Reduction in morbidity and mortality from childhood diarrhoeal disease after species A rotavirus vaccine introduction in Latin America – A Review

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Countries in Latin America were among the first to implement routine vaccination against species A rotavirus (RVA). We evaluate data from Latin America on reductions in gastroenteritis and RVA disease burden following the introduction of RVA vaccine. Published literature was reviewed to identify case-control studies of vaccine effectiveness and population-based studies examining longitudinal trends of diarrhoeal disease reduction after RVA vaccine introduction in Latin American countries. RVA vaccine effectiveness and impact on gastroenteritis mortality and hospitalization rates and RVA hospitalization rates are described. Among middle-income Latin American countries with published data (Mexico, Brazil, El Salvador and Panama), RVA vaccine contributed to a gastroenteritis-associated mortality reduction of 22-41%, a gastroenteritis-associated hospitalization reduction of 17-51% and a RVA hospitalization reduction of 59-81% among children younger than five years of age. In Brazil and El Salvador, case-control studies demonstrated that a full RVA vaccination schedule was 76-85% effective against RVA hospitalization; a lower effectiveness of 46% was seen in Nicaragua, the only low-income country with available data. A growing body of literature offers convincing evidence of "real world" vaccine program successes in Latin American settings, which may be expanded as more countries in the region include RVA vaccine in their immunization programs.

Key words: species A rotavirus - rotavirus - vaccines - Latin America

Species A rotavirus (RVA) disease is a leading cause of childhood mortality in the world, accounting for an estimated 527,000 deaths annually among children younger than five years of age (Parashar et al. 2009). In 2006, clinical trials conducted in the Americas and Europe demonstrated that two new RVA vaccines had efficacy of 85-98% against severe RVA diarrhoea (Ruiz-Palacios et al. 2006, Vesikari et al. 2006). Subsequently, these RVA vaccines, Rotarix® [(RV1), monovalent G1P(8)] (GlaxoSmithKline Biologicals, Rixensart, Belgium) and RotaTeq® [(RV5) pentavalent G1, G2, G3, G4P(8)] (Merck Vaccines, Whitehouse Station, NJ, USA) (Soares-Weiser et al. 2010), were recommended for use in children of Europe and the Americas for preventing RVA diarrhoea (WHO 2007). By January 2011, 13 of the 24 countries routinely offering RVA vaccine as part of the national immunization schedule were in Latin America.

In 1999, a previous RVA vaccine, RotaShield, was withdrawn from the United States (US) market because of its association with intussusception. The risk of intussusception with both current RVA vaccines, RV5 and RV1, was evaluated pre-licensure in clinical trials of 60,000-70,000 infants each (designed to assess a risk similar to RotaShield) and no risk was observed. In recent months, vaccine safety came under scrutiny after a post-licensure evaluation identified a short-term four-six-fold elevated relative risk of intussusception in the first-seventh days following dose 1 of RV1 in Mexico (Colindres 2010, Patel et al. 2011) and with both RV1 and RV5 in Australia (Buttery et al. 2011). These risks are substantially lower than the 30-fold increased risk in the first week after dose 1 of RotaShield (WHO 2010).

With these new risk data, ministries of health need real-world RVA vaccine benefits data to determine whether to introduce or continue RVA vaccination programs. This report summarizes Latin American hospital-based and national surveillance network data; highlighting the reduction in gastroenteritis and RVA disease burden as well as identifying changes in RVA epidemiology, following RVA vaccine introduction.

Vaccine effectiveness estimates from case-control studies and vaccine impact data from population-based time-trend analysis of RVA vaccines used currently in Latin America were evaluated. Studies were identified using a country-specific publication search strategy and were reviewed and organized by study design (disease burden trend analysis versus case-control) and by disease outcome (gastroenteritis deaths, gastroenteritis hospitalizations and RVA hospitalizations). Gross national income data was obtained from the World Bank and reported for the country of origin for each study. For disease burden trend analysis studies, published estimates of vaccine coverage and percent reduction in disease after vaccine implementation

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were reported. For case-control studies, full vaccine series was defined as three doses of RV5 or two doses of RV1 and partial vaccine series was defined as one or two doses of RV5 or one dose of RV1. Additionally, the most prevalent RVA genogroup causing gastroenteritis among cases enrolled in the case-control study was abstracted. Individual study results and ranges were summarized.

