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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

Table 1
Recommendations from the WHO-GAVI meeting in Geneva, February 2000.

1. The group strongly encouraged the rapid development of new RV vaccine candidates. Trials of new RV vaccines must assess the potential risk of IS with the use of the vaccine. Parallel testing of new RV vaccine candidates in developed and developing countries was also recommended.
2. Further studies with *RotaShield*™ were considered ethical, given the higher disease burden and potential higher benefit/risk ratio in a developing country. However, further testing must not occur without the assurance that the vaccine will be available for general use should trial results prove positive.
3. The need to conduct disease burden studies in selected developing countries was emphasized.
4. The group also encouraged research activities on the pathogenesis and epidemiology of IS and baseline incidence studies in countries interested in testing new RV vaccines.
5. WHO to provide continuing support to the national regulatory authorities of developing countries to reach international standards for vaccine regulation.
6. Laboratory surveillance of RV strains should be continued.

Note: RV, rotavirus; IS, intussusceptions.

Alliance for Vaccines and Immunization (GAVI) organized a meeting in Geneva in February 2000 with the participation of international agencies, ministries of health, scientists, and personnel from the pharmaceutical industry. The aim was to develop strategic recommendations to create appropriate conditions for the prompt clinical development, licensure and introduction of new RV vaccines into those countries with greatest medical need [21]. Surveillance of RV disease burden, strain distribution and background incidence of IS were considered essential to establish the need for vaccination and risk-benefit assessment (Table 1). Other recommendations included parallel testing of candidate RV vaccines in developed and developing countries given the differences in RV epidemiology between these settings, the development of standard licensure requirements for national regulatory authorities and the need for rigorous post-marketing surveillance for vaccine-related adverse events. This represented a new paradigm for vaccine development and required a large-scale, coordinated collaborative research approach involving public and private health institutions, international agencies and pharmaceutical companies willing to conduct the necessary studies with associated costs and risks.

Four RV vaccine candidates were available at the time of the WHO-GAVI meeting: a human neonate G3P[6] candidate (Ruth Bishop, Australia), a LLR lamb G10P[12] candidate (Lanzhou Institute of Biomedical Products, China), a five-strain human-bovine (WC3) reassortant RV candidate (*RotaTeq*™; Merck Research Laboratories, USA) and a single-strain human attenuated G1P[8] RV candidate (*Rotarix*™, GSK). Both Merck and GSK accepted the challenge, but with different scientific and commercial approaches. Based on clinical trial conduct, Merck focused its strategy predominantly towards industrialized countries, such as the United States and Europe, although vaccine safety was assessed in a number of Latin American countries (Costa Rica, Guatemala, Jamaica and Mexico, for a total of 5300 children) in one large Phase III study [22]. GSK implemented a more diverse clinical development program and proposed a strategy aiming to introduce a safe and efficacious RV vaccine first to those countries with greatest disease burden and medical need. Latin America was targeted based on the good quality of previous research, including efficacy of former RV vaccines in this region and regional epidemiological data on the burden of RV, coupled with the existence of the necessary infrastructure to conduct clinical trials. The result was the construction of one of the largest, multicenter, academic-industry research teams—the Human Rotavirus Vaccine Study Group. Over a period of 5 years, more than 10 Phase II and III clinical trials and health economic studies were undertaken in 12 low- and middle-income Latin American countries involving approximately 73,650 children.

3. Burden of rotavirus disease

Studies of the burden of RV infection in Latin American children date back to the late 1970s and early 1980s [23–31]. RV has long been recognized to be a leading cause of acute childhood GE in the region, accounting for 20–70% of GE cases depending on the study endpoints (age group, diagnostic techniques used, outpatient or inpatient setting). While diarrhea-associated deaths have fallen significantly in Latin America over the past 15 years due to improved sanitation and appropriate use of oral rehydration [32], studies within the first 2000 decade confirmed that RV infection continued to impose a high burden of disease in this region [33–37]. Cumulative estimates of RV-associated mortality risk in Latin American children under 5 years were <1:1600 in Argentina and Chile, 1:400–1:1800 in Colombia, Venezuela, Brazil and most of Central America, and 1:100–1:400 in Peru, Bolivia and low-income Central American countries [33–37]. Altogether these studies highlighted the rotavirus disease impact in the region and were of importance at the time of decision-making process for vaccine introduction in Latin American countries. Recent prospective studies suggest that RV causes 30–40% of diarrhea-associated emergency room visits and 40–70% of hospitalizations among children 36 months or younger in Argentina, Chile and Venezuela [38]. Similar hospitalization rates have been reported in Brazil (48%) and Colombia (50%) [39,40]. In Chile and Venezuela, approximately one in 70 children will be hospitalized and one in 20–30 will visit the clinic for RV disease by the age of 5 years [41–43]. In Argentina, one in six children born in 1995 visited a public hospital and one in 35 required hospitalization as a result of RV diarrhea before their third year of life [34]. Similar hospitalization rates (one in 27) were reported in another study in Cordoba, Argentina [44]. A multicenter study conducted in 11 countries of this region by the Human Rotavirus Vaccine Study Group before the initiation of the Phase III clinical trial reported 49% rotavirus positivity among children hospitalized with severe GE during the observation period, with almost all cases of severe RVGE occurring in children <24 months of age [7]. In a recent meta-analysis including 11 observational studies of RV in Latin America and the Caribbean, the proportion of gastroenteritis cases due to RV was 24.3% and the incidence of RVGE was 170 per 1000 children-years in the age group under 5 years [45].

