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Rotavirus vaccine effectiveness in Latin American and Caribbean countries: A systematic review and meta-analysis

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ABSTRACT

Introduction: There are two group A rotavirus (RVA) vaccines available worldwide since 2006: monovalent (Rotarix®, RV1) and pentavalent (RotaTeq®, RV5). Currently, 16 countries and 1 territory in Latin America and the Caribbean (LAC) have introduced RVA vaccines and since their introduction several impact and effectiveness studies have been conducted in different countries. The purpose of this study was to assess RVA vaccine effectiveness in LAC countries.

Methodology: We conducted a systematic review and meta-analysis of studies in children under-five who were admitted with laboratory-confirmed RVA diarrhea. We searched Medline, WOS, LILACS, Scopus, and other sources from 2006 to October 2013. Two independent evaluators identified the studies that met predefined selection criteria and extracted relevant information according to a protocol. Pooled estimates were obtained with fixed and random-effects models and stratified according to selected effect modifiers.

Results: Of the 806 articles meeting the initial criteria, 8 case-control studies which involved 27,713 participants (6265 cases and 21,448 controls) were included in the final analyses. The pooled estimates were calculated using different types of controls, leading to different degrees of effectiveness. The effectiveness of two doses of RV1 against rotavirus-related hospitalizations ranged from 63.5% (95% CI: 39.2–78.0) to 72.2% (95%CI: 60.9–80.2). Effectiveness ranged from 75.4% (95%CI: 64.6–82.9) to 81.8% (CI 95%:72.3–88.1) among infants <12 months for RV1, and from 56.5% (95%CI: 26.2–74.3) to 66.4% (95%CI: 54.1–75.5) for infants >12 months. The RV5 effectiveness for diarrhea with a Vesikari score >11 in infants 6 to 11 months old ranged from 76.1% (95%CI: 57.6–86.6) to 88.8% (95%CI: 78.3–94.3). Also, it showed 63.5% (95%CI: 29.4–82.6) of effectiveness against G2P [4].

Conclusion: RVA vaccines consistently showed protection against diarrhea-related hospitalizations in LAC. Results were more robust for RV1. Effectiveness was shown with different types of controls, but appeared somewhat higher with community controls. Effectiveness was higher among infants <12 months and lower in older children.

1. Introduction

Group A RVA infect nearly every child by the age of 3–5 years and are globally the leading cause of severe, dehydrating diarrhea in children under five years of age [1,2]. Globally, RVA diarrhea in 2008 resulted in 453,000 deaths in children under five, comprising 37% of deaths attributable to diarrhea and 5% of all deaths in children <5 years [3]. It was estimated for 14 countries in Latin America that RVA caused 6302 deaths and 229,656 hospitalizations annually in the absence of RVA vaccination [4]. More recently, was estimated that RVA caused approximately 197,000 deaths in 2011 which means that it still is the most important cause of diarrhea-related mortality worldwide [5].

RVA are non-enveloped dsRNA viruses with a segmented genome (11 gene segments) and based on their two outer capsid proteins, VP7 and VP4, RVA have been classified into G (glycoprotein) and P (protease-sensitive) genotypes [6,7]. In 2006, two new human, live-attenuated oral vaccines, RotaTeq® (RV5) (Merck and Co.) and Rotarix® (RV1) (GSK Biologicals, Rixensart, Belgium), were licensed. RotaTeq® (RV5) is an oral pentavalent human-bovine reassortant vaccine (G1, G2, G3, G4, P [8]) that is administered in a 3-dose schedule. Rotarix® (RV1) is an oral attenuated human

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monovalent vaccine (G1P [8]) that is administered in a two-dose schedule. These vaccines have proven to be safe and effective in clinical trials in different countries [8,9]. They are recommended for use in all countries by the World Health Organization (WHO), particularly in those countries with high diarrhea-related mortality in children <5 years [10].

As of May 2014, 16 LAC countries and one territory have introduced RVA vaccines into their universal immunization program: Brazil, El Salvador, Mexico, Nicaragua, Panama, and Venezuela in 2006; Ecuador in 2007; Bolivia in 2008; Colombia, Honduras, Peru, and Cayman Island in 2009; Guatemala, Guyana, and Paraguay in 2010; Dominican Republic in 2012 and Haiti in 2014[11,12].

