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Effect of rotavirus vaccine on childhood diarrhea mortality in five Latin American countries

Angel Paternina-Caicedo[a,e,*], **Umesh D. Parashar**[b], **Nelson Alvis-Guzmán**[a,e], **Lucia Helena De Oliveira**[c], **Andres Castaño-Zuluaga**[f], **Karol Cotes-Cantillo**[d], **Oscar Gamboa-Garay**[d], **Wilfrido Coronell-Rodríguez**[a], **Fernando De la Hoz-Restrepo**[d]

[a]Universidad de Cartagena, Cartagena de Indias, Colombia

[b]Centers for Disease Control and Prevention, Atlanta, GA, United States

[c]Pan American Health Organization/World Health Organization, Washington, DC, United States

[d]Universidad Nacional de Colombia, Bogotá, Colombia

[e]Hospital Infantil Napoleón Franco Pareja, Cartagena, Colombia

[f]IDEAR - Department of Economics, Universidad Católica del Norte, Antofagasta, Chile

Abstract

Background: The aim of this study was to estimate the association between rotavirus vaccine (RV) introduction and reduction of all-cause diarrhea death rates among children in five Latin American countries that introduced RV in 2006.

Methods: Diarrhea mortality data was gathered from 2002 until 2009 from the Pan American Health Organization Mortality Database for five “vaccine adopter” countries (Brazil, El Salvador, Mexico, Nicaragua, and Panama) that introduced RV in 2006 and four “control” countries (Argentina, Chile, Costa Rica, and Paraguay) that did not introduce RV by 2009. Time trend analyses were carried out, and effects and 95% confidence intervals (CI) were estimated.

Results: Each of the five vaccine adopter countries, except Panama, showed a significant trend in declining mortality rates during the post-vaccine period from 2006 to 2009, whereas no decline was seen in control countries during these years. Furthermore, trends of reduction of all-cause diarrhea mortality in both children <1 year of age and <5 years of age were greater in the post-vaccination period compared with the pre-vaccine period in all vaccine adopter countries (except for Nicaragua), whereas in control countries, a reverse pattern was seen with greater reduction in the early years from 2002 to 2005 versus 2006–2009. An estimatedtotal of 1777 of annual under-5 deaths were avoided in Brazil, El Salvador, Mexico, and Nicaragua during the post-vaccination period.

Conclusion: All vaccine adopter countries, except Panama, showed a significant decrease in all-cause diarrhea-related deaths after RV implementation, even after adjusting for declining

*Corresponding author. fax: +57 56625244. angel.paternina@gmail.com (A. Paternina-Caicedo).

Conflict of interest statement

Authors report no conflict of interests.

trends over time in diarrhea mortality. These data strongly support continuous efforts to increase vaccination coverage of RV vaccines, particularly in countries with high levels of child mortality from diarrhea.

Keywords

Rotavirus vaccines; Latin America and the Caribbean; Effectiveness; Ecological

1. Introduction

Diarrheal diseases cause ~750,000 annual deaths worldwide in children under-5 years of age [1]. Rotavirus disease is the single most frequent cause of diarrheal deaths in the world, causing about one-third of mortality from diarrhea [2–4]. Two efficacious and effective rotavirus vaccines (RV) to prevent severe rotavirus diarrhea were licensed in 2006 [5,6]. Efficacy of both RV1 (Rotarix; GlaxoSmithKline Biologicals; Rixensart, Belgium) and RV5 (RotaTeq; Merck Vaccines; Whitehouse Station, NJ, USA) has varied in different settings with studies showing a higher efficacy in low-mortality countries compared to high-mortality countries [7]. The World Health Organization (WHO) recommends the introduction of either RV for all countries globally, particularly those with high child mortality from diarrhea.

The evidence of reduction of severe rotavirus diarrhea resulting in hospitalization or emergency room visit after RV introduction is extensive [8], but impact of vaccination in preventing deaths has being studied less extensively. An ecological study in Mexico found a reduction of diarrheal deaths in under-5 children by 50% (95% confidence interval [CI], 29 to 39) during the 3-years post-RV implementation compared with the pre-vaccine period [9]. In Brazil, this reduction was 22% (95% CI, 6–44) in three post-introduction years [10]. Such data on mortality benefits of RV provide strong evidence to support vaccine implementation worldwide, particularly in high mortality settings.

