Efficacy and Effectiveness of Rotavirus Vaccine on Incidence of Diarrhoea among Children: A Meta-analysis

Katayi Mwila-Kazimbaya1,2*, Samuel Bosomprah1,3, Michelo Simuyandi1, Caroline C Chisenga1, Roma Chilengi1,4 and Sody Munsaka2

1Center for Infectious Disease Research in Zambia, Lusaka
2Department of Biomedical Sciences, School of Health Sciences, University of Zambia, Lusaka, Zambia
3Department of Biostatistics, School of Public Health, University of Ghana, Legon, Accra, Ghana
4School of Medicine, University of North Carolina at Chapel Hill, North Carolina, U.S

*Corresponding author: Kazimbaya KM, Centre for Infectious Disease Research in Zambia, Lusaka, Department of Biomedical Sciences, School of Health Sciences, University of Zambia, Lusaka, Zambia, Tel: +26 0211 242257-63; E-mail: katayi.kazimbaya@cidrz.org

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Abstract

Background: Introduction of rotavirus vaccines has resulted in a decrease in rotavirus related mortality and morbidity. We sought to conduct a meta-analysis to estimate the effect of rotavirus vaccine on incidence of diarrhoea.

Methods: The MEDLINE database was searched through PubMed interface using both textword and subject headings (MeSH). The search strategies were ["rotavirus vaccine effectiveness" or "rotavirus vaccine efficacy" or "rotavirus vaccine eff"][1]. The reference lists of the most recent studies identified by the search were checked for additional studies (if not already retrieved). We included both randomised trials and observational studies, which investigated the effect of rotavirus vaccine on incidence of diarrhoea.

Results: There was strong evidence of vaccine efficacy (70%) on incidence of diarrhoea (Pooled risk ratio (pRR)=0.30; 95% confidence interval (CI)=[0.24,0.38]; p<0.0001), with much lower vaccine efficacy (63%) in low-middle income countries (LMICs) (pRR=0.37; 95% CI=[0.56,69]; p<0.0001). When restricted to severe diarrhoea outcome, we found 74% vaccine efficacy (pRR=0.26; 95% CI=[0.19,0.24]; p<0.0001). For vaccine effectiveness in LMICs, we found 53% vaccine effectiveness (pRR=0.47; 95% CI=[0.36,0.62]; p<0.0001) for 1 dose; 61% effectiveness (pRR=0.39; 95% CI=[0.32,0.47]; p<0.0001) for 2 doses and 72% effectiveness (pRR=0.28; 95% CI=[0.14, 0.56]; p<0.0001) for 3 doses.

Conclusion: Incomplete dose series had lower vaccine effectiveness than vaccine efficacy in LMICs where health system capacity is low. However, a 3-dose series had similar effectiveness to vaccine efficacy, suggesting that a booster dose could present a potential benefit in LMIC.

Keywords: Meta-analysis; Efficacy; Effectiveness; Rotarix; RotaTeq; Rotavirus vaccines

Introduction

Rotavirus associated diarrhoea has been a key contributor to the morbidity and mortality among children under 5 years of age worldwide [1] and low-middle income countries (LMICs) bear the greater burden. This problem has led to the widespread introduction of Rotarix™ (GlaxosmithKline Biologicals, Belgium) and RotaTeq™ (Merck, USA) vaccines into national immunization programmes. As of December 2017, 93 countries have done so at either national, sub-national or began phased introduction of the vaccines [2]. The World Health Organization (WHO) made this recommendation after randomised clinical trials showed efficacy in high income countries (HICs) of between 80-95% [3-6].

Although subsequent trials from low and middle income countries (LMICs) showed much lower efficacy rates between 40 and 60% [7-10], the public health impact in these high burden settings was still compelling enough to continue the immunization campaigns. Several other vaccines are in the developmental and licensure phase such as Rotavin™ and RotaVac™ which have partial or restricted licensure in China, Vietnam and India [11,12]. Rotasil™ is another vaccine currently under development and was recently tested in Niger [13]. All have shown similar vaccine efficacy and effectiveness trends in LMICs [11-14].

Much data on post licensure effectiveness of rotavirus vaccines has been published on HICs which still indicate how well rotavirus vaccines have worked. LMIC researchers are now also beginning to generate more information on vaccine effectiveness in their respective locations that has shown that
vaccine responses have continued to be sub-optimal [7-10,15-17].

We will focus on consolidating vaccine efficacy and effectiveness data for globally licensed vaccines Rotarix and RotaTeq in HICs and LMICs as well as some of the steps and areas that still need to be addressed in order to improve vaccine effectiveness in LMICs.

