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Impact of a twelve-year rotavirus vaccine program on acute diarrhea mortality and hospitalization in Brazil: 2006-2018

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ABSTRACT

Background: Monitoring the impact of vaccine programs is necessary to identify changes in vaccine efficacy. We report the impact of the 12-year rotavirus vaccine program on diarrhea mortality and hospitalizations and their correlation to socioeconomic indicators.
Methods: this ecological study describes diarrhea hospitalizations and deaths from 2006 to 2018 in Brazil and correlates rotavirus vaccine coverage, hospitalizations and deaths to socioeconomic indicators and social vulnerability index (SVI) by state and region. Hospitalizations, deaths, and vaccine coverage trends were analyzed using Joinpoint regression models. Associations between hospitalizations, mortality and rotavirus vaccination coverage and socioeconomic and SVI indicators were established using Ordinary Least Square regressions.
Results: Rotavirus vaccine coverage remained stable between 2006 and 2018 (annual percentage changes (APC) [95%CI]: 4.4% [−0.3%, 9.2%]). Diarrhea hospitalization rates decreased 52.5% (−5.7% [−7.5%, −3.8%]), from 68.4 to 32.5 hospitalizations per 10,000 children <5 years-old between 2006 and 2018, with significant decreases in diarrhea mortality (−9.8% [−11.2%, −8.5%]). The Northeast region experienced the largest reductions (−13.9% [−15.7%, −12.2%]). Vaccination coverage and diarrhea-mortality were inversely correlated with the SVI.
Conclusion: The burden of childhood diarrhea has decreased over an extended period. States with high SVI, but high vaccination coverage had the largest reductions in hospitalizations and deaths.

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KEYWORDS
Acute diarrhea; rotavirus; rotavirus vaccine; mortality; hospitalization; Brazil

1. Introduction

Diarrhea is a leading cause of childhood mortality, resulting in half a million annual deaths worldwide [1]. A major cause of severe diarrhea is Rotavirus, which is responsible for a high proportion of diarrhea hospitalizations in children. Two live Rotavirus vaccines were licensed in 2006 (Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium and RotaTeq, Merck & Co. Inc., West Point, PA, USA) and were recommended by the World Health Organization (WHO) for worldwide implementation in 2009 [2]. Since then, the adoption of these and other Rotavirus vaccines by national immunization programs has reduced all-cause and rotavirus diarrhea-related hospitalizations and deaths in all countries where the vaccine has been implemented on a large scale [3–7]. However, vaccine efficacy varies between high and low-income countries, with lower effectiveness reported from African countries [8]. Brazil introduced the Rotavirus (Rotarix®) vaccine in its national immunization program in March 2006, providing two doses free of charge to infants less than 6 months old, rapidly achieving high vaccination coverage, which resulted in significant decreases in diarrhea-related hospitalizations and deaths [9]. Long-term surveillance of vaccine effectiveness however is still necessary to demonstrate the continued benefits of the vaccine on public health important outcomes, enhancing vaccine confidence and support for its continued roll out, and to identify potential changes in the epidemiology of diarrhea

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Supplemental data for this article can be accessed here.

[10]. Moreover, as the vaccine has been shown to have a lower efficacy in low-income countries [8], it is important to monitor whether vaccine efficacy varies within a large country, such as Brazil, with continental proportions and major sociodemographic differences [11,12].

We describe the impact of the rotavirus vaccination program on diarrhea-related mortality and hospitalization in Brazil, over an extended period of 12 years, and examine whether these indicators are associated with the geographical regions' socioeconomic indicators and social vulnerability index (SVI).

2. Methods

2.1. Study design and data sources

This was an ecological study of all diarrhea hospitalizations and deaths of children less than 5 years old reported in Brazil. Data on the number of diarrhea-related hospitalizations and deaths for children and the Rotavirus vaccine coverage (%) were obtained from the public-domain Brazilian Hospital Information System of the National Health System (DATASUS) (http://datasus.saude.gov.br/). All hospitalizations and deaths of children with the International Classification of Diseases (ICD-10) codes A08–A09 were included. These codes correspond to all-cause diarrhea for both mortality and hospitalizations, as there are no large-scale diarrhea databases based on etiological diagnosis. Data were obtained by year for the five regions and each of the states of the country. In addition, data on the Human Development Index (HDI) and the SVI were obtained for each region and state of the country (http://www.br.undp.org/content/brazil/pt/home.html). The HDI describes the degree of human development and is categorized into longevity, education and income domains and ranges from 0 to 1; with higher values indicating higher human development [13]. The SVI, obtained from the Brazilian Institute of Applied Economic Research (http://www.ipea.gov.br), estimates the degree of vulnerability and social exclusion of a population. This index is composed of 16 social indicators of urban infrastructure, human capital, income, and work [14] and ranges from 0 to 1, where 0 (zero) corresponds to no or very low social vulnerability and 1 to very high vulnerability.

Other social indicators, including the Gini Index (Supplementary Material) were obtained from the Brazilian Institute of Geography and Statistics [15].

2.2. Data analysis

The trends of hospitalizations, deaths, and vaccine coverage rates were analyzed using Joinpoint regression models (Joinpoint Regression Program 4.5.0.1, National Cancer Institute, USA) with Monte Carlo permutations. This method allows identifying trends and change points (i.e. the year that the trend changed) and determining annual percentage changes (APC). Trends were categorized as stable, increasing, or decreasing, according to the slope of the regression line (whether positive or negative) and based on the 95% confidence interval (95% CI) and 5% significance.