Ethics - This study did not require Institutional Review Board clearance.

Population-based time-trends of gastroenteritis burden before and after vaccine implementation - Four middle income countries in Latin America (Brazil, El Salvador, Mexico and Panama) have published reports on population-based time-trends of gastroenteritis and/or RVA disease burden reductions after RVA vaccine introduction (de Palma et al. 2010, Lanzieri et al. 2010, 2011, Richardson et al. 2010, Sáfadi et al. 2010, do Carmo et al. 2011, Molto et al. 2011, Quintanar-Solares et al. 2011, Yen et al. 2011a) (Table I). In these countries, vaccine coverage among infants younger than one year of age with at least one dose of RVA vaccine ranged from 74-94% during the post-vaccine years for which data were evaluated.

Three studies from two Latin American countries (Brazil and Mexico) have reported a decline of 22-41% in gastroenteritis mortality among children younger than five years of age in post-vaccine years; this corresponds with annual absolute reductions of ~700 infant gastroenteritis deaths in Mexico and ~1,300 infant gastroenteritis deaths in Brazil (Richardson et al. 2010, do Carmo et al. 2011, Lanzieri et al. 2011).

Five studies from four Latin American countries (Brazil, El Salvador, Mexico and Panama) have reported a decline of 17% to 51% in all cause gastroenteritis-associated hospitalizations among children younger than five years of age in post-vaccine years (de Palma et al. 2010, Lanzieri et al. 2010, do Carmo et al. 2011, Molto et al. 2011, Quintanar-Solares et al. 2011). Two studies from two Latin American countries (Brazil, El Salvador) have reported a decline of 59% to 81% in laboratory-confirmed RVA hospitalizations among children younger than five years of age in post-vaccine years (Sáfadi et al. 2010, Yen et al. 2011a).

Case-control evaluations of vaccine effectiveness - Case-control studies from Latin American settings were done in one lower income country (Nicaragua) and three middle income countries (El Salvador, Brazil and Mexico) (Table II). In Nicaragua, the vaccine efficacy for averting RVA gastroenteritis hospitalization was 46% for the full schedule of RV5 and 52% for the partial vaccine schedule (Patel et al. 2009). In the three middle income countries, the vaccine efficacy for averting RVA gastroenteritis hospitalization was 76-94% for the full schedule of RV1 (Gurgel et al. 2007, Correia et al. 2010, de Palma et al. 2010, Justino et al. 2011, Yen et al. 2011b) and 51-84% for the partial vaccine schedule (de Palma et al. 2010, Yen et al. 2011b). In Nicaragua and Brazil, the most prevalent RVA genogroup identified among cases was G2P(4) (Gurgel et al. 2007, Patel et al. 2009, Correia et al. 2010, Justino et al. 2011), in El Salvador the most prevalent RVA genogroup identified among cases was

TABLE I

National estimates of reduction in all-cause diarrhoea and species A rotavirus (RVA) disease burden after RVA vaccine introduction

