

Rotavirus Vaccine Schedules and Vaccine Response Among Infants in Low- and Middle-Income Countries: A Systematic Review

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Background. Rotavirus vaccine schedules may impact vaccine response among children in low- and middle-income countries (LMICs). Our objective was to review the literature evaluating the effects of monovalent (RV1) or pentavalent rotavirus vaccines schedules on vaccine response.

Methods. We searched PubMed, Web of Science, Embase, and ClinicalTrials.gov for eligible trials conducted in LMICs comparing ≥ 2 vaccine schedules and reporting immunologic response or efficacy. We calculated seroconversion proportion differences and geometric mean concentration (GMC) ratios with 95% confidence intervals.

Results. We abstracted data from 8 eligible trials of RV1. The point estimates for seroconversion proportions difference ranged from -0.25 to -0.09 for the 6/10-week schedule compared with 10/14. The range for the 6/10/14- compared with 10/14-week schedule was -0.02 to 0.10 . Patterns were similar for GMC ratios and efficacy estimates.

Conclusions. The commonly used 6/10-week RV1 schedule in LMICs may not be optimal. Further research on the effect of rotavirus schedules using clinical endpoints is essential.

Keywords. infant; rotavirus; vaccine; vaccine schedule; viral gastroenteritis.

Rotavirus vaccination has been recommended for all infants worldwide [1]. As of May 2016, 81 countries, including 44 low- and middle-income countries (LMICs), have introduced rotavirus vaccines into their national immunization programs [2]. Most of these countries use 1 of the 2 oral rotavirus vaccines available globally: the monovalent ([RV1] Rotarix; GlaxoSmithKline Biologicals, Rixensart, Belgium) or pentavalent ([RV5] RotaTaq; Merck & Co., Inc.; Kenilworth, NJ) rotavirus vaccine [3, 4].

The efficacy of RV1 and RV5 is low in LMICs (39%–59%) [5–7] and could be due to a number of factors including the following: interference by maternally acquired antibodies, gut microbiota composition, interference from oral polio vaccine (OPV), and/or altered enteric immunity due to the burden of coinfections and malnutrition among infants in LMICs [8]. Potential interference by maternal antibodies seems plausible

because some studies have reported high correlations (0.57–0.86) between anti-rotavirus immunoglobulin (Ig) G antibody levels in mothers and infants in LMICs [9, 10] and the potential for IgG antibodies to interfere with RV1 immune response [11, 12]. Infants in LMICs are often undernourished and have repeated exposure to a variety of enteric pathogens. This may result in chronic environmental enteropathy, which can lead to altered enteric immunity [13]. In addition, infants in LMICs are administered OPV rather than the inactivated polio vaccine, and OPV has been reported to interfere with the immune response to both RV1 and RV5 [14, 15]. These factors combined could require different timing and number of doses of RV1 or RV5 to improve the performance of these vaccines in LMICs.

Rotavirus vaccines schedules (the timing and number of doses received) are easily measured and were varied among some trials conducted in LMICs. To assess the current literature on the potential impact of the timing of vaccine schedules on vaccine response, we conducted a systematic review of randomized control trials conducted before 2016 that compared 2 or more rotavirus vaccine schedules of either RV1 or RV5 among infants in LMICs.

METHODS

Study Selection

This review was conducted after PRISMA guidelines [16]. Only randomized Phase II, III, and IV trials of RV1 or RV5

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conducted in a LMIC were eligible for this review (PICOS Table in Supplemental Table 1). Trials had to be conducted among infants who were randomized to receive a complete RV1 or RV5 series (≥ 2 doses of RV1 or ≥ 3 doses of RV5) with ≥ 2 different dosing schedules of treatment; final rotavirus vaccine dose had to be given by 24 weeks (RV1) or 32 weeks (RV5) of age. A different dosing schedule was defined as a change in the number or timing of doses of RV1 or RV5 (eg, for RV1, 6/10- versus 6/10/14-week schedules). All trials had to report measures of immunogenicity (anti-rotavirus IgA antibody concentrations as either seroconversion proportion, geometric mean concentrations or geometric mean titers) or efficacy against severe rotavirus gastroenteritis (RVGE) (polymerase chain reaction [PCR]-confirmed, wild-type) and be written in English.

Data Sources and Searches

Medline (using PubMed), Embase, and Web of Science were searched on January 19, 2016 for the terms “Rotarix” or “RIX4414” or “RotaTeq” or “WC3” and the name of all the LMICs (Supplemental Table 2). In addition, ClinicalTrials.gov was searched on February 9, 2016 using the term “rotavirus.” Supplemental Table 2 contains the exact searches performed.