The association between the HDI and SVI and hospitalization, mortality, and rotavirus vaccination coverage was established using Ordinary Least Square (OLS) regressions [16]. In the OLS model, the inclination of the regression line (positive or negative) indicates the direction of the association (direct or inverse). The residues of the model were submitted to Moran's statistics for the assessment of spatial dependence. If these were present, a spatial regression model was applied: or Spatial Error or the Spatial Lag Models. In the Spatial Error Model, spatial effects are noises that need to be removed, while the Spatial Lag Model attributes the ignored spatial autocorrelation to the response variable Y. Lagrange multiplier tests were used to the selection of the spatial model. The quality of the model was assessed by observing the Akaike, Schwarz Bayesian, R^2, Log-Likelihood, and the I Moran statistic of the residues [17] using GeoDa 1.10 (Center for Spatial Data Science, Computation Institute, The University of Chicago, USA).

2.3. Ethical considerations

The study did not require approval from an ethics committee as databases are in the public domain without individual identifiers.

3. Results

Trends on rotavirus vaccine coverage are shown in Figure 1(a). The lowest vaccine coverage was 46.5% in 2006, and the highest 95.4% in 2015. In Brazil, the vaccine coverage trend remained stable between 2006 and 2018 (APC: 4.4%; 95% CI: −0.3% to 9.2%; P = 0.1) (Table 1). All regions showed an increasing trend in relation to vaccination coverage, despite a slight decline in rates from 2015 (Figure 1(a) and Table 1). The North, Northeast, and Central-West regions showed the largest increases in vaccination, with increases of 6.6%, 5.2%, and 5.4%, respectively. All states showed an increasing trend from 2006 to 2018, excepting the Federal District (APC: 1.8%; 95% CI: −1.2% to 4.9%; P = 0.2), which had a stable trend in vaccination coverage.

A total of 46,292 diarrhea-related hospitalizations of children less than 5 years old were recorded from 2006 to 2018. The hospitalization rates ranged from 68.4 hospitalizations per 10,000 children under 5 years-old in 2006 to 32.5 in 2018, resulting a 52.5% reduction in hospitalizations (APC: −5.7%; 95% CI: −7.5% to −3.8%; P < 0.001) (Figure 1(b) and Table 2). Diarrhea hospitalization rates decreased significantly in all Brazilian regions, with the largest reductions observed in the West Central (APC: −7.9%; 95% CI: −10.7% to −5.8%; P < 0.001) and Northeast (APC: −7.1%; 95% CI: −9.0% to −5.2%; P < 0.001) regions and the smallest reductions in the North region (APC: −2.9%; 95% CI: −4.8% to −1.0%; P: 0.006). Nearly all Brazilian states had decreasing hospitalization trends. Three states in the North region (Acre [APC: 6.7%; 95% CI: −6.1% to 21.3%; P: 0.3], Amazonas [APC: 0.1%; 95% CI: −2.4% to 2.7%; P: 0.9] and Roraima [APC: 0.4%; 95% CI: −4.9% to 5.9%; P: 0.9]) and one state in the Northeast region (Maranhão [APC: −0.3%; 95% CI: −2.7% to 2.1%; P: 0.8]) showed a stable trend. One state in the North region (Tocantins [APC: 4.7%; 95% CI: 0.7 to 8.8;

