Impact of oral human rotavirus vaccine on hospitalization rates for children

Impacto da vacina oral de rotavírus humano nas taxas de hospitalizações em crianças

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Abstract

Objective: To evaluate the risk of hospitalization for acute diarrhea in children under five,in the period of ten years before and after the oral rotavirus vaccine.

Methods: Eco-descriptive-analyticstudy of the rates of hospitalization for acute diarrhea. We used hospitalization rate and the Relative Variation Rate to quantify the difference between the median in the years pre- andpost-vaccination. We used logistic regression, *odds ratio* and attributablerisk to assess for the proportion of cases that could be avoided if exposure was avoided.

Results: During the study period, the hospitalization rate was 117.41 per 10,000 children. In the pre-vaccination period, the median rate of hospitalization was 124.2/10,000 children. After the introduction of the vaccine, hospitalization rates were lower when compared to the median of the pre-vaccination years.

Conclusion: There was a reduction in the hospitalization rates for acute diarrhea, thereby suggesting that the use of the vaccine and other associated factors can reduce the number of cases.

Resumo

Objetivo: Avaliar o risco de hospitalização por diarreias agudas em crianças menores de cinco anos no período de dez anos, antes e depois da vacina oral do rotavírus.

Métodos: Estudo ecológico-descritivo-analítico das taxas de hospitalização por diarreias agudas. Utilizou-se a Taxa de Hospitalização e Taxa de Variação Relativa para quantificar a diferença entre a mediana dos anos pré-vacinais e pós-vacinais. Empregou-se a Regressão Logística, o *Odds Ratio* e Risco Atribuível para verificar a proporção de casos que poderiam ser evitados se a exposição fosse afastada.

Resultados: No período estudado a taxa de hospitalização foi de 117,41 por 10.000 crianças. Observou-se que, no período pré-vacinal, a mediana da taxa de hospitalização foi de 124,2/10.000 crianças. Após a introdução da vacina, as taxas de hospitalização foram menores quando comparadas à mediana dos anos pré-vacinal.

Conclusão: Houve redução nas taxas de hospitalização por diarreias agudas, sugerindo que o uso da vacina e outros fatores associados podem reduzir os casos.

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Introduction

Diarrhea is one of the most common childhood diseases. In developing countries, it is the leading cause of hospitalization and death among children under five, and mortality is higher in their first year of life.[1,2] In developed countries, the frequency of acute diarrhea in infants is up to two episodes/year, whereas in developing regions it can reach ten episodes/year. Basic sanitation and drinking water almost eliminated bacterial and parasiticinfections in developed countries, but rotavirus infections are still comparable between developed and developing countries.[3,4]

Younger children with rotavirus infection tend to have significantly higher risks of complications, as most cases of severe diarrhea and dehydration occur between three to 35 months.[2,5,6] In the United States, 17% of hospitalizations occurred during the first six months of life, and 40% in children up to one year of age. It is estimated that each year the rotavirus infections in children under five years of age total 27 million episodes, and result in 410,000 consultations, with 205,000 - 272,000 emergency room visits, and 20-60 deaths.[7]

In Brazil, acute diarrhea in children under five accounts for 15% of admissions. There were 1,505,800 hospitalizations from 1995 - 2005, and 39,421 deaths from diarrhea in children under one year of age.[8] In Curitiba, Paraná, as well as in 15 other Brazilian cities, there was a reduction in hospitalization rates for diarrhea; eight capitals remained stable, and two capital cities and the Federal District showed increasing rates.[8]

In 2011, Sudan became the first low-income country in Africa to introduce a rotavirus vaccine. Active hospital-based surveillance for rotavirus disease was performed in eight regional public hospitals in Sudan using a standard protocol recommended by the World Health Organization for children at two years of age.[9] From June 2009 to May 2011, rotavirus was detected in 3985 (36%) of 10,953 children hospitalized for gastroenteritis, with detection rates ranging from 25% - 48% in eight hospitals. About 61% of hospitalizations for rotavirus occurred before one year of age, and most (91%) occurred before two years of age. With the national estimates of diarrhea events, 9,800 deaths, 22,800 hospitalizations and 55,400 outpatient visits related to rotavirus were calculated annually among children under five, in Sudan.

