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Efficacy of the pentavalent rotavirus vaccine, RotaTeq® (RV5), between doses of a 3-dose series and with less than 3 doses (incomplete regimen)

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Abbreviations: ACIP, advisory committee on immunization practices; CI, confidence interval; ED, emergency department; GEE, generalized estimating equations; PD, post-dose; REST, rotavirus efficacy and safety trial; RV5, rotavirus vaccine; RVGE, rotavirus gastroenteritis

Post-hoc analyses of the Rotavirus Efficacy and Safety Trial (REST) were conducted to determine whether the pentavalent rotavirus vaccine (RV5) confers early protection against rotavirus gastroenteritis (RVGE) before completion of the 3-dose regimen. To evaluate the efficacy of RV5 between doses in reducing the rates of RVGE-related hospitalizations and emergency department (ED) visits in infants who ultimately received all 3 doses of RV5/placebo, events occurring from two weeks after the first and second doses to receipt of the subsequent dose (Analysis A) and events occurring from two weeks after the first and second doses to two weeks after the subsequent dose (Analysis B) were analyzed. In Analysis A, RV5 reduced the rates of combined hospitalizations and ED visits for G1–G4 RVGE or RVGE regardless of serotype between doses 1 and 2 by 100% [95% confidence interval (CI): 72–100%] or 82% (95% CI: 39–97%), respectively, and between doses 2 and 3, RV5 reduced the rates of combined hospitalizations and ED visits for G1–G4 RVGE or RVGE regardless of serotype by 91% (95% CI: 63–99%) or 84% (95% CI: 54–96%), respectively. Similar rate reductions were observed in Analysis B. These data suggest that RV5 provides a high level of protection between doses against hospitalizations and ED visits for RVGE starting as early as 14 days after the first dose.

Introduction

Over the years, several vaccines have been developed to protect children from rotaviruses, the leading cause of severe diarrhea in children less than 5 years of age. Two rotavirus vaccines have now been licensed in many parts of the world: a pentavalent live human-bovine reassortant vaccine (RotaTeq, rotavirus vaccine, live, oral, pentavalent; Merck, Whitehouse Station, New Jersey, US; designated RV5 by the Advisory Committee on Immunization Practices [ACIP][1]) and a live, attenuated G1P1A[8] human rotavirus vaccine (Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium; designated RV1 by the ACIP[1]).

The efficacy of RV5 following receipt of the recommended 3-dose series was evaluated in the Rotavirus Efficacy and Safety Trial (REST) in 2 ways: (1) reduction in the rates of rotavirus gastroenteritis (RVGE) hospitalizations and emergency department (ED) visits; and (2) prevention of RVGE cases.[2,3] In REST, the rate of RVGE hospitalizations and ED visits caused by G1–G4 rotaviruses was reduced by 95% (95% confidence interval [CI]: 91–97%) by RV5 through up to 2 years after completion of the vaccination schedule. The rate of RVGE hospitalizations and ED visits caused by rotaviruses of any serotype was also reduced by 95% (95% CI: 92–97%) by RV5. In REST, enrollment occurred year round and the per-protocol analyses were based on follow-up beginning 14 days after the third dose. In this paper, post-hoc analyses of REST were conducted to determine whether RV5 confers protection to infants before completion of the 3-dose regimen. These analyses may be of particular interest to health care professionals immunizing infants during, or just prior to, the rotavirus season.

