Evaluation of the rotavirus vaccine introduced into infant population in the semiarid region of the state of Paraíba, Brazil (2006 - 2013)

Avaliação da vacina para rotavírus introduzida na população infantil do semiárido paraibano (2006 - 2013)

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ABSTRACT
Acute gastroenteritis caused by rotavirus represents a clinical episode of great relevance to Brazilian public health due to its expressive mortality rate in children under five years of age. In Brazil, Rotarix® from GlaxoSmithKline, a live attenuated vaccine, has been used in children since 2006. The present study evaluated the effectiveness of vaccination in the semiarid region of Paraíba, a Brazilian state, through the notification of diarrhea cases, clinical data of the disease in the period from 2005 to 2013, and the detection of viral antigens in the feces of hospitalized children in the years 2012 and 2013. There was no significant reduction in the number of cases of diarrhea with the implementation of vaccination in the period studied, with an epidemic of diarrhea in 2013, when the number of cases increased 4 times compared to the previous period

Keywords: rotavirus, vaccine, rotarix, infantile diarrhea.

RESUMO
A gastroenterite aguda causada por rotavírus representa um episódio clínico de grande relevância para a saúde pública brasileira devido à sua expressiva taxa de mortalidade em crianças menores de cinco anos. No Brasil, a Rotarix® da GlaxoSmithKline, vacina viva atenuada, é utilizada em crianças desde 2006. O presente estudo avaliou a eficácia da vacinação no semiárido da Paraíba, estado brasileiro, por meio da notificação de casos de diarreia, dados da doença no período de 2005 a 2013, e a detecção de antígenos virais nas fezes de crianças hospitalizadas nos anos de 2012 e 2013. Não houve redução significativa no número de casos de diarreia com a implantação da vacinação no período estudado, com uma epidemia de diarreia em 2013, quando o número de casos aumentou 4 vezes em relação ao período anterior.

Palavras-chave: rotavírus, vacina, rotarix, diarreia infantil

1 INTRODUCTION

According to the World Health Organization, rotaviruses are the most important etiologic agents of severe diarrhea in infants and children under 5 years of age, and the second leading cause of death in this age group worldwide (BLACK et al., 2010; ESTES & KAPIKIAN, 2013). In 2008, about 453,000 children died from this syndrome, attributable to rotavirus infection, corresponding to 37% of all diarrhea cases (TATE et al., 2011).

The rotavirus particle has three protein layers protecting its 11 double-stranded RNA segments. The International Committee on Taxonomy of Viruses (ICTV) classifies rotaviruses into five types (A, B, C, D and E), with *Rotavirus A* (RVA) being the main species involved in childhood diarrhea.

The first rotavirus vaccine was licensed in 1998 in the United States, but due to complications such as intussusception, it was suspended in 1999 (MORENO, 2001; PETER & MYERS, 2002). The following year, another commercial monovalent live attenuated vaccine appeared, the Rotarix® vaccine, which contains the human strain G1P (O'RYAN, 2007), and was included in the Brazilian vaccine schedule in 2006, administered in two doses: the first up to the 16th week of life, and the second up to the 30th week (CILLI et al., 2011).

Several authors have reported a 90% reduction in the hospital admission rate after the use of this vaccine (ARAÚJO et al., 2007; ZLAMY et al., 2013), arguing that the vaccine is highly effective against severe acute diarrhea during the two first years of life (CORTESE et al., 2013).

The present study evaluated the results of vaccination in 12 cities in the semi-arid region of Paraíba, from 2006 to 2013, based on clinical and epidemiological data in this period, and on the tracking of rotavirus antigens in the feces of children under five years of age between September 2012 and November 2013.

2 MATERIAL AND METHODS

2.1 FAECAL SAMPLES

Stool samples (n=169) were obtained from children admitted to hospitals in their municipalities, aged between six months and five years, living in the 12 cities that form the 4th Health Regional of the State of Paraíba, during the period from September 2012 to October

2013. Feces were collected from diapers and stored for a maximum of 48 hours in the refrigerator at 4 °C.

The selection of samples for the investigation of viral antigens was based on the cases considered as severe diarrhea in children under five years of age. Detection of viral antigens was performed at room temperature of 25 °C.