We removed duplicate articles/records from the search results. Before title and abstract review of each article, we searched for missing abstracts manually. Articles without abstracts available were automatically advanced to full-text review. Two reviewers (J.F.G. and L.M.G.) screened the title and abstract of each article according to the PICOS table criteria. We retrieved and dually reviewed full-texts of articles if either reviewer determined the abstract should be evaluated further. Dual review was also completed for studies and published articles identified in the ClinicalTrials.gov search. Any discrepancies between reviewers were resolved by a third reviewer (S.B.-D.).

Data Abstraction and Quality Assessment

We abstracted data from all trials meeting the inclusion criteria. Immunogenicity and efficacy data were abstracted into a standardized table by J.F.G. and then verified by L.M.G. for each trial. For RV1, seroconversion proportion was defined as the proportion of participants with anti-rotavirus IgA antibody concentrations ≥ 20 U/mL 1 month after completing all RV1 doses (among those who were seronegative before vaccination). For RV5, seroconversion proportion was defined as the proportion of participants with at least a 3-fold rise in anti-rotavirus IgA antibody titer from baseline to 1 month after completing all RV5 doses. One-month geometric mean concentrations or titers were abstracted for RV1 and RV5, respectively. If blood samples were not collected in the month after vaccination, 2-month seroconversion proportion and geometric mean concentration or titer were abstracted.

To assess the potential bias of each included trial, J.F.G. and R.P.W. independently reviewed each trial using a standardized risk of bias tool. Any discrepancies in the responses were

discussed until consensus was reached. Each trial was classified as “low,” “medium,” or “high” risk of bias.

For studies missing sample size for immunogenicity endpoints, corresponding authors were contacted and asked to provide the sample size. If sample sizes were unavailable, they were estimated from the available information and identified as such in the results. Otherwise, raw data related to immunologic and clinical endpoints were presented as they were published.

Data Analysis

Differences in seroconversion proportions with corresponding 95% confidence intervals and ratios of geometric mean concentrations or titers with corresponding 95% confidence intervals were estimated between groups with different RV1 or RV5 schedules. This was done using the reported or estimated sample size, seroconversion proportion, and geometric mean concentrations or titers extracted from each trial. Because different schedules could be evaluated across trials, the most commonly used schedules were compared with a common referent group and were presented in figures whereas comparisons of less common schedules were presented in tables. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

There were 822 articles and 183 ClinicalTrials.gov records identified through the searches (Supplemental Figure 1). After deduplication, 639 abstracts from the database search were screened, 580 of which were excluded. Review of 59 full-text articles and 183 ClinicalTrials.gov records resulted in the inclusion of 10 articles [5, 11, 12, 17–23] representing 8 unique trials.

Missing Information

In National Clinical Trial (NCT)00346892 [21], sample size was unavailable, but the number randomized was provided. We used an exclusion/dropout rate of 30%, which was the exclusion/dropout rate in another trial (NCT00383903 [23]) conducted in South Africa around the same time period, to estimate the sample sizes of each group. Likewise, we were unable to determine the sample size for the immunogenicity cohort in Malawi from trial NCT00241644 [5, 18]. The sample size was estimated using the estimate of seroconversion proportion and 95% confidence interval to solve for the standard error and sample size. In addition, one trial, Clinical Trials Registry of India (CTRI)-2012-02-002454, did not report 95% confidence intervals for seroconversion proportion [19]. Exact confidence intervals were estimated using the sample size and seroconversion proportion estimate.

Study Characteristics

Of the 8 included trials, all evaluated different schedules of RV1 (Table 1) and none evaluated different schedules of RV5. Four of these trials were Phase II, 1 Phase III, and 3 Phase IV. The earliest trial began data collection in 2001 and the latest in 2012. Most trials evaluated the lyophilized formulation of RV1 given at the

Table 1. Characteristics of Included Trials and Trial Populations (N = 8)

