2.56	4.41	24.18	65.12
Calabria	14.64	41.52	75.55	72.43	79.91
Sicily	45.06	50.92	53.77	54.29	59.83
Sardinia	13.55	21.5	29.52	35.93	79.19

TABLE 3 Poisson regression analyses, adjusted for year of study, on variables involved in RVGE hospitalization rates in Italy from 2008 to 2018.

	Adjusted-HR	95% CI	p
% Vaccination coverage (per % unit increase)	0.987	0.986–0.988	<0.001
Year (per unit increase)	0.970	0.969–0.972	<0.001

Abbreviation: RVGE, rotavirus gastroenteritis.

Table 3 displays the results of the multivariable Poisson regression analysis. It was found that an increase in vaccination coverage is associated with a decreased risk of RVGE hospitalization (adj-HR = 0.987; 95% CI = 0.986–0.988). This reduction corresponded to a decrease in hospitalization rates of –1.25% (from –1.19% to –1.31%, $p < 0.001$) per unit increase in vaccination coverage.

Figure 1 illustrates the relationship between percentage vaccination coverage and percentage reduction in hospitalization rates based on the estimated model coefficients. According to this

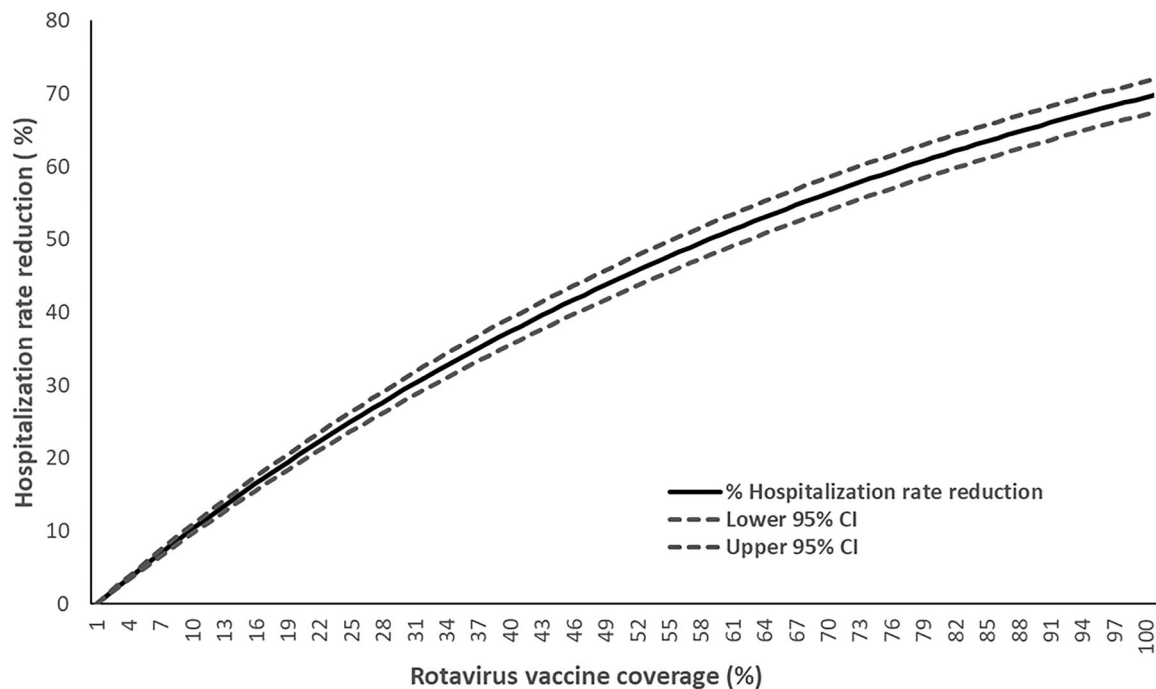


FIGURE 1 Modelization of hospitalization rates reduction by percentage increase in vaccination coverage according to the Italian observed data.

modeling, hospitalization rates would decrease by 71.6% if vaccination coverage reached 100%.

4 | DISCUSSION

RV has been the leading cause of moderate/severe acute viral gastroenteritis in infants and children for decades. In fact, several studies^{37–40} have revealed that RV is responsible for almost 50% of hospitalizations for diarrhea in children.

