Effectiveness of the Monovalent G1P[8] Human Rotavirus Vaccine Against Hospitalization for Severe G2P[4] Rotavirus Gastroenteritis in Belém, Brazil

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Background: Brazil initiated universal immunization of infants with the G1P[8] human rotavirus (RV) vaccine in March 2006. This study evaluated vaccine effectiveness (VE) against severe rotavirus gastroenteritis (RVGE) hospitalizations.

Methods: Matched case-control study conducted at 4 hospitals in Belém from May 2008 to May 2009. Cases were children hospitalized with RVGE age-eligible to have received 2 doses of the human RV vaccine (≥12 weeks of age and born after March 6, 2006). For each case, 1 neighborhood and 1 hospital control without gastroenteritis was selected, matching by birth date (±8 and ±6 weeks, respectively). Matched odds ratio of 2-dose RV vaccination in cases versus controls was used to estimate VE (1 − odds ratio × 100%).

Results: Of 538 RVGE cases, 507 hospital controls and 346 neighborhood controls included, 54%, 61%, and 74% had received both RV vaccine doses. VE against RVGE hospitalization was 75.8% (95% confidence interval [CI]: 58.1–86.0) using neighborhood controls and 40.0% (95% CI: 14.2–58.1) using hospital controls. VE in children 3 to 11 months and ≥12 months of age was 95.7% (95% CI: 67.8–99.4) and 65.1% (95% CI: 37.2–80.6) using neighborhood controls, and 55.6% (95% CI: 12.3–77.5) and 32.1% (95% CI: −3.7–55.5) using hospital controls. G2P[4] accounted for 82.0% of RVGE hospitalizations. G2P[4]-specific VE was 75.4% (95% CI: 56.7–86.0) using neighborhood controls and 38.9% (95% CI: 11.1–58.0) using hospital controls.

Conclusions: Although fully heterotypic G2P[4] was the predominant RV strain, good VE was demonstrated. VE was highest in children aged 3 to 11 months. However, protection in children ≥12 months of age, important for optimal public health impact, was significantly sustained based on estimates obtained using neighborhood controls.

Key Words: gastroenteritis, rotavirus, hospitalizations, human rotavirus vaccine, Brazil

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Rotavirus (RV) is the most common cause of acute gastroenteritis (GE) requiring medical attention or hospitalization in young children worldwide, accounting for approximately 2.4 million hospitalizations and more than half a million deaths annually among children less than 5 years of age.[1–4] The availability of safe and effective vaccines against RV offers the potential to reduce the global burden of rotavirus gastroenteritis (RVGE).[2,5,6] The World Health Organization (WHO) recommends inclusion of RV vaccination of infants into all national immunization programs.[5] Two oral RV vaccines are now available in many countries—a 2-dose human G1P[8] RV vaccine (Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) and a 3-dose live bovine-human reassortant pentavalent vaccine (Rotateq, Merck Vaccines, Whitehouse Station, NJ).[7] Both vaccines have been shown to be safe and highly effective for the prevention of RVGE in large-scale clinical trials[8–14] and postlicensure studies.[7,15–17]

The human RV vaccine is currently licensed in 13 Latin American countries. Brazil was the first country in the region to incorporate this vaccine into the national Expanded Program on Immunization, with RV vaccination available free of charge at public primary healthcare centers throughout the country since March 2006. Prior to RV vaccine introduction, RV accounted for an annual 3.5 million episodes of GE, 650,000 visits to outpatient healthcare facilities, 92,000 hospitalizations and 850 deaths among Brazilian children less than 5 years of age.[18] RV accounted for approximately 43% of all GE hospitalizations in this age group[19] and 46% of GE hospitalizations in children younger than 3 years.[20]

With RV vaccines increasingly being introduced into childhood immunization programs, monitoring vaccine effectiveness (VE) under normal operational conditions is a high priority.[21,22] In parallel, continuous surveillance of circulating RV strains is warranted during the postintroduction period to evaluate any potential impact of RV vaccination on genotype diversity.[23] We assessed the effectiveness of the human RV vaccine for the prevention of severe RVGE hospitalizations in children age-eligible to have received both vaccine doses in Belém, Brazil. To mimic the real-life scenario, the effectiveness of partial vaccination was also assessed.