In LAC, since the introduction of RVA vaccines, several studies have demonstrated their effectiveness, especially for severe diarrhea leading to hospitalizations and deaths. However, these studies have shown reductions in child hospitalization and mortality with a variation in the magnitude of the protective effect of the vaccines, also when comparing the effect of two different vaccines that are currently available [13–19]. In this paper we reviewed the benefits, limitations, and consistency of results in studies measuring RVA vaccine effectiveness in LAC children. We critically assess the similarities and differences in methodology and findings of observational studies and compare RVA vaccine effectiveness.

2. Methods

2.1. Inclusion criteria

We selected the studies using the following criteria: those conducted in LAC countries in hospitalized children <5 years; intervention restricted to monovalent or pentavalent RVA vaccines; RVA cases confirmed with laboratory diagnosis; and comparative studies where it was possible to calculate vaccine effectiveness. If data were duplicated or shared in more than one study, we included the most recent publication.

2.2. Literature search

We searched Medline (PubMed data base), LILACS, Scopus and Web of Science, from 2006 to October 2013 using key words related to rotavirus, such as “rotavirus infection”, “rotavirus disease”, “rotavirus hospitalization”, “rotavirus death” “rotavirus vaccines” and “rotavirus impact and effectiveness studies” in all countries of LAC. We also contacted 10 experts on RVA studies from LAC looking for unpublished articles, thesis, and reviewed the literature of relevant articles to locate additional publications. Additionally, we obtained and confirmed some data from researchers. There was no restriction regarding languages.

2.3. Study selection and data extraction

In the first phase three independent evaluators reviewed the abstracts in order to identify the studies that met predefined criteria. In the second phase two independent evaluators selected studies where all the relevant information should be abstracted in a data-collection form based on a standardized protocol. Disagreements between evaluators were resolved through discussion. That process was summarized in a flow chart (PRISMA) [20].

2.4. Quality assessment of the methodology

We assessed the methodological quality of the selected studies using the Newcastle–Ottawa Scale (NOS) for observational studies in meta-analysis [21]. A NOS system score ranges from 0 to 9, with 7 or higher being generally considered satisfactory.

We calculated the pooled odds ratios and the respective 95% confidence intervals using fixed and random effect models. The pooled odds ratios were converted into vaccine effectiveness (VE) using the following formula: $VE = (1 - \text{odds ratio}) \times 100$. As the case-control studies presented different control groups such as community, hospitalized controls, RVA negative test (EIA), and combined controls, we decided to summarize the effectiveness of the most common control groups established in the studies which was the hospitalized controls. However, we also pooled estimations using the other control groups when the number of studies allowed for this type of analysis.

Heterogeneity among studies was assessed through: (i) visual inspection of forest-plots; (ii) chi-squared for heterogeneity and; (iii) Higgins *I*-squared (I^2). In the case of the latter, values over 40% were considered as indicative of relevant inconsistency between studies.

The main exposition variables studied were vaccine type (RV1 or RV5) and vaccine schedule (complete or incomplete). A subgroup analysis was also performed to explore the role of potential effect modifiers such as the Vesikari score (>11 and >15), age (6 to 12 months and >12 months); Vesikari score >11 and >15 by ages 6 to 12 months and >12 months.

A sensitivity analysis was conducted both to explore possible sources of heterogeneity and assess the accuracy of our findings [22]. We performed an analysis to evaluate the impact on effectiveness by using different types of controls and removing some studies.

Statistical analysis was performed using Stata software. StataCorp 2007. Stata Statistical Software: Release 10.College Station, TX: StataCorp LP.

