Sustained Reduction of Childhood Diarrhea-Related Mortality and Hospitalizations in Mexico After Rotavirus Vaccine Universalization

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Abstract

Background.—Mexico implemented routine childhood vaccination against rotavirus in 2007. We describe trends in hospitalization and deaths from diarrhea among children aged <5 years in Mexico before and 7 years after implementation of rotavirus vaccination.

Methods.—We obtained data on deaths and hospitalizations from diarrhea, from January 2003 through December 2014, in Mexican children <5 years of age. We compared diarrhea-related mortality and hospitalizations in the postvaccine era with the prevaccine baseline from 2003 to 2006.

Results.—Compared with the prevaccine baseline, we observed a 53% reduction (95% confidence interval [CI], 47%–58%) in diarrhea-related mortality and a 47% reduction (95% CI, 45%–48%) in diarrhea-related hospitalizations in postvaccine years, translating to 959 deaths and 5831 hospitalizations averted every year in Mexican children aged <5 years. Prevaccine peaks in diarrhea-related mortality and hospitalizations during the rotavirus season months were considerably diminished in postvaccine years, with greater declines observed during the rotavirus season compared with non–rotavirus season months.

Conclusions.—We document a substantial and sustained decline in diarrhea-related hospitalizations and deaths in Mexican children associated with implementation of rotavirus

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vaccination. These results highlight the public health benefits that could result in countries that adopt rotavirus vaccination into their national immunization programs.

Keywords

rotavirus vaccines; diarrhea; mortality; hospitalizations; Mexico

Worldwide, diarrheal disease remains a leading cause of death in children aged <5 years (hereafter "under 5") [1]. Rotavirus is the most common cause of severe diarrhea in children and is most frequently associated with cases of dehydration, hospitalization, and death [2]. Globally, it is responsible for about 40% of all diarrhea-related hospitalizations and was estimated to cause 453 000 deaths in 2008 [2, 3]. Rotavirus infection has a strong seasonal pattern [4, 5]; in Mexico, approximately 60%–70% of the hospitalizations for laboratory-confirmed rotavirus infection occur during the months of October–March [6, 7].

RotaTeq (Merck & Co, Whitehouse Station, New Jersey) and Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium), the 2 rotavirus vaccines available on the global market, have been shown to be safe and effective in large-scale prelicensure studies [8–17]. Since the recommendation of the World Health Organization to introduce rotavirus vaccines into every country's national immunization program (NIP), >75 countries have implemented rotavirus vaccines [18, 19]. Mexico was one of the first nations to introduce, in May 2007, the rotavirus vaccine in its national immunization program. Rotarix was used during the first 5 years (2006–2011), administered in a 2-dose schedule. In 2011, due to known similar efficacy for both vaccines, a complete-schedule price competition was set by the government, and monovalent vaccine was substituted with pentavalent vaccine, RotaTeq, administered on a 3-dose schedule.

Monitoring the impact of rotavirus immunization against diarrhea deaths and hospitalizations during routine use will be important to better understand the potential of these vaccines. Two years after implementation of rotavirus vaccination, a 35% reduction in the mortality rate and a 40% reduction in the hospitalization rate from diarrhea were observed in children under 5. These reductions were significant in children aged 0–23 months, but not in children aged 24–59 months [20, 21]. Once 4 annual cohorts were vaccinated with the monovalent vaccine by 2010, the reduction in mortality was 50%, with a significant reduction in all subgroups of children under 5 and with no differences across regions with different socioeconomic levels of Mexico [22, 23]. In this study, we include an additional 3 years of postvaccine data to describe trends in hospitalization and deaths from diarrhea among children under 5 in Mexico before and 7 years after implementation of universal rotavirus vaccination.

METHODS

All-Cause and Diarrhea-Related Hospitalizations

We accessed data from the Ministry of Health's National System for Health Information to obtain monthly data on all-cause and diarrhea-related hospitalizations among children aged <5 years, from January 2003 to December 2014, for all of Mexico's 677 Ministry

of Health hospitals. These hospitals cover about 50% of the hospitalizations nationwide in public hospitals. *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes A00–A03, A04, A05, A06.0–A06.3, A06.9, A07.0–A07.2, A07.9, and A08–A09 were used to select diarrhea-related hospitalizations. No attempt was made to evaluate hospitalizations specifically caused by rotavirus infection because there is no systematic laboratory testing for rotavirus in children hospitalized for diarrhea in Mexico.