Trial Number	Phase	Location	Inclusion	Exclusion	Study Notes
NCT00346892 [21]	II	South Africa	<ul style="list-style-type: none"> • Healthy infants • 5–10 weeks at first dose • HIV-confirmed negative mother^a 	<ul style="list-style-type: none"> • History of (1) allergic disease, (2) clinically significant chronic GI disease, (3) serious medical condition • Confirmed or suspected immunosuppressive or immunodeficient condition • Receipt of treatment prohibited by protocol 	<ul style="list-style-type: none"> • Lyophilized formulation • Viral concentration: $1 \times 10^{5.6}$ CCID₅₀ • EPI vaccines given • 100% concomitantly received OPV (group 1) • 100% concomitantly received IPV (group 2) • Breastfeeding not restricted
NCT00388903 [23]	II	South Africa	<ul style="list-style-type: none"> • Healthy infants • 5–10 weeks at first dose • ≥ 36 weeks gestation at birth • HIV-confirmed negative mother 	<ul style="list-style-type: none"> • History of (1) allergic disease, (2) clinically significant chronic GI disease, (3) serious medical condition, (4) polio disease • Confirmed or suspected immunosuppressive or immunodeficient condition (including HIV) • Receipt of treatment prohibited by protocol 	<ul style="list-style-type: none"> • Lyophilized formulation • Viral concentration: $1 \times 10^{6.0}$ CCID₅₀ • EPI vaccines given • 100% concomitantly received OPV • Breastfeeding not restricted
NCT00345956 [17]	II	Vietnam	<ul style="list-style-type: none"> • Healthy infants • 6–10 weeks • Birth weight >2000 grams 	<ul style="list-style-type: none"> • History of allergic disease or suspected reaction • Chronic administration (since birth) of immunosuppressants or immune-modifying drugs • Planned vaccinations outside of protocol except DTPw, HBV, and OPV vaccines within 14 days of each dose • Concurrent participation in another clinical study where an investigational product is used <30 days of first dose or where any pharmaceutical product is used in study 	<ul style="list-style-type: none"> • Liquid formulation • Viral concentration: $1 \times 10^{6.0}$ CCID₅₀ • EPI vaccines given • 100% concomitantly received OPV • Breastfeeding not mentioned
NCT00432380 [17]	II	Philippines	<ul style="list-style-type: none"> • Healthy infants • 5–10 weeks at first dose • Birth weight >2000 grams 	<ul style="list-style-type: none"> • History of allergic disease or suspected reaction • Chronic administration of immunosuppressants or immune-modifying drugs 6 months before first dose; confirmed or suspected immunosuppressive or immunodeficient condition; receipt of immunoglobulins or blood products since birth or planned use in study • Planned vaccinations outside of protocol except DTPw, HBV, and OPV vaccines within 14 days of each dose and BCG at birth according to local EPI guidelines • Concurrent participation in another clinical study; use of investigational product <30 days of first dose or planned use in study • Acute disease at enrollment 	<ul style="list-style-type: none"> • Liquid formulation • Viral concentration: $1 \times 10^{6.0}$ CCID₅₀ • EPI vaccines given • 100% concomitantly received OPV • Breastfeeding not mentioned

Table 1. Continued

Trial Number	Phase	Location	Inclusion	Exclusion	Study Notes
NCT00241644 [15, 18, 20, 22]	III	South Africa Malawi	<ul style="list-style-type: none"> Healthy infants 5–10 weeks at first dose >36 weeks gestation at birth^b Birth weight >2000 grams or unknown^b Parents/guardians who investigators believe will comply with study requirements 	<ul style="list-style-type: none"> History of (1) allergic disease, (2) clinically significant chronic GI disease, (3) serious medical condition, (4) neurologic disorders or seizures, (5) confirmed rotavirus gastroenteritis, (6) acute or chronic pulmonary, cardiovascular, hepatic, or renal function abnormalities Confirmed or suspected immunosuppressive or immunodeficient condition; receipt of immunosuppressants for > 14 days since birth; family history of congenital or hereditary immunodeficiency; receipt of immunoglobulins or blood products since birth or planned use in study Previous routine vaccination except BCG, HBV, OPV at birth; planned receipt of vaccines not described in protocol within 14 days of each dose Acute disease at enrollment or gastroenteritis within 7 day preceding first dose History of experimental rotavirus vaccine use; concurrent participation in another clinical study where an investigational product is used <30 days of first dose or planned use in study 	<ul style="list-style-type: none"> Lyophilized formulation Viral concentration: 1×10^6 CCID₅₀ EPI vaccines given ≥99% concomitantly received OPV Breastfeeding not restricted
NCT01199874 [12]	IV	Pakistan	<ul style="list-style-type: none"> Healthy infants 6 weeks 0 days to 6 weeks 6 days at enrollment 	<ul style="list-style-type: none"> History of (1) intussusception, (2) abdominal surgery, (3) hypersensitivity to vaccine components Use of immunosuppressants; receipt of immunoglobulins or blood products since birth or planned use in study Concurrent participation in another trial; use of investigational product <30 days of first dose or planned use in study Birth weight <1500 grams or, if birth weight unknown, weight <2000 grams by 28 days of age 	<ul style="list-style-type: none"> Lyophilized formulation Viral concentration: 1×10^6 CCID₅₀ EPI vaccines given ≥99% concomitantly received OPV Breastfeeding not restricted
CTRI-2012-02-002454 [19]	IV	India	<ul style="list-style-type: none"> Infants <7 weeks of age attending Well Baby Clinic for routine EPI immunization 36–42 weeks gestation at birth Birth weight ≥2000 grams Guardians available for follow up 	<ul style="list-style-type: none"> History of (1) intussusception, (2) abdominal surgery, (3) congenital abdominal pain, (4) confirmed rotavirus gastroenteritis, (5) chronic diarrhea, (6) failure to thrive, (7) hypersensitivity to vaccine components Confirmed or suspected impairment of immunological function; receipt of any intramuscular, oral, or intravenous corticosteroid treatments in past 30 days Active gastroenteritis or fever (≥38.1°C) Prior rotavirus vaccination Exclusion from routine EPI immunization 	<ul style="list-style-type: none"> Lyophilized formulation Viral concentration: 1×10^6 CCID₅₀ EPI vaccines given %concomitant OPV not reported^c Breastfeeding not mentioned