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METHODS

Study Setting and Design

This was a hospital-based, age-matched case-control study in Belém, a large city in Northeastern Brazil with a population of 1,437,604 and an annual birth cohort of 24,054.[24,25] Active surveillance for RVGE was conducted at 4 large urban pediatric clinics/hospitals with a total of 294 pediatric beds, accounting for approximately 80% of all pediatric admissions for severe GE in Belém. RV strain surveillance was initiated in parallel with the case-control study and is currently ongoing.

Study design was based on the WHO generic protocol for monitoring the impact of RV vaccination on GE disease burden.[21] The protocol was reviewed and approved by the independent ethics committee of the investigational center at Instituto Evandro Chagas, Secretaria de Vigilância em Saúde, Brazilian Ministry of Health. Written informed consent was obtained from the parents/guardians of all participating children prior to study entry.

Case Definition and Enrollment

Cases were children at least 12 weeks of age born after March 6, 2006 hospitalized with laboratory-confirmed severe RVGE, defined as diarrhea (3 or more looser than normal stools within 24 hours), with or without vomiting, of less than 14 days duration requiring at least an overnight stay and intravenous rehydration therapy in one of the participating centers during the study period. As part of routine clinical practice, stool samples were collected within 48 hours of admission and tested for the presence of RV by enzyme-linked immunosorbent assay (ELISA) at the Ministry of Health's National Rotavirus Reference Laboratory, Instituto Evandro Chagas. Only children with ELISA-confirmed RVGE were eligible for inclusion as a case. Children with onset of severe RVGE more than 48 hours after hospital admission (nosocomial infections) were excluded. All ELISA-positive stool samples were tested by polymerase chain reaction at Instituto Evandro Chagas for determination of RV G and P type.

Control Definition and Enrollment

For each case, we planned to enroll 1 hospital and 1 neighborhood control. Hospital controls were children hospitalized for any reason except GE or another vaccine-preventable disease identified through review of the hospital admission log book and matched progressively to cases by date of birth (from ± 2 weeks, up to a maximum of ± 6 weeks). Neighborhood controls were children without any signs or symptoms of GE who had resided in the same neighborhood as the case for at least 3 months. Neighborhood controls were selected by interviewing neighbors to the right and left of the case home in a sequential manner until a child born within ± 8 weeks of the case was enrolled. This wider age range for neighborhood controls was used because of logistical difficulties to facilitate the enrollment of subjects.

Data Collection

After informed consent had been obtained, parents/guardians of all cases/controls were interviewed by a pediatrician or nurse to obtain information on demographics, medical history, GE symptoms and treatment prior to hospitalization (cases only), and diagnosis at hospital admission and discharge (cases and hospital controls). Study staff also reviewed medical records and recorded appropriate information for cases and hospital controls. For both cases and controls, vaccination history was confirmed by vaccination card review during the interview with the parent/guardian.

Statistical Analysis

All statistical analyses were performed using SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC). Considering RV vaccine coverage of 69.1% for the first dose and 52.1% for the full 2-dose course among controls (Pará State Secretary of Public Health, September 2007), through simulation (2000 runs) and conditional logistic regression we estimated that a total of 230 cases and 230 controls would provide a power of 97% to demonstrate that VE is higher than 50%, with an alpha level of 5%, when the true VE is 80%.

For calculation of VE of the full 2-dose course of human RV vaccine, the analysis included only pairs for which the case and the controls had received either 0 or 2 vaccine doses and who met all protocol-defined criteria. Cases were required to have received the first dose of human RV vaccine at least 14 days before the onset of severe GE to be included in this analysis. VE (%) was estimated as 1 minus the matched odds ratio of vaccination multiplied by 100 for each control group. Conditional logistic regression was used to estimate the matched odds ratio (hazard ratio using SAS code of PROC PHREG), with 95% Wald confidence limits,[26] and was repeated to include potential confounders, for which a backward elimination strategy was used to retain variables with $P \leq 0.20$.[16,27] VE of the full 2-dose course of human RV vaccine was estimated according to age (3–11 months and $\geq$12 months), severity of RVGE hospitalizations determined using the Vesikari scale,[28] and RV genotype. VE was also estimated in children who had received at least 1 vaccine dose. Finally, to include some of the subjects with missing/unknown vaccination history, in addition to the actual VE, VE was also calculated using a sensitivity analysis assuming cases and controls with missing/unknown vaccination history were vaccinated and unvaccinated, respectively, for the worst case scenario (sensitivity $-$), or the opposite for the best case scenario (sensitivity $+$).

