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 a revised version of our manuscript, “Cost-effectiveness Analyses of Rotavirus Vaccination in Vietnam.”

The comments from the reviewers were very helpful. As requested, we have addressed the concerns and comments from the reviewers and incorporated the suggested changes into the revised manuscript. We have highlighted the changes in the revised version (bold and underlined) and prepared a detailed point-by-point response to each comment (included in this letter). Please note that we have made some minor changes in the distributions of several parameters and correspondingly updated the shapes of the cost-effectiveness acceptability curves, but that there have been no changes in the base-case results of the study. Please also note that we have made some minor editorial revisions throughout the manuscript and newly provided an Appendix describing the details of the steps taken to estimate rotavirus disease incidence related parameters. We hope that BMC Public Health finds our revisions to satisfactorily address the concerns of the reviewers.

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

Sincerely,

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

Kim and colleagues present a Markov model of routine childhood rotavirus vaccination in Vietnam in order to evaluate the cost-effectiveness of vaccination. They find that vaccination is likely to be very cost-effective under WHO criteria under both health care provider and societal perspectives. This is to my knowledge the first time a study has been submitted for peer review publication that uses a Markov model in order to track partial immunity due to prior infections. There are some limitations to the work, but these are adequately discussed and are unlikely to affect the broad conclusions. Overall, the work appears to be a methodological advance from previous models of rotavirus vaccination.

We thank the reviewer for the positive overall comments.

Major compulsory revisions

1. Footnote c (page 24) does not really explain how disease incidences (page 7-8) were converted into transmission probabilities for the Markov model. Since previous infections reduce the probability of severe disease, the probabilities for various rotavirus-linked health care outcomes would depend on the state. So it doesn't appear that the incidences can be converted to probabilities without some sort of fitting technique. The paper should either clarify the technique or explain why it was not necessary.

We agree with the reviewer that our description of the process for converting incidence rates to probabilities was not sufficiently detailed and clear in the footnote. In response to the reviewer comments, we chose to provide an Appendix including a more detailed explanation on the process. Footnote c has been correspondingly revised as follows (Please note that the alphabetical order of the footnote has been changed due to the addition of another footnote placed before the original footnote c):

(Revised text)
Page 25 (Table 1, footnote d): Monthly incidence rates were converted to weekly transition probabilities within the model, assuming an exponential relationship between the cumulative incidence at different time (age) intervals and time (age). For details, see Appendix, which provides a more detailed explanation of the steps taken.

2. Page 23 – 24: What are the distributions marked “--”? Were these parameters varied in the multivariate analysis? In particular, I would imagine that many of the ratios used to calculate less severe disease outcomes are extremely uncertain yet very important (since they determine the incidence of many outcomes). Were these varied in the multivariate analysis?

In Table 1, the third column (under the subheading of “Ranges”) provides the plausible ranges of model input varied during the deterministic one-way sensitivity analysis, and the fourth column (under the subheading of “Distributions”) provides the types of distributions assigned to parameters that were simultaneously varied during the probabilistic sensitivity analysis. In both columns, the mark “--“ was used to indicate that the corresponding parameters were not varied in the sensitivity analyses. We acknowledge that the use of the mark “--“ can be confusing. We thank the reviewer for scrutinizing the
manuscript and pointing out this. We replaced the mark with the phrase “Not varied” to clearly indicate the types of parameters that were not varied for sensitivity analyses.

We fully agree with the reviewer that the ratios used to calculate non-severe rotavirus infection outcomes (i.e., mild and asymptomatic cases by the primary or sequential infections) are highly uncertain (although they were obtained from a published cohort study) and that it is important to explore uncertainty surrounding the parameters. However, due to the highly non-linear (e.g., age-specific) nature of the incidence of different rotavirus infection outcomes and the hierarchical relationships between epidemiological model input, it was not easy to vary all of the parameters during the probabilistic sensitivity analysis. As we described in the Appendix attached, in estimating the age-specific incidence of different rotavirus infection outcomes taking into account reinfection, we tried to fit our incidence model to the two empirically reported data points of cumulative probability of rotavirus infection—about 90% by the age of 24 months and about 100% by the age of 60 months—and chose not to vary the values of the parameters that were used in fitting the incidence model during the probabilistic sensitivity analysis. Instead, we varied each of the parameters one at a time for deterministic one-way sensitivity analyses, taking into account several epidemiological constraints (e.g., the empirical age-specific cumulative probability of severe outcomes and the base-case assumption that immunity by vaccine does not wane over the first 5 years of age, the size of the susceptible population should not be depleted, say, during the first year of age.)

