Diarrhoea-related hospitalizations in children before and after implementation of monovalent rotavirus vaccination in Mexico

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Abstract

Objective To assess, by socioeconomic setting, the effect of nationwide vaccination against species A rotavirus (RVA) on childhood diarrhoea-related hospitalizations in Mexico.

Methods Data on children younger than 5 years who were hospitalized for diarrhoea in health ministry hospitals between 1 January 2003 and 31 December 2011 were collected from monthly discharge reports. Human development indexes were used to categorize the states where hospitals were located as having generally high, intermediate or low socioeconomic status. Annual rates of hospitalization for diarrhoea – per 10 000 admissions – were calculated. Administrative data were used to estimate vaccine coverage.

Findings In the states with high, intermediate and low socioeconomic status, coverage with a two-dose monovalent RVA vaccine – among children younger than 5 years – had reached 93%, 86% and 71%, respectively, by 2010. The corresponding median annual rates of hospitalization for diarrhoea – per 10 000 admissions – fell from 1001, 834 and 1033 in the “prevaccine” period of 2003–2006, to 597, 497 and 705 in the “postvaccine” period from 2008 to 2011, respectively. These decreases correspond to rate reductions of 40% (95% confidence interval, CI: 38–43), 41% (95% CI: 38–43) and 32% (95% CI: 29–34), respectively. Nationwide, RVA vaccination appeared to have averted approximately 16 500 hospitalizations for childhood diarrhoea in each year of the postvaccine period.

Conclusion Monovalent RVA vaccination has substantially reduced childhood diarrhoea-related hospitalizations for four continuous years in discretely different socioeconomic populations across Mexico.
Introduction

Species A rotavirus (RVA) is the leading cause of severe childhood gastroenteritis worldwide and accounts for about 2 million hospitalizations and 453,000 deaths among young children annually. In 2006, the World Health Organization (WHO) recommended including two RVA vaccines in national immunization programmes in the Americas and Europe – after both vaccines had been found to show high efficacy and safety in clinical trials in these regions. By 2009, the same vaccines had been found to be efficacious in Africa and Asia and WHO therefore expanded its recommendation to include all children worldwide. Nearly 40 countries – most of them high- or middle-income – have introduced an RVA vaccine into their national programmes. Early evaluations after the introduction of these vaccines in high- or middle-income countries have shown a drop in hospitalizations for diarrhoea ranging from 33 to 50%. RVA vaccines have appeared to perform less well in low-income countries. The impact of RVA vaccination in different socioeconomic groups within a single country has not yet been investigated.

The evaluation of the impact of RVA vaccination in “real-world” settings is a public health priority. Although the direct protection conferred by RVA vaccines against RVA infection needs to be assessed, the broader public health benefits of such vaccines may be better appreciated by evaluating the impact of RVA vaccination on hospitalizations for diarrhoea.

The states of Mexico vary in the level of development that they have achieved and this heterogeneity provides a useful opportunity to examine possible differences in the impact of an RVA vaccine across several socioeconomic strata. After the national introduction of a monovalent RVA vaccine in 2007, substantial declines in diarrhoea-related mortality and morbidity among Mexican children were observed. In one study in Mexico, the incidence of hospitalization for diarrhoea was found to have declined since 2007. However, this decline could not be attributed to RVA vaccination unequivocally because at the time “postvaccine” data had only been collected for two years and the incidence of infection with RVA shows considerable inter-annual variation in the absence of any interventions.

In this study we describe trends in hospitalization for diarrhoea among young children in Mexico before and after the introduction of RVA vaccination. The primary aims of this analysis were to document the long-term effect of RVA vaccination on diarrhoea-related
hospitalizations and to compare the impact of such vaccination in the poorly developed states of Mexico with that seen in the country’s more developed states.

