Effect of Rotavirus Vaccine on Diarrhea Mortality in Different Socioeconomic Regions of Mexico

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KEY WORDS
rotavirus vaccines, diarrhea, mortality, Mexico

ABBREVIATIONS
CI—confidence interval
CENSIA—National Center for Child and Adolescent Health
WHO—World Health Organization

Dr Gastañaduy conducted the analysis, drafted the initial manuscript, and provided final approval of the manuscript as submitted; Drs Sánchez-Uribe and Esparza-Aguilar contributed to the acquisition of data, carried out the initial analyses, reviewed and revised the article critically, and provided final approval of the manuscript as submitted; Dr Desai carried out the initial analyses and provided final approval of the manuscript as submitted; and Drs Parashar, Patel, and Richardson contributed to the conception and design of the study, reviewed and revised the article critically, and provided final approval of the manuscript as submitted.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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WHAT’S KNOWN ON THIS SUBJECT: In Mexico, substantial declines in childhood diarrhea deaths have been documented since the introduction of the rotavirus vaccine in 2007. However, there is concern of lower vaccine effectiveness in less developed regions of Mexico with higher diarrhea-related mortality.

WHAT THIS STUDY ADDS: We documented significant and comparable declines across all 3 regions of Mexico with different levels of development, indicating equitable vaccine distribution to children with varying risk of mortality and reaffirming the beneficial effects of rotavirus vaccination against fatal diarrheal disease.

abstract

OBJECTIVE: In Mexico, declines in childhood diarrhea deaths have been documented during 2008–2010 after rotavirus vaccine introduction in 2007. Because of concerns about variation in rotavirus vaccine efficacy by socioeconomic status, we compared reductions in diarrhea mortality in the lesser developed southern region versus the more developed northern and central regions of Mexico.

METHODS: We obtained data from national vital statistics on diarrhea deaths among children aged <5 years from 2002 through 2011. We compared region-specific diarrhea mortality before (2003–2006) and after (2009–2011) vaccine introduction. Regional vaccine coverage was estimated from administrative data, and socioeconomic status was assessed by using the Human Development Index.

RESULTS: In northern, central, and southern Mexico, the 2007 Human Development Index was 0.84, 0.82, and 0.77, respectively, and by 2010 an estimated 99%, 84%, and 89% of children aged 12 months had completed rotavirus vaccination. Diarrhea mortality among children <5 years old declined from 8.3, 17.9, and 28.5 deaths per 100 000 children during 2003–2006 to 4.5, 8.1, and 16.2 in 2009–2011 in northern, central, and southern Mexico, respectively, corresponding to rate reductions of 45%, 55%, and 43%. No significant differences were observed in rate reductions between regions (P > .8).

CONCLUSIONS: After introduction of rotavirus vaccination, marked and sustained declines in diarrhea deaths were seen among children in all regions of Mexico, including in the least developed southern region with the highest baseline diarrhea mortality. This finding indicates equitable vaccine delivery to children with varying risk of mortality and reaffirms the beneficial effects of rotavirus vaccination against fatal diarrheal disease. Pediatrics 2013;131:e1115–e1120
Rotavirus is the most common cause of severe childhood gastroenteritis worldwide, leading to an estimated 453,000 deaths among children <5 years old annually. Since 2006, the World Health Organization (WHO) recommended the use of rotavirus vaccines for countries in the Americas and Eastern Europe on the basis of good vaccine efficacy and safety data from these regions. In 2009, after trials demonstrated the efficacy of rotavirus vaccines in Asia and Africa, WHO expanded the recommendation to all children worldwide. Since 2006, some 30 countries worldwide have introduced rotavirus vaccines into their routine immunization program, with introductions mostly in high- and middle-income countries with low diarrhea-related mortality. Vaccine introduction in these early adopter countries has markedly reduced the burden of severe childhood gastroenteritis, including diarrhea mortality in Brazil and Mexico where this has been specifically examined.

