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Efficacy of human rotavirus vaccine against severe gastroenteritis in Malawian children in the first two years of life: A randomized, double-blind, placebo controlled trial

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ABSTRACT

Rotavirus gastroenteritis is a major cause of morbidity and mortality among African infants and young children. A phase III, placebo-controlled, multi-centre clinical trial of a live, oral G1P[8] human rotavirus vaccine (RIX4414) undertaken in Malawi and South Africa significantly reduced the incidence of severe rotavirus gastroenteritis in the first year of life. We now report on vaccine efficacy in the Malawi cohort of children who were followed into the second year of life. A total of 1773 healthy infants were enrolled in Blantyre, Malawi into three groups. Two groups received three doses of RIX4414 or placebo at age 6, 10, and 14 weeks and the third group received placebo at 6 weeks and RIX4414 at age 10 and 14 weeks. Subjects were followed by weekly home visits for episodes of gastroenteritis until 1 year of age, and were then re-consented for further follow-up to 18–24 months of age. Severity of gastroenteritis episodes was graded according to the Vesikari scoring system. Seroconversion for anti-rotavirus IgA was determined on a subset of children by using ELISA on pre- and post-vaccine blood samples. Rotavirus VP7 (G) and VP4 (P) genotypes were determined by RT-PCR. A total of 70/1030 (6.8%, 95% CI 5.3–8.5) subjects in the pooled (2 dose plus 3 dose) RIX4414 group compared with 53/483 (11.0%, 8.3–14.1) subjects in the placebo group developed severe rotavirus gastroenteritis in the entire follow-up period (vaccine efficacy 38.1% (9.8–57.3)). The point estimate of efficacy in the second year of life (17.6%; −59.2 to 56.0) was lower than in the first year of life (49.4%; 19.2–68.3). There were non-significant trends towards a higher efficacy in the second year of life among children who received the three-dose schedule compared with the two-dose schedule, and a higher anti-rotavirus IgA seroresponse rate in the three-dose RIX4414 group. Rotavirus strains detected included genotype G12 (31%); G9 (23%); and G8 (18%); only 18% of strains belonged to the G1P[8] genotype. While the optimal dosing schedule of RIX4414 in African infants requires further investigation, vaccination with RIX4414 significantly reduced the incidence of severe gastroenteritis caused by diverse rotavirus strains in an impoverished African population with high rotavirus disease burden in the first two years of life.

1. Introduction

Diarrhoeal disease continues to represent a major threat to global child health, and was recently estimated to account for 15% of all deaths among children below 5 years of age [1]. Rotavirus is the most important aetiological agent of severe gastroenteritis, and is responsible for an estimated 453,000 childhood deaths annually [2], with over 230,000 rotavirus deaths occurring in the African continent [2,3,4]. Hence, rotavirus disease prevention in Africa through vaccination is a public health priority [5].

Two live, oral, attenuated rotavirus vaccines are globally licensed for the prevention of rotavirus gastroenteritis. These include a monovalent serotype G1P[8] human rotavirus vaccine RIX4414 (*Rotarix*, GSK Biologicals, Belgium) and a multivalent, human-bovine reassortant rotavirus vaccine (*RotaTeq*, Merck & Co, USA) which contains the most common human rotavirus G-types

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(G1–G4), and P[8], the most common human rotavirus P-type. Both vaccines are highly efficacious in preventing severe rotavirus gastroenteritis in infancy in high and middle income countries [6–8], and in 2006 were recommended by WHO for use in the Americas and Europe where evidence of efficacy had been demonstrated [9]. In countries that have adopted rotavirus vaccine in their childhood immunisation programmes, evidence of impact has been striking [10]. Importantly, evidence of reduction of diarrhoea deaths following routine rotavirus vaccination has recently been published from Mexico [11]. Finally, a recent study of *Rotarix* from Mexico and Brazil has documented that the benefit of routine rotavirus vaccination (reduction in childhood diarrhoea hospitalisations and deaths) far outweighs a small, short term risk of intussusception that may be associated with use of this live, oral vaccine [12].

In 2009, following review of vaccine performance in Africa and resource-poor settings in Latin America, a global recommendation for rotavirus vaccine use was issued [13]. This recommendation was in part informed by the results of a phase III, placebo-controlled clinical trial of RIX4414 undertaken in Malawi and South Africa [14]. In this study, vaccination with RIX4414 significantly reduced severe rotavirus gastroenteritis episodes in the first year of life in both settings, although efficacy was lower in Malawi (49.4% [95% CI 19.2–68.3]) compared with South Africa (76.9% [56.0–88.4]). Notable findings in Malawi included a high incidence of severe rotavirus disease, a wide diversity of circulating rotavirus strains and a high exposure to natural rotavirus infection early in infancy [14]. This manuscript reports on vaccine performance and circulating rotavirus strains in Malawian children for an extended period of up to 24 months of age.

