



Impact of rotavirus vaccination on childhood deaths from diarrhea in Brazil

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SUMMARY

Objectives: Rotavirus vaccination was introduced in Brazil in March 2006, targeting an annual birth cohort of approximately 3.5 million. We analyzed trends in all-cause gastroenteritis-related deaths in children <5 years of age during the pre- and post-vaccination periods.

Methods: Data from the National Immunization Program and the Mortality Information System were used to calculate vaccine coverage and mortality rates related to gastroenteritis in children <1 year and 1–4 years of age, using population estimates from the census as the denominator. Relative reductions in mortality rates were calculated for 2007 and 2008, using the 2004–2005 mean as baseline before vaccine introduction.

Results: Coverage of two doses of human rotavirus vaccine was 39% in 2006, increasing to 72% in 2007 and 77% in 2008. During 2004–2005, the gastroenteritis mortality rate in children <1 year of age was 56.9 per 100 000, decreasing by 30% (95% confidence interval (CI) 19–41) in 2007 and by 39% (95% CI 29–49) in 2008. In children 1–4 years of age, the mortality rate was 4.5 per 100 000 during 2004–2005, decreasing by 29% (95% CI 10–49) in 2007 and by 33% (95% CI 15–52) in 2008.

Conclusions: The decreased rates of childhood gastroenteritis-related deaths in Brazil following rotavirus vaccine introduction, particularly among children <1 year of age, suggest the potential benefit of vaccination.

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1. Introduction

Rotavirus infection remains the most common cause of severe, dehydrating gastroenteritis among children worldwide. Almost every child in the world, in both developed and developing countries, will be infected with rotavirus in the first 5 years of life. Approximately 611 000 childhood deaths annually are caused by rotavirus, most of them in developing countries.¹ Since only non-specific symptomatic therapies are available, prevention by vaccination is considered to be critical for effective control of rotavirus infection and may have a significant impact on the incidence of severe dehydrating rotavirus disease.¹

With the widespread use of oral rehydration therapy strategies, deaths from diarrhea have declined substantially in the developing world. Diarrhea morbidity has not had a concomitant decrease, with an estimated 3–5 billion cases of diarrhea occurring worldwide each year, mostly among children.^{2,3} In Brazil, declining trends in gastroenteritis-related mortality associated with the

increased use of oral rehydration therapy were observed in the 1980s and 1990s.⁴ Nonetheless, diarrhea remains an important cause of childhood morbidity and mortality, with rotavirus infections estimated to cause approximately 3.5 million diarrhea episodes, 655 853 outpatient visits, 92 453 hospitalizations, and 850 deaths each year in children aged ≤5 years, before vaccine introduction.⁵

Brazil was one of the first Latin American countries to include the human rotavirus vaccine into the expanded program on immunization in March 2006. A marked decline in the number of all-cause gastroenteritis hospitalizations among children aged <1 year was observed one year after vaccine introduction.^{6–8} In this study, we analyzed the trends in all-cause gastroenteritis-related mortality among children aged <5 years in Brazil before and after implementation of rotavirus vaccination.

2. Methods

2.1. Vaccine coverage

The number of first and second doses of rotavirus vaccine administered are recorded at the local level by primary health care

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workers, entered into the National Immunization Program database at the municipal level and transmitted electronically to the state and national level. The numbers for both the first and second doses and vaccine coverage are available at the National Unified Health System Database (DATASUS) website and data can be tabulated by municipality, state, region, and year. From the year 2000, the National Immunization Program started using the number of live births as recorded in the Live Birth Information System (SINASC) for vaccine coverage calculations. Whereas the coverage of SINASC has increased from 75% (range 55–102) in 1994 to 92% (range 84–100) in 2006, underreporting of live births still occurs, with the lowest coverage in the Northeast region.⁹ In addition, SINASC data used as the denominator for vaccine coverage calculations are generally from the birth cohort of the two previous years. In this study, we chose to use the census estimates for the population aged <1 year and 1–4 years to calculate rotavirus vaccine coverage for the first and second dose from 2006 to 2008, to estimate the cumulative proportion of children who had received rotavirus vaccination each year.