In clinical trials, the efficacy of rotavirus vaccines against severe rotavirus disease has been lower in low-income, high-child-mortality countries compared with high- and middle-income countries with lower child mortality. This disparity in vaccine performance may reflect factors that impair vaccine take or immune responses in high-mortality populations, such as circulating maternal antibodies, breast milk interference, concomitant enteric infections, oral polio vaccine interference, and undernutrition. Despite lower effectiveness in high-mortality settings, rotavirus vaccines are likely to have their highest life-saving potential in these regions where >90% of deaths from rotavirus diarrhea occur. However, the efficacy of rotavirus vaccines against rotavirus mortality could not be examined in clinical trials because of the very large sample size required. Consequently, monitoring the impact of rotavirus immunization against diarrhea deaths during routine use in national immunization programs will be critical for better understanding the full potential of these vaccines.

In Mexico, substantial declines in childhood deaths from diarrhea have been documented since the national introduction of rotavirus vaccine during 2007. During 2008–2010, diarrhea-related deaths among children <5 years old decreased by 46% relative to prevaccine levels from 2003 through 2006. However, because of year-to-year variations in diarrhea rates, ongoing evaluation is necessary to confirm that the observed reductions early after the introduction of vaccine are sustained, thus providing stronger support for vaccine effect rather than secular changes. In addition, potential regional differences in vaccine impact have not been previously evaluated. The level of economic development and health care infrastructure differs between the various states of Mexico: the northern and central states are more developed compared with the southern states. This heterogeneity in economic development provides an opportunity to assess whether differences in vaccine impact on diarrhea deaths exist by region.

The primary objectives of this analysis were to determine if the reductions in diarrhea deaths previously documented during 2008–2010 were sustained during 2011 and to compare postvaccination trends in diarrhea-related mortality in the lesser developed southern region of Mexico with those in the more developed northern and central regions. The high quality of Mexico’s death registration data and the heterogeneity in development between regions provided a suitable setting to examine regional differences of the impact of the rotavirus vaccine on diarrhea-related mortality.

METHODS
Diarrhea-Related Deaths
We obtained numbers of diarrhea-related deaths among Mexican children from the National Institute of Statistics, Geography, and Informatics, which gathers and codes death certificates for children <5 years of age. Data were accessed through the National System for Health Informatics and collected for the period July 2002 through December 2011. The following International Classification of Diseases, 10th Revision, codes were used for extraction: A00–A03, A04, A05, A06.0–A06.3, A06.5, A07.0–A07.2, A07.5, and A08–A09. Mexico is divided into 32 federal entities, composed of 31 states and 1 federal district (Mexico City). Numbers of diarrhea-related deaths were extracted for each federal entity. Deaths were then aggregated into 3 geographic regions: northern region (Aguascalientes, Baja California, Baja California Sur, Coahuila de Zaragoza, Chihuahua, Durango, Nayarit, Nuevo Leon, San Luis Potosi, Sinaloa, Sonora, Tamaulipas, Zacatecas), central region (Colima, Distrito Federal, Guanajuato, Hidalgo, Jalisco, Mexico, Michoacan de Ocampo, Morelos, Puebla, Queretaro de Arteaga, Tlaxcala, Veracruz, Yucatan), and southern region (Campeche, Chiapas, Guerrero, Oaxaca, Quintana Roo, Tabasco, Yucatan).

Socioeconomic Development
To assess indicators of economic development, we obtained 3 different parameters for each state: the 2007 under-5 child mortality rate, the 2007 gross domestic product per capita, and the 2007 Human Development Index. Indices were extracted from the Instituto Nacional de Estadistica y Geografia, a government entity that collates statistics of the population and economy of Mexico, and the human development reports from the United Nations Development Program.
population size was calculated for each indicator.

**Vaccine Coverage Data**

In Mexico, vaccines for children are provided by 3 health care institutions: the National Center for Child and Adolescent Health (CENSIA), part of the Ministry of Health; Instituto Mexicano de Seguro Social; and Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado. CENSIA provides vaccine for ~50% to 61% of all Mexican infants, with the Instituto Mexicano de Seguro Social and Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado covering the rest. A staggered introduction of the monovalent rotavirus vaccine started in February 2006, and eventually expanded to include all Mexican children by May 2007. Two doses given at ages 2 and 4 months were recommended. Because surveys of rotavirus vaccine coverage are not available for Mexico, we relied on administrative coverage data kept by CENSIA on the number of doses given (either 1 or 2 doses) and the population served by CENSIA. A crude estimate of rotavirus vaccine coverage was calculated by dividing the number of doses administered during 2010 by the cohort of infants eligible to receive vaccine through CENSIA.

