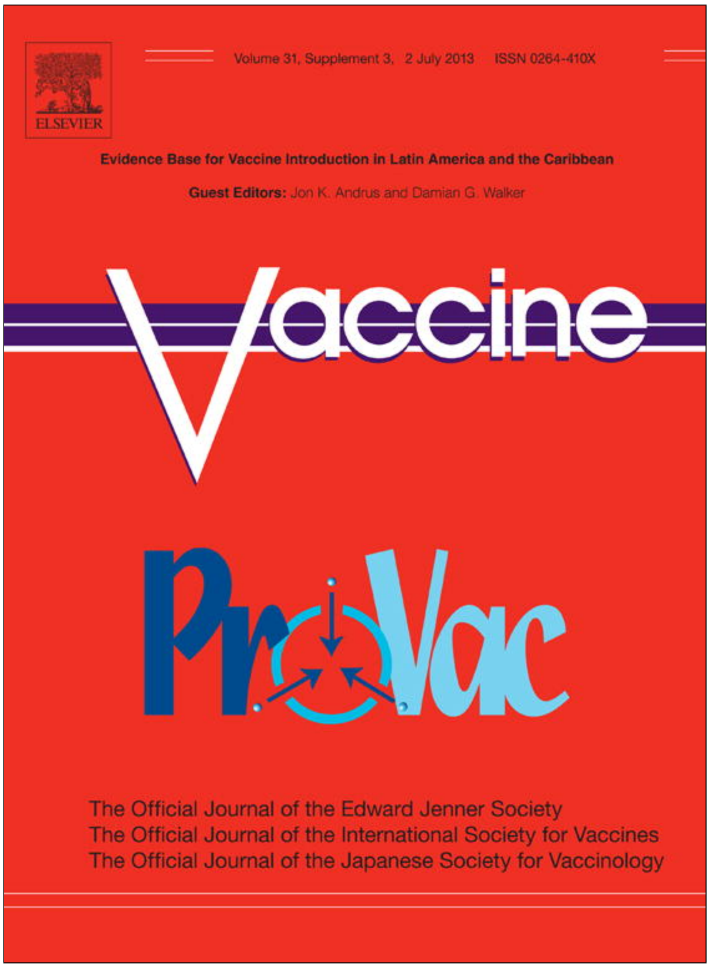
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Review

Temporal trends in diarrhea-related hospitalizations and deaths in children under age 5 before and after the introduction of the rotavirus vaccine in four Latin American countries

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ABSTRACT

Introduction: Rotavirus infection mainly affects children under 5 years of age and causes 453,000 deaths annually throughout the world. Several countries in Latin America have introduced the rotavirus vaccine and the majority have epidemiological data to measure impact following vaccine introduction.
Objective: To assess the impact of rotavirus immunization on the number of all-cause diarrhea-related deaths and hospitalizations in children under 1 and 5 years of age in Bolivia, El Salvador, Honduras and Venezuela.
Methods: Interrupted time-series analyzed with the integral method and the projection method to evaluate the pre and post-vaccine introduction trend in diarrheal disease compared to Argentina as the control country. The analysis period was from 2002 to 2010, including 2 to 4 post-vaccine years depending on the country. Information sources included records from PAHO, the Ministry of Health, public hospitals, social security, the private health system, the Expanded Programme on Immunization and UNPop 2008.
Results: Over the period studied, reductions were observed in trends of diarrhea-related deaths and hospitalizations in children under five. In diarrhea-related deaths, under the integral method, the range of reduction was between 15.7% (13.5–17.9) and 56.8% (56.0–57.5) while with the projection method was between 19.9% (4.9–34.8) and 63.7%(56.1–71.4). In diarrhea-related hospitalizations, under the integral method was 5.6% (4.1–6.7) and 17.9% (16.7–19.1)) while with the projection method was between 5.1%(1.7–8.7) and 11.1% (5.8–16.3)
Conclusions: A decrease was observed in the number of diarrhea related deaths and hospitalizations in all countries under study following introduction of the rotavirus vaccine as opposed to the control country. The impact on reduction of deaths was greater than hospitalization.

Contents

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1. Introduction

Rotavirus infection mainly affects children under 5 years of age, causing 453,000 deaths annually throughout the world [1,2], 80% of which occur in developing countries [3]. It has been estimated that in the Americas rotavirus infection causes 5000 deaths annually in children under age 5 after the introduction of the vaccine in many countries. [1].

Currently, there are two attenuated oral rotavirus vaccines licensed and prequalified by the World Health Organization (WHO). The first is the monovalent human vaccine (Rotarix®), derived from the G1 P1 human virus strain and administered in two doses, usually at 2 and 4 months of age [4]. The second is a pentavalent vaccine (RotaTeq®) made with a human-bovine reassortant virus that contains G1, G2, G3, G4, and P1 strains of human serotypes, and usually administered in three doses at 2, 4, and 6 months of age [5,6].

In 2006 and 2007, respectively, the Directing Council of the Pan American Health Organization (PAHO) [7] and the World Health Organization's Strategic Advisory Group of Experts (SAGE) [8] declared that the introduction of the rotavirus vaccine in the Americas was a priority, with the goal of preventing deaths and hospitalizations caused by this virus. This decision was based on the results of clinical trials on both vaccines, which showed 85% to 98% efficacy in the prevention of severe rotaviral diarrhea in Europe and Latin America [4–6].

