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Clinical Severity and Rotavirus Vaccination among Children Hospitalized for Acute Gastroenteritis in Belém, Northern Brazil

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ABSTRACT

In March 2006, Brazil introduced the monovalent rotavirus (RV) vaccine (Rotarix™) into the public sector. This study assessed the severity of rotavirus gastroenteritis (RVGE) according to the vaccination status among hospitalized children. We identified 1023 RVGE episodes among not vaccinated ($n = 252$), partially vaccinated ($n = 156$) and fully vaccinated ($n = 615$) children. Very severe gastroenteritis (scored ≥ 15) was reported in 16.7, 17.9 and 13.5% of not vaccinated, partially vaccinated and fully vaccinated children, respectively. There was a trend for a shorter duration of RV diarrhoea among vaccinated children than in not vaccinated children ($p = 0.07$). A protective effect of vaccination was noted when mean duration of symptoms and hospital stay are analysed, comparing unvaccinated, partially vaccinated and fully vaccinated children ($p < 0.05$). We showed a vaccination dose effect trend, with fully vaccinated children having less-severe RVGE than not vaccinated and partially vaccinated children.

KEYWORDS: rotavirus, gastroenteritis, severity, vaccination status.

INTRODUCTION

Worldwide, rotavirus (RV) infection is the leading cause of severe gastroenteritis (GE) among infants and young children, causing an estimated 453 000 deaths annually in children aged <5 years [1].

In Brazil, the live-attenuated monovalent human RV vaccine (Rotarix®; GlaxoSmithKline Biologicals, Rixensart, Belgium) was introduced into the National Immunization Program in March 2006, covering a birth cohort of >3 million infants [2]. Over the past 7 years, at least two case-control effectiveness studies were conducted in Brazil, which reaffirmed the good vaccine efficacy against severe RV disease shown during phase III trials in Latin America, including Brazil [3–7]. In addition, there have been several observational studies throughout the country showing a consistent reduction over time in the number of all-cause and RV-related GE hospitalizations and deaths among children aged <1 year [6, 8].

It has become apparent from several efficacy/effectiveness studies with RV vaccines that there is a gradient of vaccine-induced protection, with enhanced efficacy against the most severe disease, with the vaccine being least effective in preventing disease of mild to moderate severity [4, 6, 8]. In general, RV vaccine efficacy/effectiveness according to clinical severity was evaluated in fully vaccinated children, and results were presented using a 20 point scoring system, as proposed by Ruuska and Vesikari [9]. There is a lack, however, of studies assessing the RV vaccine protection in partially vaccinated children and using individual clinical indicators of severity. Because rotavirus gastroenteritis (RVGE) may eventually be identified among vaccinated children, in this study, we sought to evaluate the clinical severity of RVGE leading to hospitalization, according to the vaccination status of not vaccinated, partially vaccinated or fully vaccinated children. This study focuses on a secondary analysis of data from a previously published case-control study to determine vaccine effectiveness of a full, two-dose series of Rotarix® in preventing RVGE hospitalization in Belém, Brazil [4].

SUBJECTS AND METHODS

This was essentially a prospective, hospital-based study conducted in Belém, Northern Brazil from May 2008 to May 2011. During the first year between May 2008 and April 2009, the study was performed in four large urban paediatric/clinic hospitals. As based on previous surveillance studies [10], these paediatric/clinic hospitals received approximately 80% of all paediatric admissions for GE in Belém area. During the remainder of the 3 year study period (May 2009–May 2011), the surveillance for GE cases continued in two hospitals that accounted for approximately 50% of all hospitalizations in Belém area.

The study was approved by the Ethical Review Committee of the Instituto Evandro Chagas (IEC), Health Surveillance Secretariat, Brazilian Ministry of Health's National Reference Centre (registry number 0003.0.072.000-08). A written informed consent form was obtained from parents/legal guardians of all children before their study entry.

