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Association Between Pentavalent Rotavirus Vaccine and Severe Rotavirus Diarrhea Among Children in Nicaragua

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Context Pentavalent rotavirus vaccine (RV5), a live, oral attenuated vaccine, prevented 98% of severe rotavirus diarrhea in a trial conducted mainly in Finland and the United States. Nicaragua introduced RV5 in 2006, providing the first opportunity to assess the association between vaccination and rotavirus disease in a developing country.

Objective To assess the association between RV5 vaccination and subsequent rotavirus diarrhea requiring overnight admission or intravenous hydration.

Design, Setting, and Participants Case-control evaluation in 4 hospitals in Nicaragua from June 2007 to June 2008. Cases were children age-eligible to receive RV5 who were admitted or required intravenous hydration for laboratory-confirmed rotavirus diarrhea. For each case (n=285), 1 to 3 neighborhood (n=840) and hospital (n=690) controls were selected.

Main Outcome Measures Primary outcome was the association of RV5 and rotavirus diarrhea requiring overnight admission or intravenous hydration in the emergency department. Secondary analysis further classified disease as severe and very severe. We computed the matched odds ratio of vaccination in cases vs controls. Vaccine effectiveness was estimated using the formula 1 – matched odds ratio × 100%.

Results Of the 285 rotavirus cases, 265 (93%) required hospitalization; 251 (88%) received intravenous hydration. A single rotavirus strain (G2P[4]) was identified in 88% of the cases. Among cases and controls, respectively, 18% and 12% were unvaccinated, 12% and 15% received 1 dose of RV5, 15% and 17% received 2 doses, and 55% and 57% received 3 doses. Vaccination with 3 doses was associated with a lower risk of rotavirus diarrhea requiring overnight admission or intravenous hydration (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.36-0.82). Of the 285 rotavirus cases, 191 (67%) were severe and 54 (19%) were very severe. A progressively lower risk of severe (OR, 0.42; 95% CI, 0.26-0.70) and very severe rotavirus diarrhea (OR, 0.23; 95% CI, 0.08-0.61) was observed after RV5 vaccination. Thus, effectiveness of 3 doses of RV5 against rotavirus disease requiring admission or treatment with intravenous hydration was 46% (95% CI, 18%-64%); against severe rotavirus diarrhea, 58% (95% CI, 30%-74%); and against very severe rotavirus diarrhea, 77% (95% CI, 39%-92%).

Conclusion Vaccination with RV5 was associated with a lower risk of severe rotavirus diarrhea in children younger than 2 years in Nicaragua but to a lesser extent than that seen in clinical trials in industrialized countries.

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ROTAVIRUS IS THE MOST COMmon cause globally of severe diarrhea in children younger than 5 years, accounting for an estimated 2.4 million hospital admissions and 610 000 deaths each year.[1,2] Most (>85%) rotavirus deaths occur in developing countries, and introduction of vaccines in these regions has been prioritized by international agencies such as the World Health Organization.[3] In 2006, clinical trials of 2 new live, oral attenuated rotavirus vaccines—RotaTeq (Merck Vaccines, Whitehouse Station, New Jersey) and Rotarix (GlaxoSmith Kline Biologicals, Rixensart, Belgium)—demonstrated high efficacy (85%-98%) against severe rotavirus disease.[4,5] These

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trials were predominantly conducted in middle- and high-income countries in the Americas and Europe, and several countries in these regions have already adopted rotavirus vaccines for routine childhood immunization.[6,7]

A key outstanding question for the global community is whether rotavirus vaccines will provide protection against severe rotavirus disease in developing countries. Experience with other candidate rotavirus vaccines, as well as immunogenicity studies of vaccines against polio, cholera, and typhoid, has shown that the performance of live, oral vaccines can be impaired in developing countries.[8-12] Several host and environmental factors—such as interference by maternal antibodies, concurrent oral polio vaccine administration, breast feeding, coprevalent enteric infections, and malnutrition—could potentially impair the ability of such vaccines to generate an effective immune response.[3,8] In addition, the licensed vaccines have not been tested during community circulation of some widely prevalent and newly emerging rotavirus serotypes.[13] Therefore, the World Health Organization has recommended efficacy trials of rotavirus vaccines in developing countries in Asia and Africa before issuing a global recommendation.[14] Trials of both rotavirus vaccines are ongoing in these regions, and results of trials of RotaTeq, a pentavalent rotavirus vaccine (RV5), are expected in late 2009 or 2010.

In October 2006, RV5 was introduced in Nicaragua through a manufacturer-sponsored 3-year vaccine donation program. The decision to add RV5 vaccine to the childhood immunization schedule was motivated by a large nationwide outbreak of rotavirus diarrhea in 2005, which caused an unexpected increase in diarrhea hospitalizations and deaths and garnered substantial attention from decision makers and public health authorities.[15] The primary objective of this evaluation was to assess the association between RV5 vaccination and subsequent rotavirus diarrhea requiring overnight admission or intravenous hydration in Nicaragua.