Six Latin American countries introduced the vaccine in their immunization programs in 2006 (Brazil, El Salvador, Mexico, Nicaragua, Panama, and Venezuela); Ecuador introduced it in 2007; Bolivia in 2008; Colombia, Honduras, Peru, and the territories of the Cayman Islands in 2009; and Guatemala, Guyana, and Paraguay in 2010 [9].

Aspects related to the impact of vaccination such as mortality, morbidity, coverage rates, seasonality, serotype replacement, and the indirect benefits for people who have not been vaccinated justify monitoring the rotavirus vaccine following its introduction into Expanded Programs on Immunization (EPI) in the Latin American region, in spite of the results of randomized clinical trials [10].

To date, impact studies in Latin America pre- and post-introduction of the rotavirus vaccine have shown a reduction in disease burden. A 22% to 50% decrease in deaths from all-cause diarrhea has been observed [11–14]. For hospitalizations related to all-cause diarrhea, the decrease ranged from 17% to 51% [12,15–18] and specifically for rotavirus, hospitalizations decreased between 59% and 81% [19,20].

Based on these reported data, and due to the need to continue assessing the impact of these vaccines in Latin America, the objective of this study was to evaluate the trend in diarrhea-related deaths and hospitalizations before and after introduction of the rotavirus vaccine in Bolivia, El Salvador, Honduras, and Venezuela.

2. Methods

2.1. Design

An interrupted time-series analysis was used to assess the impact of rotavirus immunization on the number of deaths and hospitalizations related to all-cause diarrhea in children under 1 year and under 5 years of age. The study considered data from four Latin American countries that met the following criteria: rotavirus vaccine introduction in the country's national routine EPI schedule in the 2006–2009 period; national records on diarrhea-related deaths and hospitalizations for at least three years prior to the introduction of the vaccine; reliable vaccine coverage records; and no significant changes in the method for registering hospitalizations and deaths or in the health care system during the pre- and post-vaccine introduction period.

Argentina has relatively good surveillance data to serve as a control country. In addition some areas of Argentina, specifically the northwest and northeast regions, present similar sanitation conditions to the countries selected for this study. Because Argentina had not introduced the rotavirus vaccine to its EPI during the study period, it was selected as a control country in order to evaluate possible secular changes in diarrhea morbidity and mortality in the region. Table 1 shows the general characteristics of the countries selected and the periods pre- and post-vaccine introduction analyzed.

2.2. Sources and data collection

The impact of rotavirus vaccine introduction was assessed through monthly hospitalizations and mortality reports received from the Ministries of Health for at least three years prior to implementation of the vaccination program and every subsequent year available through December 2010. The time series window of the countries is detailed in Table 1. We used databases on epidemiological surveillance of rotaviral diarrhea from the PAHO recommended sentinel surveillance network and records on hospitalizations and deaths at the Ministries of Health of the countries selected for this study [21,22].

Hospitalizations and deaths from diarrhea-related causes corresponding to the following codes from the tenth version of the International Classification of Diseases (ICD-10) [23] were considered: A00–A03, A04, A05, A06.0–A06.3, A06.9, A07.0–A07.2, and A08–A09The Venezuelan surveillance systems report aggregated data for all diarrhea-related hospitalizations. Therefore, data on hospitalizations from that country were excluded from the regional analysis because that data could not be stratified.

Monthly national rotavirus vaccine coverage data reported to PAHO was used for this study. Demographic data were obtained from the United Nations World Population Prospects database for 2008 [24].

The proportion of all diarrhea cases caused by rotavirus was taken from sentinel surveillance data on hospitalized children from 0 to 5 years of age through the year 2009. This proportion was applied to all-cause diarrhea reported cases in order to estimate those attributable to rotavirus. Due to the predictable seasonality of hospitalizations and deaths and the stable proportion of all cause diarrhea caused by rotavirus over time, the proportions corresponding to 2010 were modeled by means of an exponential smoothing method [25]. The relative reduction in deaths and hospitalizations attributed to rotavirus infection and corresponding 95% confidence intervals were estimated for each analysis proposed.

2.3. Statistical time-series analysis

For the time-series analysis, two different methods were used: the integral method and the projection method. Time-series data were adjusted for changes in the population size of the target age groups. The absolute number of estimated cases took into account the age-specific rate of natural increase [24].

Table 1
Population characteristics of selected countries and the periods analyzed pre- and post-introduction of rotavirus vaccine.

Countries	Population 0–5 years of age[a,b]	All-cause deaths in children under age 5 for every 1000 live births in 2005[b]	Introduction of the vaccine	Start of TIME SERIES	Completion of the TIME SERIES
Bolivia	1,242,000	66.00	Yes (August 2008)	January 2003 (Hospitalizations) January 2004 (Deaths)	December 2010
El Salvador	710,000	27.73	Yes (April 2006)	January 2002 (Hospitalizations) January 2002 (Deaths)	December 2010
Honduras	905,000	41.59	Yes (February 2009)	January 2004 (Hospitalizations) January 2004 (Deaths)	December 2010
Venezuela	2,850,000	23.00	Yes (April 2006)	January 1998 (Cases) January 2002 (Deaths)	December 2009
Argentina	3,355,000	16.00	No (Control country)	January 2005 (Hospitalizations) January 2004 (Deaths)	December 2009

[a] Averages for the period following vaccine introduction.
[b] Based on United Nations, Department of Economic and Social Affairs, Population Division (2009). World Population Prospects: the 2008 Revision. (CD-ROM Edition) New York: United Nations.