Eligible children were aged at least 12 weeks, born after 6 March 2006 (the date when universal RV vaccination with Rotarix™ was started in Brazil, following a vaccination schedule of 2 and 4 months). Study cases included children hospitalized for laboratory-confirmed severe RVGE, defined as three or more liquid/semi-liquid motions in a 24 h period, of $<$14 days duration, requiring at least one overnight stay and intravenous rehydration therapy. According to their vaccination status, **as ascertained by reviewing vaccination cards**, enrolled subjects were categorized as fully vaccinated (children who had received two doses of Rotarix™), partially vaccinated (one dose) and not vaccinated (no written records of Rotarix™).

Data on demographics, medical history, feeding practices and specific symptoms were obtained. The severity of RVGE was graded as proposed by Ruuska and Vesikari [9], where cases with clinical scores of 1–10, $\geq$11 and $\geq$15 were defined as mild/moderate, severe and very severe, respectively. We analysed disease severity using the Ruuska and Vesikari score, whenever all required clinical parameters were available, including number of days and maximum number of looser than normal stools, duration and maximum number of episodes of vomiting, maximum fever reported, presence of dehydration and type of treatment given for rehydration.

Stool samples were routinely collected within 48 h following hospitalization and transported to IEC, where testing was performed for the presence of RV antigen using a sandwich-type commercial enzyme-linked immunosorbent assay (RIDASCREEN® Rotavirus; R-Biopharma, Darmsdadt, Germany). The tests were performed following the manufacturer's instructions and included positive and negative controls.

Data were statistically analysed using SAS version 9.1 (SAS Institute Inc., Cary, NC). Analyses were performed to evaluate the association between disease severity, and individual symptoms against vaccination status using chi-square or Fisher's exact test, as appropriate. All tests were two-tailed, and differences between variables were considered statistically significant at p-values ≤ 0.05. Multinomial logistic regression was performed to assess the effect of the risk factors such as age, vaccination status and

current feeding practices, on the disease severity measured by the Ruuska and Vesikari Clinical Score and graded as mild/moderate (1–10), severe (≥11) and very severe (≥15).

RESULTS

Altogether, there were 1023 RVGE episodes among not vaccinated ($n = 252$), partially vaccinated ($n = 156$) and fully vaccinated ($n = 615$) children during the 3 year surveillance period. The clinical severity according to the Vesikari score could be calculated for 497 (48.5%) of the 1023 RVGE episodes. The analysis of severity of RVGE by Ruuska andVesikari score according to age and vaccination (Table 1) showed that odds of having a severe disease, compared with less-severe cases, is 1.4 times less for every month increase in age ($p = 0.04$). Odds of having a severe disease was 1.46 greater for not vaccinated, compared with fully vaccinated children, and this was statistically significant ($p = 0.02$). No statistical significance was yielded when comparing the odds of developing either a severe or a very severe disease with the vaccination status. There was also no statistically significant difference if the odds of developing severe disease are analysed according to the feeding practices.

The proportion of severe RVGE cases according to the vaccination status and the intensity of individual clinical symptoms are shown in Table 2. Overall, there was a trend for shorter duration of diarrhoea among vaccinated children, as compared with not vaccinated children ($p = 0.07$). Similar proportions were observed when comparing not vaccinated, partially vaccinated and fully vaccinated children, who developed diarrhoea of the shortest (1–4 days) duration: 92.2% (202/252), 92.5% (124/156) and 95.5% (511/556). No statistically significant differences were seen among the other clinical categories according to the vaccination status, with *p*-values in the range of 0.16 (duration of vomiting in days) to 0.84 (need for intravenous rehydration).

Table 3 demonstrates the differences in the duration of general symptoms during hospitalization, according to the vaccination status. The mean duration of all individual symptoms was higher among not vaccinated children, as compared with vaccinated children (*p*-values in the range of 0.003–0.05). Overall, the mean duration (in days) of hospitalization ranged from 5.02 to 4.72 in not vaccinated and fully vaccinated children, respectively, with a *p*-value of 0.01.

