Duration of Protection of Pentavalent Rotavirus Vaccination in Nicaragua

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KEY WORDS
rotavirus, vaccine, diarrhea, vaccine effectiveness

ABBREVIATIONS
CI—confidence interval
DTP/Hib/HepB—diphtheria/tetanus/pertussis/Haemophilus influenzae type b/hepatitis B
ED—emergency department
EIA—enzyme immunoassay
OPV—oral polio vaccine
OR—odds ratio
RV5—pentavalent rotavirus vaccine
VE—vaccine effectiveness

Dr Patel participated in the design, data gathering, analysis, and manuscript preparation; approved the final version of the manuscript; had full access to all data in the study; and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Pedreira, De Oliveira, Tate, Lopman, Sanchez, Reyes, Mercado, Gonzalez, Perez, Balmaceda, Andrus, and Parashar participated in the design, data gathering and interpretation, and in manuscript revision; they approved the final version of the manuscript.

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WHAT’S KNOWN ON THIS SUBJECT: Rotavirus vaccine efficacy is lower in low-income settings with the highest child mortality due to diarrhea. In recently published clinical trials of rotavirus vaccines in Africa, waning of efficacy was also noted among children aged ≥1 year.

WHAT THIS STUDY ADDS: These data offer the first evidence of the duration of protection of the pentavalent rotavirus vaccine against severe rotavirus disease after routine use of the vaccine in a developing country setting.

abstract

OBJECTIVE: To evaluate the duration of protection of pentavalent rotavirus vaccine (RV5) against rotavirus hospitalizations in Nicaragua, a developing country in Central America.

METHODS: We conducted a case-control study at 4 hospitals from 2007 through 2010, including 1016 children hospitalized with laboratory-confirmed rotavirus diarrhea, 4930 controls with nonrotavirus diarrhea (ie, “test-negative”), and 5627 controls without diarrhea. All cases and controls were aged ≥6 months and born after August 2006. Outcomes included odds of antecedent vaccination between case-patients and controls, and effectiveness of vaccination (1 – adjusted odds ratio [OR] × 100). Duration of protection was assessed by comparing effectiveness among children aged <1 year compared with ≥1 year.

RESULTS: Indicators of socioeconomic conditions and nonrotavirus vaccination (oral polio vaccine and diphtheria/tetanus/pertussis/hepatitis A/hepatitis B) for test-negative controls were more comparable to the rotavirus case-patients than nondiarrhea controls. RV5 vaccination was associated with a significantly lower risk of rotavirus hospitalization by using test-negative controls (OR: 0.55; 95% confidence interval [CI]: 0.41–0.74) and nondiarrhea controls (OR: 0.30; 95% CI: 0.22–0.40). Risk of rotavirus hospitalization was twofold lower among RV5 vaccinated children aged <1 year (OR: 0.36; 95% CI: 0.22–0.57) compared with RV5 vaccinated children aged ≥1 year (OR: 0.70; 95% CI: 0.47–1.05).

CONCLUSIONS: RV5 provided good protection against severe rotavirus disease in Nicaragua during the first year of life, when most severe and fatal rotavirus disease in developing countries occurs. However, the decline in protection with age warrants monitoring of disease among older children and consideration of a booster dose evaluation at the end of infancy. Pediatrics 2012;130:e365–e372
Two live attenuated oral rotavirus vaccines, a pentavalent bovine-human WC3 reassortant vaccine (RV5, RotaTeq, Merck Vaccines, Whitehouse Station, NJ) and an attenuated monovalent RIX444 strain human vaccine (RV1, GlaxoSmithKline Biologicals, Rixensart, Belgium) are licensed in many countries worldwide. The World Health Organization recommends these rotavirus vaccines for all children worldwide to help control the large burden of deaths and hospitalizations from rotavirus disease among children aged <5 years. In 2006, Nicaragua, a low-middle income country in Central America with a gross national income per capita of $1110, introduced RV5 into its routine infant immunization program. A study conducted during the first season (2008) after vaccine implementation in Nicaragua showed that RV5 provided ~50% protection against rotavirus hospitalization among children up to 18 months of age. Data from this study and a similar study assessing RV1 in El Salvador suggested lower effectiveness among children 12 to 18 months compared with those <12 months of age, but the number of older vaccinated children was too few to make reliable conclusions. Recently published data from clinical trials of RV5 in poor settings of Africa and Asia also showed lower protection during the second year of life. Together, these findings raise the possibility of waning of vaccine-induced immunity in older children.