METHODS

Setting and Design

Nicaragua is a low-income country in Central America with an annual birth cohort of approximately 150 000. The Nicaragua Ministry of Health added RV5 to the routine childhood immunization schedule on October 27, 2006, recommending 3 doses of RV5 for all Nicaraguan children at ages 2, 4, and 6 months. The first dose is recommended between ages 6 and 12 weeks. Subsequent doses should be administered at 4- to 10-week intervals, and all 3 doses should be administered by age 32 weeks.

From June 2007 to June 2008, we conducted active surveillance for laboratory-confirmed cases of rotavirus diarrhea at 4 hospitals selected by the ministry on the basis of high admission census and absence of ongoing rotavirus surveillance (1 urban hospital in the capital city of Managua and 3 semiurban hospitals in Jinotepe, Masaya, and Matagalpa, respectively). We performed a case-control evaluation to assess the association between RV5 vaccination and subsequent rotavirus diarrhea by comparing antecedent rates of vaccination in cases of rotavirus diarrhea against the background rate of vaccination in 2 groups of age-matched controls.

Case Definition and Enrollment

Case children were defined as those who were admitted or required intravenous hydration for laboratory-confirmed rotavirus diarrhea and were born after August 26, 2006, making them age-eligible to receive RV5 vaccine. Because the primary goal of rotavirus vaccination is to prevent severe disease, eligible children were those with diarrhea that required either intravenous hydration or overnight admission.

To identify cases, active surveillance for patients with acute diarrhea (defined as ≥3 loose stools in a 24-hour period and with onset <14 days prior to the hospital visit) was conducted 24 hours a day in the emergency department and inpatient wards. Nurses and physicians in the wards were encouraged to notify the surveillance coordinator when treating children younger than 2 years with diarrhea. The emergency department and hospital admission log was used to further identify any child with a chief complaint of vomiting or diarrhea.

Bulk stool specimens were collected within 48 hours of admission. Specimens were stored at 2°C to 8°C prior to transfer to the national laboratory on a weekly basis, where rotavirus testing was conducted using a commercially available enzyme immunoassay (IDEIA; Oxoid, Cambridge, United Kingdom). At the national laboratory, specimens were frozen at −70°C and shipped to the Centers for Disease Control and Prevention in Atlanta, Georgia, where they were maintained at −70°C. Rotavirus-positive specimens were evaluated at the Centers for Disease Control and Prevention to determine the infecting strain, using previously described methods.[16-19]

Control Enrollment

For each case, we selected 2 groups of control children—hospital and neighborhood—individually matched to the case's date of birth (±30 days). Hospital controls were children seeking care at the emergency department 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 age-matched hospital controls were consecutively enrolled. Neighborhood controls were enrolled on a weekly basis; interviewers visited homes to the left and right of the case home until 3 controls age-matched to each case were identified. We restricted enrollment to 1 control per household and prohibited reenrollment once they were matched to a case.

Sample Size

Precision-based sample-size estimates were calculated for a matched design, using a previously described procedure,[20] under the conservative assumption that RV5 vaccination would be associated with a 60% reduction in risk of severe rotavirus diarrhea, with a confidence limit width of 30%. Assuming vaccine coverage of 50% among the

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control population during the study period and a 3:1 control-to-case ratio, we estimated that approximately 170 cases of severe rotavirus diarrhea would be sufficient for our primary analysis. In Nicaragua, incidence of rotavirus hospitalization prior to RV5 introduction was estimated to be approximately 500 per 100 000 child-years (M.P., C.P., M.O., J.J.A., unpublished data). During the prevaccine years, we estimated that approximately 400 to 500 rotavirus cases younger than 5 years were hospitalized annually at the 4 study sites, leading us to suspect that 1 year of surveillance would allow us to meet our desired sample size.

Data Collection

This evaluation was approved by human subjects offices at the Program for Appropriate Technology in Health, the Pan American Health Organization, and the Nicaragua Ministry of Health. Parents of cases and hospital controls were interviewed face-to-face during the hospital visit and, similarly, neighborhood controls were interviewed at their homes. After provision of written informed consent, information was obtained on vaccination history, demographics, socioeconomic factors, birth weight, prematurity at birth, body mass index, 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. Vaccine records at the clinic were identified on the basis of participant name, sex, and date of birth. A photocopy of the vaccination record was obtained for cases and controls, and after data entry into an electronic database, all RV5 vaccination dates were verified against this record.