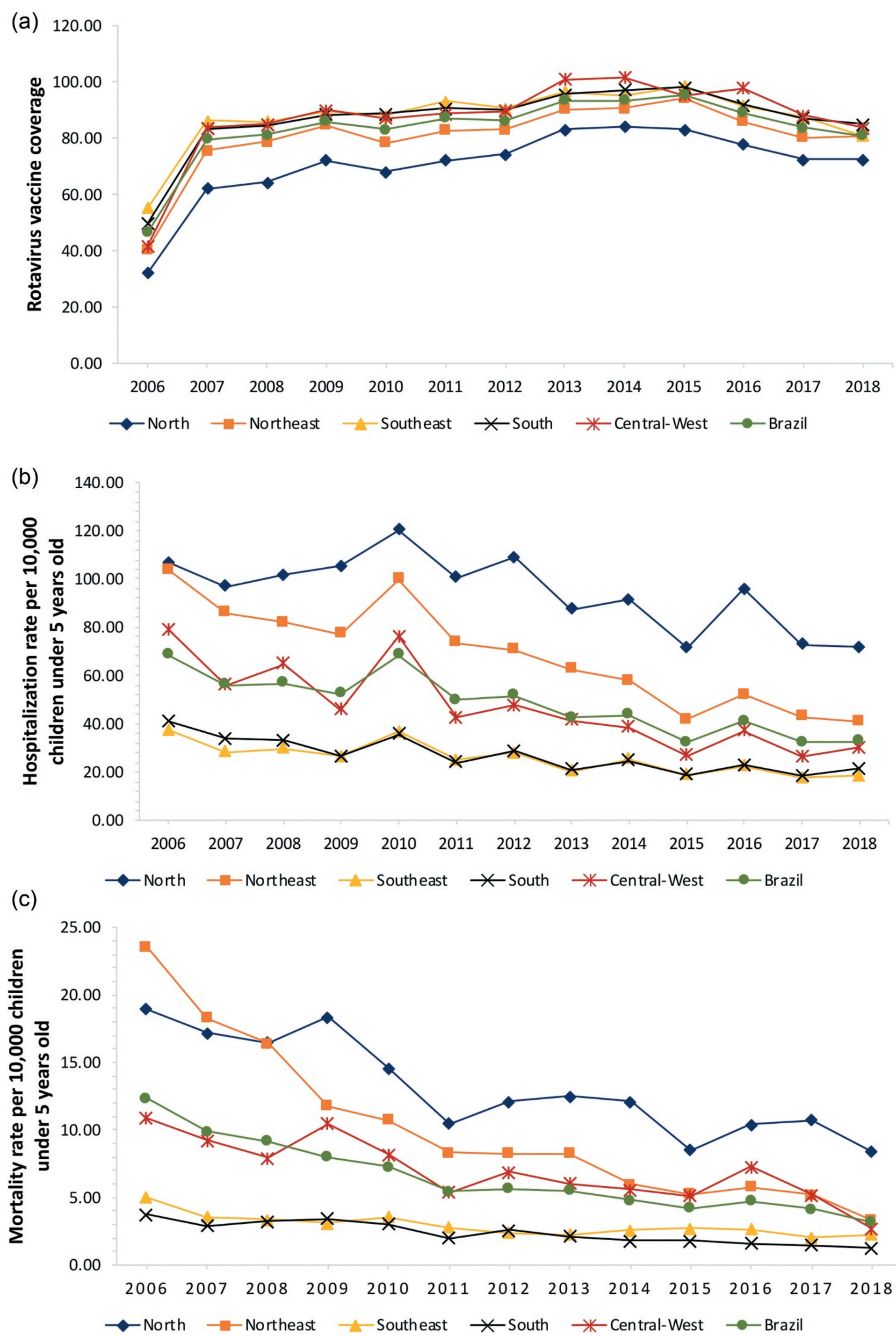

Figure 1. (a) rotavirus vaccine coverage, acute diarrhea (b) hospitalization, and (c) mortality in Brazil from 2006 to 2018.

$P < 0.001$]) and one state in the Northeast region (Ceará [APC: −4.2%; 95% CI: 6.1 to −2.2; $P < 0.001$]) had an increasing trend (Table 2 and Figure 2(a)).

There was a total of 11,137 diarrhea-related deaths in children under 5 years-old over the study period. The mortality rate ranged from 3.2 to 12.0 deaths per 10,000 children under 5 years old, with the highest and lowest rates observed in 2006 and 2018, respectively (Figure 1(c)). Overall, there was a statistically significant decrease in mortality (APC: −9.8%; 95% CI: −11.2% to −8.5%; $P < 0.001$), with the largest reductions occurring in the Northeast (APC: −13.9%; 95% CI: −15.7% to −12.2%; $P < 0.001$) and the South Regions (APC: −8.2%; 95% CI: −9.9% to −6.4%; $P < 0.001$) (Table 2). All states in the Northeast and South regions had decreasing mortality rate trends, while five of seven states in the North, three of four in the Southeast and three of four in the Central-West regions had stable trends (Table 2 and Figure 2(b)).

Table 1. Joinpoint regression analysis of rotavirus vaccine coverage in children under 5 years old from 2006 to 2018.

Region	Period	Rotarix vaccine coverage			Trend
		APC	95% CI	P-value	
North	2006–2018	6.6	13.2 to 2.1	<0.001	Increasing
Rondônia	2006–2018	3.4	1.1 to 5.7	<0.001	Increasing
Acre	2006–2018	11.9	8.9 to 15.1	<0.001	Increasing
Amazonas	2006–2018	5.2	2.5 to 7.9	<0.001	Increasing
Roraima	2006–2018	7.1	3.8 to 10.5	<0.001	Increasing
Pará	2006–2018	7.8	2.9 to 12.9	<0.001	Increasing
Amapá	2006–2018	6.5	1.7 to 11.5	<0.001	Increasing
Tocantins	2006–2018	4.6	2.5 to 6.8	<0.001	Increasing
Northeast	2006–2018	5.2	0.5 to 10.2	<0.001	Increasing
Maranhão	2006–2018	7.0	2.3 to 12.0	<0.001	Increasing
Piauí	2006–2018	5.3	2.8 to 7.9	<0.001	Increasing
Ceará	2006–2018	7.0	4.5 to 9.5	<0.001	Increasing
Rio Grande do Norte	2006–2018	6.4	1.9 to 11.1	<0.001	Increasing
Paraíba	2006–2018	2.4	0.5 to 4.3	<0.001	Increasing
Pernambuco	2006–2018	5.7	2.4 to 9.0	<0.001	Increasing
Alagoas	2006–2018	8.4	5.0 to 11.8	<0.001	Increasing
Sergipe	2006–2018	3.5	0.7 to 6.4	<0.001	Increasing
Bahia	2006–2018	4.9	1.1 to 8.8	<0.001	Increasing
Southeast	2006–2018	2.3	1.3 to 3.2	<0.001	Increasing
Minas Gerais	2006–2018	3.5	1.4 to 5.7	<0.001	Increasing
Espírito Santo	2006–2018	2.9	0.4 to 5.5	<0.001	Increasing
Rio de Janeiro	2006–2018	4.7	0.9 to 8.6	<0.001	Increasing
São Paulo	2006–2018	3.6	1.8 to 5.4	<0.001	Increasing
Central-West	2006–2018	5.4	0.3 to 10.9	<0.001	Increasing
Mato Grosso do Sul	2006–2018	3.3	0.6 to 5.9	<0.001	Increasing
Mato Grosso	2006–2018	8.8	5.7 to 11.8	<0.001	Increasing
Goiás	2006–2018	7.0	3.9 to 10.3	<0.001	Increasing
Distrito Federal	2006–2018	1.8	−1.2 to 4.9	0.20	Stable
South	2006–2018	4.2	0.1 to 8.5	<0,001	Increasing
Paraná	2006–2018	4.5	2.0 to 7.1	<0.001	Increasing
Santa Catarina	2006–2018	3.8	1.3 to 6.3	<0.001	Increasing
Rio Grande do Sul	2006–2018	5.1	2.9 to 7.4	<0.001	Increasing
Brazil	4.4	4.4	−0.3 to 9.2	0.1	Stable