In developing countries, the majority of severe rotavirus disease occurs during the first year of life. However, because up to 30% to 40% of disease can occur after the first year of life and because vaccination could further shift disease incidence to older age groups, it is important to define the duration of protection after RV5 vaccination to better understand the long-term impact of routine rotavirus vaccination.

**METHODS**

**Study Design and Setting**

Nicaragua is a low-middle income country in Central America with an annual birth cohort of ~150 000. RV5 was added to the routine childhood immunization schedule in October 2006, at 2, 4, and 6 months of age. From July 2007 to June 2010, we conducted active surveillance for laboratory-confirmed cases of rotavirus diarrhea at 4 community hospitals (1 hospital in the capital city of Managua and hospitals in Jinotepe, Masaya, and Matagalpa). We assessed duration of RV5 protection by using a case-control approach to assess vaccine effectiveness (VE) against rotavirus diarrhea among children aged <1 year versus those aged ≥1 year. To better quantify the impact of vaccination in Nicaragua at a population level, we assessed trends of national incidence of diarrhea-related hospitalizations using an interrupted time-series analysis.

**Cases**

To identify case-patients, we conducted active hospital-based surveillance for children with acute diarrhea (defined as ≥3 loose stools in a 24-hour period and with onset <14 days before the hospital visit) 24 hours a day in the emergency department (ED) and inpatient wards. We enrolled all children who were admitted or treated in the ED with intravenous hydration for laboratory-confirmed rotavirus diarrhea and were born after August 26, 2006, making them age-eligible to receive RV5 vaccine. Although most children presenting to the hospital were from the city where the hospital was located, we did not exclude children based on proximity of residence to the hospital. Bulk stool specimens were collected within 48 hours of admission. Specimens were stored at 2°C to 8°C before transfer to the national laboratory on a weekly basis, where rotavirus testing was conducted by using a commercially available enzyme immunoassay (EIA).

**Controls**

For each case, we selected 2 groups of controls: children with rotavirus-negative diarrhea and those without diarrhea. Rotavirus-negative diarrhea controls were those children who were enrolled during the surveillance for rotavirus diarrhea but tested negative for rotavirus by EIA (ie, test-negative controls). Because of the high sensitivity and specificity of detecting rotavirus by EIA, test-negative controls were unlikely to have had acute rotavirus disease and have previously proved to be a good source of controls in rotavirus VE studies when compared with community or nondiarrhea hospital controls.

We also enrolled nondiarrhea controls matched to case’s date of birth (±30 days) from 2 sources: hospital and neighborhood. Hospital controls were children seeking care at the ED or outpatient clinic or admitted to the same hospital as the case for an acute illness unrelated to diarrhea or a vaccine-preventable condition. After a rotavirus case was identified, up to 3 hospital controls were consecutively enrolled during the first 2 surveillance years. Neighborhood controls were enrolled on a weekly basis during all 3 surveillance years; interviewers visited homes to the left and right of the case home until 3 controls were identified.

**Variables**

Parents of cases and hospital controls were interviewed through face-to-face interviews during the hospital visit, and, similarly, neighborhood controls were interviewed at their homes. After written informed consent, information was obtained on vaccination history, demographics, socioeconomic factors, BMI, history of breast feeding, and medical history. For cases, we also
gathered information on clinical characteristics, treatment, and course of illness.

