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SYSTEMATIC REVIEW

REVISED **Effectiveness of Rotarix® vaccine in Africa in the first decade of progressive introduction, 2009-2019: systematic review and meta-analysis** [version 2; peer review: 2 approved]

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Abstract

Background: Randomized controlled trials of licensed oral rotavirus group A (RVA) vaccines, indicated lower efficacy in developing countries compared to developed countries. We investigated the pooled effectiveness of Rotarix® in Africa in 2019, a decade since progressive introduction began in 2009.

Methods: A systematic search was conducted in PubMed to identify studies that investigated the effectiveness of routine RVA vaccination in an African country between 2009 and 2019. A meta-analysis was undertaken to estimate pooled effectiveness of the full-dose versus partial-dose of Rotarix® (RV1) vaccine and in different age groups. Pooled odds ratios were estimated using random effects model and the risk of bias assessed using Newcastle-Ottawa scale. The quality of the evidence was assessed using GRADE.

Results: By December 2019, 39 (72%) countries in Africa had introduced RVA vaccination, of which 34 were using RV1. Thirteen eligible studies from eight countries were included in meta-analysis for vaccine effectiveness (VE) of RVA by vaccine dosage (full or partial) and age categories. Pooled RV1 VE against RVA associated hospitalizations was 44% (95% confidence interval (CI) 28-57%) for partial dose versus 58% (95% CI 50-65%) for full dose. VE was 61% (95% CI 50-69%), 55% (95% CI 32-71%), 56% (95% CI 43-67%), and 61% (95% CI 42-73%) for children aged <12 months, 12-23 months, <24 months and 12-59 months, respectively.

Conclusion: RV1 vaccine use has resulted in a significant reduction in severe diarrhoea in African children and its VE is close to the efficacy findings observed in clinical trials. RV1 VE point estimate was higher for children who received full dose than those who received partial dose, and its protection lasted beyond the first year of life.

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 2 (revision) 24 Sep 2020	✓ report	✓ report
version 1 06 Aug 2020	? report	

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> **REVISED** **Amendments from Version 1**
>
> We would like to thank our reviewer for the helpful feedback. We received useful thoughts for clarifications throughout, and we have amended the paper accordingly. We have also excluded Table 3 and merged Table 1 and Table 2 into one Table.
>
> **Any further responses from the reviewers can be found at the end of the article**

Introduction

Globally, rotavirus group A (RVA) is a leading cause of severe dehydrating acute diarrhoea in children aged <5 years[1]. In 2016, approximately 117 million episodes of rotavirus-associated diarrhoea occurred in sub-Saharan Africa, ~104,000 of which were fatal[2]. Rotavirus vaccination programmes are considered the most effective control measure for RVA disease[3,4] and six oral vaccines (RotaTeq® (RV5), Rotarix® (RV1), Rotavac®, Rotavin-mi®, Lanzhou Lamb and Rotasiil®) have been licensed[5]. In 2009, the World Health Organization recommended inclusion of two licensed RVA vaccines (Rotarix®, GlaxoSmithKline Biologicals, Belgium; and RotaTeq®, Merck, USA) into routine national immunization programmes (NIP) of all countries[6]. By July 2020, 74% of African countries (40 out of 54) had introduced an RVA vaccine into their NIP compared to the global tally of 107 out of 194 countries (55%)[7]. Of the 40 African countries with the RVA vaccine, 35 (88%) were using the RV1 vaccine.

Randomised controlled trials (RCTs) investigating the efficacy of oral RVA vaccines in sub-Saharan Africa showed a modest performance (50–80% efficacy against severe disease) compared to results from industrialized countries (90–100% efficacy)[8,9]. Despite this discrepancy, use of RVA vaccines in developing countries was encouraged on the basis of the expected absolute impact on the high RVA disease burden in low-income setting[10]. Post-vaccine introduction, a number of African countries have reported on RVA vaccine impact and effectiveness against rotavirus gastroenteritis (RVGE) and all-cause diarrhoea related hospitalisations[11]. Vaccine effectiveness is similar to vaccine efficacy but is measured in the context of routine real-world use of the vaccine to quantify the reduction in disease among those who are vaccinated compared to unvaccinated persons. Vaccine impact measures the absolute reduction in disease at population level following the introduction of the vaccine and is determined by from vaccine effectiveness, vaccine coverage, and any herd effect[12]. There have been expert reviews discussing the impact of RVA vaccine in African countries[13–15] and systematic review and meta-analysis conducted focusing on the prevalence of rotavirus infections pre- and post-vaccine introduction[16]. In this paper, we present a systematic review and meta-analysis of vaccine effectiveness of rotavirus vaccination programmes in Africa focusing on partial dose versus full dose and effectiveness stratified by age categories.

Methods

Systematic search

We conducted a systematic search in PUBMED database for articles on research conducted in African populations from January 2009 to December 2019 focusing on the rotavirus vaccination programme and adhered to PRISMA guidelines (*Extended data*: Supplementary File One, Supplementary Table 1)[17]. Publications were identified using combinations of the following key search terms: "Rotavirus", "effectiveness", "success", "impact", "effect", "potency", "performance", "vaccine", "Rotarix", "Rotateq" and names of all 54 African countries. We restricted our search to articles published in English (see *Extended data*: Supplementary File One, Supplementary Text 1 for details)[17]. Two reviewers screened the outputs identified from the searches for appropriate articles and from references of the relevant published articles to identify additional articles for possible inclusion into the analysis. The final included articles were based on agreement between the two reviewers. A third reviewer resolved any discrepancies. Information on RVA vaccine introduction status for each country and impact evaluation were inferred from VIEW-hub[18].

Inclusion criteria and outcomes

This analysis focuses on the Rotarix® (RV1) Vaccine, which is given to infants as two doses at 6 and 10 weeks of life. We aimed to include articles published from any African country that administers RV1 vaccine as part of the NIP. Observational studies (case-control) reporting on the effectiveness of RVA vaccine among children aged <5 years in their country, on RVGE or other acute gastroenteritis (AGE) hospitalization between 2009 and 2019 were included. Outcomes of interest included effectiveness RVA vaccine against hospitalization from RVGE for full dose, partial dose and, effectiveness stratified by age categories. Randomized controlled trials, review articles, editorials and conference papers were excluded from this analysis (*Extended data*: Supplementary File One, Supplementary Text 2)[17].