Data Analysis

Our primary analysis assessed the association between 3 doses of RV5 and rotavirus diarrhea requiring hospital admission or intravenous hydration in the emergency department. A secondary analysis assessed the association between RV5 and rotavirus diarrhea classified as severe (score of ≥11) and very severe (score of ≥15), using the previously described 20-point Vesikari scale.[21,22] The Vesikari scale, which has been validated and used in the rotavirus clinical trials and studies of natural rotavirus infection, allows for comparison of results across regions.

Prior to the study, we had no convincing data indicating that one control group was better than another. Thus, we enrolled neighborhood and hospital controls with the intent of pooling both groups to ensure that sufficient controls existed per each case to maximize precision for the primary and subgroup analyses. As a secondary aim, we sought to obtain estimates through the use of each of the control groups separately to determine biases that might exist with either of the 2 control groups.

Cases and controls were considered vaccinated with the respective number of doses (1, 2, or 3) if the most recent dose was administered 14 or more days before the date of the case's hospital visit (ie, the reference date). Matching was retained in the analysis. We used conditional logistic regression to estimate the matched odds ratio (OR) of vaccination in cases vs each of the control groups as well as both of the control groups combined. We repeated the regression controlling for sex, underlying chronic illness, history of breastfeeding, daycare attendance, birth weight, maternal education, ownership of a motorized vehicle, and access to electricity, telephone, or computer in the home to identify variables that changed the estimate by more than 10%. Even though we had matched controls to ±30 days of the age of the case patient, potential for residual confounding by age could still exist. Thus, we further adjusted for age in the analysis by using as the reference date the date on which the controls were the same age (in days) as the matched case when the case was hospitalized. In this analysis, each control had its own unique reference date, which could have differed from the case's reference date.

Preplanned subgroup analyses were conducted to assess the association between rotavirus diarrhea and partial-dose vaccination (ie, 1 and 2 doses of RV5) and also to assess if the association between vaccination and rotavirus diarrhea varied by age at disease onset (to assess duration of protection after vaccination). We also conducted an intention-to-vaccinate analysis whereby we assessed association between receipt of 1 or more doses of RV5 and rotavirus diarrhea.

Vaccine effectiveness was calculated as 1 – matched odds ratio × 100%. Conditional logistic regression was performed to calculate ORs with associated 95% Wald confidence limits.[23] Differences in characteristics of children with rotavirus gastroenteritis and their matched controls were assessed using the Wilcoxon rank sum test or χ^2 test. Statistical significance was designated as $P < .05$. Analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

A total of 1615 patients with diarrhea were approached. Of these, 1589 (98%) provided stool samples. Rotavirus was identified using enzyme immunoassay in 285 (18%). Children with rotavirus diarrhea were significantly older than children without rotavirus diarrhea (median age, 10 months vs 8 months, respectively; $P < .001$) but were otherwise similar. Of the 285 rotavirus case children, 251 (88%) received intravenous hydration and 265 (93%) were admitted for a median duration of 3 days; none died. Among control children, 99% of those approached agreed to participate.

Vaccine history was confirmed for all cases and controls. Among cases and controls, respectively, about 18% and 12% were unvaccinated, 12% and 15% had received 1 dose of RV5, 15% and 17% had received 2 doses, and 55% and 57% had received 3 doses. To assess up-

