Author's response to reviews

Title: Cost-effectiveness of Rotavirus Vaccination in Vietnam

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Dear Editor:

Thank you for this opportunity to submit our revised manuscript, “Cost-effectiveness Analyses of Rotavirus Vaccination in Vietnam.”

We have addressed the concern from the first reviewer and incorporated the suggested change into the manuscript (highlighted in bold and underlined). We have included a detailed point-by-point response to the comment in this letter. Please note that we have added a reference while addressing the reviewer comment and have made some minor editorial revisions throughout the manuscript. We appreciate Reviewer 2’s overall positive comments.

Thank you very much for your consideration of our revised manuscript. We look forward to hearing from you.

Sincerely,

Sun-Young Kim, PhD
**RESPONSE TO COMMENTS FROM REVIEWER 1:**

Kim and co-workers have revised their manuscript based on comments from two reviewers. The new manuscript is substantially improved, and I look forward to seeing it published. In particular, their explanation of the way key parameters in the model were estimated is much more transparent. I only have one follow-on comment.

We thank the reviewer for the positive comments.

**Major compulsory revisions**

I agree with the authors that the rate of waning of vaccine protection in Vietnam is uncertain and difficult to impute from clinical trials conducted in other countries. However, I disagree that the solution is to assume that there is no vaccine waning. When a parameter in a decision model is unknown but unlikely to be zero, the solution is to vary it within a plausible range rather than removing it from the model entirely (which would have the effect of assuming it takes a particular value, i.e. zero). If this is not possible, then I think it is important to discuss the implications in the text, particularly given that the incremental cost-effectiveness ratio of vaccination found in the study is very close to the cost-effectiveness threshold. That is, there should be a mention that the assumption of no waning in the first 5 years of age is unlikely to be realistic, and hence the model may slightly overestimate the effect of vaccination.

We recognize the importance of the points made by the reviewer, while in the base case we assume no waning of vaccine-induced immunity, in part due to the lack of empiric data, but also to facilitate comparison with previous published studies. In response to the reviewer’s point, we conducted a sensitivity analysis to assess the potential impact of vaccine immunity waning, and have incorporated the results into the manuscript.

To accomplish this analysis, we adjusted vaccine efficacy downward as a proxy for declining or waning immunity. We assumed that vaccine efficacy against severe cases would decline during each of the first 5 years of life, to model the waning vaccine-induced immunity. Since there are no 5-year efficacy data available for the vaccine, we elected to conservatively calculate a lower limit of vaccine efficacy at each age extending the 2-year efficacy data from Linhares et al.’s study (Lancet 2008;371:1181-1189) performed in Latin American infants. The estimated lower limits of vaccine efficacy (adjusted for serotype distribution) for the first 5 years of life were as follows: 77%, 66%, 57%, 49%, and 43% for age 0, 1, 2, 3, and 4, respectively. (The upper limit for each age was assumed to be 77%, which is the base-case efficacy assuming no vaccine immunity waning.) We added the results of a sensitivity analysis using this approach in the Results section and described the analysis in the methods section (as shown below). We also added relevant discussion about the implications of waning vaccine-induced immunity, the uncertainty of the magnitude, and its overall population-level impact in the Discussion section (as shown below).

(Revised text)

Page 6 (Lines 128-131, Methods):...and (4) immunity from either natural infection or
vaccination lasts over the full time horizon of 5 years, but the level of immunity depends on the number of previous infections. **We explored the impact of waning vaccine-induced immunity in sensitivity analysis.**

**Page 7 (Lines 153-161, Methods):** We assumed an average vaccine efficacy of 41% against mild rotavirus infections based on published literature [8]. **In a sensitivity analysis on waning vaccine-induced immunity, we assumed that vaccine efficacy against severe cases would decline during each of the first 5 years of life. In the absence of direct evidence on waning immunity, we applied a conservative estimate of declining vaccine efficacy over age by extending the 2-year efficacy data from Linhares et al.’s study [42] among Latin American infants. The resulting vaccine efficacy estimates (adjusted for serotype distribution) for the first 5 years of life were as follows: 77%, 66%, 57%, 49%, and 43% for age 0, 1, 2, 3, and 4, respectively.**

**Pages 12-13 (Lines 280-286, Results):** Results were moderately sensitive to rotavirus-associated mortality, waning vaccine-induced immunity, and vaccine wastage rate. **If vaccine-induced immunity waned over the five years, corresponding to a decline in age-specific vaccine efficacy from 77% in year 1 to 43% in year 5, the incremental cost per DALY changed by approximately 15%, increasing from $540 (base-case assuming no waning) to $630.** The general results were also robust to delivery cost, cost per hospitalization or outpatient visits, and the disability weight for diarrhea (Figure 3A).

**Page 16 (Lines 368-373, Discussion):** Our study has several limitations. First, although our model attempted to reflect the natural history of rotavirus infection more comprehensively, we did not model seasonality or coinfection by different serotypes of rotavirus. Second, local epidemiological data quality was variable, and country-specific data were not always available. We had to estimate values of some key epidemiological parameters (e.g., genotype-specific vaccine efficacy and incidence rates of primary and subsequent rotavirus infections) based on data from other countries. Third, our model is static and does not capture the effects of vaccination on the force of infection (the rate at which susceptible individuals get infected) in populations over time. Fourth, we did not include Rotateq®, another new rotavirus vaccine, in our analysis. Given that Rotateq® can cover more serotypes circulating in Vietnam, this vaccine may provide a higher serotype-adjusted vaccine efficacy against severe rotavirus diseases. However, a majority of the effectiveness gains from the higher vaccine efficacy may be offset by higher vaccine costs. Accordingly, we expect similar results with Rotateq®. **Fifth, while we conducted a sensitivity analysis to explore the impact of waning vaccine-induced immunity, and found an approximate 15% increase in the cost-effectiveness ratio, we did not explore the implications of specific relationships and correlations between natural immunity and vaccine induced immunity within individuals. As better data become available, these will be important to incorporate to ensure the impact of vaccination is not overestimated.**

Finally, it was not possible to project the potential impact of routine vaccination on the serotype distribution of rotavirus. Because the currently available rotavirus vaccines do not provide cross-immunity for all serotypes, and because serotypes of rotavirus are known to vary over time even in the same country [3], if routine vaccination affects the dynamics of serotype evolution in some way, future vaccine efficacy may in turn be affected considerably.