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Table 1. Rate reduction in RVGE-related health care encounters (hospitalizations and ED visits) between vaccine doses[a] attributable to G1–G4 rotavirus

G1–G4 RVGE[b]	Interval (N)	Health care encounter	Vaccine	Placebo	Efficacy (%)	95% CI (%)
			Counts (n)/evaluable (n)			
Analysis A[c]	Doses 1 to 2 (58,851)	Hospitalizations	0/29,417	6/29,434	100	15–100
		ED visits	0/29,417	9/29,434	100	49–100
		Combined hospital and ED visits	0/29,417	15/29,434	100	72–100
	Doses 2 to 3 (59,061)	Hospitalizations	0/29,496	10/29,565	100	55–100
		ED visits	2/29,496	12/29,565	83	25–98
		Combined hospital and ED visits	2/29,496	22/29,565	91	63–99
Analysis B[d]	Doses 1 to 2 (58,851)	Hospitalizations	0/29,413	12/29,438	100	64–100
		ED visits	0/29,413	17/29,438	100	76–100
		Combined hospital and ED visits	0/29,413	29/29,438	100	87–100
	Doses 2 to 3 (59,019)	Hospitalizations	0/29,473	18/29,546	100	77–100
		ED visits	3/29,473	16/29,546	81	34–97
		Combined hospital and ED visits	3/29,473	34/29,546	91	72–98

N, number of evaluable infants who received 3 doses of vaccine or placebo; RVGE, rotavirus gastroenteritis; CI, confidence interval; ED, emergency department. [a]Given that the interval between doses was to be 4–10 weeks, the range of follow up was 14–56 days per infant in Analysis A and 14–69 days per infant in Analysis B. [b]The most common rotavirus serotype identified was G1, followed by a few samples that contained G2, G4, and G3 rotavirus strains. Between doses 1 and 2 among placebo recipients, the distribution of the rotavirus serotypes in the total number (n = 29) of RVGE-related health care encounters in Analysis B, which also includes the 15 health care encounters in Analysis A, was G1 (n = 22), G2 (n = 4), G3 (n = 1), and G4 (n = 2). Between doses 2 and 3, the distribution of the rotavirus serotypes in the total number (n = 34) of RVGE-related health care encounters in Analysis B, which also includes the 22 health care encounters in Analysis A, among vaccine recipients was G1 (n = 3) and among placebo recipients was G1 (n = 31) and G3 (n = 3). [c]Analysis A: ≥14 days post dose 1 (PD1) up to dose 2 and ≥14 days PD2 up to dose 3. [d]Analysis B: ≥14 days PD1 through 13 days PD2 and from ≥14 days PD2 through 13 days PD3.

Results

Efficacy between doses against health care encounters attributable to G1–G4 RVGE in infants who received all 3 doses. In Analysis A, the reduction in the rate of combined hospitalizations and ED visits for G1–G4 RVGE between doses 1 and 2 was 100% (95% CI: 72–100%) and between doses 2 and 3 was 91% (95% CI: 63–99%) (**Table 1**). There were only 2 RVGE-associated health care encounters among vaccine recipients, and both encounters were ED visits that occurred between doses 2 and 3. In contrast, there were 37 RVGE-associated health care encounters among placebo recipients: 15 between doses 1 and 2 and 22 between doses 2 and 3. Sixteen of the 37 health care encounters were hospitalizations. Although Analysis B extended the follow-up interval, the reduction in the rate of combined hospitalizations and ED visits for G1–G4 RVGE was identical to that of Analysis A [100% between doses 1 and 2 and 91% between doses 2 and 3, with small changes to the CIs (**Table 1**)]. Only 1 additional RVGE-associated health care encounter, an ED visit between doses 2 and 3, was observed in the vaccine group, whereas 26 additional encounters were observed in the placebo group, 14 between doses 1 and 2 and 12 between doses 2 and 3. Under both analysis strategies, vaccine efficacy against G1–G4 RVGE hospitalizations was 100% between doses. Overall, G1 was the most common serotype identified (detailed breakdown provided in footnote, **Table 1**).