Methods

Search strategy for identification of studies

The MEDLINE database was searched through PubMed interface using both textword and subject headings (MeSH). The search strategies were [“rotavirus vaccine effectiveness” or “rotavirus vaccine efficacy” or “rotavirus vaccine eff**”], which retrieved 858 studies. The reference lists of the most recent studies identified by the search were checked for additional studies (if not already retrieved).

Criteria for including studies for the review

In the efficacy analysis we included randomised clinical trials reporting efficacy of Rotarix (RV1) and RotaTeq (RV5). In the effectiveness analysis we included observational studies reporting population effectiveness of Rotarix (RV1) or RotaTeq (RV5) against hospital admission for rotavirus gastroenteritis (RVGE) or acute gastroenteritis (AGE) for incomplete and complete doses in all countries regardless of whether they are included in national immunisation programmes or privately offered. Duplicates were removed, as were cost effective, genotype specific, impact, methodological and review articles, leaving 68 articles for inclusion in the analysis. Efficacy data included overall efficacy and severe rotavirus related gastroenteritis, whilst effectiveness data included efficacy against hospital admission. All studies published until October 2017 was eligible for inclusion.

Data extraction

Two authors (K.M-K, SB) extracted data from the studies using data extraction form designed to capture relevant data for this purpose and the differences (if any) were reconciled. For the efficacy studies, the measure of effect for the meta-analysis was risk ratio (RR), which measures cumulative incidence more accurately. For studies that reported odds ratio, we recalculated risk ratios by reconstructing the 2x2 tables from data in the original paper because odds ratios usually overestimate risk ratios especially where the incidence of the outcome is common (>10%).

The recalculation was convenient because efficacy studies are required to report the unadjusted result as primary analysis [18]. For the effectiveness studies, we did not recalculate the measure of effect because the primary analysis was adjusted effect. All studies measured diarrhoea severity using Vesikari scores of 11 [19] or Clarke score of 16 [20]. We followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) in the conduct of this review. Severe diarrhoea was defined as Vesikari score of 11 or greater. Any diarrhoea was defined as mild or moderate or severe.

Statistical analysis

We calculated a weighted average of the effect measures across studies using ‘metan’ command in Stata. Forest plot was also presented. The ‘metan’ command is flexible for any measure of effect because it requires either the frequencies of events in exposed and unexposed group (the approach we used in the efficacy studies) or the logarithm of the effect measure and its standard error (the approach we used in the effectiveness studies). For studies that reported zero events, we replaced the zeros with 0.5 before performing the meta-analysis. For the effectiveness studies, we calculated the standard error of the log-risk ratio or log-odds ratio by back-transforming the relevant confidence intervals as reported in the papers. Studies conducted in different epidemiological settings are likely to vary, so we performed a chi-squared test of heterogeneity.

If there was evidence of heterogeneity, the individual study effect estimates were combined using random effects meta-analysis, which incorporates between-study variability in the weighting. P-values less than 0.05 were considered to show strong evidence of association. Published studies may not be representative of all valid studies undertaken and this can bias meta-analysis. We assessed publication bias using Harbord’s modified test for small-study effects [21]. All analyses were performed using Stata 15 MP (StatCorp, College Station, TX, USA).

Results

Overview of included studies

The search identified a total of 858 studies out of which 228 were duplicates (Figure 1). Of the 630 non-duplicated studies, we excluded 98 cost-effectiveness, 67 genotype specific, 13 impact, 21 reviews, and 7 methodological studies leaving a total of 424 studies. After applying the eligibility criteria, we further excluded 357 studies leaving a total of 67 full text articles for analysis out of which 16 were severe RVGE efficacy, 4 overall efficacy, and 47 efficacy against hospital admission studies (Figure 1).

Characteristics of included studies

27 studies investigated the efficacy of rotavirus vaccine on incidence of diarrhoea, out of which 7 studies investigated the overall efficacy of the vaccines [22-31] while 20 studies investigated efficacy on severe diarrhoea (Table 1) [4,5,31-45]. 23 studies were in LMICs while 4 studies were in HICs contributing a total sample size of 135,486 (Table 1). Data from the HICs included data from multicenter trials that was not
disaggregated by country. 13 investigated RV1 and 6 investigated RV5 (Table 1).