2.2 DETECTION OF VIRAL ANTIGENS

Was used the RIDA®Quick Rotavirus/Adenovirus Combi test marketed by R-Biopharm®, which detects rotavirus and adenovirus antigens in feces. It is a rapid immunochromatographic test, available in individually packed cartridges. About 50mg of feces was suspended in the extraction buffer, vortexed for five minutes and sedimented for two minutes. Then, four drops of the supernatant were transferred to the cartridge, with readings carried out up to a maximum of five minutes. The test results were interpreted as follows: positive adenovirus occurs when a blue band (T1) appears next to the green control band (C), and positive rotavirus occurs when a green band (C) appears next to the red control band (T2). The test detects Rotavirus A VP6 protein, and adenovirus capsid proteins.

2.3 DATA FROM THE 4TH REGIONAL MANAGEMENT OF THE HEALTH DEPARTMENT OF THE STATE OF PARAÍBA, BRAZIL

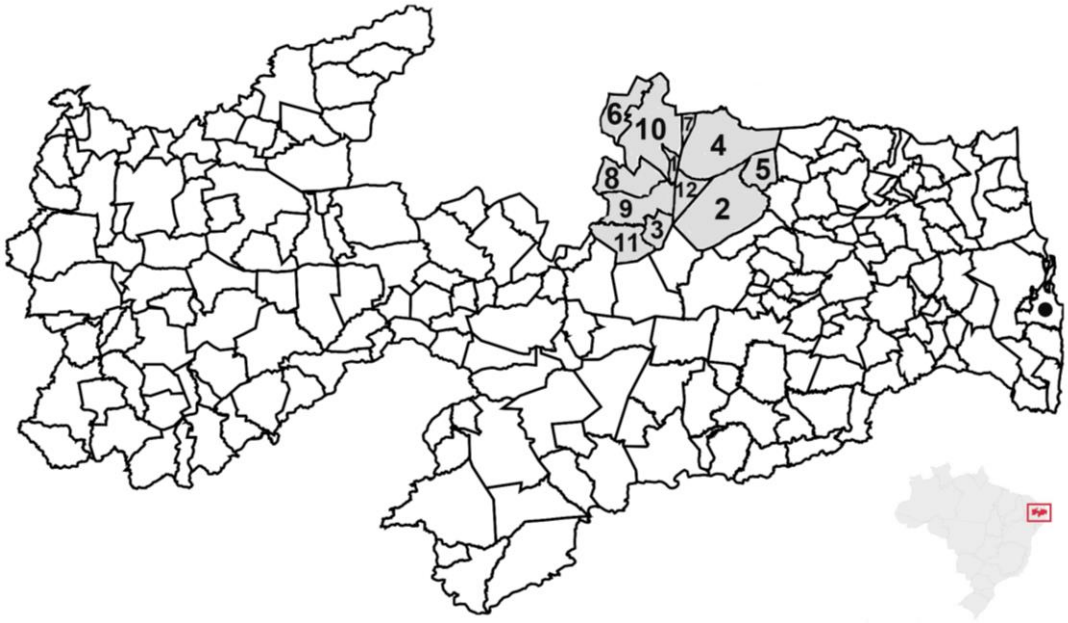
The data provided for the 12 cities correspond to the number of cases of acute diarrheal disease in the child population in the period from 2005 to 2013, to the number of patients undergoing clinical management adopted by the Ministry of Health, Brazil, between 2005 and 2013, and to the vaccination coverage for rotavirus (Rotarix®) from 2006 to 2013.

These cities constitute the 4th Regional Health Management of the State of Paraíba, numbered and presented in alphabetical order, they are: 1- Baraúna, 2- Barra de Santa Rosa, 3- Cubati, 4 - Cuité, 5- Damião, 6- Frei Martinho, 7- Nova Floresta, 8- Nova Palmeira, 9- Pedra Lavrada, 10- Picuí, 11- Seridó, and 12- Sossêgo (Figure 1). The 4th Region corresponds to 6.27% of the state territory and includes 2.8% of the residents of the State of Paraíba and 3.4% of children aged 1 to 4 (IBGE, 2016).

