RESEARCH PAPER

Immunogenicity of different dosing schedules of the human live attenuate rotavirus vaccine (RV1) in infants and children: a meta-analysis

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ABSTRACT

Rotavirus immunization strategies have become part of a comprehensive global public health program to control rotavirus-associated gastroenteritis, particularly in infants and children in developing countries. Several studies have reported the efficacy of different rotavirus vaccine dosing schedules, but with mixed findings. Therefore a systematic review of the published literature on rotavirus vaccination dosing schedules using the live attenuated RV1 rotavirus vaccine in infants and children, including randomized controlled clinical trials (RCTs), published between January 1998 to January 2018 was conducted, with meta-analysis of the published data. The literature search was performed using six databases. The initial review identified 495 publications, of which three satisfied the selection eligibility criteria. The three studies that assessed RV1 rotavirus vaccine immunogenicity compared a two-dose vaccination schedule with a three-dose vaccination schedule. The use of a three-dose vaccination schedule did not show a statistically significant seroconversion rate when compared with a two-dose vaccination schedule (OR = 0.87; 95% CI: 0.65–1.17; $p = 0.298$). Analysis of included studies with one-month follow-up time showed that the three-dose vaccination schedule did not result in have significantly increased geometric mean concentrations (GMCs) compared with the two-dose vaccination schedule ($p = 0.311$). Rotavirus immunogenicity did not increase significantly with the three-dose schedule at 6, 10 and 14 weeks with the two-dose schedule at 10 and 14 weeks. These findings indicate that further controlled studies should be undertaken to support the optimum immunization schedules for rotavirus in terms of clinical effectiveness and cost-effectiveness, particularly for infants and children in developing countries.

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Introduction

Worldwide, rotavirus is a leading cause of severe diarrhea among infants and young children under 5 years of age, particularly in developing countries. In 2016, the World Health Organization (WHO) estimated that rotavirus-associated gastroenteritis was, responsible for approximately 215, 000 child deaths worldwide (range, 197, 000–233, 000). Each year an average of 40% (range 34–45%) of hospitalization admission for diarrhea among children under 5 years of age are due to rotavirus infection and approximately 90% of all rotavirus-associated fatalities occur in developing or low-income countries, including in Africa and Asia.^{1,2} The median age for primary rotavirus infection ranges from 6–9 months in low-income and middle-income countries, whereas the first episode of rotavirus infection may be delayed until 2–5 years in developed or high-income countries.³

Rotaviruses are non-enveloped dsRNA viruses in the (family, *Reoviridae*), and have been classified into G-type and P-type according to their outer capsid antigens, VP7

and VP4, respectively.⁴ At least 12 different VP7 antigens and 15 different VP4 antigens have been identified and there are 6 G-P combinations, including G1P[8], G2P[4], G3P[8], G4P[8], G9P[8] and G12P[8], which account for approximately 80% of all human rotavirus infections.⁴

Rotavirus infection can result in severe diarrhea with vomiting and fever that can result in dehydration with shock, electrolyte imbalance, and in some cases, death. Rotavirus cannot be treated with antibodies and other drugs, which means that the prevention of infection with the use of vaccines is essential.¹ Currently, two live attenuated oral rotavirus vaccines are available, RV1 or RotarixTM (GSK Biologicals) and RV5 or RotaTeq[®] (Merck & Co. Ltd.), which have been licensed in more than 100 countries worldwide. Also, three newer vaccines, ROTAVAC[®] (Bharat Biotech International Ltd., India), Lanzhou lamb rotavirus vaccine (LLR) (Lanzhou Institute of Biomedical Products, China) and BRV-PV or ROTAILL[®] (Serum Institute of India) have also been licensed for use and are less costly.^{5–7}

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RV1 (RotarixTM) is a live-attenuated human rotavirus vaccine that originated from a G1P[8] strain that was isolated from a case of infantile gastroenteritis, and is usually administered as a two-dose series.¹ The first dose of the RV1 vaccine is administered to infants from the age of six weeks, and then there should be an interval of at least four weeks before the second dose.⁸ Factors that may reduce the performance of rotavirus vaccine may be overcome by altering the vaccination programme, including the use of different schedules of vaccination, or different intervals between doses.