Table 1. Continued

Trial Number	Phase	Location	Inclusion	Exclusion	Study Notes
NCT01575197 [11]	IV	Ghana	<ul style="list-style-type: none"> • Healthy infants • 42–55 days at enrollment • Guardians able to follow study procedures 	<ul style="list-style-type: none"> • History of intussusception or abdominal surgery • Receipt of immunoglobulins or blood products since birth or planned use in study • Concurrent participation in another intervention trial or use of investigational product in study • Birth weight <2000 grams or <36 weeks gestation at birth, if available • Prior rotavirus vaccination • Planned relocation before study completion • Another child living in same compound is already enrolled in study until vaccine is introduced in EPI system in Navrongo, at which point a child in the same compound who is <16 weeks of age can be enrolled 	<ul style="list-style-type: none"> • Lyophilized formulation • Viral concentration: 1×10^6 CCID₅₀ • EPI vaccines given • 100% concomitantly received OPV • Breastfeeding not mentioned

Abbreviations: BCG, bacille Calmette-Guérin vaccine; CCID₅₀, 50% cell culture infective dose; CTRI, Clinical Trials Registry of India; DTPw, diphtheria, tetanus, whole cell pertussis vaccine; EPI, expanded program on immunization; GI, gastrointestinal; HBV, hepatitis B vaccine; HIV, human immunodeficiency virus; IPV, inactivated poliovirus vaccine; NCT, National Clinical Trial; OPV, oral polio vaccine.

^aHIV status was only confirmed after 2002 rotavirus season.

^bSouth Africa only.

^cExact percentage not reported; the recommended polio schedule from the Indian Academy of Pediatrics Committee on Immunization is OPV (birth, 6 months, and 9 months) and IPV (6, 10, 14 weeks).

licensed concentration concomitantly with routine vaccines, including OPV. Most trials had similar inclusion and exclusion criteria for the study populations. Half of the trials were conducted in Asian LMICs whereas the other half were conducted in African LMICs. Several of the trials conducted in Africa were conducted in South Africa. All trials had medium or low risk of bias (Supplemental Table 3). Trials (N = 3) with a medium risk of bias had moderate to high attrition and/or did not adequately describe the method of treatment randomization.

Intermediate Outcomes

Seroconversion proportions and geometric mean concentrations were available for all trials (Table 2). The seroconversion proportion ranged from approximately 0.3 to approximately 0.8 across the different schedules evaluated by country and trial. Geometric mean concentrations of postimmunization anti-rotavirus IgA ranged from 19.7 U/mL to 176.3 U/mL across different schedules by country and trial.

Differences in Seroconversion Proportions

Differences in seroconversion proportions comparing 6/10- versus 10/14-week schedules and 6/10/14- versus 10/14-week schedules are presented in Figure 1. In general, seroconversion proportions for the 6/10-week schedule were lower than for the 10/14-week schedule. Only 2 of these estimated differences, trial NCT00346892 in South Africa [21] and NCT01575197 in Ghana [11], were statistically significantly different than the null (no difference between schedules). By contrast, seroconversion proportions for the 6/10/14-week schedule were similar or slightly higher than seroconversion proportions for the 10/14-week schedule.