Paraíba – PB

- Capital: João Pessoa

Figure 1: Map of the 12 cities in the semiarid region of the State of Paraíba: 1- Baraúna, 2- Barra de Santa Rosa, 3- Cubati, 4- Cuité, 5- Damião, 6- Frei Martinho, 7- Nova Floresta, 8- Nova Palmeira, 9- Pedra Lavrada, 10- Picuí, 11- Seridó, 12- Sossêgo. The position of the Brazilian state of Paraíba is displayed in the lower right corner. Source: IBGE (2016).



2.4 STATISTICAL ANALYSIS

Demographic and epidemiological aspects of our results were compiled into a database and subjected to descriptive statistical analysis using Graph Prism v.7.0 software for Windows.

2.5 ETHICAL CONSIDERATIONS

The study was developed with the approval of the Ethics Committee of the Federal University of Paraíba, CAEE: 01841412.4.0000.5188, according to Resolution 466/12 of the National Health Council of the Ministry of Health, Brazil.

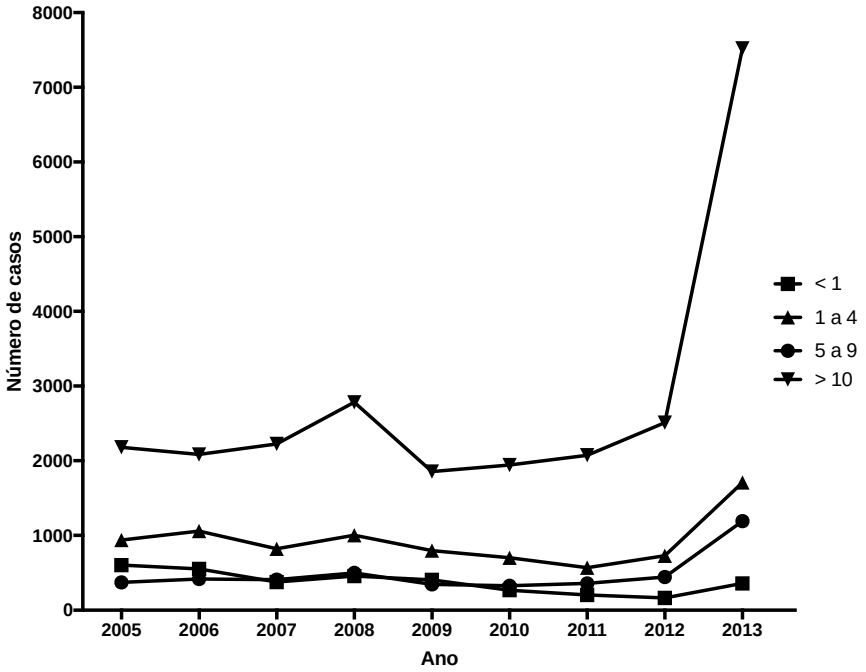
3 RESULTS

3.1 ACUTE DIARRHEAL SYNDROME CASES FROM 2005 TO 2013

The results revealed a higher prevalence of diarrheal episodes in the population of patients over ten years of age, followed by the age group from 1 to 4 years, in the period from 2005 to 2013 (Figure 2), with an oscillation in 2008 (n = 3,000) within the group of patients older than ten years. In the 2012-2013 period, there was a significant increase in the number of cases compared to the previous year: > 200% in the panel of children over ten years of age (n

= 2500 to n = 7523); 168% in children between 5 and 9 years old (n = 444 to n = 1191); 134% in the age group from 1 to 4 years (n = 729 to n = 1708); and 119%, in the age group below one year old (n = 164 to n = 359).