Diarrhea-Related Deaths

For the period from January 2003 through December 2014, we obtained data on diarrhea-related deaths among Mexican children under 5 from the National Institute of Statistics, Geography, and Informatics and the Ministry of Health's General Directorate of Health Information, which collects information from all death certificates. We used the same *ICD-10* codes used to select diarrhea hospitalizations to select diarrhea-related deaths.

Vaccine Coverage

The Mexico National Health and Nutrition Survey for 2012 reports coverage with a complete rotavirus vaccine schedule of 63% for children <1 year and 80% for those <2 years of age [24]. Coverage from the National Health and Nutrition Survey 2012 could be underestimated due to underreporting of doses applied in the national immunization and health card [25].

Other studies using administrative coverage data (doses administered/the estimated target population) have estimated the coverage rate for a complete vaccine series to be 90% for children aged <1 year [22, 23, 25]. Administrative coverage could be imprecise because the estimated population, in some scenarios, could be higher or lower than the number of actual targeted population.

Prevaccine and Postvaccine Periods

The prevaccine period was defined as January 2003 to December 2006; 2007 was considered a transition year after vaccine introduction. Postvaccine period was considered according to age group to account for the moment when the first vaccinated cohort reached the age group: <12 months from January 2008 to December 2014, 12–23 months from January 2009 to December 2014, and 24–59 months from January 2010 to December 2014. In addition, according to the timing of detection of rotavirus in sentinel laboratory surveillance in Mexico, we defined the rotavirus season as occurring from November to March.

Statistical Analysis

All analyses were restricted to children <5 years of age and were stratified by age: 11 months, 12–23 months, and 24–59 months. National Population Council population estimates were used as denominators [26].

We compared median annual diarrhea mortality rates and median annual absolute number of diarrhea-related deaths in the prevaccine and postvaccine periods. We also compared the median absolute number and rate of diarrhea-related deaths during the peak rotavirus season in the prevaccine and postvaccine periods.

Overall numbers of diarrhea-related hospitalizations from January 2003 to December 2014 were examined. Because the catchment populations of the study hospitals were not known, rates of hospitalization for diarrhea per 100 hospitalizations from all causes were calculated. The median annual rate of diarrhea-related hospitalizations in the prevaccine period was compared with the postvaccine period. To improve specificity of vaccination effect on rotavirus disease, we also restricted our analysis to hospitalizations during the rotavirus season among children <5 years of age.

Diseases recorded on the same information systems where we obtain the deaths and hospitalizations due to diarrhea were used as controls to show that the reduction effect seen in diarrhea mortality and hospitalizations was not an artifact of the record or an unspecific trend. As controls we have included congenital heart malformation mortality for diarrhea deaths, and hospitalization due to injuries for diarrhea hospitalizations.

We estimated the national reductions in diarrhea-related hospitalizations that could reasonably be attributed to the rotavirus vaccinations by extrapolating the rates of diarrhea-related hospitalization per 100 all-cause admissions—observed in the Ministry of Health hospitals, which attend to about 50% of the population—to the total number of hospital admissions for all causes observed countrywide.

We calculated 95% confidence intervals (CIs) for the rate reductions in diarrhea-related deaths and diarrhea-related hospitalizations by CI for comparing 2 independent proportions. A 2-sided *P* value of <.05, as calculated with a χ^2 test, was considered significant. Analyses were performed with Microsoft Excel (Microsoft Corporation, Redmond, Washington).

RESULTS

Mortality

From January 2003 to December 2014, there were 14 808 registered deaths in Mexican children under 5, with 66.2% occurring in children 0–11 months, 22.3% in children 12–23 months, and 11.5% in children 24–59 months of age. Monthly mortality showed the strong seasonal pattern of high peaks in cold months from January to April, mainly in the prevaccine period. After the introduction and universalization of the rotavirus vaccines, seasonal peaks were drastically reduced and seasonality become less evident (Figure 1).