3. Results

3.1. Identification and characteristics of selected studies

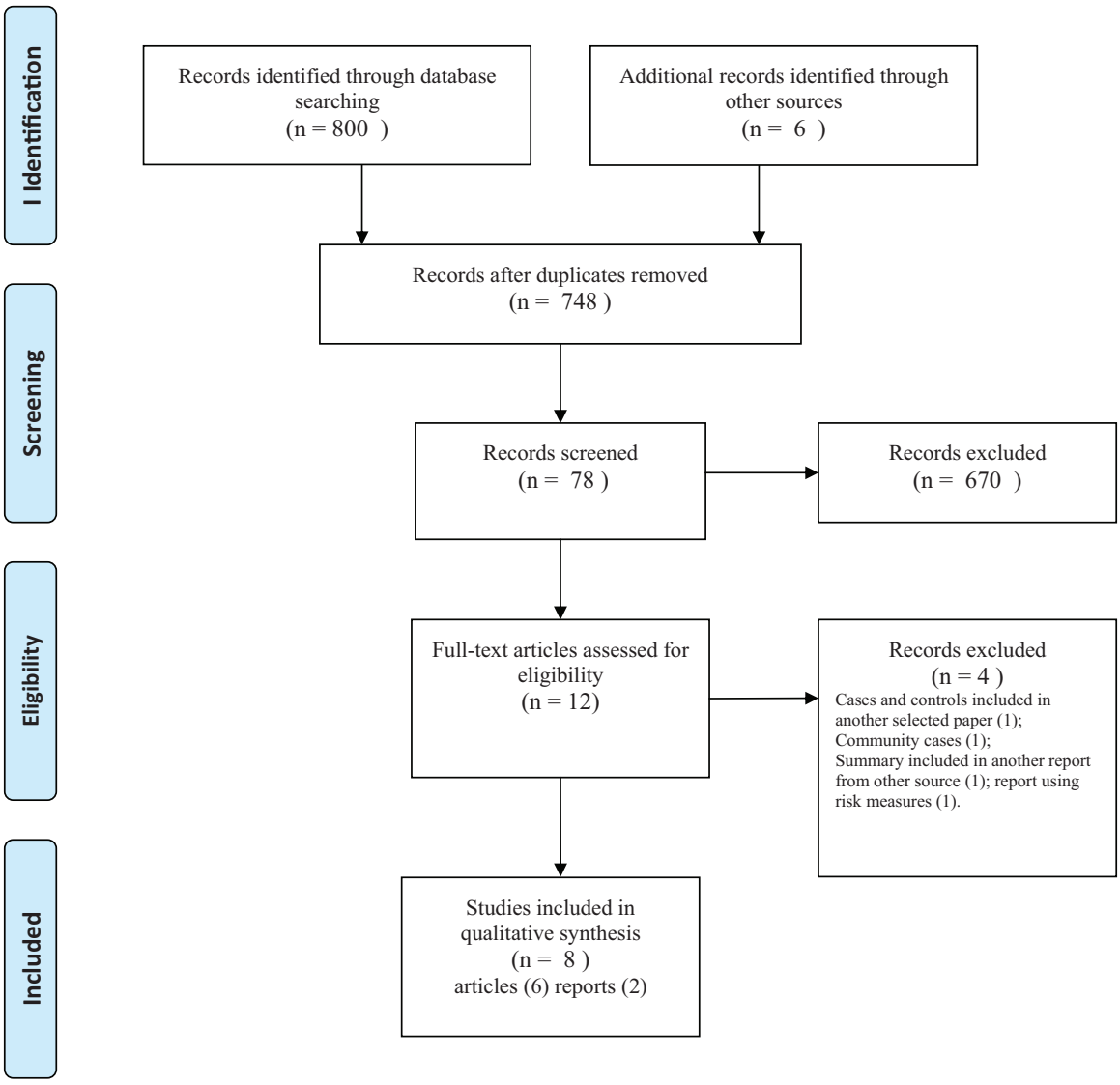
We selected 806 records meeting protocol eligibility criteria and excluded 58 duplicated articles. We excluded an additional 670 articles that did not meet the selection criteria after a thorough revision of titles, abstracts and, in many cases, methodologies. After reviewing the full text of 12 records, four were excluded (Fig. 1).

The remaining eight records were case-control studies considered to have a satisfactory methodological quality based on NOS score 7 or higher. Two studies had not been published when the systematic review was conducted and were located by contacting specialists [23,24].

The final eight studies included a total of 27,713 participants (6265 cases and 21,448 controls) and all of them were among children <5 years of age. Six studies estimated VE for the RV1 vaccine and two for the RV5 vaccine. From the selected studies, three were conducted in Brazil, two in Nicaragua, and one in each of the following countries: Bolivia, Colombia and El Salvador. Severe diarrhea hospitalizations were the main outcome to estimate VE of complete vaccination schedules using different types of controls (Table 1). Six case-control studies were designed using individual matching, at least for age, and one used frequency matching. The pooled measures of VE for the different outcome definitions showed an important variation according to the type of control. We could not perform any meta-analysis including all of the eight case-control studies together due to the different interventions and specific objectives across studies.