4. Circulating rotavirus strains

Studies on RV serotype circulation in Latin America during the last 20 years showed similar patterns to those observed in other parts of the world [6,46]. In preparation for the large Phase III safety and efficacy trial of the human RV vaccine, a prospective, hospital-based surveillance study was undertaken in 75 centers in 11 Latin American countries [7]. At the time of this study, G1 was the most common strain overall (51%), followed by G4 and G3, with G9 emerging as an important serotype in Brazil and Mexico. Interestingly, very different serotype patterns were observed between countries during the same season [7]. It has been suggested that some strains, such as G9 serotype, may cause more severe disease [47]; however, this has not been supported by other studies [48]. As observed in other regions [6,48–52], the distribution of RV serotypes in Latin America fluctuated over time with particular serotypes temporarily predominating during given seasons in individual countries, e.g. G4P[8] in 1998–2000 followed by G9P[8] during 2002–2005 in Paraguay [53,54], G1P[8] in Colombia, Uruguay, Brazil and Argentina [55–58], G9P[8] in Ecuador [59],

G2P[4] in Mendoza and Buenos Aires, Argentina in the late 1990s [60,61], and G3P[8] in Mexico City during the late 1980s [48].

Uncommon RV serotypes infecting children in the region had been occasionally reported. These included G types 12, 10, 8 and 5 and P types [1], [6] or [9], mostly as isolated cases [6,46,58,60,62–64]. It was suggested that a mutated G4 strain may have been responsible for a large outbreak of RVGE in Nicaragua in 2005 [65].

An extensive meta-analysis study of circulating serotypes before introduction of rotavirus in Latin America and the Caribbean concluded that G1P[8], G2P[4] and G9P[8] were the most prevalent P-G combinations, accounting for17.9%, 9.1% and 8.8% of isolates, respectively [45].

5. Intussusception in pre-licensure surveillance studies

In light of the experience with *Rotashield*™, knowledge on IS epidemiology and background incidence was considered critical before mass vaccine use. Studies were then generated in an important number of Latin American countries. IS incidence rates were 51 per 100,000 infant population in Chile [66], 30 per 100,000 infant population in Panama [67] and 47 per 100,000 live births in Venezuela [68]. A retrospective study conducted in Venezuela reported an annual hospitalization rate for IS of 35 per 100,000 in infants under 1 year [69]. Prior to the Phase III trial of the human RV vaccine in Latin America, a large IS surveillance study was conducted in 11 countries in the region [70]. The incidence of IS in infants under 1 year was found to range from 3.8 per 100,000 population in Brazil to 105.3 per 100,000 population in Argentina, with a mean incidence of 51 per 100,000. This wide range of incidence rates seems to be in line with global observations that the incidence of IS varies over time and between regions, even within individual countries [71]. Demographic and clinical characteristics of IS cases were as expected from previous studies. Most IS (89%) occurred during the first year of life, with peak incidence between 4 and 8 months of age and a predominance in boys of (male: female ratio, 1.3:1). Careful surveillance has not revealed any increased risk of IS in large phase III studies of new vaccines to date [22,72].