Vaccination history was obtained from the parent and was considered confirmed if the parent showed a vaccination card with the date of vaccination, type of vaccine used, and the name of the child. If parents reported vaccination but did not possess a card, confirmation was obtained by review of vaccine cards at the clinic where the child was reportedly vaccinated.

**Sample Size for VE**

We estimated 900 case-patients for computing VE of 50% and 30% among children aged <1 and ≥1 year, respectively, under the following assumptions: vaccine coverage = 90%; type 1 error = .05; type II error = .80.12

**Statistical Methods: Case-Control**

Our primary aim was to compute VE of 3 doses of RV5 against rotavirus hospitalization among children aged <1 year compared with children ≥1 year. To assess for a potential gradient in protection by severity, we repeated this analysis for VE against rotavirus diarrhea with a clinical severity score of ≥11 and ≥15 on a 20-point Vesikari scoring scale similar to that used in the RV5 clinical trials.13,14 We first conducted bivariate analyses to assess for differences in indicators of socioeconomic condition and non-RV5 vaccination rates between rotavirus case-patients and the 2 groups of controls to identify potential confounders or biases for the association between RV5 vaccination and rotavirus disease. Differences were assessed by using the Wilcoxon rank-sum test or \( \chi^2 \) test.

To determine VE, we constructed 2 separate logistic regression models for test-negative and nondiarrhea controls. Analysis was restricted to case-patients and controls aged ≥6 months, thus making them age-eligible to have received the full series of RV5. For the analysis using test-negative controls, we used an unconditional logistic regression model to calculate odds ratios (ORs) with associated 95% confidence intervals (CIs).15 Potential confounders were screened by calculating adjusted ORs individually for each potential confounder. Confounders were defined as any variables that changed the OR between vaccination status and rotavirus diarrhea by >10%. The final model included age at hospitalization (in months), month/year of birth, and hospital, in addition to vaccination status.

Because nondiarrhea controls were matched to case-patients by date of birth, we used a conditional logistic regression model to calculate ORs with associated 95% CIs for this analysis. Because of the high vaccination rates in the community and therefore the small number of unvaccinated controls, we screened for potential confounding by using the same process and criterion described for test-negative controls. No variables met this criterion, and so the final conditional model included vaccination status as the only independent variable.

VE was calculated as 1 – the OR \( \times \) 100%. Statistical significance was designated as a \( P \) value <.05. Analyses were done with SAS statistical software (version 9.2).

**Statistical Methods: Trends Analysis**

We assessed the impact of RV5 vaccination on national diarrhea hospitalizations from all causes by age in Nicaragua using an interrupted time series analysis. We obtained national data on all-cause diarrhea admissions from Ministry of Health hospitals. Because these hospitals provide services to >85% of the Nicaraguan population,16 annual population data from the Nicaraguan census was used to calculate national rates. By using an interrupted time-series analysis, we examined rates of diarrhea admissions before (2001–2005) and after (2007–2010) rotavirus vaccine introduction. Because of a nationwide health care worker strike during 2006 that affected data collection for 6 months, data from 2006 were excluded.17 Analysis was stratified by age groups for which data were available (<1 year and 1–4 years). Rotavirus disease is highly seasonal in Nicaragua with a majority of the rotavirus hospitalizations occurring between February through May (ie, peak rotavirus season).18 Thus we stratified the trends analysis by season (peak rotavirus season versus nonrotavirus season). For the regression analysis, a generalized linear model was fit to the time-series data, assuming that diarrhea admissions were Poisson distributed. We first computed monthly rates of diarrhea-related deaths and admission “expected” to occur in the absence of a rotavirus vaccination program by fitting the model to prevaccine data (2001–2005). We adjusted for seasonality by including calendar month and for secular trends by including calendar year in the model. Because no secular decline was observed, the final model was based on prevaccine data including a constant and terms for month and population. This model was used to estimate expected values in the vaccine era. We then compared the absolute number of diarrhea admissions observed in the vaccine era with those expected in the absence of vaccination, as computed by the model, to assess the potential impact of vaccination. Finally, we calculated the rate ratio and 95% CI of diarrhea admissions in the vaccine era compared with prevaccine years, with the inclusion of an indicator variable for the period after rotavirus vaccine introduction; again we controlled for seasonal and population trends.
Ethics Statement
This case-control evaluation was approved by human subjects’ offices at the Program for Appropriate Technology in Health and the Nicaragua Ministry of Health and determined to be public health practice at the Centers for Disease Control and Prevention.

