Vaccine 32 (2014) 3035–3040

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effectiveness of the monovalent rotavirus vaccine in Colombia: A case-control study

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ARTICLE INFO

Article history:
Received 18 June 2013
Received in revised form 12 March 2014
Accepted 17 March 2014
Available online 31 March 2014

Keywords:
Rotavirus
Vaccine
Diarrhea
Vaccine effectiveness

ABSTRACT

Objective: To assess the effectiveness of the monovalent rotavirus vaccine (RV1) to prevent rotavirus diarrhea admissions to emergency departments (ED) in Colombia.
Methods: A multicenter case-control study was carried out in six Colombian cities from 2011 to January, 2013. Cases were laboratory confirmed rotavirus diarrhea patients admitted to ED of selected health centers. Controls were patients with non-rotavirus diarrhea. Vaccination status was card-confirmed. Vaccine effectiveness and 95% confidence intervals (CI) were calculated from the conditional logistic regression models using the formula 1 − adjusted odds ratio × 100.
Results: 1051 fecal samples were collected from 193 cases and 858 controls. Vaccination history was confirmed on 173 cases (90%) and 801 controls (93%). Among the rotavirus-positive samples with vaccination history, 57% were G2P[4], 9.8% G9P[8], 6% G9P[6]. Median age of cases (17 months) was greater than controls (15 months) ($P < 0.001$), and mothers of cases had lower level of education ($P = 0.025$). The adjusted effectiveness was 79.19% (95% CI, 23.7 to 94.32) among children 6–11 months of age and −39.75% (95% CI, −270.67 to 47.24) among those >12 months of age. Against overnight rotavirus hospitalizations, RV1 provided protection of 84.42% (95% CI, 22.68 to 96.86) among children 6–11 months of age, and −79.49% (95% CI, −555.8 to 51.08) among those >12 months.
Conclusions: RV1 provided significant protection against rotavirus hospitalization among children under 1 year of age in the Colombian setting. The observation of lower effectiveness in children >12 months requires further assessment.

1. Introduction

Rotavirus-related diarrhea causes ~200,000 to 453,000 annual deaths worldwide without vaccination [1–3]. Two efficacious rotavirus vaccines are currently recommended by the World Health Organization (WHO) for use in all children worldwide [4,5], a monovalent rotavirus vaccine, hereafter called RV1 (Rotarix; GlaxoSmithKline Biologicals; Rixensart, Belgium), and a pentavalent rotavirus vaccine (RotaTeq; Merck Vaccines; Whitehouse Station, NJ, USA). Trials for these vaccines have demonstrated that efficacy is higher (~85–98%) in low-income settings compared to high-income settings (~50%) [5,6].

Postlicensure effectiveness of both rotavirus vaccines has varied in several studies throughout the world [7–14]. The reasons for the lower effectiveness of the vaccines in high-mortality settings remain unclear but could be related to competing enteric pathogens, micronutrient malnutrition, breastmilk interference, or circulating antibodies [15]. The effectiveness of the vaccines may also differ after routine programmatic use compared to their expected performance based on clinical trials conducted under ideal, controlled conditions [16]. In addition, studies in Africa and low-income countries in Asia have also shown efficacy to be lower in the second year of life [17]. Some evidence also suggests that protection against strains heterotypic to the vaccine might

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http://dx.doi.org/10.1016/j.vaccine.2014.03.064
0264-410X/

decline among older children [8]. For these reasons, assessing the effectiveness of rotavirus vaccination after routine public health use of the vaccine is crucial.

In January of 2009, mass RV1 vaccination was implemented in the Expanded Program on Immunization (EPI) of Colombia, an upper-middle income country in South America, with two doses being recommended at 2 and 4 months of age. De la Hoz [18] estimated in a modeling study a potential 27% reduction of diarrhea hospitalizations in Colombia after the introduction of the RV1, assuming an effectiveness of 85% and 95% vaccine coverage. However, effectiveness of RV1 has not been assessed in the country. Thus, our primary objective was to assess the effectiveness of RV1 against severe rotavirus diarrhea in Colombia.