The RV1 rotavirus vaccine has been shown to be effective in reducing the incidence of infantile diarrhea with a recommended two-dose schedule that includes (RV1 vaccination at 6 weeks and 10 weeks of age, and again) at one or two years after the initial two-dose vaccination. A Cochrane systematic review showed that two doses of RV1 rotavirus vaccine provided a 97.5% anti-rotavirus IgA seroconversion rate in children from Hong Kong.⁹ The efficacy and immunogenicity were compared between a three-dose schedule for RV1 rotavirus vaccination at 6, 10, and 14 weeks of age, and a two-dose schedule at 10 and 14 weeks of age in two previous clinical trials from Africa.^{10,11}

One study estimated this oral vaccine efficacy against severe rotavirus-associated gastroenteritis did not show statistically significant differences between two-dose schedule, at 10 and 14 weeks of age (mean, 58.7%; 95% CI, 35.7–74%), and the three-dose schedule, at 6, 10 and 14 weeks of age (mean, 63.7%; 95% CI, 42.4–77.8%), respectively. However, there was a slight, but nonsignificant, trend toward an increase anti-rotavirus IgA seroconversion rate and efficacy of the vaccine with a three-dose schedule.¹⁰ In another immunogenicity study, infants receiving the RV1 rotavirus vaccine

with the 10-week and 14-week vaccination schedule and compared the immune responses with the 6-week and 10-week vaccination schedule.¹¹

To our knowledge, no previous systematic literature reviews have been conducted to specifically assess differences in efficacy and immunogenicity between different rotavirus vaccine schedules. Therefore, the aims of this study were to do a systematic review of the literature and undertake a meta-analysis to determine the immunogenicity of the human rotavirus vaccine, RV1, with different dosing schedules and to determine whether there are differences in the seroconversion rate and geometric mean concentrations (GMCs) between two-dose and three-dose RV1 vaccination regimens for infants and children.

Results

A systematic review of the literature identified 495 publications, of which three satisfied the selection eligibility criteria. The process of publication selection is shown in the study flow diagram in Figure 1. There were 241 duplicate studies that were removed using EndNote reference manager. Five review articles were excluded. The following studies were also excluded: two meta-analysis studies of rotavirus vaccination,^{12,13} and one paper that considered the same population in a clinical trial,¹⁰ a study with incomplete data,¹⁴ and one published randomized controlled trial (RCT) that used a different protocol for the follow-up time.¹⁵ Finally, three studies were selected as being eligible for meta-analysis.^{16–18} Two studies accessed different dosing schedules on the immunogenicity of the RV1 rotavirus vaccine,^{16,17} and one study accessed the immunogenicity and efficacy of the RV1 rotavirus vaccine in two cohorts.¹⁸

Figure 1. Flow diagram of the publication selection process.

Table 1. Study characteristics of vaccine trials included.

Reference	Country	Study design (phase)	Sample size	Mean age (week)	Study design	Sex (%)		OPV co-administered (%)	Anti-rotavirus IgA seroconversion rate (%)		GMCs of anti-rotavirus IgA (U/mL)	
						Male	Female		2-Dose schedule (95%CI)	3-Dose schedule (95%CI)	2-Dose schedule (95%CI)	3-Dose schedule (95%CI)
Madhi (2012)	South Africa	RCT (III)	205	6.2	Double-blind	50.7	49.3	> 99	57.1 (44.7–68.9)	66.7 (54.0–77.8)	59.4 (37.5–93.9)	94.3 (56.5–157.4)
Ali (2014)	Pakistan	RCT (IV)	630	6.3	Open-label	51.5	48.5	> 99	38.5 (31.2, 46.3)	36.7 (29.8, 44.2)	24.4 (19.5, 30.6)	25.8 (20.5, 32.5)
Armah (2016)	Ghanaian	RCT (IV)	456	6.3	Open-label	48.9	51.1	100	37.4 (29.8–45.7)	43.4 (35.5–51.6)	26.5 (20.7–34.0)	32.6 (24.7–43.2)

Note. RCT, randomized controlled trial; OPV, oral polio vaccine; GMCs, geometric mean concentrations.