2.3.1. Integral method

This methodology uses the cumulative case distribution calculated based on the integral over the course of the time series and makes possible a quantitative and qualitative (visual) analysis of changes [26].

Based on the date of vaccine introduction into each country's National Immunization Program, an estimate was obtained using the least-squares linear regression of the integral curve pre- and post-introduction of the vaccine, using the following formulae:

$$C_o(t) = \int_{t_0}^{t} N_o(t)\,dt$$

$$C_e(t) = C_o(t_v) + r(t - t_v)$$

where $C_o(t)$ is the integrated value of the cases observed following introduction of the vaccine and $C_e(t)$ is the integrated value of cases adjusted by regression that would be expected in the absence of the vaccine. The number of cases expected in the absence of vaccine is obtained by projecting the linear regression line prior to introduction of the vaccine.

In estimating the net effect of vaccination using quantitative analysis, the cumulative number of actual cases (number of cases observed: N_o) were compared following introduction of the vaccine (t_v) with the projection of cases that would have occurred if the vaccine had not been introduced (t_f) (number of cases expected: N_e), using the following formula:

Number of cases averted $= \int_{t_v}^{t_f} (N_e(t) - N_o(t))\,dt$, where the difference between the cumulative values of expected cases and observed cases during the post-vaccination period is calculated. Expected cases are estimated based on the slope of the integral curve during the pre-vaccination period.

For qualitative analysis, the slopes of the integral curves associated with the incidence of events were compared. A potential impact can thus be inferred for each country pre- and post-vaccination if there is an observed change in slope when compared to the control country.

In order to facilitate visual comparison of the qualitative behavior of the time series in each country, the maximum values corresponding to the last value available in the time series were standardized in integral curves, acquiring values between 0 and 1.

Data were analyzed by means of linear regression by using the best adjustments for each series, comparing the differences between intervention countries and the control country.

2.3.2. Projection method

This method was used to obtain a more detailed analysis of the time series, eliminating the stochastic noise and seasonality components of the global trend from the original monthly data curve.

First, least-squares non-linear regression was applied to the data curve. Subsequently, using the Levenberg–Marquardt algorithm [27] and the Hodrick–Prescott filter [28] for trend analysis, the impact of change compared the actual trend of the time series (N_o) with what could be expected without vaccination (N_e). In this way, similar to the regression method, the cases averted through vaccination were quantified using the formula: $N_e - N_o$.

3. Results

The number of cases observed over the post-vaccination study period was less than the number of expected cases modeled in the absence of vaccination programs, suggesting a reduction in diarrhea-related deaths and events in all the countries studied. Fig. 1 shows the number of diarrhea-related deaths and hospitalizations reported by the different countries during the study time period. It also shows the results of the best adjustments for each series, comparing the intervention countries and the control country.

In the post-introduction period, a total of 2231 diarrhea-related deaths were observed in contrast with the 4430 (integral method) to 5337 (projection method) expected in children under age 5 in Bolivia, El Salvador, Honduras, and Venezuela (Table 2). 110,227 diarrhea-related hospitalizations were observed in contrast with 120,146 (projection method) to 120,518 (integral method) expected in Bolivia El Salvador, and Honduras. In Venezuela, 1,582,480 cases of diarrhea were registered in the under 5 age group (hospital discharges and outpatient cases) compared to the 1,858,700 (integral method) to 1,887,080 (projection method) expected for the same period (Table 3).

Using the integral method, mortality trends due to all-cause diarrhea in children under age 5 during pre- and post-vaccination showed that mortality reduction ranged from 15.7% (CI95%: 13.5%–17.9%) in Honduras to 56.8% (CI95%: 56.0%–57.5%) in Venezuela. Using the projection method, reduction in mortality ranged from 19.9% (CI95%: 4.9%–34.8%) in Honduras to 63.7% (CI95%: 56.1%–71.4%) in Venezuela (Table 2).

The assessment of impact on diarrhea-related hospitalizations for Bolivia, El Salvador, and Honduras revealed a decrease in the number of hospitalizations following vaccine introduction,