2.2. Mortality data

The Brazilian Ministry of Health is responsible for maintaining mortality data based on death certificates. The Mortality Information System (Sistema de Informação de Mortalidade – SIM) contains data for primary cause of death obtained from death certificates, and using the International Classification of Diseases (ICD), 10th Revision (since 1998). Data collected from death certificates are recorded and analyzed for consistency at the municipal level, transmitted electronically to the state and national level, and made available for direct tabulation on the DATASUS website. Annual databases usually take up to two years to be finalized. The coverage of the SIM is calculated based on the number of observed deaths (reported to the system) divided by the number of expected deaths (based on census projections) for all ages and for the age group <1 year. From 1991 to 2006, the coverage increased from 78% to 89% overall and from 56% to 72% in the age group <1 year. By 2006, the coverage had increased in all regions, reaching $\geq 85\%$, except the Northeast region, where only 54% of expected deaths in children <1 year were reported.⁹

We obtained data on all-cause gastroenteritis-related deaths among children <5 years of age during 1998–2008 from the Mortality Information System using the codes A00 to A09 of the ICD 10th Revision. Annual rates of all-cause gastroenteritis-related mortality were calculated using the population estimates from the census as a denominator. The mean rate of all-cause gastroenteritis-related mortality during 2004–2005 was used as baseline to compare with post-vaccination years 2007 and 2008. This baseline period was chosen because a declining trend was already in evidence for the past decades and would artificially increase the presumed impact of vaccination. We considered 2006 a transitional year and excluded it from the analysis because vaccination was introduced during this year and coverage was suboptimal. Analysis was stratified according to age groups <1 year and 1–4 years and by region. The absolute and relative reduction in deaths and mortality rate were calculated, with 95% confidence intervals.¹⁰ Analysis was performed using SAS statistical software, version 9.1 and Microsoft Excel.

3. Results

3.1. Vaccine coverage

From March 2006 to December 2008, more than 13.5 million doses of human rotavirus vaccine were administered to children

<1 year of age, 56% as first doses and 44% as second doses. Coverage of one dose of human rotavirus vaccine was 60% in 2006, 85% in 2007, and 90% in 2008. Lower vaccine coverage was observed for the second dose: 39% in 2006, 72% in 2007, and 77% in 2008. In 2008, an estimated 38% of the population 1–4 years of age had received one vaccine dose, with 28% having received two doses. Vaccine coverage varied by region, being highest in the South and Southeast regions, where the coverage of the second dose reached 88% and 84% in 2008, respectively, and remained the lowest in the North (66%) and Northeast (69%) regions. All regions achieved over 80% vaccine coverage for the first dose in 2008.

3.2. All-cause gastroenteritis-related mortality

Of 33 363 gastroenteritis-related deaths among children <5 years of age reported in Brazil during 1998–2008, 27 375 (82%) were in children <1 year of age. This age group has seen a marked decline in the number and rates of gastroenteritis-related deaths over the past decade (Fig. 1).

During 2004–2005, considered the baseline period before vaccine introduction, the mean number of gastroenteritis-related deaths observed in children <1 year was 1994 and in those aged 1–4 years was 516, of which 1185 (59%) and 231 (45%), respectively, occurred in the Northeast region. A reduction in the number of gastroenteritis-related deaths in children <1 year of age was observed in all regions in 2007 and 2008 (Fig. 2), by 36% (range 27–55) and 45% (range 37–64), respectively. The highest reduction rate in children <1 year of age was observed in the South region (54%) in 2008, whereas the absolute number of gastroenteritis-related deaths in the Northeast region fell from a mean of 1185 during 2004–2005 to 751 (by 37%) in 2007 and 661 (by 44%) in 2008. In children 1–4 years of age, gastroenteritis-related deaths decreased by 28% (range 15–48) in 2007 and by 34% (range 0–48) in 2008, with the highest reduction rates observed in the North and Mid-West regions.

The gastroenteritis-related mortality rate in children aged <1 year fell from a mean of 56.9 per 100 000 during 2004–2005, to 39.6 in 2007 and 35.0 in 2008, representing relative reductions of 30% (95% confidence interval (CI) 19–41) and 39% (95% CI 29–49), respectively. The highest mortality rates were observed in the Northeast region, with a mean of 112.4 per 100 000 during 2004–2005, decreasing by 35% (95% CI 29–41) in 2007 and by 42% (95% CI 37–48) in 2008 (Table 1). In children aged 1–4 years, the gastroenteritis mortality was 4.5 per 100 000 during 2004–2005, decreasing by 29% (95% CI 10–49) in 2007 and by 33% (95% CI 15–52) in 2008. The relative reduction in this age group was significant in both years only in the North and Mid-West regions (Table 1).