2. Methods

2.1. Study design

A phase III, double-blind, randomized, placebo-controlled multicentre study was undertaken in South Africa and Malawi as previously reported [14]. In Malawi, children were enrolled in four health centres in Blantyre, the largest city in the Southern region of the country. Healthy infants were randomized at their first Expanded Program on Immunisation (EPI) clinic visit into three groups. One group received three doses of placebo at 6, 10, and 14 weeks of age and a second group received three doses of RIX4414 at the same age. The third group received placebo at 6 weeks and RIX4414 at 10 and 14 weeks. The study was designed to reflect, as far as possible, the conditions under which rotavirus vaccine would be administered under "real-life" conditions in a typical African infant population. Thus, all EPI vaccines including oral poliovirus vaccine (OPV) were co-administered; HIV-infected or -exposed infants were included; and no restriction on breastfeeding around the time of vaccination was imposed.

2.2. Enrolment and follow-up

Enrolment was conducted between October 2006 and July 2007. Subjects were initially followed-up until 12 months of age [14]. At age 1 year, parents/guardians were given the opportunity to enter their children into a period of extended follow-up, the conclusion of which was subject to a time cut-off of January 2009. Subjects were seen at the study clinic at the time of vaccination (~6, 10 and 14 weeks of age), at one month following the third dose of vaccine/placebo (~age 18 weeks of age), at one year of age and, for those subjects who agreed to follow-up beyond one year, at final visit (18–24 months of age). In addition, study staff visited the subjects' homes at weekly intervals throughout the study period. Parents were encouraged to bring the subjects to clinic in the event of illness (unscheduled visits). In the case of severe illness requiring inpatient care, children were hospitalized at the Queen Elizabeth Central Hospital (QECH), a tertiary referral hospital in Blantyre. Voluntary testing of infants for HIV infection using ELISA and PCR was undertaken as previously described [14].

2.3. Assessment and investigation of gastroenteritis episodes

Gastroenteritis was defined as the passage of three or more looser-than-normal stools in a 24 h period, with or without vomiting. Parents completed a diary card for each gastroenteritis episode, the severity of which was graded according to the Vesikari scoring system with severe disease defined by a score of $\geq$11 [15]. Parents were asked to collect a stool specimen at soon as possible after the onset of gastroenteritis. Stool samples were frozen at −70 °C until shipped to GSK Biologicals, Rixensart, Belgium for rotavirus testing by ELISA (*Rotaclone*, Meridian Biosciences, Cincinnati, OH), following which G and P types were determined at DDL Diagnostic Laboratory (Voorburg, The Netherlands) by a testing algorithm using RT-PCR and reverse hybridization [16].

2.4. Vaccine immunogenicity

Serum for anti-rotavirus IgA determination was obtained immediately prior to administration of the first dose of vaccine/placebo in a ~10% systematically selected subset of subjects (at ~6 weeks of age) and at one month following receipt of the third vaccine/placebo dose in all subjects (at ~18 weeks of age). Serum was frozen at −20 °C prior to investigation for anti-rotavirus IgA by ELISA (GSK Biologicals), with an assay cut-off at 20 U/ml. Seroconversion was defined as the presence of a demonstrable IgA titre at one month post-vaccination, in those infants without demonstrable pre-vaccination antibody.

2.5. Statistical analysis

Infants who had received the complete vaccination course and had entered the efficacy surveillance period comprised the according-to-protocol (ATP) efficacy cohort. Efficacy analysis began at 2 weeks after receipt of the 3rd dose of vaccine/placebo, and finished at final follow-up visit (age 18–24 months). The primary endpoint was the assessment of pooled vaccine efficacy (two dose RIX4414 plus three dose RIX4414) against severe rotavirus gastroenteritis up to one year of age for the combined Malawi and South African populations [14]. Supplementary analyses were performed to calculate country-specific vaccine efficacy against severe- and any severity-rotavirus gastroenteritis and severe all-cause gastroenteritis, in children followed up to 2 years of age, for the two- and three-dose schedules. All subjects who agreed to follow up beyond one year of age and who complied with the study protocol were included in the supplementary analyses, regardless of event(s) in the first year of life. Vaccine efficacy against a particular event was calculated using the formula VE = (1 − relative risk) × 100, where relative risk = cumulative incidence of the event in the vaccinated group/cumulative incidence of the event in the placebo group. Ninety-five percent confidence intervals for vaccine efficacy were derived from the exact confidence interval for the Poisson rate ratio for each analysis [17]. A *p*-value was also calculated using a two-sided Fisher's exact test. The incidence rate in a group was computed as the number of infants reporting at least one event (the first event only was included) divided by the total follow-up time for each parameter or subgroup with corresponding 95% confidence intervals [18]. The number of events prevented (per 100 infants per year) was obtained as 100 times the difference in