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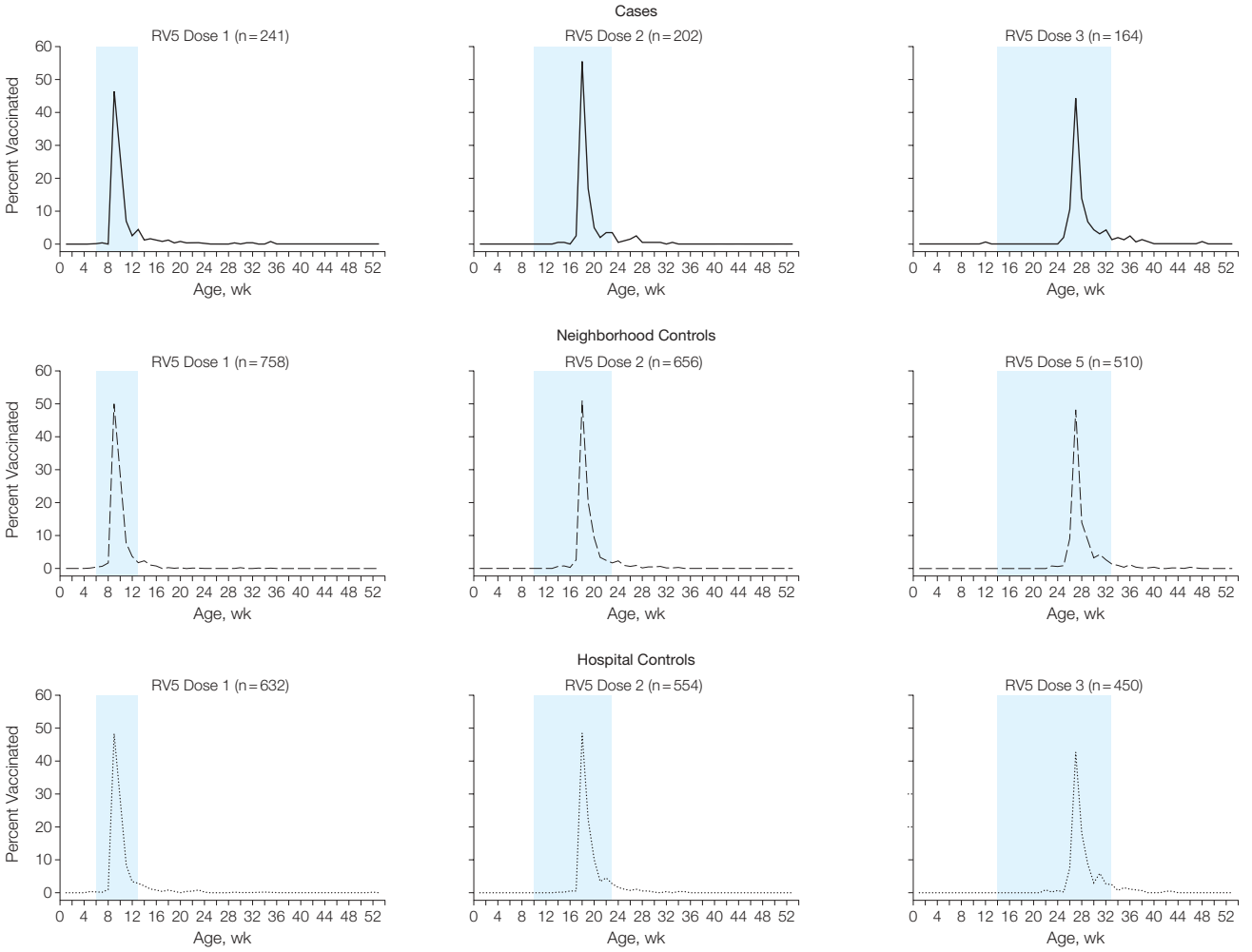
take at the study sites, we determined rates of vaccination among the 2 control groups and children with diarrhea who tested negative for rotavirus. Among children in these cohorts who were older than 8 months and age-eligible to receive vaccination, 9% were unvaccinated, 4% had received 1 dose of RV5, 9% had received 2 doses, and 77% had received 3 doses. Less than 10% of the children were vaccinated outside the recommended age windows of vaccine administration (FIGURE). Ninety-four percent of the vaccination records without any RV5 doses indicated receipt of 1 or more doses of the diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenza* type b vaccine.

The median enrollment time after case admission was 9 days for community controls and 40 days for hospital controls. For community controls, 97% of the matched sets had 3 controls per case. For hospital controls, 68% of the matched sets had 3:1 matching, while 32% had either 1:1 or 1:2 matching. Hospital controls with 3:1 matching were older (median age, 12 months) than those with less than planned matching (median age, 9 months). No other differences in socioeconomic parameters and demographics existed between these 2 hospital groups.

Compared with neighborhood and hospital controls, cases were more likely to attend daycare, and their mothers were less likely to have received higher education (TABLE 1). Including demographic and socioeconomic variables in the model and further adjusting for age did not alter the findings and therefore were not incorporated in the final model.

Children receiving 3 doses of RV5 had a lower risk of rotavirus diarrhea requiring either overnight admission or intravenous hydration (OR, 0.54; 95% confidence interval [CI], 0.36-0.82), with an estimated vaccine effectiveness of 46% (95% CI, 18%-64%) (TABLE 2). Differences between the estimates were not statistically significant ($P = .82$) when using either neighborhood (OR, 0.55; 95% CI, 0.35-0.86) or hospital controls (OR, 0.51; 95% CI, 0.32-0.82). No differences in

Figure. Age at Rotavirus Vaccination of Cases and Controls, Nicaragua



Blue tinted columns indicate recommended ages (dose 1, 6-12 weeks; 10-22 weeks; dose 3, 14-32 weeks) for vaccination with pentavalent rotavirus vaccine (RV5).

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estimates were observed across the 4 study sites. The odds of rotavirus diarrhea with 1 dose of RV5 (OR, 0.48; 95% CI, 0.28-0.82) and 2 doses (OR, 0.49; 95% CI, 0.30-0.82) did not differ significantly from the odds with 3 doses (Table 2). However, differences existed in the duration of follow-up after each vaccine dose: while more than 65% of case children who received only 1 or 2 doses of vaccine had onset of illness within 12 weeks of their last dose, only 30% of cases in 3-dose recipients had onset during this interval. Restricting the analysis only to cases requiring hospitalization (265/285 [93%]) or to those requiring intravenous hydration (251/285 [88%]) yielded estimates similar to those for all cases (Table 2).

