Author's response to reviews

Title: Robustness of the healthcare utilization results from the Rotavirus Efficacy and Safety Trial (REST) evaluating the human-bovine (WC3) reassortant pentavalent rotavirus vaccine (RV5)

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Author's response to reviews: see over
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Re: Robustness of the REST Health Care Utilization Data

Dear Colleagues:

We sincerely appreciate the generally favorable review of our work with the detailed critiques from both expert consultants. Our responses to the reviewers’ many helpful suggestions are enumerated below and identified in a marked copy of the revised paper. A clean version of the manuscript is also provided.

Reviewer #1

Major compulsory revisions

1. The main point of the paper is to compare vaccine-related rate reductions in health care encounters between the original, less externally valid figures reported in the NEJM paper (PP, G1-G4 serotypes only) and those in this re-analysis (MITT, all serotypes). However, the paper as it is written does not make it very easy to do a direct comparison. It would be helpful to readers to provide the original figures for comparison when the new ones are reported. For example, on page 11 to provide the rate reduction against G1-G4, on page 12 to provide the PP rate reduction and so forth. Some (though not all) of this information can be obtained from the tables, but it would be helpful if direct comparisons were made in the text.

We have included the reduction in the rate of hospitalizations and ED visits due to RV5 for the G1-G4 serotypes based on the PP analysis in the Results section under the subheading Comparison of the results based on the PP analysis regardless of serotype for the overall study population. The rate reductions based on the PP and MITT analyses for serotypes G1-G4 and the PP analysis regardless of serotype for the overall study population. The rate reductions based on the PP and MITT analyses for the G1, G3, G4, and G9 serotypes were included in the Results section under the subheading Comparison of the PP and MITT analyses stratified by serotype. The rate reduction for G1-G4 RVGE based on the PP analysis was included in the Results section under the subheading Comparison of results for RVGE and AGE healthcare encounters by intensity of surveillance for the PP analysis.

2. I don’t think the authors can claim that “the estimates of rate reductions in health care utilization were consistent regardless of differences in study population, timing of healthcare encounters, intensity of surveillance,
serotypes and geographical region”. What the paper shows is that there is (as expected) a small but not negligible reduction in the protective effect of vaccination when moving from a PP to MITT population, or from G1-G4 serotypes to all serotypes. I think a milder claim e.g. “the estimates of rate reduction in healthcare utilization remained very high” is more justifiable.

We have revised the wording of the first paragraph of the Discussion.

3. The differences between the PP rate reduction in the NEJM paper and the MITT rate reduction in this paper could be due to a number of reasons, the most obvious being: (i) inclusion of more of the vaccinated infants excluded from the PP analysis who are less likely to benefit from vaccination and (ii) inclusion of the time period during which infants only received one or two doses of vaccine, as well as the time period immediately following vaccination when vaccine-induced antibody titres have not reached protective levels. It would be useful if there could be some attempt to separate out the two effects as far as possible. For example, the authors could conduct a separate MITT including as many participants as possible but only counting events occurring two weeks after the final vaccine dose. (There would obviously be some differences between the included cohort in MITT and the new MITT2, but at least there would be some basis for comparison which is better than guessing.)

The reduction in the rate of hospitalizations and ED visits due to RV5 from 14 days after dose 1 until 14 days after dose 3 for subjects completing the three dose regimen was summarized in a review article for RotaTeq in Vaccine in December 2009. A more in depth article on this subject has also been submitted to Vaccine. The results demonstrated that high protective efficacy was achieved for hospitalizations and ED visits during this period. The reduction in the rate of hospitalizations and ED visits for all serotypes was a little lower than the analyses limited to the G1-G4 serotypes but the protective efficacy remained high. We referenced the published article in the first paragraph of the Discussion.