Methods

Data sources

All-cause and diarrhoea-related hospitalizations

Monthly data on all-cause and diarrhoea-related hospitalizations among children younger than 5 years were collected – from an electronic database of Mexico’s National System for Health Informatics – for the period from 1 January 2003 to 31 December 2011 and for all of Mexico’s 591 health ministry hospitals. No attempt was made to evaluate hospitalizations specifically for RVA infection because testing for RVA is rare in Mexico. However, studies in Mexico and other Latin American countries have indicated that 62 to 68% of hospitalizations for diarrhoea occur during the winter months and that about 40% of such hospitalizations throughout the year are due to rotavirus infection.

To allow for a thorough examination of the temporal trends in hospitalization for diarrhoea, we confined our analysis to data from the 346 health ministry hospitals that had no lapses in reporting over our study period of 2003–2011. Together, these 346 hospitals represent 31 (97%) of the 32 Mexican states, all parts of Mexico and all levels of socioeconomic development in the country, and they cover about 38% of the hospitalizations that occur nationwide. In terms of the percentage of patients lacking social security, the 245 excluded hospitals were very similar to the 346 included hospitals (25.1% versus 25.4%; $P = 0.7$).

In 2004, the National System for Health Informatics expanded to include records of health care encounters at all hospitals throughout Mexico. This expansion allowed us to estimate – for the period from 2004 to 2011 – the national reductions in diarrhoea-related hospitalizations among children younger than 5 years that could be reasonably attributed to RVA vaccination.

Vaccine coverage and socioeconomic categories

Administrative data kept by Mexico’s National Centre for Child and Adolescent Health [Centro Nacional para la Salud de la Infancia y la Adolescencia] were used to estimate RVA vaccine coverage. Through government health facilities, the National Centre supplies RVA vaccine to about 50 to 61% of infants in Mexico; the rest is provided by the Mexican Social Security Institute [Instituto Mexicano de Seguro Social] and the Institute for Social Security
and Services for State Workers [Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado]. Two doses of the monovalent RVA vaccine – given at the ages of 2 and 4 months – are recommended. Every month each government health facility sends to the National Centre’s vaccine registration system the numbers of first and second doses of the RVA vaccine that the facility has administered. Coverage with two doses of the RVA vaccine in 2010 was estimated by dividing the number of second doses given by the population of infants served by the National Centre in the same year.21

To investigate possible differences in vaccine impact by level of development, the Mexican states represented by the study hospitals were grouped into lower (n = 10), intermediate (n = 11) and high socioeconomic status (n = 10) using the human development indexes reported for these states in 2007.22,23 The corresponding population-weighted mean human development indexes24 were 0.77 (range: 0.73–0.79), 0.81 (range: 0.80–0.83) and 0.87 (range: 0.84–0.91), respectively. In general, the level of socioeconomic development of the southern states of Mexico was lower than that of the central and northern states.

Data analysis
Overall numbers of diarrhoea-related hospitalizations from 1 January 2003 to 31 December 2011 were examined. Because the catchment populations of the study hospitals were not known, rates of hospitalization for diarrhoea per 10,000 hospitalizations from all causes were calculated. The median annual rate of diarrhoea-related hospitalizations during the baseline, “prevaccine” period of 2003 to 2006 was compared with the corresponding value for the “postvaccine” period of 2008 to 2011. Since RVA vaccination was still being rolled out in Mexico during the year, 2007 was considered a transitional year and excluded from this part of the analysis.

Rate ratios (RR) were calculated so that monthly and annual diarrhoea-related hospitalization rates in each of the postvaccine years could be compared with the corresponding prevaccine rates. The RRs were stratified by age group – 0–11, 12–23 and 24–59 months – and socioeconomic category. Although RVA testing or coding is not routinely conducted in the study hospitals, in Mexico approximately 60 to 70% of the hospitalizations for laboratory-confirmed RVA infection occur during the months of December to May.19 Seasonal changes in diarrhoea-related hospitalizations were therefore specifically assessed before and after the introduction of the RVA vaccine.
Ninety-five per cent confidence intervals (95% CI) were calculated around the relative reductions in the rates of diarrhoea-related hospitalization. Statistical significance in \( \chi^2 \) tests was assessed. A \( P \)-value of less than 0.05 was considered indicative of a statistically significant difference.

