Rotavirus Vaccine Safety and Effectiveness in Infants With High-Risk Medical Conditions

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abstract

OBJECTIVES: Rotavirus vaccination has 87% to 100% effectiveness against severe rotavirus acute gastroenteritis (AGE) in healthy infants in high-income countries. Little is known whether infants with medical risk conditions (MRCs) are equally protected and if the vaccine is equally well tolerated. We conducted a quasi-experimental prospective multicenter before-after cohort study to assess the vaccine effectiveness (VE) and safety profile of the human rotavirus vaccine (HRV) among MRC infants that required prolonged or frequent postnatal care.

METHODS: The Netherlands has no national rotavirus immunization program, but HRV was implemented in routine care for MRC infants in 13 Dutch hospitals. Participants in the before and after cohort, HRV unvaccinated and vaccinated, respectively, were followed for occurrence of (rotavirus) AGE. VE of at least 1 dose was estimated by using time-to-event analysis for severe rotavirus AGE. Vaccine-related serious adverse event (AEs) after HRV were retrieved systematically from medical charts. Solicited AEs after vaccinations were prospectively collected and compared between vaccination time points with or without HRV.

RESULTS: In total, 1482 high-risk infants with MRC were enrolled, including 631 in the before and 851 in the after cohorts; 1302 infants were premature (88.3%), 447 were small for gestational age (30.2%), and 251 had at least 1 congenital disorder (17.0%). VE against severe rotavirus AGE was 30% (95% confidence interval [CI]: −36% to 65%). Overall, the observed number of rotavirus hospitalizations was low and not significantly different between the cohorts (2 and 2, respectively). The rate of vaccine-related serious AE was 0.24 per 100 vaccine doses. The adjusted risk ratio for any AE after HRV vaccination compared with other routine vaccinations was 1.09 (95% CI: 1.05 to 1.12) for concomitant administration and 0.91 (95% CI: 0.81 to 0.99) for single HRV administration. Gastrointestinal AEs were 10% more frequent after HRV.

CONCLUSIONS: In contrast to previous findings among healthy term infants, in routine use, HRV offered limited protection to vulnerable medical risk infants. HRV is generally well tolerated in this group in single administration, but when coadministered with routine vaccines, it is associated with higher risk of (mostly gastrointestinal) AE. Our study highlights the importance of studying vaccine performance in subgroups of medically vulnerable infants.

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WHAT'S KNOWN ON THIS SUBJECT: National immunization programs worldwide recommend rotavirus vaccines for all infants. Currently available evidence on rotavirus vaccines effectiveness and safety is, however, largely based on healthy term infants. Medical risk infants experience more vaccine adverse events.

WHAT THIS STUDY ADDS: Rotavirus vaccination with human rotavirus vaccine offers limited protection against rotavirus gastroenteritis in vulnerable medical risk infants. Medical risk infants experienced 10% more (gastrointestinal) adverse events after rotavirus vaccination. This study emphasizes the importance of studying risk group specific vaccine performance.

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Rotavirus is a frequent cause of acute gastroenteritis (AGE) in children <5 years of age.[1] Since the global introduction of vaccines against rotavirus in 2006, hospitalizations for rotavirus AGE have decreased substantially.[2] Worldwide, over 98 countries have now included rotavirus vaccination in their national immunization program (NIP).[3] The majority of countries use 1 of 2 globally licensed live-attenuated oral rotavirus vaccines; Rotarix (GlaxoSmithKline, Belgium) or RotaTeq (Merck and Co, United States). In high-income countries, high rotavirus VE against severe rotavirus AGE has been consistently reported for both vaccines, with overall VE of >80% for a full series of either vaccine.[4–6] Yet, these estimates are primarily based on results from healthy infants[4–6] and limited data on the performance of rotavirus vaccines in infants with underlying medical conditions, which may influence their vaccine response and/or their risk of severe rotavirus AGE, is available. These medical risk conditions (MRCs) include premature birth, low birth weight, and severe congenital disorders. There is reason to assume vaccine responses may be different in these medical risk infants because of immaturity or conditions compromising immune functioning to some extent.[7–9]

Findings on rotavirus vaccine safety and tolerability in preterm infants from previous studies indicate that rates of adverse events (AEs) are similar to those observed among term infants.[10,11] However the trials included a limited number of infants with low gestational ages (GAs), and for Rotarix no infants with GA <27 weeks were included. Moreover, inclusion criteria required that infants were healthy and medically stable at time of enrollment. This may have selected for a relatively healthy study population of premature infants, which may influence AE rates.[10,11] More real-world data on safety and tolerability of rotavirus vaccination in unbiased populations with MRCs are needed to guide clinicians in the individual assessment of risks and benefits of rotavirus vaccination.

In the absence of a universal rotavirus vaccination program in the Netherlands, a pilot with routine rotavirus vaccination was initiated in a selection of hospitals for MRC infants diagnosed with ≥1 of these MRCs and who received prolonged or frequent postnatal care. An earlier study showed these infants are at increased risk of severe or complicated rotavirus AGE.[12] The human rotavirus vaccine (HRV; Rotarix) was used throughout the project. The implementation of HRV for MRC infants was combined with a before-after cohort study to evaluate rotavirus VE. In addition, the safety and tolerability of rotavirus vaccination was studied.

