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Rotavirus Genotypes Circulating in Brazil Before and After the National Rotavirus Vaccine Program: A Review

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Abstract

We describe the rotavirus genotypes before and after rotavirus vaccine introduction in Brazil. 86 studies reported 6,884 (15.2%) rotavirus-episodes among 45,305 children. Rotavirus caused 22.4% and 11.6% of cases before and after vaccine introduction. G1P[8] and G9P[8], and G2P[4] and heterotypic-strains were most common before and after vaccine introduction. The vaccines may have selected heterotypic strains in this highly-vaccinated population.

Key-words: Rotavirus; Rotavirus genotypes; Rotavirus vaccine; Brazil

Introduction

The advent of the rotavirus vaccines in 2006 was followed by major decreases in diarrhea-related hospitalizations and deaths.[2,3] in countries adopting the vaccines.

Brazil incorporated the G1P[8] rotavirus vaccine (Rotarix®; GlaxoSmithK-line Biologicals, Rixensart, Belgium) into its immunization program in 2006, with substantial reductions in diarrhea-related morbidity and mortality. Early studies after vaccine introduction reported that a high proportion of the rotavirus-diarrhea cases remaining were due to the G2P[4] genotype, a heterotypic strain for which the vaccine has lower efficacy.[3,4] The high proportion of G2P[4] strains could have been due to chance, as rotavirus genotypes vary from year to year; but could also be due to the selection of heterotypic genotypes for which the vaccine has lower efficacy.[5] Although it is difficult to establish the cause of this selection, it could be expected that a temporal coincidence should wane over time, as genotypes are regularly replaced by others, or that a selective immunological pressure would allow heterotypic strains to stay for a longer period or to be replaced by other heterotypic strains.

We reviewed the frequency and proportion of rotavirus genotypes in Brazil before and after vaccine introduction, to explore whether there is evidence to support either of these hypotheses.

Methods

We reviewed the distribution of rotavirus genotypes in Brazil before (1986-2006)[6] and after vaccine introduction (2006-2015) by searching publications in MEDLINE, the Latin American and Caribbean Health Sciences Literature (LILACS), SCOPUS, the Scientific Electronic Library Online (SciELO), the Cochrane Library and the Pan American Health Organisation Library. We used the terms “Brazil”, “rotavirus” and related terms. Two reviewers screened the titles and abstracts and selected original articles of children with acute gastroenteritis reporting rotavirus

genotypes. References cited in the articles were searched to identify further publications. We excluded reviews/opinion papers, studies of diarrhea >2 weeks' duration, nosocomial infections and rotavirus B or C.

Data was extracted using pre-defined tables. Children co-infected with other pathogens were considered rotavirus-positive. Percentages were calculated using the number of studies reporting a given variable as the denominator.

The proportion of rotavirus genotypes were analyzed by time (≤1995, 1996-2000, 2001-2006, 2007-2010 and 2011-2015) and region.[6] Brazil has five regions. The South and Southeast with subtropical/tropical climate, cold and dry winters and rainy summers and good socio-economic indicators. The Central-West with tropical climate, dry winters and rainy/hot summers. The Northeast, with semi-arid land and tropical climate, rainy warm winters and poor sanitary conditions and the Northern region with equatorial climate, low population density and poor socio-economic conditions.

Rotavirus strains were classified by their surface neutralizing antigens (VP7 and VP4) as homotypic to G1P[8], partially heterotypic (G1 or P[8] combined with non-G1 or Non-P[8]) and fully heterotypic (nzon-G1 and non-P[8]). The proportions of homo/partially and fully heterotypic strains were analyzed over time. P-values <0.05 were considered statistically significant.

Results

A total of 1,436 publications were identified (1,157 before/279 after vaccine introduction). Of these, 158 articles were assessed in full, but only 86 reported rotavirus genotypes. Sixty-six (76.7%) were cross-sectional, five (5.8%) cohorts, five (5.8%) case-control, four (4.6%) case series, two (2.3%) clinical trials and four (4.6%) did not report the design. Sixty-seven studies

were hospital-based, three community-based, three ambulatory clinics and 13 did not report the setting (Table, Supplemental Digital Content 1, http://links.lww.com/INF/C840).

Overall, 6,884 (15.2%) of 45,305 children were rotavirus-positive, including 3,364 (22.4%) of 15,033 children before and 3,520 (11.6%) of 30,275 children after vaccine introduction ($p<0.001$). The proportion of rotavirus-positive samples ranged from 3.1% to 40%.

The G1P[8] genotype was reported before and after vaccine introduction in all regions. G5P[8] was reported before 1995 in all regions and then disappeared from 2000. G9 with P[8], P[6] or P[4] was reported between 1996-2000 in the Southeast and West-Central regions and by all regions after 2001. G4 with P[6] and P[8] were reported from all regions before 1995, then by the Southeast between 1996-2000 and the South, Southeast and West Central regions after 2001. G12P[8] was reported in the South between 2001-2006 and in the North and Northeast regions between 2007-2015. G2P[4] was reported in 4 of the 5 regions before the vaccine and from all the regions after vaccine introduction.