In addition, we included two additional analyses for hospitalizations and ED visits based on rotavirus gastroenteritis regardless of serotype. One excluded protocol violators. The other excluded protocol violators and health care contacts in the first 14 days after receiving dose 1. These analyses should separate #2 above (inclusion of the time period during which infants only received one or two doses of vaccine, as well as the time period immediately following vaccination when vaccine-induced antibody titres have not reached protective levels) from #1 (inclusion of more of the vaccinated infants excluded from the PP analysis who are less likely to benefit from vaccination). These additional analyses were included in the Results section under Comparison of the results based on the PP analysis regardless of serotype and the MITT analysis regardless of serotype for the overall study population.
4. Also, the authors describe well the participants excluded from the MITT analysis. However, they do not describe the participants included in the MITT analysis but excluded from the PP – presumably some of these exclusions contribute to the higher PP rate reduction.

Actually, this information is included in the Results section. Under the subheading Comparison of the results based on the PP analysis for serotypes G1-G4 and the PP analysis regardless of serotype, we show that there were 40 additional hospitalizations and ED visits attributable to RVGE when the case definition is expanded to include all serotypes. Under the subheading Comparison of the results based on the PP analysis for serotypes G1-G4 and the PP analysis regardless of serotype, we included the following sentences: There were 151 additional hospitalizations and ED visits in the MITT analysis compared with the PP analysis regardless of serotype. Of this total, 43 hospitalizations and ED visits (14 RV5, 29P) occurred among protocol violators and 107 hospitalizations and ED visits (21 RV5, 86P) occurred prior to 14 days after dose 3. There was also one additional ED visit occurring more than 14 days after dose 3 in an RV5 recipient classified as not evaluable in the PP analysis.

Discretionary revisions

1. The original NEJM paper also provided the PP clinical efficacy of the vaccine against rotavirus gastroenteritis of any severity. Would it be possible to now provide MITT figures for the same endpoint?

The NEJM provided the clinical efficacy of the vaccine against rotavirus gastroenteritis of any severity for the G1-G4 serotypes among infants beginning immediately after dose 1. It was 60% (95% CI: 51.5, 67.1) for the first season. We referenced this result in the Discussion as well as the clinical efficacy of the vaccine based on the PP and MITT analysis regardless of serotype for the first season which was 71.8% (95% CI: 64.5, 77.8) and 50.9% (95% CI: 41.6, 58.9) respectively.

Reviewer #2

Minor Essential Revisions:

1. Baseline characteristics of the included subjects must be given.

We have included a table with the age, race, and sex of evaluable subjects for
the G1-G4 PP analysis and the MITT analysis regardless of serotype. This table is referenced in the Results section under the subheading Infants included in the PP and MITT analyses.

2. Analysis of efficacy by gestational age and birth weight

Clinical efficacy and HCU efficacy analyses for premature infants based on the REST trial have already been published in the Pediatric Infectious Disease Journal: Safety and Efficacy of the Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine in Healthy Premature Infants; Volume 26:12; 2007; 1099 – 1104. Briefly, there were 2070 infants between 25 and 36 gestational weeks who received at least one dose of vaccine or placebo. Among the infants who completed the vaccination regimen, RV5 was associated with a 100% reduction in the rate of hospitalizations and ED visits due to G1-G4 rotavirus gastroenteritis. The rate reduction was also 100% for the PP analysis regardless of serotype and 95.5% for MITT analysis regardless of serotype. We have added the reference to the Discussion in the second paragraph.

Information on birth weight was not collected in REST.

Discretionary Revisions:

1. What is the advantage over exclusive breastfeeding of the rota virus vaccine?

A comparison of infants never breastfed, sometimes breastfed, and exclusively breastfed for clinical efficacy regardless of severity based on the REST trial has already been published in the Pediatric Infectious Disease Journal: Efficacy of Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine Based on Breastfeeding Frequency; Volume 27: 7; 2008; 656 – 8. Briefly, the results showed that the efficacy against rotavirus gastroenteritis of any severity for infants never breastfed, sometimes breastfed, or exclusively breastfed was 68.3%, 82.2%, and 68.0% respectively. The efficacy against severe RVGE was 100%, 95.4%, and 100% respectively.