Efficacy between doses against health care encounters attributable to RVGE regardless of serotype in infants who received all 3 doses. In Analysis A, the reduction in the rate of combined hospitalizations and ED visits due to RVGE regardless of serotype was 82% (95% CI: 39–97%) between doses 1 and 2 and 84% (95% CI: 54–96%) between doses 2 and 3 (**Table 2**). Among vaccine recipients, there were 7 health care encounters, 3 between doses 1 and 2 and 4 between doses 2 and 3; 1 of the health care encounters was a hospitalization. Among placebo recipients, there were 42 health care encounters, 17 between doses 1 and 2 and 25 between doses 2 and 3; 18 of the 42 health care encounters were hospitalizations. The reduction in the rate of combined hospitalizations and ED visits was slightly greater in Analysis B (**Table 2**). Two additional RVGE-related health care encounters among the vaccine recipients (1 between doses 1 and 2 and 1 between doses 2 and 3) and 31 among the placebo recipients (15 between doses 1 and 2 and 16 between doses 2 and 3) were captured in Analysis B. Among the vaccine recipients, none of the additional health care encounters were hospitalizations. Among placebo recipients, 16 of the 31 additional health care encounters were hospitalizations. Overall, vaccine efficacy against RVGE hospitalizations between doses ranged from 90% to 100%. G1 was the most common serotype identified (detailed breakdown provided in footnote, **Table 2**).

Efficacy of RV5 against RVGE-related health care encounters among the subset of infants who received less than 3 doses (incomplete regimen). Subject compliance in REST was high, with 59,210 infants (86%) having received 3 doses of RV5 or placebo.[2] In REST, among infants who received only 1 dose or only 2 doses, the number of health care encounters was small, and the rate reductions in RVGE-associated combined hospitalizations and ED visits were not statistically significant.

Table 2. Rate reduction in RVGE-related health care encounters (hospitalizations and ED visits) between vaccine doses[a] attributable to rotavirus of any serotype

RVGE of any serotype[b]	Interval (N)	Health care encounter	Vaccine	Placebo	Efficacy (%)	95% CI (%)
			Counts (n)/evaluable (n)			
Analysis A[c]	Doses 1 to 2 (58,856)	Hospitalizations	0/29,422	8/29,434	100	42–100
		ED visits	3/29,422	9/29,434	67	<0–94*
		Combined hospital and ED visits	3/29,422	17/29,434	82	39–97
	Doses 2 to 3 (59,064)	Hospitalizations	1/29,497	10/29,567	90	30–100
		ED visits	3/29,497	15/29,567	80	29–96
		Combined hospital and ED visits	4/29,497	25/29,567	84	54–96
Analysis B[d]	Doses 1 to 2 (58,858)	Hospitalizations	0/29,420	15/29,438	100	72–100
		ED visits	4/29,420	17/29,438	76	28–94
		Combined hospital and ED visits	4/29,420	32/29,438	88	65–97
	Doses 2 to 3 (59,033)	Hospitalizations	1/29,484	19/29,549	95	67–100
		ED visits	4/29,484	22/29,549	82	46–95
		Combined hospital and ED visits	5/29,484	41/29,549	88	69–96

N, number of evaluable infants who received 3 doses of vaccine or placebo; RVGE, rotavirus gastroenteritis; CI, confidence interval; ED, emergency department. *Not statistically significant. [a]Given that the interval between doses was to be 4–10 weeks, the range of follow up was 14–56 days per infant in Analysis A and 14–69 days per infant in Analysis B. [b]In addition to rotavirus serotypes G1 to G4, between doses 1 and 2, 4 nontypeable and 3 G9 RVGE-related health care encounters were detected among vaccine and placebo recipients, respectively. Between doses 2 and 3, G9 ($n = 3$), G8 (n = 1), G10 (n = 1), and nontypeable (n = 2) RVGE-related health care encounters were also detected among placebo recipients, whereas 2 additional nontypeable RVGE-related health care encounters were detected among vaccine recipients. [c]Analysis A: ≥14 days post dose 1 (PD1) up to dose 2 and ≥14 days PD2 up to dose 3. [d]Analysis B: ≥14 days PD1 through 13 days PD2 and from ≥14 days PD2 through 13 days PD3.