The proportion of hospital admissions for severe GE and the proportion of severe GE hospitalizations attributable to RV were calculated with exact 95% confidence interval [CI]. Demographic characteristics, age distribution, disease seasonality, severity and distribution of RV G and P types were also tabulated. Due to non-normality, sparse or unbalanced data, demographic characteristics were compared between cases and each set of controls using the Fisher exact test for categorical variables and the Mann-Whitney Wilcoxon 2 sample test for continuous variables. Two-sided P values of <0.05 were considered statistically significant.

RESULTS

Study Population

Between May 14, 2008 and May 28, 2009, 10,828 age-eligible children were hospitalized at the participating centers, 4692 (43.3%) of whom were hospitalized due to severe GE. Of these, 80.2% (3763/4692) provided stool samples for testing, 24.1% of which were positive for RV by ELISA (906/3763). The proportion of ELISA-confirmed severe RVGE hospitalizations varied by age and was highest in children aged 12 to 23 months, with 53.2% (482/906) of RVGE hospitalizations occurring in this age group. The proportion of severe RVGE hospitalizations varied over time, peaking during July and August 2008 and April 2009 (Fig. 1).

A total of 538 RV-positive children were enrolled as cases (59.4% of those testing positive for RV in the screened population), 522 of whom had a matched hospital and/or neighborhood control (97.0%). Differences between the screened and enrolled RV-positive subjects, with respect to age distribution or area of residence that could impact the results, were not identified. Overall, 368 RV-positive children were not included as a case in the final according-to-protocol analysis. Because of logistic reasons (eg, child was discharged from the hospital and moved away from the study area, address could not be found, etc.), it

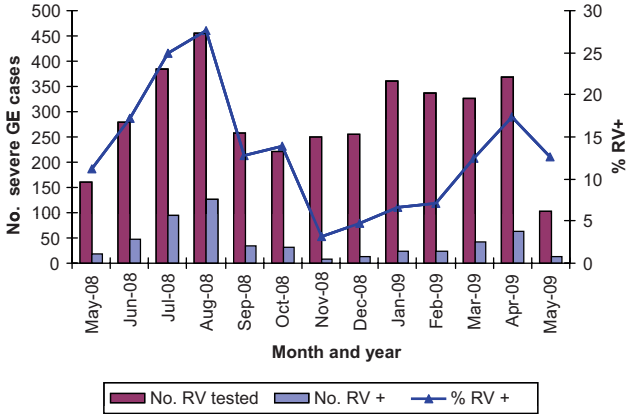

FIGURE 1. Seasonal distribution of severe GE cases and the proportion of cases attributable to RVGE by month of year in Belém, Brazil (May 14, 2008–May 28, 2009).

was not possible to obtain written informed consent from parents/guardians for 317 subjects. In the additional 51 subjects for whom informed consent had been obtained, reasons for exclusion from the according-to-protocol analysis were stool sample collected more than 48 hours after admission (15 subjects), nosocomial diarrhea (15 subjects), diarrhea did not meet the protocol definition (13 subjects), previous enrollment (3 subjects), persistent diarrhea (2 subjects), doubtful history of diarrhea (1 subject), outside the age group (1 subject), and birth date unknown (1 subject). It was not possible to enroll both a matched hospital and a neighborhood control for all cases. Among children screened as hospital controls, 516 of 885 (58.3%) were enrolled and 507 met the criteria for inclusion in the case-control analysis. There was an uneven temporal distribution of cases and hospital controls (>90% of the hospital controls were acute respiratory infections), leading to a significant difference in the time period of their recruitment into the study (month, year). While most of the cases occurred during July to August 2008 (150/538; 28%), respiratory illnesses (hospital controls) peaked in October to November 2008 (145/507; 28.6%). In the former period, for instance, there were too few hospitalizations for acute respiratory infections to match a large number of RVGE hospitalizations.

The absolute median (range) difference between date of birth of cases and hospital controls was 1 (0–6) week. The median duration of hospitalization for both cases and hospital controls was 5 days. Among children screened as neighborhood controls, 348 of 387 (89.9%) were enrolled and 346 met the criteria for inclusion in the case-control analysis. The absolute median (range) difference between date of birth of cases and neighborhood was 3 (0–8) weeks.