**Table 1: Features of studies included in vaccine efficacy analysis**

| Reference   | Country/Region       | Demo     | Vaccine Type | Sample Size | Loss to Follow Up | Study Duration (months) | Efficacy | Vaccinated No Diarrhoea | Vaccinated No Diarrhoea | Non-Vaccinated No Diarrhoea | Non-Vaccinated No Diarrhoea |
|-------------|----------------------|----------|--------------|-------------|-------------------|-------------------------|----------|------------------------|--------------------------|-------------------------------|-------------------------------|
| Araujo et al. [82] | Brazil LMIC       | RV1      | 2155         | 1           | 8                 | 64.5                    | 460      | 22                     | 130                      | 19                            |                               |
| Armah et al. [10] | Ghana, Mali and Kenya LMIC | RV5      | 5468         | 134         | 17.5               | 64.2                    | 2712     | 21                     | 2735                     | 58                            |                               |
| Armah et al. [10] | Ghana LMIC         | RV5      | 5468         | 134         | 18.2               | 65                      | 3255     | 15                     | 3235                     | 42                            |                               |
| Armah et al. [10] | Mali LMIC          | RV5      | 5468         | 134         | 18.2               | 1                       | 2835     | 4                      | 2844                     | 4                             |                               |
| Armah et al. [10] | Kenya LMIC         | RV5      | 5468         | 134         | 16                 | 83.4                    | 1892     | 2                      | 1876                     | 12                            |                               |
| Bhandari et al. [26] | India LMIC    | Rotavac  | 4532         | 101         | 20                 | 56.3                    | 4298     | 56                     | 2123                     | 64                            |                               |
| Cunliffe et al. [27] | Malawi LMIC | RV1      | 9            | 19           | 49.7               | 989                     | 41       | 445                    | 38                       |                               |                               |
| Feikin et al. [33] | Kenya LMIC        | RV5      | 1308         | 185         | 7                  | 83.4                    | 569      | 2                      | 552                      | 12                            |                               |
| Iwata et al. [28] | Japan HIC         | RV5      | 762          | 4           | 7                  | 100                     | 355      | 0                      | 346                      | 10                            |                               |
| Lau et al. [31] | China, Hong Kong LMIC | RV1      | 3025         | 20           | 100                | 1494                   | 0        | 1491                   | 8                        |                               |                               |
| Li et al. [32] | China LMIC        | RV1      | 3333         | 13           | 24                 | 75                      | 1567     | 8                      | 1541                     | 32                            |                               |
| Linhares et al. [32] | Latin America LMIC | RV1      | 1428         | 248          | 20                 | 83.1                    | 7195     | 10                     | 7023                     | 58                            |                               |
| Madhi et al. [94] | SA and Malawi LMIC | RV1      | 4939         | 206          | 12                 | 61.2                    | 2918     | 56                     | 1373                     | 70                            |                               |
| Madhi et al. [94] | South Africa LMIC | RV1      | 973          | 206          | 12                 | 81.5                    | 1929     | 15                     | 928                      | 32                            |                               |
| Madhi et al. [94] | Malawi LMIC       | RV1      | 505          | 206          | 12                 | 49.7                    | 989      | 41                     | 445                      | 38                            |                               |
| Mo et al. [35] | China LMIC        | RV5      | 4040         | 1           | 12                 | 78.9                    | 1916     | 11                     | 1885                     | 52                            |                               |
| Phua et al. [29,31] | Hong Kong, Singapore and Taiwan HIC | RV1      | 1051         | 155          | 21                 | 96.1                    | 5261     | 1                      | 5206                     | 51                            |                               |
| Ruiz-Palacios et al. [4] | Latin America LMIC | RV1      | 2016         | 239          | 12                 | 84.8                    | 8997     | 12                     | 8781                     | 77                            |                               |
| Sow et al. [22] | Mali LMIC         | RV5      | 1960         | 36           | 12                 | 1                       | 782      | 41                     | 754                      | 71                            |                               |
| Tregnaghi et al. [38] | Latin America LMIC | RV1      | 6568         | 34           | 7.4                | 81.6                    | 4204     | 7                      | 2080                     | 19                            |                               |
| Vesikari et al. [101] | Europe HIC      | RV1      | 3994         | 23           | 5.7                | 95.8                    | 2567     | 5                      | 1242                     | 60                            |                               |
47 studies investigated vaccine effectiveness (Table 2) [5-16,40-77]. 29 studies were from HICs [5,47,48,60-62,72-74,78-84] and 18 were from LMICs (Table 2) [7-16,40-47,50-54,67-79]. 20 studies evaluated RV1, 10 studies evaluated RV5 and 11 studies evaluated the use of either RV1 or RV5. The total sample size across all the studies was 777,809 (Table 2).