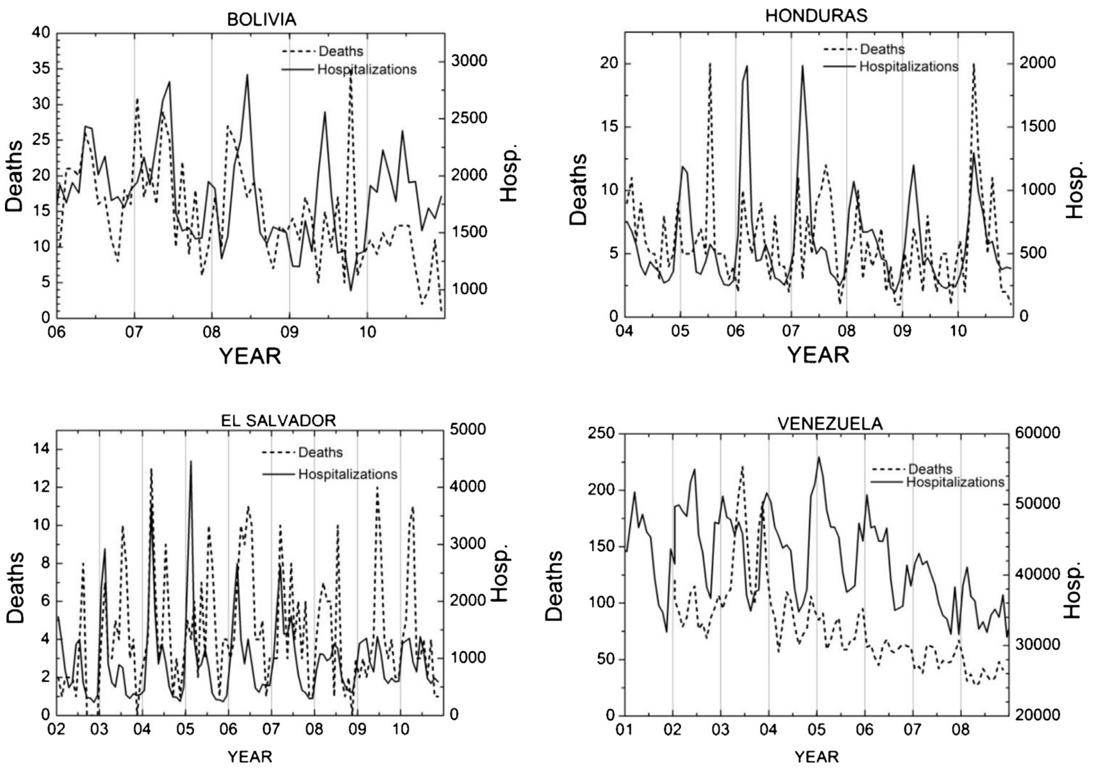

Fig. 1. Number of deaths and hospitalizations for the countries included during the entire study period. All causes. The graphs show the number of deaths (dashed line) and hospitalizations (solid line) for the countries included during the entire study period. The *y* axis shows the absolute number of events, hospitalizations are shown on the left, deaths are shown on the right and the years are shown on the *x* axis.

ranging from 5.6% (CI95%: 4.1%–6.7%) in El Salvador to 17.9% (CI95%: 16.7%–19.1%) in Honduras using the integral method, and 5.1% (CI95%: 1.7%–8.7%) in El Salvador to 11.1% (CI95%: 5.8%–16.3%) in Honduras using the projection method (Table 3).

The reduction in the proportion of deaths attributed to all-cause diarrhea did not vary considerably in the 0 to 1 year age group compared with the 0 to 5 year group (Table 2), but the reduction in hospitalizations was greater in the 0 to 1 year age group (Table 3). Of the total number of deaths in the 0 to 5 year age group, the majority occurred in the 0 to 1 age group, accounting for 96% of deaths in Bolivia, 96%, 75% in El Salvador, 66% in Honduras, and 66% in Venezuela.

Trends in diarrhea-related deaths and hospitalizations in children under age 5 in countries where the vaccine was introduced were different than the control country (Argentina). In the control country, the cumulative number of deaths and hospitalizations maintained the same slope over time, while the study countries showed a drop in the slope following introduction of the vaccine

Table 2
Number of observed and expected deaths related to all-cause diarrhea following rotavirus vaccine introduction in children, by age group, in selected countries.

Country	Age range	Integral method				Projection method			
		Observed deaths	Expected deaths	Difference	Δ% (CI 95%)	Observed deaths	Expected deaths	Difference	Δ% (CI 95%)
Bolivia	0–1 year	303	430 ± 4	127 ± 4	29.5% (28.2%–30.8%)	303	376 ± 40	73 ± 40	19.4% (2.3%–36.5%)
	0–5 years	314	487 ± 5	173 ± 5	35.5% (34.1%–36.9%)	314	546 ± 50	232 ± 50	42.5% (32.0%–53.0%)
El Salvador	0–1 year	188	178 ± 2	−10 ± 2	–5.6% (–8.0%–-3.2%)	188	211 ± 20	23 ± 20	10.9% (0–27.8%)
	0–5 years	253	240 ± 3	−13 ± 3	–5.4% (–8.3%–-2.8%)	253	395 ± 60	142 ± 60	35.9% (16.5%–55.4%)
Honduras	0–1 year	85	99 ± 4	14 ± 4	14.1% (7.2%–21.1%)	85	85	0	0% (0–0.0)
	0–5 years	129	153 ± 2	24 ± 2	15.7% (13.5%–17.9%)	129	161 ± 15	32 ± 15	19.9% (4.9%–34.8%)
Venezuela	0–1 year	1010	2510 ± 10	1500 ± 10	59.8% (59.4%–60.1%)	1010	2770 ± 300	1760 ± 300	63.5% (55.6%–71.4%)
	0–5 years	1535	3550 ± 32	2015 ± 32	56.8% (56.0%–57.5%)	1535	4235 ± 450	2700 ± 450	63.7% (56.1%–71.4%)
Argentina	0–5 years	423	425 ± 1	–	0.4% (0.3%–0%)	–	–	–	–
Total[a]	0–1 year	1586	3217 ± 20	1631 ± 20	50.7% (50.1%–51.3%)	1586	3442 ± 360	1856 ± 360	53.9% (44.3%–63.6%)
Total[a]	0–5 years	2231	4430 ± 42	2199 ± 42	49.6% (48.7%–50.6%)	2231	5337 ± 575	3106 ± 575	58.2% (49.2%–67.2%)

Note: Deaths for the entire period, from the introduction of rotavirus vaccination through the last information available, adjusted for population growth.
[a] The total does not include Argentina.