2. Methodology

A hospital based case-control study was designed to assess effectiveness of RV1 in Colombian children, following recommendations by the WHO generic protocol for assessment of rotavirus vaccine effectiveness [16]. Seven hospitals in six cities throughout the country were chosen on the basis of WHO rotavirus surveillance guidelines recommending selection of hospitals that admit >250 children for gastroenteritis per year. The selected cities belong to different geographical regions within the country: Cartagena, Leticia, Neiva, Pereira, Pitalito and Valledupar.

2.1. Population

2.1.1. Cases

Active surveillance was conducted at all hospital emergency departments (ED) for children presenting with acute diarrhea, defined as ≥3 loose stools in a 24-h period. Inclusion criteria for a rotavirus cases were: laboratory confirmed rotavirus; onset of diarrhea <14 days prior to the emergency department (ED) visit; eligibility to receive at least one dose of RV1 which was defined as being born after January 1, 2009 and being at least 8 weeks of age when presenting at the ED. Cases were excluded when we were unable to obtain parental consent or verify vaccination status through parental card or vaccination registry.

2.1.2. Controls

Controls for this study were patients with non-rotavirus diarrhea, based on the rapid diagnostic test, who were older than 8 weeks of age and were born after January 1, 2009. Controls were not matched in the present study.

2.1.3. Laboratory analysis

Rotavirus testing was conducted using the rapid diagnostic test (RIDA® QUICK Rotavirus/Adenovirus Combi) in the selected hospitals. All positive and 20% of negative samples (for quality control) were refrigerated at −2 to −8 °C for 24–48 h before transfer to a central laboratory where they were stored frozen at −20 to −70 °C. Then the samples were transferred to the Colombian National Institute of Health (*Instituto Nacional de Salud*, INS), where confirmatory ELISA tests were performed for rotavirus (Ridascreen ELISA tests of r-Biopharm®) and strains were genotyped for VP7 and VP4 by RT-PCR using the procedure described by Hull et al. [19].

2.2. Data collection

A standard questionnaire was filled by trained health care personnel by interviewing the parents, and contained social, demographic, clinical and vaccination data. Variables included date of birth, sex, family income, socioeconomic status (family income), family education level, clinical characteristics, treatment, and course of illness [20].

We stratified data according to overnight hospitalization and according to the previously applied 20-point Vesikari severity scale. The Vesikari scale was calculated for all patients with rotavirus diarrhea admitted to ED. Because a majority (∼80%) of the ED cases were Vesikari ≥11, to assess whether a gradient in effectiveness by disease severity existed for RV1 in our study population, we classified cases with severity ≥15 as "very severe rotavirus diarrhea" [20].

Vaccination history was ascertained by written verification of the vaccination card for each patient. When this card was not available, electronic records of vaccination were verified when available, and home visits were made to confirm vaccination status of each child when electronic records of vaccination was not available.

2.3. Sample size and data analysis

For sample size calculations, we initially assumed vaccination coverage of 60% in controls, an expected effectiveness of 60%, a confidence level of 95% and an assumed case:control ratio of 1:5. Under those assumptions, we estimated that a total of 145 cases and 725 controls would be necessary to achieve the desired effectiveness with 80% power.

Our main objective was to assess vaccine effectiveness of 2 doses of RV1 against all rotavirus visits to the ED, an outcome important to the Colombian Ministry of Health. Because rotavirus vaccine has a gradient in efficacy according to severity of disease, secondary objectives included assessing effectiveness against overnight rotavirus hospitalizations, or cases with Vesikari score ≥11 and ≥15. We also conducted an "intention-to-vaccinate" analysis whereby we assessed effectiveness of ≥1 dose of RV1.

Bivariate analyses were first conducted to assess for differences in demographic and socioeconomic variables between cases and controls. For the analysis of categorical variables, chi-square or exact Fisher test was applied, as appropriate; for continuous variables, the Kruskal–Wallis rank test was used to assess statistical significance because continuous variables were not normal, according to the Shapiro–Wilk test.