Table 2. Assessing risk of bias in included studies.

References	Selection bias		Performance blinding	Detection bias	Reporting bias	Attrition bias	Other bias	Jadad score
	Randomization	Allocation concealment						
Madhi (2012)	Low	Low	Low	Low	Low	Low	Unclear	5
Ali (2014)	Low	Low	High	Unclear	Low	Low	Unclear	3
Armah (2016)	Low	Low	High	Unclear	Low	Low	Unclear	3
Risk of bias	Interpretation		Within a study		Across studies			
Low	Plausible bias unlikely to seriously alter the results.		Low risk of bias for all key domains.		Most information is from studies at low risk of bias.			
Unclear	Plausible bias that raises some doubt about the results.		Unclear risk of bias for one or more key domains.		Most information is from studies at low or unclear risk of bias.			
High	Plausible bias that seriously weakens confidence in the results.		High risk of bias for one or more key domains.		The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.			

Table 1 summarizes the characteristics of the Identified studies. To assess the immunogenicity of the RV1 rotavirus vaccine, the concentration of anti-rotavirus IgA antibody in the serum was measured using an enzyme-linked immunosorbent assay (ELISA)¹⁹ The proportions of rotavirus IgA seroconversion of the participants between the groups were compared by calculating the odds ratio (OR) and 95% confidence interval (CI) during the study (α -value > 0.05). As shown in Table 2, the quality of the three studies varied considerably, the data on the risk of bias are presented in the supplementary material.^{20,21}

Serum anti-rotavirus IgA seroconversion rates

Seroconversion was defined as a serum concentration of anti-rotavirus IgA antibodies < 20U/mL in 6-week subjects who were seropositive (≥ 20 U/mL) after vaccination. Because the study heterogeneity analysis showed $p = 0.441$ and $I^2 = 0.0\%$, the fixed-effects model was applied. Meta-analysis (Figure 2) resulted in a pooled OR of 0.87 (95% CI, 0.65–1.17), which indicated that immunization using the RV1 rotavirus vaccine in a two-dose schedule at 10 weeks and 14 weeks showed a lower trend but did not show a statistically significant seroconversion rate compared with the three-dose RV1 rotavirus vaccine schedule at 6, 10, and 14 weeks ($p = 0.368$). The publication bias was assessed separately using funnel plots (Figure 3) and Egger's tests (Figure 4). The funnel plot data showed that the studies were not quite symmetrically distributed, but Egger's test showed a result of $p = 0.492$, which supported that no publication bias existed and that the data from the forest plot analysis was credible.

Serum geometric mean concentrations (GMCs) of anti-rotavirus IgA

The meta-analysis (Figure 5) of included studies with a one-month follow-up time showed that the three-dose vaccination schedule did not result in significantly increased geometric mean concentrations (GMCs) when compared with the two-dose vaccination schedule ($p = 0.311$). The study heterogeneity test showed that $I^2 = 0.0\%$ and $p = 0.452$. The funnel plot shown in Figure 6, demonstrates that the studies were almost symmetrically distributed. However, the Egger's test results, presented in Figure 7, showed that all three studies were in the 95%CI range, and the Egger's test showed $p = 0.178$, which indicates a lack of publication bias, and that the findings of the forest plot were credible.