**Data Analysis**

Trends of diarrhea-related mortality were examined over the entire surveillance period (from July 2002 through December 2011). Median rates of diarrhea-related death for each surveillance year were calculated by using corresponding population estimates for Mexico from the National Population Council. We compared region-specific diarrhea mortality rates and absolute reductions in number of diarrhea deaths before (2003–2006) and after (2009–2011) vaccine introduction. Analysis was restricted to children <5 years of age and was stratified by age ≤11 months, 12 to 23 months, and 24 to 59 months, and by region. Because the rotavirus vaccine was recommended for all infants in 2007 and coverage was still increasing during the early years of the vaccine program, we considered 2007 and 2008 as transitional years and excluded these years from this part of the analysis.

We calculated 95% confidence intervals (CIs) for the rate reductions in diarrhea-related death. A $\chi^2$ test was used to estimate significance; $P$ values <0.05 indicated statistical significance. Analyses were performed with Microsoft Excel (Microsoft Corporation, Redmond, WA).

**RESULTS**

**Socioeconomic Indicators**

An analysis of the mean indicators of development by region in Mexico indicates that the southern region has a higher under-5 mortality rate and lower gross domestic product per capita and Human Development Index compared with the northern and central regions (Table 1).

**Vaccine Coverage**

On the basis of CENSIA administrative data, 3 830 932 second rotavirus vaccine doses were administered to a target population of 4 677 341 children <5 years of age in Mexico during 2010, for a vaccine coverage of 82% (Table 2). Two-dose vaccine coverage was ≥68 across the 3 age groups and regions. In general, coverage was highest among children <24 months of age and in the northern states of Mexico (Table 3).

**Diarrhea-Related Deaths**

**Overall Trends**

Before nationwide introduction of the rotavirus vaccine in 2007, diarrhea deaths among children <5 years followed a predictable seasonal pattern, with almost two-thirds of all deaths occurring from December to May (Fig 1). Nearly 67% of the deaths were among children ≤11 months of age, whereas 23% and 10% were among those 12 to 23 months and 24 to 59 months of age, respectively. After introduction of the vaccine, there was a clear flattening of the winter peak in diarrhea-related mortality compared with previous years. During 2008, the first year after vaccine introduction, reduction in diarrhea deaths was most prominent among infants, the only age group that would have been vaccinated. After 2009, a reduction in deaths was observed in the 12- to 23-month age group and was sustained to the end of 2011.


When comparing the number of diarrhea-related deaths by age group in the pre- and postvaccine years, reductions in diarrhea mortality were observed across all age groups in Mexico (Table 2). The greatest relative reductions in rates of diarrhea-related deaths were seen among children <24 months of age. Although the relative reduction was lower among children ≥24 months

**TABLE 1** 2007 Mean Indicators of Development

<table>
<thead>
<tr>
<th>Region</th>
<th>Under-5 Mortality Rate (per 1000 Live Births)</th>
<th>GDP per Capita, US$</th>
<th>Human Development Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern</td>
<td>16.4</td>
<td>10 553</td>
<td>0.94</td>
</tr>
<tr>
<td>Central</td>
<td>18.8</td>
<td>8 508</td>
<td>0.82</td>
</tr>
<tr>
<td>Southern</td>
<td>23.2</td>
<td>5 707</td>
<td>0.77</td>
</tr>
</tbody>
</table>

* A regional weighted mean based on population size was calculated for each indicator. GDP, gross domestic product.

b A measurement of development that combines indicators of life expectancy, educational attainment, and income, expressed as a value between 0 and 1.
of age, only 10% of diarrhea deaths occurred in this age group, and reductions were significant for all age groups. Absolute reductions in the number of diarrhea-related deaths were substantially greater among infants <12 months of age.