In 2006, oral human rotavirus vaccine was included in the National Immunization Program, as a strategy to reduce intestinal diseases in children under five, impacting morbidity and mortality from the disease. After its introduction, there was a 14% reduction in hospitalization rates for acute diarrhea, with a mean hospitalization of 115.74 cases before the introduction, 85.84 cases in 2006 and 59.94 cases in 2007, a reduction of 25.8% and 48.0% respectively.[6]

Given the above, this study aimed to evaluate the risk of hospitalization for acute diarrhea in children under five,in the state of Paraná, from 2000 - 2009, comparing the periods before and after the introduction of oral human rotavirus vaccine.

Methods

This was an eco-descriptive-analytic study of infant hospitalization rates for diarrhea registered in the Unified Health System (UHS) of the State of Paraná. The study population consisted of all children under five, living in the State of Paraná, who were hospitalized for acute diarrheal diseases from January 2000 - December 2009. Data were collected from the Hospital Information System of the UHS, which was established in 1982 by the Ministry of Health, with the function of monthly and continuous documenting ofUHS hospital information, using the A00-A09 codes, related to intestinal infectious diseases of the International Classification of Diseases (ICD-10). Vaccination coverage was calculated through the percentage of vaccinated individuals in the target population, in relation to the total population. This denominator was obtained in SINASC database.

The coverage of oral human rotavirus vaccine can be understood as the proportion of children

under five who received the full course of vaccination, in relation to children in the population under one year of age, whose doses were applied at the correct ages (epidemiological adequateness) and proper time intervals (immunologicaladequateness). We evaluated the accessibility and the dropout rate, which allowed us to analyze the percentage of children who had not had a complete scheme of this vaccine, although they had received the first dose. We obtained the hospitalization rate by dividing the number of hospitalizations for acute diarrhea by the population of children under five, then multiplying the quotient by 10,000. We used the Relative Variation Rate to quantify the difference between the pre-vaccination median with the annual rates post-vaccination. The population was obtained from the 2000 censusfrom the IBGE, and the intercensal estimatesfor other years. For the age variable,the following categories were considered: younger than one year, one year, two, three and four yearsof age. Data were collected at the Maringá 15th Regional Health Unit by a properly trained researcher from the State University of Maringá.

The data were stored in the Excel program. The unadjustedoddsratio (OR), the point estimate and the 95% confidence interval were subsequently calculated. Stratified analyses were performed with the application Epi Info®, and logistic regression was calculated using SAS® software. The attributable risk was calculated to assess for the proportion of cases that could be avoided if the exposure was prevented, with the category of four years being used as a baseline for the lower incidence presented in this age group.

The development of the study met national and international standards of ethics in research involving human subjects.

Results

In the period between 2000-2009,there were 103,654 hospitalizations registered in the State of Paraná for a population of 8,828,162 children under five, with a hospitalization rate of 117.41 per 10,000 children.

Children younger than one year accounted for 31.1% of hospital admissions; children one year of age accounted for30.6%; 17.9% weretwo-year-old children; 11.7% werethree-year-old children; and 8.8% werefour-year-old children. Of the total sample, 45.5% were female and 54.5% were male.

In the pre-vaccination period (2000-2005), the median hospitalization rate was 124.2/10,000 children. After the introduction of the vaccine, hospitalization rates were lower when compared to the median of the pre-vaccination years. The 2009 year variation rates compared to the median in the pre-vaccination years were negative, indicating a reduction in hospitalization ranging from (-9.4%) to (-32.1%). Children younger than one year had a higher variation rate (-32.1%), followed by the one-year-old children (-30.7%) and the two-year-old children (-25.8%), with a reduction inversely proportional to age being observed (Table 1).

The age group younger than one year was the one that showed a significant reduction ($p<0.001$) in hospitalization rates in the post-vaccination years, compared to the median of the pre-vaccination years. It should be noted that, among the age groups, this was the one with the highest median. For the year 2008, there was an increase in hospitalization rates in all age groups when compared to 2007 and 2009. The analysis of the age group by hospitalization rates shows that four-year olds presented the lowest rates for all pre- and post-vaccination years (Table 1).