Discussion

The World Health Organization (WHO) have reviewed the effects of rotavirus vaccination in infants and children, and have recommended that infants receive a first dose of the RV1 rotavirus vaccine from six weeks of age, and complete the two-dose regimen with the RV1 vaccine before 16 weeks of age.⁸ However, a study conducted in the USA reported that 23% of children were older than the recommended age for the first vaccination.²² Also, another previously published study concluded that more than 30% of children were vaccinated late, and that delayed vaccination was more common in rural areas urban areas compared with urban areas.²³ The interference of maternal antibody and replication of the oral poliovirus vaccine have been cited as potential causes of low immunogenicity to rotavirus vaccine in children at younger ages, but three recent randomized controlled trials evaluated withholding and encouraging breastfeeding at the time

Figure 2. Forest plots showing the pooled odds ratio (OR) of anti-rotavirus immunoglobulin A (IgA) seroconversion, following rotavirus vaccination with RV1, with 95% confidence intervals (CIs) and using a fixed-effects model.

Figure 3. Funnel plots of reporting bias for rotavirus vaccination and anti-rotavirus IgA seroconversion.

of vaccination found no statistically significant difference in anti-rotavirus IgA seroconversion between compared groups.²⁴⁻²⁶ A recent study showed that a short delay in the rotavirus vaccination program could still improve the rotavirus vaccine response in low-income and middle-income countries.²⁷ Furthermore, when the rotavirus vaccines were co-administered with oral polio vaccine (OPV), a reduced immune response to rotavirus vaccine in children at younger ages has been reported.²⁸ Therefore, it is necessary to undertake further studies to compare the immunogenicity between two doses of rotavirus vaccine administered at earlier ages and two doses of vaccine administered at later ages, with other potential confounders, in the meta-analysis.

The use of rotavirus vaccines is now considered to be an important child public health strategy to control infection in countries with high fatality rates from rotavirus-associated gastroenteritis. In the present systematic review of the literature and meta-analysis of the use of the live attenuated RV1 rotavirus vaccine in infants and children, the results of different dose-schedules of rotavirus vaccines were studied to determine whether increasing the number of doses increases the proportion of children responding to the vaccine. The evidence from one published randomized controlled trial (RCT) on the use of the RV1 rotavirus vaccine compared a two-dose vaccination strategy given at 10 and 14 weeks of age with three dose vaccination strategy given at 6, 10 and 14 weeks of age and showed a non-significant difference (44.3%, and 44.4%, respectively) on vaccine immunity after a six-month follow-up period.¹⁵

The findings of this meta-analysis are supported by the previously published RCTs that evaluated RV1 rotavirus vaccine from Malawi and South Africa, which did not detect significant differences in vaccine immunogenicity or efficacy between the three-dose and two-dose immunization schedule.^{14,15} Although this meta-analysis showed no significant differences between these two RV1 vaccinated groups, the two-dose group, and the three-dose group, there was a significant trend towards higher seroconversion rates in three-dose schedule compared with the two-dose schedule when the RV1 vaccine was given at the early age of 6 weeks and 10 weeks, which suggested that a third dose of rotavirus vaccine might provide the optimum immunization regimen for protection from rotavirus infection. Reduced immunity may explain this difference over time. Therefore, adding a third dose of rotavirus vaccine at a later time in infancy or childhood might provide longer-lasting immune protection.^{10,14,17}

Figure 4. Egger's test results of publication bias for rotavirus vaccination and anti-rotavirus IgA seroconversion.

Figure 5. Forest plot of the levels of rotavirus vaccination geometric mean concentrations (GMCs) analyzed by the weighted mean differences (WMD).

To increase the impact of the importance of rotavirus vaccination programs on child public health policy makers, there remains a strong need to conduct more clinical studies to compare the current World Health Organization (WHO) recommended two-dose vaccine schedule and a three-dose vaccine schedule. Also, the efficacy of the three-dose RV1 rotavirus vaccination schedule requires evaluation against severe rotavirus gastroenteritis over two rotavirus epidemic seasons. As the present study showed, a two- years follow-up that compared the two-dose schedule with the three-dose schedule, showed that the three-dose schedule of RV1 rotavirus vaccine provide increased protection for children through the second year, compared with the first year of life. This finding means that the three-dose schedule of rotavirus vaccine might be considered in future child public

health programs for the prevention of rotavirus-associated gastroenteritis in high-risk populations.