Another set of parameters that were not directly varied during the probabilistic sensitivity analysis is the serotype-specific vaccine efficacy. Since our Markov model does not distinguish rotavirus serotypes, we elected not to vary the values of the model input directly within the model. Instead, we used the data in adjusting the overall vaccine efficacy against severe rotavirus gastroenteritis and varied the value of vaccine efficacy against severe cases based on the plausible range identified using the serotype-specific efficacy. Lastly, the parameters of which mathematical definition includes some ‘initial’ parameters (that are assigned numerical values without being a function of other parameters) were not directly varied in sensitivity analyses. Those parameters were indirectly varied as the initial parameters were varied during the sensitivity analyses.

Please note that two of the parameters reported in Table 1 in the original manuscript (the ratio of symptomatic vs. severe cases during the primary infection and the corresponding ratio for the secondary infection) were not ‘initial’ parameters and were marked with “--”. For clarity, we have removed the two variables from Table 1 and included some “initial” variables that were missing in the original version. Please also note that we have updated the distributions of some parameters (while no base-case values have been changed) and added a few new footnotes to the table for more details.

3. Shouldn’t waning vaccine immunity be considered, seeing that clinical trials show a decrease in vaccine efficacy between first and second follow-up periods? (See for example Vesikari et al. Lancet 370:1757)
This is an excellent point. We fully agree with the reviewer that it is important to consider potential waning of vaccine immunity over time in evaluating rotavirus vaccines and recognized the presence of the reference the reviewer mentioned. However, we also reasoned that waning of vaccine immunity in a local setting is likely to be affected by the local serotype distribution of rotavirus (as with the case of vaccine efficacy in Vietnam estimated in the current analysis). Given that there have been no local clinical trial data on vaccine efficacy for Vietnam and that serotype distribution of rotavirus is known to vary across different regions, in part for the practical reason and in part for comparability with previous studies performed in the Asian setting, we elected to assume no vaccine immunity waning over the time horizon of 5 years for the base-case of the current analysis.

4. Line 116-117: “Vaccinated infants received the second dose at the age of 4 months but the period between the first and second doses provides the same level of immunity as a full-dose course” [30]. I’m not sure you can be so confident about this. The paper referred to (Salinas et al, 2005) does find a difference in rotavirus incidence between first and second doses, and after the second dose (3% compared to 1%). Ruiz Palacios et al (2006 NEJM 354:11) also found slightly lower efficacy between first and second dose. It does seem that the difference may be small and it may be difficult to interpret since there may be age and other confounding factors involved. But it would be safer to say that the model assumed efficacy after first dose is the same as after the second dose because the evidence is difficult to interpret.

We thank the reviewer for the useful suggestion. We acknowledge that the level of efficacy between the first and second doses can be possibly lower than the one after a full-dose course. However, we agree with the reviewer that the reported difference in vaccine efficacy between the inter-dose period and the period after a full 2-dose course is hard to interpret. For example, we recognized the difference in the incidence (3% vs. 1%) between the two periods in the article the reviewer mentioned, but we considered the difference negligible, as the reviewer also mentioned, given that there might be some confounding factors such as age or ad-hoc changes in the subject children’s nutrition status (which might in turn affect the level of general immunity of subjects). Accordingly, in the original version of the manuscript, we chose to make an assumption that “the period between the first and second doses provides the same level of immunity as a full-dose course.”

Although we meant to state that we made such an assumption (rather than assertion) by including the phrase “based on the following base-case assumptions” in the preceding line (line 115), we agree that it would be better if we state clearly that the evidence from the literature is difficult to interpret. Accordingly, responding to the reviewer’s suggestion, we inserted a sentence in a parenthesis in line 117 as below:

(Revised text)
Pages 5-6 (Lines 118-121): (1) vaccinated infants received the second dose at the age of 4 months but the period between the first and second doses provides the same level of immunity as a full-dose course (although some clinical trials [30] report different incidence rates between the inter-dose period and the period after the 2nd dose, we assumed the same level of vaccine efficacy for the two different periods since the evidence from the literature is difficult to interpret);
Minor essential revisions

1. Line 30-38: Could the authors cite particular papers for each assertion about previous models to indicate what they have in mind?

In response to the reviewer suggestion, we have provided specific references corresponding to each statement as below.