Vaccine efficacy on incidence of diarrhoea (severe and/or any)

There was evidence of substantial variability between studies (I²=74.4%, p<0.0001) with about 74.4% of the pooled between-study heterogeneity attributable to the variability in the true effect (Figure 2A). There was strong evidence of vaccine efficacy (70%) on incidence of diarrhoea (Pooled risk ratio (pRR)=0.30; 95% confidence interval (CI)=(0.24, 0.38); p<0.0001) (Figure 2A).

Table 2: Features of studies included in vaccine effectiveness analysis.

| Reference | Country/ Region | Dem o | Sample Size | Vaccine Type |
|-----------|-----------------|------|-------------|--------------|
| Abeid et al. [52] | Zanzibar | LMI C | 805 | RV1 |
| Adlhoch et al. [59] | Germany | HIC | 368 | RV1/RV5 |
| Araki et al. [65] | Japan | HIC | RV1/RV5 |
| Armah et al. [101] | Ghana | LMI C | 657 | RV1 |
| Beres et al. [7] | Zambia | LMI C | 529 | RV1 |
| Boom et al. [48] | USA | HIC | 205 | RV5 |
| Braeckman et al. [45] | Belgium | HIC | 431 | RV1 |
| Cardellino et al. [75] | Nicaragua | LMI C | RV5 |
| Castilla et al. [57] | Spain | HIC | 6792 | RV1/RV5 |
| Chang et al. [55] | China | HIC | 1088 | RV1 |
| Chang et al. [55] | China | HIC | RV5 |
| Cortese et al. [44] | USA- RV1 | HIC | 593 | RV1 |
| Cortese et al. [44] | USA-RV5 | HIC | 593 | RV5 |
| Cotes-Cantillo et al. [42] | Colombia | LMI C | 974 | RV1 |
| de Palma et al. [40] | El Salvador | LMI C | 323 | RV1 |
| Desai et al. [83] | USA | HIC | 122 | RV1/RV5 |
| Field et al. [72] | Australia | HIC | 459 | RV5 |
| Fuji et al. [62] | Japan | HIC | 244 | RV1/RV5 |
| Gastanaduy et al. [83] | Botswana | LMI C | 610 | RV1 |
| Gastanaduy et al. [83] | Guatemala | LMI C | 1417 | RV1/RV5 |
| Gheorghita et al. [85] | Moldova | LMI C | 957 | RV1 |
| Gosselin et al. [60] | Canada | HIC | 11203 | RV1/RV5 |
| Groome et al. [81] | South Africa | LMI C | 1974 | RV1 |
| Ichihara et al. [46] | Brazil | LMI C | 2176 | RV1 |
When stratified by country income status, we observed strong evidence of vaccine efficacy (96%) in HICs (pRR=0.04; 95% CI=[93, 98]; p<0.0001) while an efficacy of 63% was observed in LMICs (pRR=0.37; 95% CI=[56, 69]; p<0.0001) (Figure 2A). We observed evidence of publication bias in terms of small-study effect (bias=-2.55; Harbord’s modified test p=0.017) (Figure 2B). When restricted to severe diarrhoea as the outcome, we also found strong evidence of vaccine efficacy (74%) (pRR=0.26; 95% CI=[0.19,0.24]; p<0.0001) (Figure 3). For any diarrhoea outcome, the efficacy was 53% (pRR=0.47; 95% CI=[0.36,0.60]; p<0.0001) (Figure 4).

In a secondary analysis to assess the efficacy of specific vaccine type, we found similar results. RV1 showed an efficacy of 76% (pRR=0.24; 95% CI=[0.17, 0.33]) while RV5 showed an efficacy of 60% (pRR=0.40; 95% CI=[0.31, 0.53]) (Figure 5).
Vaccine effectiveness on incidence of diarrhoea

In assessing the effect of rotavirus vaccine in real world setting, we found strong evidence of about 78% reduction in incidence of diarrhoea due to the vaccine (pRR=0.22; 95% CI=(0.18, 0.28); p<0.0001). This effect was influenced by the number of vaccine doses; we observed that as the number of dose increases so does the vaccine effectiveness (Figures 6A-6C). For 1 vaccine dose, the vaccine effectiveness in LMIC was 53% (pRR=0.47; 95% CI=(0.36, 0.62); p<0.0001) (Figure 6A). For 2 doses, the effectiveness in LMIC was 61% (pRR=0.39; 95% CI=(0.32, 0.47); p<0.0001) (Figure 6B). For 3 doses, the effectiveness in LMIC was 72% (pRR=0.28; 95% CI=(0.14, 0.56); p<0.0001) (Figure 6C).
Discussion

Results from both the efficacy and effectiveness trials show that rotavirus vaccines have been effective in reducing the scourge of rotavirus associated diarrhoea. Our analysis was able to consolidate data that shows HICs have consistently higher efficacy and effectiveness rates than LMICs; and is true for both RV1 and RV5.