Table 1. Median hospitalization rates for acute diarrhea, and variation rates between periods, by age

Age (years)	Median HR 2000-2005	HR 2006	VR (%)	HR 2007	VR (%)	HR 2008	VR (%)	HR 2009	VR (%)	p<0.001
<1	202.7	155.1	-23.5	141.3	-30.3	167.5	-17.4	137.7	-32.1	0.001
1	191.5	196.9	+2.8	158.7	-17.1	193.5	+1.1	132.8	-30.7	0.467
2	107.2	107.3	+0.1	96.2	-10.3	125.5	+17.1	79.6	-25.8	0.297
3	66.3	71.9	+8.5	59.4	-10.4	79.0	+19.2	56.8	-14.3	0.141
4**	49.9	50.3	+0.7	48.4	-3.2	55.0	-10.1	45.3	-9.4	-
Total	124.5	114.8	-7.8	98.4	-20.9	121.4	-2.5	88.5	-28.9	0.009

HR - Hospitalization rate; VR - Variation rate; ***baseline* Category

Table 2. Probability of hospitalization for acute diarrhea in children under five

Age (years)	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	χ^2
<1											
OR	6.78	5.95	4.49	3.49	3.44	3.28	3.12	2.95	3.08	3.07	1358.70
CI	6.2-7.3	5.5-6.4	4.1-4.8	3.2-3.7	3.2-3.7	3.0-3.5	2.9-3.3	2.7-3.2	2.8-3.3	2.8-3.3	
P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
1											
OR	4.65	5.00	4.19	3.54	3.63	3.62	3.97	3.32	3.57	2.96	181.14
CI	4.2-5.0	4.6-5.3	3.8-4.5	3.3-3.8	3.3-3.8	3.3-3.8	3.7-4.2	3.0-3.5	3.3-3.8	2.7-3.2	
P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
2											
OR	2.26	2.62	2.3	2.22	2.04	2.1	2.14	2.0	2.3	1.76	0.060
CI	2.0-20.4	2-2.4	2.1-2.4	2.0-2.3	1.8-2.2	1.9-2.2	1.9-2.3	1.8-2.1	2.1-2.4	1.6-1.9	
P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
3											
OR	1.3	1.44	1.35	1.45	1.31	1.31	1.43	1.23	1.44	1.26	5.27
CI	1.2-1.5	1.3-1.5	1.2-1.4	1.3-1.5	1.2-1.4	1.2-1.4	1.3-1.5	1.1-1.3	1.3-1.5	1.1-1.3	
P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Stratified analysis											
MH	3.13	3.63	3.06	2.66	2.59	2.56	2.65	2.35	2.58	2.24	13.73
CI	3.0-3.2	3.5-3.7	3.1-2.9	2.5-2.7	2.5-2.6	2.4-2.6	2.5-2.7	2.2-2.4	2.4-2.6	2.1-2.3	
P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.001	<0.01	<0.01

OR - *Odds Ratio*; CI - Confidence Interval; P - significance level; MH - Mantel-Haenszelstatistic

The age group of those under one yearof age showed the greatestinteraction with the vaccine (p<0.001). The other age groupswere different from the first, and equal when compared to each other. The odds ratio for hospitalization in children under one year of age reduced the risk by half in the ten years evaluated, but it is still the age group at greatest risk of hospitalization (Table 2).

It was also found that all age groups had decreased rates of hospitalization in the study period (2000-2009), with a statistically significant reduction (p<0.001). At the age of two, this analysis was not significant (Table 2).

In the analysis of the pre-vaccination period, it was observed that children under one,and one-year-old children had a risk (OR_{MH}=4.40 and OR=4.05, p<0.001) of hospitalization for acute diarrheal disease when compared to older children (Table 3). In the period after the introduction of the vaccine, taking the age of four as a baseline, it was observed that the probability of hospitalization for acute diarrheal disease decreased. For the period of 2006-2009, the age groupsyounger than one year and the one-year-olds had a risk (OR=3.06 andOR=3.5, respectively) of hospitalization that was greater when compared to older ages. This analysis concerning the age should be carefully performed, because in the post-vaccination period, one-year-old children had a higher risk of hospitalization for acute diarrhea compared to children under one (Table 3).

