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

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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 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.


## 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

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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 $100(\exp(\beta\text{-coefficient}) - 1)$, 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).

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