

Rotarix™: an example of a recently developed oral vaccine against rotavirus for infants

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Introduction

Rotavirus gastroenteritis (RVGE) is the leading cause of severe diarrhoeal disease in infants and young children between 6-24 months of age world-wide. Prospective epidemiological studies have shown that already 20% of acute rotavirus gastroenteritis occurs during the first 6 months of life.¹ It has recently been estimated that world-wide in children under 5 years of age, 611,000 (range 454,000-705,000) rotavirus-related deaths occur each year, with the majority of these deaths occurring in developing countries - the Asian subcontinent, Africa, and Latin America.² Every year in Africa, rotavirus is estimated to cause 170,000 to 210,000 deaths in children under 5 years of age³ and approximately 145,000 of these deaths occur in sub-Saharan Africa alone.⁴ In other low-income countries such as Bangladesh, rotavirus is estimated to cause 6,000-14,000 deaths each year in children under 5 years of age,⁵ whereas in India, up to a 100,000 deaths are recorded every year.⁶

Re-hydration (orally or intravenously) with salts and electrolytes is a well-known and effective life-saving treatment against dehydrating RVGE. Although extensive education programmes on oral re-hydration have been successfully implemented and are still actively pursued, vaccination is considered as the most effective public health tool to reduce the burden of rotavirus disease. Efforts to develop vaccines have been underway since the 1980s. In low-income countries, an effective vaccine would also substantially reduce childhood mortality rates.

Because rotavirus disease is associated almost exclusively with infection of the epithelium of the small intestine, the most rational approach to vaccine development has been via oral administration of an antigen capable of inducing a virus-specific mucosal immune response. The 'Jennerian' concept of using vaccines based on a heterologous live, attenuated animal strain such as bovine^{7,8} or simian⁷ rotaviruses to protect against human rotavirus disease has been applied since the 1980s. Studies with RV vaccine candidates using monovalent animal RV strains showed however variable protection rates and led to the development of multivalent vaccine candidates with reassortant strains bearing one or more human RV G or P proteins. The first rotavirus vaccine was launched in the United States (USA) - a tetravalent rhesus and human reassortant rotavirus vaccine (*RotaShield*).⁹ Although *RotaShield* was shown to be safe and effective in pre-licensure trials, it was withdrawn from the USA due to an association with an increased risk of intussusception (IS) occurring shortly after vaccination and

particularly following the first dose.¹⁰ The withdrawal of *RotaShield* led also to discontinuation of trials in developing countries (Africa, Bangladesh) and meant that rotavirus disease remained a world-wide burden.

This temporal relationship of a rotavirus vaccine with a rare event such as IS has dramatically impacted on the development of second-generation rotavirus vaccines, especially with respect to the demonstration of safety.

RotaShield is a trade mark of Wyeth Lederle Laboratories.

GlaxoSmithKline Biologicals' rotavirus vaccine

GlaxoSmithKline Biologicals' rotavirus vaccine *Rotarix* contains a live attenuated human G1P[8] rotavirus strain, RIX4414, derived from the 89-12 parent strain through passaging and cloning. The 89-12 strain was isolated in 1988 from a child during an epidemic in Cincinnati, USA. It was chosen as a vaccine candidate since natural infection with this virus provided excellent protection against subsequent rotavirus disease.¹¹ Several small size clinical studies demonstrated that two doses of 89-12 administered with a two-month interval were immunogenic and efficacious with mild reactogenicity.¹²⁻¹⁴

RIX4414 has been evaluated in phase I, II, and III clinical trials enrolling more than 100,000 infants in Europe, Africa, Asia, Latin America, and the USA.¹⁵⁻²³ Clinical trials addressing questions of specific interest for developing countries were initiated in South Africa and Bangladesh under the RAPID (Rotavirus Action Partnership for Immunization and Development) programme (*) and the Rotavirus Vaccine Program (RVP) at the Program for Appropriate Technology in Health (PATH) in Seattle, WA, USA and GlaxoSmithKline Biologicals.²⁰⁻²² During the phase II studies,¹⁵⁻²² the tolerability and immunogenicity of different viral concentrations (range from 10⁴ to 10⁶ foci-forming units (ffu)), different ages at first dose, different intervals between doses of RIX4414, and the absence of interference with routine childhood vaccines including oral polio vaccine (OPV) were evaluated. The vaccine was well tolerated at all studied viral concentrations and dosing schedules, with a reactogenicity profile similar to that of the placebo in terms of the incidence of fever, diarrhoea, vomiting, loss of appetite, cough/runny nose, and irritability on the day of vaccination and for seven to 14 subsequent days. In terms of safety, a large phase III clinical trial conducted with 63,225 infants in 11 countries in Latin America and Finland demonstrated that the administration of two doses of RIX4414 was not associated with an increased risk of IS.²³

In all studies, the immunogenicity of the vaccine was measured as a seroconversion rate of anti-rotavirus IgA antibody, defined as the percentage of subjects with anti-rotavirus IgA antibody concentrations ≥ 20 U/ml in post-