Differences in the less commonly used schedules are presented in Table 3. There was no difference in seroconversion proportions between the 6/10/14- and 6/10/14/18/22-week schedules in India. However, there was a statistically significant lower seroconversion proportion for the 8.8/13.2-week schedule compared with the 8.6/17.4-week schedule in Vietnam. The seroconversion proportion for the 6.5/15.1-week schedule was lower than the 10.6/15.2-week schedule, although not statistically significant.

Ratios of Geometric Mean Concentrations

The ratios of geometric mean concentration levels comparing the 6/10- and 6/10/14-week schedules to the 10/14-week schedule are presented in Figure 2. These ratios followed a similar pattern to the differences in seroconversion proportions. In general, the geometric mean concentration was lower, although not statistically significantly lower, for the 6/10- versus 10/14-week schedules. Similar to the results for difference in seroconversion proportion, the geometric mean concentrations were similar or slightly higher for 6/10/14- versus 10/14-week schedules.

For less commonly used schedules, the geometric mean concentration was significantly lower for 8.8/13.2-week schedule compared with the 8.6/17.4-week schedule. The responses were

Table 2. One-Month Seroconversion Percentage and GMCs by Trial and Country for Different Schedules of the Monovalent Rotavirus Vaccine Administered Concomitantly With Routine Vaccines, Including Oral Polio Vaccines Unless Otherwise Indicated

Trial Number	Trial Month/Year	Location	Schedule	N	Seroconversion ^a % (95% CI)	GMC (U/mL) (95% CI)
NCT00346892 ^b	November/2001–Oct/2003	South Africa	6/10	64 ^d	36 (23–50)	28.1 (18.2–43.2)
			10/14	63 ^d	61 (43–76)	48.6 (29.9–78.9)
			6/10 ^c	41 ^d	43 (29–58)	32.6 (20.7–51.3)
			10/14 ^c	42 ^d	55 (39–70)	56.7 (32.5–98.9)
NCT00383903	September/2003–February/2004	South Africa	6/10/14	133	44.4 (35.8–53.2) ^e	30.7 (24.0–39.3) ^e
			10/14	131	44.3 (35.6–53.2) ^e	29.3 (23.0–37.3) ^e
NCT00345956 ^f	September/2006–March/2007	Vietnam	8.8/13.2	130	56.2 (47.2–64.8)	48.7 (36.1–65.8)
			8.6/17.4	119	81.5 (73.4–88.0)	176.3 (123.8–251.1)
NCT00432380 ^f	March/2007–September/2007	Philippines	6.5/15.1	120	59.2 (49.8–68.0)	75.6 (52.5–109.0)
			10.6/15.2	120	70.0 (61.0–78.0)	68.0 (50.1–92.1)
NCT00241644	October/2005–July/2007	South Africa	6/10/14	66	66.7 (54.0–77.8)	94.3 (56.5–157.4)
			10/14	70	57.1 (44.7–68.9)	59.4 (37.5–93.9)
		Malawi	6/10/14	83 ^d	57.1 (42.2–71.2)	51.2 (26–102)
NCT01199874	April/2011–September/2012	Pakistan	6/10	46	29.7 (23.1–37.3)	19.7 (16.2–23.9)
			6/10/14	62	36.7 (29.8–44.2)	25.8 (20.5–32.5)
			10/14	60	38.5 (31.2–46.3)	24.4 (19.5–30.6)
CTRI-2012-02-002454 ^c	March/2012–December/2012	India	6/10/14	15	46.7 (21.3–73.4) ^g	72.9 (30.9–172.3)
			6/10/14/18/22	22	45.5 (24.4–67.8) ^g	60 (35.3–102.2)
NCT01575197	September/2012–February/2013	Ghana	6/10	142	28.9 (22.1–36.8)	22.5 (17.4–28.2)
			6/10/14	143	43.4 (35.5–51.6)	32.6 (24.7–43.2)
			10/14	139	37.4 (29.8–45.7)	26.5 (20.7–34.0)

Abbreviations: CI, confidence interval; CTRI, Clinical Trials Registry of India; GMC, geometric mean concentration; Ig, immunoglobulin; NCT, National Clinical Trial.