By extrapolating the rates of diarrhoea-related hospitalization per 10 000 all-cause admissions – observed in the 346 study hospitals – to the total number of hospital admissions for all causes observed countrywide, the national reductions in diarrhoea-related hospitalizations in Mexico that could reasonably be attributed to the RVA vaccinations were estimated. The numbers of reported hospital admissions for the entire country were available for the years 2004 to 2006 (prevaccine) and 2008 to 2010 (postvaccine) and for two age groups of young children: those younger than 12 months and those aged from 12 to 59 months.

All analyses were performed using SAS version 9.2 (SAS Institute, Chicago, United States of America) and Excel (Microsoft, Redmond, USA).

Results

Coverage

By 2010, a total of 3 830 932 second doses of monovalent RVA vaccine had been administered to the National Centre for Child and Adolescent Health’s target population of 4 677 341 children younger than 5 years. This was equal to a national two-dose coverage of 82% (Table 1). Two-dose coverage was at least 69% across all the age groups and socioeconomic categories that we considered (Table 1). In general, coverage was relatively higher among children younger than 24 months and in the states with high or intermediate socioeconomic status.

Diarrhoea-related hospitalizations

Overall trends

Before the introduction of RVA vaccination nationwide, diarrhoea-related hospitalizations were distinctly seasonal in Mexico (Fig. 1). About 67% of such hospitalizations occurred between the months of December and May – i.e. during the autumn–winter peak of RVA activity in Mexico. In 2008, a moderate decrease in the number of diarrhoea-related hospitalizations was noted among children younger than 12 months – that is, among the first birth cohort that received the RVA vaccine. After 2009, clear blunting of the seasonal peaks
extended to include all children aged less than 24 months. By 2011, declines were also noted among children between the ages of 24 and 59 months. The number of diarrhoea-related hospitalizations observed among children younger than 5 years in each of the four years following vaccine introduction was substantially less than that observed in any study year before the vaccine was introduced.

Changes in the seasonality of diarrhoea-related hospitalizations were also observed following the introduction of the RVA vaccine. In the prevaccine period, monthly rates of such hospitalizations peaked in January and February (Fig. 1). However, the monthly rates did not peak until March in 2007 and 2008 and not until April and May in 2008 to 2011.

**Prevaccine versus postvaccine years**

During the prevaccine period, a median of 15 398 diarrhoea-related hospitalizations were reported annually among children younger than 5 years at the 346 study hospitals. This corresponds to an annual rate of hospitalization for diarrhoea of 945 cases per 10 000 hospital admissions (Table 1). During the postvaccine period, the corresponding median annual number of diarrhoea-related hospitalizations was 10 577 – corresponding to an annual rate of 590 cases per 10 000 admissions; by comparison with the prevaccine values, this represented a rate reduction of 38% ($P < 0.001$). Overall, an absolute reduction of 4821 childhood hospitalizations was observed each year across the 346 study hospitals following vaccine introduction. About 93% of this reduction – 4463 of the 4821 hospitalizations – was observed in the months of December through May. Although significant postvaccine reductions in the rates of diarrhoea-related hospitalization were seen in all the age groups that we investigated, the greatest declines were observed among children younger than 24 months (Table 1).