Effectiveness data from real world setting results have also indicated that incomplete vaccine series are able to provide some protection to infants though to a lesser extent than a complete series. The incomplete series had a much lower effectiveness in LMIC than vaccine efficacy in LMIC. Incomplete series is common in LMICs where inadequate health facilities and long distances to health facilities exist. We found that a 3-dose vaccine series had effect similar to vaccine efficacy in LMIC, making it a logical argument for a booster dose especially in LMICs.

Improved vaccine effectiveness: Terrain à forte

The differences in efficacy and effectiveness in HICs and LMICs however still remain the main discussion point as there is need for further reduction in rotavirus associated mortality and morbidity [85]. Various factors have been postulated as contributing to this observed effect. Host factors such as genetics, malnutrition, enteric environmental dysfunction (EED), maternal factors such as antibodies passed onto the infant, various components of breast milk, exposure to HIV and other environmental factors including poor sanitation, concurrent infection with other pathogens have all been postulated to influence vaccine effectiveness [86-97].

Another factor postulated to possibly have an effect is strain diversity in HICs and LMICs. Both RV1 and RV5 are vaccines originally designed by HIC researchers from strains present in HIC regions. However, research has indicated that the vaccines are not strain specific but cross-cutting without evidence of vaccine induced selection pressure [43,98,99]. Nonetheless, the increased strain diversity being observed in many LMICs requires seroepidemiological vigilance to ensure tracking of any emerging strains such as P[4]G2 that may account for reduced efficacy through limited cross protection [100-104].

Despite greater understanding of contributing factors to reduced vaccine efficacy, we are faced with the fact that a lot of these factors are almost impossible to resolve. The high maternal immunity that is passed onto the child is a consequence of where one lives and poor water, sanitation and hygiene (WASH) that cannot easily be changed. Unless this is addressed, mothers will continue to pass these, on to their infants. The same applies to the EED; in order to change the micro biome that exists in individuals, it will require interventions that address which organisms are first introduced into the system. Additionally in low income settings with low availability of funds, the use of formula is not a feasible solution to address the issue of maternal antibodies passed onto the child during breast feeding.

Genetic makeup has also been included in the list of factors affecting vaccine effectiveness. Despite advances in science, genetics is still a growing area and we have not yet reached a point where we can change ones genetic code if one is pre-disposed towards a disease even in the developed settings. Thus, genetic predisposition is another unsolvable in the quest for better vaccine effectiveness. Another key area is that of
mal(nutrition) in LMICs. Again, despite great efforts being made worldwide, the magnitude of this problem renders it unsolvable for years to come. Unless we can find a world in which all children are able to have sufficient food and the right kind of food, this too shall remain a hindrance to our efforts to obtain better vaccine effectiveness.

Future perspectives

Despite the many hindrances to achieving better vaccine effectiveness in LMICs there are still many other areas that are available to work on. The next generation of vaccines can be targeted to areas that maybe within our control such as alternative routes of administration; short course full dose regimen. The ease of use and lower cost of oral vaccines is the main reason for their inclusion in national immunisation programmes. However, the large number of interfering factors has led us to reassess their use. As is the case with Polio, we may have to go the parenteral route to effectively circumvent the problems encountered via the oral route [105].

Another way of dealing with interference is the adjustment of the vaccine schedule; a neonatal dosing schedule has been proposed as potentially beneficial to improved vaccine immunogenicity [106,107]. A booster dose has also been proposed as viable option for enhanced vaccine immune responses of current vaccines in use [108]. While use of the expanded programme on immunization (EPI) was recommended in order to reach as many infants as possible, there may be larger benefits in offering immunization options outside of this schedule. This could be in the form of changing the time to one at which maternal antibodies are waning or as early as possible to ensure adequate protection from early exposure. Nonetheless, these options need to be weighed against the challenge of low coverage in LMIC [109], when venturing outside of the EPI.

Lastly, use of effective adjuvants has not been fully explored in rotavirus immunology [110]. This is particularly key when considering neonates in whom the immune system is naïve [111,112]; and yet it’s a practical window to beat the early exposure of infants to pathogens [88].

Conclusion

While current rotavirus vaccines have saved many lives in LMIC settings, there are still clear gaps in vaccine performance. This paper has comprehensively shown the differences and need for concerted effort to improve vaccine performance in these areas where in fact, vaccines are most needed.

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