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vaccination sera (for subjects seronegative before vaccination). The anti-rotavirus IgA antibody seroconversion rates ranged from 45% to 96% with the higher end observed in studies conducted in Finland,^{15,16} USA¹⁸ and Singapore,¹⁹ and the lower end in the studies conducted in Latin America,¹⁷ South Africa,^{20,21} and Bangladesh.²²

It is not straightforward to explain the observed variance in seroconversion rates. The higher levels of maternal antibodies, as expected in countries with more frequent exposures of the mothers to wild type circulating rotaviruses,²⁰ might have an inhibitory influence on the vaccine take. Breast milk has also been named to have a natural protective effect against RV disease in very young infants and could therefore, in the countries where breastfeeding is customary, explain some of this variability. Other factors such as malnutrition, genetic differences, and the pressure on the immune system of other circulating infectious pathogens will also contribute to the variability.

Absence of interference of RIX4414 on OPV seroprotection rates was demonstrated²⁰ and antibody responses against other co-administered routine vaccines used in the different countries were similar in groups receiving RIX4414 and placebo.^{18,24-26}

As no correlate of protection exists for this type of vaccine, the clinical protection was studied in phase II and phase III studies. In all trials, administration of two doses of the human-based RV vaccine was efficacious. In two pilot efficacy studies conducted in Finland¹⁶ and Latin America¹⁷ the vaccine showed excellent clinical protection against severe rotavirus gastroenteritis (90% (95%CI: 10-100)¹⁶; 86% (95%CI: 63-96)¹⁷). Efficacy of RIX4414 vaccine was well maintained with vaccine efficacy 85% (95%CI: 42-97)¹⁶ over two consecutive rotavirus seasons. In the large phase III study conducted in Latin America,²³ a cohort of 15,183 infants was followed until their second birthday (24 months). The main outcome measure was the protection achieved by the vaccine against severe RVGE and RV hospitalisation defined as diarrhoeal RV episodes requiring hospitalisation and/or re-hydration (WHO treatment B or C). For the first efficacy period of follow-up (mean duration: seven months), efficacy against severe RVGE and RV-associated hospitalisation was 85% (95% CI: 72-92). Protection against severe RVGE caused by G1P[8] and pooled non-G1 RV types was demonstrated to be significant. Interestingly, during this period, hospitalisation for any cause of gastroenteritis was reduced by 40% (95% CI: 28-50). Protection was maintained for a mean duration of 20 months with a vaccine efficacy against severe RVGE during the combined efficacy period of 80.5% (95% CI: 71.3-87.1).²⁷

Finally, a European phase III study was conducted in 3,994 infants in several countries to determine efficacy, immunogenicity, and safety of *Rotarix*TM when co-administered with routine childhood vaccines. Overall protective efficacy was strong, with rates of 87% (95% CI: 80-92) against any RVGE, 96% (95% CI: 90-99) against severe RVGE²⁸ and 100% against RV hospitalisations during the first follow-up period (RV season following vaccination) and well sustained during the second follow-up period.²⁹ Significant and sustained protection during two consecutive rotavirus seasons was demonstrated against severe RVGE

caused by different circulating rotavirus serotypes such as G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8].³⁰ Protective efficacy of 90% (95% CI: 9-100) was already observed after the first dose up to before the second dose of vaccine.³¹ In this study, the immune responses related to co-administered vaccines (*Infanrixhexa*TM, *Infanrixquinta*TM, *Prevenar*TM or *Meningitec*TM) were not impaired.²⁴⁻²⁶

Rotarix, *Infanrixhexa* and *Infanrixquinta* are trademarks of the GlaxoSmithKline group of companies. *Prevenar* and *Meningitec* are trademarks of Wyeth Pharmaceuticals.

Conclusion

Rotarix (RIX4414), a live attenuated human rotavirus vaccine administered in two oral doses has been proven to be highly effective and well-tolerated in infants in different socio-economic and geographic settings where multiple RV types circulate. Demonstrated significant reduction in severe RVGE and hospitalisation will be of major public health impact in developed and developing countries. One might even expect a lowering effect on childhood mortality rates. This newly developed two-dose RV vaccine protects children early in life (before the peak of the disease) and can be easily co-administered with all other recommended childhood vaccines and integrated in existing EPI schedules. Clinical studies are still ongoing addressing specific questions such as HIV-infected infants, efficacy in some specific populations, e.g. premature infants, infants in day-care centres, Asian and African infants, etc, and will generate even more data in the near future.

Rotarix has now been licensed in more than 100 countries across the world and is available for use in most of them. It is the only RV vaccine with a WHO pre-qualification label allowing UN agencies and others to make large purchases for use in mass vaccination campaigns. Sustained efforts at many levels (health authorities and recommendation bodies) are still of utmost importance to bring this vaccine to the populations where it is most needed and make it available to all infants.

*The RAPID partnership consists of public sector partners (including the World Health Organization, US Agency for International Development, National Institutes of Health, Children's Vaccine Program, and the Centers for Disease Control), academic institutions (International Centre for Diarrhoeal Disease Research, Bangladesh and Medical University of Southern Africa), and GlaxoSmithKline Biologicals.

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