In the prevaccine years, there was a median number of 1198 diarrhea-related deaths annually in children 0–11 months, 421 in children 12–23 months, and 175 in children 24–59 months of age, with median annual mortality rates of 52.7, 18.6, and 2.6 deaths per 100 000, respectively. In the postvaccine period, the median number of annual deaths was reduced to 563 in children 0–11 months, 158 in children 12–23 months, and 114 in children 24–59 months of age, with median annual mortality rates of 25.4, 7.1, and 1.7 deaths per 100 000, respectively. This represents significant reductions in the mortality rate of 52% (96% CI, 45%–59%), 62% (96% CI, 50%–73%), and 34% (96% CI, 15%–55%) in children 0–11 months, 12–23 months, and 24–59 months of age, respectively. Overall in children under 5, we observed a 53% reduction (95% CI, 47%–58%) in diarrhea-related mortality rates

post–vaccine introduction, with about 959 deaths averted every year in children under 5 (Table 1).

The reductions were more evident when the analysis was restricted to the rotavirus season, showing a reduction in mortality rate of 67% in children under 5 during the rotavirus season, which highlights the impact on the diarrhea mortality of the rotavirus vaccination (Table 2).

As a control, in the same population, in the same information system, in the same periods, mortality due to congenital heart malformations did not show any reduction (Table 1; Figure 1).

Hospitalizations

From January 2003 to December 2014, there were 189 837 diarrhea-related hospitalizations in children under 5, with 42.3% occurring in children 0–11 months, 32.2% in children 12–23 months, and 25.4% in children 24–59 months of age. Monthly hospitalization rates also showed a clear seasonal pattern of high peaks in cold months, mainly in the prevaccine period. After the introduction of rotavirus vaccines, seasonal peaks were considerably reduced, with declines sustained throughout the postvaccine period (Figure 2).

In prevaccine years, the median number of annual hospitalizations was 8212 in children 0–11 months, 5823 in children 12–23 months, and 3728 in children 24–59 months of age, with median annual hospitalization proportions of 5.6, 20.2, and 7.9 hospitalizations per 100 hospitalizations in children of these ages, respectively. In the postvaccine periods, the median number of annual hospitalizations was reduced to 4926 in children 0–11 months, 3445 in children 12–23 months, and 3562 in children 24–59 months of age, even when the total number of hospitalizations increased by 26%. These median frequencies corresponded to median annual hospitalization proportions of 2.7, 10.2, and 5.5 diarrhea patients per 100 hospitalizations, respectively. This represents significant reductions in hospitalizations of 52% (96% CI, 50%–54%), 49% (96% CI, 47%–52%), and 30% (96% CI, 26%–34%) in children 0–11 months, 12–23 months, and 24–59 months of age, respectively. Overall, in children under 5, we estimate a 47% reduction (95% CI, 45%–48%) in diarrhea-related hospitalizations, with about 5831 hospitalizations averted every year in children under 5 in Ministry of Health (MOH) hospitals (about 11 662 in the country). As a control, in the same population, in the information system, in the same periods, hospitalizations due to injuries did not show a significant important reduction (Figure 2; Table 3).

In prevaccine years, 55% of diarrhea-related hospitalizations occurred during the rotavirus season. After the introduction of the rotavirus vaccine, during the rotavirus season, diarrhea-related hospitalizations decreased 66% in children under 5, with reductions of 68% in the group of 0–11 months and 12–23 months. In postvaccine years, only 33% of all diarrhea-related hospitalizations occur during the rotavirus season, showing a specific impact of the rotavirus vaccines with more important reductions in the rotavirus seasons (Table 4).

DISCUSSION

Rotavirus vaccine has contributed significantly toward reaching the Millennium Development Goal 4 target in counties where rotavirus vaccines have been introduced [27].