Despite individual country analyses with time-trend data and other statistical tools, multi-country analyses that account for confounders are not available in current literature. This issue can be dealt with a longitudinal panel-data analysis of several units of observations over-time, that adjust the association of time-invariant parameters of each country unlike time series or cross-sectional data analysis, resulting in a more adequate and unbiased estimation [11,12]. We performed the present study in order to have a better understanding of the potential reduction of all-cause diarrhea-related deaths in children under-5 years old from five countries in the Americas which were early adopters of RV in 2006. To support the role of RV in reducing diarrhea deaths, we also compared diarrhea mortality trends in four “control” countries that did not introduce RV during the same time period.

2. Methods

This ecological study aimed to analyze the association between the introduction of RV and the incidence of diarrhea-related mortality for five countries in LAC that introduced the vaccine in 2006. To accomplish this goal, pre and post vaccination diarrhea-related death

rates among children <5 years of age were compared nationwide for each country, in the pre- and post-vaccine years between 2002 and 2009.

2.1. "Vaccine adopter" and "control" countries

"Vaccine adopter" countries selected for the analysis were: Brazil, El Salvador, Mexico, Nicaragua, and Panama as countries that introduced RV in 2006. Argentina, Chile, Costa Rica, and Paraguay were "control" countries that did not introduced RV by 2009, the end of our study period.

2.2. Source of mortality and vaccine coverage data

Mortality data was gathered from the Pan American Health Organization/World Health Organization (PAHO/AMRO–WHO) Mortality Regional Database. This database is composed of data collected from national vital registration systems in all countries in the American region. The causes of death according to this source are official estimates for each country and are grouped using the International Classification of Diseases version 10 (ICD-10). Deaths with ICD-10 codes for diarrhea and gastroenteritis of presumed infectious origin (A09X) were chosen for this analysis. Mortality data was disaggregated by prespecified age-groups (0–1 year of age, 1–2 years of age, 2–4 years of age; and total under-5 years of age).

Vaccine coverage that evidenced the impact of RV1/RV5 introduction on all-cause diarrhea deaths from LAC countries was derived from a previous study by de Oliveira et al. in 2011 [13]. That study used data from across Latin Americas for countries that introduced RV1/RV5 by 2009. Data for this estimation included direct estimates from National Expanded Program on Immunization (EPI), data surveillance from rotavirus sentinel surveillance network, rotavirus vaccine purchase records from PAHO's Revolving Fund, and reports from international evaluations in Ecuador and El Salvador [13].

2.3. Data analysis

Death rates for diarrhea in each country were calculated using age- and cause-specific deaths as numerators and population denominators obtained from demographic projections carried out by the Economic Commission for Latin America and the Caribbean (ECLAC) [14]. All analyses were performed in Excel (Microsoft, Redmond, WA) and Stata 13 (StataCorp, College Station, TX). A p-value <0.05 was considered statistically significant.

Several analytic models were constructed to compare pre- and post-vaccine introduction diarrhea mortality rates for "vaccine adopter" countries:

Model 1 (unadjusted relative reduction of rates): Diarrhea mortality rates in the pre-vaccine period (2002 to 2005) were compared with rates in the post-vaccine period (2006 to 2009); relative rate reductions (RRR) with 95% confidence intervals (95% CI) were calculated.

Model 2 (segmented linear regression): A segmented linear regression model was fit to data from the five countries to compared diarrhea mortality rates in the pre-

and post-vaccine period [15]. In order to correct for auto-correlation, and according to recommendations by Judge et al. [15,16], the Prais–Winsten method was used to estimate the adjusted effect of the RV1/RV5 vaccine in vaccine adopter countries.

Model 3 (time-trend analysis): A Poisson regression model was constructed for the pre- and post-vaccination period. Trends were reported according to the following equation 100(exp(β-coefficient) − 1), and 95% CI were calculated through robust standard errors.

Model 4 (longitudinal analysis): A longitudinal panel-data analysis was carried out in order to assess the association between rates of diarrhea-related mortality from 2002 to 2009 and mass introduction of RV. The dependent variable was entered in the model as continuous, and the exposure variable as mass introduction or not of RV (as a dummy variable). These models were estimated using fixed-effects linear panel-regression, and coefficients were accompanied by 95% CI. Several longitudinal panel-data models were estimated, with one for every age-group. The models were examined for: (1) all selected countries; (2) “vaccine adopter” countries with RV introduction in 2006; and (3) “control” countries with no RV introduction as of 2009, with a dummy variable assuming RV introduction in 2006.