Of the 285 rotavirus cases, 94 (33%) were classified as mild to moderate (score ≤10), 191 (67%) as severe (score ≥11), and 54 (19%) as very severe (score ≥15). No association was identified between RV5 vaccination and rotavirus disease of mild to moderate severity (OR, 0.87; 95% CI, 0.42-1.83). In contrast, 3 doses of RV5 vaccine significantly reduced the risk of severe (OR, 0.42; 95% CI, 0.26-0.70) and very severe (OR, 0.23; 95% CI, 0.08-0.61) rotavirus diarrhea. Thus, effectiveness of 3 doses of RV5 was estimated to be 58% (95% CI, 30%-74%) against severe and 77% (95% CI, 39%-92%) against very severe rotavirus diarrhea (TABLE 3).

In the intention-to-vaccinate analysis, effectiveness of 1 or more doses of RV5 was 47% (95% CI, 22%-64%) against rotavirus diarrhea requiring overnight hospitalization, 61% (95% CI, 38%-75%) against severe rotavirus diarrhea, and 74% (95% CI, 35%-90%) against very severe rotavirus diarrhea.

Strain characterization was conducted on 262 patients with adequate volume of specimens; among these, 231 (88%) were G2P[4], 14 (5%) were G1P[8], and the remaining were a variety of uncommon and mixed strains. For G2P[4] cases alone, RV5 vaccination was associated with a reduction in rotavirus disease requiring admission or intravenous hydration (OR, 0.49; 95% CI, 0.31-0.77) and in severe (OR, 0.35; 95% CI, 0.20-0.61) and very severe rotavirus diarrhea (OR, 0.18; 95% CI, 0.06-0.53).

Table 1. Comparison of Cases With Acute Rotavirus Gastroenteritis and Matched Controls

Characteristic	No. (%)				
		Controls			
	Cases (n = 285)[a]	Neighborhood (n = 840)[b]	*P* Value[c]	Hospital (n = 690)[d]	*P* Value[c]
Male	159 (56)	434 (52)	.23	396 (57)	.63
Chronic underlying illness	5 (2)	30 (4)	.12	58 (8)	<.001
History of breastfeeding	263 (92)	785 (93)	.50	638 (92)	.92
Daycare attendance	56 (20)	73 (9)	<.001	73 (11)	<.001
Premature birth	29 (10)	51 (6)	.02	87 (13)	.27
Maternal education					
None	14 (5)	27 (3)	.001	43 (6)	.02
Primary	110 (39)	256 (30)		230 (33)	
Secondary	144 (51)	456 (54)		342 (50)	
Tertiary	14 (5)	96 (11)		74 (11)	
No. of children in household, median (range)[e]	2 (1-36)	2 (1-12)	.34	2 (1-10)	.38
No. of persons in household, median (range)[e]	6 (2-22)	6 (2-22)	.59	6 (2-18)	.72
Socioeconomic parameters					
Rooms in home, median (range)[e]	5 (1-12)	5 (1-25)	.22	5 (1-15)	.02
Electricity in home	270 (95)	808 (96)	.13	640 (93)	.37
Ownership of motorized vehicle	45 (16)	163 (19)	.17	135 (20)	.17
Telephone in home	199 (70)	564 (67)	.40	502 (73)	.34
Computer in home	12 (4)	77 (9)	.007	61 (9)	.01

[a] Hospitalized or emergency department patients with acute gastroenteritis who had stool testing positive for rotavirus.
[b] Community controls matched by neighborhood and age (±1 mo).
[c] For comparison of cases and respective controls. Values were computed using the χ^2 test for differences in categorical variables and the Wilcoxon rank sum test for differences in continuous variables.
[d] Hospital- or clinic-based patients with acute nongastroenteritis illness matched by age (±1 mo).
[e] Two cases and 10 controls living in an orphanage account for the extreme observations of median children, persons, and rooms in a household.

We assessed whether the association between vaccination and reduction in risk of rotavirus disease varied by time interval since vaccination. Because most children (95%) received the full RV5 series by the recommended age limit of 8 months, the age at disease onset was closely correlated with time since vaccination—that is, children aged 8 to 11 months had disease onset 0 to 120 days since RV5 vaccination, and those older than 12 months had disease onset more than 120 days since vaccination. Risk of severe diarrhea after RV5 vaccination was lower among children aged 8 to 11 months (OR, 0.31; 95% CI, 0.13-0.76) compared with children aged 12 to 19 months (OR, 0.68; 95% CI, 0.32-1.47); however, the CIs overlapped (*P* = .19). In contrast, the association of RV5 vaccination with the odds of very severe diarrhea was sustained in both age groups, children aged 8 to 11 months (OR, 0.39; 95% CI, 0.08-1.90) and children aged 12 to 19 months (OR, 0.13; 95% CI, 0.03-0.59).