Table 3. Likelihood of hospitalization, attributablerisk and adjusted *odds ratio* by age and pre- and post-vaccination periods

Age(years)	Pre-vaccination	Post-vaccination	AR%	Adjusted OR	p-value
<1					
OR	4.4	3.06	30.45	3.89	<0.001
CI	4.2-4.5	2.9-3.1			
MH	11685.02	3533.93			
P	0.01	0.01			
1					
OR	4.05	3.5	13.54	3.84	<0.001
CI	3.93-4.17	3.37-3.64			
MH	10026.61	4734.56			
P	0.01	0.01			
2					
OR	2.19	2.07	5.48	2.14	<0.001
CI	2.12-2.26	1.99-2.16			
MH	2434.48	1279.46			
P	0.01	0.01			
3					
OR	1.37	1.35		1.36	<0.001
CI	1.32-1.42	1.29-1.41	1.46		
MH	318.14	179.26			
P	0.01	0.01			
Vaccination period				1.16	<0.001
Stratified analysis					
OR	2.97	2.46	17.17		
CI	2.94-3.04	2.44-2.53			
adjusted MH	2.98	2.48			
χ^2MH	21683.31	8611.36			
P	0.01	0.01			

OR - *Odds Ratio*; MH - Mantel-Haenszelstatistic; IC - Confidence Interval; P - significance level

Through calculation of the attributable risk, it was observed that children under one year had a 30% decreased rate of hospitalization, a difference between the pre- and post-vaccination periods, and, as one ages, the likelihood of hospitalization decreases.The Mantel-Haenszel chi-squarestatistic revealed that for the set of all analyzed ages, the risk of hospitalization for diarrheal diseaseafter vaccination decreased by 17% (Table 3).

The logistic regression confirmed the statistically significant predisposition for all ages, with a risk of 3.89 and 3.84 for hospitalization for children in the age under one year andequal to one year, respectively (Table 3).

Discussion

An ecological study design does not allow direct interpretation of results at the individual level. Also, the number of hospitalizations for all causes of diarrhea is secondary data, without independent validation, from health administration and subject to reporting bias. However, it was noted that diarrheal diseases showed particular characteristics,such as anoutbreak incidence.In addition to seasonality, diarrheal diseases presented with temporal variation amongthe years, important factors to be considered in new proposals.

In this study, we found a reduction in hospitalization rates due toacute diarrhea, in children under five for all stratified age groups, suggesting that the use of oral human rotavirus vaccine was associated with the reduction in cases, following a national trend of decrease in hospitalization rates for acute diarrhea.[3,5,8]

This reduction in hospitalization rates for acute diarrhea, after the introduction of the vaccine,was confirmed in a study conducted in the United States, which found a 50% increase in hospitalizations for diarrhea in children 6-23 months, in the second year after the oral human rotavirus vaccine.[10] Also, one case-control study that evaluated the efficacy of the vaccine in sentinel hospitals in El Salvador observed a significant protection for all admissions for diarrhea among children under five, with a 40% and 51% reduction in cases in 2008 and 2009, respectively, when compared to 2006.[11]

The study conducted in Brazil, in 2006 and 2007, found a 14% reduction in the hospitalization rates for acute diarrhea by region, with a mean hospitalization rate of 115.74 cases per 10,000 children before the introduction of the vaccine, 85.84 in 2006 and 59.94 in 2007 (a reduction of 25.8% and 48%, respectively).[6] Meanwhile,in the city of São Paulo, a reduction of 29% in hospitalizations for diarrhea of any cause was found after oral human rotavirus vaccine.[5]

Identifying the causes of diarrhea is essential,-so that appropriate measures are instituted for its prevention. A studyat the University of Würzburg Hospital (Germany),with 650 patients with proven diarrhea treated between April 2005 and May 2008, aimed to analyze the clinical features and laboratory data of the different pathogens causing diarrhea. Rotavirus was the most common pathogen identified, followed by norovirus, adenovirus and *Salmonella* spp. Nosocomial infections were most commonly caused by norovirus. Rotavirus was the most common agent when there was simultaneous detection of two or more viruses. Rotavirus infections were significantly more severe, with a higher frequency of diarrhea and elevated liver enzymes. Patients infected with *Salmonella* spp showed significantly higher values for C-reactive protein, hemo-sedimentation velocity, and fever. Younger children showed significant scores for gastroenteritis and airway inflammation. Respiratory symptoms and systemic inflammation parameters differed between the different pathogens.[12]

A study comparing the proportion of hospitalizations for diarrhea attributable to rotavirus found increased hospitalization rates in recent years, 21% between 1986 and 1999, 39% between 2000 and 2004, both in developed and developing countries.[13] After this period, there was a reduction in hospitalization rates compared to other causes of diarrhea, suggesting the importance of oral human rotavirus vaccine in reducing hospitalization rates. It should be added that high admission rates may be related to viral infections, which do not have their rates reduced with the basic measures of sanitation and clean water.[3]