Reference	Country	Per capita national income ($)	Pre-vaccine year(s)	Post-vaccine year(s)	RVA vaccine coverage (%)	Decline in disease	
						Vaccinated age groups[b] (%)	Children under five years of age (%)
Gastroenteritis mortality							
Richardson et al. (2010)	Mexico	8,960	2003-2006	2008	74	41	35
Lanzieri et al. (2010)	Brazil	8,070	2004-2005	2008	90	30-39	41
do Carmo et al. (2011)	Brazil	8,070	2002-2005	2007-2009	82[c,d]	22-28	22
Gastroenteritis hospitalization							
do Carmo et al. (2011)	Brazil	8,070	2002-2005	2007-2009	82[c,d]	21-25	17
Lanzieri et al. (2010)	Brazil	8,070	1998-2005	2007	78[d]	26-48	31
Molto et al. (2011)	Panama	6,570	2003-2005	2008	94	15-31	37
Quintanar-Solares et al. (2011)	Mexico	8,960	2003-2006	2009	89	43-52	40
de Palma et al. (2010)[a]	El Salvador	3,370	2006	2009	-	Not available	51
RVA hospitalization							
Yen et al. (2011a)	El Salvador	3,370	2006	2008-2009	77[c]	79-86	69-81
Sáfadi et al. (2010)	Brazil	8,070	2004-2005	2007-2008	82[c]	73-82	59

a: Jan-June estimates; *b*: children under one or two years of age depending on year of vaccine introduction; *c*: annual average over the post-vaccine; *d*: RVA dose 2 coverage years.

G1P(8) (de Palma et al. 2010) and in Mexico the most prevalent RVA genogroup identified among cases was G9P(4) (Yen et al. 2011b).

Since RVA vaccine introduction, significant and sustained declines in gastroenteritis disease burden have been documented in multiple Latin America settings, illustrating the health benefits of RVA vaccines. Of particular note, reductions in gastroenteritis mortality, an outcome that was not evaluated in clinical trials, were documented in the two largest countries of the region that have introduced RVA vaccine (Brazil and Mexico), underscoring the life-saving potential of these vaccines. Furthermore, the drastic reduction in gastroenteritis deaths confirms pre-vaccine estimates of RVA-attributable mortality which had been questioned because they were based upon the assumption that the proportion of deaths due to RVA equates that proportion of hospitalizations due to RVA. In addition to mortality benefits, large reductions in gastroenteritis-associated hospitalizations and RVA hospitalizations were observed, which has important implications for reductions in health care utilization costs. The observed reductions were among children under five years of age and included only one or two vaccinated birth cohorts. Interestingly, studies from the US have found reductions in RVA among older children ineligible for vaccine, suggesting the possibility of indirect benefits from a herd immunity effect (Lopman et al. 2011). As the vaccine program continues throughout the Latin American region, a larger proportion of children under five years of age will have been vaccine eligible as infants and the real-world direct and indirect vaccine impact may become even more dramatic.

The field effectiveness of RV1 in Brazil and El Salvador was comparable to the overall 85% efficacy observed in the pivotal pre-licensure trial of RV1 in 11 Latin American countries. Interestingly, RV5 effectiveness in Nicaragua, the only low income Latin American country with available data, was lower and was similar to that seen in African and Asian settings. This dichotomy suggests that factors related to income (e.g., concurrent enteric infections, malnutrition) may, in part, explain the differences in vaccine efficacy by setting. Of note, however, the efficacy of RV1 in a poor region of Mexico during a G9P(4) outbreak was comparable to that in other middle income settings. Further evaluations of effectiveness of both RVA vaccines in impoverished Latin American settings, such as in Bolivia, which introduced vaccine in 2008, are needed to help assess the full significance of these observations.