6. Health economic studies of rotavirus burden

Extensive health economic evaluation was performed in the region during the period of decision making processes occurring within the continent. Researchers from Latin American and Emory University, supported by GSK, conducted studies to evaluate the cost and health burden of RV disease and the cost-effectiveness value of RV vaccination compared to the existing situation in eight countries from the region (Argentina, Brazil, Chile, Dominican Republic, Honduras, Mexico, Panama and Venezuela) [73–79]. All studies highlighted the significant RV disease burden on Latin American healthcare systems resulting in an average of 246 outpatient visits, 24 hospitalizations and 0.6 deaths for every 1000 live births during the first 5 years of life and a total annual cost (medical plus direct and indirect non-medical costs) of approximately US$86 million. As might have been expected, health burden (measured in disability-adjusted life-years [DALYs]) was generally highest in lower-income countries and greatest cost burden (cost per child) occurred in higher-income countries [76]. It was concluded that a RV vaccination program in Latin America would reduce both disease burden (deaths averted: 50–75%) and healthcare costs (51–75%) [80]. According to the criterion established by the WHO [80], RV vaccination was considered a very cost-effective health intervention in six countries and cost-effective in all countries, even in Honduras which had a very low income (gross domestic product [GDP] per capita: US$1001) [75]. Local cost-effectiveness results were important for GAVI and other organizations in their role of financial assistance for universal use of RV vaccine in the poorest countries. Of particular importance in this context was the PAHO's Revolving Fund for Vaccine Procurement which operates through a system of bulk purchasing; since 2007 the Fund has secured the supply of rotavirus vaccines, at affordable prices, for the national immunization programs of countries in the Americas. Of note, during the Sixth International Symposium on Rotavirus and Rotavirus Vaccines, held in Mexico in July 2004, representatives of the Ministries of Health of Latin America launched the Mexico City Declaration to put forward a call to action that would facilitate introduction of rotavirus vaccines in the Americas region [81]. This would include a concerted effort including PAHO and its Revolving Fund for Vaccine Procurement, the GAVI and vaccine manufactures.

7. Clinical studies of the human rotavirus vaccine

The vast rotavirus vaccine research experience in Latin America dates back to the late nineties with the simian–human quadrivalent reassortant strain that resulted in the licensure of *RotaShield*™ in the United States of America (USA) in 1998 [82]. One of the pivotal trials was conducted in Venezuela with an efficacy of 88% efficacy against severe rotavirus gastroenteritis during the first year of life. Unfortunately, however, the use of *RotaShield*™ was short-lived since it was withdrawn within 1 year of its introduction owing to an association with intussusception [9,10]. The conduct of such early, large catchment vaccine trials in Latin America was instrumental for the implementation of further strategies to evaluate the new generation vaccines, mostly *Rotarix*™, albeit also with *RotaTeq*™. The decision of launching these new studies in Latin America was taken mainly in light of a recommendation made during a meeting in Geneva in 2000, organized by WHO and GAVI, which denoted a new paradigm for vaccine development: trials were to be conducted in parallel in industrialized and developing countries [21].

A fundamental clinical study providing evidence for natural protection, key for vaccine development, was performed in Mexico [83]. This study demonstrated that in Mexican children two natural infections conferred 100% protection against a subsequent symptomatic rotavirus infection and that repeated asymptomatic infections were common. Protection against symptomatic rotavirus infections became the main target and outcome variable for future vaccine studies. The efficacy and safety of the human RV vaccine *Rotarix*™ was extensively evaluated in large randomized, Phase II and III placebo-controlled trials involving more than 73,650 children in Latin America and Europe [84]. Results of a randomized, double-blind, placebo-controlled Phase II study in three Latin American countries (Brazil, Mexico and Venezuela) revealed *Rotarix*™ to be safe, immunogenic and effective for the prevention of severe GE in healthy infants [85]. Two oral doses of the vaccine ($10^{4.7}$, $10^{5.2}$ or $10^{5.8}$ focus-forming units [ffu]) or placebo were administered at 2 and 4 months of age concomitantly with other routine infant immunizations (oral poliovirus vaccine given at least 14 days apart). A total of 2155 infants (1618 vaccines and 537 placebo recipients) were followed up to 1 year of age. Protective efficacy against severe and any RVGE from 15 days post-dose 2 was higher in the $10^{5.8}$ ffu group (86% and 70%, respectively) than in the other two vaccine groups. The vaccine was found to be well tolerated, with rates of adverse events similar to placebo. A post hoc analysis from this study to evaluate vaccine efficacy (VE) in mild to moderate malnourished children showed two doses of the human RV vaccine to confer high protection against severe RVGE equally to both malnourished and normal weight infants [86].

Table 2
Protective efficacy of *Rotarix*™ in Latin American infants during the first 2 years of life from 2 weeks post-dose 2 (mean duration of follow-up, 20 months) [87].

Type of GE	*Rotarix*™ (N^a = 7205)		Placebo (N^a = 7081)		Vaccine efficacy	
	N^b	%[b]	n^b	%[b]	%[b]	95% CI[c]
RVGE						
Severe	32	0.4	161	2.3	80.5	71.3, 87.1
Hospitalization	22	0.3	127	1.8	83.0	73.1, 89.7
Severe RVGE according to typed						
G1 wild-type	10	0.1	55	0.8	82.1	64.6, 91.9
Pooled non-G1 (G2, G3, G4, G9)	24	0.3	105	1.5	77.5	64.7, 86.2
GE due to any cause						
Severe	342	4.7	551	7.8	39.0	30.1, 46.9
Hospitalization	265	3.7	429	6.1	39.3	29.1, 48.1

[a] Number of subjects included in each group.
[b] Number/percentage of subjects reporting at least one specified episode in each group.
[c] 95% confidence interval.
[d] Subjects appear in more than one category if more than one G-type was identified in the stool sample.