After the implementation of universal rotavirus vaccination in Mexico in 2007, substantial declines in childhood diarrhea deaths and admissions were observed [20–23]. Seven years after the introduction of rotavirus vaccines in the NIP, diarrhea mortality continues to decrease, with a decline of 53% in diarrhea deaths, representing about 6328 averted deaths since vaccine introduction. All-cause diarrhea-related hospitalizations have also declined since 2007, with the highest impact observed during rotavirus seasons. During these months, a reduction of 66% was seen for all diarrhea hospitalizations, with 37 050 hospitalizations adverted during fall/winter seasons in MOH hospitals, and about 74 099 in the country.

We examined all-cause diarrhea-related deaths and hospitalizations, as we did not have verifiable information on laboratory-confirmed rotavirus events. Consequently, the results could be affected by secular trends in diarrhea related to other pathogens to some extent. Nevertheless, the seasonal pattern of all diarrhea-related deaths and hospitalizations follow the same fall/winter seasonality of rotavirus, allowing us to indirectly assess the effect of vaccination on the mortality and the proportion of diarrhea-related hospitalizations. In addition, the stepped shape of the reduction by age groups, as they became vaccine eligible, support the effect of the rotavirus vaccine. In initial reports, no statistically significant reduction was observed in diarrhea mortality or diarrhea hospitalizations in children 24–59 months of age. It was not until the entire annual cohort of under-5 children was vaccinated that reduction was observed in the group of children 24–59 months of age. Finally, there was a noticeable flattening of the seasonal peaks in diarrhea mortality and diarrhea-related hospitalizations, with the greatest decrease seen during the rotavirus season, further supporting a role for rotavirus vaccination in the observed decline.

Additionally, the data sources we used may have been subject to some underreporting and classification error. Nevertheless, underreporting would likely be similar during the periods before and after the introduction of the vaccination program, and thus unlikely to produce major bias. Furthermore, to exclude the possibility of bias from changes in the reporting system, we used other conditions as a control, and it was reassuring that these control conditions did not demonstrate any secular trend.

Our findings are in accord with other Latin American findings, with decreases of 17%–55% in all-cause diarrhea hospitalizations and effectiveness against rotavirus diarrhea hospitalizations ranging from 17% to 94% [28–33]. Mexico's reductions in diarrhea-related deaths are similar to other Latin American countries, which report a decline of 22%–50% [32, 34, 35]. These results highlight the public health benefits that could result in countries that adopt rotavirus vaccination as part of their NIPs.

In summary, we documented a substantial and sustained decline in diarrhea-related hospitalizations and deaths in Mexican children associated with implementation of rotavirus vaccination. These data highlight the real-world value of vaccination and should encourage

other countries to consider vaccination as a strategy to reduce the burden of severe childhood diarrhea.