RESULTS
Case-Control Analysis
From July 2007 to June 2010, we enrolled 1178 children with rotavirus diarrhea who met the study case-definition and of whom, 1016 (86%) were ≥6 months of age. Of these, 928 (91%) were hospitalized and 741 (63%) had severe rotavirus diarrhea as classified by Vesikari severity score ≥11. Of those with severe rotavirus diarrhea, 20% had severity score ≥15.

In comparison with nondiarrhea controls, rotavirus case-patients had significantly lower indicators (P < .001) of socioeconomic condition at home (motorized vehicle, telephone, and computer), and their mothers were significantly less likely (P < .001) to have received higher education (Table 1). Although rotavirus diarrhea case-patients were significantly older (P < .001) and more likely to attend day care (P < .001) than test-negative controls, they otherwise had similar characteristics and socioeconomic indicators.

Overall, vaccination rates were high for RV5 and other concomitantly administered vaccines (oral polio vaccine [OPV] and diphtheria/tetanus/pertussis/Haemophilus influenzae type b/hepatitis B [DTP/Hib/HepB], Table 2), and ~95% of those immunized received vaccination before 6 months of age. When considering all rotavirus cases ≥6 months of age, risk of severe rotavirus diarrhea was significantly lower by using test-negative controls (OR, 0.55; 95% CI: 0.41–0.74) and nondiarrhea controls (OR: 0.30; 95% CI: 0.22–0.40) (Table 2). However, although rotavirus case-patients and test-negative controls had similar rates of vaccination with OPV and DTP/Hib/HepB, rotavirus cases were significantly less likely to have received these vaccines (98%) compared with nondiarrhea controls (100%; P < .001). This finding, together with the socioeconomic differences noted earlier, suggest that test-negative controls better represented the source population for the case-patients.

By using test-negative controls, RV5 vaccination was associated with a significantly lower risk of rotavirus hospitalization among children <1 year (OR: 0.36; 95% CI: 0.22–0.57) compared with children aged ≥1 year (OR: 0.70; 95% CI: 0.47–1.05) (Table 3). Thus, effectiveness of RV5 was twofold greater among children aged 6 to 11 months (64%; 95% CI: 43–78) compared with those aged ≥12 months (30%; 95% CI: −5 to 53; P = .02). A similar pattern of decreasing VE by time since vaccination was noted for rotavirus diarrhea of severity score ≥11 (P = .05).

No statistically significant decline in VE by age occurred among children with rotavirus diarrhea of severity score ≥15 (P = .99).