METHODS

The Risk group Infant Vaccination Against Rotavirus (RIVAR) project piloted the implementation of a selective rotavirus vaccination program for MRC infants in pediatric secondary and tertiary care hospitals. The primary objectives of the RIVAR project were to (1) assess the feasibility of implementing and executing this selective rotavirus vaccination program in routine hospital and outpatient care for MRC infants and (2) determine VE against severe rotavirus AGE in MRC infants. Secondary objectives included safety and tolerability assessment and VE against rotavirus AGE of any severity.

The medical ethic board of the University Medical Center Utrecht declared that the RIVAR study was not covered by the Medical Research Involving Human Subjects Act. Rotavirus vaccine was implemented into routine care, and study procedures were noninvasive.

Here, we describe the results of the primary end point of VE and secondary end point of vaccine safety/tolerability. The study protocol was registered in the Dutch trial registry.[13]

Study Setting

Dutch hospitals with an NICU or post–intensive care (IC)/high care ward were invited to participate in the project. Hospitals could participate if they were willing to (1) implement rotavirus vaccination for MRC infants in their routine neonatal care and (2) recruit and enroll eligible infants in the before-after cohort study.

Thirteen Dutch hospitals, at 15 locations, with a NICU or post–intensive care/high care unit participated in the RIVAR study. Hospitals enrolled in a stepped-wedge order (ie, at different points in time); the first hospitals enrolled in November 2014 and the last in April 2016 (Fig 1).

Implementation of a Hospital-Based Selective Rotavirus Vaccination Program

After enrollment, each hospital entered a preparatory pre-implementation year during which local operational procedures were developed for patient selection, rotavirus vaccine delivery, administration, and documentation. In the second year, rotavirus vaccination was locally implemented, at different time points, for all infants with a qualifying MRC and was continued thereafter.

At the start of the preimplementation year, the participating site initiated screening