When stratifying by region, an annual median of 245, 1044, and 518 under-5 diarrhea-related deaths were reported in Mexico during the 2003–2006 baseline prevaccine period for the northern, central, and southern regions, respectively (Table 3). Diarrhea mortality decreased from 8.3, 17.9, and 28.5 deaths per 100 000 children during 2003–2006 to 4.5, 8, and 16.1 in 2009–2011 in northern, central, and southern Mexico, respectively, corresponding to rate reductions of 45% (95% CI: 29%–61%; P < .001), 55% (95% CI: 47%–63%; P < .001), and 43% (95% CI: 31%–53%; P < .001). No significant differences were observed in rate reductions between regions (P > .8). Absolute reductions in number of deaths were 125, 624, and 255 and in rates of death were 3.8, 9.8, and 12.4 deaths per 100 000 children in the northern, central, and southern regions, respectively. The absolute reductions translated to ~1000 childhood deaths averted every year in Mexico after vaccine introduction for years 2009 through 2011. In each of the 3 regions, significant reductions ranging from 39% to 57% and 60% to 62% were observed among children aged <12 months and 12 to 23 months, respectively, in whom 90% of the diarrhea deaths occurred. Among children aged 23 to 59 months, reductions were lower (17%–31%) but confidence limits were wide.

**DISCUSSION**

Our findings of significant reductions in diarrhea death of ~50%, which were sustained for 4 continuous years, provide

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<table>
<thead>
<tr>
<th>Region and Age Group</th>
<th>2010 Two-Dose Vaccine Coverage,a, %</th>
<th>No. of Diarrhea-Related Deaths</th>
<th>Diarrhea-Related Rate of Death per 100 000</th>
<th>Absolute Reduction</th>
<th>Relative Reduction in Rate of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Northern</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤11 Months</td>
<td>99</td>
<td>169</td>
<td>85</td>
<td>30.3</td>
<td>16.2</td>
</tr>
<tr>
<td>12–23 Months</td>
<td>100</td>
<td>56</td>
<td>20</td>
<td>9.4</td>
<td>3.8</td>
</tr>
<tr>
<td>24–59 Months</td>
<td>79</td>
<td>21</td>
<td>15</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td>All ages (0–59 mo)</td>
<td>91</td>
<td>245</td>
<td>120</td>
<td>8.3</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Central</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤11 Months</td>
<td>84</td>
<td>735</td>
<td>302</td>
<td>66.5</td>
<td>28.9</td>
</tr>
<tr>
<td>12–23 Months</td>
<td>94</td>
<td>217</td>
<td>74</td>
<td>17.7</td>
<td>7.1</td>
</tr>
<tr>
<td>24–59 Months</td>
<td>68</td>
<td>81</td>
<td>54</td>
<td>2.2</td>
<td>1.7</td>
</tr>
<tr>
<td>All ages (0–59 mo)</td>
<td>78</td>
<td>1044</td>
<td>420</td>
<td>17.9</td>
<td>8</td>
</tr>
<tr>
<td><strong>Southern</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤11 Months</td>
<td>89</td>
<td>263</td>
<td>165</td>
<td>81.9</td>
<td>50.2</td>
</tr>
<tr>
<td>12–23 Months</td>
<td>100</td>
<td>164</td>
<td>54</td>
<td>4.4</td>
<td>16.6</td>
</tr>
<tr>
<td>24–59 Months</td>
<td>62</td>
<td>75</td>
<td>45</td>
<td>6.7</td>
<td>4.6</td>
</tr>
<tr>
<td>All ages (0–59 mo)</td>
<td>83</td>
<td>518</td>
<td>263</td>
<td>28.5</td>
<td>16.1</td>
</tr>
</tbody>
</table>

a Prevaccine and postvaccine values are the median of the yearly sums of diarrhea-related death for each period and for each age group.

b Because the Ministry of Health at times delivers vaccine to a larger operative region than planned, coverage in certain age groups for 2010 exceeds 100%.

P values were calculated with the use of χ² tests. Sum-rank test showed no differences in rate reductions across regions (P > .8).
strong suggestive evidence of the beneficial effects of rotavirus vaccination against fatal rotavirus disease in Mexico. Moreover, the similarity in reductions in the lowest and highest income sectors of Mexico indicates equitable distribution of vaccine and that the vaccine is reaching children at the highest risk of dying in this country. Before rotavirus vaccine introduction, diarrheal disease was estimated to cause ~5% of deaths among children <5 years of age in Mexico and ~3000 deaths annually. Combining regional reductions, we estimated an annual reduction of ~1000 childhood diarrheal deaths in Mexico after vaccine introduction. In addition, largely because of substantially greater baseline rates of diarrheal mortality seen in the south, the number of deaths prevented per population was highest in this region.