3.2. Effectiveness of Group A RVA vaccines

VE according to different subgroups used primarily hospital controls. If the study was not designed using hospital controls, we performed an analysis using another type of control.



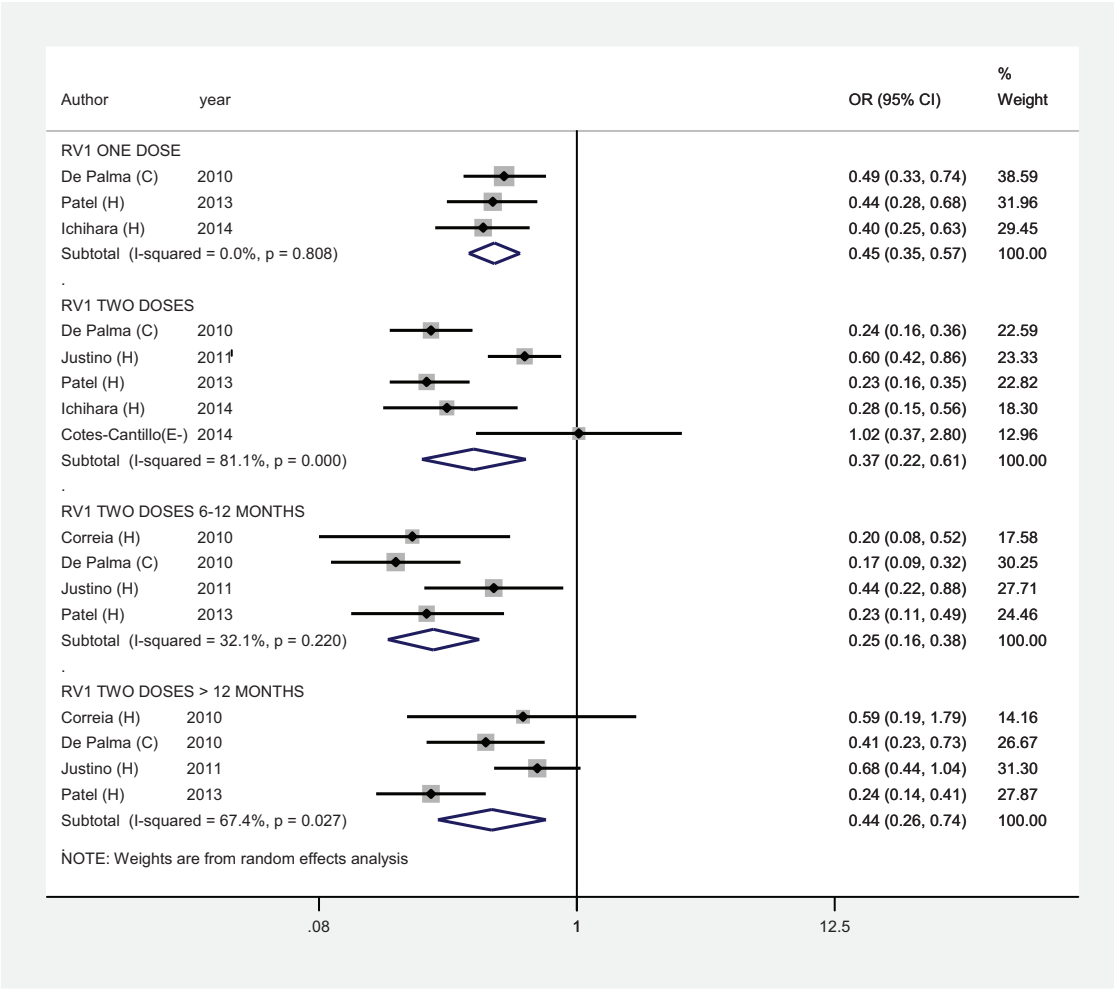
*PRISMA [20]

Fig. 1. Flow of information through the different phases of a systematic review*. * PRISMA [20].

Table 1
Characteristics of 8 case-control studies selected for the meta-analysis by year, country, vaccine, objective, number of cases and controls.