Demographic characteristics are shown in Table 1. Median age of study participants was 17 months, 52.6% were male, all were American Hispanic or Latino and 90.4% lived in Belém. Of note, the proportion of hospital controls that lived in Belém was lower than for neighborhood controls (87.6% and 95.7%, respectively).

RV Vaccination History

In all, 68.0% of cases, 76.3% of hospital controls, and 85.3% of neighborhood controls had received at least 1 dose of the human RV vaccine, with 53.7% of cases, 60.7% of hospital controls, and 74.0% of neighborhood controls having completed the full 2-dose course (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A695). The percentage of vaccinated subjects that received the first vaccine dose between 8 and 12 weeks of age was 87.2%, 80.4%, and 86.8%, in the 3 groups, respectively. The respective proportions of vaccinated subjects who had completed the full 2-dose course by 24 weeks of age were 77.3%, 76.2%, and 85.4%.

Most subjects had received other recommended vaccinations. However, for most vaccines, coverage rates were 5% to 6% lower in hospital controls than in neighborhood controls.

Vaccine Effectiveness

VE of 2 doses of the human RV vaccine for the prevention of severe RVGE hospitalization was 75.8% (95% CI: 58.1–86.0) using neighborhood controls and 40.0% (95% CI: 14.2–58.1) using hospital controls (Table 2). VE in cases and hospital controls that lived in the same district was 52.9% (95% CI: −9.1 to 79.7). VE was higher in children aged 3 to 11 months than in those aged ≥12 months (95.7% [95% CI: 67.8–99.4] versus 65.1% [95% CI: 37.2–80.6] using neighborhood controls and 55.6% [95% CI:

TABLE 1. Demographic Characteristics of Study Participants in Belém, Brazil (May 14, 2008–May 28, 2009)

Characteristic	Cases N = 538	Hospital Controls		Neighborhood Controls		Total N = 1391
		N = 507	*P*	N = 346	*P*	
Gender, %						
Male	50.7	52.9	0.500	54.9	0.240	52.6
Female	49.3	47.1		45.1		47.4
Age, mo						
Median (range)	16 (3–36)	18 (3–36)	0.008	17 (3–36)	0.240	17 (3–36)
Age group, %						
3–5 mo	2.6	2.4		1.4		2.2
6–11 mo	22.9	19.3		19.1		20.6
12–23 mo	53.9	53.6		57.5		54.7
≥24 mo	20.6	24.7		22.0		22.4
Living in Belém at the time of the study, %						
Yes	89.8	87.6	0.280	95.7	0.001	90.4
No	10.2	12.4		4.3		9.6

P values were calculated using exact Fisher exact test for categorical variables and Mann-Whitney-Wilcoxon 2 sample test for continuous variable.

TABLE 2. Effectiveness of the Human RV Vaccine for the Prevention of Hospital Admissions for Severe RVGE in Belém, Brazil (May 14, 2008–May 28, 2009)

	Neighborhood Controls					Hospital Controls				
	Vaccine Effectiveness			Sensitivity		Vaccine Effectiveness			Sensitivity	
	N	%	95% CI	−	+	N	%	95% CI	−	+
Full 2-dose series										
Overall	249	75.8	58.1–86.0	71.2	77.8	312	40.0	14.2–58.1	21.3	52.0
3–11 mo	64	95.7	67.8–99.4	95.7	95.8	77	55.6	12.3–77.5	48.1	58.6
≥12 mo	185	65.1	37.2–80.6	58.1	68.8	235	32.1	−3.7–55.5	7.5	49.3
Full 2-dose series by RVGE severity (Vesikari score)										
Mild/moderate (1–10)	149	72.7	43.0–87.0	66.7	75.7	187	25.6	−20.2–54.0	2.6	42.0
Severe (≥11)	100	78.8	52.1–90.6	75.8	80.0	125	53.7	20.2–73.1	39.0	62.0
Very severe (≥15)	23	90.0	21.9–98.7	90.0	90.0	25	28.6	−125.1–77.3	0.0	37.5
Full 2-dose series against fully heterotypic G2P[4]	222	75.4	56.7–86.0	70.5	77.6	286	38.9	11.1–58.0	22.2	51.6
Full 2–dose series against pooled non-G2P[4] types	42	70.0	−9.0–91.7	70.0	70.0	46	50.0	−33.2–81.2	8.3	60.0
Full or partial series vaccination										
Overall	331	62.3	42.3–75.4	58.4	65.5	444	44.2	23.1–59.6	26.0	54.3
3–11 mo	91	88.9	63.4–96.6	88.9	89.3	120	60.5	28.2–78.3	52.6	62.5
≥12 mo	240	48.0	16.5–67.6	42.0	53.6	324	34.9	4.3–55.6	10.6	50.6

Sensitivity −, cases and controls with other or unknown RV vaccination status are assumed respectively vaccinated and unvaccinated.
Sensitivity +, cases and controls with other or unknown RV vaccination status are assumed respectively unvaccinated and vaccinated.
N indicates number of matched pairs; RV, rotavirus; RVGE, rotavirus gastroenteritis.