^aPercentage of seronegative participants with postvaccination anti-rotavirus IgA antibody concentrations of ≥ 20 U/mL.

^bVaccine with viral concentration of $1 \times 10^{5.6}$ median cell culture infective dose.

^cConcomitant inactivated polio vaccine.

^dExact sample size not reported; sample size estimated.

^eTwo-month seroconversion percentage/GMC.

^fLiquid formulation of vaccine.

^gExact 95% CI estimated.

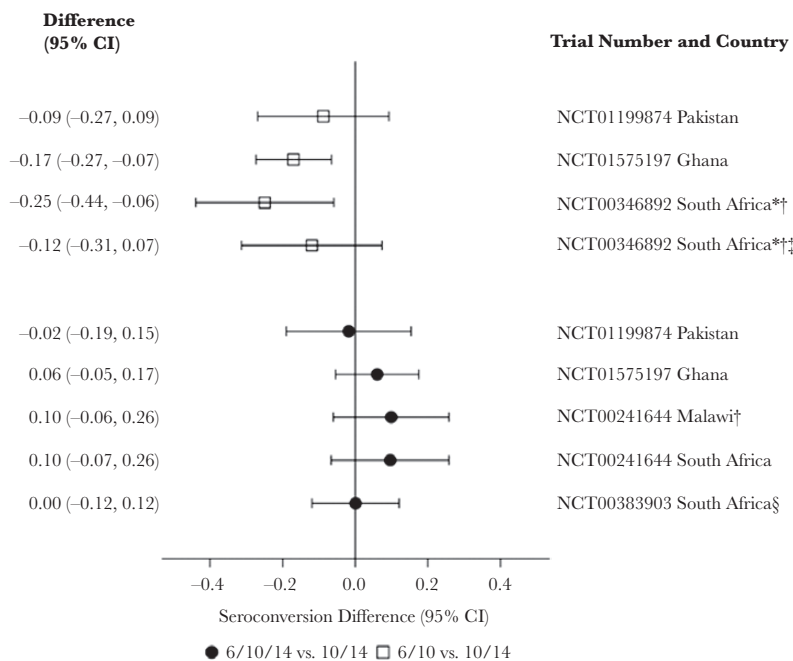


Figure 1. One-month seroconversion proportion differences comparing different monovalent (RV1) rotavirus vaccine schedules from 5 trials conducted in low- and middle-income countries with concomitantly administered oral polio vaccines unless otherwise indicated. *RV1 viral concentration $10^{5.6}$; †Estimated sample size used; ‡Concomitant inactivated polio vaccine; §2-month seroconversion difference. CI, confidence interval.

Table 3. Summary of Seroconversion Proportion Differences and Ratios of GMCs by Trial and Country of the Monovalent Rotavirus Vaccine for Vaccine Schedules Less Commonly Reported

Trial Number Trial Month/Year	Location	Schedule	Seroconversion Proportion Difference (95% CI)	Ratio of GMC (95% CI)
CTRI-2012-02-002454 ^a March/2012–December/2012	India	6/10/14 6/10/14/18/22	0.01 (–0.32 to 0.34) (Reference)	1.2 (0.4 to 3.3) (Reference)
NCT00345956 ^b September/2006–March/2007	Vietnam	8.8/13.2 8.6/17.4	–0.25 (–0.36 to –0.14) (Reference)	0.3 (0.2 to 0.4) (Reference)
NCT00432380 ^b March/2007–September/2007	Philippines	6.5/15.1 10.6/15.2	–0.11 (–0.23 to 0.01) (Reference)	1.1 (0.7 to 1.8) (Reference)

Abbreviations: CI, confidence interval; CTRI, Clinical Trials Registry of India; GMC, geometric mean concentration; NCT, National Clinical Trial.

^aConcomitant inactivated polio vaccine.

^bLiquid formulation of vaccine.

similar or slightly higher for the 6/10/14-week schedule compared with the 6/10/14/18/22-week schedule. The responses were also similar or slightly higher for the 6.5/15.1-week schedule compared with the 10.6/15.2-week schedule.

Comparison of Efficacy

One trial (NCT00241644 [5, 18, 20, 22]), conducted in South Africa and Malawi, reported vaccine efficacies by schedule using clinical outcomes (Table 4). In South Africa, the 6/10/14-week schedule had slightly higher efficacy compared with the 10/14-week schedule. However, these efficacy estimates, particularly for the second year and cumulative 2-year efficacy, had large variability. In Malawi, the efficacy for the 6/10/14-week schedule was largely indistinguishable from the 10/14-week schedule for the first-year efficacy, but the 6/10/14-week schedule had

a numerically higher efficacy compared with the 10/14-week schedule during the second year, although the estimates were very imprecise.

