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Effectiveness of rotavirus vaccine against hospitalized rotavirus diarrhea: A case–control study☆

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ABSTRACT

Rotavirus is one of the leading cause of hospitalization and outpatients visits among children under five years. This study evaluated overall and genotype-specific vaccine effectiveness of oral monovalent rotavirus vaccine (G1P[8] strain) in preventing hospital admission of Brazilian children with rotavirus acute diarrhea.

A hospital based case–control study was conducted in five Regions of Brazil using the National Rotavirus Acute Diarrhea Surveillance System from July 2008 to August 2011. A total of 215 cases (aged 4–24 months) admitted with confirmed rotavirus diarrhea were recruited and 1961 controls hospitalized without diarrhea were frequency matched by sex and age group to cases.

Two-dose adjusted vaccine effectiveness (adjusted by year of birth and the frequency matching variables) was 76% (95%CI: 58–86) lasting for two years. Effectiveness controlled by the available potential confounders was 72% (95%CI: 44–85), suggesting no appreciable confounding by those factors for which adjustment was made. In a half of the cases the rotavirus genotype was G2P[4] and in 15% G1P[8]. Genotype-specific VE (two doses) was 89% (95%CI: 78–95), for G1P[8] and 76% (95%CI: 64–84) for G2P[4]. For all G1, it was 74% (95%CI: 35–90), for all G2, 76% (95%CI: 63–84), and for all non G1/G2 genotypes, 63% (95%CI: −27–99). Effectiveness for one dose was 62% (95%CI: 39–97).

Effectiveness of two-dose monovalent rotavirus vaccine in preventing hospital admission with rotavirus diarrhea was high, lasted for two years and it was similar against both G1P[8] and G2P[4]. Based on the findings of the study we recommend the continued use of rotavirus in the Brazilian National Immunization Program and the monitoring of the early emergence of unusual and novel rotavirus genotypes.

1. Introduction

Acute diarrhea (AD) is a frequent cause of child hospitalization and outpatient visits in children under 5 years [1]. In Brazil, before introduction of the rotavirus vaccine in 2006, about 120.000 hospitalizations a year occurred due to AD in children under five years (*DATASUS/Ministry of Health of Brazil, 2006*).

Rotavirus is the leading cause of severe acute diarrhea in children in developed and in developing countries and is the major cause of death in poor countries [2,3]. Seven groups of rotavirus have been identified (A to G) and group A (RV-A) is responsible for more than 90% of human rotavirus infections [4]. RV-A has great genetic diversity due almost 60 serotypes (G and P) and the most

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common strains are: G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8] [5]. In Brazil, between 12% and 42% of children under 5 years with diarrhea had positive stool samples for RV-A before the introduction of the RV-A vaccine. This increased from 22% to 38% in children hospitalized for AD [6,7]. More than 51 genotype combinations were reported and the most common genotypes described were G1P[8], G9P[8] and G2P[4] [8].

Vaccination is the better measure to prevent rotavirus [1,2,9] and its adoption has been recommended by World Health Organization [10]. An attenuated monovalent human RV-A (G1P[8] strain; Rotarix®) and a pentavalent bovine-human reassortant (G1,G2,G3, G4 and P[8] strains; RotaTeq®) are licensed worldwide. Rotarix® was introduced in the Brazilian National Immunization Program (BNIP) in 2006 in a two-dose schedule at 2 and 4 months of age and co-administered with tetravalent, pneumococcal and poliovirus vaccines.

RV-A vaccine efficacy against severe RV-A AD varied between more than 90% Europe and Asia, 85% in Latin America, 72% in South Africa to 49% in Malawi [11–14]. Three case–control studies carried out in a high income country (Belgium) [15] and in low to middle-income countries (El Salvador and Bolivia) [16,17] found a two-dose vaccine effectiveness of 90%; 76% and 77% respectively and a one-dose effectiveness of 91%; 51% and 56% respectively against hospitalization by RV-A AD. In Brazil, two small case controls studies showed a range of 40–85% effectiveness in preventing hospitalization caused by G2P[4] [18,19]. The reason for variation in vaccine protection is not clear and has been attributed to antigen diversity, malnutrition and higher incidence of other enteric pathogens [20]. There is strong suggestion of cross protection among genotypes [11–14].