Table 3
Number of observed and expected hospitalizations due to all-cause diarrhea following rotavirus vaccine introduction in children, by age group, in selected countries.

Country	Age range	Integral method				Projection method			
		Observed hospitalizations	Expected hospitalizations	Difference	Δ% (CI 95%)	Observed hospital-izations	Expected hospital-izations	Difference	Δ% (CI 95%)
Bolivia	0–1 year	21,772	24,987 ± 80	3215 ± 80	12.9% (12.3%–13.4%)	21,772	25,281 ± 520	3509 ± 520	13.8% (10.3%–17.7%)
	0–5 years	46,646	51,220 ± 420	4574 ± 420	8.9% (7.4%–10.4%)	46,646	52,288 ± 650	5642 ± 650	10.8% (9.0%–12.6%)
El Salvador	0–1 year	20,790	22,464 ± 250	1674 ± 250	7.5% (5.4%–9.5%)	20,790	21,930 ± 400	1140 ± 400	5.2% (1.7%–8.7%)
	0–5 years	51,229	54,250 ± 410	3021 ± 410	5.6% (4.1%–6.7%)	51,229	53,965 ± 920	2736 ± 920	5.1% (1.8%–8.3%)
Honduras	0–1 year	4948	6780 ± 60	1832 ± 60	27.0% (25.7%–28.3%)	4948	6190 ± 190	1242 ± 190	20.1% (15.1%–25.0%)
	0–5 years	12,352	15,048 ± 110	2696 ± 110	17.9% (16.7%–19.1%)	12,352	13,893 ± 410	1541 ± 410	11.1% (5.8%–16.3%)
Venezuela[a]	0–1 year	58,4910	786,260 ± 7500	201,350 ± 7500	25.6% (24.2%–27.0%)	584,910	722,610 ± 14,200	137,700 ± 14,200	19.1% (15.9%–22.2%)
	0–5 years	1,582,480	1,858,700 ± 11000	276,220 ± 11,000	14.9% (13.9%–15.8%)	1,582,480	1887,080 ± 21,000	304,600 ± 21,000	16.1% (14.2%–18.0%)
Argentina	0–5 years	1,974,266	1,975,000	734 ± 10	0.03% (0.25%–0.32%)	–	–	–	–
Total[b]	0–1 year	47,510	54,231 ± 390	6721 ± 390	12.4% (11.1%–13.6%)	47,510	53,401 ± 1110	5891 ± 1110	11.1% (7.3%–14.7%)
Total[b]	0–5 years	110,227	120,518 ± 940	10,291 ± 940	8.5% (7.1%–9.9%)	110,227	120146 ± 1980	9919 ± 1980	8.3% (5.2%–11.3%)

Note: Hospitalizations for the entire period, from vaccine introduction through the last information available, adjusted for population growth.
[a] In Venezuela, outpatient and inpatient cases combined were reported since no disaggregated data were available.
[b] Venezuela and Argentina are excluded from this result.