Data extraction

The following details were extracted from the eligible studies; study design, sample size, country, vaccine type, age groups, cases vaccinated, controls vaccinated, reported vaccine effectiveness and 95% confidence intervals (CIs). Extracted data was entered into data collection forms created in Microsoft Excel (Extended data: Supplementary File Two)[17].

Assessment of risk of bias

The Newcastle–Ottawa scale (NOS) was used to assess the risk of bias (ROB) among the case-control studies[19]. The NOS was used to evaluate the selection of participants, comparability of study groups, and the ascertainment of exposure or outcome of interest.

A study was assigned a maximum of 9 points based on selection (4 stars), comparability (2 stars) and exposure (3 stars),

for a maximum of 9 points, by using a star allocation scheme according to the coding manual developed by collaboration between Universities of Newcastle and Ottawa[20]. Studies scoring zero in any of the categories were classified as having high ROB. Studies scoring 1 point in any of the categories were classified as having moderate ROB, and those scoring 2 points or more in all categories were classified as having low ROB.

Data management and analysis

Meta-analysis was stratified (full and partial dose) for RV1 vaccine effectiveness and by age categories (<12 months, 12–23 months, <24 months, and 12–59 months). We used study reported vaccine effectiveness (VE) estimates $\sqrt{VE = (1 - OR) * 100\%}$ to obtain the respective $\sqrt{OR = 1 - (VE/100)}$ and the respective log transformed odds ratio (OR). A random effects model was used to estimate the pooled VE while accounting for variations of the true effect size due to varying geographical settings of the studies.

Heterogeneity was assessed by the chi-squared test for heterogeneity and quantified by I^2 index [(Q-df) / Q x 100 %] where Q is the Cochran's heterogeneity statistics and the degrees of freedom (df). I^2 values of 25–49%, 50–74% and >=75% were categorized as low, moderate, and high heterogeneity respectively[21]. Forest plot was used to present the pooled ORs with their corresponding 95% CI. To check for publication bias, funnel plot was used, and Eggers test employed to assess funnel plot asymmetry. All statistical analyses were conducted using STATA version 15.1 (StataCorp College Station, Texas), and where applicable admetan package was used[22].

Quality of the evidence

Two reviewers independently assessed the quality of evidence using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) approach[23]. Quality of evidence was graded as high, moderate, low, or very low. GRADE starts with a baseline rating of 'high quality of evidence" for RCTs, and "low quality of evidence" for non-RCTs[24]. Given that only observational studies were included in this review we assessed the quality of evidence starting-off as "low quality" and downgraded or upgraded accordingly. Reasons for downgrading included high risk of bias, inconsistency or heterogeneity, indirectness of the findings, imprecision of the point estimates, and publication bias. The quality of evidence was upgraded if data showed a large effect, a dose-response effect, or if all the plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed.

Results

Search outcome

A total of 324 published articles were identified based on our defined search criteria. Of these, 13 met our inclusion criteria for the meta-analysis (Figure 1 and Table 1). All the 13 studies reported the full dose vaccine effectiveness and five studies also reported on effectiveness of partial dose of RV1 vaccine as well. The included studies originated from eight countries. The large majority of studies were excluded from the analysis after

screening the title and abstract (n=259). Fifty-two studies were excluded after full-text screening. Of these, 28 were due to evaluation of the impact of RVA vaccines, 13 were systematic reviews, four were rotavirus symposium report, and rotavirus strain distribution respectively, two were evaluating the effectiveness of RVA pentavalent vaccine (RotaTeq®), and one was an informative interview (Figure 1; see *Extended data*: Supplementary File One, Supplementary Text 2 for details)[17]. All the studies included in this review used enzyme immunoassay (EIA) to identify rotavirus infection (Extended data: Supplementary File Two)[17].

Risk of bias in the included studies

ROB in the included studies was assessed, and none was found to have a high risk of bias. The assessment using NOS was based on selection, comparability, and exposure. With regard to selection; most studies had adequate selection and representativeness of cases, controls were selected within the same population as cases, and it was difficult to ascertain if the history of rotavirus among the control was considered. With regard to comparability; confounding was controlled through adjusting for age, date of birth, and month and year of admission in the analysis for the majority of the studies. Lastly, exposure was ascertained through the vaccination cards held by a guardian or parent. It was difficult to ascertain whether the non-response rate was considered in the analysis of most studies (see *Extended data*: Supplementary File Three for details)[17].

Pooled vaccine effectiveness of Rotarix® (RV1) vaccine

Pooled RV1 VE against rotavirus-associated hospitalization was estimated as 44% (95% CI 28–57%) among children who received partial dose versus 57% (95% CI 49–64%) among children who received the full dose. There was no statistical evidence of heterogeneity for studies reporting estimates for both full ($I^2 = 0.0$, $p = 0.98$) and partial dose ($I^2 = 0.0$, $p = 0.97$) (Figure 2). When stratifying by age (<12 months, 12–23 months, <24 months and 12–59 months), full dose of RV1 had an effectiveness of 61% (95% CI 50–69%), 55% (95% CI 32–71%), 56% (95% CI 43–67%), and 37% (95% CI 14–53%), respectively (Figure 3). Statistically significant heterogeneity ($I^2 = 71.9$ %, $p = 0.003$) was observed for 12–59 months age category. No heterogeneity was observed in other age stratification ($I^2 = 0.0$ %, p >0.05). Four and three studies reported VE for children aged 12–23 and <24 months, respectively. These estimates should however be interpreted with caution due to few numbers of studies used. Publication bias was not observed among the studies that reported on effectiveness of RV1 vaccines (Figure 4). This was supported by eggers regression intercept (-0.43; 95 % CI -1.2 to 0.37; p=0.273).