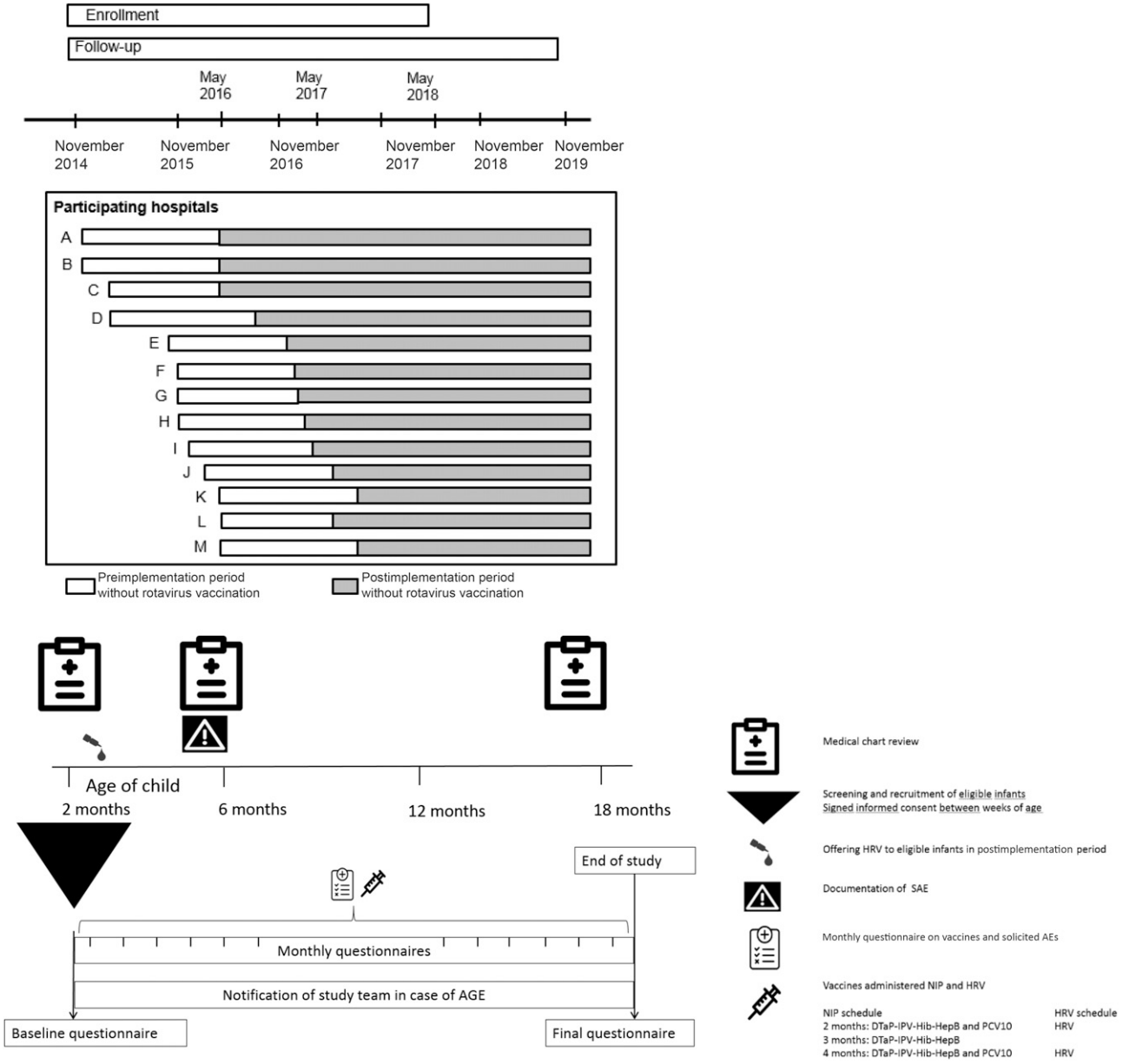

FIGURE 1

Schematic outline of study data collection and procedures. A, Implementation of a hospital-based selective rotavirus vaccination program: A screening log was recorded for infants with at least 1 of the qualifying MRC. Exclusion criteria were known hypersensitivity to the vaccine components, history or predisposition of intussusception, and/or diagnosis of severe combined immunodeficiency syndrome. During the preimplementation period, eligible infants received standard of care only without rotavirus vaccination. After implementation, eligible infants were offered rotavirus vaccination free of charge. Rotavirus vaccination status was documented in the screening log for each eligible infant. We also logged any serious adverse reaction as documented in the medical chart. Hospitals continued screening and vaccination until end of the project in November 2019. The first dose HRV was administered by a health care professional at the study site between 6 and 14 weeks of age. The second dose was by default administered by parents at home, following detailed instructions, with a minimal interval of 4 weeks and no later than 23 weeks and 6 days of age. Alternatively, the second dose could be delivered at the site and administered by a health care professional. B, Before–after cohort study: Eligible infants were not approached for participation in the cohort study if parents were not proficient in Dutch language, the child was in custody or in an unstable home situation, the infant had a poor medical prognosis, or the infant was discharged from follow-up (including transfer to another nonparticipating hospital) before 6 weeks of age. After informed consent, parents received a baseline questionnaire on household composition, socioeconomic status, and pregnancy, followed by short monthly questionnaires and a final questionnaire at 18 months of age. The monthly questionnaire consisted of 7 items on respiratory and gastrointestinal symptoms during the past month, received vaccinations of the NIP and rotavirus, and solicited AEs and health care attendance in the 7 days after vaccination, type of feeding, and day care attendance. The final questionnaire at 18 months contained a modified quality of life questionnaire. Finally, trained research staff collected data from the participating child's hospital medical record at 6 weeks and 5 and 18 months of age, including rotavirus vaccination status, any rotavirus vaccine-related SAE, and dates of vaccine administration, information on all hospitalizations, supportive therapy, medical treatment, and complications. DTaP-IPV-Hib-HepB, hexavalent diphtheria–tetanus toxoids–accelular pertussis–inactivated polio–Haemophilus influenzae type B–hepatitis B vaccine; PCV10, 10-valent pneumococcal vaccine.

of all hospitalized infants <14 weeks of age for prematurity (GA before 36 weeks), low birth weight (<2500 g), and/or presence of a severe congenital disorder (for qualifying conditions, see Supplemental Fig 3). Infants still hospitalized or receiving outpatient care between 6 and 14 weeks of postnatal age (corresponding with the age-window for first dose rotavirus vaccination) were eligible. The HRV (containing attenuated human rotavirus G1P8 genotype, licensed by GlaxoSmithKline, Belgium, since 2006)[14] was used throughout the project and given as 2 oral doses. HRV vaccination status was documented for each eligible infant postimplementation. In addition, medical charts were reviewed for all HRV-vaccinated infants to check for any vaccine-related serious adverse event (SAE).

Before-After Cohort Study

Parents of eligible infants were approached for participation in the cohort study with active follow-up for occurrence of AGE until 18 months of age. Enrollment started early in the preimplementation year and continued in each hospital until 12 to 18 months after implementation of the selective rotavirus vaccination program. The "before" cohort thus included infants who received standard of care only. The "after" cohort included infants who were routinely offered rotavirus vaccination. Throughout follow-up, parents completed monthly questionnaires. These contained yes or no questions on AGE symptoms, date and type of received immunizations, solicited AEs, and AE-related health care in the 7 days after vaccinations (Fig 1). Parents were also asked to notify the study team whenever symptoms of AGE developed in their child and instructed to collect a fecal sample as soon as possible. A 7-day AGE symptom diary was completed along with a questionnaire on health care attendance. Research staff collected additional medical data from infant hospital records up to 18 months of age. For a schematic overview of the study, see Fig 1.

Microbiologic Analysis

Fecal samples were tested by multiplex realtime polymerase chain reaction (PCR) for presence of rota-, noro-, adeno- (type 40/41), and astrovirus. Details of the laboratory analysis are described in the Supplemental Information.

Definitions

AGE was defined as acute diarrhea or looser than normal stools >3 times per 24 hours, and/or forceful vomiting.[15] Reports of AGE were derived from 3 different sources: as per protocol reported by parents, not reported but documented on monthly questionnaires, or retrieved form medical chart review (elaborated in Supplemental Information). AGE severity was based on symptom diaries by using the modified Vesikari score.[16,17]

Vaccine-related SAE was defined as any reaction that was fatal, life-threatening, disabling, or incapacitating; required inpatient treatment or prolonged existing hospitalization; or required intervention to prevent the previously stated outcomes and was considered related to rotavirus vaccination as judged by the treating physician and documented in the patient medical record. In addition, we described "vaccine failure" when rotavirus AGE led to hospitalization and occurred at least 14 days after second HRV dose.

Solicited AE were fever, rash, irritability, loss of appetite, vomiting, looser and/or bloody stools. We defined vaccine administration concomitant when vaccination dates were identical for at least 1 NIP vaccination and HRV (NIP+HRV) vaccination or if dates were a maximum of 3 days apart, such that the 7-day postvaccination period for reporting solicited AE covered both vaccinations.