APC: annual percentage change

The distribution of the SVI by state is shown in Figure 3. The SVI was inversely associated with the state vaccination coverage (coefficient: −85.4; P < 0.001)., while there was no association between HDI and state vaccination coverage. There also were no associations between the SVI or the HDI and the hospitalization and mortality rates. Further sub-analysis of individual domains of the SVI identified that the urban infrastructure (coefficient: −26.4; P = 0.02) and human capital (coefficient −84.1; P = 0.009) domains were inversely associated with vaccination coverage, while the human capital (coefficient 119.0; P < 0.001) and income and work (coefficient: 87.2; P < 0.001) domains were directly associated with the mortality rates. There were no associations between the domains and hospitalization rates (Table 3).

Similarly, a sub-analysis of the individual components of both the HDI and SVI identified seven indicators associated with vaccine coverage, including the percentage of children aged 0–5 and 6–14 years old not attending school, the proportion of the population with household income per capita ≤ half the 2010 minimum wage, the education index, the percentage of adults with complete elementary school, low income among individuals at work and the Gini index. Two components were also associated with mortality (the percentage of employers aged ≥18 years-old and the degree of formalization of employees ≥18 years old) nut no components were associated with the hospitalization rates. Rotavirus vaccine coverage, diarrhea hospitalizations, and mortality did not have a geographic association. The regression model indicated high vaccine coverage was directly associated with lower diarrhea mortality (coefficient −0.601948; P = 0.031) but not with diarrhea hospitalization rates (coefficient −0.00571481; P = 0.26).

4. Discussion

The introduction of rotavirus vaccination represented a step change in our ability to prevent acute diarrhea and to reduce infant morbidity and mortality. Rotavirus, historically a pathogen responsible for most severe cases of acute gastroenteritis in children under 5 years old, often represented 40%-50% of acute diarrhea hospitalizations and consultations to emergency services before the immunization era [18,19] and their impact on diarrhea hospitalizations and mortality was reported soon after their large-scale introduction [5,7,20–23]. Although the effectiveness of the rotavirus vaccine on the burden of diarrheal disease has already been reported [4,21,24], the assessment of the continued effectiveness of the rotavirus vaccination program after a prolonged period of implementation is necessary to confirm that vaccine efficacy has not changed over the years and that rotavirus incidence continues to be low, as other potential pathogens could have filled the ecological niche left empty by rotaviruses or the emergence of vaccine escapees.

Our study includes information of an uninterrupted twelve-year mass vaccination program with a cohort of *circa* 3.0 million live births eligible for vaccination for each year. Our analysis identified a stable trend in vaccination coverage and substantial reductions in diarrhea-related hospitalizations and deaths in Brazil. Despite the slight decline in vaccination coverage in all regions from 2015 to 2018, vaccine coverage rates still remaining above 80%. Diarrhea-related hospitalizations and mortality have continued to decrease throughout both periods, suggesting that diarrhea reduction follows a long term decreasing trend that started before the advent of the vaccines [21–23,25]. The 62% and 74% reductions in childhood diarrhea hospitalizations and deaths occurring in the study period have invariable been attributed to the Rotavirus vaccines. However, similar reductions had occurred in other Latin American countries, which are attributed to water and sanitation and nutritional improvements, with decreases in all-cause diarrhea hospitalizations and deaths before and after vaccine introduction [21]. Rotavirus is transmitted from person-to-person mainly via fecal-oral route and, in settings with well-established urban and sanitation infrastructure, rotavirus is responsible for about 10% of episodes of acute diarrhea [9,26,27], suggesting that environmental control measures alone are insufficient to stop transmission [28–30]. Effective control, therefore, requires a multi-pronged approach and the reduction in the incidence of acute diarrhea after vaccine introduction is likely to have benefited from the synergistic effect of the long-term environment and sanitation improvements.

The slight decrease in rotavirus vaccine coverage since 2015 coincided with the decline of other vaccines in the country [31]. This was due, in part, to the misinformation spread through

Table 2. Joinpoint regression analysis of hospitalization and mortality rates in children ≤5 years old due to infectious diarrhea in Brazil from 2006 to 2018.