Among infants who received only 1 dose of RV5/placebo, the number of health care encounters was small for the G1–G4 RVGE analysis (RV5, 3 G1-related events; placebo, 6 G1-related events) and the RVGE of any serotype analysis [RV5, 6 events (3 G1-related, 1 G9-related and 2 nontypeable); placebo, 7 events (6 G1-related and 1 nontypeable)]. Among the 5,408 evaluable infants who received only 1 dose (2,738 in the RV5 group and 2,670 in the placebo group), the rate reduction in combined hospitalizations and ED visits for G1–G4 RVGE was 52% (95% CI: <0–92%). The rate reduction in combined hospitalizations and ED visits for RVGE of any serotype among the 5,409 evaluable infants who received only 1 dose (2,738 in the RV5 group and 2,671 in the placebo group) was 18% (95% CI: <0–75%).

Similarly, among infants who received only 2 doses of RV5/placebo, the number of health care encounters was also small for the G1–G4 RVGE analysis (RV5, 1 G3-related event; placebo, 3 G1-related events) and the RVGE of any serotype analysis [RV5, 1 G3-related event; placebo, 4 events (3 G1-related and 1 G9-related)]. Among the 2,457 evaluable infants who received only 2 doses (1,202 in the RV5 group and 1,255 in the placebo group), the rate reduction in combined hospitalizations and ED visits for G1–G4 RVGE was 64% (95% CI: <0–99%), whereas the rate reduction in combined hospitalizations and ED visits for RVGE of any serotype among the 2,456 evaluable infants who received only 2 doses (1,202 in the RV5 group and 1,254 in the placebo group) was 73% (95% CI: <0–100%).

Discussion

In REST, both the safety and efficacy of the complete regimen of RV5 were demonstrated in nearly 70,000 infants.[2] The prespecified time frame to measure the efficacy of RV5 in reducing the rate of RVGE-associated health care encounters (i.e., hospitalizations and ED visits) in REST started 14 days after completion of the 3-dose regimen. Given that many infants are routinely vaccinated during the season when rotavirus is circulating and risk of illness is greatest, post-hoc analyses were conducted to evaluate the efficacy of RV5 before completion of the 3-dose regimen. Although REST was not designed or powered to examine the efficacy between doses, vaccine efficacy between doses among infants who ultimately completed the 3-dose vaccination schedule was retrospectively examined. A separate analysis among the small number of infants who received only 1 dose or only 2 doses of vaccine in REST also was conducted.

In the post-hoc analyses of infants who completed the 3-dose regimen, a high level of protection against RVGE-related hospitalizations and ED visits combined caused by serotypes G1–G4 and rotavirus of any serotype between doses was demonstrated by RV5. Vaccine efficacy against G1–G4 RVGE-related hospitalizations and ED visits was 100% between doses 1 and 2 and 91% between doses 2 and 3 regardless of whether the analysis time frame ended at the subsequent dose or 13 days after the subsequent dose. Similarly, vaccine efficacy against hospitalizations

and ED visits for RVGE of any serotype was 82% to 88% between doses 1 and 2 and 84% to 88% between doses 2 and 3. Based on the vaccine schedule, these data suggest the potential for RV5 to provide high efficacy and rapid protection in young infants during the immunization schedule. Between doses, vaccine efficacy against hospitalizations alone was 100% for G1–G4 RVGE and 90% to 100% for RVGE caused by any serotype. These results may be of interest because rotavirus-related health care encounters can occur in young infants. In the era before universal vacccination in the US, 17% of rotavirus hospitalizations occurred in infants less than 6 months of age.[4] Circumstances in Europe may be similar to those in the US,[5] although variation among European countries exists.[6,7]

The efficacy between doses of RV1, whose complete vaccine regimen consists of 2 doses, against RVGE was evaluated in a European Phase III study that enrolled over 4,000 infants. From the day of dose 1 up until dose 2, vaccine efficacy was 100% (95% CI: <0–100%) against severe RVGE and 90% (95% CI: 9–100%) against RVGE of any severity.[8,9] In a larger Phase III study that enrolled infants from Latin America and Finland, the efficacy of RV1 against severe RVGE in the Latin American cohort was 51% between doses 1 and 2 and 61% from dose 1 until 14 days after dose 2, with wide CIs given the small number of cases.[9] Because the trials for the two vaccines were conducted differently, the results between the trials can not be directly compared.