Sensitivity analysis

Sensitivity analysis was carried out by excluding Armah *et al.* 2016[25] in our meta-analysis of full and partial dose VE. This study reported full dose vaccine effectiveness of 18% (95% CI -81-63%). This was due to high vaccine coverage (93–100%) immediately after its introduction in Ghana making it difficult to arrive at robust VE estimate[25]. VE estimate for full dose by excluding this study in our meta-analysis was
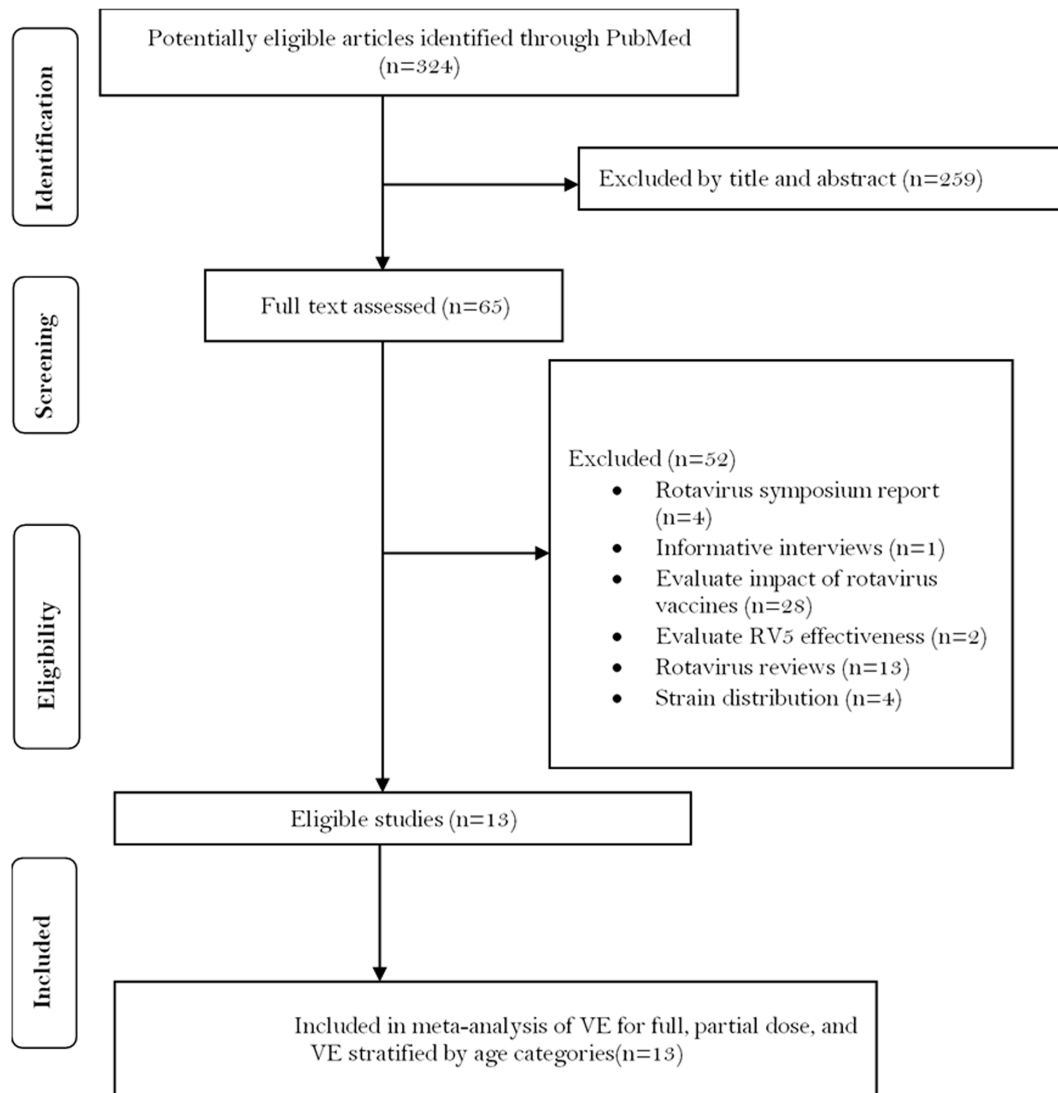
Figure 1. Identification of studies included in the systematic review. VE=Vaccine effectiveness.

58% (95% CI 50–65%) (*Extended data*: Supplementary File One, Supplementary Figure 1)[17]. More so, sensitivity analysis was carried out to ascertain the source of high heterogeneity when meta-analysis was stratified by age categories. A study by Mujuru *et al.* 2019[26] was dropped from analysis because the author stated that VE estimate for this aged group lacked precision and was non-significant[26]. VE estimate for full dose after this study was dropped from analysis was 61% (95 % CI 42–73%) and no heterogeneity was observed in any of the age stratification (*Extended data*: Supplementary File One, Supplementary Figure 2)[17].

Quality of evidence
Pooled VE for full and partial dose had moderate quality of evidence. We started at the low quality of evidence because

our pooled effects were based on case-control studies (observational studies). No considerable bias was detected using the NOS, all studies were conducted in Africa and directly address review questions, and no heterogeneity or imprecision which was observed to warrant downgrading. However, the evidence was upgraded to moderate quality since the magnitude of the effect was high and consistent throughout the included studies (Table 2).

Our effect estimate based on age categories had low quality of evidence. The evidence was downgraded by one for imprecision due to the few numbers studied used within the different age categories. However, we upgraded the evidence by one since the reported estimates are consistent within the different age categories. No further adjustment was made as

Table 1. Characteristics of case-control studies included in analysis of vaccine effectiveness.

