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Review Article

Clinical development, registration, and introduction of human rotavirus vaccine: The Latin American experience

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ABSTRACT

Rotavirus (RV) is the leading cause of severe gastroenteritis (GE) among infants and young children worldwide, accounting for 453,000 deaths in children aged <5 years. In Latin America rotavirus causes an estimated 15,000 deaths annually and accounts for 20–70% of acute gastroenteritis cases requiring hospitalization. This results in an estimated annual cost of approximately US$86 million. The most common G type has been G1 (~50%), followed by G4, G3 and G9, although regional and temporal variations are significant. There are currently two effective rotavirus vaccines: a single-strain, human attenuated-based (*Rotarix*™, GlaxoSmithKline Biologicals), and a five-strain, bovine-human reassortant vaccine (*RotaTeq*™, Merck and Company). The pioneering strategy behind the development and licensure of *Rotarix*™ was part of a new paradigm for global vaccine research and development focusing on introduction first in countries with greatest medical needs. *Rotarix*™ demonstrated high efficacy and a good safety profile in Phase II and III clinical trials performed in Latin America. In the pivotal phase III study involving 11 Latin American countries a 2-year efficacy of 81% (95% CI: 71–87) was achieved against severe rotavirus acute gastroenteritis. A high protective efficacy was observed against severe rotavirus gastroenteritis caused by G1 and non-G1 strains. *Rotarix*™ proved to be safe regarding intussusception (IS) in a two-dose vaccine schedule beginning at 6–12 weeks of age.

First registered in Mexico in July 2004, *Rotarix*™ gained World Health Organization (WHO) prequalification in February 2007 and has been introduced for routine use into the universal mass vaccination programs of Brazil, Panama, Mexico, Venezuela, Ecuador, Guatemala, Honduras, Colombia, Paraguay, Bolivia, Peru, and El Salvador. The main factors influencing the decision-making process of introducing rotavirus vaccines in Latin American countries included: (a) demonstration of good efficacy/safety profiles; (b) political decision to decrease mortality; (c) decision from ministries of health; (d) availability of data on the disease burden; (e) cold chain available; and, importantly (f) the use of PAHO's Revolving Fund for the purchase of vaccines. Post-licensure studies have shown 76% (95% CI: 64–84%) effectiveness in El Salvadoran children and 76% (95% CI: 58–86%) to 85% (95% CI: 53–94%) in Brazil. Observational studies in Panama, Mexico, El Salvador and Brazil reported reduction in all-cause diarrhea-related hospitalizations at rates of 22–37%, 11–40%, 35–48%, and 17–48%, respectively. The decline in diarrhea-associated deaths reached 35% (95% CI: 29–39%) in Mexico and ranged from 22% (95% CI: 6–45%) to 33% (95% CI: 15–52%) among Brazilian children. A low, increased risk of intussusception was detected among Mexican

Abbreviations: WHO, World Health Organization; GAVI, Global Alliance for Vaccines and Immunization; DALY, disability adjusted life-years; GDP, gross domestic product; PAHO, Pan American Health Organization; RVGE, rotavirus gastroenteritis; PATH, The Program for Appropriates Technologies in Health; CDC, US Centers for Disease Control and Prevention; CVP, The Children Vaccine Program of the Bill and Melinda Gates Foundation; SVI, Sabin Vaccine Institute; NIH, National Institutes of Health; USIAD, US Agency for International Development.

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infants within 7 days after first vaccine dose [odds ratio, 5.8 (95% CI: 2.6–13)]. Continuous and expanding post-licensure rotavirus surveillance studies are needed to better assess the effect of universal vaccination in Latin American countries and elsewhere.

Contents

1. Introduction

On a global scale rotavirus (RV) is the most important cause of severe gastroenteritis (GE) among children, accounting for one-third of all diarrheal hospitalizations and nearly half a million deaths annually [1–3]. It is estimated that RV causes about 15,000 deaths, 75,000 hospitalizations, and 2 million outpatient visits per year in Latin America and the Caribbean [4–5]. A great diversity in serotype-composition over time of co-circulating RV strains has been reported worldwide, with strains bearing G1-type specificity being dominant in Latin America at the time pivotal clinical trials with RV vaccines were performed [6,7].

Vaccination is considered the most effective public health strategy to prevent RV disease and reduce the global burden of RVGE [8]. The first commercialized RV vaccine, *RotaShield*™, was licensed in the United States in 1998 and recommended by the Advisory Committee on Immunization Practices (ACIP) for routine immunization of infants. However, this vaccine was withdrawn from the market before its first year, based on evidence of an association with intussusception (IS), an uncommon adverse event [9,10]. This event resulted in several international initiatives designed to expedite the development and introduction of new RV vaccines, particularly in those countries with greatest medical needs. Almost one decade after the withdrawal of *RotaShield*™ two live-attenuated oral rotavirus vaccines were licensed in 2006 and made available commercially: a single-strain vaccine composed of an attenuated human G1P[8] strain (*Rotarix*™; GlaxoSmithKline Biologicals) and a five-strain human-bovine (G1, G2, G3, G4 and P[8] strains) reassortant vaccine (*RotaTeq*™; Merck and Company). *RotaTeq*™ and *Rotarix*™ were tested in more than 70,000 infants each before licensure, proving to be safe and highly efficacious (>85%) against severe rotavirus gastroenteritis [11]. Results were made available recently from phase III trials completed in Africa and Asia [12–15], where an overall lower – though significant – protective efficacy was achieved when compared to pivotal clinical studies conducted in Latin America, Europe and the USA. In October 2009 the availability of these additional data from Africa and Asia led WHO to recommend that rotavirus vaccines should be included into all countries' Expanded Program of Immunization (EPI) worldwide, especially in those with high diarrhea-associated mortality [16].

Several recent, post-licensure studies have been conducted in Latin American countries to assess vaccine effectiveness against severe RVGE and the vaccine impact on childhood morbidity and mortality [15,17–20]. Overall, vaccine effectiveness against hospitalization for severe RVGE surpassed 75%. In addition, a significant reduction was seen in hospitalizations for all-cause diarrhea among children in Panama, Mexico and Brazil [15,17]. Recent investigations in Mexico and Brazil have also demonstrated that the vaccine has had a major impact on diarrhea-related deaths [18–20]. Although the large phase III trial with *Rotarix*™ in Latin America convincingly demonstrated a lack of association between the vaccine and intussusception at the level observed for *RotaShield*™, post-licensure case-series and case-control studies in Mexico and Brazil indicate a low increased risk of developing intussusception (IS) in the 7-day window after vaccination [15].

A number of analyses on the economic impact of rotavirus vaccination in Latin American countries have shown a favorable cost-effectiveness ratio with an important impact of vaccine cost in the models [11]. The role of PAHO's Revolving Fund, the GAVI Alliance and vaccine manufacturers has been crucial in this context; and as a consequence, there are currently 12 Latin American countries that have introduced *Rotarix*™ into their National Immunization Programs [5]. Of these 10 use the revolving fund, two purchase the vaccine through direct government-industry negotiation and three receive GAVI support.

This paper reviews the novel pioneering strategy underlying the development of the human RV vaccine *Rotarix*™ (GlaxoSmithKline [GSK] Biologicals, Rixensart, Belgium), with particular focus on its clinical development, licensure, introduction, and early post-licensure impact in Latin America.

2. A new paradigm for vaccine development

In light of the urgent need to accelerate the development of new RV vaccines, the World Health Organization (WHO) and Global