SYSTEMATIC REVIEW

Effectiveness of Rotarix® vaccine in Africa in the first decade of progressive introduction, 2009-2019: systematic review and meta-analysis [version 1; peer review: 1 approved with reservations]

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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.

**Keywords**
Rotavirus, vaccine effectiveness, systematic review, meta-analysis, Africa

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Introduction

Globally, rotavirus group A (RVA) is a leading cause of severe dehydrating acute diarrhoea in children aged <5 years. In 2016, approximately 117 million episodes of rotavirus-associated diarrhoea occurred in sub-Saharan Africa, ~104,000 of which were fatal. Rotavirus vaccination programmes are considered the most effective control measure for RVA disease and six oral vaccines (Rotatiq® (RV5), Rotarix® (RV1), Rotavac®, Rotavin-mi®, Lanzhou Lamb and Rotasil®) have been licensed. In 2009, the World Health Organization recommended inclusion of two licensed RVA vaccines (Rotarix®, GlaxoSmithKline Biologicals, Belgium; and Rotatiq®, Merck, USA) into routine national immunization programmes (NIP) of all countries. 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%). 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). 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. 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. There have been expert reviews discussing the impact of RVA vaccine in African countries and systematic review and meta-analysis conducted focusing on the prevalence of rotavirus infections pre- and post-vaccine introduction. 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. Two reviewers screened the outputs (Extended data: Supplementary File One, Supplementary Table 1). Publications were identified using combinations of the following key search terms: “Rotavirus”, “effectiveness”, “success”, “impact”, “effect”, “potency”, “performance”, “vaccine”, “Rotarix”, “Rotatiq” 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). 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.

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).

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).

Assessment of risk of bias

The Newcastle–Ottawa scale (NOS) was used to assess the risk of bias (ROB) among the case-control studies. 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. 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 \( \sqrt{VE} = \{1 - OR\} \times 100\% \) to obtain the respective \( OR = 1 - \{VE/100\} \) 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 \( (Q-df) / Q \times 100 \% \) 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. 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.

Quality of the evidence
Two reviewers independently assessed the quality of evidence using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. 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. 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; Table 1 and Table 2). 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 for several reasons as detailed in the following figure.
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)⁶⁶.

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 (Table 3). 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 (Table 3; see Extended data: Supplementary File Three for details)⁶⁶.

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 (I² = 0.0, p = 0.98) and partial dose (I² = 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 (I² = 71.9 %, p = 0.003) was observed for 12–59 months age category. No heterogeneity was observed in other age stratification (I² = 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. 2016²⁷ 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 estimate²⁷. VE estimate for full dose by excluding this study in our meta-analysis was 58% (95% CI 50-65%) (Extended data: Supplementary File One, Supplementary Figure 1)⁶⁶. More so, sensitivity analysis was carried out to ascertain the source of high heterogeneity

Table 1. Characteristics of case-control studies included in analysis of RVA vaccine effectiveness for full and partial dose.

| Study | Country       | Sample size | Cases vaccinated (N/Total) | Control vaccinated (N/Total) | Adjusted VE (95% CI) |
|-------|---------------|-------------|---------------------------|-------------------------------|----------------------|
|       |               |             | Partial          | Full                  | Partial          | Full                  |
|       |               |             | (N/Total)        | (N/Total)             | (N/Total)        | (N/Total)             |
|       |               |             |                 |                     |                 |                     |
| Groome et al. 2014²⁴ | South Africa | 1974        | 126(540)         | 278/540             | 334/1434         | 856/1434             | 40 (16-57)     | 57 (40-68) |
| Bar-zeev et al. 2015²⁵ | Malawi       | 392         | NR              | 81/109              | NR              | 234/283             | NR              | 64 (24-83) |
| Beres et al. 2016²⁶ | Zambia       | 316         | 1/18            | 8/18                | 28/298           | 182/298             | 62 (-261 to 96) | 56 (-34 to 86) |
| Armah et al. 2016²⁷ | Ghana        | 655         | NR              | 196/207             | NR              | 426/448             | NR              | 18 (-81 to 63) |
| Ganstanaduy et al. 2016²⁸ | Botswana     | 610         | 37/242          | 162/242             | 51/368           | 288/268             | 48 (1-72) | 54 (23-73) |
| Bar-zeev et al. 2016²⁹ | Malawi       | 933         | NR              | 241                | NR              | 692                | NR              | 58.3 (20.2-78.2) |
| Plattis-mills et al. 2017³⁰ | Tanzania      | 220        | NR              | 57/71              | NR              | 121/149             | NR              | 74.8 (-8.2 to 94.1) |
| Abeid et al. 2017³¹ | Tanzania     | 691         | NR              | 157/179            | NR              | 480/512             | N/R             | 57 (14-78) |
| Mokomane et al. 2018³² | Botswana     | 610         | 37/242          | 162/242             | 51/368           | 288/268             | 48 (1-72) | 54 (23-73) |
| Jani et al. 2018³³ | Tanzania     | 609         | NR              | 110/119            | NR              | 470/490             | NR              | 49 (-30 to 80) |
| Mjuuru et al. 2019³⁴ | Zimbabwe     | 1467        | NR              | 37/1398            | NR              | NR                 | NR              | 61 (21-81) |
| Khagayi et al. 2020³⁵ | Kenya        | 509         | 7/40            | 51/83              | 41/110           | 308/365             | 54 (-20 to 83) | 64 (35-80) |
| Bennett et al. 2018³⁶ | Malawi       | 1318        | NR              | 275/1019           | NR              | NR                 | NR              | 61.89 (28.04-79.82) |