12.3–77.5] versus 32.1% [95% CI: −3.7 to 55.5] using hospital controls in the 2 age groups, respectively).

During hospitalization, 58.4% of RVGE cases were rated as mild/moderate (Vesikari score, 1–10), 41.6% as severe (Vesikari score, ≥11), and 9.7% as very severe (Vesikari score, ≥15). Using neighborhood controls, VE of 2 doses of the human RV vaccine was 72.7% (95% CI: 43.0–87.0), 78.8% (95% CI: 52.1–90.6), and 90.0% (95% CI: 21.9–98.7) for the prevention of mild/moderate (Vesikari score, 1–10), severe (Vesikari score, ≥11), and very severe (Vesikari score, ≥15) RVGE, respectively. Respective VE estimates using hospital controls were 25.6% (95% CI: −20.2 to 54.0), 53.7% (95% CI: 20.2–73.1), and 28.6% (95% CI: −125.1 to 77.3).

Strain characterization was conducted on all enrolled 538 RV-positive cases. G2P[4] was the most common RV type, accounting for 82.0% (441/538) of cases. Of the 97 (18%) non-G2P[4] strains identified, 1 was G1P[6] (0.2%), 11 were G1P[8] (2.0%), 16 were G2P[6] (3.0%), 2 were G9P[4] (0.4%), 1 was G9P[6] (0.2%), 2 were G9P[8] (0.4%), 11 were G12P[6] (2.0%), 48 were mixed types (8.9%), and 5 were untypeable (0.9%).

VE of 2 doses of the human RV vaccine for the prevention of severe G2P[4] RVGE was 75.4% (95% CI: 56.7–86.0) using neighborhood controls and 38.9% (95% CI: 11.1–58.0) using hospital controls. For RVGE caused by pooled non-G2P[4] types, VE of 2 doses of the human RV vaccine was 70.0% (95% CI: −9.0 to 91.7) using neighborhood controls and reached 50% (95% CI: −33.2 to 81.2) using hospital controls.

In children who had received at least 1 vaccine dose, VE using neighborhood controls was 62.3% (95% CI: 42.3–75.4) overall, 88.9% (95% CI: 63.4–96.6) in children aged 3–11 months, and 48.0% (95% CI: 16.5–67.6) in those aged ≥12 months. Corresponding VE using hospital controls was 44.2% (95% CI: 23.1–59.6) overall and 60.5% (95% CI: 28.2–78.3) and 34.9% (95% CI: 4.3–55.6) in the 2 age groups, respectively.

After controlling for potential confounders (or risk factors) in the conditional logistic regression model (Tables, Supplemental Digital Content 2 and 3, http://links.lww.com/INF/A696 and http://links.lww.com/INF/A697), VE was 73.6% (95% CI: 53.9–84.9) and 43.3% (95% CI: 8.4–64.8) using neighborhood and hospital controls, respectively. Age ≥1 year was significantly associated with RVGE using neighborhood controls. For hospital controls, time period of recruitment into the study, the presence of underlying medical conditions and diet including breast-feeding also had a significant impact on VE. Results of the sensitivity analysis for the primary objective ranged from 71.2% to 77.8% using neighborhood controls and from 21.3% to 52.0% using hospital controls (Table 2).