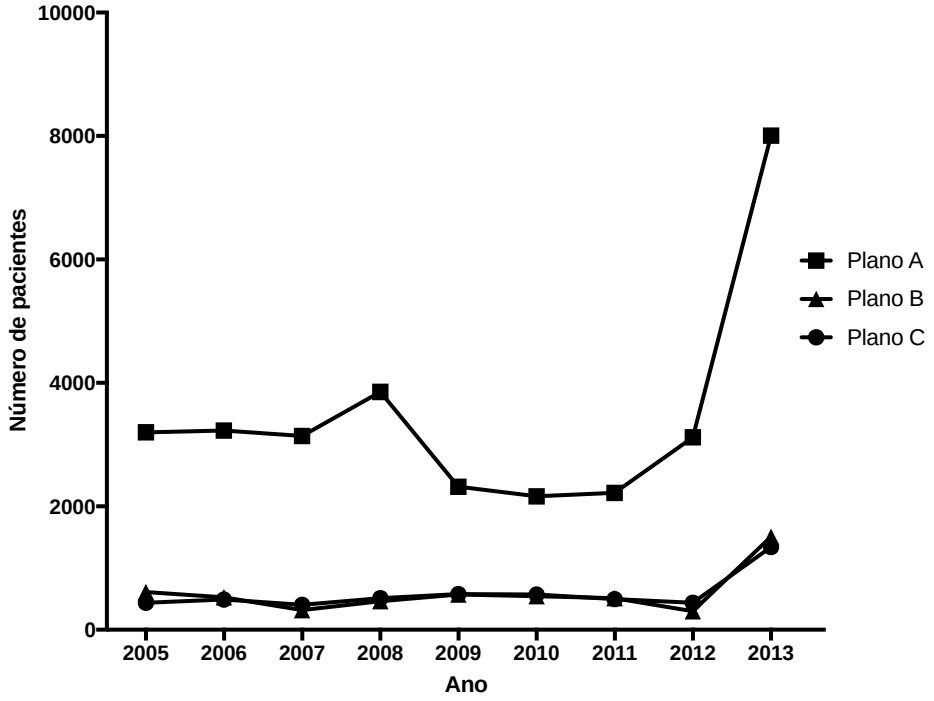
Figure 2: Number of cases of acute diarrheal disease in children up to 9 years of age and in children over 10 years of age from 2005 to 2013 in 12 cities in the semi-arid region of Paraíba, Brazil.



3.2 ASSESSMENT OF CASES ACCORDING TO DISEASE SEVERITY

According to the guidelines of the Ministry of Health, inpatients in the Unified Health System (SUS) with diarrhea are submitted to one of three treatment plans called A, B and C (Figure 3). In plan A, the patient is instructed to perform rehydration at home. In plan B, the patient is rehydrated in the hospital, while plan C is applied to patients with severe diarrhea. In the study period covered in this work, about 3.000 cases were treated in plan A from 2005 to 2012, except in 2008, when this number reached more than 4.000. In the same period, the number of patients submitted to plans B and C were equal (n = 300). However, in the short period of 2012-2013, the number of cases increased dramatically, almost 170% for plan A (n = 8.006), and about 333% for categories B and C, respectively (n = 1,300 in each case). Note that there was a relative and absolute increase in the severity of the cases (category C). Figure 3 shows the evolution of these categories.

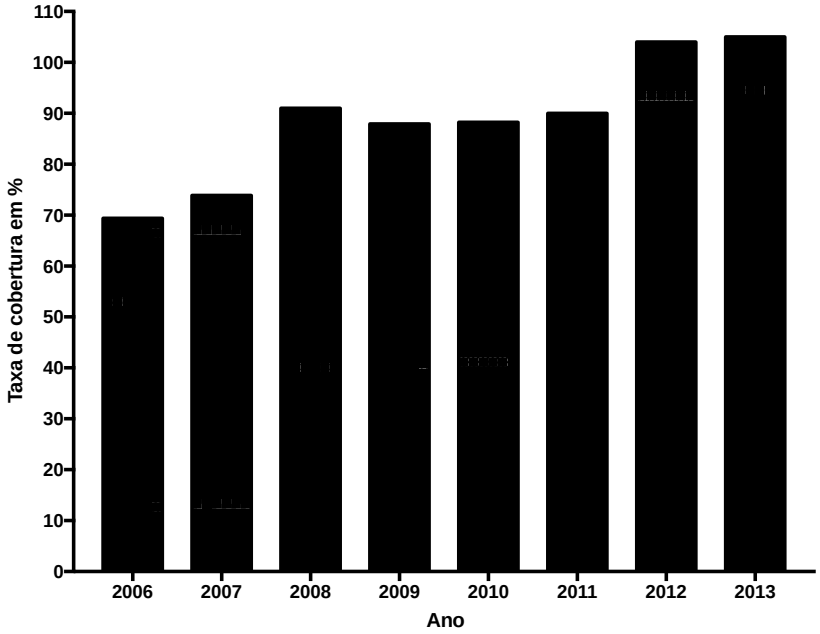
Figure 3: Graph showing the numbers of patients with acute diarrhea undergoing treatment plans A (square), B (triangle) and C (circle) prepared by the Ministry of Health (MS), Brazil. Initially, the patient was evaluated by the health professional to determine his hydration status (severity of the disease). After this evaluation, the patient was treated according to the "MANAGEMENT OF PATIENTS WITH DIARRHEA, MS, Brazil". Plan A refers to preventing dehydration at home; plan B oral rehydration at the health unit; plan C corresponds to severe dehydration, to be treated in the hospital unit.