VE: Vaccine effectiveness; NR: Not recorded; CI: Confidence interval.
### Table 2. Characteristics of case-control studies included in analysis of RVA vaccine effectiveness stratified by age categories.

| Study            | Country      | Age        | Sample size | Cases vaccinated (N/Total) | Control vaccinated (N/Total) | Adjusted VE (95% CI) |
|------------------|--------------|------------|-------------|----------------------------|-----------------------------|----------------------|
|                  |              |            |             | Partial/Full               | Partial/Full                | Partial dose/Full     |
| Groome et al. 2014 | South Africa | 18w–23m    | 1974/638    | 126/540/278/540            | 334/1434/231/947            | 40 (16-57) / 39 (9-59) / 40 (-7 to 66) / 57 (40-68) / 54 (32-68) / 61 (35-77) |
|                  |              | 18w–11m    | 1336/638    | 92/389/207/389             | 231/947/103/487             |                      |
|                  |              | 12–23m     | 34/151      | 71/151                     | 289/487                     |                      |
| Bar-zeev et al. 2015 | Malawi      | <12m       | 392/307     | NR/81/109                  | NR/234/283                  | 64 (24-83)           |
| Ganstanaduy et al. 2016 | Botswana                     | 4–11m      | 425/185     | 26/162/108/162             | 202/263/80/105             | 52 (8-75) / 67 (8-89) |
|                  |              | ≥12m       | 122/90      | 5480/1310                 |                            |                      |
| Bar-zeev et al. 2016 | Malawi      | <12m       | 634/272     | NR/167/71                  | NR/467/201                  | 70.6 (33.6-87.0) / 31.7 (-140.6 to 80.6) |
|                  |              | 12–23m     | 217/71      | NR/71                     | NR/71                       |                      |
| Abeid et al. 2017 | Tanzania    | 5–23m      | 691/217     | NR/157/179                | NR/480/512                  | 57 (14-78) / 56 (-2 to 81) / 57 (-30-86) |
|                  |              | 5–11m      | 474/121     | NR/94/107                 | NR/345/367                  |                      |
|                  |              | 12–23m     | 217/71      | NR/63/72                  | NR/135/145                  |                      |
| Jani et al. 2018 | Tanzania    | 5–23m      | 609/119     | NR/110/119                | NR/490/400                  | 49 (-30 to 80)       |
| Mujuru et al. 2019 | Zimbabwe    | 6–11m      | 1467/2121   | 371/398>NR                | NR/61/18-81                 |                      |
| Khagayi et al. 2020 | Kenya      | <12m       | 273/175     | 33/55/18/28               | NR/184/218/124/147         | 67 (30-84) / 72 (10-91) |
| Bennett et al. 2018 | Malawi      | <12m       | 1318/1318   | NR/190/795/78/285         | NR/16/19/4/13               | 74.88 (44.59-88.61) / 31.69 (-139.03 to 80.48) |
|                  |              | 12–23m     | 1318/1318   | NR/795/78/285             | NR/16/19/4/13               |                      |

VE: Vaccine effectiveness; NR: Not recorded; CI: Confidence interval; age (m/w): Age in months or weeks
Table 3. Risk of bias assessment for studies included in evaluation of rotavirus vaccine effectiveness in Africa using Newcastle Ottawa-scale. Details on how the assessment score was reached are described in the Extended data: Supplementary File Three.