Because this was an unmatched study, we used unconditional logistic regression models to assess RV1 effectiveness. Cases and controls were deemed vaccinated if RV1 dose was administered 14 days before being present at the ED. The analysis compared two (full series), or ≥one dose (intention to vaccinate) of RV1 to zero doses in cases and controls. For substantive reasons, the base models adjusted for age in months and birth quarter/year. We also assessed confounding by including hospital, demographic and socioeconomic variables in the model, choosing to retain those that changed the effectiveness estimates by more than 10%. Although the study was not designed to provide adequate power to assess statistical significant differences in age-groups, we assessed for differences in vaccine effectiveness by age (as a proxy for duration of protection). For this analysis, we stratified cases between 6 and 11 months and greater than 12 months, using all non-rotavirus diarrhea patients older than 6 months as controls. Because ∼94% of all vaccinated children had received RV1 before 6 months of age, vaccination status was not changing after this age and thus unlikely to be a confounder. Thus, only birth quarter and year was included in the base model.

After calculating the odds ratio (OR) with 95% confidence intervals (95% CI) trough unconditional logistic regression, we estimated effectiveness of the vaccine using the formula [21]: $(1 - \mathrm{OR}) \times 100\%$. Statistical significance for all analyses was designated as P-value <0.05. Analyses were conducted using Stata (Stata v. 11; StataCorp; TX, USA).

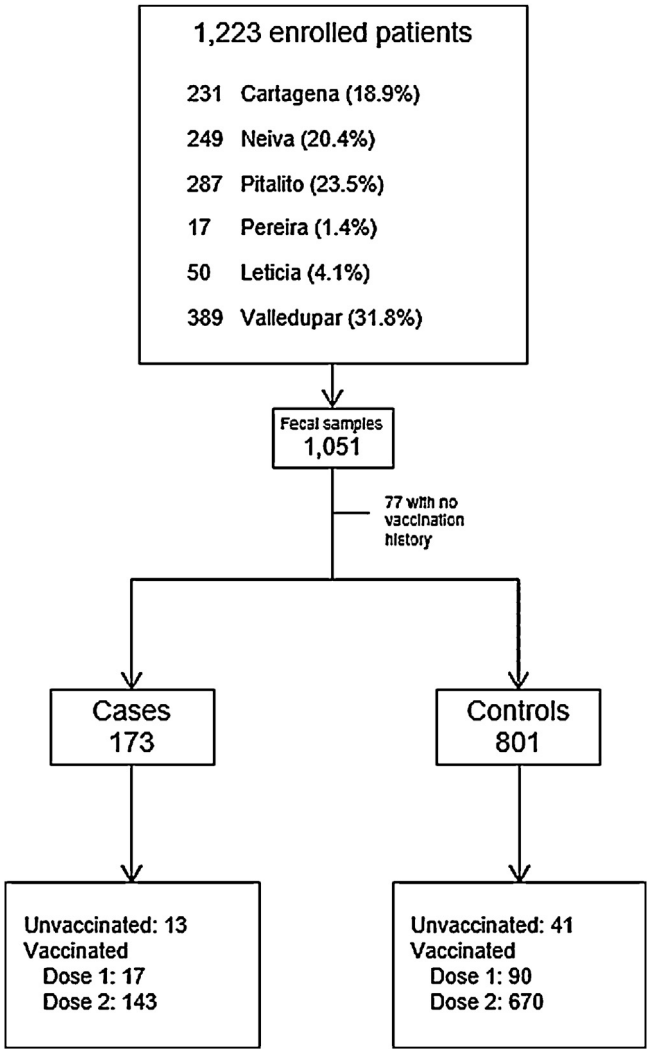

Fig. 1. Flow-chart of included patients.

3. Ethics statement

This case-control evaluation was approved by the ethical committee of Universidad Nacional de Colombia.

4. Results

4.1. Case-control analysis

A total of 1223 patients were enrolled in the present case-control study (Fig. 1). Of these patients, 172 did not have sufficient stool sample for enrollment. Among 1051 patients with a stool sample, a total of 193 rotavirus-positive cases (18.3%) and 858 rotavirus-negative controls (81.7%) were identified.