Finally, based on the panel-data analysis, and to assess the count of deaths prevented by the intervention based on the longitudinal panel-data analysis, linear predictions were estimated by year from the longitudinal panel-data analysis in rates, which were then converted to absolute frequencies based on population estimations for each year. Averages of these estimations for the four year-periods were then reported.

3. Results

3.1. Vaccine coverage data

Five countries in LAC introduced the vaccine in 2006: Brazil, El Salvador, Mexico, Nicaragua and Panama. According to Oliveira et al. [13] and PAHO data [17], in 2007 Brazil had a coverage for the last dose of rotavirus vaccine of 76.0%, El Salvador of 58%, Mexico of 35.9%, Nicaragua of 79.0%, and Panama of 68.4%. In 2009, vaccination coverage with the last dose of rotavirus vaccine was 81.9% in Brazil, 61.4% in El Salvador, 88.7% in Mexico, 94.4% in Nicaragua and 77.0% in Panama.

3.2. Diarrhea mortality rates in vaccine adopter and control countries

In each of the five vaccine adopter countries except Panama, significant reductions in diarrhea mortality rates ranging from about 30–50% were observed in each age group, when comparing aggregate rates in pre- and post-vaccine periods (Table 1). Countries that did not introduce rotavirus vaccine also showed a significant reduction of all-cause diarrhea mortality, when comparing the same aggregate time periods (2006–2009 versus 2002–2005). The quasi-experimental approach controlling for secular trends and serial correlation also found lower all-cause diarrhea mortality rate in the post-vaccine versus pre-vaccine period in under-1 and under-5 year old children in all vaccine adopter countries, except for Panama, as well as in the control countries (Table 1).

3.3. Time-trend analysis of reduction in diarrhea mortality in vaccine adopter and control countries

Each of the five vaccine adopter countries, except Panama, showed a significant trend in declining mortality rates during the post-vaccine period from 2006 to 2009 (Table 2 and Fig. 1A). Furthermore, trends of reduction of all-cause diarrhea mortality in both children <1 year of age and <5 years of age were greater in the post-vaccination period compared with the pre-vaccine period in all vaccine adopter countries, except for Nicaragua (Fig. 1).

Trends in control countries that did not introduced the vaccine are shown in Fig. 2.

In contrast, in each of the four control countries (Table 2 and Fig. 1B), under-5 mortality rate did not change between 2006 and 2009 and, except for Paraguay, the under-1 mortality rates also did not change significantly. Furthermore, the declining trend in diarrhea mortality was greater in the years from 2002–2005 versus 2006–2009 in each of the four countries for both <5 and <1 year age groups, except for the <1 year age group in Paraguay.

3.4. Longitudinal analysis

Longitudinal analysis using fixed-effects panel-data analyses showed a significant reduction in diarrhea mortality rates in countries that introduced the vaccine in 2006. In contrast, analysis in countries that did not introduce the vaccine showed no significant effect (Table 3).

3.5. Estimated reduction in diarrhea deaths in vaccine adopter countries

Analysis also showed that Brazil, El Salvador, Mexico, and Nicaragua reduced all-cause diarrhea deaths by 1777 annually in under-5 children during study period. Brazil would have prevented 977 annual all-cause diarrhea deaths during the study period, 50 annual deaths in El Salvador, 702 in Mexico, and 49 deaths in Panama.

4. Discussion

Several lines of evidence support that RV played a role in the reduction of diarrhea-related deaths in the vaccine adopter countries. First, all vaccine adopter countries, except Panama, showed a significant decrease of all-cause diarrhea deaths in children under-5 years old after vaccine implementation compared with pre-vaccine years and these declines persisted even after adjusting for the declining secular trend in mortality prior to vaccine implementation. Second, trends of reduction of all-cause diarrhea mortality in both children <1 year of age and <5 years of age were greater in the post-vaccination period compared with the pre-vaccine period in all vaccine adopter countries (except for Nicaragua), whereas in control countries, a reverse pattern was seen with greater reduction in the early years from 2002–2005 versus 2006–2009.

Our study has several strengths. First, similar to vaccine adopter countries, control countries also showed a significant reduction when aggregate diarrhea mortality rates over time periods were compared, but more sophisticated analyses examining and controlling for secular trends showed clear differences in the patterns between vaccine adopter and control countries. Second, the consistency of results across different models that we deployed

provides reassurance in the validity of the findings. Finally, we used high quality data from international sources that is gathered and published after an extensive validation process.