With respect to infants who received only 1 dose or only 2 doses of RV5 or placebo, the number of RVGE-related health care encounters observed was small. Although the estimates were positive, the efficacy was not statistically significant in either evaluation. However, higher protection against RVGE-attributable health care encounters was generally provided by 2 doses than by only 1 dose.

The efficacy against RVGE cases of any severity, which was measured in the clinical efficacy substudy of REST, was analyzed in a similar manner as the efficacy between doses and after only 1 dose or only 2 doses against RVGE-related health care encounters. The cohort in the clinical efficacy substudy was less than one-tenth the entire size of REST and the efficacy outcomes in these evaluations were generally not statistically significant (data not shown).

Although some protection is likely conferred with less than 3 doses of RV5, only the complete 3-dose vaccine series was prospectively studied in Phase III trials and may provide more durable and optimal protection. Because REST was not designed to evaluate the efficacy of RV5 with less than 3 doses, conclusions drawn from these analyses should be interpreted cautiously.

However, the effectiveness of partial vaccination with RV5 has been evaluated since licensure in routine clinical use in the US.[10] Fecal specimens from children with acute gastroenteritis 15 days to 23 months of age were collected over a 5-month period. One, 2 and 3 doses of RV5, respectively, were 69% (95% CI: 13–89%), 81% (95% CI: 13–96%) and 88% (95% CI: 68–96%) effective at preventing ED visits or hospitalizations from rotavirus disease when children with acute respiratory infection and rotavirus negative gastroenteritis were used as the combined control group.[10] Similar findings were observed by the New Vaccine Surveillance Network, a program coordinated by the US Centers for Disease Control and Prevention designed to evaluate the impact of new vaccines at several sites in the US.[11] Based upon data from the 2007 and 2008 rotavirus seasons, their results showed that 1, 2 and 3 doses of RV5 were 71% (95% CI: 17–90%), 72% (95% CI: 1–92%) and 88% (95% CI: 47–97%), respectively, effective at preventing RVGE-related ED visits and hospitalizations. A consistent pattern of reduction of all-cause and rotavirus-related gastroenteritis has been repeatedly observed after introduction of RV5. These significant reductions have been observed in other postlicensure disease surveillance and effectiveness studies in the US[12-14] and other countries that have introduced RV5 into their childhood immunization schedules.[14-19]

Conclusions. RV5 is a 3-dose vaccine that protects infants against RVGE. RV5 provided a high level of protection between doses against hospitalizations and ED visits for RVGE starting as early as 14 days after the first dose. This may be particularly beneficial to infants being immunized during, or just prior to, the rotavirus season.

Patients and Methods

Study design. REST was a large-scale, placebo-controlled, multicenter, randomized clinical trial that enrolled nearly 70,000 infants year round.[2,3,20] Healthy infants between 6 and 12 weeks of age at dose 1 were randomized 1:1 to receive 3 oral doses of RV5 or placebo as outlined in **Figure 1A**.

Post-hoc analyses. Efficacy between doses of RV5, as measured by a reduction in the rate of RVGE-related health care encounters, including hospitalizations and ED visits, among infants who received all 3 doses of RV5 or placebo was evaluated to examine whether the vaccine confers early protection before completion of the 3-dose regimen (**Fig. 1B**). The efficacy of RV5 for infants who received only 1 dose or only 2 doses of vaccine or placebo was also evaluated (**Fig. 1B**). RVGE was defined exactly as it was in REST.[2] Reverse transcription polymerase chain reaction and sequencing was used to genotype all rotavirus-positive stool samples.[2] In REST, the per-protocol measures of efficacy were assessed beginning 14 days post-dose (PD) 3 to allow time for an immune response to the last dose to develop (**Fig. 1A**) and a consistent approach was used for the between-dose and less-than-3-dose analyses.

