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Efficacy, safety and immunogenicity of a human rotavirus vaccine (RIX4414) in Hong Kong children up to three years of age: A randomized, controlled trial

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ABSTRACT

Background: A phase III, double-blind, randomized, controlled trial was conducted in Hong Kong to evaluate the efficacy, safety and immunogenicity of a human rotavirus vaccine, RIX4414 (*Rotarix*™) against severe rotavirus gastroenteritis in children up to three years of age.
Methods: Healthy infants aged 6–12 weeks were enrolled between 08-December-2003 and 31-August-2005 and received two oral doses of either RIX4414 vaccine ($N = 1513$) or placebo ($N = 1512$) given 2 months apart. Vaccine efficacy was assessed from two weeks post-Dose 2 until the children were two and three years of age. Anti-rotavirus IgA seroconversion rate was calculated pre-vaccination and 1–2 months post-Dose 2 using ELISA (cut-off = 20 U/mL) for 100 infants. Safety was assessed until the children were two years of age; serious adverse events (SAEs) were recorded throughout the study period.
Results: In children aged two and three years of life, vaccine efficacy against severe rotavirus gastroenteritis was 95.6% (95% CI: 73.1%–99.9%) and 96.1% (95% CI: 76.5%–99.9%), respectively. The seroconversion rate 1–2 months after the second dose of RIX4414 was 97.5% (95% CI: 86.8%–99.9%).

Abbreviations: ARSN, Asian Rotavirus Surveillance Network; ATP, According-to-protocol; $CCID_{50}$, Cell culture infectious dose; DTPa, Diphtheria-tetanus-acellular pertussis; DTPw, Diphtheria-tetanus-whole cell pertussis; ELISA, Enzyme-linked immunosorbent assay; GMCs, Geometric mean concentrations; Hib, *Haemophilus influenzae* type b; ICD, International Classification of Diseases; IPV, Inactivated polio vaccine; OPV, Oral polio vaccine; RT-PCR, Reverse transcriptase polymerase chain reaction; RVGE, Rotavirus gastroenteritis; SAE, Serious adverse event; U/mL, Units per milliliter; WHO, World Health Organization.

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At least one SAE was recorded in 439 and 477 infants who were administered RIX4414 and placebo, respectively (p-value = 0.130). Six intussusception cases were reported (RIX4414 = 4; placebo = 2) and none was assessed to be vaccine-related.
Conclusion: RIX4414 was efficacious, immunogenic and safe in the prevention of rotavirus gastroenteritis for at least two years post-vaccination in Hong Kong children.

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1. Introduction

In 2008, diarrhea attributable to rotavirus infection was estimated to have resulted in 453,000 deaths worldwide (95% CI: 420,000–494,000) in children aged less than 5 years [1]. An estimated 41% (188,000) of these deaths occurred in the Asian region [1]. The World Health Organization (WHO) recommends that rotavirus vaccines should be used in all countries, and considered a priority especially in countries with high rotavirus-related mortality [2].

Rotavirus is prevalent throughout Asia and is an important cause of gastroenteritis requiring hospitalization and medical care in children aged less than 5 years [3]. Data derived through passive surveillance of rotavirus underestimated the disease burden in Hong Kong [4] and highlighted the need for active rotavirus surveillance [5]. The first phase of the Asian Rotavirus Surveillance Network (ARSN) conducted across: China, Hong Kong, Indonesia, Malaysia, Myanmar, South Korea, Taiwan, Thailand and Vietnam between 2001–2003 [3,5], showed that rotavirus accounted for 30–55% of hospitalization in children aged less than 5 years with the lowest rotavirus-positivity rate (30%) recorded in Hong Kong [3].

In 2006, two new rotavirus vaccines, RIX4414 (*Rotarix*™; GlaxoSmithKline, Belgium) and (*Rotateq*™; Merck Vaccines) became available [1]. In studies undertaken in the Americas and Europe, both were reported to be highly efficacious and were not associated with any safety concerns in children during the first two years of life [6–9].