| Study                | Country     | Study design | Selection score | Comparability score | Exposure score | Overall score | Bias         |
|----------------------|-------------|--------------|-----------------|--------------------|----------------|---------------|--------------|
| Bar-zeev et al. 2015 | Malawi      | Case-control | 3               | 2                  | 2              | 7             | Low risk     |
| Armah et al. 2016    | Ghana       | Case-control | 3               | 2                  | 2              | 7             | Low risk     |
| Bar-zeev et al. 2016 | Malawi      | Case-control | 3               | 2                  | 2              | 7             | Low risk     |
| Bennett et al. 2016  | Malawi      | Case-control | 3               | 2                  | 2              | 7             | Low risk     |
| Mokomane et al. 2018 | Botswana    | Case-control | 3               | 2                  | 2              | 7             | Low risk     |
| Abeid et al. 2017    | Tanzania    | Case-control | 2               | 2                  | 2              | 6             | Low risk     |
| Ganstanaduy et al. 2016 | Botswana     | Case-control | 3               | 2                  | 2              | 7             | Low risk     |
| Plats-Mills et al. 2017 | Tanzania     | Case-control | 3               | 2                  | 2              | 7             | Low risk     |
| Groome et al. 2014   | South Africa | Case-control | 3               | 2                  | 2              | 7             | Low risk     |
| Beres et al. 2016    | Zambia      | Case-control | 3               | 2                  | 2              | 7             | Low risk     |
| Jani et al. 2018     | Tanzania    | Case-control | 3               | 2                  | 2              | 7             | Low risk     |
| Khagayi et al. 2020  | Kenya       | Case-control | 3               | 2                  | 2              | 7             | Low risk     |
| Mujuru et al. 2019   | Zimbabwe    | Case-control | 3               | 2                  | 2              | 7             | Low risk     |

Risk of bias assessment for the 13 studies included in meta-analysis. A score is given (*) if each of the item in selection or exposure was satisfied. Two stars (**) is given for comparability if the study adjusted for age at admission and any other important factor.

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.
when meta-analysis was stratified by age categories. A study by Mujuru et al. 2019 was dropped from analysis because the author stated that VE estimate for this aged group lacked precision and was non-significant. 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).

**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.

**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...
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.

was upgraded to moderate quality since the magnitude of the effect was high and consistent throughout the included studies (Table 4).

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 no considerable bias was detected by the NOS and all studies were conducted in Africa and directly addressed the review question (Table 5).

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 effectiveness (VE = 58%, 95% CI: 50-65%) compared to partial dose (VE = 44%, 95% CI: 28-57%). We found that the pooled VE was falling 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%).

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%) 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. We have also shown evidence of protection against RVA-associated severe diarrhoea beyond the first year of life.

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 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 was lower with a partial dose compared to full dose, thus increased coverage should be encouraged to 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.
Table 4. 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<sup>1</sup> VE; partial dose (OR 95% CI) | Adjusted<sup>1</sup> VE; partial dose (OR 95% CI) | Overall adjusted<sup>1</sup> 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 | Low | Low | Low | High | Upgraded by 1 | MODERATE |
| No downgrade<sup>2</sup> | No downgrade<sup>3</sup> | No downgrade<sup>4</sup> | Did not downgrade<sup>5</sup> | |

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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), see Table 3.
3 There was no statistical heterogeneity (I² = 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)<sup>5</sup>, 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 5. Assessment of quality of evidence for vaccine effectiveness (VE) by age categories.

| Effectiveness of RVA vaccine in Africa stratified by age categories | Cases vaccinated (n/Total) | Control vaccinated (n/Total) | Adjusted<sup>1</sup> VE; <12 m (OR 95% CI) | Adjusted<sup>1</sup> VE; 12-23 m (OR 95% CI) | Adjusted<sup>1</sup> VE; <24 m (OR 95% CI) | Adjusted<sup>1</sup> VE; 12-59 m (OR 95% CI) | Overall adjusted<sup>1</sup> 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 | Upgraded by 1 | MODERATE |
| No downgrade<sup>2</sup> | No downgrade<sup>3</sup> | No downgrade<sup>4</sup> | Downgraded by 1<sup>1</sup> | |

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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), see Table 3.
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 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).<sup>5</sup> The studies were all conducted in African countries and directly address the review question.
6 The magnitude of effect was high consistently throughout all included studies. Quality of evidence was upgraded by 1.

Data availability

Underlying data

Adobe 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

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/WJOF7N16.

This project contains the following extended data:

• Supplementary File One.docx
  o Supplementary Text 1. Search strategy of peer-reviewed articles.
  o Supplementary Text 2. Inclusion/exclusion criteria for the systematic review and meta-analysis.
  o Supplementary Figure 1. Estimated pooled vaccine effectiveness for complete dose of RV1 against laboratory-confirmed rotavirus infection with Armah et al. 2016 excluded.
  o 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 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/WJOF7N16.