DISCUSSION

Overall, a small body of literature reported the effect of RV1 or RV5 schedules on vaccine immunogenicity or efficacy in LMICs. We identified 8 trials, all of which evaluated different schedules of RV1. These studies had relatively similar inclusion and exclusion criteria.

In general, the 6/10-week schedule was not as immunogenic as the 10/14-week schedule in LMICs. A 3-dose RV1 schedule at 6/10/14 weeks had similar or slightly higher immunogenicity and efficacy compared with a 2-dose schedule at 10/14 weeks.

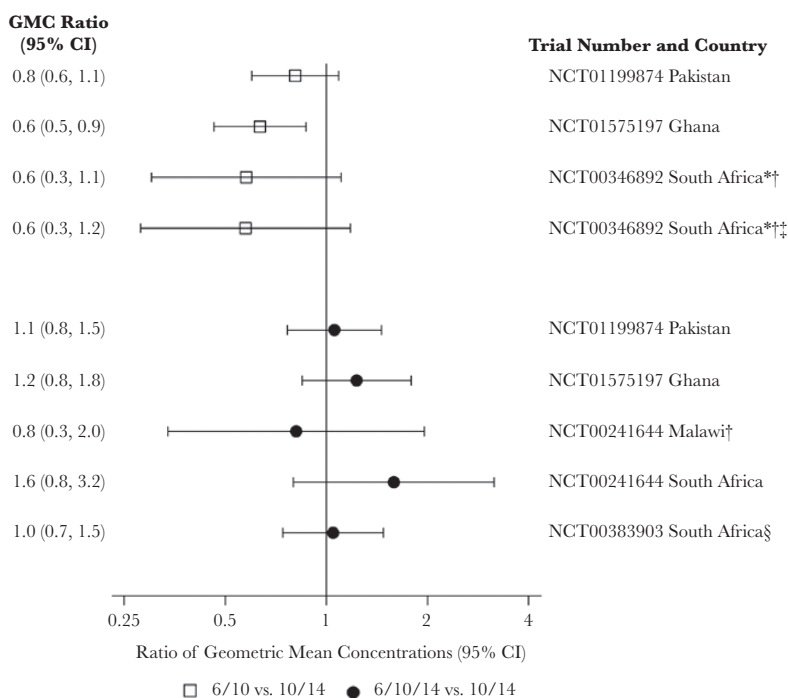


Figure 2. One-month ratios of geometric mean concentrations comparing different monovalent (RV1) rotavirus vaccine schedules from 5 trials conducted in low- and middle-income countries with concomitantly administered oral polio vaccines unless otherwise indicated. *RV1 viral concentration $10^{5.6}$; †Estimated sample size used; ‡Concomitant inactivated polio vaccine; §2-month ratio of GMCs. CI, confidence interval; GMC, geometric mean concentration.

Table 4. Rotavirus Vaccine Efficacy Against Severe Rotavirus Gastroenteritis Comparing Different Schedules From Trial NCT00241644

Location	Schedule	N ^a	One Year Efficacy (95% CI)	Second Year Efficacy (95% CI)	Cumulative Two-Year Efficacy (95% CI)
South Africa	10/14	971	72.2 (40.4 to 88.3)	3 (-43 to 82)	32 (-71 to 75)
	6/10/14	973	81.5 (55.1 to 93.7)	76 (-143 to 100)	85 (35 to 98)
Malawi	10/14	525	49.2 (11.1 to 71.7)	2.6 (-101.2 to 52.6)	34.0 (-2 to 57.7)
	6/10/14	505	49.7 (11.3 to 72.2)	33.1 (-48.6 to 70.9)	42.3 (8.8 to 64.0)

Abbreviations: CI, confidence interval.

^aSample size in each arm for 1-year efficacy analysis.

However, as mentioned previously, this was a relatively small body of evidence, and the estimates for each schedule within each trial had a large amount of variability. Consequently, moderate differences that appear between different vaccine schedules may be due to random variability. More importantly, these studies, in large part, relied on immunogenic assessment of the response to the vaccine. Currently, there is no known correlate of protection for anti-rotavirus IgA levels [24, 25]. Therefore, even an association between vaccine schedule and immunogenicity does not provide evidence of a difference in disease protection. However, the pattern observed in the immunogenicity data was similar to the pattern seen with clinical outcomes in one trial, although the 6/10-week and 10/14-week schedules were not compared using clinical outcomes.