The primary end points were defined as follows:

1. VE of at least 1 dose of HRV (as at least the first dose was given on-site) against severe rotavirus-related AGE from 14 days postdose 1 until 18 months of age.
2. The impact of the selective HRV vaccination program defined as the relative reduction in rotavirus-related hospitalization (including symptomatic nosocomial infection) during follow-up comparing infants enrolled in the preimplementation versus postimplementation periods.

Prespecified secondary end points included (1) the effectiveness of a full series of HRV against severe rotavirus-related AGE, (2) the protective effectiveness of at least 1 dose of HRV against rotavirus-related AGE of any severity, (3) vaccine safety, defined as the number of vaccine-related SAE per 100 vaccine doses, and (4) tolerability of at least 1 solicited AE in the 7 days after receipt of either NIP vaccines, concomitant NIP+HRV or, HRV only.

Next, we performed subgroup analyses for infants born at GA 32 to 37 weeks, 30 to 32 weeks, <30 and <27 weeks, term infants with congenital disorders, and infants with >1 MRC.

As post hoc analysis, we added all-cause (severe) AGE as outcome for all specified primary end points. This was decided because a stool sample was missing from a

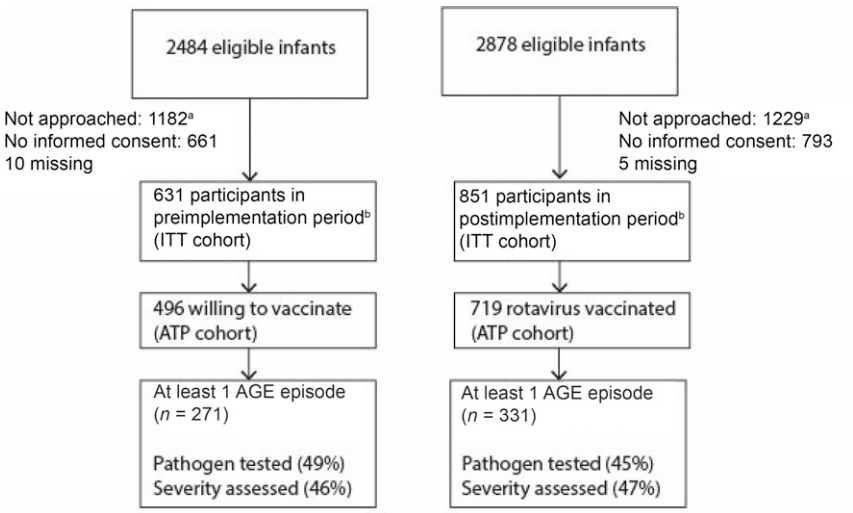

FIGURE 2

Flowchart of recruitment and cohort groups. [a] Reasons for not approaching were as follows: 596 vs 663 were discharged or referred (50.4% vs 53.9%), 201 vs 177 had no Dutch speaking parent (17.0% vs 14.4%), 193 vs 96 had unstable home situation (16.3% vs 7.8%), 82 vs 103 had poor prognosis (6.9% vs 8.4%), 110 vs 190 had other unspecified reason (9.3% vs 15.5%). Missing refers to missing information on whether infant was not approached or no consent was obtained. [b] A total of 82 missing information on willingness to vaccinate and 6 missing information on vaccination status. *n* = number with characteristic.

substantial proportion of AGE episodes (eg, without a rotavirus test result) and previous studies have estimated up to 50% of severe AGE in infants are caused by rotavirus.[18–20] In addition, we quantified the probability of incorrectly estimating VE because of sparse confirmed rotavirus events.

Statistical Analyses Plan

1. For the primary analysis of VE, we used Cox regression modeling of the time to first episode of severe rotavirus AGE as a function of vaccination status with age (between 2 and 18 months) modeled as time-variable. Infants were censored at their first severe episode or when lost to follow-up. Rotavirus vaccination was modeled as a time-dependent covariate thereby accounting for weeks of observation in vaccinated infants before dose 1 and the initial 14 days after dose 1, when protection from vaccination is considered to be still minimal. VE was defined as 1 minus the hazard rate (HR) × 100%. More details are described in the Supplemental Information.
2. The impact of the HRV selective vaccination program was estimated from the proportion of infants with rotavirus-related hospitalization in the postimplementation versus the preimplementation period, expressed as 1 minus the risk ratio (RR). We used a mixed model with a binomial distribution, and RRs were obtained from odds ratio by using the method described by Knol et al.[21] To account for potential cluster effects within hospitals, type of study site (academic versus general hospital) was added as a random intercept to the model.

For the secondary analyses of VE after a complete HRV series and subgroup analyses, we used the Cox model as described above. For VE against rotavirus AGE episodes of any severity, accounting for multiple episodes within one individual, we used negative binomial regression with VE calculated as 1 minus the incidence rate ratios (IRRs) ×100%. Person-time of observation was included as offset in the model. To calculate posterior probability of VE in our study population, we used Bayesian analysis, with uninformative priors, of the Cox model for the primary outcome of VE against severe rotavirus AGE. All-cause AGE analyses were performed by using the same methods as described above.