		Hospitalization rate				Mortality rate			
Region	Period	APC	95% CI	P-value	Trend	APC	95% CI	P-value	Trend
North	2006–2018	−2.9	−4.8 to −1.0	0.006	Decreasing	−6.2	−8.0 to −4.4	<0.001	Decreasing
Rondônia	2006–2018	−6.9	−9.3 to −4.5	<0.001	Decreasing	−4.4	−10.8 to 2.4	0.2	Stable
Acre	2006–2018	6.7	−6.1 to 21.3	0.3	Stable	−3.0	−3.2 to 9.5	0.3	Stable
Amazonas	2006–2018	0.1	.2.4 to 2.7	0.9	Stable	−1.2	−4.4 to 2.2	0.5	Stable
Roraima	2006–2018	0.4	−4.9 to 5.9	0.9	Stable	−6.6	−20.2 to 9.5	0.4	Stable
Pará	2006–2018	−3.0	−4.7 to −1.3	<0.001	Decreasing	−11.1	−14.5 to −7.6	<0.001	Decreasing
Amapá	2006–2018	−5.0	−9.3 to −0.5	<0.001	Decreasing	−1.5	−11.4 to 9.5	0.8	Stable
Tocantins	2006–2018	4.7	0.7 to 8.8	<0.001	Increasing	−9.7	−16.8 to −2.0	<0.001	Decreasing
Northeast	2006–2018	−7.1	−9.0 to −5.2	<0.001	Decreasing	−13.9	−15.7 to −12.2	<0.001	Decreasing
Maranhão	2006–2018	−0.3	−2.7 to 2.1	0.8	Stable	−14.0	−17.0 to −10.8	<0.001	Decreasing
Piauí	2006–2018	−6.0	−8.0 to −3.8	<0.001	Decreasing	−13.8	−18.8 to −8.4	<0.001	Decreasing
Ceará	2006–2018	−4.2	6.1 to −2.2	<0.001	Increasing	−11.5	−16.1 to −6.7	<0.001	Decreasing
Rio Grande do Norte	2006–2018	−7.9	−10.8 to −5.0	<0.001	Decreasing	−7.9	−14.8 to −0.4	<0.001	Decreasing
Paraíba	2006–2018	−9.5	−12.3 to −6.6	<0.001	Decreasing	−24.1	−31.1 to −16.3	<0.001	Decreasing
Pernambuco	2006–2018	−11.6	−13.9 to −9.3	<0.001	Decreasing	−13.5	−16.8 to −8.4	<0.001	Decreasing
Alagoas	2006–2018	−12.2	−14.1 to −10.4	<0.001	Decreasing	−14.7	−19.3 to −9.9	<0.001	Decreasing
Sergipe	2006–2018	−9.6	−16.5 to −2.1	<0.001	Decreasing	−12.3	−16.9 to −7.5	<0.001	Decreasing
Bahia	2006–2018	−10.0	−11.7 to 8.2	<0.001	Decreasing	−13.2	−16.7 to −9.6	<0.001	Decreasing
Central-West	2006–2018	−7.9	−10.7 to −5.8	<0.001	Decreasing	−6.8	−9.7 to −3.8	<0.001	Decreasing
Mato Grosso do Sul	2006–2018	−4.1	−6.6 to −1.6	<0.001	Decreasing	−12.5	−17.9 to −6.7	<0.001	Decreasing
Mato Grosso	2006–2018	−5.6	−8.5 to −2.5	<0.001	Decreasing	−2.0	−6.5 to 2.6	0.3	Stable
Goiás	2006–2018	−11.4	−14.4 to −8.3	<0.001	Decreasing	−1.6	−7.2 to 11.3	0.7	Stable
Distrito Federal	2006–2018	−7.2	−11.5 to −2.7	<0.001	Decreasing	−10.8	−20.7 to 0.2	0.1	Stable
Southeast	2006–2018	−5.2	−7.4 to −3.0	<0.001	Decreasing	−5.8	−7.9 to −3.7	<0.001	Decreasing
Minas Gerais	2006–2018	−6.7	−9.4 to −3.9	<0.001	Decreasing	−8.3	−14.4 to −1.7	<0.001	Decreasing
Espírito Santo	2006–2018	−3.1	−5.6 to −0.5	<0.001	Decreasing	−7.3	−14.4 to 0.4	0.1	Stable
Rio de Janeiro	2006–2018	−9.0	−11.7 to −6.1	<0.001	Decreasing	−3.8	−9.8 to 2.6	0.2	Stable
São Paulo	2006–2018	−4.3	−6.1 to −2.6	<0.001	Decreasing	−7.2	−12.0 to −2.2	0.0	Stable
South	2006–2018	−5.75	−7.7 to −6.3	<0.001	Decreasing	−8.2	−9.9 to −6.4	<0.001	Decreasing
Paraná	2006–2018	−4.1	−6.4 to −1.8	<0.001	Decreasing	−12.2	−18.3 to −5.7	<0.001	Decreasing
Santa Catarina	2006–2018	−4.1	−6.2 to −2.0	<0.001	Decreasing	−8.4	−15.9 to −0.2	<0.001	Decreasing
Rio Grande do Sul	2006–2018	−11.4	−17.5 to −4.9	<0.001	Decreasing	−7.1	−11.4 to −2.5	<0.001	Decreasing
Brazil	2006–2018	−5.7	−7.5 to −3.8	<0.001	Decreasing	−9.8	−11.2 to −8.5	<0.001	Decreasing