DISCUSSION

This study demonstrated the effectiveness of 2 doses of the human RV vaccine for the prevention of severe RVGE hospitalizations, predominantly due to the G2P[4] strain, in Belém, Brazil, one of the settings where the pivotal Latin American Phase III trial of this vaccine was conducted.[8,11] The effectiveness of 2 doses and at least 1 dose of human RV vaccine was comparable to the findings of previous clinical trials in the region.[11,29]

The effectiveness of RV vaccines against the fully heterotypic G2[P4] strain is currently of particular interest, since this strain seems to be showing natural re-emergence in Latin America and many other parts of the world.[19,30–35] The human RV vaccine has been shown to provide broad protection against circulating G1 and non-G1 strains in randomized controlled clinical trials, with G2P[4]-specific efficacy ranging from 45% to 86%.[8,10–12] A meta-analysis of results from 6 randomized controlled clinical trials indicated a VE of 81% against G2P[4] RVGE of any severity and of 71% against severe G2P[4] RVGE.[36] We found the human RV vaccine to provide a high level of protection against hospitalization for G2P[4] RVGE, in line with the results of another recent study in Recife, Brazil, which had an unmatched case-control design and demonstrated VE of 77% against severe G2P[4] RVGE requiring hospital admission or emergency department treatment in children 6 to 11 months of age.[17]

Duration of protection is another important factor influencing the potential public health impact of RV vaccines. VE of 83% to 85% against hospitalization for severe GE caused by the fully

heterotypic G2P[4] type was seen in children aged 6 to 11 months and nonsignificant results in children ≥12 months in the Recife study.[17] We also observed highest VE in children 3 to 11 months of age (96%), with lower but still significant protection in children ≥12 months of age (65%) using neighborhood controls. Vaccine efficacy was also found to be slightly lower during the second year of follow-up in the Phase III study in Latin America (79% vs. 83% during the first year).

The proportion of severe GE hospitalizations attributable to RV was low in this study compared with that reported in Belém and other regions in Brazil prior to RV vaccine introduction (43%–46%).[19,20] Similarly, the proportion of RV-positive cases among children with diarrhea accessing emergency services decreased from 24% in 2006 to 7% in 2008 in Aracaju, Brazil, with greatest reductions seen in the youngest age groups.[37] A marked decline in hospitalizations for all-cause gastroenteritis among children younger than 1 year following the introduction of RV vaccination in Brazil has also recently been reported.[38] While earlier studies in Brazil and Latin America found approximately 50% of RV cases to occur in children aged <12 months and 80% in those aged <24 months,[20] most RVGE occurred in children 12 to 23 months of age in this study, followed by infants aged 3 to 11 months and children aged >24 months. It is possible that the age distribution and severity of RVGE may change after vaccine introduction, with less severe cases occurring among older children. However, protection against RVGE during the first 2 years of life is particularly important, as this is the time when RV infections are most severe.

Although we used an age-matched case-control design and obtained a large sample size, the marked differences in VE using the 2 different control groups are striking. Case-control studies are an effective method of monitoring VE in real-life conditions, particularly during the early phases of vaccine introduction.[21] However, choice of control group can have a significant impact on VE estimates.[21,39–41] For RV infection, neighborhood controls provide the advantage of controlling for key potential confounding factors which could impact on risk of developing severe RVGE, particularly sociodemographic status and general access to vaccination and medical care. In contrast, greater variability in such factors may occur among hospitalized controls. Hospitalization and emergency department visits are recognized to be potential markers of under-vaccination, even in children with access to healthcare.[42] In Belém, vaccination is performed at primary healthcare centers with well-defined catchment areas and not in hospitals, and vaccination coverage varies greatly geographically.[43] VE increased when we attempted to augment comparability of hospital controls to neighborhood controls by restricting analysis to cases and hospitals controls that lived in the same districts in Belém. In this study, a higher proportion of hospital controls than cases and neighborhood controls resided outside of the Belém area. Furthermore, coverage rates for most routine childhood vaccines were lower in hospital controls than neighborhood controls. In addition, a higher proportion of hospital controls had missing or unknown RV vaccination status which may explain the greater variability in the sensitivity analysis using this group. One possible limitation of our study in this context was that hospital controls were not screened for RV infection. According to routine clinical practice in each participating hospital and the generic WHO protocol followed,[21] stool samples were only tested for the presence of RV by ELISA if GE was present at admission.

In summary, results of this study show a considerable reduction in the proportion of severe GE hospitalizations attributed to RV in children younger than 3 years in Belém, Brazil following introduction of the human RV vaccine. Good VE was demonstrated versus fully heterotypic G2P[4], which was the predominant RV strain throughout the study period. VE was highest in children 3 to 11 months of age. However, our results also suggest that the vaccine affords protection in older children ≥12 months of age, based on estimates obtained using neighborhood controls. Ongoing surveillance studies should further demonstrate the public health benefits afforded by this RV vaccine in community settings.

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