Among children younger than 5 years, the rates of diarrhoea-related admission to the study hospitals in the states with high, intermediate and low socioeconomic status fell from 1001, 834 and 1033 per 10 000 admissions in 2003 to 2006 to 597, 497 and 705 per 10 000 admissions in 2008 to 2011, respectively. These changes correspond to rate reductions of 40% ($P < 0.001$), 41% ($P < 0.001$) and 32% ($P < 0.001$), respectively (Table 1). Substantial and significant reductions – ranging from 40 to 51% – were seen in all regions among children younger than 24 months. Although significant reductions were also noted among children between the ages of 24 and 59 months, the corresponding CIs were wider and these reductions represented only about 5% of the overall fall that was observed.
Changes in diarrhoea-related hospitalizations with respect to the prevaccine period were evident in each postvaccine year (Appendix A, available at: https://dl.dropboxusercontent.com/u/97573266/Appendix%20A.pdf). In 2008, statistically significant reductions were only observed among children younger than 12 months. Starting in 2009, significant reductions were also seen among children between 12 and 23 months of age. By 2010, the reductions seen among children 24 months of age or older had also reached statistical significance. The magnitude of the reductions increased with each postvaccine year. The RRs for the years 2008, 2009, 2010 and 2011 – 0.95, 0.66, 0.57 and 0.55, respectively – were all statistically significant ($P < 0.001$).

In all of the socioeconomic categories and age groups considered, the postvaccine reductions in diarrhoea-related hospitalizations largely occurred during the autumn and winter seasons, which is when hospitalizations peaked in the prevaccine period (Fig. 2, Fig. 3 and Appendix A). The greatest reductions were seen in January in states with high or intermediate socioeconomic status and in February in states with low socioeconomic status (Fig. 3). Nationwide, the greatest reductions were seen in January across all age groups (Appendix A). During 2008, statistically significant RRs that exceeded 1 were noted in all regions, especially in March and April (Fig. 3). However, the results of age-stratified analysis indicated that the increases seen in diarrhoea-related hospitalizations in March–April 2008 were the result of hospitalizations of children who were then more than 12 months of age (Appendix A). Few such children had received the RVA vaccine by April 2008. After 2009, significant reductions in diarrhoea-related hospitalizations of children aged less than 5 years were evident in all months of each year (Fig. 3). For children aged 24–59 months, statistically significant RRs that exceeded 1 were noted during April and May in 2008, 2009 and 2010 (Appendix A) – when vaccine uptake was still increasing in this age cohort. In 2011, no increase was apparent during April and May. In this year, the reductions observed from December through March continued, leading to an annual RR of 0.76 (Appendix A).

**Estimated national reduction**

It was estimated that 16 537 hospitalizations for diarrhoea among children younger than 5 years were averted annually in Mexico between 2008 and 2011 as the result of RVA vaccination (Table 2).

**Discussion**
After implementation of RVA vaccination in 2007, substantial declines in paediatric admissions for diarrhoea were observed throughout Mexico. Four observations strongly support a role of RVA vaccination in these declines. First, over 90% of the postvaccine reduction was observed over the 6 months of each year – December through May – when two thirds of childhood hospitalizations due to RVA infection are known to occur.19 Second, the impact was greatest among children who were younger than 24 months – the age group that is most at risk of severe RVA-related disease.25 Third, the declines appeared to affect each age group after that age group became eligible for RVA vaccination. Fourth, significant declines were recorded in each of the four years that followed the introduction of RVA vaccination.

Over 16 500 diarrhoea-related hospitalizations were estimated to have been averted nationally every year after the RVA vaccine was introduced in Mexico. If all children in Mexico received two doses of RVA vaccine by their fifth birthdays, one hospitalization could be prevented per 120 infants vaccinated. This analysis highlights the substantial economic and public health benefits that could result in countries that incorporate RVA vaccination into their national programmes.

Among Mexican children younger than 5 years we recorded a nationwide reduction in diarrhoea-related hospitalizations of about 38%. This level of reduction is in line with the results of Latin American trials in which the vaccine was found to be associated with 39 to 42% fewer hospitalizations for diarrhoea of any cause.5,26 Four Latin American countries recorded declines of 17 to 51% in gastroenteritis hospitalizations in the first two years after an RVA vaccine was introduced.27 Since about 40% of Mexican children who were hospitalized with diarrhoea in the prevaccine period were found to be infected with RVA,18 a 40% reduction in diarrhoea-related hospitalizations after an RVA vaccine is introduced is, presumably, the best result for Mexico that might be expected.