3.3 VACCINATION COVERAGE CARRIED OUT BY THE 4TH REGIONAL HEALTH MANAGEMENT OF THE STATE OF PARAÍBA, BRAZIL, BETWEEN 2006 AND 2013

Figure 4 shows the vaccine coverage rates from the year of its implementation in the Brazilian immunization schedule, in 2006, until 2013. Coverage reached about 70% in 2006 and 75% in the following year. In 2008, these numbers increased to 91%, although they dropped to 88% in the following couple of years (2009-2010). In 2011, coverage reached 90% of the target population, reaching 100% in 2012 and 2013.

Figure 4: Graph of Rotarix® vaccination coverage in 12 cities in the semi-arid regions of Paraíba during the period from 2006 to 2013.



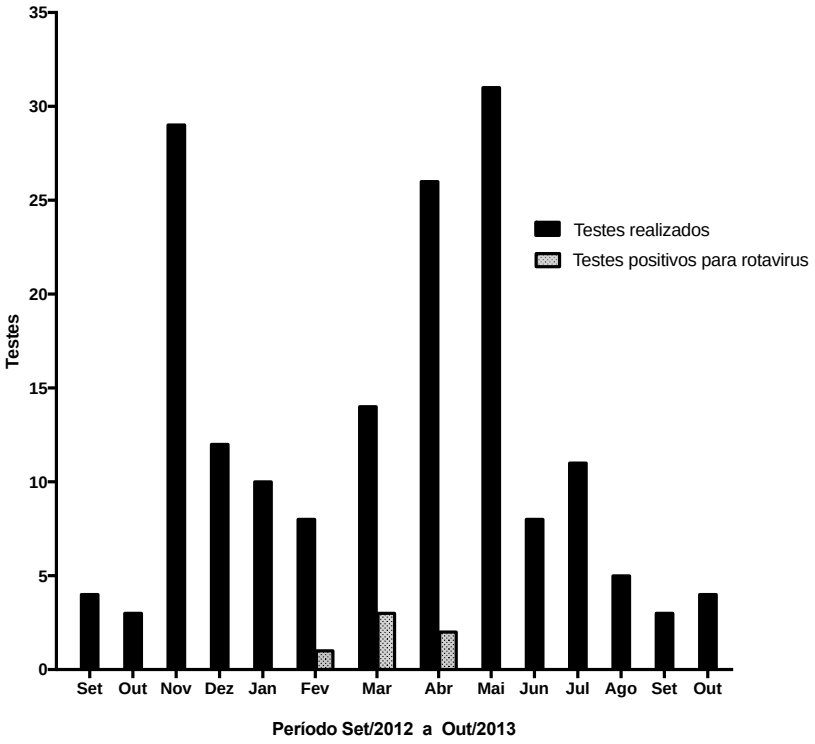
3.4 DISTRIBUTION OF TESTS CARRIED OUT IN THE 12 CITIES

Most of the 169 rotavirus' antigen tests performed in children hospitalized for severe acute diarrhea were performed in the municipalities of Cuité (n = 45) and Picuí (n = 89). No tests were performed on children from Cubati, Pedra Lavrada and Seridó. Regarding the distribution by gender, there were no significant differences.