(Revised text)
Page 2 (Lines 28-38): There is also high uncertainty around the incidence of infection, as rotavirus infection is often asymptomatic, and even symptomatic cases can only be diagnosed definitively through laboratory testing, which is not usually performed even in medical facilities in developed countries [16]. For these reasons, most previous studies have estimated the avertable disease burden through vaccination based only on the estimated incidence of symptomatic rotavirus diarrhea (not rotavirus infection itself) and proportions of severe cases requiring medical treatment or leading to deaths, based on surveillance data [13-19, 23]. Further simplifying assumptions are typically: one episode of rotavirus diarrhea at maximum and full protection against subsequent rotavirus diarrhea during the first 5 years of life of a birth cohort [13-15, 17, 19,23]. The potential impact of the dimensions that are not incorporated in previous models on the cost-effectiveness of rotavirus vaccines have received less attention thus far.

2. Line 132: Was the disability weight of 0.119 from GBD study for diarrhoeal diseases in general or for rotavirus gastroenteritis?

The disability weight of 0.119 obtained from the GBD study was for an episode of diarrhoeal diseases in general. Since we were not able to obtain any rotavirus gastroenteritis-specific disability weights, we used the disability weight of 0.119 for diarrhoeal diseases. We made this more clear by adding a phrase as below.

(Revised text)
Page 6 (Lines 134-137): Health losses associated with nonfatal outcomes (i.e., outpatient clinic visits or hospitalizations) were calculated using the disability weights of 0.119 for an episode of diarrhea in general obtained from the GBD study and assuming a duration of 6 days [19].

3. Line 272: Does human papilloma virus have multiple transmission routes?

Yes, it has been reported that human papillomavirus (HPV) can be transmitted through multiple routes such as “vertical (from mother to newborns) [Rice et al.]” and “skin-to-skin contact (or finger-genital) [Sonnext C et al.]” as well as “sexual contact,” which is the most common way the virus is transmitted.

References:

4. Line 274: Isn’t this model also a static model? (as mentioned on line 340)

Yes. As we acknowledged in the subsection for limitations in the Discussion (line 340), our model is also a static one. When we mentioned in Lines 274-276 that “…most previous studies have evaluated the impact of rotavirus vaccines using a simple static model, not fully incorporating all key features of rotavirus infection, and the potential impact of the features that are not incorporated in the models has remained unexplored,” we meant to emphasize (in the sentences that followed the statement) that our model attempted to incorporate key features of rotavirus infection in a more comprehensive way extending the previous static model while our model was also a static model as the previous ones.

5. Could Figure 2A compare model results to those from the Velazquez et al. cohort study (as it is mentioned on line 234 that they have the same pattern)?

Although we obtained estimates of most key parameters regarding the ratios of different rotavirus infection outcomes from the Velazquez et al. study, another set of key data—the age-specific cumulative probability of hospitalized rotavirus gastroenteritis—were obtained from a published article that reported local data in Vietnam. Accordingly, the graph for cumulative probability of rotavirus infection under no vaccination presented in Figure 2A in the current study may not be (and does not need to be) in exactly the same shape as the one from the Velazquez et al. study (Figure 1). In comparing the two figures, Figure 1 (from Velazquez et al. study) and Figure 2A (from the present study), we could not perform any statistical tests due to the lack of detailed data for Figure 1. However, when we visually compared the two figures (both are pasted in below for the ease of reference), the two graphs showed a very similar pattern, for example, in terms of the curvature of each line corresponding to the same order of infection.
Figure 2A. Cumulative probability of rotavirus infection under no vaccination.
Discretionary revisions
1. Line 365: I agree that value of information analysis would be very useful. It doesn’t look like it would be very difficult to add on to the existing analysis that the authors have already done, and would definitely provide invaluable information to policy makers.

We thank the reviewer for the thoughtful suggestion to improve our work. We have elected not to incorporate this discretionary revision in the current paper because we believe that a value of information analysis would be sufficiently different than what is presented in the present paper, and would require additional methodological explanation, so it is better reserved for future work.
RESPONSE TO COMMENTS FROM REVIEWER 2:

This is a very nice paper exploring the cost-effectiveness of a rotavirus vaccination program in Vietnam. The analysis is solidly rooted in epidemiological and clinical effectiveness data from Vietnam and other settings, and is more detailed than previous cost-effectiveness analyses for developing countries (ref 13-15). I only have a few comments to improve the manuscript:

We thank the reviewer for the overall positive remarks about our manuscript.