Study	Country	Age (m/w)	Sample size	Cases vaccinated (N/Total)		Control vaccinated (N/Total)		Adjusted VE (95% CI)	
				Partial	Complete	Partial	Complete	Partial dose	Full dose
Beres et al. 2016[27]	Zambia	>=6m	316	1/18	8/18	28/298	182/298	62 (-261 to 96)	56 (-34 to 86)
Bar-zeev et al., 2015[28]	Malawi	<12m	392	NR	81/109	NR	234/283	NR	64 (24-83)
Armah et al. 2016[25]	Ghana	6-<24m	655	NR	196/207	NR	426/448	NR	18 (-81 to 63)
Bar-zeev et al., 2016[29]	Malawi	<60m <12m 12-23m	933 634 272	NR NR NR	241 167 71	NR NR NR	692 467 201	NR NR NR	58.3 (20.2-78.2) 70.6 (33.6-87.0) 31.7 (-140.6 to 80.6)
Plattis-mills et al., 2017[30]	Tanzania	<60m	220	NR	57/71	NR	121/149	NR	74.8 (-8.2 to 94.1)
Abeid et al., 2017[31]	Tanzania	5-23m 5-11m 12-23m	691 474 217	NR NR NR	157/179 94/107 63/72	NR NR NR	480/512 345/367 135/145	N/R N/R N/R	57(14-78) 56(-2 to 81) 57(-30-86)
Ganstanaduy et al., 2016[32]	Botswana	>=4m 4-11 ≥12	610 425 185	37/242 26/162 11/80	162/242 108/162 54/80	51/368 38/368 13/105	288/368 202/368 86/105	48(1-72) 42(-23 to 73) 63(-33 to 90)	54(23-73) 52(8-75) 67(8-89)
Groome et al., 2014[33]	South Africa	18w-23m 18w-11m 12-23m	1974 1336 638	126/540 92/389 34/151	278/540 207/389 71/151	334/1434 231/947 103/487	856/1434 567/947 289/487	40(16-57) 39(9-59) 40(-7-66)	57(40-68) 54(32-68) 61(35-77)
Mujuru et al. 2019[26]	Zimbabwe	6-11m >=12m	1467 2121	371/398 482/505	NR NR	NR NR	NR NR	NR NR	61 (21-81) -48 (-148 to 11)
Mokomane et al. 2018[34]	Botswana	>=4m	610	37/242	162/242	51/368	288/368	48 (1-72)	54 (23-73)
Jani B et al. 2018[35]	Tanzania	5-23m	609	NR	110/119	NR	470/490	NR	49 (-30 to 80)
Khagayi et al. 2020[36]	Kenya	<60m <12m >=12m	509 273 175	7/40 NR NR	51/83 33/55 18/28	41/110 NR NR	308/365 184/218 124/147	54 (-20 to 83) NR NR	64(35-80) 67(30-84) 72(10-91)
Bennett A et al. 2018[37]	Malawi	<60m <12m 12-23m	1318 1318 1318	NR NR NR	275/1019 190/696 78/285	NR NR NR	NR NR NR	NR NR NR	61.89 (28.04-79.82) 74.88 (44.59-88.61) 31.69 (-139.03 to 80.48)

VE: Vaccine effectiveness; NR: Not recorded; CI: Confidence interval; Partial dose: One dose of Rotarix; Full dose: Two doses of Rotarix; age (m/w): Age in months or weeks.
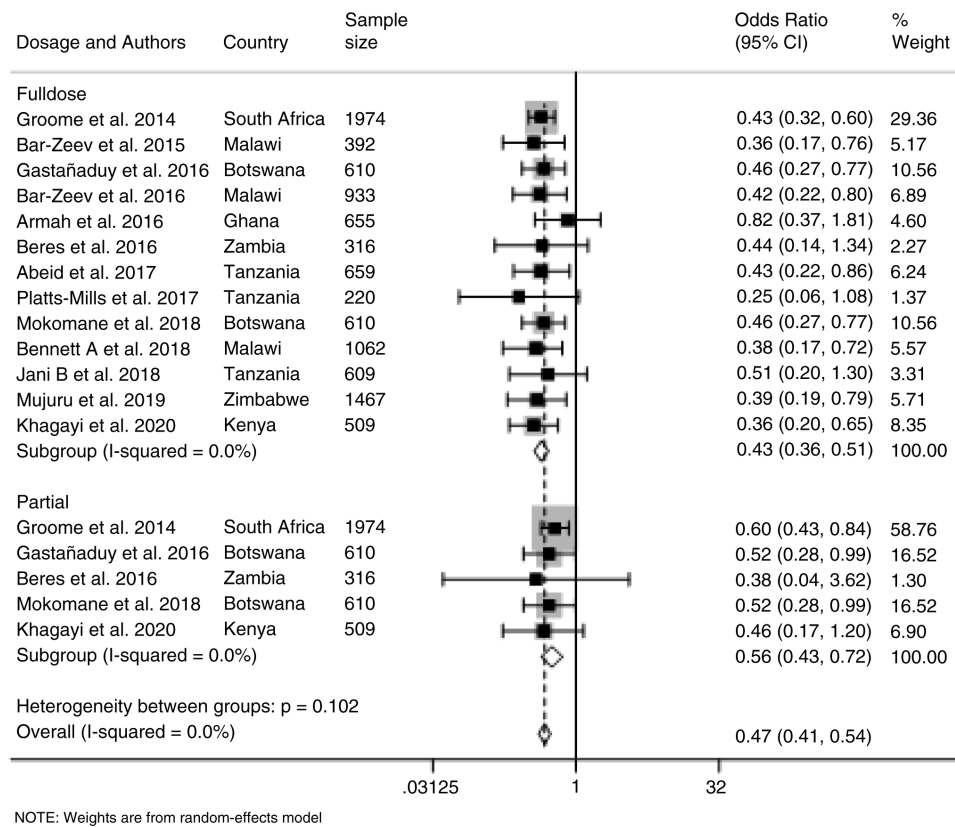
Figure 2. Forest plot of vaccine effectiveness of full and partial doses against hospitalization for rotavirus gastroenteritis. Studies are plotted starting with the earliest published to the recent. Each study is represented by a black box and a horizontal line, which correspond to the odds ratio and 95% CI, respectively. The vertical line in the middle corresponds to an odds ratio of 1.0. The diamond represents the overall pooled odds ratio with the 95% CI given by its width. I-squared shows the degree of heterogeneity with p-value indicating whether there was statistically significant heterogeneity between the studies and among the groups. Fulldose stands for two doses of the Rotarix while Partial represents one dose of Rotarix.

no considerable bias was detected by the NOS and all studies were conducted in Africa and directly addressed the review question (Table 3).

Discussion

Majority of African countries have introduced the Rotarix® vaccine into their NIP and there is a need to continue making a case for continued vaccination of African children against rotavirus infection. We present pooled VE from case-control studies in the continent showing that full-dose of RV1 vaccine had higher vaccine effectiveness point estimate (VE = 58%, 95% CI: 50-65%) compared to partial dose (VE = 44%, 95% CI: 28-57%). We found that the pooled VE was within range of vaccine efficacy observed during clinical trials in Africa (50–80%).

The confidence intervals (CI) of our VE estimates for full and partial dose were overlapping. Similar evaluation outside Africa by Hungerford *et al*. (2017) shows that full dose of RV1 vaccine had an effectiveness of 89% (95% CI 84-92%)

and partial dose had an effectiveness of 62% (95% CI 55-69%)[38]. Another study evaluating effectiveness in individuals in Latin American and the Caribbean found pooled VE for full dose of RV1 against rotavirus hospitalization was 63.5% (95% CI 39.2-78.0%) when using hospital control and 72.2% (95% CI 60.9-80.2%)[39] for community control. Evidently, these estimates of VE are higher than our findings in Africa, hence portraying a similar scenario to the pre-licensure evaluation of rotavirus vaccine efficacy whereby efficacy in high-income countries were higher than low-income countries[9]. We have also shown evidence of protection against RVA-associated severe diarrhoea beyond the first year of life. All the studies included in this review used enzyme immunoassay (EIA) to identify rotavirus infection. Therefore, the sensitivity and specificity of the tests could not have affected vaccine effectiveness across all studies.