Given the year-to-year and regional variability in RVA strain prevalence, interpreting RVA genotype epidemiology after RVA vaccine introduction is particularly challenging and underscores the importance of ongoing monitoring of vaccine effectiveness against a broad range of serotypes (Jiang et al. 2010). A predominance in G2P(4) RVA strains was observed in Nicaragua and Brazil after the introduction of RV5 and RV1, respectively (Gurgel et al. 2007, Patel et al. 2009, Correia et al. 2010, Justino et al. 2011). Because this strain differs from the RV1 vaccine strain by G-type, P-type and genogroup and also from the RV5 vaccine strain which contains the G2 reassortant, but not the P(4) reassortant, monitoring of G2P(4) is of particular interest after the introduction of vaccine. However, several observations from the studies in Latin America suggest that this predominance was likely due to secular variation and unrelated to vaccine pressure. First, the effectiveness of both vaccines against G2P(4) was similar to that against other G and P-type strains in the clinical trials from similar income settings. Second, although G2P(4) was the predominant strain in Brazil in the first year after RVA vaccine introduction, it was soon replaced by non-G2 strains in subsequent years (Carvalho-Costa et al. 2011). Third, in El Salvador, a G2P(4) predominance occurred in the year before vaccine introduction, but G1P(8) became the dominant strain after vaccine introduction (de Palma et al. 2010). Lastly, in the short term there is no evidence of widespread emergence of a vaccine-resistant strain of RVA. Thus, it would be prudent to interpret the changing ecology of RVA strains after vaccine in the context of vaccine effectiveness studies or changes in absolute disease burden.

This assessment of RVA vaccine impact in Latin American settings was limited by variation in methodology used between studies. Studies that examined

TABLE II

Case-control studies evaluating full vaccine schedule and partial vaccine schedule vaccine efficacy against species A rotavirus hospitalization[a]

Study	Country	Per capita national income ($)	Prevalent strain	Full (%)	Partial (%)
Patel et al. (2009)	Nicaragua	1,000	G2P(4)	46	52
de Palma et al. (2010)	El Salvador	3,370	G1P(8)	76	51
Gurgel et al. (2007)	Brazil	8,070	G2P(4)	79	-
Justino et al. (2011)	Brazil	8,070	G2P(4)	76	-
Correia et al. (2010)	Brazil	8,070	G2P(4)	85[b]	-
Yen et al. (2011b)	Mexico	8,960	G9P(4)	94	84

a: most infants included in the analysis of partial vaccine schedule are between vaccine doses; *b*: among six-11 months old infants.

time-trends used variable pre and post-vaccine year(s), with country specific differences in vaccine introduced, introduction date and vaccine coverage rates. Although most studies assessed the vaccine impact for children younger than five years of age using annual rates, one study presented vaccine impact for just the RVA season (de Palma et al. 2010), which would likely overestimate the rate reduction. Our assessment includes studies from a lower-middle income and upper-middle income countries; however, local factors (e.g. health care access, vaccine coverage rates, RVA epidemiology) make it difficult to tease out the effect, if any, of income per capita. Among case-control studies, case definitions of RVA disease were based upon laboratory testing, however, control groups varied between children with RVA-negative gastroenteritis, acute respiratory infections, as well as healthy children in the community. These control groups are meant to reflect the source populations from which the cases arose and the use of different groups between studies makes comparisons challenging. Finally, most of the data for effectiveness of partial schedule was based on cases between doses and thus effectiveness close to vaccination that should be interpreted with caution.

In conclusion, data generated from countries in Latin America that have introduced RVA vaccine provide evidence of substantial reductions in both diarrhoea deaths and hospitalizations among children. These documented benefits of vaccination have been compared with the small risk of vaccine-associated intussusception identified in post-licensure trials and World Health Organization and other regulatory agencies have affirmed that the vaccine benefits outweigh the risks (Jiang et al. 2010). For example, in Brazil and Mexico combined, RVA vaccine has been estimated to cause 150 excess annual intussusception cases, but has also prevented approximately 140,000 diarrhoea hospitalizations and 1,300 diarrhoea deaths annually among children under five years of age. Furthermore, because vaccine benefits have been documented in both developing and developed countries of Latin America, they highlight the value of RVA vaccines in improving child in all regions of the world. In countries of Asia and Africa where more than 85% of RVA deaths occur, widespread use of RVA vaccines is anticipated in the next one-two years with funding support through the GAVI Alliance (2011). Given the successful experience of RVA vaccines in Latin America, the global use of RVA vaccines could have a substantial impact on diarrhoeal morbidity and mortality and thus will accelerate reaching the fourth Millennium Development Goal of reduced child mortality.

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