The peak in diarrhoea-related hospitalizations among Mexican children younger than 5 years was delayed by about two months with respect to the prevaccine period following the introduction of the RVA vaccine. In the United States, peak RVA activity was similarly delayed by about 8 weeks after vaccine introduction.28 These changes in seasonality probably reflect diminished transmission of RVA and the slower development of RVA disease in partially immunized populations. Interestingly, this hypothesis is supported by the increased rates of diarrhoea-related hospitalization recorded – in the present study – among mainly unimmunized children 24 months of age or older in April and May in 2008, 2009 and 2010.
By 2011, most children in this age group had been immunized against RVA and the increase seen in April and May in the three previous years was not observed.

In clinical trials, the efficacy of RVA vaccines was found to be lower in low-income settings than in middle- or high-income settings.\textsuperscript{10–12} Subsequent studies in Latin America have shown that a licensed RVA vaccine contributed to a reduction of 46\% in RVA-related hospitalizations in a low-income country as opposed to a reduction of 76 to 94\% in three middle-income countries.\textsuperscript{27} This disparity is thought to be related to environmental and host-related factors that are common to resource-limited settings and either reduce the uptake of oral RVA vaccines or impede the development of a robust immune response – or both.\textsuperscript{29} Some of these factors include enteric infections, interference from oral polio vaccine, neutralizing breast milk and transplacental antibodies, undernutrition and comorbidities such as infection with human immunodeficiency virus.\textsuperscript{29} In the present study, the reduction in diarrhoea-related hospitalizations was relatively smaller in the Mexican states with lower levels of socioeconomic development, but it was still statistically significant. In addition, in recent trials in Chiapas, the poorest of Mexico’s states, the effectiveness of the monovalent RVA vaccine was shown to be as high as that recorded in some middle- and high-income countries.\textsuperscript{30} Furthermore, RVA vaccines are expected to have the greatest impact in resource-limited settings because of the relatively high baseline rates of RVA gastroenteritis found in such settings.

The factors that reduce vaccine effectiveness in Africa and Asia – where RVA vaccination is still being rolled out – generally differ from those encountered in Latin America and may have a greater effect on vaccination success.\textsuperscript{29,31} Ongoing research focusing on strategies to improve vaccine performance – such as delaying breastfeeding at the time of vaccination, increasing the number of doses administered, and giving zinc or probiotic supplements – could prove crucial in maximizing the benefits of RVA vaccines in these settings.\textsuperscript{29,31}

Our study has several important limitations. Because RVA testing is rarely conducted at health ministry facilities in Mexico, data on hospitalizations for RVA-specific gastroenteritis were not available. Thus, we cannot confirm that the observed “postvaccine” reductions in hospitalizations for diarrhoea were solely attributable to vaccination against RVA. Nonetheless, the declines occurred primarily during the peak months of RVA activity, correlated with vaccine coverage by age group and region, and showed gradual, stepwise increases – over several years – with increasing vaccine uptake. Changes in the catchment populations of the study hospitals and in referral and reporting practices may have affected
the recorded temporal trends in diarrhoea-related hospitalization. However, our evaluation was limited to hospitals with continuous reporting during the study period – and the number of hospitalizations from other causes remained fairly stable over the same period. Although inter-annual “natural” variability in the prevalence of RVA infection could have had some impact on our findings, it is not likely to have led to a sustained reduction in hospitalizations for diarrhoea over a four-year period. The effect of other concurrent interventions – such as improvements in sanitation, hygiene and food and water quality – may also have contributed to the observed declines. However, these interventions do not explain the magnitude of the declines or the remarkable consistency in trends across Mexico’s regions. By examining trends in diarrhoea-related hospitalizations, we only investigated the impact of RVA vaccination on severe diarrhoea. The effects of such vaccination on less severe outcomes – such as those generally observed in outpatient and community settings – also need to be investigated. Differences across regions in baseline rates of diarrhoea-related hospitalization and in the proportions of such hospitalizations attributable to rotavirus may have affected the absolute reductions seen in diarrhoea-related hospitalizations. However, these differences should not affect the RRs that we have presented. Lastly, the heterogeneity in income, state of development and vaccine impact among different communities within states could not be evaluated.