This analysis had some limitations. Primarily, the number of studies reporting effectiveness of RV1 vaccine was still low compared to the number of countries that have introduced
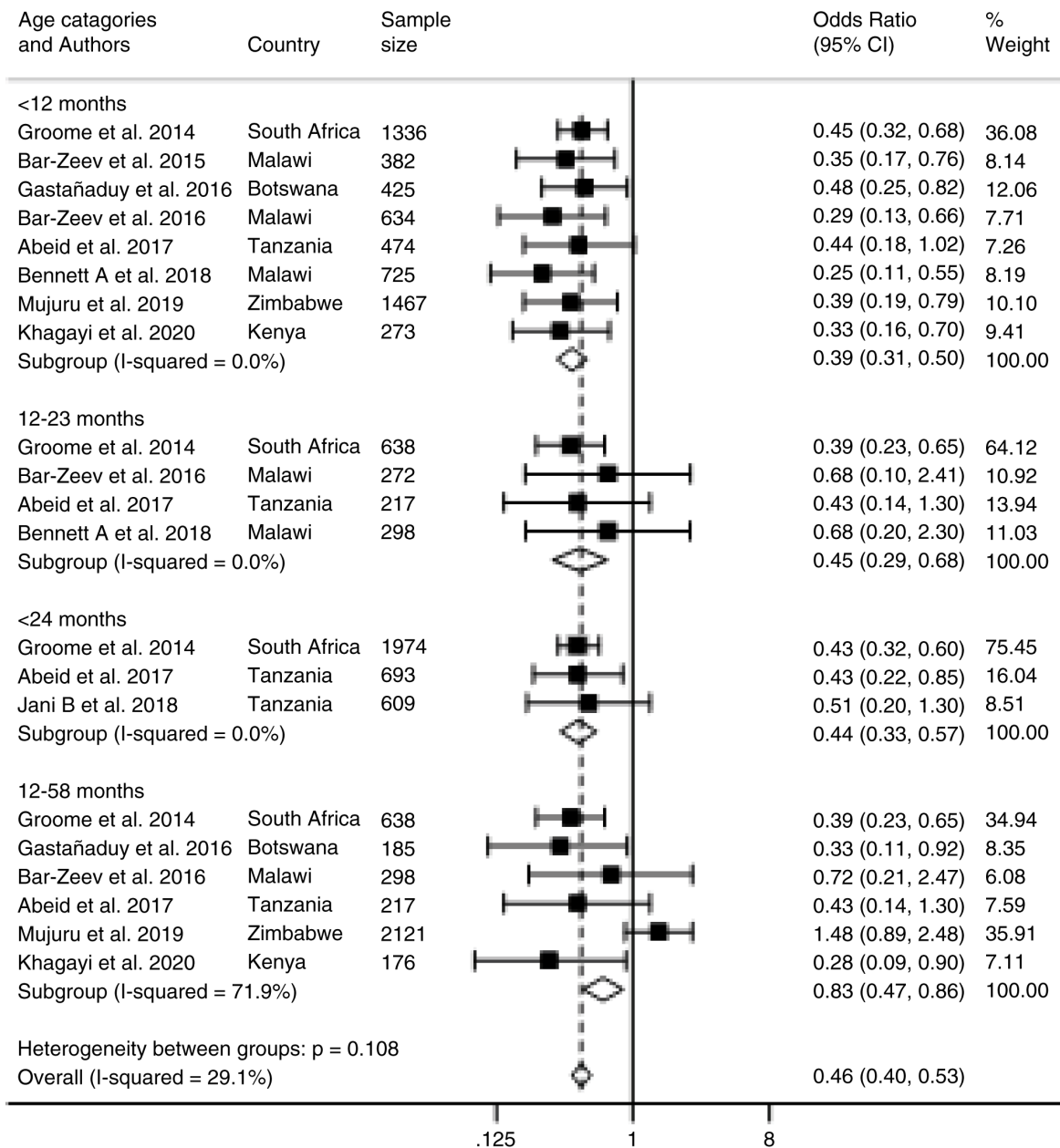
Age catagories and Authors	Country	Sample size		Odds Ratio (95% CI)	% Weight
<12 months					
Groome et al. 2014	South Africa	1336		0.45 (0.32, 0.68)	36.08
Bar-Zeev et al. 2015	Malawi	382		0.35 (0.17, 0.76)	8.14
Gastañaduy et al. 2016	Botswana	425		0.48 (0.25, 0.82)	12.06
Bar-Zeev et al. 2016	Malawi	634		0.29 (0.13, 0.66)	7.71
Abeid et al. 2017	Tanzania	474		0.44 (0.18, 1.02)	7.26
Bennett A et al. 2018	Malawi	725		0.25 (0.11, 0.55)	8.19
Mujuru et al. 2019	Zimbabwe	1467		0.39 (0.19, 0.79)	10.10
Khagayi et al. 2020	Kenya	273		0.33 (0.16, 0.70)	9.41
Subgroup (I-squared = 0.0%)				0.39 (0.31, 0.50)	100.00
12-23 months					
Groome et al. 2014	South Africa	638		0.39 (0.23, 0.65)	64.12
Bar-Zeev et al. 2016	Malawi	272		0.68 (0.10, 2.41)	10.92
Abeid et al. 2017	Tanzania	217		0.43 (0.14, 1.30)	13.94
Bennett A et al. 2018	Malawi	298		0.68 (0.20, 2.30)	11.03
Subgroup (I-squared = 0.0%)				0.45 (0.29, 0.68)	100.00
<24 months					
Groome et al. 2014	South Africa	1974		0.43 (0.32, 0.60)	75.45
Abeid et al. 2017	Tanzania	693		0.43 (0.22, 0.85)	16.04
Jani B et al. 2018	Tanzania	609		0.51 (0.20, 1.30)	8.51
Subgroup (I-squared = 0.0%)				0.44 (0.33, 0.57)	100.00
12-58 months					
Groome et al. 2014	South Africa	638		0.39 (0.23, 0.65)	34.94
Gastañaduy et al. 2016	Botswana	185		0.33 (0.11, 0.92)	8.35
Bar-Zeev et al. 2016	Malawi	298		0.72 (0.21, 2.47)	6.08
Abeid et al. 2017	Tanzania	217		0.43 (0.14, 1.30)	7.59
Mujuru et al. 2019	Zimbabwe	2121		1.48 (0.89, 2.48)	35.91
Khagayi et al. 2020	Kenya	176		0.28 (0.09, 0.90)	7.11
Subgroup (I-squared = 71.9%)				0.83 (0.47, 0.86)	100.00
Heterogeneity between groups: p = 0.108					
Overall (I-squared = 29.1%)				0.46 (0.40, 0.53)	