Median age was 17.4 months (interquartile range [IQR], 11.3–21.8) and 14.9 months (IQR, 8.4–19.4) for cases and controls ($P < 0.001$) included in the analysis. Of the 173 included cases with vaccination data, 58 (33%) were less than 12 months of age (Fig. 2). Among diarrhea patients <12 months with vaccination history, 11.7% were positive for rotavirus compared to 22.1% among those >12 months of age (Fig. 2). Of patients with available clinical data, 92/170 (54.1%) cases, and 425/777 (54.7%) controls were hospitalized overnight. Median time of hospitalization was 1 day (IQR, 1–2.5) in cases and 1 day (IQR, 1–2) in controls ($P = 0.81$).

Table 1
Comparison of characteristics between rotavirus diarrhea cases and non-rotavirus diarrhea controls.

	Cases ($n = 173$)	Controls ($n = 801$)	*P*-value
Age			<0.001
<6 Months	12 (6.9%)	115 (14.4%)	
6–11 Months	36 (20.8%)	247 (30.8%)	
12–17 Months	54 (31.2%)	199 (24.8%)	
18–23 Months	37 (21.4%)	120 (15%)	
>24 Months	34 (19.6%)	120(15%)	
History of breast feeding	140/167 (83.8%)	683/792 (86.2%)	0.418
Day care attendance*	12/161 (7.5%)	57/774 (7.4%)	0.969
Sex			0.518
Male	105 (60.7)	463 (58.0%)	
Female	68 (39.3%)	335 (42.0%)	
Mother education level*			0.025
None	7(5.5%)	17(2.3%)	
Primary	62 (48.4)	316 (43.4)	
High school	50 (39.1%)	336 (46.1%)	
Technical	9 (7.0%)	37 (5.1%)	
University	0 (0.0)	22 (3.02%)	
Family income*			0.273
Less than minimum salary	97 (77.0%)	531 (73.7%)	
Between 1 and 2 minimum salaries	29 (23.0%)	176 (24.4%)	
>2–4 Minimum salaries	0 (0.0%)	13 (1.8)	
Hospital of study			<0.001
Cartagena	35 (20.2%)	97 (12.1%)	
Neiva	56 (32.4%)	186 (23.2%)	
Pitalito	24(13.9%)	244 (30.5%)	
Pereira	2 8 (1.2)	10 (1.2)	
Leticia	0 (0.0%)	33 (4.1)	
Valledupar	56 (32.4%)	231 (28.8%)	

* This data was collected for cases and controls with available data on rotavirus vaccination and case/control status.

A significant difference in maternal education was observed between cases and controls ($P = 0.03$) but no difference was observed in sex ($P = 0.52$), family income ($P = 0.27$), history of breastfeeding ($P = 0.41$), and daycare attendance ($P = 0.98$) (Table 1).

Among rotavirus cases with clinical data allowing for calculation of Vesikari score and vaccination history available, 131/165 (79.39%) had score ≥11 and 63/165 (38.18%) had score ≥15.

Sufficient volume of stool was available for strain characterization from 71.1% (123/173) of the cases with vaccination history. Among these samples, 56.9% were G2P[4], 9.8% G9P[8], 6% G9P[6]. The remaining strains were mixed and non-typeable genotypes for G or P-type. G1 was not identified in any of the enrolled cases. No homotypic strains were observed during the study period.

4.2. Effectiveness

Vaccine history was confirmed for 90% (173/193) of the cases and for 93% (801/858) of the controls. Among cases and controls respectively, about 7.5% (13/173) and 5.1% (41/801) were unvaccinated. When considering those who were unvaccinated or vaccinated with 1 dose, 57% (17/30) of the cases versus 69% (90/131) of the controls received one doses of the vaccine. When considering those unvaccinated or vaccinate with 2 doses of RV1, 92% (143/146) of the cases versus 94% (670/711) of the controls received two doses of the vaccine.