COMMENT

In this first evaluation of the performance of RV5 given as part of the routine childhood immunization program of a developing country, a complete 3-dose vaccine series was associated with a 45% to 49% reduction in risk of rotavirus diarrhea requiring admission or intravenous hydration in children younger than 2 years at the 4 hospitals. The magnitude of risk reduction increased with severity of illness, with a 58% reduction in severe (Vesikari score ≥11) rotavirus diarrhea and a 77% reduction in very severe (Vesikari score ≥15) rotavirus diarrhea in our study population.

These findings are consistent with studies of protection conferred by natural rotavirus infection, which show that

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while repeat infections and episodes of rotavirus diarrhea of milder severity can occur among young children, protection increases with increasing severity of episodes of rotavirus disease.[24-26] In addition, our findings are also in agreement with evidence from rotavirus vaccine trials indicating vaccines to be more efficient in preventing severe disease than milder disease.[5,8,27] Thus, while RV5 may only halve rotavirus-associated hospital admissions or emergency department treatment of young children in Nicaragua, its impact on the most severe disease, including rotavirus mortality, could be more substantial.

The reduction in risk of severe rotavirus disease associated with RV5 vaccination in Nicaragua is lower than the reduction of 86% to 96% against rotavirus-associated health care utilization in the prelicensure trial in Finland and the United States and the 84% to 100% reduction in emergency department visits and hospitalizations for rotavirus diarrhea in a postlicensure evaluation in the United States.[5,28] Our findings are not unexpected, given that efficacy of previous candidate rotavirus vaccines has also tended to be lower in developing countries compared with industrialized countries,[8,29,30] a phenomenon that might be explained by potential differences in host and environmental factors that could adversely affect vaccine performance.[3,8,31] Data for RV5 and other oral rotavirus vaccines have shown a slightly lower immune response to rotavirus vaccines when given concomitantly with vs separately from oral polio vaccine, although the relevance of the immunogenicity data to efficacy remains unclear.[32-35] Because oral polio vaccine was coadministered to all children vaccinated with RV5 in our evaluation, we were unable to assess the association between severe rotavirus disease and RV5 given with and without oral polio vaccine.

Two surface rotavirus proteins (G and P) induce homotypic and heterotypic neutralizing antibody responses suspected to be important for protective immunity after natural infection and rotavirus vaccination.[36] The 2 gene segments encoding the G and P proteins segregate independently and combine to form many strains, 5 of which

Table 2. Association Between Rotavirus Vaccination and Rotavirus Disease Requiring Hospital Admission or Intravenous Hydration

	1-Dose Vaccinees[a]			2-Dose Vaccinees[a]			3-Dose Vaccinees[a]		
Rotavirus Group	No./Total (%)[b]	Matched OR (95% CI)[c]	VE (95%CI)[d]	No./Total (%)[b]	Matched OR (95% CI)[c]	VE (95%CI)[d]	No./Total (%)[b]	Matched OR (95% CI)[c]	VE (95%CI)[d]
Requiring hospital admission or intravenous hydration									
Cases	34/85 (40)			42/93 (45)			158/209 (76)		
Controls									
Neighborhood	119/217 (55)	0.50 (0.29 to 0.88)	50 (12 to 71)	137/235 (58)	0.51 (0.30 to 0.87)	49 (13 to 70)	486/584 (83)	0.55 (0.35 to 0.86)	45 (14 to 65)
Hospital	108/186 (58)	0.45 (0.25 to 0.83)	55 (17 to 75)	120/198 (61)	0.47 (0.27 to 0.82)	53 (18 to 73)	382/460 (83)	0.51 (0.32 to 0.82)	49 (19 to 68)
Combined	227/403 (56)	0.48 (0.28 to 0.82)	52 (18 to 72)	257/433 (59)	0.49 (0.30 to 0.82)	51 (18 to 70)	868/1044 (83)	0.54 (0.36 to 0.82)	46 (18 to 64)
Requiring admission									
Cases	31/80 (39)			42/91 (46)			143/192 (74)		
Controls									
Neighborhood	116/213 (54)	0.48 (0.27 to 0.88)	52 (14 to 73)	125/222 (56)	0.59 (0.35 to 1.02)	41 (–2 to 65)	442/539 (82)	0.57 (0.36 to 0.91)	43 (9 to 64)
Hospital	106/181 (59)	0.40 (0.22 to 0.76)	60 (24 to 78)	111/186 (60)	0.51 (0.29 to 0.90)	49 (10 to 71)	350/425 (82)	0.51 (0.32 to 0.83)	49 (17 to 68)
Combined	222/394 (56)	0.45 (0.26 to 0.78)	55 (22 to 74)	236/408 (58)	0.56 (0.33 to 0.93)	44 (7 to 67)	792/964 (82)	0.56 (0.36 to 0.85)	44 (15 to 63)
Requiring intravenous hydration									
Cases	30/76 (39)			37/83 (45)			138/184 (75)		
Controls									
Neighborhood	106/192 (55)	0.49 (0.27 to 0.88)	51 (12 to 73)	119/205 (58)	0.51 (0.29 to 0.89)	49 (11 to 71)	428/514 (83)	0.52 (0.32 to 0.85)	48 (15 to 68)
Hospital	97/167 (58)	0.42 (0.22 to 0.82)	58 (18 to 78)	109/179 (61)	0.45 (0.25 to 0.81)	55 (19 to 75)	334/404 (83)	0.53 (0.33 to 0.88)	47 (12 to 67)
Combined	203/386 (56)	0.46 (0.26 to 0.80)	54 (20 to 74)	228/384 (59)	0.48 (0.28 to 0.82)	52 (18 to 72)	762/918 (83)	0.52 (0.34 to 0.81)	48 (19 to 66)