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Figure 3. Forest plot of vaccine effectiveness against hospitalization for rotavirus gastroenteritis stratified by age groups. Studies are plotted starting with the earliest published to the recent. Each study is represented by a black box and a horizontal line, which correspond to the odds ratio and 95% CI, respectively. The vertical line in the middle corresponds to an odds ratio of 1.0. The diamond represents the overall pooled odds ratio with the 95% CI given by its width. I-squared shows the degree of heterogeneity with p-value indicating whether there was statistically significant heterogeneity between the studies and among the groups.

RV1. We only used data from the limited number of studies that have been published to date. Including more studies in a future meta-analysis will improve our certainty of the pooled VE estimates from the African continent both for the different age categories and for partial- and full-dose assessment.

In conclusion, we show that RV1 vaccine effectiveness is substantial in Africa and is occurring within the range of efficacy findings observed in clinical trials. The pooled vaccine effectiveness point estimate was lower with a partial dose compared to full dose, thus increased coverage should be encouraged to
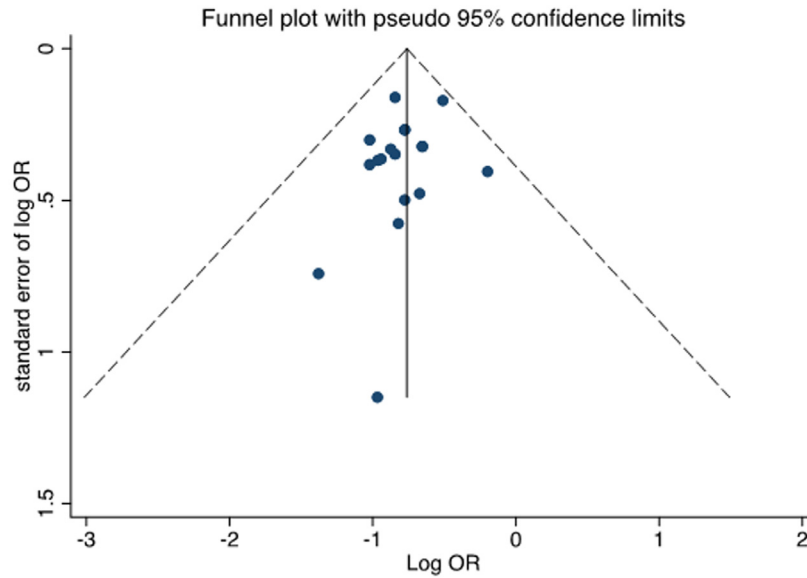
Figure 4. Funnel plot to assess publication bias among studies evaluating effectiveness of RV1 vaccine against hospitalization for laboratory-confirmed rotavirus gastroenteritis. The triangle represents the estimates of the included studies that reported on the effectiveness of full and partial dose of RV1 vaccine. The log of the odds ratio is plotted on the horizontal axis, against the standard error of the log odds ratio. The vertical line in the funnel plot indicates the random effect summary estimate and the sloping two lines indicate the expected 95% CIs for a given SE.

Table 2. Assessment of quality of evidence for vaccine effectiveness (VE) of partial and full dose.

Effectiveness of RVA vaccine in Africa for partial and full dose		Cases vaccinated (n/Total)	Control vaccinated (n/Total)	Adjusted[1] VE; partial dose (OR (95% CI))	Adjusted[1] VE; partial dose (OR (95% CI))	Overall adjusted[1] VE; partial or full dose (OR (95% CI))	Number of participants (number of studies)
		335/ 3468	5948/6519	0.56 (0.43 – 0.72)	0.43 (0.36 – 0.51)	0.47 (0.41 – 0.54)	9987 (13 studies)
Certainty of assessment using GRADE approach	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Magnitude of effect	Overall certainty of evidence
	Case control	Low No downgrade[2]	Low No downgrade[3]	Low No downgrade[4]	Low Did not downgrade[5]	High [6]Upgraded by 1	⊕⊕⊕O MODERATE

Assessment of quality of evidence of vaccine estimates from different age categories. Quality of evidence is graded as high, moderate, low, or very low as a result of downgrading or upgrading the VE estimates. Reasons for downgrading include high risk of bias, inconsistency or heterogeneity, indirectness of the findings, imprecision of the point estimates, and publication bias. The quality of evidence is upgraded if data shows a large effect, a dose-response effect, or if all the plausible residual confounding reduce the demonstrated effect or suggest a spurious effect if no effect was observed.

[1] Adjusted for age and date of admission in most of the studies.

[2] No considerable risk of bias was detected using the Newcastle-Ottawa scale (NOS).

[3] There was no statistical heterogeneity (I^2 = 0%), there was also low methodological heterogeneity given that all included studies used similar study design.

[4] The studies were all conducted in African countries and directly address the review question.

[5] We did not downgrade for imprecision although some studies had wide confidence intervals. We conducted sensitivity analysis by removing Beres *et al*. 2016 (*Extended data*: Supplementary File One, Supplementary Figure 3)[17], which had widest CI was removed from the meta-analysis and concluded it did not change the pooled estimate.

[6] The magnitude of effect was high consistently throughout all included studies. Quality of evidence was upgraded by 1.

Table 3. Assessment of quality of evidence for vaccine effectiveness (VE) by age categories.