DISCUSSION

The present study suggests that children who underwent a full RV vaccination schema (two doses of Rotarix® at 2 and 4 months of age) are less likely to develop severe RVGE requiring hospitalization than either partially vaccinated or not vaccinated children. These results were obtained from an exploratory analysis performed within a long-term (May 2008–May 2011) hospital-based study for RVGE among children in Belém, Northern Brazil, with the primary objective

Table 1. Clinical severity of RVGE, according to age and vaccination status among children in Belém, Brazil

Characteristics	Severity score[a]	ß	Standard error	*p*-value	Odds ratio	95% CI	
						LL	UL
Age at disease	≥11–<15[b]	−0.3830	0.18	0.04	0.68	0.48	0.97
	≥15[c]	−0.4103	0.24	0.09	0.66	0.41	1.07
Partially vs. fully vaccinated	≥11–<15	0.1271	0.21	0.54	1.14	0.76	1.70
	≥15	0.3996	0.25	0.11	1.49	0.91	2.45
Unvaccinated vs. fully vaccinated	≥11–<15	0.3786	0.17	0.02	1.46	1.05	2.03
	≥15	0.3994	0.22	0.07	1.49	0.97	2.28

[a]20 point Ruuska andVesikari score.
[b]Severe episode.
[c]Very severe episode.
ß = Regression linear coefficient.

Table 2. Proportion of RVGE cases according to the vaccination status and the intensity of individual symptoms during hospitalization

Characteristics	Categories	Not vaccinated ($N = 252$)		Partially vaccinated ($N = 156$)		Fully vaccinated ($N = 615$)		*p*-value
		$n^{\S}$	%	*n*	%	*n*	%	
Number of days of diarrhoea	1–4 days	202	92.2	124	92.5	511	95.5	0.07*
	5 days	9	4.1	9	6.7	17	30.2	
	≥6 days	8	3.6	1	0.7	7	1.3	
Maximum number of looser than normal stools per day	1–3	48	21.8	20	15.0	119	22.5	0.23
	4–5	74	33.6	58	43.6	189	35.7	
	≥6	98	44.5	55	41.4	222	41.9	
Duration of vomiting (days)	1	76	39.2	50	45.9	202	48.3	0.16
	2	55	28.4	28	25.7	117	28.0	
	≥3	63	32.5	31	28.4	99	23.7	
Maximum number of episodes of vomiting per day	1	42	22.0	27	24.8	121	29.5	0.23
	2––4	90	47.1	48	44.0	188	45.8	
	≥5	59	30.9	34	31.2	101	24.6	
Maximum fever reported [measured rectally]	37.1–38.4°C	12	9.2	7	9.7	35	13.3	0.64
	38.5–39.9°C	69	52.7	42	58.3	137	51.9	
	≥39°C	50	38.2	23	31.9	92	34.8	
Dehydration	No dehydration	1	0.4	2	1.30	3	0.5	0.64
	Mild/moderate (1–5%)	16	6.5	10	6.5	31	5.1	
	Severe (≥6%)	121	49.0	85	55.2	313	51.7	
Oral rehydration	Yes	67	26.6	36	23.1	130	21.1	0.23*
	No	185	73.4	119	76.3	484	78.7	
	Unknown	0	0.0	1	0.64	1	0.16	
IV rehydration	Yes	251	99.6	156	100	611	99.3	0.84
	No	1	0.4	0	0.0	4	0.7	

N = Number of severe RVGE hospitalizations; $n^{\S}$ = number of patients from whom data could be obtained; % = n/number of subjects with available results × 100; *p*-values: Chi-square test to test the association between the vaccination status and the intensity of the symptoms; **p*-values: Fisher's exact test to test the association between the vaccination and intensity of symptoms.

of evaluating the effectiveness of Rotarix™ full series vaccination in preventing severe RV disease (May 2008–May 2009), with continued monitoring of RV strains during additional 2 years [4, 11].