TABLE 1 Comparison of Characteristics of Rotavirus-Positive Case-Patients and Controls Who Were ≥6 Months of Age, July 2007 Through June 2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases*</th>
<th>Controls</th>
<th>P Value</th>
<th>Nondiarrhea*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, mo (range)</td>
<td>14 (6–41)</td>
<td>11 (6–44)</td>
<td>&lt;.001a</td>
<td>14 (6–42)</td>
<td>.72a</td>
</tr>
<tr>
<td>Male, (%)</td>
<td>534 (54)</td>
<td>2315 (58)</td>
<td>.002</td>
<td>2515 (52)</td>
<td>.98</td>
</tr>
<tr>
<td>Chronic underlying illness, (%)</td>
<td>29 (3)</td>
<td>115 (3)</td>
<td>.97</td>
<td>270 (6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of breastfeeding, (%)</td>
<td>832 (92)</td>
<td>3775 (94)</td>
<td>.01</td>
<td>4542 (95)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Daycare attendance, (%)</td>
<td>143 (14)</td>
<td>383 (10)</td>
<td>&lt;.001</td>
<td>707 (15)</td>
<td>.71</td>
</tr>
<tr>
<td>Premature birth, (%)</td>
<td>98 (10)</td>
<td>404 (10)</td>
<td>.63</td>
<td>336 (7)</td>
<td>.004</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>None, (%)</td>
<td>45 (4)</td>
<td>178 (4)</td>
<td>152 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school, (%)</td>
<td>347 (34)</td>
<td>1264 (32)</td>
<td>1442 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary school, (%)</td>
<td>543 (54)</td>
<td>2161 (53)</td>
<td>2586 (54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertiary school, (%)</td>
<td>73 (7)</td>
<td>387 (10)</td>
<td>603 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median no. of children in household (range)</td>
<td>2 (1–35)</td>
<td>2 (1–52)</td>
<td>.12d</td>
<td>2 (1–26)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Median no. of people in household (range)</td>
<td>6 (2–30)</td>
<td>6 (2–47)</td>
<td>.67d</td>
<td>6 (2–28)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Socioeconomic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Median rooms in home (range)</td>
<td>5 (1–15)</td>
<td>5 (1–51)</td>
<td>.03d</td>
<td>5 (1–53)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Electricity in home, (%)</td>
<td>863 (97)</td>
<td>3848 (96)</td>
<td>.44</td>
<td>4637 (97)</td>
<td>.79</td>
</tr>
<tr>
<td>Own motorized vehicle, (%)</td>
<td>148 (14)</td>
<td>658 (16)</td>
<td>.11</td>
<td>1048 (22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Telephone in home, (%)</td>
<td>672 (88)</td>
<td>2721 (68)</td>
<td>.24</td>
<td>3424 (71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Computer in home, (%)</td>
<td>47 (5)</td>
<td>240 (6)</td>
<td>.08</td>
<td>580 (12)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

a Hospitalized or ED patients with acute gastroenteritis who had EIA stool testing positive for rotavirus.
b Hospitalized or ED patients with acute gastroenteritis who had EIA stool testing negative for rotavirus.
c Neighborhood and nondiarrhea hospital controls were matched by age (± 30 d) and either neighborhood or hospital/clinic, respectively.
d P value for Wilcoxon rank-sum test.
By using nondiarrhea controls, the effectiveness of RV5 against rotavirus hospitalization was 70% (95% CI: 59–78) for children of all ages 73% (95% CI: 54–84) for children aged 6 to 11 months, and 68% (95% CI: 51–79) for children aged ≥12 months of age (Table 3). No significant differences in VE were observed when restricting the analysis to children with rotavirus diarrhea of severity score ≥11 or ≥15.

**Trends Analysis**

During the 4 rotavirus seasons after RV5 introduction in Nicaragua (2007–2010), all-cause diarrhea hospitalization rates during the peak rotavirus season declined significantly (Table 4) among children aged <1 year (relative risk, 0.81; 95% CI: 0.67–0.97), who had a vaccination coverage of 79%. These reductions occurred during February to May, peak months of rotavirus activity in Nicaragua (Fig 1). No reduction was observed among children aged 1 to 4 years (relative risk, 1.01; 95% CI: 0.81–1.24). Because this age group had older unvaccinated age cohorts, vaccination coverage among 1- to 4-year-olds was 35% during 2008–2010, which increased from 11% in 2008% to 59% in 2010. No significant reduction was observed among either of the age groups during the nonrotavirus season months of the study years.