Author	Year	Country	Vaccine	Study objective	Number of cases	Type and number of controls
Correia et al.	2010	Brazil	RV1	VE against severe diarrhea and hospitalization caused by infection with fully heterotypic G2P4 strains	70	Hospital = 416 EIA test negative = 484
De Palma et al.	2010	El Salvador	RV1	VE of 2 doses of the vaccine against rv diarrhea requiring hospital admission	323	Neighborhood = 969
Justino et al.	2011	Brazil	RV1	VE of 2 or 1 dose of vaccine in hospitalized children	538	Neighborhood = 346 Hospital = 507
Mast et al.	2012	Nicaragua	RV5	VE in reducing risk of RVA resulting in hospitalization and emergency department visit with 3 doses of vaccine	502	Neighborhood = 1685 Hospital = 1894 Combined = 3579
Patel et al.	2012	Nicaragua	RV5	To define the duration of protection of 3 doses of vaccine	1016	EIA test negative = 4930 Neighborhood and hospital = 5627
Patel et al.	2013	Bolivia	RV1	VE against hospital admission with 2 doses of vaccine	400	Hospital = 1200 EIA test negative = 718
Ichihara et al.*	2013	Brazil	RV1	VE in preventing hospitalization against RVA and genotype specific with 2 doses of vaccine	215	Hospital = 1961
Cotes-Cantillo et al.*	2013	Colombia	RV1	VE against severe diarrhea with 2 doses of vaccine	173	Rapid test negative for RVA confirmed for EIA test negative = 711

* Ichihara and Cotes-Cantillo were selected from specialist reports in 2013 and published in 2014.



RV1: Monovalent vaccine

C: Community control

H: Hospital control

E-: EIA test negative

Fig. 2. Monovalent rotavirus vaccine effectiveness, according number of doses and age. RV1: monovalent vaccine. C: community control. H: hospital control. E-: EIA test negative.

Fig. 2 presents the results obtained in our study using random-effect models due to the heterogeneity of estimates across studies.

The pooled estimate of three studies [13,19,25] which assessed VE of one dose of RV1 was 55.5% (Fig. 1); however, when we performed the analysis using EIA test negative as a control group in the Patel et al. study [13], the pooled VE was reduced to 49.8%.

As shown also in Fig. 2, five studies [13,23–26] evaluated VE of two doses of RV1 against RVA hospitalizations and the pooled measure was 63.5%. When the VE estimate with hospitalized controls was replaced by community controls, used in the Justino et al. study [26], the VE improved to 72.2%.

VE for two doses of RV1 in children from 6 to 12 month was 75.4% in the primary analysis [13,26–28], and improved to 81.8% when the alternative estimate using community controls of Justino et al. [26] was considered. Regarding the VE in children >12 month, effectiveness was also improved, when using the community control of Justino et al. [26], increasing to 66.4% compared with the results shown on Fig. 2 [13,26–28].

The random-effects pooled measure including three studies [23,25,26] for RV1 Vesikari >11 score in all ages presented a VE of 48.2% (Table 2). A sensitivity analysis was done without considering the Cotes-Cantillo et al. study [23], to explore the degree of VE variation. The results changed significantly and VE was 65.0% (95%CI: 40.6 to 79.3). For RV5 Vesikari >11, including two studies [14,18], pooled VE was 68.4%. Analysis for RV1 Vesikari >15 contemplated three studies [23,25,26] and VE was 39.2% (Table 2). Sensitivity analysis disregarding Cotes-Cantillo et al. [23] showed a pooled VE of 65.3% (95%CI: −98.6 to 91.5), which is similar to the previous analysis, with both estimates presenting large confidence intervals.

Some of the studies [14,18,23,25] allowed to stratify the subset with Vesikari >11 score by age. The pooled VE in children from 6 to 12 months was 76.2% and 76.1% for RV1 and RV5, respectively, with no substantial heterogeneity between them. However, it is important to note that these analyses contemplated only two studies for RV1 and two for RV5 (Fig. 1). The same analysis for RV5 was performed with community controls [14,18], increasing the VE to

Table 2
Summary of RV1 and RV5 effectiveness, according type of control and Vesikari subgroups, using random effects model.