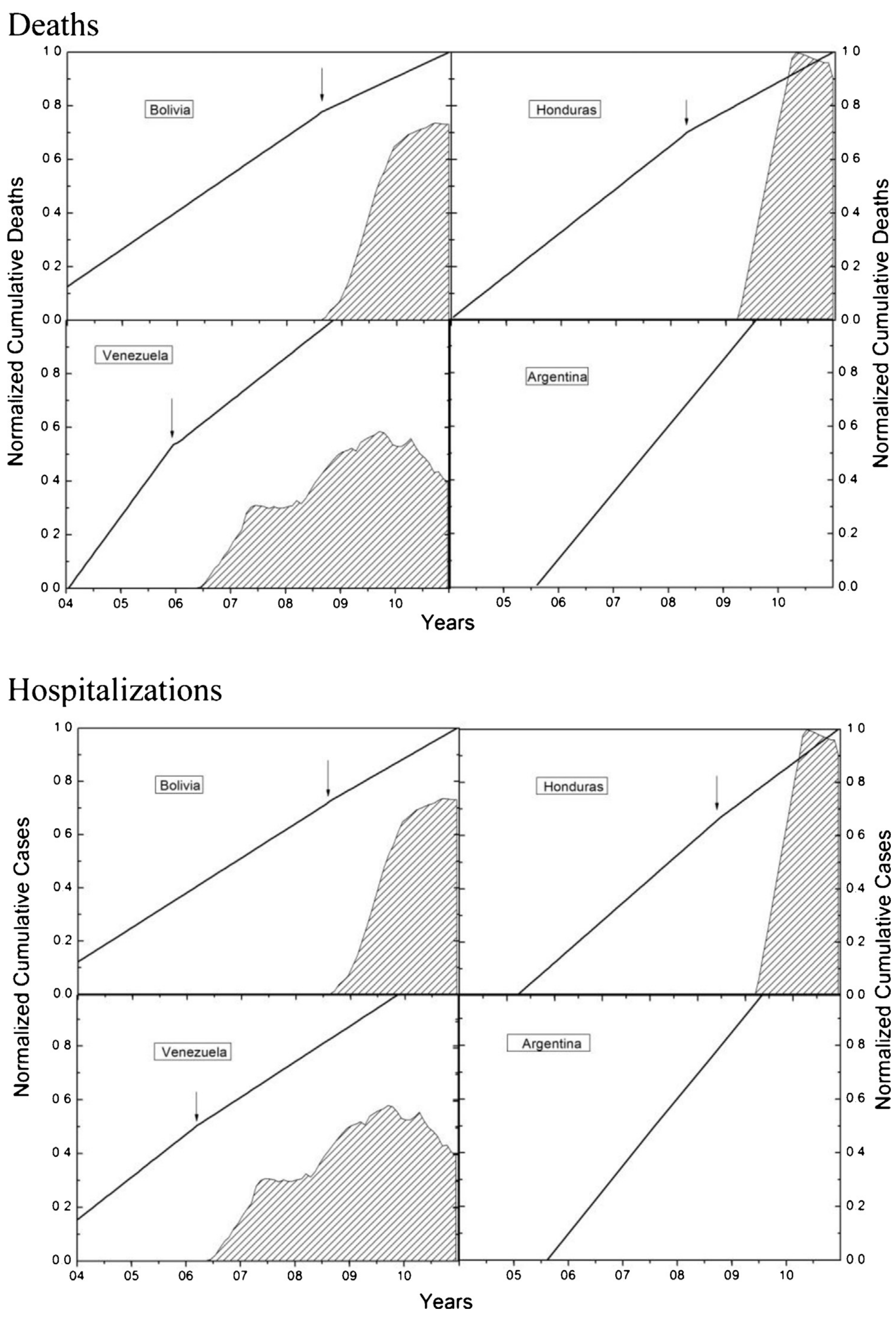

Fig. 2. All-cause diarrhea-related deaths and hospitalizations of children under five in countries where the vaccine has been introduced and in the control country (Argentina). Cumulative number of all-cause diarrhea-related deaths (top) and hospitalizations (bottom) observed in children under five, normalized to the total number of cases during the analyzed period. The arrow indicates when the vaccine was introduced and the shaded area shows cumulative vaccine coverage. It can be noted that in the control country (Argentina), there was no change in the slope, whereas this did occur in other countries where the vaccine was introduced. The *Y* axis indicates the cumulative number of cases, normalized to the total number of cases during the whole period. The quality of the data corresponding to El Salvador deaths was not good enough to be studied with the integral method, as can be observed in Table 2.

(Fig. 2). Due to the high degree of variability observed in the number of events over time in El Salvador, it could not be included in this graph.

Fig. 3 shows a decrease of mean value in the number deaths and hospitalizations in children under 5 years old using the projection method. The shaded areas in Figs. 2 and 3 represent the percentage of cumulative vaccine coverage following vaccine introduction.

The proportion of all-cause diarrhea attributed to rotavirus and the seasonality of cases are shown for each country in Fig. 4.

4. Discussion

Unlike the majority of rotavirus impact studies conducted in Latin America, this analysis evaluates several countries concurrently, using the same design, and comparing them with a control country. This makes it possible to estimate a decreasing trend in rotavirus disease burden regionally following vaccine introduction, so that possible secular changes can be evaluated.