Vaccine safety was reported by describing each vaccine-related SAE in terms of diagnosis, infant characteristics, timing in relation to HRV vaccination, and, where applicable, results of fecal testing. All eligible infants with at least 1 HRV administration were included in the safety analysis, irrespective of participation in the cohort study. For the tolerability outcome of at least 1 AE, data from cohort participants were used in mixed model with binomial distribution and a random intercept per infant. We estimated odds ratios for type of vaccine administration (NIP, HRV, or NIP+HRV), adjusting for age at vaccination. Odds ratios were

TABLE 1 Comparison of Characteristics Between Before and After Cohort Participants

	ITT			ATP		
	Preimplementation Period: All Infants (N = 631)[a]	Postimplementation Period: All Infants (N = 851)[a]	P	Preimplementation: Willing to Vaccinate (n = 496)	Postimplementation: Vaccinated (n = 719)	P
Male sex, *n* (%)	361 (57.2)	456 (53.8)	.19	286 (57.7)	381 (53.0)	.11
Multiple births, *n* (%)	158 (25.0)	230 (27.1)	.37	115 (23.8)	193 (26.8)	.15
Premature birth (gestation <37 wk), *n* (%)	549 (87.6)	753 (88.8)	.47	432 (87.8)	635 (88.3)	.79
GA in weeks + days among those premature (SD)	31 + 4 (3 + 1)	31 + 6 (2 + 6)	.03*	31 + 3 (3 + 1)	32 + 1 (2 + 5)	<.001*
Small for GA,[b] *n* (%)	176 (27.9)	271 (31.8)	.10	135 (27.2)	238 (33.1)	.03*
Presence of severe congenital disorder,[c] *n* (%)	126 (20.0)	125 (14.7)	.01*	95 (19.2)	106 (14.7)	.04*
Length of postnatal hospital stay (IQR), d	29 (44)	27 (38)	.53	31 (43)	27 (35)	.17
Total hospitalization days during follow-up (IQR), d	35 (48)	33 (42)	.35	37 (48)	31 (41)	.13
Vaccinated within NIP, *n* (%)	539 (85.4)	753 (88.5)	.08	484 (97.6)	652 (90.7)	<.001*
Age at first vaccination in days (median, IQR)	62 (48–76)	60 (40–80)	.007[d,]*	62 (50–74)	59 (39–79)	<.001[d,]*
Day care ever, *n* (%)	319 (56.5)	464 (59.4)	.28	289 (58.6)	398 (59.6)	.74
Average age at start (IQR), mo	6 (1–11)	5 (1–9)	.06	6 (1–12)	5 (1–9)	.01*
Breastfed ever, *n* (%)	355 (62.7)	481 (61.4)	.61	312 (63.3)	403 (60.2)	.29
Average duration of exclusive breastfeeding (SD), wk	16.8 (7.0)	16.3 (7.3)	.40	16.6 (6.9)	16.4 (7.4)	.69
Socioeconomic status,[e] *n* (%)			.59			.36
Higher	398 (71.3)	568 (72.9)		352 (71.5)	492 (74.1)	
Moderate	134 (24.0)	183 (23.5)		119 (24.2)	153 (23.0)	
Lower	26 (4.7)	28 (3.6)		21 (4.3)	19 (2.9)	
Young sibling (≤5 y) in household, *n* (%)	134 (24.4)	167 (21.5)	.22	118 (24.2)	148 (22.4)	.46
Young sibling attending day care, *n* (%)	87 (22.0)	94 (17.3)	.07	77 (21.8)	81 (17.5)	.13
Parental origin,[f] *n* (%)			.92			.75
European parent(s)	471 (84.1)	652 (83.3)		417 (84.8)	557 (83.4)	
Non-European parent(s)	35 (6.3)	31 (6.5)		28 (5.7)	38 (5.7)	
Mixed	54 (9.6)	80 (10.2)		47 (9.6)	73 (10.9)	
Median age of parent(s) (IQR)	32.5 (27–38)	33 (27–39)	.60	32.5 (27–38)	33 (27–39)	.23
Mean No. months with completed follow-up (SD)	14.5 (7.2)	14.5 (6.9)	.84	16.4 (5.5)	14.9 (6.5)	<.001*
No. with complete follow-up until 18 mo of age, *n* (%)	421 (66.7)	526 (61.8)	.05	380 (76.6)	450 (62.6)	<.001*

Percentages are derived excluding subjects with missing data on the variable.

[a] 82 missing information on willingness to vaccinate and 6 missing information on vaccination status.

[b] Small for GA was based on the 10th percentile cutoff for perinatal growth in Dutch infants (Hoftiezer L, Hof MHP, Dijs-Elsinga J, Hogeveen M, Hukkelhoven CWPM, van Lingen RA. From population reference to national standard: new and improved birthweight charts. *Am J Obstet Gynecol.* 2019;220(4):383.e1-383.e17; Hoftiezer L, Dijs-Elsinga J, van Dillen J, et al. Perined population curves. Published 2018. Available at: https://www.perined.nl/publicaties1/geboortegewichtcurven. Accessed May 28, 2019).

[c] Qualifying conditions in Supplemental Fig 3.

[d] Rank-sum test.

[e] Based on highest parental education.

[f] Based on parental origin (World Population by Country 2020, n.d.).

* Statistical significance ($P < .05$).