This three-year study was conducted in high-income regions of Southeast and East Asia (Singapore, Hong Kong and Taiwan) to evaluate the efficacy, safety and immunogenicity of the RIX4414 vaccine. The overall efficacy results have been previously presented elsewhere [10,11] and this publication describes specific data pertaining to the efficacy, safety and immunogenicity of RIX4414 vaccine in a pediatric population in Hong Kong.

2. Materials and methods

2.1. Study design and infants

This phase III, randomized, double-blind, placebo-controlled study (NCT00197210) was conducted at eight public hospitals in Hong Kong. The study protocol and related documents were approved by the ethics committee of the individual study centers and the study was conducted in accordance with Good Clinical Practice guidelines. Parents or legal guardians of the participating infants provided written consent before any study-related procedure was undertaken.

Healthy infants 6–12 weeks of age were equally randomized (1:1 blocking scheme) to receive two doses of either RIX4414 vaccine/placebo at 2 and 4 months of age.

Participants received a combined diphtheria-tetanus-acellular pertussis [DTPa], inactivated poliovirus [IPV] and *Haemophilus influenzae* type b [Hib] vaccine (*Infanrix*™ *IPV/Hib*; GlaxoSmithKline, Belgium) concomitantly with the study vaccines according to the local vaccination schedules. Alternatively, if requested, participants could receive diphtheria-tetanus-whole cell pertussis [DTPw], and oral poliovirus vaccine [OPV] at Maternal and Child Health Centres for routine vaccination. According to Hong Kong government policy, infants received a birth dose of Bacillus Calmette-Guérin, hepatitis B and OPV vaccines. Two weeks lapsed between the administration of any OPV dose and the RIX4414 vaccine/placebo; the second and third doses of hepatitis B vaccines were administered at 1 and 6 months of age. Infants were ineligible to participate if they had previously received any investigational drug/vaccine 30 days before the study, had allergy to any of the vaccine components, or were immunosuppressed or had a history of chronic gastrointestinal disease.

2.2. Study objectives and end points

The first co-primary objective of this study was to evaluate the efficacy of the RIX4414 vaccine against severe rotavirus gastroenteritis from two weeks after the second vaccine dose until two years of age. The second co-primary objective was to assess the safety of the vaccine with regard to occurrence of definite intussusception within 31-days following each vaccine dose.

2.3. Vaccine

Each dose of the lyophilized formulation of RIX4414 (*Rotarix*™, GlaxoSmithKline, Belgium) vaccine contained at least $10^{6.0}$ median cell culture infectious dose ($CCID_{50}$) of live, attenuated human G1P[8] rotavirus. The placebo had the same constituents and appearance as the active vaccine but without the vaccine viral strain. Both, the RIX4414 vaccine and placebo were reconstituted in a calcium carbonate buffer before oral administration. RIX4414 vaccine lot numbers RVC018A42, RVC019A43 and RVC021A44 were used. Lot numbers DD05A003A, DD05A003B and DD05A003C were used for the calcium carbonate buffer and RVC020A41PL was used for placebo.

2.4. Assessment of efficacy

The surveillance for gastroenteritis episodes started from the first dose of RIX4414 vaccine/placebo and continued until the children were three years of age. A gastroenteritis episode was defined as the occurrence of diarrhea [three or more, looser than normal stools within a day] with or without vomiting. If there was an interval of five or more symptom-free days between the two gastroenteritis episodes, they were considered as two different episodes. Hospital/medical facility surveillance ensured that all gastroenteritis cases requiring hospitalization and/or re-hydration therapy (equivalent to WHO plan B [oral re-hydration therapy for children with some dehydration in a medical facility] or C [intravenous re-hydration for severe dehydration in a medical facility]) [12] were recorded. Study personnel accessed computerized admission databases in the study centers on a daily basis to determine whether any study participants had been admitted to public hospitals. In addition, study personnel contacted families by telephone at least every month to determine any admissions to private hospitals.

For each qualifying episode of gastroenteritis, parents/guardians of infants completed a gastroenteritis diary card every day until

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