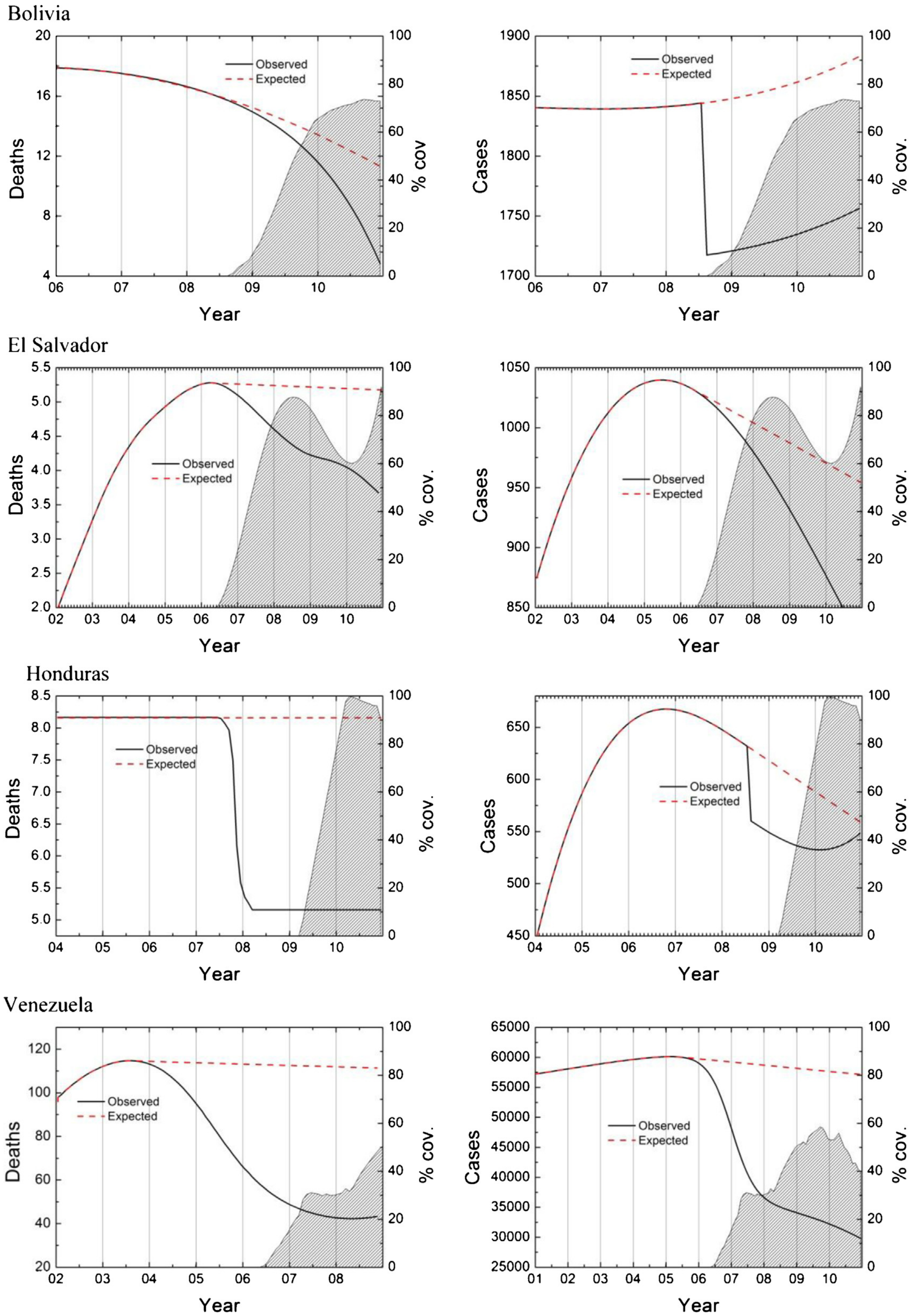

Fig. 3. All-cause diarrhea-related deaths and hospitalizations observed vs. expected
The graphs show deaths (right) and hospitalizations (left) observed and expected for the different countries. The solid line shows the trend observed and the dotted line corresponds to the projection of the trend in the absolute number of deaths (adjusted for population growth based on time series behavior prior to vaccine introduction). The shaded area represents cumulative coverage percentage since introduction of the vaccine, on a scale of 0–100% shown on the right ordinates.

The results show an absolute decrease of approximately 10,000 hospitalizations and between 2000 and 3000 fewer diarrhea-related deaths in children under 5 years old for all of the countries studied following introduction of the rotavirus vaccine as mentioned previously. Venezuela did not have disaggregated data on inpatient and outpatient cases and has therefore not been included in calculations on the reduction of the estimated number of hospitalizations.

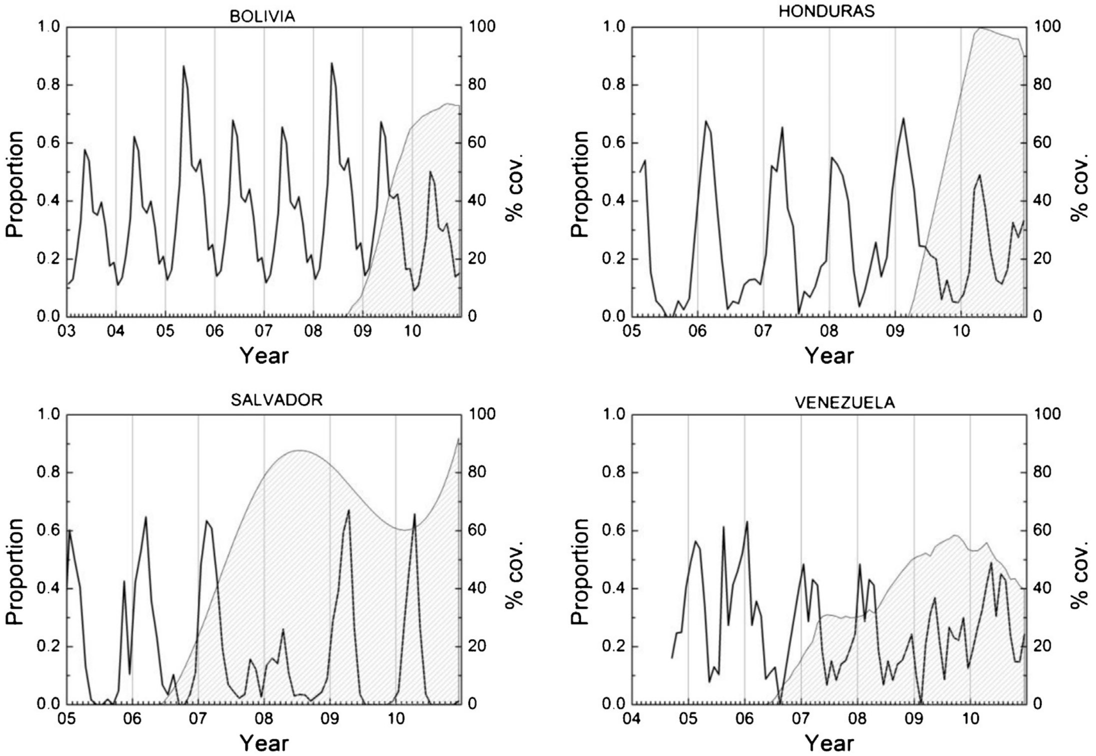

Fig. 4. Monthly ratio of rotavirus diarrhea to total diarrhea cases
On the *y* axis, the proportion of rotavirus diarrhea cases is shown for the different follow-up years shown on the *x* axis.