The results of this compiled evidence are consistent with the hypothesis that immune response to vaccination may be dampened or negated by maternal antibodies, differences in profiles of microbiota, or other immunologic factors. However, by assessing vaccine schedule alone, it is impossible to know the mechanism through which this effect, if it exists, occurs. Maternal antibodies passively acquired in utero (anti-rotavirus IgG) may partially, or fully, inhibit the immune response to rotavirus vaccine doses given at 6 weeks. Although transplacentally acquired antibodies decay exponentially with a half-life of approximately 35 to 40 days, there is considerable individual variability in the rate of clearance [26]. In addition, the critical level at which maternally acquired antibody concentrations are low enough to elicit a robust immune response to rotavirus vaccines in infants is unknown. One study has examined the clearance rate of passively acquired anti-rotavirus antibodies in 54 Mexican infants and found a gradual decline until 4 months of age and then an increase in anti-rotavirus IgG, likely due to the infant's active immunity to rotavirus infections [27]. Another study of the natural history of rotavirus infection found that children with maternal antibodies in cord blood were less likely to experience symptomatic rotavirus infection before 3 months of age compared with those without maternal antibodies [28]. Furthermore, one study in India even demonstrated the ability of pre-existing anti-rotavirus IgG antibodies in infant blood to neutralize the effect of a new rotavirus vaccine (ORV-116E) [29]. These data suggest it is possible passively acquired antibodies could interfere with the immunologic response to

rotavirus vaccines given to very young infants. However, other infant characteristics, including the microbiota of young infants in LMICs and other factors affecting enteric immunity, may influence any effect of vaccine schedules that is observed.

The implementation of immunization programs for rotavirus vaccines is extremely complex. Currently, the World Health Organization recommends that rotavirus vaccines be given as soon as possible after 6 weeks of age [30] and that 62% of the 37 LMICs administering RV1 in their routine immunization program use the 6/10-week schedule [2, 31]. The 6/10-week schedule may not be as immunogenic as the 10/14-week schedule, which suggests vaccination could start at 10 weeks rather than 6 week. However, in some LMICs countries, initial vaccination is already delayed, and there is concern that starting vaccination later may lead to prolonged vaccination time or missing vaccination altogether. In addition, due to the potential fear of increased risk of intussusception [32], there is a recommendation that RV1 and RV5 be given before 32 weeks if at all possible [30]. Furthermore, the timing of first rotavirus infection is thought to occur early in LMICs (median 6–9 months) [33]. It is important that rotavirus vaccines be provided in a timely manner to prevent severe RVGE. Although the additional dose at 14 weeks could improve immunogenicity, the additional capacity and cost associated with this decision may not be justified based on the current evidence.

There are some limitations and strengths of this systematic review. This is the first review to summarize data on RV1 or RV5 schedules and the impact it has on vaccine response among children in LMICs. We were limited in our ability to report and use the exact sample size for some trials, but we did evaluate the effect of schedule on vaccine response. This will be helpful given the paucity of data in low-resource settings at this time. In addition, we were able to present comparisons not directly reported in some trials and to estimate seroconversion proportion differences and ratios of geometric mean concentrations using the same methods to ease comparison across trials. The summarization of these data highlights the importance of assessing the effect of RV1 and RV5 schedules on vaccine performance using clinical endpoints, because there is the potential that schedules could affect the incidence of severe RVGE, and alterations in schedules could result in the prevention of more severe RVGE episodes.

CONCLUSIONS

In conclusion, 8 trials have assessed the impact of different RV1 schedules on vaccine response in LMICs, whereas none have reported information for RV5 schedules. Seroconversion proportions and geometric mean concentrations were generally lower for the 6/10-week schedule compared with the 10/14-week schedule. The administration of 3 doses of RV1 on the 6/10/14-week schedule had similar or slightly higher seroconversion proportions, geometric mean concentrations, and efficacies against severe RVGE compared with the 10/14-week schedule. The commonly used 6/10-week schedule of RV1 in LMICs may not be optimal for protection. Further research on the effect of RV1 and RV5 schedules using clinical endpoints is critical, because if altering schedules could confer better protection, even small improvements gained by altering vaccine schedules could translate into the prevention of thousands of severe RVGE episodes each year.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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