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Review

Rotavirus genotypes circulating in Brazil before national rotavirus vaccination: A review

Ricardo Q. Gurgel [a,b,*], Nigel A. Cunliffe [c,1], Osamu Nakagomi [c,d,1,2], Luis E. Cuevas [b,c,1]

[a] *Postgraduate Nucleus, Rua Claudio Batista SN, Barrio Sanatorio, Federal University of Sergipe, Aracaju, Brazil*
[b] *Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, United Kingdom*
[c] *Department of Medical Microbiology & GUM, University of Liverpool Duncan Building, Daulby Street, Liverpool, Merseyside L69 3GA, United Kingdom*
[d] *Department of Molecular Microbiology and Immunology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan*

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Abstract

Background: Rotavirus vaccine was recently introduced in Brazil, which has the potential to greatly reduce childhood deaths from diarrhoea. To provide baseline data to assess the effect of mass rotavirus vaccination on the ecology of circulating rotavirus strains, we systematically analysed published studies in the pre-vaccine era.
Aims: To describe the distribution of rotavirus genotypes in Brazil prior to vaccine introduction.
Methods: Systematic literature searches in health-related databases from 1986 to 2006. Information extracted and analysed by time and region.
Results: 117 studies with 48,401 participants were included. Of these, 3036 were infected with rotavirus. More than 51 genotype combinations were reported, the distribution of which changed over time.P[8]G1 (43%) was the most frequent genotype throughout, followed by P[8]G9 (22%) and P[4]G2 (7%). The detection rate of P[8]G9 increased, while P[4]G2 decreased during the study period. There was a high frequency of G/P combinations between 1995 and 2000 and a low frequency before and after these years.
Conclusions: While considerable diversity of rotavirus strains was recognized during the pre-vaccine era, three strains comprised 72% of the total analysed. These data provide a baseline against which any changes in circulating rotavirus strains post-vaccine introduction can be measured.

Keywords: Rotavirus; Brazil; Genotypes; Review; Diarrhoea

Contents

* Corresponding author at: Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, United Kingdom. Tel.: +44 1517057132; fax: +44 1517053329.
E-mail addresses: ricardoqg@infonet.com.br (R.Q. Gurgel), N.A.Cunliffe@liv.ac.uk (N.A. Cunliffe), onakagom@nagasaki-u.ac.jp (O. Nakagomi).
[1] Tel.: +44 1517064382.
[2] Tel.: +81 95 819 7061; fax: +81 95 819 7064.

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1. Introduction

Rotavirus vaccines were recently introduced into national childhood immunization programmes of the USA (Rota Teq®, Merck and Co., Whitehouse Station, NJ, USA), and Brazil, Panama and Venezuela (Rotarix®, Glaxo-SmithKline, Research Triangle Park, NC, USA) (Glass et al., 2006). This represents the most significant public health intervention in the global effort to reduce the morbidity and mortality associated with childhood diarrhoea, since the advent of oral rehydration therapy in the 1950s (Darrow and Pratt, 1950a,b). Rotavirus is the leading cause of severe diarrhoea in infants and young children worldwide. It is estimated to cause 39% of childhood diarrhoea-related hospitalizations. Application of this proportion to the World Health Organization estimates of diarrhoea-related childhood deaths would indicate an estimated 611,000 (range 454,000–705,000) rotavirus-related deaths per year (Parashar et al., 2006). Although its incidence is similar in developed and developing countries (Kosek et al., 2003; Parashar et al., 2003), the case fatality rate among hospitalized children is much higher in low-income countries (Parashar et al., 2003).