The data revealed a substantial drop in deaths and hospital admissions occurring after the vaccine had been introduced in Bolivia, Honduras and Venezuela, as shown in Fig. 2. The change in trend appears to happen before the introduction of the vaccine, but this is an artifact of the mathematical method. Regardless of when this change in trend happens, its sole presence suggests impact of the vaccine. If vaccination had no effect, all the curves would be similar to that of the control country (Argentina), which showed a constant slope throughout the whole period.

In the case of Honduras, a decrease was observed in rotaviral disease prior to introduction of the vaccine. This discrepancy in the temporal association may be due to an artificial increase in the number of cases during 2004–2006 as a result of improvements in the surveillance system that resulted in an increase in number of reported cases. However, this observed decrease in rotaviral disease could also be due to the introduction of the vaccine in neighboring countries (Nicaragua and El Salvador in 2006 and Guatemala in 2008) with which Honduras has a continuous population exchange due to inter-regional migration.

The observed reduction in the number of deaths is consistent with the results of studies conducted in Brazil [12,14,29], Panama [11], and Mexico [13]. As in the studies conducted previously in Brazil [12,15], Panama [16], Mexico [17] and El Salvador [18], a decreasing trend was also observed in the number of hospitalizations related to all-cause diarrhea in children under age 5.

Generally, a greater reduction was observed in the number of deaths than in hospitalizations, although this was not as apparent in Honduras and El Salvador. In the case of Honduras, the reduction in deaths and hospitalizations was similar. This may be due to a lack of statistical power given the low absolute number of cases, which makes it difficult to observe differences between events.

In the case of El Salvador, a more pronounced decreasing trend can be observed in the number of deaths than in hospitalizations using the projection method, although this was not observed using the integral method. This may be due to the low number of cases, as well as their high temporal variability.

The greater reduction observed in the number of deaths compared to the reduction in hospitalizations could be due to the fact that the vaccine is particularly effective in preventing severe diarrhea. This is consistent with studies conducted in El Salvador and Nicaragua, where the drop in mortality was more pronounced than the drop in hospitalizations following vaccine introduction [18,23,30]. It is possible that many of the deaths during the pre-rotavirus vaccination period occurred in children who had not been hospitalized due to poor access to health care, which may contribute to this difference. In addition, the majority of deaths or serious cases are found in children under 1 year of age, which is the group that would obtain the greatest protection from the vaccine [31].

The cumulative number of deaths and hospitalizations sustained the same trend over time in the control country (Argentina). In contrast, a decrease could be observed in the four countries that introduced the vaccine, reinforcing the validity of the results obtained, in addition to suggesting certain stability in the health care systems in the region. While it is possible that some structural differences exist, the better quality of water supply and sanitation services found in the control country are not important factors that influence the transmission of rotavirus disease [32,33]. Moreover, some areas of Argentina, specifically the northwest and northeast regions, present similar water and sanitary conditions to the countries selected for this study. Beyond these considerations, situations such as changes in social and health conditions, improvement in access to health care systems, and variations in the reporting patterns of surveillance systems may influence the results.

The results were robust given two different analysis methods used; a difference in disease burden reduction was observed in relation with the control country, and both methods were consistent with previously published studies. The impact of the vaccine would be even more evident had under-reporting in the pre-vaccine introduction period been considered.

In all of the countries, over 65% of total deaths among children 0 to 5 years ocurred in children under 1 year old. This result reinforces the reliability of the reports obtained, since the most serious cases of diarrhea generally occur in children under 1 year old.

Due to the lack of disaggregated information in the 0 to 5 age group, it was not possible to develop an analysis by age sub-groups. It was only possible to report results with a breakdown for 0 to 5 years of age and 0 to 1 year of age, which makes it difficult to prove in all the scenarios proposed that there is a greater impact in children 0 to1 year of age in relation with the 2 to 5 year age group in each scenario proposed.

It was not possible to categorize cases of diarrhea by severity because of study design. Our only indicator of severity of cases was the number of deaths.

The reduction in rotavirus disease burden correlated with vaccine introduction in the countries selected for this study, even though the post-vaccine introduction time series were limited (two to four years) and increase in coverage has been gradual. Although it has not been observed that greater vaccine coverage is associated with greater reduction in morbidity and mortality, it is clear that coverage and morbidity/mortality curves follow an inverse pattern in each study country.

Unresolved questions include impact of vaccination in the medium- and long-term, serotype replacement, and changes in the disease profile. Additional research based on epidemiological surveillance studies of rotavirus will be needed to answer these questions.

This study shows results consistent with other studies conducted on the impact of the rotavirus vaccine in reducing diarrhea-related hospitalizations and deaths in Latin American countries. Furthermore, the study provides evidence of disease burden reduction following the introduction of rotavirus vaccine, especially in diarrhea-related deaths in four countries of Latin America, using two different methods. These findings have important global health policy implications to help decision makers considering the introduction of rotavirus vaccine to their national immunization schedules.

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