Abbreviations: CI, confidence interval; OR, odds ratio; VE, vaccine effectiveness.
[a] Cases and controls were considered vaccinated with the respective number of doses (1, 2, or 3) if the most recent dose was administered 14 or more days before the date of the case's hospital visit.
[b] Total indicates the sum of infants with no vaccination plus those receiving either 1, 2, or 3 doses of pentavalent rotavirus vaccine.
[c] Conditional logistic regression was used to compute odds ratio of vaccination (1, 2, or 3 doses) vs no vaccination among cases and controls (neighborhood controls, hospital controls, and both combined). Adjusting for potential confounding did not change the results; thus, the unadjusted results are presented.
[d] Vaccine effectiveness was calculated as 1 – matched odds ratio × 100%.

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are commonly detected worldwide: G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8]. Components of the RV5 vaccine include all of these antigens except G9 and P[4], the latter being 1 of the 2 antigens in the G2P[4] strain that was detected in 88% of the samples in Nicaragua during the study. Because the P protein also elicits neutralizing antibodies,[37] the possibility exists that the effectiveness of RV5 in Nicaragua might have been affected by the predominance of this relatively uncommon G2P[4] strain. During the RV5 clinical trial in Finland and the United States, vaccination conferred 88% (95% CI, <0%-98%) protection against G2[P4] strains, but the data should be interpreted with caution, given that only 8 children in the placebo group were infected with the strain.[5] The fact that G1 rotavirus strains constituted 86% of the circulating strains during the clinical trial suggests that careful monitoring during the postintroduction period of the impact of vaccination on disease from non-G1 strains is warranted, particularly in developing countries where strain diversity is common.[13]

The epidemiology of severe rotavirus disease indicates that for vaccines to have a substantial public health impact, they need to provide protection against severe rotavirus disease beginning early in life through at least age 2 years.[38] Our sample size was insufficient to assess whether the association of RV5 and severe rotavirus diarrhea diminishes with time since vaccination. While we did observe lower odds of severe disease (score ≥11) among younger children (8-11 months) compared with older children (12-19 months), the difference was not statistically significant.

We also assessed the association of partial vaccination with rotavirus diarrhea. The overall reduction in risk associated with partial immunization with 1 or 2 doses of vaccine appeared similar to that associated with complete vaccination. It is important to note that most of the case children (65%) who received only 1 or 2 doses of vaccine had onset of illness within 12 weeks of their last dose; only 30% of the 3-dose recipients had onset during this interval. Thus, the reduction in risk after partial vaccination may not be directly comparable to the risk reduction after 3 doses. However, obtaining protective immunity from 1 dose of the vaccine, even for a short period, could be a substantial advantage in developing countries where up to one-third of the burden of severe rotavirus disease, including deaths, may occur among children younger than 6 months.[39,40] While these data on partial-dose analysis identified some interesting information, the small sample sizes and the overlapping CIs are of concern. These results should be interpreted with caution and need to be evaluated in future studies.