Some limitations should be considered. First, it is possible that other community, public health and clinical interventions could have contributed to the declining diarrhea trend in post-vaccine years in vaccine adopter countries. Also, because we did not have information on laboratory-confirmed rotavirus diarrhea deaths, our analyses could be affected by secular trends in diarrhea mortality related to other pathogens. For example, it is possible that the lack of a post-vaccine decline in diarrhea deaths in Panama, largely related to an increase in mortality in 2007, could be due to the occurrence of a diarrheal outbreaks of a pathogen other than rotavirus (e.g., norovirus) in that year. This requires further examination as additional years of data become available.

In conclusion, our study confirms previous reports showing decline in childhood diarrhea mortality after rotavirus vaccine introduction in Mexico and Brazil and also extends these observations to El Salvador and Nicaragua. Furthermore, our inclusion of control countries and several analytic approaches generated more robust findings than that of previous ecologic studies. Our data strongly encourages expansion of rotavirus vaccine programs in countries around the world, particularly in low income setting with high childhood mortality from diarrhea.

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Disclaimer

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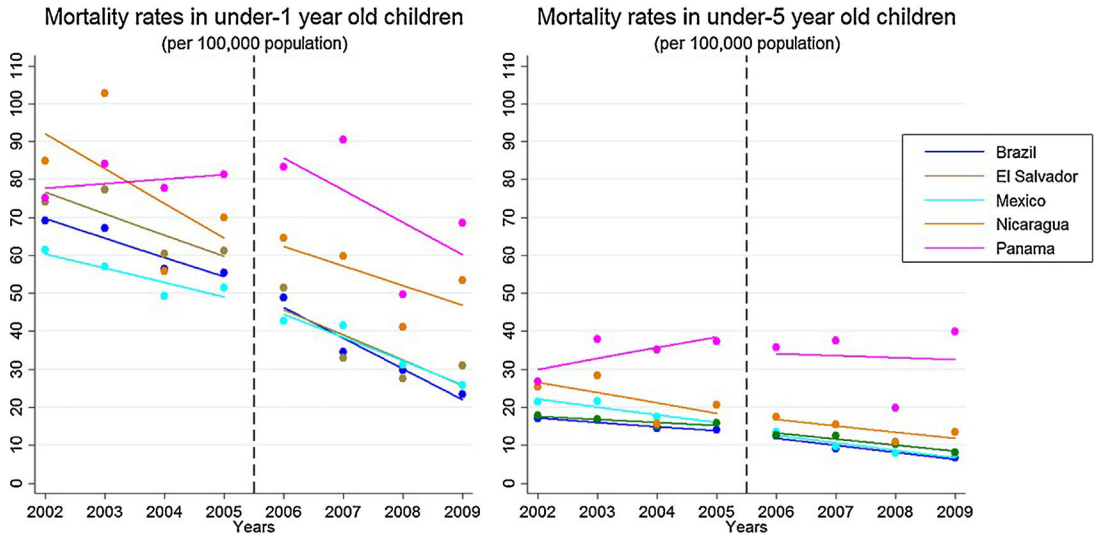

Fig. 1.

Linear time-trends of diarrhea-related deaths in children before and after RV vaccination in selected Latin American countries who introduced the vaccine by 2006.