APC: annual percentage change

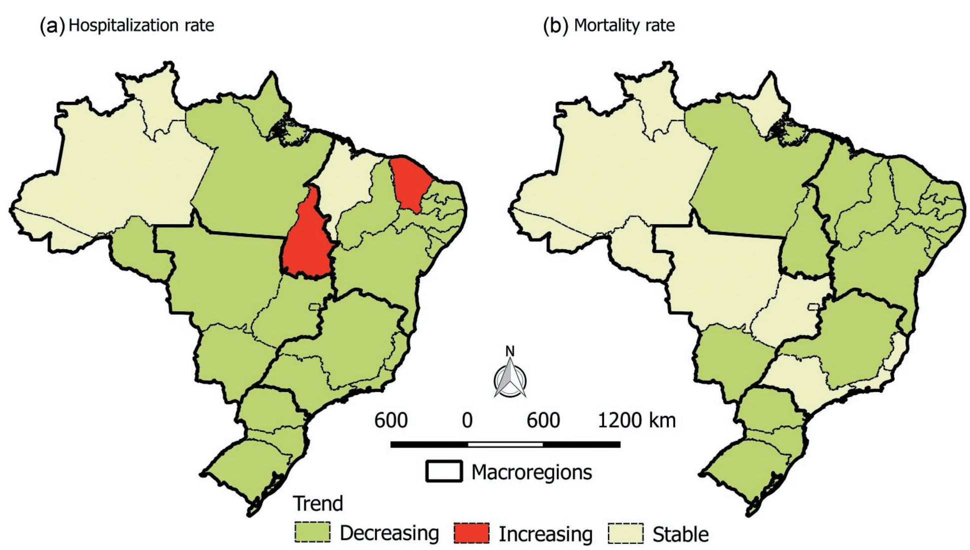

Figure 2. Distribution of the trend of the indicators of (a) hospitalization and (b) mortality by Brazilian state.

social media [32], as caregivers of unvaccinated children believe misinformation of the role of the vaccines and fear adverse events, with 67% believing at least one factually inaccurate vaccine statement. The main source of misinformation is messaging apps and low income and low education population groups are more likely to believe false news [32].

Recent reviews of the causes and contributing factors for the low Rotavirus vaccine performance in low- and middle-income countries (LMIC) reported that enteric pathogens, malnutrition, microbiota dysbiosis, and environmental enteropathy [33,34], the passive transfer of Immunoglobin antibodies through maternal milk [34,35] and the concomitant use of

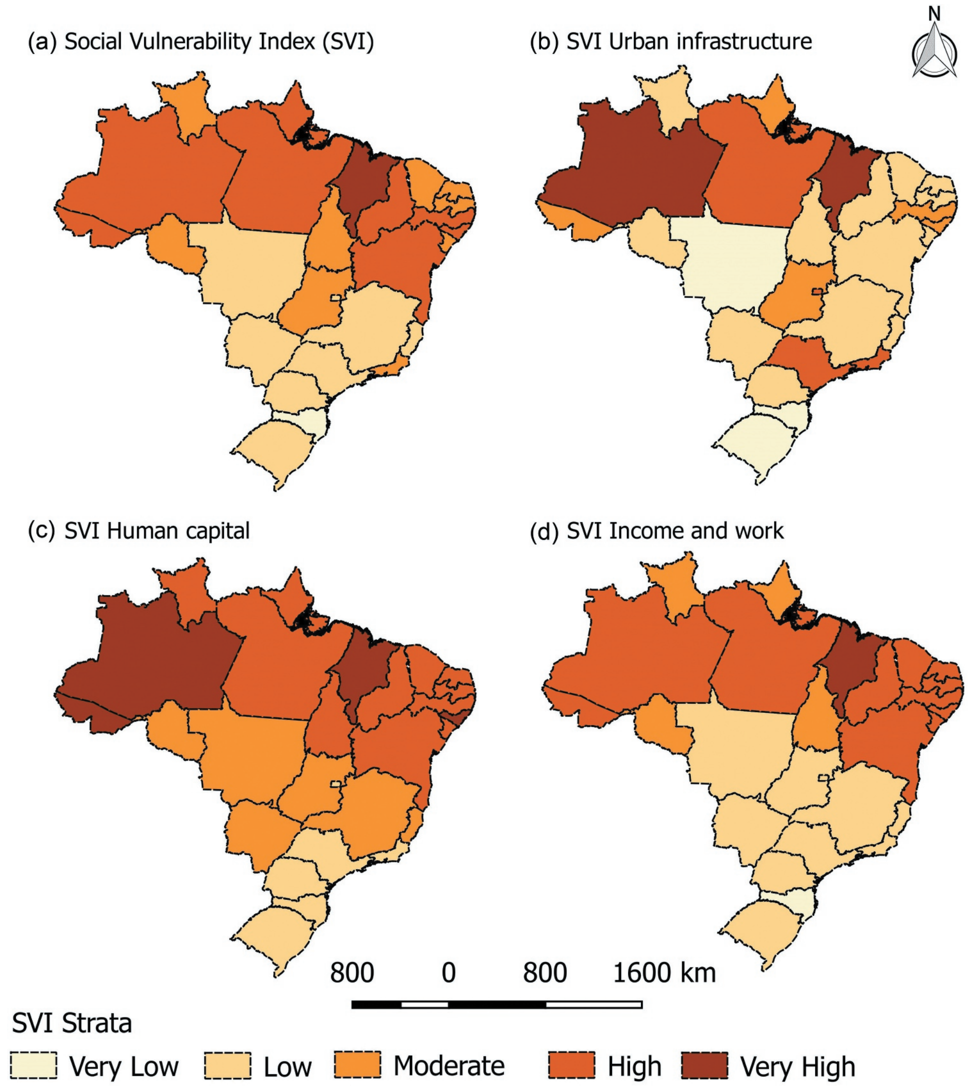

Figure 3. Distribution of the Social Vulnerability Index (SVI) and their SVI domains by Brazilian state.

Rotavirus and Polio oral vaccines could reduce vaccine efficacy [35]. These two last factors however may not play a significant role in Brazil, as only about one-third of the mothers breast-feed exclusively their infants up to 6 months [36] of age and mothers may have a lower concentration of immunoglobulins because of the low Rotavirus prevalence in recent years. Moreover, in 2012 Brazil replaced the oral Polio vaccines for the inactivated Polio vaccine for the two first doses, at 2 and 4 months of age, which would have removed any possible interference.