In conclusion, the sizable declines seen in diarrhoea-related hospitalizations among Mexican children since 2007 are probably related to vaccination against RVA. Sustained reductions were observed over a four-year period and across distinct socioeconomic categories throughout Mexico. An estimated 66 000 hospitalizations have probably been averted since – and because of – the initiation of Mexico’s programme of vaccination against RVA. Our evaluation highlights the value of the RVA vaccine against diarrhoea-related hospitalizations in “real world” circumstances. It also supports WHO’s recommendation that RVA vaccination be introduced in Africa and Asia, where more than 85% of the world’s cases of severe RVA disease occur. As RVA vaccines are introduced in these challenging settings, studies of vaccine effectiveness and RVA-specific hospital-based monitoring could offer valuable measures of the vaccine’s impact. In countries that have adopted the vaccine, continued surveillance remains essential to elucidate the vaccine’s long-term impact on the burden of diarrhoeal disease.

**Competing interests:**
None declared.
References


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Table 1. **Annual rates of diarrhoea-related hospitalizations in children younger than 5 years, Mexico, 2003–2011**

<table>
<thead>
<tr>
<th>Socioeconomic category&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Age (months)</th>
<th>Vaccine coverage&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>No. of DR hospitalizations&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Rate reduction&lt;sup&gt;d&lt;/sup&gt; % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>≤ 11</td>
<td>100</td>
<td>823</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>12–23</td>
<td>100</td>
<td>2050</td>
<td>1049</td>
</tr>
<tr>
<td></td>
<td>24–59</td>
<td>88</td>
<td>792</td>
<td>698</td>
</tr>
<tr>
<td></td>
<td>0–59</td>
<td>93</td>
<td>1001</td>
<td>597</td>
</tr>
<tr>
<td>Intermediate</td>
<td>≤ 11</td>
<td>84</td>
<td>580</td>
<td>302</td>
</tr>
<tr>
<td></td>
<td>12–23</td>
<td>100</td>
<td>2200</td>
<td>1113</td>
</tr>
<tr>
<td></td>
<td>24–59</td>
<td>79</td>
<td>850</td>
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<td></td>
<td>0–59</td>
<td>86</td>
<td>834</td>
<td>497</td>
</tr>
<tr>
<td>Low</td>
<td>≤ 11</td>
<td>85</td>
<td>668</td>
<td>401</td>
</tr>
<tr>
<td></td>
<td>12–23</td>
<td>100</td>
<td>2703</td>
<td>1531</td>
</tr>
<tr>
<td></td>
<td>24–59</td>
<td>51</td>
<td>1077</td>
<td>893</td>
</tr>
<tr>
<td></td>
<td>0–59</td>
<td>71</td>
<td>1033</td>
<td>705</td>
</tr>
<tr>
<td>All</td>
<td>≤ 11</td>
<td>89</td>
<td>684</td>
<td>358</td>
</tr>
<tr>
<td></td>
<td>12–23</td>
<td>100</td>
<td>2301</td>
<td>1195</td>
</tr>
<tr>
<td></td>
<td>24–59</td>
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<td>888</td>
<td>733</td>
</tr>
<tr>
<td></td>
<td>0–59</td>
<td>82</td>
<td>945</td>
<td>590</td>
</tr>
</tbody>
</table>

CI, confidence interval; DR, diarrhoea-related.