According to official data from the Expanded Program on Immunization, vaccine coverage rates in the Northern and North-Eastern regions of Brazil are in general lower than in other regions, possibly because of limited access to the health services in these country's less-developed settings [12]. Vaccine coverage rates in Northern Brazil ranged from 64.3 to 72.3% from 2008 to 2011, therefore allowing for a comparison of clinical severity between RVGE episodes that occurred among fully vaccinated, partially vaccinated and not vaccinated children in Belém, Brazil. This appears to be in line with our study, where the majority of subjects (around 75%) were previously vaccinated with at least one dose of Rotarix™, with 60.1% of them having received a full-course vaccination.

It is well known that RV vaccination strategies target mainly severe RVGE, which may course with dehydration and electrolyte disturbances, and that protection against more severe episodes is evident even among partially vaccinated [4, 13, 14]. To our knowledge, however, there have been no studies to

Table 3. Differences in the duration of general symptoms during hospitalization according to the vaccination status

Symptoms	Parameters	Not vaccinated (0 dose) $N = 252$	Partially vaccinated (1 dose) $N = 156$	Fully vaccinated (2 doses) $N = 615$	*p*-value
Number of days of fever	*n*	132	74	264	0.003
	Mean	1.79	1.59	1.50	
	SD	0.99	0.74	0.91	
	Minimum	1.00	1.00	1.00	
	Maximum	6.00	4.00	9.00	
Number of days of diarrhoea	*n*	219	134	535	0.01
	Mean	2.58	2.40	2.27	
	SD	1.37	1.20	1.19	
	Minimum	1.00	1.00	1.00	
	Maximum	9.00	6.00	8.00	
Duration of vomiting in days	*n*	194	109	418	0.05
	Mean	2.13	1.96	1.88	
	SD	1.30	1.15	1.10	
	Minimum	1.00	1.00	1.00	
	Maximum	11.00	6.00	6.00	
Number of days of behaviour change before or during hospitalization*	*n*	229	141	548	0.009
	Mean	2.10	2.11	1.92	
	SD	1.04	0.97	0.98	
	Minimum	1.00	1.00	1.00	
	Maximum	6.00	5.00	8.00	
Duration of hospitalization in days	*n*	252	156	615	0.01
	Mean	5.02	4.88	4.72	
	SD	1.59	1.45	1.39	
	Minimum	2.00	1.00	1.00	
	Maximum	14.00	16.00	16.00	

N = Number of severe RVGE hospitalizations; n = number of subjects in a given category;
p-value: Kruskal–Wallis test to test the difference between vaccination status and duration; SD = standard deviation; *irritability, lethargy, convulsions and others.

assess whether the clinical severity of RVGE episodes differ between vaccinated and not vaccinated children. In general, our data showed that rates of very severe RVGE episodes were similar between not vaccinated (16.7%) and partially vaccinated (17.9%) children, both of which being higher than for those children who were fully vaccinated (13.5%). Although the administration of a full-series, two-dose vaccination schema is strongly recommended to achieve protection with Rotarix® [15], our findings appear to account for broadening the benefits of a partially completed RV vaccine series, a condition that may not be too rare in less-developed settings, like ours. In addition, the data from our secondary analysis suggest that a significant protection against the most severe RVGE can be reached early in the course of vaccination, and this may be of particular relevance if initiated, for instance, in the midst of an epidemic season.