TABLE 2 AGE Events and Vaccine AE During Follow-up in ITT and ATP Before and After Cohorts

	ITT		ATP	
	Preimplementation Period: All Infants (N = 631), n (%)	Postimplementation Period: All Infants (N = 851), n (%)	Preimplementation: Willing to Vaccinate (n = 496), n (%)	Postimplementation: Vaccinated (n = 719), n (%)
All-cause AGE				
Any AGE	549	674	499	597
Severe AGE	68/252 (27.0)	79/227 (25.8)	62/228 (27.2)	71/279 (25.4)
AGE hospitalization	43 (7.8)	64 (9.5)	42 (8.4)	58 (9.7)
Rotavirus AGE				
Any rotavirus AGE	49	68	47	67
Severe rotavirus AGE	18/42 (42.9)	20/64 (31.3)	17/39 (43.6)	17/59 (28.8)
Rotavirus hospitalization	2 (4.1)	2 (2.9)	2 (4.3)	2 (3.0)

Denominator changes for categories of severe all-cause and severe rotavirus AGE episodes, because of missing data on severity if AGE was unreported.

transformed into RR by using the method described above. The number of solicited AE per vaccine administration was compared by using IRR. Comparisons were performed for the subgroup of fever and gastrointestinal AE (vomiting, bloody and/or looser stools) and for AE-related health care attendance. For the number of solicited AE experienced after vaccine administration, we estimated adjusted IRR using negative binomial regression.

All analyses were performed according to protocol (ATP), in which all preimplementation infants whose parents indicated willingness to receive HRV were compared with all postimplementation infants who received ≥1 dose of HRV. Only for the impact of HRV on hospitalization, we performed an intention to treat (ITT) analysis in which all infants in the preimplementation period were compared with all infants in the postimplementation period irrespective of HRV vaccination status. For tolerability analyses, infants receiving any vaccination of the primary series were compared with infants receiving the primary series and HRV vaccination. This is because our interest is in AEs of the added rotavirus vaccine administration. To guide recommendations of rotavirus vaccination, we also analyzed subgroups of infants with MRCs separately.

Data analysis were performed by using the statistical software of RStudio version 3.6.1. Packages; *survminer*, *survival*, *lme4*, *MASS*, *rstanarm*, *timeseries*.

RESULTS

Between November 2014 and April 2016, a total of 13 hospitals with 15 locations started in the preimplementation period of the RIVAR project and subsequently implemented rotavirus vaccination between May 2016 and November 2017. Throughout the project, a total of 2484 medical risk infants in the preimplementation and 2878 in the postimplementation period met the eligibility criteria (Fig 2). Between November 2014 and April 2016, 631 of these high-risk infants were recruited in the "before" cohort and contributed to 9125 person-months of observation. An additional 851 high-risk infants were enrolled in the "after" cohort, between May 2016 and July 2018, and contributed to 12 302 person-months. Follow-up of the last cohort participant was completed in December 2019.

Among 1482 cohort participants 1302 infants were born premature, 447 were small for GA, and 251 had 1 or more congenital disorders. The median length of postnatal hospital stay was 28 days (interquartile range [IQR], 38 days), and total median number of hospitalization days (including initial admission) during follow-up was 34 (IQR, 44 days).

The characteristics of participants in the before and after cohort were comparable (Table 1). There was a small difference in the participation rate in the NIP (7% less participation in the HRV-vaccinated group) and in completeness of follow-up (number of participants with complete follow-up is 14% lower in HRV-vaccinated group). A total of 719 infants in the after cohort were HRV immunized. Of those, 28.4% was vaccinated during postnatal hospital stay, 5.2% were vaccinated at discharge, and 66.4% were vaccinated postdischarge at the outpatient clinic.

For 599 infants, information on (date of) both first and second dose administration was complete (83.3%). Within the 3-day window, 225 infants received both HRV and NIP vaccines and 61% received them on the same day.

A total of 1223 AGE episodes were identified during follow-up (Table 2). A fecal sample was collected from 564 (46.1%) episodes. Rotavirus was detected in 117 AGE samples (20.7%). Severe (≥11 Vesikari score) rotavirus-positive AGE occurred in 18 infants in the before cohort and 20 infants in the after cohort. Hospitalization due to rotavirus AGE was reported in 2 vs 2 infants.

Coprimary outcome:

TABLE 3 Primary and Secondary Outcomes

Outcome	Estimate	95% CI	VE (95% CI), %
Effectiveness against severe rotavirus AGE ≥14 d after HRV administration[a]	HR 0.70	0.35 to 1.40	30 (−36 to 65)
Impact on rotavirus AGE hospitalization in postimplementation period	RR 0.76	0.10 to 6.37	24 (−537 to 90)
Effectiveness against rotavirus AGE of any severity among HRV-vaccinated infants[b]	IRR 1.02	0.69 to 1.50	−2 (−50 to 31)
Effectiveness against severe rotavirus AGE ≥14 d after full course HRV[a]	HR 0.62	0.31 to 1.21	38 (−21 to 69)
Effectiveness against severe all-cause AGE ≥14 d after HRV administration[a]	HR 0.81	0.55 to 1.19	19 (−19 to 45)
At least one solicited AE after concomitant NIP+HRV vaccination[c]	RR 1.09	1.05 to 1.12	
At least 1 solicited AE after HRV only vaccination[c]	RR 0.91	0.81 to 0.99	
No. solicited AE after NIP+HRV vaccination[c]	IRR 1.08	0.99 to 1.19	

[a] Adjusted for day care attendance and rotavirus epidemic intensity.
[b] Adjusted for day care attendance and parental educational level.
[c] Tolerability outcome, therefore no vaccine effectiveness was calculated.