**DISCUSSION**

With a sample size of >1,000 rotavirus cases and 10,000 controls enrolled over 3 years, this is one of the largest postlicensure evaluations of field effectiveness of routine childhood vaccination against rotavirus. Our study provides evidence for significant protection from RV5 against severe rotavirus diarrhea among infants in Nicaragua for 3 surveillance years, which is consistent with data from the recent RV5 clinical trials from similar developing countries in Asia and Africa. This finding of good VE against rotavirus hospitalization (~64%) and severe rotavirus disease (~70%) among infants <1 year of age was reassuring because most of the severe childhood rotavirus disease in developing-country settings, particularly deaths, occurs in this age group. Consistent with the protection from vaccine, we also noted a nationwide decline in diarrhea hospitalizations in infants during the rotavirus seasons of 2007 through 2010. However, protection was lower among children aged ≥1 year using test-negative controls and reduction in diarrhea rates was absent among the 1- to 4-year-olds during 4 postvaccination years in Nicaragua, including the most recent year when...
∼59% of the children in this age group were vaccinated. These findings indicate that the duration of protection from vaccination may be suboptimal. However, because coverage is still increasing in this age group, ongoing monitoring of disease will be crucial in future years.

Our findings are consistent with data from clinical trials in developing countries that also showed a sharp decline in RV5 efficacy in the second year of life.\textsuperscript{4,5} In contrast to developing-country settings, efficacy of RV5 was sustained at a high level through 3 years of life in industrialized countries.\textsuperscript{8,10,20} The restriction of this finding to developing-country settings implicates other contributory factors unique to poor settings as an explanation for the decline in protection.

Immunogenicity after rotavirus vaccination is significantly lower in poor settings compared with high-income settings.\textsuperscript{21} Thus, any waning in vaccine-induced immunity might have a greater influence on efficacy among children in developing settings compared with those in developed regions with higher baseline antibody titers after vaccination. Reduced circulation of rotavirus in the community after vaccination or perhaps acquisition of immunity from natural rotavirus infection over time are other possible explanations for the decreasing efficacy with age, but this phenomenon should have also led to decline in protection in industrialized settings.

It is important to note that a decline in efficacy was not observed among children hospitalized with very severe rotavirus disease (ie, Vesikari score $\geq 15$). In Nicaragua, ∼20% of the children admitted to the hospital had very severe rotavirus disease. Sustained efficacy against this subgroup of children admitted to the hospital had very severe rotavirus disease. Sustained efficacy against this subgroup of children was particularly reassuring because it serves as a good proxy for efficacy against rotavirus mortality, which has not been evaluated in

\begin{table}
\centering
\begin{tabular}{llll}
\hline
Age & Vaccine Coverage\textsuperscript{a} & Rate Reduction in Diarrhea Hospitalizations During 2007–2010 (95\% CI)\textsuperscript{b} & \\
   & & Peak Rotavirus Month\textsuperscript{c} & Nonrotavirus Months\textsuperscript{c} \\
\hline
$<1$ y & & & \\
2007 & 26 & 0.74 (0.52–1.06) & 1.35 (1.13–1.60) \\
2008 & 74 & 0.85 (0.61–1.18) & 1.03 (0.85–1.25) \\
2009 & 77 & 0.83 (0.59–1.15) & 1.26 (1.06–1.50) \\
2010 & 86 & 0.81 (0.57–1.13) & 1.20 (1.00–1.44) \\
All years & 79 & 0.81 (0.67–0.97) & 1.21 (1.08–1.36) \\
1–4 y & & & \\
2007 & 0 & 0.88 (0.60–1.32) & 1.31 (1.07–1.60) \\
2008 & 11 & 1.03 (0.71–1.50) & 1.12 (0.90–1.39) \\
2009 & 35 & 1.07 (0.74–1.54) & 1.32 (1.08–1.62) \\
2010 & 59 & 1.01 (0.70–1.47) & 1.44 (1.19–1.75) \\
All years & 35 & 1.01 (0.81–1.24) & 1.30 (1.14–1.48) \\
\hline
\end{tabular}
\textsuperscript{a}Coverage on January 1 of corresponding year, estimated on basis of vaccination records among control children born after August 2006 (thus eligible to receive rotavirus vaccine) who received at least 1 dose of vaccine.
\textsuperscript{b}Reduction in diarrhea hospitalizations during 2007–2010 compared with 2001–2005 from Poisson regression models; 2006 excluded due to nationwide healthcare strike leading to partial reporting.
\textsuperscript{c}Peak rotavirus months in Nicaragua include February, March, April, and May; non-rotavirus months include January, July to December.
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Monthly number of vaccine age-eligible children with severe diarrhea and rotavirus positive diarrhea, 4 hospitals, Nicaragua, July 2007 through June 2010.}
\end{figure}
clinical trials. Because Nicaragua has a relatively small birth cohort, the absolute number of children dying from diarrhea was insufficient for assessing the effect of vaccine against lethal diarrhea. However, large declines in rotavirus mortality have been noted in Mexico and Brazil after the introduction of a rotavirus vaccine.10,22,23