The safety and efficacy of *Rotarix*™ were further evaluated in a large-scale, randomized, double-blind, Phase III trial involving a total of 63,225 healthy infants from 11 Latin American countries and Finland. Subjects received two oral doses of the vaccine (n = 31,673) or placebo (n = 31,552) at approximately 2 and 4 months of age [72]. Severe GE episodes were identified by active surveillance. VE was evaluated in a subgroup of 20,169 infants (10,159 vaccines and 10,010 placebo recipients). *Rotarix*™ was found to provide high protection against severe RVGE as well as significantly reducing the rate of severe GE from any cause, and was not associated with an increased risk of IS. VE against severe RVGE and RV-associated hospitalization during the first year of life was 85% ($p < 0.001$) and reached 100% against more severe RVGE. Hospitalization for diarrhea of any cause was reduced by 42% (95% CI: 29–53%; $p < 0.001$). During the 31 days after each dose, six vaccine recipients and seven placebo recipients had definite IS (difference in risk, −0.32 per 10,000 infants; 95% CI: −2.91–2.18; $p = 0.78$).

A subset of 15,183 Latin American infants participating in this trial (7669 vaccines and 7514 placebo recipients) were followed for severe GE of any cause and safety from dose 1 up to 2 years of age [87]. Efficacy follow-up for GE episodes was undertaken from 2 weeks post-dose 2 (2-years efficacy follow-up period; mean duration, 20 months). VE against severe RVGE was 80.5% (95% CI: 71.3–87.1) (Table 2). Significant protection was demonstrated individually for G1, G3, G4 and G9 types, as well as against pooled non-G1 strains (G2, G3, G4 and G9), with a trend for protection against G2P[4] strains. VE for hospitalization due to RVGE reached 83.0% (73.1–89.7) and for GE due to any cause was 39.3% (29.1–48.1). No cases of IS were reported during the second year of follow-up.

In a recent double-blind, placebo-controlled study conducted across six Latin American countries, two doses of *Rotarix*™ proved to be highly efficacious [82% (95% CI: 54–94%)] against severe RVGE by 12 months of age, when co-administered with routine EPI vaccines, including OPV [88].

Based on these findings, it was concluded that two oral doses of human RV vaccine are safe in Latin American infants and provide sustained high protection against severe RVGE due to G1 and non-G1 strains and related hospitalizations during the first 2 years of life, when the disease burden is the highest.

8. Country-specific rotavirus vaccine introduction initiatives

One of the first recommendations from WHO was that RV vaccination should be included into the National Immunisation Programs of regions where vaccine efficacy data have suggested a significant public health impact and where appropriate infrastructure and financing mechanisms are available [82]. Subsequently, when the efficacy of rotavirus vaccines became evident in Asian and African countries, WHO recommended that all infants worldwide should be vaccinated against rotavirus, particularly in those regions where mortality rates in children <5 years of age are ⩾10% [89]. This recommendation was regarded as crucial in the acceleration towards achievement of the fourth Millennium Development Goal 4 of a two-thirds reduction in the mortality rate among children aged <5 years. *Rotarix*™ is currently licensed for vaccination of infants in 123 countries in the Americas, Europe, Australia, Africa and Asia, of which 27 have incorporated the vaccine into their national or regional immunization programs. As of September 2011, 12 Latin American countries have introduced *Rotarix*™ into their national expanded program on immunization (EPI), including: Brazil (in 2006), Ecuador (2007), El Salvador (2006), Mexico (2007), Panama (2006), Peru (2009), Colombia (2009), Guatemala (2009), Honduras (2009), Bolivia (2008), Paraguay (2010), and Venezuela (2006) (Fig. 1, Table 3). Just following completion of large phase III trials conducted in Latin America, *Rotarix*™ was first licensed in Mexico during July 2004, where the creation of a Special Vaccine Expert Committee led to mass introduction of the vaccine in two steps: initial implementation in only 14 of the 32 states (those with the highest rates of diarrhea deaths), followed by nationwide use starting in March 2007. The fact that Latin American countries were the first in the developing world to introduce rotavirus vaccination into their national immunization programs provided these countries with several lessons that have covered technical, operational, financial and political issues [4,5]. The human RV vaccine was only, after polio, the second oral vaccine introduced into the universal mass vaccination programs of the region, requiring several programmatic adjustments, including the implementation of surveillance programs for vaccine safety, rotavirus strains circulation and impact evaluation. This has served as a model for several countries worldwide which have recently introduced universal rotavirus vaccination or are in the process of adopting rotavirus vaccines in their national immunization programs. Following the GAVI Alliance's inclusion of RV vaccines to the list of interventions available for eligible countries in Latin America and its utilization by PAHO's Revolving Fund, broader implementation of RV vaccination in the region took place [90]. Of the 12 Latin American countries that have adopted universal mass vaccination with *Rotarix*™ in their public sector, 10 are currently utilizing the PAHO's Revolving Fund in the process of purchasing the vaccine at the lowest price in the market. It should be pointed out in this context that GAVI approval of applications from Bolivia, Guyana (*RotaTeq*™ in use) and Honduras, led to