Our findings are unique in establishing an association between the SVI, rotavirus vaccination coverage, and mortality, with the worst socioeconomic indicators associated with lower vaccination coverage and increased mortality. Although all regions of the country experienced reductions in hospitalizations and mortality rates, these reductions were less steep in the South and Southeast regions, which have the best social and economic indicators, than the Northeast region, with the worst social and economic conditions. This was unexpected as the rotavirus vaccine has been shown to be more effective in high-income countries than in LMIC [6,21]. The Northeast region of Brazil had the highest decline in hospitalization rates and the second highest decline in deaths, suggesting regions with severe socioeconomic deprivation benefitted considerably more from the high vaccine coverage rates.

Although we only have anecdotical evidence, factors that affect low vaccine efficacy, as malnutrition and breast milk [33,34] may play a less prominent role in Brazil. For example, undernutrition is less common and has been replaced by obesity, while breastfeeding is less common among younger generations, and the prevalence of other infections such as malaria has largely been eliminated except than the Amazonian region.

In the North region, which has poor socio-economic indicators and living conditions, the reduction in hospitalization rates was lower than expected, as the region has similar social and economic indicators than the Northeast. Factors that could play a role are the higher number of villages without primary health-care services, which may hinder disease prevention, awareness of hygiene practices and vaccine use and reduce the opportunities for vaccination [37,38]. Conversely, this region achieved significant reductions in mortality,

Table 3. Spatial lag model between rotavirus vaccine coverage, hospitalization and mortality rates and socioeconomic indicators, Brazil, 2006–2018.

	Rotavirus-vaccine coverage		Hospitalization		Mortality	
Social determinants	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value
Block 1- Synthetic indicators of social vulnerability and human development						
Constant	127.8	0.00133	2611.73	0.11596	−6.94113	0.83779
Social Vulnerability Index (SVI)	−85.4	0.00150	219.237	0.84140	27.7111	0.23402
Human Development Index (HDI)	−21.3	0.59612	−3069.29	0.10206	4.15583	0.91340
Block 2- Social Vulnerability Index domains						
Constant	112.7	0.00000	−42.3172	0.86962	−9.79261	0.00748
SVI Urban infrastructure	−26.4	0.02007	53.5585	0.92156	−5.16754	0.47068
SVI Human capital	−84.1	0.00872	31.6206	0.98326	119.017	<0.0001
SVI Income and work	33.4	0.23449	1510.22	0.28921	87.2292	<0.0001
Block 3- Human Development Index (HDI) domains						
Constant	5.46	0.94135	799.415	0.76471	38.8407	0.51398
HDI Longevity	57.3	0.71244	3174.47	0.57043	−30.7117	0.80413
HDI Education	64.7	0.32833	−3981.12	0.10066	−11.9713	0.81883
HDI Income	−12.5	0.87685	−567.55	0.84515	−1.21521	0.98496
Block 4- SVI Urban Infrastructure indicators						
Constant	85.3	0.00000	673.581	0.00050	10.1865	0.00329
% of people in households with inadequate water supply and sewage	85.3	0.13407	4.68223	0.62016	−0.0297418	0.86566
% of population living in urban households without garbage collection service	0.54	0.28477	−10.8064	0.55782	−0.307157	0.37420
% of people living in households with a per capita income below half the minimum wage (in 2010) and spending more than an hour to work	−0.14	0.28477	−15.4313	0.22589	−0.292306	0.21902
Block 5- SVI Human Capital indicators						
Constant	93.1	0.00001	743.542	0.28728	−5.41726	0.66301
Infant mortality	−0.9	0.32422	−22.063	0.59359	−0.383776	0.60663
% of children aged 0–5 years-old who not attending school	−0.2	0.00566	−9.85047	0.49194	0.468188	0.08094
% of people aged 6–14 years-old who not attending school	−5.9	0.00239	82.5062	0.26334	1.86167	0.16571
% of women aged 10–17 years-old who had children	8.9	0.05355	−206.815	0.27770	−5.24612	0.13277
% of mothers who are heads of household, who complete elementary school and with child under 15 years-old	0.6	0.39341	39.6639	0.20164	−0.0705729	0.89741
Illiteracy rate of population aged ≥15 years-old.	0.4	0.70778	10.3425	0.79816	0.461057	0.52921
% of children living in households where none of the residents have completed elementary school	0.03	0.94177	20.7857	0.34526	−0.0747096	0.84897
% of people aged 15–24 years-old who do not study, do not work and have a per capita household income equal to or less than half the minimum wage (in 2010)	−0.5	0.62626	−32.8931	0.43852	−0.0903655	0.90527
Block 6- SVI Income and work indicators						
Constant	86.5	0.00004	570.175	0.43545	12.6567	0.30911
Proportion of persons with per capita household income equal to or less than half the minimum wage (in 2010)	0.9	0.04565	11.2683	0.58579	0.331953	0.34657
Population unemployment rate of persons aged ≥18 years-old	−0.9	0.43090	−46.3278	0.46675	−1.28536	0.23802
% of people aged ≥18 year-old without elementary school	−0.2	0.77779	7.46703	0.76941	0.00742866	0.98625
% of people in households with per capita income below half the minimum wage (in 2010) and dependent on the elderly	10.4	0.36700	−84.0648	0.67560	−3.5623	0.30027
Occupancy rate of people aged 10–14 years-old	0.3	0.81915	−22.081	0.71499	−0.037787	0.97051
Block 7- HDI Longevity						
Constant	43.4	0.52029	1680.54	0.49548	−48.9212	0.28382
Life expectancy at birth	0.5	0.56202	−15.6899	0.63898	0.744588	0.23166
Block 8- HDI Education						
Constant	10.7	0.89965	2277.05	0.54515	41.437	0.43625
Education index	13,528.7	0.03014	73,417.2	0.77532	−4065.91	0.26951
% of people aged ≥18 years-old who completed elementary school	−135.5	0.03036	−757.163	0.76914	40.5458	0.27213
School attendance index	1228.5	0.84147	−274,395	0.31547	−1753.9	0.64546
% of children aged 5–6 years-old in school	−2.3	0.87932	682.017	0.31715	3.65387	0.70054
% of children ages 11–13 years-old in the final years of elementary school or with complete fundamental	−3.2	0.83194	671.266	0.31158	4.9008	0.59654
% of people aged 15–17 years-old with complete elementary school	−2.7	0.85969	703.6	0.30556	3.85336	0.68705
% of people aged 18–20 years-old with complete high school	−3.0	0.84949	688.111	0.32789	4.9418	0.61482
Block 9 – HDI Income						
Constant	81.4	0.00000	629.85	0.00045	2.82477	0.33918
Per capita income	0.0	0.78223	−0.147384	0.48379	0.00429165	0.27583
Block 10 – Other indicators of social vulnerability and human development						
Constant	1144.5	0.19771	8281.55	0.84635	468.917	0.35389
Illiteracy rate in people aged ≥18 years-old.	−25.3	0.18639	−154.647	0.86620	5.8621	0.58400
Illiteracy rate in people aged ≥25 years-old	19.4	0.21869	194.201	0.79896	−4.37245	0.62214
Per capita income of those vulnerable to poverty	−0.5	0.44745	−12.1334	0.69852	−0.247088	0.49933
% income due to personal work	−0.5	0.03955	−3.16924	0.96141	0.0489985	0.94850
Gini index	−462.3	0.01804	4882.62	0.67614	−70.072	0.60560
% of employees aged ≥18 years-old in formal work	2.8	0.74408	−235.351	0.58884	−9.37376	0.08377
% of employees aged ≥18 years-old in unformal work	−3.3	0.67812	−140.696	0.72681	−3.83863	0.41708
% of workers aged ≥18 years-old in public sector	2.8	0.75321	−215.507	0.62853	−8.4125	0.12348
% of self-employed workers aged ≥18 years-old	−4.00	0.62396	−137.78	0.73628	−4.45832	0.35609
% of employers aged ≥18 years-old	16.0	0.20658	−100.368	0.86945	−18.3372	0.02390