Figure one describes the frequency and distribution of genotype combinations over time (for a full frequency see Table, Supplemental Digital Content 2, http://links.lww.com/INF/C841). The most frequent combinations were G2P[4] (53%), G1P[8] (20%) and G9P[8] (10%). However, their distribution varied over time. Before vaccination, G1P[8] was the most frequent strain (43%) and G9P[8] (22%) and G2P[4] (7%) had lower frequencies. G1P[8] represented 8% of all genotypes in 2007-2010 and 23% in 2011-2016. G9P[8] increased before vaccine introduction from 0% before 1995 to 9% and 32% between 1996–2000 and 2001-2006, respectively, and decreased after vaccine introduction to 6% in 2007-2010 and 1% in2011-2015. G2P[4] decreased from 19% before 1995 to 12% and 1% in 1996–2000 and 2001-2006 and then increased to 74% in 2007-2010 and decreased to 45% in 2011-2015.

Before the vaccine, G1P[8]-homotypic strains represented 46%, 12% and 55% of the strains in <1995, 1996-2000 and 2001-2006, respectively. After vaccine introduction, homotypic strains represented 8% and 23% of strains in 2007-2010 and 2011-2015, respectively ($p<0.001$). Partially heterotypic strains represented 27%, 51% and 41% of strains <1995, 1996-2000 and 2001-2006, respectively. After vaccine introduction, partially heterotypic strains represented 10% and 16% in 2007-2010 and 2011-2015, respectively. Fully heterotypic strains in turn represented 25%, 38% and 3% of strains <1995, 1996-2000 and 2001-2006, respectively (Fig., Supplemental Digital Content 3, http://links.lww.com/INF/C842). After vaccine introduction, fully heterotypic strains represented 83% and 59% of strains in 2007-2010 and 2011-2015 ($p<0.001$).

Discussion

Rotavirus G and P types in Brazil have changed significantly in recent decades, with major changes occurring after the rotavirus-vaccine introduction. Genotypes variation over time was well documented before the vaccine introduction and strains were usually replaced by other genotypes within one and two years.[6,7] This variation is likely due to the natural ecology of rotavirus. In Europe, for example, there are variations in genotype distributions between the peak and nadir rotavirus-seasons and year on year.[7] Globally, four G-P combinations G1P[8], G2P[4], G3P[8] and G4P[8] accounted for 88% of rotavirus infections between 1973 and 2003, and the proportion of cases attributed to a specific genotype varied across continents. For example, G1P[8], caused >70% of cases in North America, Europe and Australia, but only 23%-30% of cases in Africa, South America and Asia. Other genotypes such as G9P[8] and G12P[8] also emerged worldwide between 1990 and 2006[8] and the widespread changes illustrate that major

and frequent changes occurred naturally before the vaccines and that these changes were not geographically homogeneous .

In Brazil, the proportion of G1P[8] strains fluctuated before the vaccine (≤1995 and 2001-2006). G1P[8] and G9P[8] were the most frequent genotypes immediately before the vaccine (>75% of all strains reported), which was similar to surveillance reports in other countries in the region. Our results also describe an unusual increase of heterotypic strains after the vaccine introduction in Brazil. Heterotypic strains had accounted for 3% of all strains in 2001-2006, but represented 83% of strains reported after vaccine introduction. A high proportion of studies reported that G2P[4] was the main strain detected after the vaccine introduction. Furthermore, although G2P[4] strains decreased in 2009-2012, they continued to be the main strain identified until 2015. Furthermore, although other strains replaced G2P[4] in recent years, these emerging strains were nearly invariably heterotypic, suggesting that the vaccine may have favored their survival.

The studies that supported the Rotarix vaccine registration reported an overall efficacy of about 85% against severe diarrhea and -hospitalisations,[5] with a higher vaccine efficacy against fully homotypic G1P[8] strains (91%), marginally lower against partially heterotypic (87%) and lowest against fully heterotypic strains (41%).[5] A post-marketing review of the vaccine confirmed its lower efficacy against G2P[4] in Latin America (39%) and Europe (58%) [9].

A meta-analysis of the Rotarix and Rotateq vaccines in Latin America has recently reported that their effectiveness against hospitalizations and severe diarrhea were similar (73% and 74%, respectively).[10] Rotarix elicited a slightly lower protection against fully heterotypic strains. However, its large-scale use and the herd immunity attained when used in national immunization

schemes has resulted in a significant impact on the overall burden of diarrhea, with significant reductions in hospitalizations and deaths.[9,10]

Our study has the limitation that studies did not report yearly data or had fairly rudimentary geo-referencing, restricting the description of strain changes to full years and large regions. However, it is clear that there have been major genotype changes over time and in all geographical regions. Despite the diversity of these changes, there was a consistent shift towards non-G1P[8] strains after vaccine introduction, with the G2P[4] strain representing 70% of the cases identified. Further surveillance is needed to continue monitoring the emergence of unusual genotypes and the continued efficacy of the vaccines.

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Legend of figure

Figure. Rotavirus G and P genotype combinations by study period.

Supplemental Digital Content

Table, Supplemental Digital Content 1. Characteristics of studies included in review.

Table, Supplemental Digital Content 2. G and P combinations by study period, Brazil 1990–2015.

Figure, Supplemental Digital Content 3. Distribution of the proportion of homotypic, heterotypic and partially heterotypic rotavirus genotypes by study period.

Figure 1