Effectiveness of RVA vaccine in Africa stratified by age categories dose	Cases vaccinated (n/Total)	Control vaccinated (n/Total)	Adjusted[1] VE; <12 m (OR (95% CI))	Adjusted[1] VE; 12-23 m (OR (95% CI))	Adjusted[1]VE; <24 m (OR (95% CI))	Adjusted[1]VE; 12-59 m (OR (95% CI))	Overall adjusted[1] VE; age categories (OR (95% CI))	Number of participants (number of studies)
	3090/4336	5924/6835	0.39 (0.31-0.50)	0.45 (0.29-0.68)	0.44 (0.33-0.57)	0.63 (0.47 – 0.86)	0.46 (0.40 – 0.53)	11171 (21 studies)
Certainty of assessment using GRADE approach	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Magnitude of effect	Overall certainty of evidence	
	Case control	Low	Low	Low	Low	High	⊕⊕OO Low	
		No downgrade[2]	No downgrade[3]	No downgrade[4]	Downgraded by 1[5]	[6]Upgraded by 1		

Assessment of quality of evidence of vaccine estimates from different age categories. Quality of evidence is graded as high, moderate, low, or very low as a result of downgrading or upgrading the VE estimates. Reasons for downgrading include high risk of bias, inconsistency or heterogeneity, indirectness of the findings, imprecision of the point estimates, and publication bias. The quality of evidence is upgraded if data shows a large effect, a dose-response effect, or if all the plausible residual confounding reduce the demonstrated effect or suggest a spurious effect if no effect was observed.

[1] Adjusted for age and date of admission in most of the studies.

[2] No considerable risk of bias was detected using the Newcastle-Ottawa scale (NOS).

[3] There was statistical heterogeneity (Figure 4). We conducted sensitivity analysis by dropping Mujuru et al. 2019 from analysis because the author stated that VE estimate for this aged group lacked precision and was non-significant. No heterogeneity was observed after dropping this study. There was also low methodological heterogeneity given that all included studies used similar study design.

[4] The studies were all conducted in African countries and directly address the review question.

[5] We downgraded for imprecision by 1 due to small number of studies used in some groups, see Figure 3.

[6] The magnitude of effect was high consistently throughout all included studies. Quality of evidence was upgraded by 1.

reap the full benefits of this vaccine. Although the quality of evidence in the age-category based analysis was lower, the data so far appear to support the notion that VE of RV1 is high beyond the first year of life in African children.

Data availability
Underlying data
Havard Dataverse: Replication Data for: Effectiveness of Rotarix® vaccine in Africa in the first decade of progressive introduction, 2009–2019: systematic review and meta-analysis https://doi.org/10.7910/DVN/WJOF7N[17].

This project contains the following underlying data:
- Age_categories.tab
- NMurunga_Rotarix_MetaAnalysis_codebook.pdf
- NMurunga_Rotarix_MetaAnalysis_Readme.txt
- Partial_complete_dose.tab
- RV_effectiveness.do

Extended data
Havard Dataverse: Replication Data for: Effectiveness of Rotarix® vaccine in Africa in the first decade of progressive introduction, 2009–2019: systematic review and meta-analysis https://doi.org/10.7910/DVN/WJOF7N[17].

This project contains the following extended data:
- Supplementary File One.docx
  - Supplementary Text 1. Search strategy of peer-reviewed articles.
  - Supplementary Text 2. Inclusion/exclusion criteria for the systematic review and meta-analysis.
  - Supplementary Figure 1. Estimated pooled vaccine effectiveness for complete dose of RV1 against laboratory-confirmed rotavirus infection with Armah et al. 2016 excluded.
  - Supplementary Figure 2. Estimated pooled vaccine effectiveness for complete dose of RV1 against laboratory-confirmed rotavirus infection stratified by age categories after excluding Mujuru et al. 2019.
  - Supplementary Figure 3. Estimated pooled vaccine effectiveness for complete dose of RV1 against laboratory-confirmed rotavirus infection with Beres et al. 2016 excluded.
- Supplementary File Two.tab (data collection form)
- Supplementary File Three.pdf (Risk of Bias Assessment for All Case Control Studies Included in Vaccine

Effectiveness Evaluation using Newcastle Ottawa Scale).

Reporting guidelines
Harvard Dataverse: PRISMA checklist for 'Effectiveness of Rotarix® vaccine in Africa in the first decade of progressive introduction, 2009–2019: systematic review and meta-analysis' (Supplementary File One, Table 1), https://doi.org/10.7910/DVN/WJOF7N[17].

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

Acknowledgements

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Open Peer Review

Current Peer Review Status: ✓ ✓

Version 2

Reviewer Report 11 November 2020

https://doi.org/10.21956/wellcomeopenres.17919.r41126

✓

Julia M Baker [ID]
Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

In this study, Murunga *et al.* examine two important questions: 1) the full vs. partial dose vaccine effectiveness of RV1 in African countries and 2) effectiveness across age groups. Investigation into these questions will further guide vaccination strategies in a setting where the burden of rotavirus is greatest. Overall, this is a thoroughly conducted study with several relevant sensitivity analyses and quality assessments. The manuscript well describes the results and interpretation of findings.

Major comments:
- Please provide more detail regarding your random effects model. Did you use a random intercept, random slopes, or both? How did you account for variations in effect size?

Minor comments:
- In Table 1, the "Partial dose Full dose" heading should be separated into two columns to correspond with the rows below.

- In Table 1, some of the studies indicate age groups greater than a certain age (e.g. >=6m). Please indicate the maximum age for these as well. Were they all <60m?

- Please clarify what the grey shaded areas represent in Figure 2.

- It seems worth elaborating more on the age stratified results in the discussion section (while noting that the quality of the evidence is poor). These results may be helpful for addressing questions about potential waning immunity.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Partly

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Vaccine effectiveness evaluation.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 16 October 2020

https://doi.org/10.21956/wellcomeopenres.17919.r40602

✔ **Sergio George**
Faculty of Medicine, University of Chile, Santiago, Chile

Miguel O'Ryan [iD]
[1] Programa de Microbiología, ICBM, Facultad de Medicina, Universidad de Chile, Santiago, Chile
[2] Instituto Milenio de Inmunidad e Inmunoterapia, Facultad de Medicina, Universidad de Chile, Santiago, Chile

All comments have been addressed

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatric infectious diseases, vaccines, enteric infections

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

- -

Version 1

Reviewer Report 18 August 2020

https://doi.org/10.21956/wellcomeopenres.17758.r39864

? Sergio George
Faculty of Medicine, University of Chile, Santiago, Chile

Miguel O'Ryan (iD)

[1] Programa de Microbiología, ICBM, Facultad de Medicina, Universidad de Chile, Santiago, Chile
[2] Instituto Milenio de Inmunidad e Inmunoterapia, Facultad de Medicina, Universidad de Chile, Santiago, Chile

Nickson Murunga and collaborators present a comprehensive review and meta-analysis, pooling data from identified studies to determine effectiveness of RV1 (Rotarix®) in Africa during the last 10 years.