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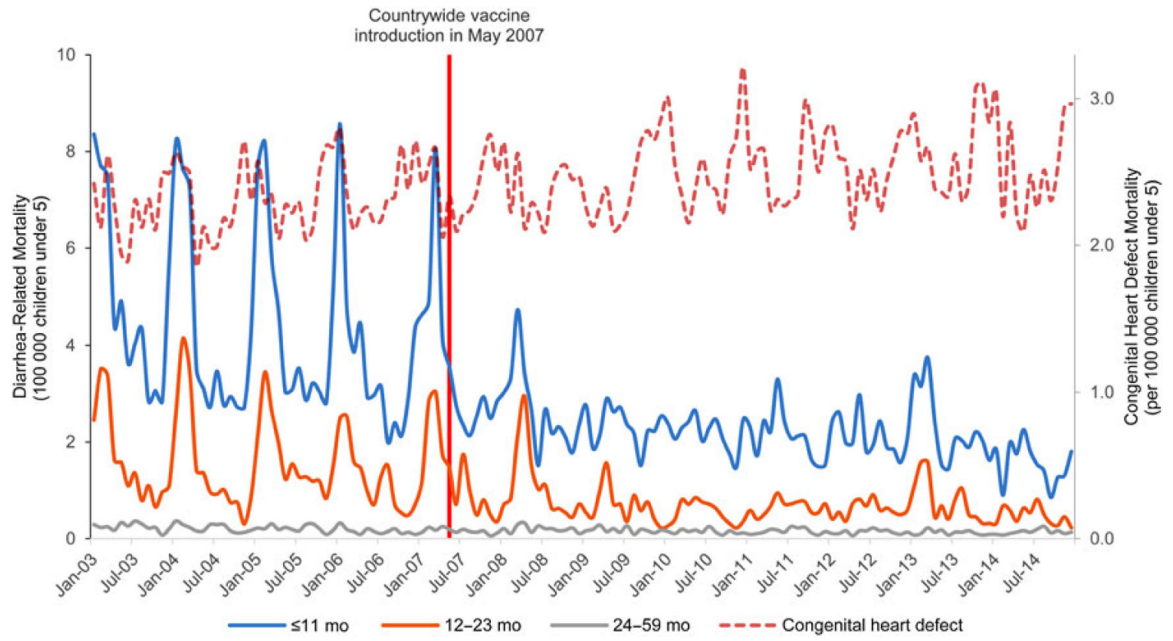
Figure 1.
Diarrhea-related mortality among children aged   59 months from 2003 through 2014 in
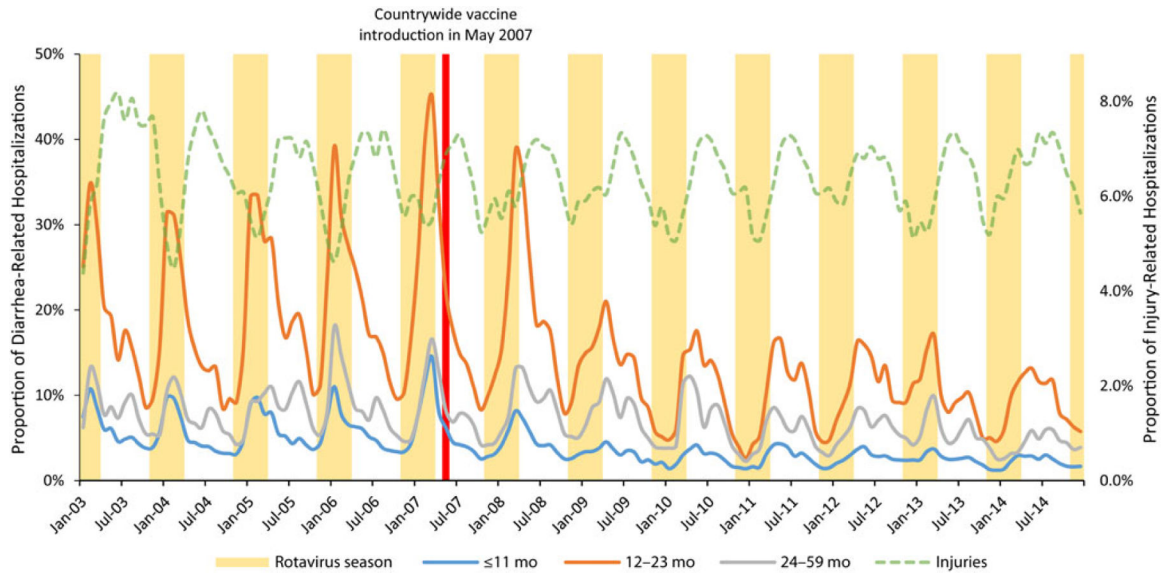Mexico, by age group.

Figure 2.
Proportion of diarrhea-related hospitalizations among children aged 59 months from 2003 through 2014 in Mexico, by age group.

Table 1.

Changes in Diarrhea-Related Mortality Among Children <5 Years of Age in the Postvaccine Period Compared With the Prevaccine Period, by Age Group

Age Group	Median Annual No. of Diarrhea-Related Deaths		Median Annual Diarrhea-Related Death Rate (No. of Deaths per 100 000 Under-5 Children)		Absolute Reduction			
	Prevaccine	Postvaccine	Prevaccine	Postvaccine	No. of Deaths	Death Rate (No. of Deaths per 100 000 Under-5 Children)	Relative Reduction in Death Rate, % (95% CI)	P Value
All ages (0–59 mo)	1794	835	15.8	7.5	959	8.3	53 (47–58)	<.001
11 mo	1198	563	52.7	25.4	635	27.3	52 (45–59)	<.001
12–23 mo	421	158	18.6	7.1	264	11.5	62 (50–73)	<.001
24–59 mo	175	114	2.6	1.7	61	0.9	34 (15–53)	<.001
Congenital heart defect 0–59 mo	3177	3362	27.9	30.1	−186	−2.2	−8 (−13 to −3)	<.001

P values were calculated with the use of a χ^2 test. Negative values imply relative increase. Prevaccine period was defined as January 2003 to December 2006. Postvaccine period: age 11 months from January 2008 to December 2014, age 12–23 months from January 2009 to December 2014, and age 24–59 months from January 2010 to December 2014.