The divergence in VE by control groups, with consistently higher VE when using nondiarrhea controls compared with test negative controls, warrants discussion. The case-control method assumes that the vaccinated and unvaccinated members of the community have a comparable risk of developing disease. With 95% of the test negative and 96% nondiarrhea controls having received RV6 (fully vaccinated versus unvaccinated), the unvaccinated group in our study was highly selected. Thus, despite the large sample size, the high coverage lowered our probability of identifying a comparable control group from the population. The 1% absolute difference in RV5 vaccination between the 2 control groups led to an absolute difference in VE of 25%. Misclassification of rotavirus cases as controls could enrich the controls with unvaccinated children thus lowering VE, which might occur if sensitivity of the EIA is low. However, several lines of evidence support that test-negative controls more accurately reflected the source population for the case-patients. First, the test-negative controls were similar to rotavirus case-patients with regard to indicators of socioeconomic conditions and non-rotavirus vaccines (OPV and DTP/Hib/HepB), whereas significant differences between nondiarrhea controls and rotavirus case-patients existed. Second, because of the nearly universal vaccination coverage among infants during the surveillance period, the 19% observed reduction in all-cause diarrhea hospitalizations among infants would equate to an estimated vaccine protection against rotavirus hospitalizations of ~60%, under the assumption that a third of the diarrhea hospitalizations were due to rotavirus before vaccine introduction. This was comparable to VE obtained by using the test-negative controls (64%; 95% CI: 43–78) against rotavirus hospitalizations among children aged 6 to 11 months. Lastly, the test-negative VE results were similar to those from the first year of surveillance using non-diarrhea controls,2 when vaccination coverage and chances of obtaining biased controls were lower than in subsequent years of nearly universal coverage.

In summary, our study provides evidence for good RV5 protection against severe rotavirus diarrhea over 3 surveillance years in a developing-country setting, with significant population level benefits against infant diarrhea hospitalizations. The findings of decreased VE and absence of disease reduction in children ≥1 year of age are consistent with findings of reduced protection in older children seen in the clinical trials from Asia and Africa. It should be noted that because a majority of the severe rotavirus disease and deaths in developing countries occurs among infants, reducing disease in the first year of life is a priority for most developing-country rotavirus vaccine programs. However, ongoing monitoring of rotavirus specific disease incidence in older groups will also be crucial, particularly for assessing the need for a potential booster dose of rotavirus vaccination at the end of the first year of life (eg, concurrently with measles vaccination) in developing country settings. Clinical studies to assess the safety and non-interference of such a booster dose with measles vaccination, and whether it improves immune response sufficiently to provide sustained protection in developing countries should also be considered.

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