The manuscript is well-written and precise (with some grammar mistakes that can be reviewed) with an adequate description of the search strategy and analysis process, although with the characteristic technical descriptions that requires expertise for appropriate evaluation. The search leads to a rather small (unfortunately not more data is available) but reasonably robust number of overall participants. The study should be reviewed by an expert in meta-analysis methods to assure that the methods used in this study are correct.

Specific comments:
Introduction
- Authors should explain and detail differences between terms "effectiveness" and "impact". As mentioned in background, RVA vaccine implementation in Africa was based on expected impact on disease, despite clinical trials showed lower efficacy compared to industrialized countries. Studies published post vaccine introduction are focused on its impact and/or effectiveness, and this review focuses only in those studies assessing effectiveness. It is possible to assume that "impact" refers to overall effect of vaccine in a population (which includes vaccinated and non-vaccinated subjects) and "effectiveness" refers to direct effect of vaccine (only in vaccinated subjects). However, in order to be understandable to general scientific community authors should specify this difference.

Methods:
- The fact that the term "impact" was included in the search strategy followed by exclusion of 28 studies focusing on impact of vaccine on diarrhea hospitalization and diarrhea

associated mortality is unclear.

○ Authors should specify if "partial dose" refers to 1 dose of Rotarix, and "complete dose" to 2 doses in all studies included in this review.

○ There is no mention of diagnostic tests used to identify rotavirus infection in the different studies. As sensitivity and specificity differs between tests, this variable may affect effectiveness results in different studies.

Results:
○ Table 1 and 2 are excessively redundant (they can be merged).

○ Table 3 is not required; it can be reduced to one sentence highlighting the only different study (Abeid *et al.*).

○ The reasoning provided for the sensitivity analysis are unclear; is this standard methodology?

○ Tables 4 and 5 are somewhat difficult to understand, should be better explained.

Discussion:
○ More caution in the full dose vs partial dose conclusion as there is no significant difference.

○ Authors compare results of this meta-analysis with a study performed in Latin America which used both hospital and community controls. This lead to ask if all studies included in this meta-analysis used only hospitalized controls, and if so, was it because studies from a non-hospital setting were not found in the literature search?

○ "...falling within range" may be misleading, better "within range".

○ Evidently, this estimates, should be these estimates.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatric infectious diseases, vaccines, enteric infections.

We confirm that we have read this submission and believe that we have an appropriate level

of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 07 Sep 2020

Nickson Murunga, Kenya Medical Research Institute (KEMRI)-Wellcome Trust Research Programme, Kilifi, Kenya

Introduction Section

1. Authors should explain and detail differences between terms "effectiveness" and "impact".As mentioned in background, RVA vaccine implementation in Africa was based on expected impact on disease, despite clinical trials showed lower efficacy compared to industrialized countries. Studies published post vaccine introduction are focused on its impact and/or effectiveness, and this review focuses only in those studies assessing effectiveness. It is possible to assume that "impact" refers to overall effect of vaccine in a population (which includes vaccinated and non-vaccinated subjects) and "effectiveness" refers to direct effect of vaccine (only in vaccinated subjects). However, in order to be understandable to general scientific community authors should specify this difference.

Authors Response: Thanks for pointing this out, we have clarified the difference in the revised manuscript.

2. The fact that the term "impact" was included in the search strategy followed by exclusion of 28 studies focusing on impact of vaccine on diarrhea hospitalization and diarrhea associated mortality is unclear.

Authors Response: Impact was included in our search strategy because during our screening we realized some papers titled reporting on the impact of rotavirus vaccine had within their results section an estimate of local vaccine effectiveness. Excluding impact in our search strategy will have excluded some of the papers that have reported on vaccine effectiveness. An example is a paper by Plats-Mills et al. 2017 "Impact of Rotavirus Vaccine Introduction and Post introduction Etiology of Diarrhea Requiring Hospital Admission in Haydom, Tanzania, a Rural African Setting".

3. Authors should specify if "partial dose" refers to 1 dose of Rotarix, and "complete dose" to 2 doses in all studies included in this review.

Authors Response: Thank you for pointing this out. We have added this clarification in Tables and Figure 2 legends.

4. There is no mention of diagnostic tests used to identify rotavirus infection in the different studies. As sensitivity and specificity differs between tests, this variable may affect effectiveness results in different studies.

Authors Response: Thank you for pointing this out. We have included this in our revised version.

Results Section

5.   Table 1 and 2 are excessively redundant (they can be merged).

Authors Response: We have merged the two tables. Included in our revised manuscript.

6.   Table 3 is not required; it can be reduced to one sentence highlighting the only different study (Abeid et al.).

Authors Response: Thank you for the observation. This has been amended in our revised manuscript.

7. The reasoning provided for the sensitivity analysis are unclear; is this standard methodology?

Authors Response: Yes. This is a standard methodology. Sensitivity analysis is one of the strategies for addressing heterogeneity see https://training.cochrane.org/handbook/current/chapter-10#section-10-11.

8.   Tables 4 and 5 are somewhat difficult to understand, should be better explained.

Authors Response: Thanks for this observation. More explanation is provided in our revised manuscript.

Discussion:

9.   More caution in the full dose vs partial dose conclusion as there is no significant difference.

Authors Response: This has been rephrased in our revised manuscript.

10. Authors compare results of this meta-analysis with a study performed in Latin America which used both hospital and community controls. This lead to ask if all studies included in this meta-analysis used only hospitalized controls, and if so, was it because studies from a non-hospital setting were not found in the literature search?

Authors Response: Thank you for noting this. From our literature search, only one study from Malawi (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4374102/) used both hospital and community control. A similar magnitude of vaccine effectiveness was established for both controls. Therefore, only hospital control was included in this meta-analysis.

11. "…falling within range" may be misleading, better "within range".

Authors Response: Corrected.

12. Evidently, this estimate, should be these estimates.

Authors Response: Corrected**.**

Competing Interests: No competing interests were disclosed.