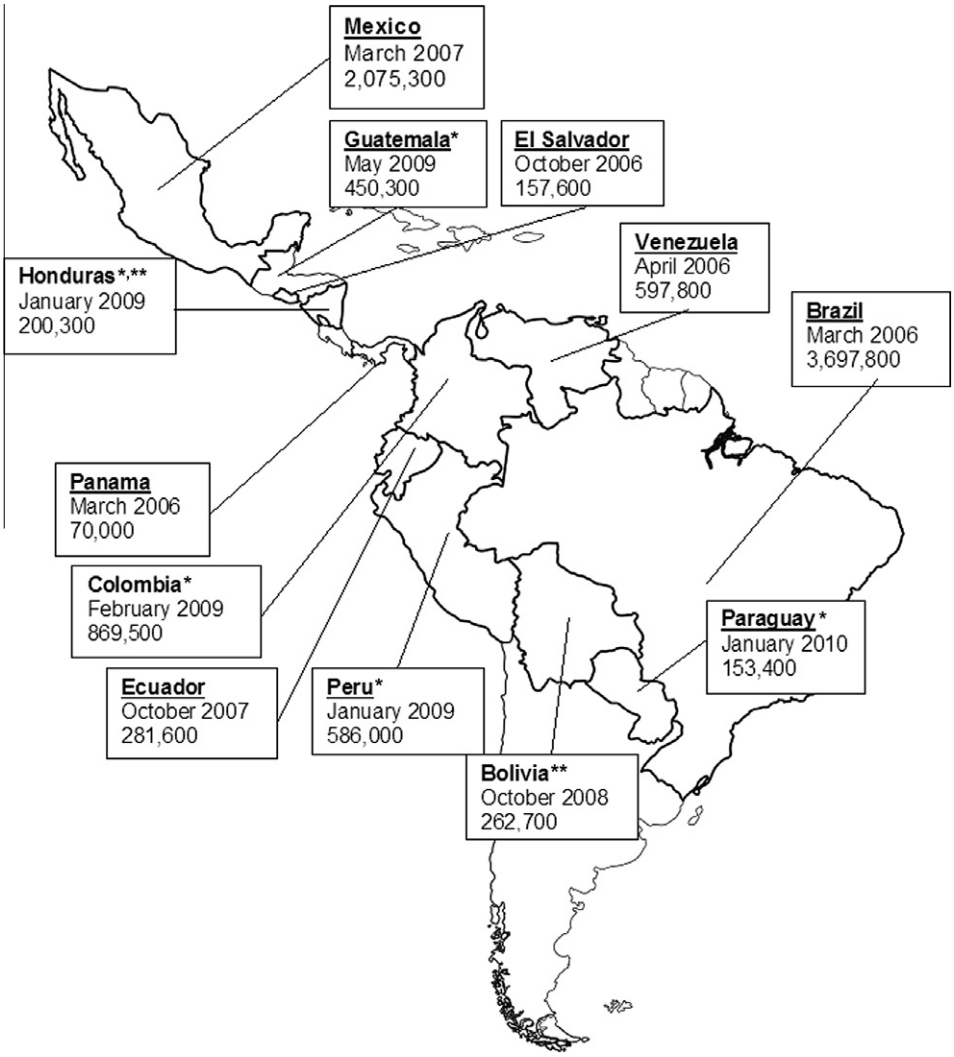

Fig. 1. Latin American countries that have incorporated *Rotarix*™ into their expanded program on immunization (September 2011) (dates of introduction and birth cohorts). *More recent data available from health authorities from each country and Pan American Health Organization. **Support provided by GAVI.

introduction of RV vaccine in these countries occurring as from 2008 [90]. Early after starting the implementation of rotavirus vaccines into the national immunization programs, it was estimated that about 77% of the 2007 birth cohort in Latin America was eligible to receive *Rotarix*™ free of costs, for a total of more than 18 million doses administered.