<sup>a</sup> The socioeconomic status of the state in which the reporting hospital was located, based on the human development index of the state for the year 2007.

<sup>b</sup> RVA vaccine coverage with two doses, as recorded in 2010. As the Ministry of Health may deliver vaccine to a region larger than that planned, the recorded coverage, which is based on the size of the planned target population, can exceed 100%.

<sup>c</sup> Per 10 000 all-cause admissions. Prevaccine and postvaccine rates – shown for 2003–2006 and 2008–2011, respectively – are based on the sums of the monthly median numbers of diarrhoea-related hospitalizations and all-cause admissions at 346 health ministry hospitals. To account for differences in vaccine coverage by age group and postvaccine year, the postvaccine values for children aged ≤ 11, 12–23 and 24–59 months were based on the number of diarrhoea-related hospitalizations over 2008–2011, 2009–2011 and 2010–2011, respectively.

<sup>d</sup> Rate reduction in the postvaccine period with respect to the prevaccine period.
Table 2. **Estimated numbers of diarrhoea-related admissions averted nationwide among children younger than 5 years after introduction of rotavirus vaccine in 2007, Mexico, 2003–2011**

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>DR hospitalizations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Annual no. of admissions for any cause&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Estimated annual no. of DR admissions&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Average no. of DR admissions averted annually&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 11</td>
<td>684</td>
<td>358</td>
<td>301 625</td>
<td>316 941</td>
</tr>
<tr>
<td>12–59</td>
<td>1431</td>
<td>1020</td>
<td>197 853</td>
<td>196 489</td>
</tr>
<tr>
<td>0–59</td>
<td>945</td>
<td>590</td>
<td>499 478</td>
<td>519 731</td>
</tr>
</tbody>
</table>

CI, confidence interval; DR, diarrhoea-related.

<sup>a</sup> Per 10 000 all-cause admissions, as reported by 346 health ministry hospitals.

<sup>b</sup> Number of admissions reported nationally for the prevaccine period (2004–2006) and the postvaccine period (2008–2010).

<sup>c</sup> Estimates made by assuming that the national annual rates of hospitalization for diarrhoea were the same as the rates recorded in the 346 study hospitals.

<sup>d</sup> Estimates for the postvaccine period of 2008–2011.
Fig. 1. Monthly numbers of diarrhoea-related hospitalizations among young children, Mexico, 2003–2011

Note: the numbers are the totals reported by 346 health ministry hospitals.
Fig. 2. **Seasonality in diarrhoea-related hospitalizations among young children before the introduction of a rotavirus vaccine, Mexico, 2003–2006**

Note: In each plot, the median numbers of diarrhoea-related admissions in children younger than 60 months in each month of the year in 2003 to 2006 are shown as a black line. The range of values is indicated by the green shading. The figure shows the values recorded in all 346 health ministry study hospitals and – in separate plots – the values recorded in the study hospitals located in states with generally high, intermediate or low socioeconomic status.
Fig. 3. **Comparison of the prevaccine and postvaccine monthly rates of diarrhoea-related hospitalization among young children, Mexico, 2007–2011**

Note: Postvaccine rates were compared with the prevaccine values by calculating rate ratios. A rate ratio was calculated for each postvaccine month by dividing the rate of diarrhoea-related hospitalizations among children younger than 60 months – recorded in that month, per 10 000 admissions, in the 346 health ministry study hospitals – by the corresponding median rate recorded in 2003 to 2006. The vaccine was introduced in May 2007. The figure shows the values recorded in all 346 study hospitals and – in separate plots – the values recorded in the study hospitals located in states with generally high, intermediate or low socioeconomic status. Error bars indicate 95% confidence intervals. Before the vaccine was introduced, rates of diarrhoea-related hospitalization in young children peaked between December and March. These “peak” months are indicated by the green shading.