Study/country	Type of control	Weight (%)	Heterogeneity, I^2%	Summary VE	95%CI
Vesikari >11 all ages by vaccine RV1 and RV5					
De Palma et al.—BOL	Community	21.6			
Justino et al.—BRA	Hospital	20.6	79.2	**48.2***	**−83.6 to 97.6**
Cotes-Cantillo et al.—COL	EIA test negative	11.8			
Mast et al.—NIC		22.7	0	**68.4****	**56.4 to 77.1**
Patel et al.—NIC		23.3			
Vesikari >15 all ages by vaccine RV1					
De Palma et al.—BOL	Communiny	25.4			
Justino et al.—BRA	Hospital	25.1	78.4	**39.2***	**−97.5 to 84.9**
Cotes-Cantillo et al.—COL	EIA test negative	22.9			
Vesikari >11 in children from 6 to 11 months by vaccine RV1 and RV5 with complete schedule					
De Palma et al.—ELS	Community	27.43			
Cotes-Cantillo et al.—COL	EIA test negative	7.6	0	**76.2***	**47.9 to 89.1**
Mast et al.—NIC	Hospital	23.9			
Patel et al.—NIC	Hospital	41.1	0	**76.1****	**57.6 to 86.6**
Vesikari >11 in children >12 months by vaccine RV1 and RV5 with complete schedule					
De Palma et al.—ELS	Community	26.7			
Cotes-Cantillo et al.—COL	EIA test negative	14.8	77.7	**22.8***	**−1.91 to 79.6**
Mast et al.—NIC	Hospital	29.9			
Patel et al.—NIC	Hospital	28.6	0	**61.6****	**42.8 to 70.8**

* RV1 (monovalent vaccine).
** RV5 (pentavalent vaccine).
ELS—El Salvador; BRA—Brazil; COL—Colombia; NIC—Nicaragua; BOL—Bolivia.

88.8% (95%CI: 78.3 to 94.3), and using combined controls, VE was 76.0% (95%CI: 68.0 to 82.0).

Two studies measured RV1 effectiveness in the subgroup Vesikari >15, by age [23,25]. The pooled VE for 6 to 11 months was 82.0% (CI 95%:20.8 to 95.9) using community controls for the De Palma et al. study [25] and EIA test negative for the Cotes-Cantillo et al. study [23]. In the subgroup Vesikari >15, age >12 months, the pooled VE was 81.8% (CI 95%:29.9 to 95.3). In both age groups, the accuracy of the pooled estimates was affected by the large confidence intervals in the Cotes-Cantillo et al. study [23]. The random effects pooled VE from three studies of RV1 [13,24,26] was 63.5% (95%CI: 29.4 to 82.6) for the genotype G2P [4] in all ages with a complete vaccination schedule.

4. Discussion

According to our knowledge, this is the first meta-analysis studying RVA effectiveness in LAC which is the main strength of this study. Overall, our findings showed that both vaccines, RV1 and RV5, protected against RVA-diarrhea hospitalizations, especially in children <5 years with a complete vaccination schedule, for whom the effectiveness estimate was around 75%. We highlight the 63.5% effectiveness of RV1 against genotype G2P [4] since this strain seems to be naturally re-emerging in Latin America [29]. Also of interest was the pooled 55.4% VE for one dose of RV1 among infants <12 months. That implies substantial protection in settings where it is difficult to reach children to complete vaccination schedules and, when it is not possible to administer the complete schedule before 12 months of age. Another important point to be considered is that a significant proportion of RVA cases occur before the age in which the vaccine schedule should be completed [30].

In general, we did not find significant differences in the magnitude of the pooled measures for the main outcomes when compared with the results of the selected studies included in our meta-analysis. Overall, the magnitude of VE across studies indicated the vaccine afforded substantial protection in several countries, which was consistent across different programmatic conditions, peak seasons of RVA infection, and environmental and social and economic status.

The results from this study represent the protective effect of the vaccines in the "real world", which is often lower compared to the artificial settings of clinical trials. The efficacy of the RV1 against severe RVA gastroenteritis and against RVA-associated hospitalization was 85%, and reached 100% in the case of more severe RVA gastroenteritis in the clinical trial [9]. For the RV5, the efficacy was 94.5% for hospitalizations and emergency visits related to RVA genotypes G1–G4 causing gastroenteritis [8]. This discrepancy of RVA efficacy and the effectiveness of immunization programs for RVA is consistent with results that have been reported in the literature in low and middle income countries of Africa [31].