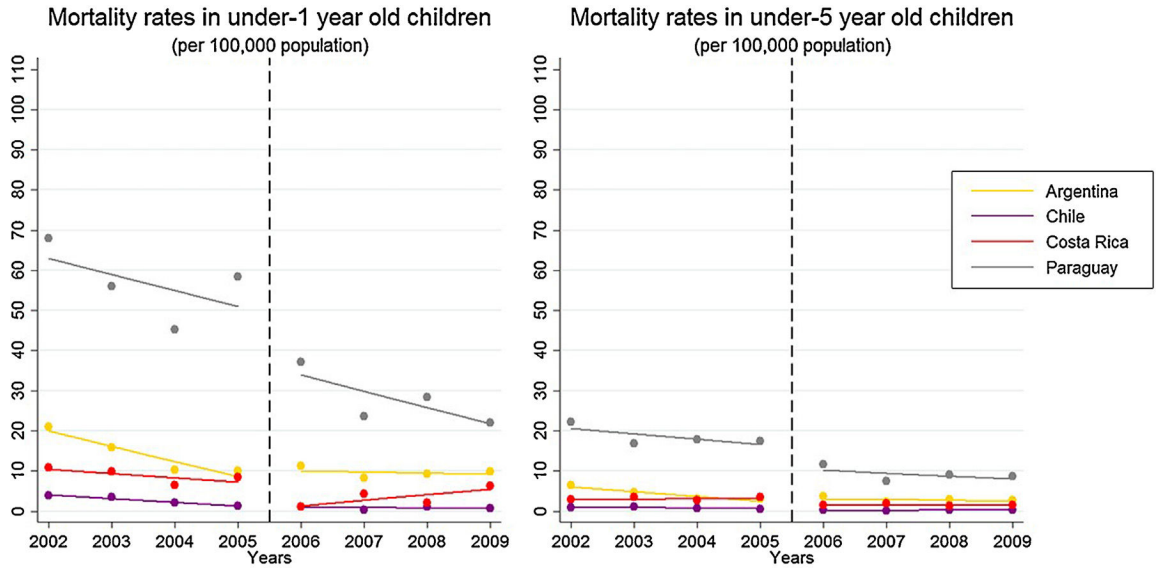

Fig. 2.

Linear time-trends of diarrhea-related deaths in children before and after RV vaccination in "control" Latin American countries who did not introduced the vaccine by 2009.

Table 1

Unadjusted relative reduction of rates (model 1) and segmented linear regression (model 2) of all-cause diarrhea deaths four-year post-introduction in countries exposed to vaccination in 2006.

	Unadjusted relative reduction of rates (Model 1)						Segmented linear regression (Model 2)
	Number of annual deaths		Death rates (per 100,000 population)		Reduction of death rates	Relative reduction of death rates (95% CI)	β-Coefficient (95% CI)
	Expected (2002–2005)	Observed (2006–2009)	Expected (2002–2005)	Observed (2006–2009)			
Brazil (RV1)							
<1 year	2031	1128	62.1	34.1	−28.0	45.0 (43.0 to 47)	−8.94 (−15.79 to −2.09) **
<5 years old	2505	1465	15.5	9.0	−6.5	42.1 (40.2 to 44.0)	−1.99 (−3.56 to −0.42) **
El Salvador (RV1)							
<1 year	111	57	68.3	35.8	−32.5	47.6 (38.5 to 55.3)	−15.63 (−26.14 to −5.12) **
<5 years old	154	77	19.1	9.6	−9.5	49.5 (42.0 to 55.9)	−4.45 (−7.37 to −1.52) **
Mexico (RV5)							
<1 year	1204	757	54.8	35.3	−19.5	35.6 (32.6 to 38.4)	−6.18 (−9.87 to −2.48) **
<5 years old	1798	1162	16.4	10.8	−5.6	33.9 (31.4 to 36.3)	−1.36 (−2.28 to −0.44) **
Nicaragua (RV5)							
<1 year	135	96	78.3	54.7	−23.6	30.1 (20.3 to 38.6)	−14.97 (−19.92 to −10.03) **
<5 years old	189	123	22.5	14.3	−8.2	36.4 (28.7 to 43.2)	−3.54 (−4.43 to −2.64) **
Panama (RV1)							
<1 year	47	43	79.5	73.0	−6.5	8.2 (−12.9 to 25.3)	−1.07 (−3.67 to 1.52)
<5 years old	102	97	34.3	33.3	−1.0	3.0 (−11.5 to 14.5)	1.25 (−0.25 to 2.75)
Argentina							
<1 year	409	277	14.26	9.62	−4.6	32.5 (21.4 to 42.0)	N.E.
<5 years old	610	407	4.29	2.84	−1.5	33.8 (25.0 to 41.6)	N.E.
Chile							
<1 year	31	9	2.75	0.80	−1.9	70.9 (38.9 to 86.2)	N.E.
<5 years old	50	17	0.88	0.30	−0.6	65.7 (40.5 to 80.2)	N.E.
Costa Rica							
<1 year	33	13	8.90	3.41	−5.5	61.6 (27.1 to 79.8)	N.E.
<5 years old	57	29	3.12	1.54	−1.5	50.6 (22.8 to 68.4)	N.E.
Paraguay							

	Unadjusted relative reduction of rates (Model 1)						Segmented linear regression (Model 2)
	Number of annual deaths		Death rates (per 100,000 population)		Reduction of death rates	Relative reduction of death rates (95% CI)	β-Coefficient (95% CI)
	Expected (2002–2005)	Observed (2006–2009)	Expected (2002–2005)	Observed (2006–2009)			
<1 year	384	198	56.8	27.7	−29.1	51.2 (42.1 to 58.9)	N.E.
<5 years old	605	315	18.5	9.1	−9.4	50.8 (43.7 to 57.1)	N.E.

N.E.: Not estimable.