Rotavirus has been confirmed to be the single most important cause of severe diarrhea among children worldwide, accounting for ~40% of all hospitalizations for diarrhea. However, given the inherent challenges associated with laboratory confirmation of diarrheal deaths, few studies have sought an enteric pathogen from children who died of diarrhea. Thus, the global burden of rotavirus deaths has been estimated by using the assumption that the prevalence of rotavirus among those children who die of diarrhea. The sustained reductions in diarrhea deaths of 44% to 56% among children <5 years old after the introduction of rotavirus vaccine in Mexico provides a “probe study” confirming the validity of this critical assumption.

Although previous studies have revealed that efficacy against rotavirus disease of any severity varies by socioeconomic status, efficacy and effectiveness have been less variable against very severe disease, which could be a better proxy for efficacy against fatal disease. The similarity in reductions in diarrhea deaths in regions of Mexico with high and low socioeconomic status is also consistent with this finding. Consequently, the possibility exists that the lower efficacy against rotavirus in poor settings might not necessarily translate to lower efficacy against deaths. Nonetheless, childhood diarrhea-related mortality rates in southern Mexico are considerably lower compared with those seen in countries of Africa and Asia. Importantly, because these countries may differ substantially from Mexico with regard to factors that impair vaccine effect, the homogeneity in regional reductions seen in Mexico may not necessarily extend to other areas of the world. Thus, as vaccines are introduced across these higher mortality settings, efforts to assess the effect of vaccine against rotavirus deaths will be valuable for understanding the full impact of rotavirus vaccine. That we were able to reveal significant reductions in diarrhea fatalities reflects the high quality of Mexico’s mortality surveillance data and reiterates that similar monitoring of diarrhea-related deaths could prove useful in other countries introducing rotavirus vaccines.

Several limitations should be considered. Our evaluation cannot provide confirmatory evidence that the noted reduction in diarrhea death was due to rotavirus vaccination. For example, declining secular trends in diarrhea, resulting from improved sanitation, safe food and water, and promotion of other preventive and treatment strategies, may have contributed to the observed reductions. Similarly, because we were unable to examine deaths due to rotavirus specifically, reductions may not be attributable solely to vaccine. In addition, seasonal variability, changing coding practices, and underreporting of deaths could conceivably have affected trends in diarrhea-related deaths. Despite these limitations, several notable findings support the contention that rotavirus vaccine played a major role. First, the initial reductions (in 2008) were seen only among infants, the first age group eligible to receive rotavirus vaccine. After 2009, when
coverage increased among older children, vaccine impact was noted among children aged 12 to 23 months old. Second, there was notable blunting of the seasonal peak of diarrhea mortality, with the greatest decrease seen during rotavirus season, from December to May, when two-thirds of hospitalizations due to rotavirus occur in Mexico. Third, the higher levels of reductions in hospitalizations due to rotavirus occur in regions where rotavirus vaccine coverage increased among children aged 12 to 23 months old, across all regions, correlated with higher vaccine coverage in this age group. Last, the reductions declined among children aged 12 to 23 months old, across all regions, correlated with higher vaccine coverage and effect, level of development and access to care, and the relative importance of rotavirus as a cause of death may differ significantly across regions and could have influenced our results. Despite these caveats, the robust and uniform reduction in diarrhea deaths evident throughout Mexico is encouraging and suggests vaccine success.

CONCLUSIONS

In summary, our assessment revealed large and consistent reductions in childhood diarrhea-related death across all 3 regions of Mexico, with distinct levels of development, which are likely related to rotavirus vaccine introduction. These findings indicate equitable vaccine delivery to children with varying risk of mortality and reaffirm the beneficial effects of rotavirus vaccination against fatal diarrheal disease. Our results additionally support the WHO recommendation for rotavirus vaccine introduction in high-mortality, resource-limited settings. Over the next few years, as rotavirus vaccines are introduced in these regions, continued monitoring of diarrhea-related deaths, ongoing rotavirus surveillance, and case-control vaccine effectiveness studies are essential to precisely quantify the impact of rotavirus vaccination worldwide.

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