In this meta-analysis, all studies were case-controls, their case definitions were based on WHO recommendations [32], effectiveness was measured by adjusting for potential confounding variables, and presence of RVA was tested by EIA. Also, cases and controls established the vaccination status based on records which show a degree of accuracy in measuring the main exposure. Many of them remark the exclusion criteria of controls when infants presented a vaccine-preventable disease, avoiding selection bias. Those features give confidence that the studies included in the meta-analysis are homogenous. However, we found an important variation regarding the type of controls in the studies identified. Primarily, we tried to analyze the data using hospital controls, but some of the studies did not use this type of controls as mentioned in Section 3. Consequently, we performed different analysis using different control groups and the effectiveness consistently increased when we included community controls in the pooled measure for all of the outcomes studied.

These findings deserve special attention because it has been recognized that case studies using multiple control groups occasionally produce discordant results [33]. Also, some authors consider the presence of a control selection bias if results are different depending on the control group utilized. However, the case-control approach is widely used to evaluate VE and all of the observational studies must control confounding variables to ensure estimates are not biased. Nevertheless, protocol studies must evaluate the possibility of a control selection bias which is liable to be introduced when they are not representative of the population producing the cases [34]. Some of the studies in this meta-analysis, and

also other authors, refer that neighborhood controls provide the advantage of controlling potential confounding variables, particularly, socio-demographic status and vaccination access [25,26,33]. On the other hand, it is recognized that the "ideal" control group rarely exists in epidemiologic studies [35].

Our study has some limitations, especially regarding the issue discussed above, where different types of controls were used in the studies and different subgroups were also analyzed across the studies. This has shown a variation in the estimates resulting from studies with different types of controls, but the pooled measure of some critical endpoints was performed with a few studies. This also hampered the analysis of the publication bias and the performance of meta-regression. Some of the analyses are not sufficiently robust to conclude the real effectiveness in these different subgroups. This was of particularly concern in the case of RV5, which was assessed in only two studies, one of them sponsored by the vaccine manufacturer. On the other hand, consistent results from different outcomes provided wider and complementary perspectives of the performance of RVA vaccination. Another possible limitation refers to selecting only case-control studies as mentioned before. The definition and selection of controls from studies were assessed with a good score in the NOS. However, it could be possible that this score did not identify some of the weaknesses of the study design, in particular, the control selection.

The studies of Cotes-Cantillo et al. [36] and Justino et al. [26] presented discrepant VE results when compared with other studies, since they showed that the estimation of effectiveness had an important variation in its magnitude. The sensitivity analyses, when we excluded Cotes-Cantillo et al. study [23], significantly increased the effectiveness of the outcomes in the meta-analysis which also occurred when the community control from the Justino et al. study [26] was used. Authors explored some explanations for this discrepancy. In the Justino et al. [26] study, it is recognize that hospital controls are under-vaccinated; in the Cotes-Cantillo et al. study [23] – which found a lower VE – authors raised the issue of the high vaccine coverage when the study was conducted.

In the systematic review we found a significant number of studies in LAC that measured the impact of these vaccines, focusing mainly on RV1, but they were conducted with different designs and estimation measures; thus, it was not possible for us to include them in the meta-analysis. However, all of these studies showed that vaccines had a significant impact in reducing RVA-diarrhea hospitalizations in children under five years of age [16,17,37] which is consistent with the vaccine effectiveness results presented in our findings.

In LAC, 16 countries and one territory had introduced the RVA vaccines up to May 2014, but few of them performed studies measuring effectiveness, according to our systematic review. Nonetheless, it would be difficult to conduct effectiveness studies in other LAC countries due to the high vaccine coverage in most of them [38], which hampers the contrast of the odds of exposure between cases and controls. Fifty seven countries – mostly middle-and high-income countries – have introduced RVA vaccines into their national immunization programs [39]. Therefore, there are many opportunities to conduct effectiveness studies in countries where coverage still allows it, as well as in those that will be introducing the vaccines in the future. These studies should consider analyzing the same outcomes and using the same group of controls that could generate a meta-analysis involving a greater number of studies in different settings.

In summary, in our meta-analysis on RVA vaccine effectiveness in LAC we found evidence that these vaccines provide good protection against hospitalizations caused by RVA diarrhea in children from 6 to 12 months; lower protection with incomplete schedule and in children >12 months, especially when considering RV1, since there was a greater number of studies to meta-analyze. This evidence ratifies the importance of these vaccines as a public health intervention, reducing the burden of severe RVA disease and supports WHO recommendation to introduce the vaccine into the routine immunization program [10].

Conflict of interest statement

We declare that we have no conflicts of interest.

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