Brazil is also one of the few countries in Latin America that developed the capacity to produce the human RV vaccine. In this regard, an agreement was signed in January 2008 between GSK and the Brazilian Ministry of Health, aiming at full local manufacture of the vaccine at Fundação Oswaldo Cruz, Rio de Janeiro, within 4–5 years. The development of a full manufacturing capacity is currently in a relatively advanced stage [Akira Homma, personal communication].

9. Post-licensure studies with *Rotarix*™

The need for conducting vaccine-effectiveness evaluations under "real conditions" gained high priority with the progressive introduction of *Rotarix*™ into the national immunization programs of several countries across Latin America [91]. To date three case-control studies to assess vaccine effectiveness have been performed in Latin America: one in El Salvador (a lower-middle income country, according to the World Bank), and two in Brazil (an upper-middle income country) (Table 3) [15,92–94]. In El Salvador two doses of *Rotarix*™ were highly effective [76% (95% CI: 64–84%)] against hospitalizations for rotavirus gastroenteritis, as compared to the healthy controls [92]. In Recife, North-eastern Brazil, vaccine effectiveness rates were both of 77% using RV negative controls (95% CI: 42–91%) and children with ARI [93]. In a large case-control study conducted in Belém, Northern Brazil, vaccine effectiveness rates were as high as 78% (95% CI: 58–86%) using neighborhood [94]. In a recent case-control study to assess vaccine field effectiveness in Mexico, *Rotarix*™ was shown to provide 94% (95% CI: 16–100%)] against hospitalization caused the unusual, fully heterotypic G9P[4] RV strain [95].

To date, population-based time-trends of all-cause/RV gastroenteritis burden reductions after implementation of *Rotarix*™ were assessed in Panama, Mexico, El Salvador and Brazil (Table 3) [18,96–99]. There were four studies conducted in upper middle income countries (Panama, Mexico and Brazil) that reported a 17–40% reduction in all-cause gastroenteritis hospitalizations in children aged <5 years [18,96–99]. In El Salvador (a lower middle income country), reduction rates of 69–81% were reported in hospitalizations for RVGE [98]. Results from an active surveillance in one sentinel hospital in São Paulo, Brazil, have also demonstrated a 42% decline in hospitalizations for RV-related GE from 2004 to 2008 [100].

Table 3
Rotarix™ introduction into the expanded program on immunization in Latin America, vaccine effectiveness and impact on morbidity and mortality.

Country, income level[c]	Date of introduction into the EPI	Decision-making process used by EPI[a]/MoH[b]	GAVI countries and PAHO collaboration	Vaccine coverage in 2010	Vaccine effectiveness in case-control studies[d] (95% CI) [d]	Health impact of vaccination	
						Outpatient visits and/or hospitalizations for AGE	Mortality for AGE
Bolivia, Lower middle	October 2008	–[e]	Purchase through the use of PAHO's Revolving Fund and support by GAVI	76%	–	–	–
Brazil, Upper middle	March 2006*	Decision from MoH Availability of epidemiological data Cold chain availableLarge G9 outbreak	Purchase of vaccines made directly from the MoH at reduced prices (U$7–8 per dose)	83%	85% (53–94%) using RV-negative GE as controls[93]76% (56–86%) using neighborhood controls [94]	48% reduction in children <1 year of age [99] 17% reduction in children <5 years of age [18] 42% reduction in rotavirus AGE in children <5 years of age [100]	39% and 33% reduction rates in infants and <5 years children, respectively [19] 22% reduction in children <5 years [18]
Colombia, Upper middle	February 2009	–	Purchase through the use of PAHO's Revolving Fund	74%	–	–	–
Ecuador, Lower middle	October 2007	Based on demonstration of good efficacy/safety profiles WHO pre-qualification PAHO funding available	Purchase of vaccines through the use of PAHO's Revolving Fund	97%	–	–	–
El Salvador, Lower middle	October 2006	Significant RV disease burden High mortality rate associated with rotavirus	First vaccine doses purchased directly by MoH and thereafter through the use of PAHO's Revolving Funds	92%	76% (58%–86%) using neighborhood controls [92]	35%–81% reduction in children <5 years [98]	–
Guatemala, Lower middle	May 2009	–	Purchase through the use of PAHO's Revolving Fund	38%	–	–	–
Honduras, Lower middle	January 2009	–	Purchase through the use of PAHO's Revolving Fund and support by GAVI	–	–	–	–
Mexico, Upper middle	March 2007**	High incidence of diarrhea deaths in 14 states Demonstration of good efficacy/safety profilesCost-effectiveness analysis	Purchase of vaccines based on local decision, made directly by the MoH at reduced prices (US$15 per course-2 doses)	90%	–	11–40% reduction in children <5 years [97]	35% reduction in infants [20]
Panama, Upper middle	March 2006***	Decision from MoH within program to improve health in the country	First vaccine doses purchased directly by MoH and,as from 2008, through the use of PAHO's Revolving Fund	89%	–	–	–
Paraguay, Lower middle	January 2010	–	Purchase through the use of PAHO's Revolving Fund	56%	–	–	–
Peru, Upper middle	January 2009	–	Purchase through the use of PAHO's Revolving Fund	75%	–	–	–
Venezuela, Upper middle	April 2006****	Political decision to decrease mortality Availability of funds Local data such as cost-effectiveness analysisStrong recommendation from vaccine investigators	First vaccine doses purchased directly by MoH and thereafter through the use of PAHO's Revolving Funds	49%	–	–	–