Rotavirus, a 70-nm icosahedral virus, is a member of the genus *Rotavirus*, family *Reoviridae* and is a non-enveloped particle with triple-layered wheel-like capsid containing 11 segments of double stranded RNA in its core. Each segment with the exception of the 11th encodes a single protein. Protein VP7 defines the G serotype (for glycoprotein) and VP4 defines the P serotype (for protease-sensitive) (Kapikian et al., 1981). These proteins have independent neutralisation properties and are used in a binary classification system. Based on serological assays, there are 14 P serotypes (nine recovered from humans) and, based on molecular characterization, 26 P genotypes (10 recovered from humans). There are 15 G serotypes, of which 11 (G1–G6, G8–G10, G12 and G15) have been recovered from humans. Because the genes encoding VP7 and VP4 segregate independently, numerous G and P combinations are possible (Hoshino and Kapikian, 2000). The 4 G/P combinations most frequently detected worldwide were reported in 2005 as P[8]G1, P[4]G2, P[8]G3 and P[8]G4 (Gentsch et al., 2005; Santos and Hoshino, 2005), although G9 with both P[6] and mostly P[8] has become one of the most common combination in several places (Kheyami et al., 2008; Rodrigues et al., 2007), including Brazil (Carmona et al., 2006).

The global disease burden attributed to rotavirus infection (Dennehy, 2007; Glass and Parashar, 2006; Glass et al., 2006; Kapikian et al., 1981; Parashar et al., 2003; Santos and Hoshino, 2005) stimulated the development of rotavirus vaccines. The first licensed rotavirus vaccine (RotaShield®, Wyeth Laboratories, Marietta, PA, USA), was a rhesus-human reassortant rotavirus vaccine designed to cover the four most prevalent human G serotypes (G1–G4). Although highly effective in preventing severe rotavirus gastroenteritis, its association with cases of intussusception (Dennehy, 2007; CDC, 1999; Murphy et al., 2001; Simonsen et al., 2001) lead to the withdrawal of the vaccine in 1999, less than 1 year after its introduction (Peter and Myers, 2002; CDC, 1999). Although the strength of this association has been questioned (Simonsen et al., 2005), it nevertheless created additional requirements for larger clinical trials to examine safety issues of two new live, oral, rotavirus vaccines (Ruiz-Palacios et al., 2006; Vesikari et al., 2006).

RotaTeq® is a live, attenuated vaccine comprising a bovine (strain WC3) background (Clark et al., 1996) into which G1–G4 genotypes and the P1A[8] genotype were inserted by reassortment to create a pentavalent vaccine (Heaton et al., 2005). Rotarix® is a live, attenuated vaccine prepared from a G1 P1A[8] human strain isolated from a child (Bernstein et al., 1999). Rotarix® was introduced in the national immunization programme of Brazil in March 2006 with two doses provided free of charge to infants at 2 and 4 months of age, and 1,353,867 vaccine doses were distributed in 2006 (http://www.datasus.gov.br) (Brazil, 2006).

The large-scale introduction of the Rotarix® vaccine in Brazil creates an opportunity to assess its effect on virus ecology, as rotavirus strains for which the vaccine is not fully protective may theoretically emerge through selective immune pressure. If changes in circulating rotavirus strains occur post-vaccine introduction, they will need to be interpreted in the context of their historical prevalence in the country.

This study reviews the frequency and profile changes over time of the rotavirus strains reported from Brazil before vaccine introduction. This information will be useful to assess changes in serotype distribution following the introduction of the rotavirus vaccine, creating a baseline for comparison over time.

2. Methods

A systematic search of the literature was performed in MEDLINE, Latin American and Caribbean Health Sciences Literature (LILACS), Scientific Electronic Library Online (SciELO), Cochrane Library and Pan American Health Organisation (PAHO) Library databases using the keywords “rotavirus” and “Brazil” from 1986 to 2006. Additional searches were conducted using the terms “rotavirus” and “vaccine” in February 2007 to identify papers that quoted subsets of genotypes from Brazil before the introduction of the vaccine. In total, 1330 publications were identified and their abstracts were read. Papers with data on genotype strains, or likely to contain relevant epidemiologic information, were retrieved. One hundred sixty-three papers were identified in MEDLINE (the first database searched); three were identified in LILACS; two in SciELO; and one in the PAHO Library. One hundred and seventeen papers had original data on rotavirus and 58 had rotavirus genotypes. All references cited in these papers were searched to identify further publications, but none was identified. Review or opinion articles without original data or with repeated figures were reviewed and genotype/serotype data was extracted