Among infants who completed the 3-dose vaccination series and were not protocol violators (i.e., per-protocol population), vaccine efficacy between doses was measured using 2 analyses that differed with regard to the time interval used: (1) Analysis A, defined as ≥14 days PD1 up to dose 2 and ≥14 days PD2 up to dose 3; and (2) Analysis B, defined as ≥14 days PD1 through 13 days PD2 and from ≥14 days PD2 through 13 days PD3 (**Fig. 1B**). In both analyses, 14 days PD1 or PD2 was used as the starting point to allow time for an immune response to develop, consistent with the time frame used to evaluate the per-protocol efficacy of the vaccine.[2] However, in Analysis B, the analysis interval extended 13 days beyond the next dose to capture any RVGE-related events occurring before the effect of an immune response to the subsequent dose might be expected. The interval between doses was to be 4 to 10 weeks, and the follow-up times for the analyses of efficacy started and ended at the indicated time intervals (**Fig. 1B**). In addition, vaccine efficacy

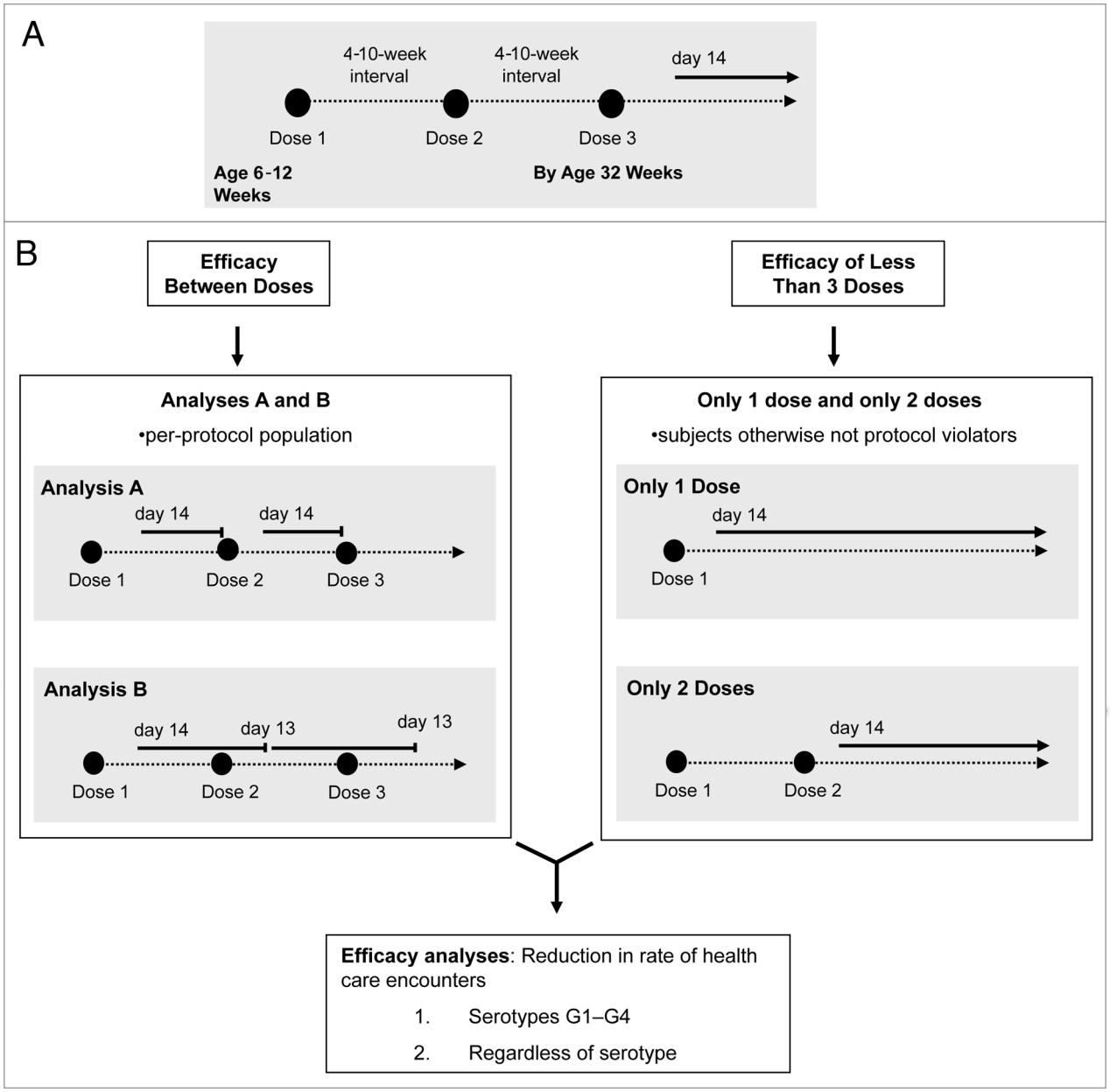

Figure 1. Overview of REST and the post-hoc analyses performed. (A) In REST, the first dose was given at 6 to 12 weeks of age, the last dose was given no later than 32 weeks of age, and the interval between doses was 4 to 10 weeks. The main measures of efficacy were assessed beginning 14 days PD3. (B) Post-hoc analyses of RV5 efficacy between doses and with less than 3 doses. All analyses of efficacy began 14 days after the receipt of a dose (indicated by the dark circles). REST, Rotavirus Efficacy and Safety Trial.

of only 1 dose or only 2 doses of RV5 was measured beginning 14 days after the receipt of the last dose among infants who did not complete the 3-dose regimen, but who were not otherwise protocol violators (**Fig. 1B**). For all analyses, infants were followed for 2 years after vaccination and efficacy against G1–G4 (i.e., human G serotypes contained in the vaccine) RVGE and RVGE of any serotype were determined.