In the analysis of the likelihood of hospitalization for acute diarrhea, a sharp drop for children under one year of age was observed before the introduction of oral human rotavirus vaccine, possibly related to other protective factors, such as the use of oral rehydration therapy, and the improvement of factors such as socioeconomic status, maternal education, breastfeeding and nutritional status of children.[1,10]

Age has been a risk factor for diarrheal disease, the severity of these episodes increased in both developing and developed countries. The attributable risk for children under one, and for one-year olds, showed a higher vaccine protection, but the OR revealed the frailty of this group regarding acute diarrhea. This fact can be observed in a case-control study which found statistically significant frequency of rotavirus infection among patients under 24 months of age (69%),compared to children aged two years or more (31%).[14]

In the present study, the incidence of diarrheal episodes in children under one was 3.8 times higher when compared with children one to four yearsof age. This same bias was observed in a case-control study[9] in the northeasternregion of Brazil, which demonstrated the risk of hospitalization of children under one year of age, with a probability 4.4 times higher, and 3.6 in the post-vaccinationperiod,compared with four-year-old children. In southern Brazil, the risk of children under one year being ill was 3.59 times higher than in children one to four years old.[6]

It was observed that the risk for two-year-old children changed a little, with a small reduction in the year 2009, and that the pre- and post-vaccination periods remain virtually unchanged (Table 2) although they present a variation rate of (-25.8%).

In the natural history of rotavirus infections, 90% of children up to the second year of life would present an infection[6] of greater severity that would require hospital care and the availability of the vaccine for all children, according to the age group. This would also reduce the risk of bias in the analysis of admission rates, suggesting that the introduction of the vaccine has reduced the percentages of hospitalization rates for some age groups. It should be noted that the younger the child, the stronger the association, i.e., the greater the probability of occurrence of the disease, probably because the likelihood of hospitalization for this age shows little variability over the years.

A study conducted in 18 states, with acute gastroenteritis hospitalization rates in children under five years of age, before and after rotavirus vaccination, found that the average rate for the years 2000-2006 was 101.1/10,000 children, compared to rates of 85.5 and 55.5/10,000 children in 2007 and 2008 (16% and 45% lower, respectively). Children aged 0-2 monthshad a reduction of 28%; those aged 6-23 months had a 50% reduction, and children aged 3-5 months and 24-59 months had reductions ranging from 42% to 45%. It was concluded that the introduction of the vaccine was associated with a dramatic reduction in hospitalizations for acute gastroenteritis in US children, regardless of age.[10]

Measures to improve sanitation, such as clean water, garbage collection, wastewater piping, combating vectors, pluvial drainage and the promotion of personal and home care are important strategies and present concrete results for the reduction of hospitalization rates for acute diarrhea. However theyare not sufficient,and prevention through immunizationis required. The World Health Organization has also supported the member states of the African countries, since 2006, to establish the sentinel surveillance of rotavirus diarrhea in children under five, through the use of standardized guidelines. This strategy is very important to generate country-specific data and document and demonstrate rotavirus gastroenteritis load in the country.[15] The collected data are being used by politicians to guide appropriate intervention decisions for diarrhea control, including importance and the timing of the introduction of new rotavirus vaccines in national immunization programs.

The use of oral human rotavirus vaccine is a breakthrough in the health of children under five, and the data on the impact of viral gastroenteritis have important implications for the evaluation of health policies, such as promoting breastfeeding,

improving weaning practicesat the proper age, and the introduction of complementary food.

It is crucial to determine how many of the still remaining admissions of children under five years of age are caused by rotavirus, and what the vaccination status is for these children. The wide variety of circulating strains, and factors such as a cold, dry climate, urban clusters with high population density, being in childcaresettings and other indoor environments, increase their potential for transmission.

Conclusion

There was a reduction in hospitalization rates for acute diarrhea in children under five years of age in the state of Paraná, suggesting that the use of oral human rotavirus vaccine and other associated factors can reduce cases of acute diarrhea.

Collaborations

Masukawa MLT and Uchimura NS state that they contributed to the writing, critical review of the relevant intellectual content, and final approval of the version to be published. Moriwaki AM; Santana RG and Uchimura TT collaborated in the study design, analysis, data interpretation, article writing, critical review of the relevant intellectual content, and final approval of the version to be published.

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