The introduction of RV-A vaccination was followed by a reduction in child hospitalization due to all causes of AD in Brazil, El Salvador and Mexico ranging from 17 to 51% [21–23] and a reduction in mortality from AD in children under 5 years in Brazil of 22% and in Mexico of 41% [24].

This study will evaluate the overall effectiveness of the oral monovalent vaccine, used in routine health services, in preventing Brazilian child hospitalization with RV-A AD. It will also evaluate overall and genotype-specific VE by time since second dose vaccination (up to two years), and genotype-specific VE.

2. Methods

2.1. Study design

This was a hospital based case–control study, frequency-matched by sex and age group. Hospitals were general hospitals which received children with a large range of diseases coming from a similar geographical catchment area. Seventeen of the hospitals enrolled in the RV-A AD National Surveillance System were invited to participate in the study, based on having had a large number of RV-A positive samples in 2007, adequate level of organization of the unit and data accessibility. After consultation and agreement on logistical arrangements with the Federal Health Surveillance (SVS/MS), the epidemiological surveillance of the hospitals and of the states, the Central Public Health and National Reference Laboratories, 10 hospitals located in five macro-regions of Brazil (6 state capital cities and 4 municipalities) were selected.

3. Participants

3.1. Eligible children

Children were eligible to participate in the study if they were admitted in the study hospitals, were aged 4 to 24 months (and therefore old enough to have received their second dose of rotavirus vaccine) and did not have diarrhea up to three weeks before admission or during hospitalization. All eligible children were listed and screened to exclude children who had any health condition presumed to reduce vaccine effectiveness (immunodeficiency, gastrointestinal disease (e.g. diverticulitis), malformations or neoplasm conditions related to vaccine effectiveness, general signs and symptoms, infectious and parasitic diseases), those who had received the second dose of vaccine in the 15 days before hospitalization, or whose vaccination did not follow the BNIP schedule. All that fulfilled the specific criteria for either effective's case or control were included. This aimed to select controls from the population that produced the cases, as cases hospitalized by AD or by other diseases were likely to come from the same population given the universal health care system in Brazil.

3.2. Potential cases and controls

Inclusion criteria for potential cases were: admission with AD (defined as three or more liquid stools in 24 h, up to 14 days before admission), stool sample was collected until 48 h after admission and positive for RV-A and stay in hospital for at least 24 h. Children were included in the study in the first hospitalization only and had no associate disease.

Inclusion criteria for controls were: admission from the same hospitals of the cases with respiratory, genitourinary, musculoskeletal, nervous systems, skin and subcutaneous tissue, ear and mastoid processes, eye and adnexa diseases, and external causes. Controls were not included if they had a previous history of RV-A diarrhea or had a vaccine-preventable disease (as children who did not receive one vaccine are more likely to not receive other vaccines).

All potential controls fulfilling the criteria above undergone a further selection for frequency matching, so that the all effective controls had the same distribution of the main confounding variables (sex and age group on admission: 4–6 months; 7–11 months and 12–24 months) as the cases. This approach aimed to select from the pool of potential controls, an effective control group with the same distribution of confounders as the effective cases; in the situation in which more controls than needed were available in the frequency matched groups they were selected at random. Random selection of frequency matched effective controls from the pool of potential controls was done using the "sample" command of the Stata version 11.0

3.3. Effective cases and controls

Cases: All potential cases fulfilling the criteria above and had stools positive for rotavirus confirmed by the reference laboratory were included.

Controls: All potential controls fulfilling the criteria above and random selected for frequency matching were included.

One stool sample was collected up to 48 h after admission as part of the RV-A AD Surveillance System. Samples were stored and transported to the LACENs of each State where the hospital was located, according to the guidelines of the General Coordination of Public Health Laboratories/Ministry of Health of Brazil (CGLAB/SVS/MS). RV-A investigation was done by Enzyme Immune Assay (EIA), using commercial kits, following the manufacture' recommendation (Dako® or Oxoide®).

3.4. Laboratory investigation of potential cases

All positive samples for RV-A and 25% of negative samples were sent to a reference laboratory. According to the LACEN localization, this was either the National Reference Laboratory (Evandro Chagas Institute [Belém, PA], or a Regional Reference Laboratory (Adolfo Lutz Institute [São Paulo, SP], and Oswaldo Cruz Institute [Rio de Janeiro, RJ]). Results were confirmed by EIA and polyacrylamide gel electrophoresis (PAGE) according to Leite et al. [25].