(*Continued*)

Table 3. (Continued).

Social determinants	Rotavirus-vaccine coverage		Hospitalization		Mortality	
	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value
Degree of formalization of the employed aged ≥18 years-old	−7.5	0.05149	127.906	0.46685	5.19898	0.02412
% of employed with complete elementary school aged ≥18 years-old	−3.8	0.20253	131.483	0.37017	−0.145139	0.93050
% of employed with complete high school aged ≥18 years-old	3.8	0.18161	−129.217	0.35040	0.425746	0.78618
% of employed with undergraduate aged ≥18 years-old	0.3	0.92545	−80.0032	0.56394	−2.41423	0.15105
Average income of employed persons aged ≥18 years-old	0.0	0.55681	0.626465	0.67693	0.0262186	0.15203
% of employed persons without income aged ≥18 years-old	−3.6	0.61685	−149.88	0.67306	−4.47391	0.28883

possibly due to the vaccine preventing the most severe cases of acute diarrhea, if not hospitalizations. Similar findings have been reported from studies on vaccine effectiveness in other LMIC [8,39,40].

Despite the substantial gains in recent years, Brazil still has considerable diarrhea hospitalization and mortality rates in regions with high SVI. The high hospitalization rates may be explained by the diversity of pathogens co-circulating with rotavirus and, potentially, variations in rotavirus strains. Norovirus incidence has increased among children presenting to emergency pediatric services, especially in highly vaccinated rotavirus populations [41–43]. In addition, rotavirus genotypes have changed significantly in recent decades, with an unusual increase of strains heterotypic to the monovalent Rotavirus vaccine, which elicits a slightly lower protection against fully heterotypic strains [25].

Our study has several limitations. Data were obtained from routine information systems and represent information on patients who sought treatment and were reported, and thus children with mild diarrhea episodes and those not seeking health services are under-represented, generating potential bias. Secondary data in ecological studies are also unsuitable to establish disease causality, and therefore, the study only provides evidence of statistical associations and limits the possibility of exploring confounders. In addition, the data reported refer to cases of acute diarrhea without a defined etiology.

5. Conclusion

Brazil is an excellent example of a successful and large-scale rotavirus vaccination program, with its free provision of vaccines and high vaccination coverage rates in a large cohort of children. Despite the country's major social and economic disparity and inequity, hospitalization and mortality rates in children have reduced in all regions. Conversely, our findings also highlight the influence of social vulnerability on rotavirus vaccine coverage and mortality, with the worst socioeconomic indicators occurring in areas with low vaccination coverage and with lower reductions in mortality. The lower vaccine coverage observed in the last 3 years has not resulted in increases on diarrhea mortality or hospitalizations but highlights the need for continued surveillance and the need to implement new strategies to increase immunization coverage.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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