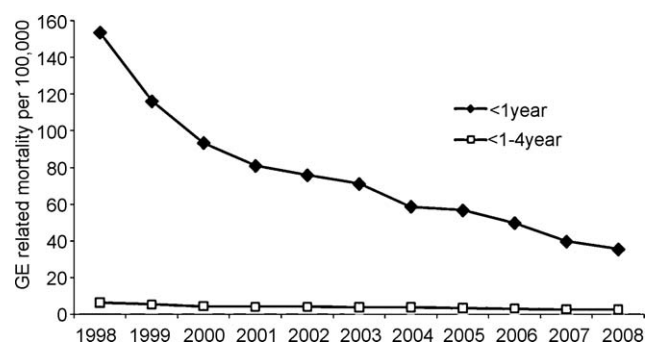


Fig. 1. Trends over time of gastroenteritis-related deaths by age group, Brazil, 1998–2008.

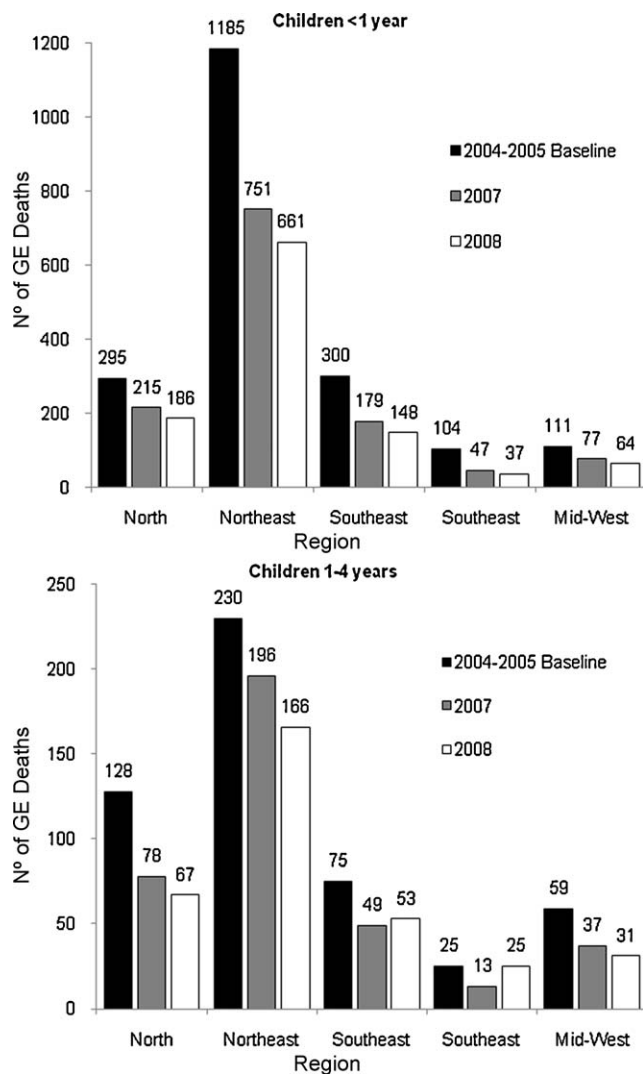


Fig. 2. Number of gastroenteritis deaths by region among children <1 and 1–4 years of age in 2007 and 2008 compared to the 2004–2005 baseline period, Brazil.

4. Discussion

Brazil introduced the human rotavirus vaccine into the childhood schedule in 2006 and uptake of the vaccine has increased over time. Although this was an ecological study and

decreasing mortality trends have been in evidence over the past decades, the introduction of rotavirus vaccination has likely contributed to the observed reduction in both absolute numbers and rates of mortality related to childhood gastroenteritis, particularly in children <1 year of age, in whom the highest mortality rates due to diarrheal diseases have been observed for the past decade.

In Brazil, the mortality rate from all-cause gastroenteritis in children <1 year of age nationwide decreased by 30–39% during 2007–2008 relative to 2004–2005, whereas the mortality rate from lower respiratory tract infections in children <1 year of age decreased by 12–16% in the same period.¹¹ The Brazilian Family Health Program has been successful in reducing childhood mortality, particularly due to diarrheal diseases and lower respiratory infections, through promotion of breastfeeding, immunization, and the prevention and treatment of infectious diseases. The strongest reductions in mortality due to diarrhea have been observed in municipalities with higher coverage of the Family Health Program during 2000–2005.¹² The continued expansion of such programs, reaching nearly half of the Brazilian population by 2007–2008,¹³ together with the increased coverage of the water supply and sewage systems and the overall increase in education level in the population >15 years of age,⁹ have had an important impact on childhood mortality rates, particularly due to infectious diseases and diarrhea. Nonetheless, the strongest reductions in mortality rates due to gastroenteritis in the South and Southeast regions, with the highest rotavirus vaccine coverage, also suggest the benefit of vaccination.