All base vaccine effectiveness for analyses in all cases and control estimates were adjusted for age and birth quarter. For sub-group analyses by age, the effectiveness was adjusted by birth quarter. No other confounders were identified.

Overall, the effectiveness of RV1 against rotavirus diarrhea ED visits of all severity was 79.19 (23.7 to 94.32) among children 6–11 months of age in comparison to −39.85 (95% CI, −270.67 to 47.24) among those >12 months of age (Table 2).

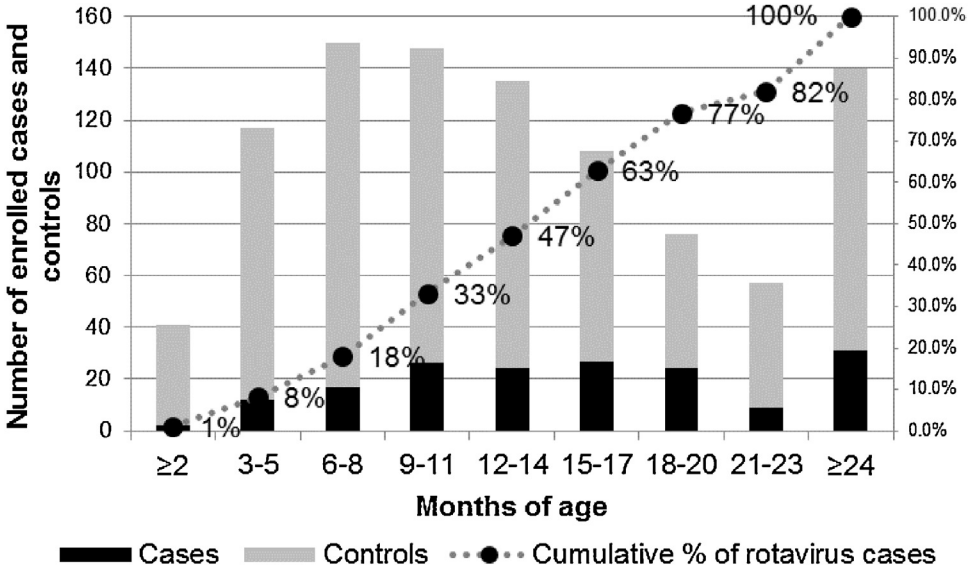

Fig. 2. Number of rotavirus diarrhea cases and non-rotavirus diarrhea controls distributed by age-groups.

Table 2
Effectiveness of the monovalent rotavirus vaccine against rotavirus disease in Colombia.

	Cases	Controls	Odds ratio	Vaccine effectiveness
All severity cases				
All ages				
Dose 0	13	41	Reference	Reference
Dose 2	143	670	0.84 (0.39 to 1.78)	(−78.74 to 60.47)
Age 6–11 months				
Dose 0	4	27	Reference	Reference
Dose 2	27	628	0.21 (0.06 to 0.76)	79.19 (23.7 to 94.32)*
Age ≥ 12 months				
Dose 0	7	27	Reference	Reference
Dose 2	112	628	1.4 (0.53 to 3.71)	−39.85 (−270.67 to 47.24)
Hospitalized patients				
All ages				
Dose 0	6	41	Reference	Reference
Dose 2	78	670	1.02 (0.37 to 2.81)	−2.19 (−181.8 to 62.45)
Age 6–11 months				
Dose 0	3	27	Reference	Reference
Dose 2	12	628	0.16 (0.03 to 0.77)	84.42 (22.68 to 96.86)*
Age ≥ 12 months				
Dose 0	3	27	Reference	Reference
Dose 2	64	628	1.79 (0.49 to 6.58)	−79.49 (−558.47 to 51.08)
Severe cases (Vesikari ≥ 11)				
All ages				
Dose 0	7	41	Reference	Reference
Dose 2	110	670	1.54 (0.59 to 4.02)	−54.18 (−302.62 to 40.95)
Age 6–11 months				
Dose 0	2	27	Reference	Reference
Dose 2	21	628	0.37 (0.07 to 2.02)	62.62 (−101.73 to 93.07)
Age ≥ 12 months				
Dose 0	5	27	Reference	Reference
Dose 2	86	628	1.65 (0.55 to 4.89)	−64.52 (−388.83 to 44.63)
Very severe cases (Vesikari ≥ 15)				
All ages				
Dose 0	4	41	Reference	Reference
Dose 2	52	670	2.14 (0.58 to 7.94)	−114.28 (−694.65 to 42.21)
Age 6–11 months				
Dose 0	2	27	Reference	Reference
Dose 2	11	628	0.33 (0.05 to 2.08)	66.63 (−107.52 to 94.63)
Age ≥ 12 months				
Dose 0	2	27	Reference	Reference
Dose 2	40	628	2.56 (0.52 to 12.66)	−155.87 (−1165.58 to 48.27)