1. The adjusted HR for severe rotavirus AGE was 0.70 (95% confidence interval [CI]: 0.35 to 1.40) for rotavirus vaccinated versus unvaccinated infants in ATP analysis, resulting in a VE of 30% (95% CI: −36% to 65%, Table 3) after at least 1 dose of HRV. Attending day care and an increase in rotavirus epidemic intensity significantly increased the hazard of severe rotavirus AGE. Characteristics of these severe rotavirus AGE are presented in Supplemental Table 6.
2. The impact of the selective HRV vaccination program defined as the relative reduction in rotavirus-related hospitalization in the postimplementation versus preimplementation period was 24%, RR 0.76 (95% CI: 0.10–6.37).

Effect estimates for all primary and secondary outcomes are presented in Table 3. A complete HRV series was 38% (95% CI: −21% to 69%) effective against severe rotavirus AGE, and VE against rotavirus of any severity was −2% (95% CI: −50% to 31%).

Among 2342 HRV-vaccinated infants, 11 vaccine-related SAE were documented (incidence rate 0.24 per 100 vaccine doses). SAEs included intussusception ($n = 2$), necrotizing enterocolitis ($n = 2$), sepsis, hospitalization ($n = 2$), lactose intolerance, and cardiorespiratory events ($n = 3$). All infants recovered and there were no deaths. Detailed information on the SAEs is provided in Supplemental Table 5. Data on AE for at least 1 vaccine administration were available for 1257 participants. In the 7 days after 3446 vaccine administrations, any AE was reported for 1571 vaccine administrations (45.6%); of these, 150 AE were followed by health care contact (3.4%). Overall, there was a 12% difference in solicited AE occurrence after NIP (44.3%) versus NIP+HRV (56.1%) vaccine administration (Table 4). Overall, AE were reported less frequently after single HRV

TABLE 4 Solicited AE After Receipt of NIP Vaccines, Concomitant NIP + HRV, or HRV Only Vaccination as Part of the Primary Series

Reported AEs	NIP Only Vaccination ($n = 1583$)	Concomitant NIP + HRV Vaccination ($n = 353$)	HRV Only Vaccination ($n = 213$)	*P*
At least 1 solicited AE, *n* (%)	669 (44.3)	198 (56.1)	81 (38.6)	<.00*
Fever	286 (18.1)	74 (21.0)	10 (4.7)	<.00*
Gastrointestinal	92 (5.8)	61 (17.3)	40 (18.8)	<.00*
Mean No. solicited AEs (SD)	1.51 (0.80)	1.58 (0.81)	1.77 (0.95)	<.00[a]*
No. solicited AE, *n* (%)[c]				.09
1	445 (28.1)	116 (32.9)	41 (19.2)	
2	183 (11.6)	56 (15.9)	25 (11.7)	
>2	71 (4.5)	26 (7.4)	15 (7.0)	
Any AE-related health care attendance, *n* (%)	78 (4.9)	19 (5.4)	9 (4.2)	.85[b]
Type of health care, *n* (%)[c]				.15[b]
General practitioner	17 (1.1)	3 (0.8)	4 (1.9)	
Outpatient clinic	4 (0.3)	2 (0.6)	1 (0.5)	
Emergency department	12 (0.8)	—	—	
Hospitalization	45 (2.8)	14 (4.0)	4 (1.9)	

[a] Analysis of variance test.
[b] Fisher exact test.
* Statistical significance ($P < .05$).

administration (38.6%), but gastrointestinal AE were more frequent after single HRV (17.3%) and concomitant NIP+HRV (18.8%) compared with NIP administration (5.8%). The adjusted RR for at least 1 solicited AE in the 7-day postvaccination period was 1.09 (95% CI: 1.05 to 1.12) for concomitant NIP+HRV versus NIP only and 0.91 (95% CI: 0.81 to 0.99) for HRV only vaccination. Analysis of the number of AE per vaccine administration yielded comparable results with an adjusted IRR of 1.08 (95% CI: 0.99 to 1.19) for NIP+HRV versus NIP only (Table 3).

Post hoc and prespecified subgroup analyses are described in the Supplemental Information. For VE against severe all-cause AGE, we found 19% (95% CI: −19% to 45%).

DISCUSSION

In this prospective multicenter study, we evaluated VE and the safety profile of HRV among infants with MRC and prolonged care using the quasi-experimental design of a before-after cohort study. We found VE after at least 1 dose of the HRV to be substantially lower than previously estimated for healthy infants. The point estimate for VE against severe rotavirus AGE was 30% in ATP analysis, with an upper limit of the 95% CI at 65%. We were unable to demonstrate statistical significance for any of the prespecified VE outcomes. Our findings indicate that ∼1 in 200 high-risk infants experienced a vaccine-related SAE after a 2-dose HRV course, but all resolved without long-term sequelae. Administration of HRV with or without concomitant administration of NIP vaccines was generally well tolerated, although risk of AE increased by 8%. Reassuringly, this increased rate of (gastrointestinal) AE did not result in more frequent health care attendance for AE among NIP versus NIP+HRV-vaccinated infants.