AGE, Acute gastroenteritis; A, available.
[], Corresponding reference number.
Other issues related to vaccine introduction in some countries, as follows: *Tech transfer agreement between Fiocruz/MoH and GSK, manufacturing in 4–5 years; **Creation of a Special Vaccine Expert Committee for decision; ***Medical community "positive-pressure" was critical, as a result of participation in phase III trial; ****Weakness due to concomitant measles outbreak, promotion and training needs and acceptability issues in some states.
[a] Expanded Program on Immunization.
[b] Ministries of Health.
[c] According to the World Bank.
[d] For information on the pre-licensure multicenter efficacy information, see topic clinical studies of the human rotavirus vaccine.
[e] Information currently not available.

To date the mortality impact of rotavirus vaccination has been evaluated in three studies only conducted in Mexico and Brazil [15,18–20]. Overall there was a decline in the range of 22–41% in all-cause GE mortality among children aged <5 years in the post-vaccination period [15,101].

Data are currently available from one study that evaluated concomitantly the potential risk of IS in Brazil and Mexico after routine use of *Rotarix*™ [102]. A small, albeit significant, increased risk of IS was observed within 7 days following the first vaccine dose among Mexican infants [odds ratio, 5.8 (95% CI: 2.6–13.0)]. A lower risk of IS was identified in Brazil after the second dose only, with an odds ratio of 1.9 (95% CI: 1.1–3.4). Data are also available from preliminary analyses of a post-marketing active surveillance study for IS under way in 66 hospitals across Mexico, covering a birth cohort of approximately 500,000 infants [103]. Taken the available data from Mexico and Brazil together, there is a signal of a small, transient increased risk of intussusception temporarily associated with administration of *Rotarix*™. Nevertheless, such a potential risk appears substantially lower than that reported for the human-rhesus tetravalent reassortant vaccine *RotaShield*™ (Wyeth), suggesting that the substantive benefits of rotavirus vaccination far outweigh the risk of intussusception.

10. Future challenges

The importance of post-marketing surveillance (PMS) following the introduction of new RV vaccines has been well-recognized [82]. Latin American clinical researchers in association with GSK were committed to evaluate *Rotarix*™ in PMS settings to further document both the safety profile of the vaccine and the overall public health impact when administered under universal mass vaccination conditions. A large PMS safety study was to be conducted in Mexico, specifically designed to evaluate the temporal association between vaccine administration and definite IS, observed with the *RotaShield*™ vaccine. PMS case-control studies were also planned to be conducted in El Salvador, Panama and Brazil to assess vaccine effectiveness for the prevention of RVGE hospitalizations. Although some of these studies have been extended to perform a long-term monitoring of circulating RV strains in children hospitalized for acute GE, a significant amount of data are currently emerging on the efficacy of *Rotarix*™ under "real conditions" in Latin America. PMS studies are indeed essential to monitor RV strain circulation following the introduction of RV vaccines into routine use, in an attempt to assess whether or not there is any long-term interaction between rotavirus vaccination and the strain ecology. Of note is the recent apparent predominance of the G2P[4] serotype in Northeastern Brazil [104,105]. Interpretation of these findings is limited by the small sample sizes, short duration of surveillance and lack of any comparison groups in these studies. However, it is noteworthy that G2P[4] RV strains have been previously documented to display a cyclic pattern of occurrence in Brazil [106,107]. Furthermore, despite low vaccine coverage (~50%) and 100% predominance of G2P[4] strains, *Rotarix*™ was found to provide high protection against severe RVGE among vaccinated children [108]. Indeed, severe RVGE occurred in only 7% of vaccinated children compared with 26% of non-vaccinated subjects ($p < 0.05$), with a calculated odds ratio (OR) of 0.20 (95% CI: 0.029–1.24) [78]. RV strain-specific surveillance conducted over several years will be essential to fully elucidate this situation. The PMS case control study in Brazil include an extended period of strain surveillance of at least 3 years. Recent studies in Brazil, El Salvador, Mexico and Panama have demonstrated a significant decline in hospitalizations for all-cause GE and GE-related deaths in children aged <5 years after introduction of a rotavirus vaccine [19,20,96–99]. This suggests that continuous gathering of data on hospitalizations for GE and GE-related deaths in Latin America and elsewhere may prove useful in assessing the effect of universal RV vaccination.