While the findings of this meta-analysis showed that the immunogenicity of the RV1 rotavirus vaccine did not increase significantly with three-dose schedule at 6, 10, and 14 weeks compared with the two-dose vaccination schedule at 10, and 14 weeks, a previously published study from South-India compared the three-dose vaccination schedule with a five-dose vaccination schedule, adding two doses at 18 and 22 weeks of age.²⁹ The findings of this study showed that five doses of the RV1 rotavirus vaccine did not increase the proportion of seroconversion in infants compared with the three-dose vaccination schedule. Based on the findings from this meta-analysis, combined with the results from previously published studies on rotavirus vaccination schedules for

Figure 6. Funnel plots of reporting bias for rotavirus vaccination geometric mean concentrations (GMCs).

infants and children, additional strategies should be investigated in different populations to improve immunity and efficacy of rotavirus vaccination. Recently, one study was undertaken to evaluate the benefit of reducing infant mortality from diarrhea due to rotavirus infection through the administration of a booster dose of RV1 rotavirus vaccine at 9 or 12 months of age.³⁰ Data from this study indicated that using this vaccination strategy significantly reduced infant mortality from diarrhea due to rotavirus infection, especially in developing countries.³⁰ It has been reported that the mortality rate from diarrhea due to rotavirus infection significantly higher in developing or low-income countries and lower-middle-income countries compared with developed or high-income countries.³¹ Since rotavirus vaccines are most

needed in high-mortality rate areas, such as developing or low-income countries and lower-middle-income countries, the two-dose RV1 rotavirus vaccination schedule might provide a more cost-effective strategy in these settings.³² Because of the cost of vaccines, vaccine efficacy, the degree of immunity provided, the safety of use of the vaccine, and the practicalities of vaccine program implementation, these considerations all need to be considered by public health physicians and families. Also, the appropriate booster dose of rotavirus vaccine still requires further investigation to achieve ideal clinical and cost-effectiveness. Therefore, there is an urgent need for further research to address these issues and to increase the availability and effectiveness of rotavirus vaccination in regions with high infants mortality rates due to gastroenteritis associated with rotavirus infection.

In conclusion, a systematic review of the published literature on rotavirus vaccination dosing schedules using the live attenuated RV1 rotavirus vaccine in infants and children, including randomized controlled clinical trials (RCTs), published between January 1998 to January 2018 was conducted. Three studies were identified with a meta-analysis of the published data. The three-dose rotavirus vaccination schedule did not result in increased immunogenicity, but the research data included only the results after one-month of follow-up, and analysis of the long-term effects of rotavirus vaccine remain to be undertaken. The limitations of this study included the low number of publications identified, and the fact that they were all from developing or low-income countries, and lacked comparison with findings from developed or high-income countries. Also, two included open-label studies were considered to be of 'high risk' following quality assessment, and although 'blinding' of patient identity and data is important in clinical trials, there

Figure 7. Egger's test results of publication bias for rotavirus vaccination geometric mean concentrations (GMCs).

is no evidence that non-blinded studies show a higher degree of bias in non-blinded clinical trials.³³ Heterogeneity analysis of the published studies supported the credibility of the data provided in the meta-analysis data. The main conclusions of this study are that further clinical and epidemiological studies are required to provide ways to improve rotavirus vaccine immunity and provide further information to vaccination policy-makers and healthcare professionals when considering rotavirus vaccination programs in economically deprived areas.