In our analysis it was shown that in regards to individual clinical parameters, there was no statistically significant difference in the likelihood of developing a severe RV disease if partially and fully vaccinated children are compared. In contrast, not vaccinated children were much more prone to develop severe and very severe RVGE if compared with fully vaccinated children. Of interest, it was observed that the dose-effect trend in protecting against severe RV disease

became more evident when analysed in regards to the mean duration of individual symptoms, which was higher among not vaccinated children, as compared with vaccinated children. Because the longer duration of symptoms may lead to prolonged hospital stay, our data highlight previous findings that RV vaccination reduces the burden of RV disease in Brazil at a reasonable cost-effectiveness ratio [8, 16]. One limitation from our study was that we were not able to assess the overall Ruuska and Vesikari score for all patients because complete information on all symptoms was only available for a subgroup of them.

Since the introduction of RV vaccination in Brazil in 2006, a significant reduction in GE-related hospitalizations and deaths was observed across the country, particularly among children aged <1 year [8]. Our analysis demonstrating that less-severe RV disease is observed among (partially or fully) vaccinated children, as compared with not vaccinated children, suggests that intensity of clinical parameters (particularly the duration of symptoms) might have accounted to this outcome.

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REFERENCES

1. Tate JE, Burton AH, Boschi-Pinto C, *et al.* 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:136–41.
2. Brazilian Ministry of Health [Technical note 193/2012: chance in recommended age for administration of measles-mumps-rubella vaccine and oral rotavirus vaccine from January 2013]. Brasília, Brazil: National Immunization Program, Secretariat of Epidemiologic Surveillance, Ministry of Health, 2012.
3. Correia JB, Patel MM, Nakagomi O, *et al.* Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe diarrhea caused by serotypically unrelated G2P [4] strains in Brazil. J Infect Dis 2010;201:363–9.
4. Justino MCA, Linhares AC, Lanzieri TM, *et al.* Effectiveness of the monovalent G1P [8] human rotavirus vaccine against hospitalization for severe G2P [4] rotavirus gastroenteritis in Belém, Brazil. Pediatr Infect Dis J 2011;30:396–401.
5. Linhares AC, Velázquez FR, Pérez-Schael I, *et al.* Efficacy and safety of oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. Lancet 2008;371:1181–9.
6. Linhares AC, Justino MC. Rotavirus vaccination in Brazil: effectiveness and health impact seven years post-introduction. Expert Rev Vaccines 2014;13:43–57.
7. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, *et al.* Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Eng J Med 2006;354:11–22.
8. O'Ryan M, Lucero Y, Linhares AC. Rotarix®: vaccine performance 6 years postlicensure. Exp Rev Vaccines 2011;10:1645–59.
9. Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical diarrhoeal episodes. Scand J Infect Dis 1990;22:259–67.
10. Linhares AC, Macias-Parra M, Sáez-Llorens X, *et al.* Rotavirus gastroenteritis in Latin America: A hospital-based study in children under 3 years of age. Trials Vaccinol 2012;1:36–41.
11. Guerra SFS, Linhares AC, Mascarenhas, JDP, *et al.* Rotavirus surveillance for three years following the introduction of rotavirus vaccine into Belém, Brazil. J Med Virol 2015;87:1303–10.
12. DATASUS. Imunizações. Cobertura por ano e região. http://tabnet.datasus.gov.br/cgi/deftohm.exe?pni/cnv/pniuf.def (13 September 2013, date last accessed).
13. Salinas B, Linhares AC, Ruiz-Palacios GM, *et al.* Evaluation of safety, immunogenicity and efficacy of an attenuated rotavirus vaccine, RIX4414. A randomized, placebo-controlled trial in Latin American infants. Pediatr Infect Dis J 2005;24:807–16.
14. Wang FT, Mast C, Glass JR, *et al.* Effectiveness of an incomplete RotaTeq® (RV5) vaccination regimen in preventing rotavirus gastroenteritis in the United States. Pediatr Infect Dis J 2013;32:278–83.
15. WHO. Rotavirus vaccines: an update. Wkly Epidemiol Rec 2009;84:533–40.
16. Constenla DO, Linhares AC, Rheingans RD, *et al.* Economic impact of a rotavirus vaccine in Brazil. Health Popul Nutr 2008;26:388–96.