Hallowell et al. conducted a systematic review considering pre-vaccine RV hospitalization rates stratified by mortality stratum (high-, medium-, or low-mortality countries) of several countries; they assessed that the median RV hospitalization rate was 535 (IQR: 388–766) per 100 000 children younger than 5 years old in low-mortality countries, 238 (IQR: 210–659) in medium-mortality countries, and 349 (IQR: 279–490) in high-mortality countries. According to the authors, these differing findings may reflect group- and country-specific differences in access to care or healthcare behavior patterns.¹² In Italy, the average hospitalization rate in the pre-vaccine era (years 2008–2015) was 448 per 100 000 children younger than 3 years of age. Our findings are comparable to the aforementioned data.

RV vaccination has been found to be extremely effective, having a significant impact on RVGE hospitalizations, as well as emergency room and primary healthcare visits, in all European countries where a tailored immunization program has been introduced.⁴¹ For instance, after the introduction of the RV vaccination and with a vaccination coverage ranging from 60% to 85% after the first year of universal

mass immunization, the frequency of RVGE hospitalizations in European countries decreased.^{18–20}

In 2013, within 12 months of the introduction of the RV immunization program for the infants in the United Kingdom, acute gastroenteritis-related hospitalizations decreased significantly. In detail, the first year of the program was associated with a 77% reduction in laboratory-confirmed RV hospitalizations, followed by reductions of 80%–88% in succeeding years.⁴²

The deployment of RV universal immunization within Italian borders resulted in a significant decrease in RVGE hospitalization rates from 2016 to 2018 (–38.45%), which is a further significant finding. This reduction was smaller than the one reported in the United Kingdom; this modest decline may be attributed to a lower vaccination coverage rate.

According to the study by Costantino et al., hospitalizations due to RVGE decreased by 35% in Sicily after the first year of universal RV vaccination (2013), with a regional vaccination coverage of 25% in the same year.^{29–31} These results are consistent with our findings, and assuming a countrywide vaccination coverage of 25%, our model predicts a 27% reduction in RVGE hospitalizations.

We also observed a statistically significant 2.98% reduction in RVGE hospitalizations for each year of the study (2.84%–3.11%, $p < 0.01$), although this trend could be partially explained by the recent trend to hospitalize only the most severe cases, effectively reducing the absolute number of hospitalizations over time. This trend may also be due to a form of herd immunity that has emerged in recent years; however, the heterogeneity of vaccination coverage between Italian regions and the absence of individual data made it extremely difficult to examine this trend.

Our study has limitations that should be discussed further. First, the use of HDRs may have underestimated the true burden of RVGE as not all reported cases may have been confirmed by laboratory testing.⁴³ However, inpatient data is an adequate proxy for overall RVGE rates across the 11-year period and is sufficient to depict the trend. Second, our model was ineffective in assessing the role and impact of herd immunity over time. It should be highlighted, however, that we observed only a few years after the introduction of the vaccine, and thus the influence of herd immunity should be negligible. As a third point, this is an ecological study, thus we cannot quantify the risk of hospitalization based on the vaccination status of the individual.

Despite the possible limitations, to the best of our knowledge, this study is the first in the world to compare, on a nationwide scale, the reduction in hospitalization rates with the percentage increase in vaccination coverage. Finally, and most importantly, our data strongly support RV immunization as an effective public health strategy that, only with a very high vaccination coverage, could lead to a further and significant reduction in the hospital admission rates of children with RVGE.

AUTHOR CONTRIBUTIONS

Prof. Emanuele Amodio contributed to development of study methods, including data standardization and linkage, developed the statistical analysis plan, performed the descriptive analysis, interpreted the results, drafted the initial manuscript, and reviewed and revised the manuscript. Prof. Francesco Vitale conceptualized and designed the study, contributed to development of study methods, contributed to interpretation of the results, and critically reviewed the manuscript for important intellectual content. Dr. Antonio D'Anna contributed to development of study methods, contributed to the data analysis and the interpretation of the results, and critically reviewed the manuscript for important intellectual content. Dr. Dario Genovese conceptualized and designed the study, was responsible for data linkage and standardization, supervised the work, interpreted the results, and reviewed and revised the manuscript. Dr. Francesco Leonforte and Dr. Maria G. Verso contributed to the interpretation of the results, critically reviewed the manuscript for important intellectual content, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for major aspects of the work.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data set generated during and/or analyzed during the current study is available from the corresponding author on reasonable request.

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