Note: All estimations were adjusted by age, birth quarter, dehydration, and vomit; no other variables from Table 1 altered the VE estimates by >10%.
* Statistically significant.

We also examined effectiveness stratified by hospitalization and clinical severity. Against overnight rotavirus hospitalizations, RV1 provided protection of 84.42 (95% CI, 22.68 to 96.86) among children 6–11 months of age, and −79.49 (95% CI, −558.47 to 51.08) among those >12 months. Against rotavirus diarrhea with Vesikari score ≥11, VE was 62.62 (95% CI, −101.73 to 93.07) for children 6–11 months, and −64.52 (95% CI, −388.83 to 44.63) among those >12 months of age. Against rotavirus diarrhea with Vesikari score

≥15, VE was 66.63 (95% CI, −107.52 to 94.63) for children 6–11 months, and −155.87 (95% CI, −1165.58 to 48.27) among those >12 months of age.

In the present study, the sensitivity of the rapid diagnostic test used in each of the hospitals compared to the ELISA test used in central lab was 82.7% (95% CI, 76.3–89.3) and specificity was 94.2% (95% CI, 90.1–97.6).

5. Discussion

In this first assessment of the effectiveness of RV1 against rotavirus diarrhea requiring ED treatment in Colombia, we identified several findings that further strengthen our understanding on the performance of RV1, particularly under routine programmatic use of the vaccine. First, our results indicate that RV1 provided an effectiveness of 84.42% against rotavirus hospitalizations among children 6–11 months of age. Second, although confidence limits overlapped, the point estimate for the effectiveness of RV1 was lower among children >12 months of age. Third, the study was not powered to assess effectiveness against individual strain types, but the predominant strains circulating in Colombia during this study period were largely fully heterotypic (G2P[4], G9P[6]) or partially heterotypic (G9P[8]) to the RV1 strain (G1P[8]). Fourth, compared to previous surveillance findings in Colombia which found that ∼55% of rotavirus hospitalizations occurred among children <1 year of age, in our study only 33% of the cases occurred among those <1 year of age [22]. The decrease in the proportion of rotavirus cases occurring among children <1 year of age after the introduction of vaccine is consistent with the moderate to high effectiveness of RV1 in this age group.

Rotavirus vaccines provide a higher level of protection against hospitalization and severe disease compared to infection of mild and moderate severity [23]. The overall effectiveness in our study was lower compared to the RV1 clinical trial in Latin America likely because we enrolled children with less-severe rotavirus diarrhea. The primary outcome in the RV1 trial was overnight hospitalization. Our study was not primarily powered to assess effectiveness against hospitalization and only 54% of the cases were hospitalized. Effectiveness against hospitalization among children <1 year 12 months of age in our study was similar to efficacy in the clinical trial. Moreover, the median duration of hospitalization (1 day) in our study was also lower than previously reported study in Colombia from 2004 (3 days), suggesting the possibility that rotavirus disease is milder during the postvaccination era compared to prevaccine years in Colombia [22]. While we do not have baseline data from the same hospitals against which the current surveillance data can be directly compared, the shorter duration of hospitalization and shift in age distribution of cases to children >1 year of age in our study suggests vaccine could have impacted the severity of rotavirus disease and likely reduced the burden in young children at the highest risk of dehydrating disease.