Although some preliminary data indicate a small, transient increase of IS following the first vaccine dose in Mexico, it is important to maintain continued surveillance in several countries across Latin America for episodes of IS and other serious adverse events following the progressive introduction of RV vaccination in Latin America. Of particular importance in the near future would be studies addressing the possible impact on vaccine performance of: (a) alternative schedules possibly including a neonatal vaccination; (b) altering breastfeeding practices; (c) introducing an interval in relation to polio vaccination; (d) using zinc or probiotic supplementation; and (e) the issue of apparent waning immunity in the second year of life [3,15]. In addition to this, further studies are needed to assess the impact of universal RV vaccination on key epidemiological issues including herd protection and herd immunity among unvaccinated infants, age distribution of rotavirus cases, changing seasonality and duration of protection. Although a progressive introduction of RV vaccination was seen in Latin America and elsewhere during the past 5 years, concerted efforts should be maintained and strengthened between PAHO, GAVI, the manufacturers, other international partners and country authorities in order to make vaccines available at the lowest prices for those countries with the highest needs. In parallel with this there is an urgent need for efforts to raise awareness of the scientific evidence currently available which reasonably reassures the safety, efficacy, effectiveness and the substantial health impact of rotavirus vaccines. It seems important to build a broad scientific-based advocacy initiative for rotavirus vaccination, stressing the current benefits over risk of vaccination mainly to decision makers, potential donors, scientific community, medical societies, opinion leaders and official advisory bodies.

11. Conclusions

The withdrawal of the first licensed RV vaccine, *RotaShield*™, yielded important lessons for the development of following generations of RV vaccines. The pioneering RV vaccine development strategy undertaken by Latin American researchers and the manufacturer represented a new paradigm for global vaccine research and development. This Human Rotavirus Vaccine Study Group undertook a systematic development program including burden of disease and IS baseline studies, Phase II and III trials to evaluate the safety, immunogenicity and efficacy of the human RV vaccine (*Rotarix*™), health-economics assessments, and post-marketing surveillance to assess vaccine effectiveness, safety and impact on morbidity, mortality and RV strain circulation. This has resulted in pioneering early vaccine introduction in a developing region of the world, before introduction into western industrialized countries with a reasonably high, albeit improbable level of vaccine coverage. By first registering the vaccine in middle-income and developing countries, it has been possible to accelerate vaccine implementation into universal mass vaccination programs and help to close the vaccine access gap between industrialized nations and less developed societies. A number of pharmacoeconomic analyses indicate that mass immunization with rotavirus vaccines in Latin America is a cost-effective measure if vaccines can be purchase at affordable prices. In the post-licensure period at least two case-control, studies in Latin America have reassured the effectiveness of *Rotarix*™ under "real world conditions". Moreover, post-licensure observational studies conducted in early introducer Latin American countries revealed substantial nationwide reductions in both gastroenteritis deaths and hospitalizations among infants and young children. As to safety, although a small, transient clustering of intussusception cases has been detected within 7 days

after first dose in Mexico and second dose in Brazil, the potential risk appears to be sufficiently low in order not to outweigh the significant benefits of rotavirus vaccination. Continuous surveillance studies are needed to better assess the effect of rotavirus vaccines on the burden of severe childhood gastroenteritis in Latin America, as well as to further evaluate any potential risk of intussusception following the progressive introduction of rotavirus vaccination.

Conflict of interest

All investigators were funded for study development by GlaxoSmithKline Biologicals.

Romulo E. Colindres, Thomas Breuer, Eduardo Ortega-Barria were employed by GlaxoSmithKline Biologicals at the time of this study.

Irene Perez Schael, Miguel O'Ryan, Xavier Sáez-Llorens, Alexandre C. Linhares and F.R. Velázquez have received funding for conferences and/or expert advise related with the development of *Rotarix*™.

Role of funding source

GlaxoSmithKline (GSK) Biologicals was the funding source and was involved in all stages of the study conduct and analysis. GSK Biologicals also funded all costs associated with the development and the publishing of the present manuscript. The corresponding author had full access to the data and was responsible for submission of the publication.

Authors' contribution

All authors have actively participated in the process of writing and reviewing the manuscript and have approved the final manuscript version for submission.

Trademark

RotaShield™ is a registered product of which was licensed in the United States, was withdrawn from the market after less than 1 year following an association with intussusception (IS).

Rotarix™ is a registered product of GlaxoSmithKline Biologicals.

RotaTeq™ is a registered product of Merck Research Laboratories, USA.

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