This evaluation has some limitations that we attempted to address. Accurate and complete ascertainment of vaccination is critical for such evaluations. While logistical reasons prevented us from blinding interviewers to knowledge of case and control status, we were able to verify vaccination by review of the vaccine record for all participants, thus minimizing any potential bias. Records of nonvaccination are not typically available; however, most (94%) of the children who were not vaccinated with RV5 had a record for vaccination with the combination vaccine against diphtheria, tetanus, pertussis, hepatitis B, and *H influenza* type b and oral polio vaccine that are given at the same ages, increasing our confidence in the accuracy of data on nonvaccination with RV5. Misclassification of vaccinees is possible; however, any such misclassification would likely have been low and equal in both cases and controls and thus unlikely to affect our estimates substantially. Also, the confounding effects of age and socioeconomic factors were controlled for through matching by age and by hospital or neighborhood. Because RV5 doses were administered in fairly tight age windows in this setting, we examined the potential for residual confounding by age; restricting analyses to cases and controls matched on exact age produced results consistent with overall estimates.

Table 3. Association Between Rotavirus Vaccination and Rotavirus Disease by Severity, Classified Using the 20-Point Vesikari Score, Among 3-Dose Vaccinees[a]

Group	No./Total (%)[b]	Matched OR (95% CI)[c]	VE (95%CI)[d]
Vesikari severity score ≤10			
Cases	48/63 (76)		
Controls			
Neighborhood	147/186 (79)	0.77 (0.34 to 1.74)	23 (–74 to 66)
Hospital	104/139 (75)	0.96 (0.42 to 2.20)	4 (–120 to 58)
Combined	251/325 (77)	0.87 (0.42 to 1.83)	13 (–83 to 58)
Vesikari severity score ≥11			
Cases	110/146 (75)		
Controls			
Neighborhood	338/396 (85)	0.48 (0.28 to 0.82)	52 (18 to 72)
Hospital	278/321 (87)	0.37 (0.20 to 0.66)	63 (34 to 80)
Combined	616/717 (86)	0.42 (0.26 to 0.70)	58 (30 to 74)
Vesikari severity score ≥15			
Cases	28/39 (72)		
Controls			
Neighborhood	86/99 (87)	0.27 (0.09 to 0.82)	73 (18 to 91)
Hospital	81/93 (87)	0.14 (0.04 to 0.55)	86 (46 to 96)
Combined	167/192 (87)	0.23 (0.08 to 0.61)	77 (39 to 92)

Abbreviations: CI, confidence interval; OR, odds ratio; VE, vaccine effectiveness.
[a] Cases and controls were considered vaccinated with 3 doses of vaccine if the most recent dose was administered 14 or more days before the date of the case's hospital visit.
[b] Total indicates the sum of infants with no vaccination plus those receiving 3 doses of pentavalent rotavirus vaccine.
[c] Conditional logistic regression was used to compute odds ratio of complete vaccination (3 doses) vs no vaccination among cases and controls (neighborhood controls, hospital controls, and both controls combined).
[d] Vaccine effectiveness was calculated as 1 – matched odds ratio × 100%.

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To avoid bias from selection of control children representing a source population with different risks of exposure and disease than the case children, we used 2 groups of controls: hospital and neighborhood. While the point estimates of effect were consistently somewhat higher with hospital controls, the results were comparable and differences were not statistically significant. We had no strong reason for preferring one control group to another prior to the study. However, for the hospital group, we were able to enroll the planned number of 3 controls for only 68% of the cases, whereas for the neighborhood group, 97% of the rotavirus cases had 3 controls. Hospitalized control children with full 3:1 matching were younger than those with 2:1 or 1:1 matching, because children with acute conditions other than diarrhea are typically younger than 1 year. This age effect with the hospital controls might have affected the precision of the estimates computed using hospital controls for the subgroup analyses but should not affect the validity of our primary findings.

In summary, RV5 was associated with lower odds of severe rotavirus diarrhea in Nicaragua but to a lesser extent than observed during the clinical trial in industrialized countries. The reduction in risk associated with RV5 vaccination increased with increasing disease severity. Our study period coincided with a season when G2P[4], a less common rotavirus strain, predominated. Further monitoring is necessary in Nicaragua to assess vaccine performance against diverse circulating strains and to better assess whether reduction in risk of severe rotavirus diarrhea is sustained through the first 2 to 3 years of life. In addition, it remains unclear whether the findings in Nicaragua would apply to other developing countries with different circulating strains and host conditions. Studies in other developing countries, including results of ongoing efficacy trials in Asia and Africa, will allow a more complete assessment of performance of these vaccines in challenging settings. If results of studies in developing countries consistently demonstrate lower reduction in risk, identifying hurdles to successful oral rotavirus immunization may prove critical for improving the effectiveness in target populations most likely to benefit from rotavirus vaccination.

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Patterns and structure. Everywhere we look we see them. What appears random and chaotic also has order. And on Earth much of the order is linked to interrelationships that drive constant change. Cycles and rhythms. Pulses and flows. Changes in magnetic fields. Continental plates moving. Water cycles. Seasons changing. Life and death. Process and connection. Nature flows through webs of structure and shifting time: from ocean to cloud to rain to river to ocean. Natural rhythms.

—Payson R. Stevens (1946-)

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