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

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We thank Prof. D. James Nokes of KEMRI-Wellcome Trust for comments and suggestions on the analysis and presentation of this work.

References

1. Luchef A, Timnetelsky MDS: Group A rotavirus gastroenteritis: post-vaccine, era genotypes and zoonotic transmission. Einstein (Sao Paulo). 2016; 14(2): 278–87. PubMed Abstract | Publisher Full Text | Free Full Text

2. Troeger C, Khalil IA, Rao PC, et al.: Rotavirus Vaccination and the Global Burden of Rotavirus Diarrhea Among Children Younger Than 5 Years. JAMA Pediatr. 2018; 172(10): 958–65. PubMed Abstract | Publisher Full Text | Free Full Text

3. Tate JE, Parashar UD: Rotavirus vaccines in routine use. Clin Infect Dis. 2014; 59(9): 1291–301. PubMed Abstract | Publisher Full Text

4. Rodrigo C, Salman N, Tatochenko V, et al.: Recommendations for rotavirus vaccination: A worldwide perspective. Vaccine. 2010; 28(31): 5100–8. PubMed Abstract | Publisher Full Text

5. O’Ryan M: Rotavirus Vaccines: a story of success with challenges ahead [version 1; peer review: 3 approved]. F1000Res. 2017; 6: 1517. PubMed Abstract | Publisher Full Text | Free Full Text

6. Meeting of the immunization Strategic Advisory Group of Experts, April 2009-:conclusions and recommendations. Wkly Epidemiol Rec. 2009; 84(23): 220–36. PubMed Abstract

7. Global Introduction Status. Rota Council.

8. Vesikari T: Rotavirus vaccination: a concise review. Clin Microbiol Infect. 2012; 18 Suppl 5: 57–63. PubMed Abstract | Publisher Full Text

9. Jiang V, Jiang B, Tate J, et al.: Performance of rotavirus vaccines in developed and developing countries. Hum Vaccin. 2010; 6(7): 532–42. PubMed Abstract | Publisher Full Text | Free Full Text

10. Rotavirus vaccines. WHO position paper - January 2013. Wkly Epidemiol Rec. 2013; 88(5): 43–64. PubMed Abstract

11. Sow SO, Steele AD, Mwenda JM, et al.: Reaching every child with rotavirus vaccine: Report from the 10th African rotavirus symposium held in Bamako, Mali, Vaccine. 2017; 36(42): 5011–4. PubMed Abstract | Publisher Full Text | Free Full Text

12. Shah MP, Tate JE, Mwenda JM, et al.: Estimated reductions in hospitalizations and deaths from childhood diarrhea following implementation of rotavirus vaccination in Africa. Expert Rev Vaccines. 2017; 16(10): 987–95. PubMed Abstract | Publisher Full Text | Free Full Text

13. Weldegebriel G, Mwenda JM, Chakauya J, et al.: Impact of rotavirus vaccine on rotavirus diarrhoea in countries of East and Southern Africa. Vaccine. 2018; 36(7): 7124–30. PubMed Abstract | Publisher Full Text

14. O’Ryan M, Giaquinto C, Benninghoff B: Human rotavirus vaccine (Rotarix): focus on effectiveness and impact 6 years after first introduction in Africa. Expert Rev Vaccines. 2015; 14(8): 1099–112. PubMed Abstract | Publisher Full Text

15. Godfrey O, Zhang W, Ampomsem-Boateng C, et al.: Evidence of rotavirus vaccine impact in sub-Saharan Africa: Systematic review and meta-analysis. PLoS One. 2020; 15(4): e0232113. PubMed Abstract | Publisher Full Text | Free Full Text

16. Nickson M, Grieve PO, Marla FM, et al.: “Replication Data, for: Effectiveness of Rotarix® vaccine in Africa in the first decade of progressive introduction, 2009–2019: systematic review and meta-analysis”. Harvard Dataverse, V2. 2020. UNF:6:Q1+MU8Loq14f+U0UV+IYZMA== [fileUNF]. http://www.doi.org/10.7910/DVN/WJOF7N16

17. VIEW-hub: Home. Reference Source

18. Wells GA, Shea B, O’Connell D, et al.: The Newcastle-Ottawa Scale (NOS) for Assessing the Quality if Nonrandomized Studies in Meta-Analyses - ScienceOpen. Reference Source
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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](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/](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.