The gastroenteritis mortality rates in Brazil have varied greatly by region, being highest in the North and Northeast, which are the most impoverished regions in the country. The rates observed in the Northeast region were up to five times the rates observed in the South and Southeast regions. Several studies have indicated the importance of diarrheal diseases as a public health problem in the Northeast and the benefit of other health interventions in the last decades in reducing related deaths, such as the increased use of oral rehydration therapy, increased breastfeeding duration, better nutrition, improved water supply, hygiene and sanitation, and the implementation of the Family Health Program.^{4,14,15} Nonetheless, the burden of diarrheal diseases remains high in the region and is likely underestimated, since access to health care may be limited and nearly half of the expected deaths in children <1 year of age may not have been reported according to 2008 estimates.^{9,16}

Other studies in the state of Sergipe, Northeast Brazil, have shown important reductions in the burden of rotavirus and non-rotavirus diarrhea, as well as consultations and hospitalizations due to all-cause diarrhea, post-vaccine introduction.^{7,8,17} On the

Table 1
Changes in childhood gastroenteritis-related mortality rates (per 100 000) in Brazil in 2007 and 2008, compared with the baseline period (2004–2005), by region and age group.

Age group	Region	2004–2005 mean mortality rate ^a	2007		2008	
			Mortality rate	% Reduction (95% CI)	Mortality rate	% Reduction (95% CI)
<1 year	North	82.1	65.4	20 (6–34)	59.2	28 (15–41)
	Northeast	112.4	73.4	35 (29–41)	64.9	42 (37–48)
	Southeast	22.6	14.7	35 (23–47)	12.8	44 (32–55)
	South	22.3	12.4	44 (25–63)	10.3	54 (36–71)
	Mid-West	45.2	32.1	29 (8–50)	27.2	40 (21–58)
	All	56.9	39.6	30 (19–41)	34.9	39 (29–49)
1–4 years	North	8.6	5.7	34 (15–53)	5.1	40 (23–58)
	Northeast	5.4	4.7	12 (–5–29)	4.0	25 (10–40)
	Southeast	1.4	1.0	31 (6–56)	1.1	23 (–4–50)
	South	1.3	0.8	40 (0–80)	1.6	–22 (–89–46)
	Mid-West	5.8	3.8	35 (9–62)	3.2	45 (21–69)
	All	4.5	3.2	29 (10–49)	3.00	33 (15–52)

CI, confidence interval.

^a Baseline values are the mean gastroenteritis-related mortality rates for 2004–2005.

other hand, the additional costs of vaccine introduction in this area were not offset by the decrease in the number of cases of diarrhea and hospitalizations.¹⁷ Nonetheless, deaths were not included in the analyses, the burden of rotavirus disease could not be expressed in terms of DALYs (disease-adjusted life years), and a longer period of analysis may be needed to demonstrate a new health intervention becoming cost-saving. We observed a reduction in the rates of childhood death from gastroenteritis in children <1 year of age in 2007 and 2008, representing a substantial decrease in the absolute numbers of deaths, particularly in the Northeast region.

Of note, significant reductions in mortality rates from all-cause gastroenteritis were observed among children aged 1–4 years in Brazil nationwide and in the North and Mid-West regions. The cumulative proportion of children 1–4 years of age vaccinated with either one or two doses in this age group was still low in 2008, suggesting factors other than vaccination may have played a role. Nonetheless, indirect effects on non-vaccinated individuals through reduced viral transmission in the community (e.g., herd immunity) also needs to be further investigated. In the USA, the reduction in hospitalization rates for acute gastroenteritis noted among age groups too young or too old to be vaccinated with the pentavalent rotavirus vaccine, and the change in the seasonal pattern of rotavirus, with a delayed season onset and peak in 2008, raised the possibility of herd immunity.¹⁸ In Sao Paulo, Southeast Brazil, the onset of rotavirus activity in the 2007 and in 2008 seasons also appeared to have been delayed when compared with the prevaccine rotavirus seasons, and an overall reduction in hospitalizations for all-cause gastroenteritis among children <5 years of age (29%), as well as in the number of rotavirus-specific acute gastroenteritis cases in children 3–5 years of age (29%), an age group too old to be vaccinated, were also observed after the introduction of the human rotavirus vaccine.⁷