Statistical analysis. The exact binomial method for ratios of Poisson counts was used to evaluate the rate reduction for rotavirus-related hospitalizations and ED visits in the vaccine group compared with the placebo group.[21] This approach was the same as the analysis technique used in REST,[2] with the exception that exact methodology was used rather than the generalized estimating equations (GEE), because GEE is not optimal in small samples.

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Author's Contributions

All of the authors made contributions to the conception and design of the post-hoc analyses, acquisition of data or analysis and interpretation of data. They actively participated in drafting the article or revised it for important intellectual content. The report was critically reviewed and subsequently approved by each co-author. All the academic authors have served as investigators for Merck.

Conflict of Interest

P.H.D. has no other conflict of interest. Compensation received from Merck & Co., Inc., was directly related to the reasonable costs of conducting the research as specified in the research agreement. T.V. has been a consultant and speaker for Merck & Co., Inc., Sanofi Pasteur-Merck Sharp & Dohme (SPMSD), MedImmune, Novartis and GlaxoSmithKline Biologicals (GSK); any compensation received from Merck & Co., Inc., was directly related to the reasonable costs of conducting the research as specified in the research agreement from Merck & Co., Inc., DOM received no compensation from Merck & Co., Inc., for conduct of the research described in this report; he has been a consultant to Merck & Co., Inc., GSK, PATH, NIAID; a speaker for Merck & Co., Inc., and GSK; and a grant recipient from Merck & Co., Inc., R.F.I., M.J.D., M.G.G. and M.J.D. are employees of Merck & Co., Inc., and may own stock or stock options in the company. P.M.H. and M.C. were employed by Merck, at the time the primary study was conducted and may own stock or stock options in the company.

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