The Netherlands currently has no national rotavirus vaccine policy, and uptake in the private market is low.[22,23] Our findings raise the question whether the benefits of rotavirus vaccination outweigh the possible risks of vaccine-related SAE in this particular population, especially in a setting with low rotavirus incidence as currently seen in the Netherlands.[24,25] Alternatively, protecting these infants through herd immunity, resulting from universal vaccination of healthy infants, may result in a more favorable risk/benefit ratio. Indirect protection against rotavirus hospitalizations has been estimated 48% (95% CI: 39% to 55%), which is higher than our estimate of direct protection from vaccination in MRC infants.[26]

This low VE after at least 1 dose of HRV among infants with MRC is unexpected and deserves further discussion. We hypothesize that certain host and pathogen factors could be of influence. For instance, prematurity, lower GA is known to be associated with poorer vaccine responses for some, but not all, vaccines.[27] In a trial, HRV immune responses in premature infants were found to be of protective levels in 85.7% of 147 infants, although this proportion declined with younger GA.[10] Immaturity of the gut and immune system and consequently a poorer rotavirus vaccine response may explain in part the lower VE in our study (with generally lower GA). In addition, the gut microbiome is a known factor of influence on HRV immune response. Some microbiota species are associated with lower rotavirus vaccine immunoglobulin A responses,[28] and their presence in premature infants is different from in healthy term infants, depending on gestational maturity.[29] However, we also found low VE in term infants with congenital pathology, suggesting that other mechanisms are involved as well. It is important to mention that based on the eligibility criteria, participants in our cohort represent a particularly vulnerable group of infants with prolonged care (between 6 and 14 weeks of age). For example, the average length of postnatal hospital stay was 28 days and 28% of infants were still hospitalized when HRV vaccinated. In addition, we could confirm receipt of the second HRV dose in 83.3% of infants, and protection is known to be lower after 1 dose of HRV (range 60%–92%).[30,31] However, our VE estimate for a complete two-dose course was not substantially higher (38%). Despite extensive instructions, maladministration of the second dose, given by parents themselves, cannot be completely ruled out. Alternatively, altered genotype diversity may have influenced our results; protection is primarily against the outer membrane proteins, defining the antigenetically distinct rotavirus G- and P-genotypes.[32] Although HRV elicits both homotypic and heterotypic immunity against antigenetically distinct rotavirus G- and P-genotypes, strain-specific VE has been estimated at 94%, 87%, and 71% for homotypic, fully, and partially heterotypic rotavirus genotypes, respectively.[33] During our study period (2015–2019), partially heterotypic (G3P8, G4P8, and G9P8) strains were dominant. The homotypic G1P8 did not exceed 14% in any of the study years,[34] as has been noticed in other high-income countries.[35,36] VE in our study may have been somewhat influenced by this genotype distribution.

Some limitations need to be addressed. First, fewer than

expected rotavirus-positive AGE episodes ($n = 117$) were detected, reducing the anticipated statistical power of the study. The expected cumulative severe rotavirus incidence for this population was 4% during 18 months of follow-up. We found only 2.7%. This may be explained by incomplete pathogen ascertainment due to lack of fecal sampling during AGE episodes and the local change in rotavirus epidemiology. A shift toward a biennial pattern resulted in a national trend toward lower rotavirus cases in infants between 2014 and 2019.[12,22,25] In post hoc analysis, we therefore analyzed all-cause AGE as outcome, which is a nonspecific but more sensitive measure of effect. VE against all-cause AGE was 19%, in line with our analysis of rotavirus specific VE. Furthermore, a post hoc power calculation confirmed that the probability that our study had incorrectly estimated low VE, when true VE would be >60% (the estimate used in the sample size calculation) was small (<.05).

Second, we encountered lower than expected inclusion rates, for which we expanded the number of sites (13 instead of 8 hospitals), and had a higher than the anticipated loss to follow-up (30%), despite substantial efforts to keep parents of participants engaged in completing questionnaires and reporting AGE. The multiple and complex health issues that many parents of a child with MRC encounter during infancy may be barriers to full engagement in an observational study like ours. Mean follow-up, however, was at least 1 year after vaccination (14.5 months) and our adjusted Cox model takes observation time into account, thereby minimizing risk of bias resulting from differential loss to follow-up. Furthermore, for the observed vaccine-related SAE, we cannot confirm or exclude causality between the event and administration of HRV. In our evaluation, we relied on clinical judgement by the treating physician, considering timing of the event in relation to vaccine administration and/or type of SAE and patient comorbidities. At most, we can therefore conclude that a causal link is plausible. For some vaccine-related SAE, other vaccines coadministered with HRV may also have triggered the event. Finally, the AE assessment was based on parent reporting, which may be subject to variability in perception. Although fever, vomiting, and loose stools can be assessed objectively, we cannot rule out that reporting may have been influenced by whether infants received the newly introduced HRV, which could increase parent's attentiveness to AE. This effect is likely small because percentages of parent reported AE between the 2 groups were similar. Differences were only observed for gastrointestinal AEs, which is in line with previous results on tolerability of HRV.

CONCLUSIONS

In this population of infants with MRC and prolonged care, at least 1 dose of HRV offered limited protection against severe rotavirus AGE. We observed a higher incidence of vaccine-related SAE in this population than previously reported for healthy infants. HRV administration is generally well tolerated but is associated with ~10% higher risk of gastrointestinal AEs when coadministered with NIP vaccines. Clinicians must outweigh the risks and benefits of HRV for this particular patient group. The findings are in contrast with those for HRV in healthy infants and underline the importance of conducting separate studies on vaccine performance in specific vulnerable populations.

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ABBREVIATIONS

AE: adverse event
AGE: acute gastroenteritis
ATP: according to protocol
CI: confidence interval
GA: gestational age
HR: hazard rate
HRV: human rotavirus vaccination
IQR: interquartile range
IRR: incidence rate ratio
ITT: intention to treat
MRC: medical risk condition
NIP: national immunization program
PCR: polymerase chain reaction
RIVAR: Risk group Infant Vaccination Against Rotavirus
RR: risk ratio
SAE: serious adverse event
VE: vaccine effectiveness

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