** p-Value <0.05.

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Table 2

Time-trends analysis (model 3) of diarrhea-related mortality in Latin American countries four years pre and post −vaccination.

	Trend 2002–2005 [100(e^{β} − 1)] (95% CI)	**Trend 2006–2009 100(e^{β} − 1)] (95% CI)**
Countries that *did* introduced the vaccine in 2006 (exposed)		
Brazil (RV1)		
<1 year	−7.96 (−9.87 to −6.02) **	−21.36 (−23.66 to −18.98) **
<5 years old	−7.1 (−8.63 to −5.55) **	−18.84 (−21.71 to −15.87) **
El Salvador (RV1)		
<1 year	−7.96 (−11.42 to −4.36) **	−17.32 (−28.13 to −4.88) **
<5 years old	−10.36 (−13.39 to −7.23) **	−18.84 (−25.08 to −12.07) **
Mexico (RV5)		
<1 year	−6.66 (−9.8 to −3.42) **	−16.06 (−19.79 to −12.17) **
<5 years old	−4.64 (−7.57 to −1.62) **	−14.05 (−18.93 to −8.88) **
Nicaragua (RV5)		
<1 year	−11.09 (−20.31 to −0.79) **	−9.08 (−18.1 to 0.94)
<5 years old	−11.21 (−20.49 to −0.85) **	−10.65 (−19.15 to −1.25) **
Panama (RV1)		
<1 year	1.53 (−1.21 to 4.34)	−11.03 (−20.92 to 0.09)
<5 years old	8.8 (−0.24 to 18.65)	−1.6 (−18.17 to 18.32)
Countries that *did not* introduced the vaccine (unexposed) *		
Argentina		
<1 year	−23.61 (−29.49 to −17.24) **	−3.16 (−12.47 to 7.14)
<5 years old	−24.4 (−31.15 to −16.99) **	−7.72 (−16.87 to 2.44)
Chile		
<1 year	−28.03 (−33.71 to −21.86) **	−4.57 (−24.15 to 20.07)
<5 years old	−17.23 (−27.83 to −5.07) **	18.07 (−4.24 to 45.59)
Costa Rica		

		Trend 2002–2005 [$100(e^{\beta} - 1)$] (95% CI)	Trend 2006–2009 $100(e^{\beta} - 1)$] (95% CI)
	<1 year	−11.03 (−20.86 to 0.03)	51.29 (8.91 to 110.16)**
	<5 years old	2.71 (−4.47 to 10.43)	−4.68 (−12.78 to 4.17)
Paraguay			
	<1 year	−6.62 (−16.94 to 4.99)	−13.58 (−20.11 to −6.52)**
	<5 years old	−6.77 (−13.06 to −0.03)**	−7.54 (−17.38 to 3.46)

*Control countries that did not introduced the vaccine by 2009.

**Significant trend (p-value <0.05).

Table 3

Fixed-effects longitudinal analysis (model 4) to estimate the association between mass introduction of rotavirus vaccine and all-cause diarrhea mortality rate reduction.

	Adjusted results 100 × β log-coefficient (95% CI)	Crude results 100 × β log-coefficient (95% CI)
Main effects with all selected nine countries (exposed and unexposed) *		
<1 year old	−9.7 (−19.8 to 0.4) (p = 0.057)	−22 (−31.8 to −12.3) (p = 0.001)
Under-5 years old	−3.1 (−5.8 to −0.5) (p = 0.026)	−6.2 (−9.3 to −3) (p = 0.002)
Sensitivity analysis: including only countries with vaccination (exposed countries) *		
<1 year old	−8.1 (−19.3 to 3.1) (p = 0.115)	−22 (−34.5 to −9.5) (p = 0.008)
Under-5 years old	−4.7 (−8.2 to −1.2) (p = 0.020)	−6.2 (−10.2 to −2.1) (p = 0.014)
Sensitivity analysis: Assuming vaccination in 2006 forunexposed countries **		
<1 year old	−3.1 (−15 to 8.7) (p = 0.460)	−8.6 (−27 to 9.8) (p = 0.235)
Under-5 years old	−1.4 (−6.5 to 3.8) (p = 0.463)	−2.8 (−8.7 to 3.1) (p = 0.229)

* Adjusted by percentage population living under rural areas, gross national income, health expenditure as percentage of gross domestic product, and DPT-vaccine coverage.

** Adjusted by percentage population living under rural areas, gross national income, and health expenditure as percentage of gross domestic product. Since rotavirus vaccination was not part of vaccine schedule, no adjustment by DPT-vaccine coverage was made.