The RV1 has provided good protection against disease from a broad range of heterotypic and homotypic rotavirus strains in high and middle income settings, and one low-middle income setting (Bolivia) [8,9,12,24]. However, two studies from impoverished settings in Brazil and Australia have identified the possibility of lower effectiveness against the fully heterotypic G2P[4] strain among children >12 months compared to those younger than 12 months of age [8,12]. In Colombia, we also observed declining effectiveness of RV1 with increasing age, during years when G2P[4] predominated. Although our study was not powered to assess effect modification of vaccine performance by age, the marked difference in point estimates of effectiveness between the two age groups is consistent with the findings from Brazil and Australia. Ongoing monitoring through robust surveillance and effectiveness studies in a variety of settings is warranted to confirm these findings [8,12].

Our results should be interpreted with several caveats. Methodological weaknesses of case-control studies related to the high vaccine exposure in Colombia (94% 2-dose coverage in controls) reduced our power to assess effectiveness and increased chances of bias. With such high coverage rates, it is increasingly probable that the control population is less likely to represent the source population from which the cases arise. Establishing prevaccine disease surveillance would facilitate the interpretation of case-control and postvaccine surveillance results, but this was not done in Colombia. It should be noted that some of our estimates were negative which implies that vaccination with RV1 caused rotavirus diarrhea. This however is unlikely because our case-definition for vaccinated children only included children developing rotavirus diarrhea 14 days after vaccination, and the negative estimates of effectiveness likely reflect the limited sample size. Our primary case-definition included all ED visits for diarrhea of any severity and thus it should be strongly noted that results of VE against all ED visits would not be applicable to more dehydrating disease requiring hospitalization. When comparing results with other settings, it should also be noted that to increase specificity for rotavirus disease our case-definition only used acute diarrhea, and did not include children with vomiting alone. We also controlled for the statistically significant differences in maternal education between cases and controls, although the differences were not meaningful. It is possible that children with rotavirus negative diarrhea are related to other viruses (e.g., norviruses) or bacterial etiologies which might have a stronger association with lower socioeconomic status than rotavirus which tends to affect all children before they reach 5 years of age. We were unable to identify vaccination records in 10% and 7% of cases and controls which might have introduced some bias if differential exposure rates occurred between these groups. Additionally, we could not verify records of schedule completeness for other vaccines in all sample patients because some records were obtain electronically only for rotavirus. Lastly, while children with diarrhea who are test-negative for rotavirus have emerged as a good source of controls due to the high sensitivity and specificity of the rotavirus assays, possible misclassification error may have occurred due to diagnostic assay errors. Such misclassification should only bias estimates toward the null.

6. Conclusions

In summary, RV1 provided good protection against severe and all-severity rotavirus infections during the first year of life. The small sample size and high vaccination coverage posed limitations in determining effectiveness against rotavirus hospitalization and duration of protection, and highlights the importance of adequate disease surveillance before vaccine introduction. The potential decline in protection among older children and appearance of non-vaccine strains after RV1 introduction warrants ongoing monitoring.

Disclaimer

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

Financial disclosures

None (all authors).

Funding

This study was funded by Administrative Department of Science Technology and Innovation of Colombia (COLCIENCIAS) through contract 304, 2010.

Conflicts of interest statement

None (all authors).

Acknowledgments

We are deeply thankful to all research staff in all study sites, among them Maria del Pilar Sanchez, MD (Cartagena, Bolívar) and Dioselina Pelaez, Lady Contreras and Jairo Mendez of the National Institute of Health of Colombia. The authors are in debt with the Hospitals: San Antonio de Pitalito, E.S.E Carmen Emilia Ospina, E.S.E Eduardo Arredondo Daza, Hospital Napoleón Franco Pareja, E.S.E Salud Pereira, Hospital San Rafael de Leticia and with the Health Departmental Secretaries of the departments of Bolívar, Cesar, Huila, Risaralda and Amazonas for their support in the present study.

We finally would like to acknowledge the anonymous peer-reviewers for the throughout revision of the manuscript.

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