Abbreviation: CI, confidence interval.

Table 2.

Changes in Diarrhea-Related Mortality Among Children <5 Years of Age in the Postvaccine Period Compared With the Prevaccine Period During Rotavirus Season

Age Group	Median No. of Diarrhea-Related Deaths		Median Diarrhea-Related Death Rate (No. of Deaths per 100 000 Under-5 Children)		Absolute Reduction in No. of Deaths per 100 000 Under-5 Children		Relative Reduction in Death Rate, % (95% CI)	P Value
	Prevaccine	Postvaccine	Prevaccine	Postvaccine	No. of Deaths	Death Rate		
All ages (0–59 mo)	997	325	8.8	2.95	672	5.9	67 (60–74)	<.001
11 mo	684	232	30.1	10.5	452	19.6	65 (56–74)	<.001
12–23 mo	241	54	10.6	2.4	187	8.2	77 (63–91)	<.001
24–59 mo	72	39	1.1	0.6	33	0.5	45 (16–74)	<.001
Congenital heart defect 0–59 mo	1423	1516	12.5	13.3	−0.9	−1.1	−9 (−16 to −1)	<.001

P values were calculated with the use of a χ^2 test. Negative values imply relative increase. Prevaccine period was defined as January 2003 to December 2006.

Abbreviation: CI, confidence interval.

Table 3.

Changes in Diarrhea-Related Hospitalizations Among Children <5 Years of Age in the Postvaccine Period Compared With the Prevaccine Period, by Age Group

Age Group	Median Annual No. of Diarrhea-Related Hospitalizations		Median Annual Diarrhea-Related Hospitalizations, %		Absolute Reduction Proportion of Hospitalizations	Relative Reduction in Hospitalizations, Proportion (95% CI) %	P Value
	Prevaccine	Postvaccine	Prevaccine	Postvaccine			
All ages (0–59 mo)	17 763	11 933	8.0	4.3	3.7	47 (45–48)	<.001
11 mo	8212	4926	5.6	2.7	2.9	52 (50–54)	<.001
12–23 mo	5823	3445	20.2	10.2	10.0	49 (47–52)	<.001
24–59 mo	3728	3562	7.8	5.5	2.3	30 (26–34)	<.001
Injuries 0–59 mo	14 145	17 518	6.37	6.26	0.12	2 (0–4)	.09

P values were calculated with the use of a χ^2 test. Prevaccine period was defined as January 2003 to December 2006. Postvaccine period: age 11 months from January 2008 to December 2014, age 12–23 months from January 2009 to December 2014, and age 23–59 months from January 2010 to December 2014.

Abbreviation: CI, confidence interval.

Table 4.

Changes in Diarrhea-Related Hospitalizations Among Children <5 Years of Age in the Postvaccine Period Compared With the Prevaccine Period During Rotavirus Season

Age Group	Median No. of Diarrhea-Related Hospitalizations		Median Diarrhea-Related Hospitalizations, Proportion		Absolute Reduction Proportion of Hospitalization	Relative Reduction in Hospitalizations, Proportion (95% CI) %	P Value
	Prevaccine	Postvaccine	Prevaccine	Postvaccine			
All ages (0–59 mo)	9748	3952	9.8	3.4	6.4	66 (64–68)	<.001
11 mo	4573	1719	7.0	2.2	4.8	68 (65–71)	<.001
12–23 mo	3507	1143	24.5	7.8	16.7	68 (65–72)	<.001
24–59 mo	1668	1090	8.3	4.2	4.1	50 (45–55)	<.001

P values were calculated with the use of a χ^2 test.

Abbreviation: CI, confidence interval.