Methods

Publication selection and eligibility criteria

A literature review was conducted and analyzed based on the recommendation of the Cochrane handbook and the current Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.^{20,34} A previously published meta-analysis was used as a reference for the design of the study.³⁵ The literature review included multi-center or single-center randomized clinical trials (RCTs), that included infants under two years of age, who received two or three doses of the RV1 live attenuated rotavirus vaccine. The required comparators included standard treatment, placebo, or no intervention, and the RV1 rotavirus vaccine immunization schedule was conducted using two doses at 10 and 14 weeks of age, and three doses at 6, 10, and 14 weeks of age. Immunogenicity following vaccination was determined by the rotavirus IgA seroconversion rate, and serum anti-rotavirus IgA geometric mean concentrations (GMCs) were used as a measure of immunogenicity compared across different groups.

Publication exclusion criteria included non-human studies, non-RCTs, different vaccine regimens, studies involving participants aged more than 2- years- old, or studies not using the RV1 rotavirus vaccine.

Literature searches and data collection

A systematic literature search was conducted independently by three of the study group authors (Xiting Dai, Ruolan Bai and Zhenhua Ji). Published studies in the English language were identified using the following databases: PubMed, the Cochrane Library, Web of Science, Medline, ClinicalTrials.gov, the Scientific Electronic Library Online (SciELO) database. The literature review was conducted from January 1998 to January 2018.

Data extraction was performed by two authors based on the study inclusion and exclusion criteria. Data were collected on vaccine type and dose, vaccine schedule, the number of participants, mean age and age range, country, and period of follow-up. Immunogenicity indices tested following rotavirus vaccination included IgA seroconversion rate and serum anti-rotavirus IgA geometric mean concentration (GMC), estimated using the weighted mean difference (WMD). WMD was defined as an absolute difference between the GMCs in the two-dose and three-dose vaccination groups. The odds ratio (OR) was defined as the ratio of the IgA antibody seropositive cases that occurred in the two-dose and three-dose vaccinated groups.

Risk of bias and data analysis

The guidelines from the Cochrane Handbook and Jadad quality scores were used to assess the quality of each of the included studies.^{20,21} Data was analyzed using STATA version 12.0. To evaluate the standard error (SE) a calculation was performed using the formula: $SE = (95\% \text{ CI, upper limit-lower limit}) / 3.92$.³⁶ Two models of analysis, the fixed-effects model and the random-effects model, were used with STATA for meta-analysis, with assessment of study heterogeneity. Statistical heterogeneity evaluated the variability in the effects of the intervention effects, which was measured by Cochran's Q, which is calculated as the weighted sum of the differences (squared) between the effects of individual studies and the pooled effects of all the studies, and the I^2 statistic, which represents the percentage of variation across studies that are not due to heterogeneity, but that occur by chance. The interpretations of the I^2 value was as follows: 40%, heterogeneity may not be important; between 30–60%, moderate heterogeneity; between 50–90%, a large degree of heterogeneity; and between 75–100%, significant heterogeneity. When significant study heterogeneity was explored using the forest plot, this implied incorrect data extraction into STATA. The Cochrane collaboration guidelines recommend methods to determine the causes of heterogeneity.^{20,34} However, if the heterogeneity among the included studies was moderate to large, following subgroup analysis or meta-regression testing ($I^2 > 75\%$), the meta-analysis was discontinued. In forest plots, each study is represented by a block at the point estimate of intervention effect with a horizontal line extending either side of the block. The area of the block indicates the weight assigned to that study in the meta-analysis while the horizontal line depicts the 95% confidence interval. The horizontal axis of the invalid line vertical line is '1'. If the line of a 95% confidence interval in a study spans an invalid vertical line, indicating that the analysis is not statistically significant. In funnel plots, it is most common to plot the effect estimates on the horizontal scale, and thus the measure of study size on the vertical axis. In the absence of bias the plots should approximately resemble a symmetrical funnel. Publication bias was investigated by applying Egger's test for asymmetry of the funnel plots, indicating publication bias and other biases.³⁷

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Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the authors.

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