A hospital-based surveillance study conducted in Brazil during 2005–2006 has found that the percentage of samples positive for rotavirus was 43% in children hospitalized with acute gastroenteritis and/or requiring rehydration therapy. This proportion varied from 21% in the South to 53% in the Southeast region.¹⁹ A recent meta-analysis of studies conducted in Latin America and the Caribbean, estimated that the proportion of diarrhea due to rotavirus in inpatients in Brazil is 25.7% (95% CI 20.7–30.9).²⁰ The effectiveness against very severe rotavirus infection might best reflect effectiveness against the fraction of diarrhea deaths attributable to rotavirus, and was estimated to be 74% in a recent review, suggesting that a rotavirus vaccination program has the potential to substantially reduce child mortality in low-income countries if appropriately implemented.²¹ Later studies conducted in the Northeast and North regions in Brazil have estimated 76% to 95% effectiveness of the human rotavirus vaccine in preventing severe rotavirus gastroenteritis hospitalizations, predominantly due to G2P[4].^{8,22,23}

We have observed an increase in the uptake of vaccine over time, with more than 80% of children having had at least one dose of rotavirus vaccine in 2008, demonstrating a successful integration of the human rotavirus vaccine into the national immunization program. However, the coverage of the second dose remains suboptimal in the Northeast and North regions, where the highest burden of all-cause gastroenteritis resulting in childhood deaths is observed. Therefore, increasing vaccine coverage should lead to the greatest impact on preventing childhood deaths.

The reduction in mortality rates due to all-cause gastroenteritis in children <1 year of age in Brazil was comparable to that observed in Mexico in 2008 following rotavirus vaccine introduction during 2006–2007.²⁴ The results of this study are also in line with a previous study reporting a decrease in hospitalizations due to all-cause gastroenteritis in children <1 year of age,^{6,7} suggesting a potential benefit of vaccination. Nonetheless, our findings need to be interpreted with caution since this was an ecological study and

decreasing trends in childhood diarrhea deaths and mortality were already in evidence before vaccine introduction. Other interventions that have contributed to the decrease in gastroenteritis-associated mortality in the past decades (oral rehydration therapy, breastfeeding, nutrition, water supply, hygiene and sanitation, and the Family Health Program) were not considered in the analysis. To counterbalance this fact, we used as baseline a short period of two years before vaccine introduction, when mortality seemed to have reached a steady state. We were unable to evaluate the reduction in mortality rates during rotavirus season months in regions with marked seasonality of rotavirus disease (South and Southeast regions), since monthly distribution of deaths is not readily available from the DATASUS website. The use of the administrative method to calculate vaccine coverage has the advantage of providing national estimates readily available to monitor program implementation, however, some population-based surveys have indicated that it may overestimate vaccine coverage and does not consider inequalities regarding access to health care and vaccination.^{25,26} Other limitations are related to the reliability of data, as for the ascertainment of cause of death and underreporting, as well as for the population estimates used as the denominator. Deaths from diarrhea affecting the poorest families may be reported less often than other childhood deaths, despite the increasing trend in reporting infant deaths. With falling fertility rates, the population <1 year of age may be overestimated by the census,⁹ thus yielding an underestimation of vaccine coverage and childhood mortality rates.

This study highlights the potential impact of the introduction of rotavirus vaccine in preventing deaths from gastroenteritis in Brazil. An additional 14 countries in Latin America have already included the vaccine in their immunization programs. Access to vaccine and impact of vaccination might differ among countries. Complementing studies designed to directly measure vaccine effectiveness, secondary databases can be useful tools for continuous monitoring and documentation of vaccine coverage and the effect of vaccination on childhood morbidity and mortality. Additionally, regression models including smaller analysis units (e.g., municipalities) exploring the multiple factors with a potential effect on childhood deaths from diarrhea, as well as mathematical transmission models using different vaccine coverage levels, may be useful to estimate the direct and indirect effect of vaccination following introduction.

Conflict of interest

ACL, IC, and MHC were funded through their institutions by GlaxoSmithKline Biologicals to carry out the study protocol. DAK, EOB and REC are employees of GlaxoSmithKline Biologicals. TML was employed by GlaxoSmithKline Biologicals at the time of this study.

Role of funding source

Study sponsors were involved in the study design, in the analysis and interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication.

Ethical approval

The study protocol has been submitted, reviewed, and approved by the Ethics Committee of Instituto Evandro Chagas.

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