3.5 DETECTION OF VIRAL ANTIGENS FROM SEPTEMBER 2012 TO OCTOBER 2013

Figure 5 shows the detection of rotavirus' antigens between September 2012 and November 2013. We found 6 samples positives for rotavirus (3.6%) and 7 positives for adenovirus (4.1%) in the months of February, March and April 2013. No cases of co-infection were detected in the sample.

Figure 5: Graph showing the distribution of the amounts of tests performed to detect rotavirus viral antigens between September 2012 and October 2013 in a sample of 169 children. Rotavirus antigens were detected in February 2013 (1 case), March 2013 (3 cases) and April 2013 (2 cases).



4 DISCUSSION

Immunization coverage with Rotarix® in the 4th Regional Management of Paraíba reached its objective in the period 2006-2013 (Figure 4), despite the social inequalities detected in the region (NÓBREGA et al., 2011; BRANCO et al., 2014).

There was no significant reduction in cases of diarrheal episodes in children <1 year of age in the period (Figure 2), the target population of the vaccine. It also did not decrease morbidity from gastroenteritis in children, despite the inclusion of Rotarix® in the national immunization program. In 2013, seven years after the implementation of the vaccine, there was an increase in all age groups examined, highlighting the group of patients over ten years of age (Figure 2). However, during this period, the number of rotavirus antigens in these patients was very low (Figure 5), totaling only 3.5% of cases hospitalized for acute diarrhea.

In the period from 2012 to 2013, we detected an outbreak of diarrhea in children in the region (Figure 3); the number of less serious cases, grouped in SUS Treatment Plan A, increased about three times, and the severe cases, grouped in Plans B and C increased four times, despite the vaccination coverage reached 100% in 2012.

Some studies report that the effectiveness of vaccine coverage is not the same worldwide because of the circulating genotypes. In Asia and Africa, more than half of children under 6

months are infected and reinfected with the different genotypes circulating in the region (GLADSTONE, 2011). We question the possibility of a similar effect in our study.

Rearrangements between the vaccine strain and circulating strains have already been detected in Brazil (ROSE et al., 2013). Luchs et al. (2014) evaluated the selective pressure that the vaccine strain exerts on the population. The study revealed that, in adults with acute diarrhea, there was a predominance of the G2P[4] genotype from 2006 to 2011. In addition, before the vaccination period, between 2004 and 2005, the predominant genotypes were G9P[8] and G1P [8]. These data reveal that the presence of the vaccine strain can put pressure on the replacement of new strains in areas where the vaccine is being administered.

Before the use of the vaccine in Brazil, Santos & Hoshino (2005) published a study on the Rotarix® genotype, the G1P[8]. They found that the Rotarix® vaccine strain accounts for more than 70% of rotavirus infections in North America, Europe and Australia. About 30% in South America and Asia, and 23% in Africa, where the relative frequency of the G8 genotype is as high as the G3 or G4 genotypes. In South America, they observed that the uncommon G5 genotype plays a significant role in the epidemiology of rotaviruses. O'Ryan (2007) also found that the effectiveness of Rotarix® may be different in different regions, suggesting that each region would need its own vaccine.

It is possible that the low number of rotavirus infections detected by the test is due to a low sensibility of the test to identify of circulating genotypes in that region during the period studied. In addition, we suspect that the fact that the introduction of the vaccine did not change the endemic level of rotavirus disease in the region, and the outbreak of 2012-2013, may be due a low efficacy of the vaccine for the population of that region.

5 CONCLUSION

Little is known about the evolution and diversity of certain rotavirus genotypes present in a given region, as well as about the consequences of the use of vaccines on the frequency of circulating genotypes.

As for the literature data on the effectiveness of Rotarix®, they do not seem to agree with what happened in the semiarid region of the State of Paraíba in the afore mentioned period. If vaccination did not reduce the number of diarrheal cases in the region, then it is possible to conclude that the contribution of this rotavirus morbidity was not efficiently removed by the vaccine, as has been reported in other places of the world.

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