Discretionary Revisions:

1) The authors focus their analysis on Rotarix, a monovalent 2-dose vaccine, and do not consider Rotateq, a tetravalent 3-dose vaccine. Would the results change substantially if the authors had considered Rotateq, which requires 3 doses but covers more serotypes circulating in Vietnam, including G1-G4?

This is a great point. As the reviewer pointed out, our analysis did not include another new rotavirus vaccine Rotateq®. (Again, as we mentioned in the text, this was because this vaccine has not been evaluated in clinical trials conducted in low-income countries. Some previous studies that evaluated both Rotarix® and Rotateq® have reported similar results for the two different vaccines (i.e., the incremental cost-effectiveness ratios of the two vaccines were in the same order of magnitude), but in general the incremental cost-effectiveness ratios for Rotateq® were slightly higher than those for Rotarix®, probably due to the difference in vaccine costs derived from different numbers of doses required for a full course (2 vs. 3 doses for Rotarix® and Rotateq®, respectively). Analogously, if we had included Rotateq® the main difference in the results would have occurred from two main sources – vaccine efficacy and vaccine costs (which are calculated as per dose vaccine price multiplied by the total number of doses required and adjusted for the vaccine wastage rates). However, we do not expect any substantial difference in the final results since a majority of the increased effectiveness gains with Rotateq® (probably from any higher level of vaccine efficacy adjusted for the serotype distribution, as the reviewer mentioned) is likely to be offset by the increased vaccine costs compared with the costs with Rotarix®. Since we feel that this should be mentioned clearly in the text, we stated this as an additional limitation in the Discussion section as follows:

(Revised text)

Pages 15-16 (Lines 353-358, Discussion): 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 a higher vaccine costs of the vaccine. Accordingly, we expect similar results with Rotateq®.

2) The authors used an estimate of 5$ for the cost of a single rotavirus vaccine dose in their base case scenario, but the current price agreed for developing countries (Brazil) is 7$. Using a base scenario of 5$, the rotavirus program appears to be “very” cost effective (i.e. very close to the per capita GDP), but there is no guarantee that the cost of Rotarix will actually go down at this point. Besides, setting the cost at 5$ seems arbitrary, and it would be more fair to use 7$ as
a base case scenario. Further, in addition to the sensitivity analyses, the authors could estimate a threshold for the cost of vaccine, below which the program does become “very” cost-effective (which should be around 5$).

We thank the reviewer for the helpful suggestions. While we agree with the reviewer that $7 per dose could be a better base-case scenario value in evaluating the cost-effectiveness of rotavirus vaccination in Vietnam, we chose to keep our base case value for per dose vaccine price. This is partly because of our reasoning that for lowest income countries like Vietnam a lower price may be agreed based on the past experience of tiered pricing that was often observed in the vaccine market and partly because of comparability with previous studies of rotavirus vaccination performed in low income countries.

Instead, responding to the reviewer comments, we have performed one-way sensitivity analysis with vaccine price set at $7. We also performed a threshold analysis of vaccine price. The results of the additional sensitivity analyses were added in the Results section.

(Revised text)
Page 10 (Lines 222-226, Methods): To explore uncertainty around parameters, we conducted univariate sensitivity analysis over the plausible ranges of key parameters (Table 1). As an extension of the univariate sensitivity analysis we performed a threshold analysis to identify the maximum per-dose vaccine price at which vaccination would still have a cost-effectiveness ration below the per-capita GDP in Vietnam.

Page 12 (Lines 261-270, Uncertainty analysis, Results): In univariate analyses, results were most sensitive to vaccine price, rotavirus-associated mortality, ratios of hospitalizations and outpatient visits to deaths, vaccine efficacy against severe gastroenteritis, and the discount rate (Figure 3A). For example, when the vaccine unit price was set at $1, the incremental cost-effectiveness was $100/DALY averted, but the corresponding value was $1,080/DALY averted with a vaccine price of $10 per dose. The corresponding ratio was $755/DALY averted when the price was set at $7 per dose (which is the recently agreed tiered price of in Brazil). In the threshold analysis for the vaccine price, the program would be cost-effective based on a benchmark of $580/DALY averted (equal to the per-capita GPD of Vietnam) at prices up to $5.41 per dose, and would be cost-effective based on a benchmark of $1,740/DALY (three times GDP per-capita) at prices up to $32.4 per dose.

3) The model used in this analysis does not include the effects of herd immunity. Indeed, if vaccine coverage is expected to be as high as 90-98% in Vietnam, transmission of rotavirus is expected to decline in the community, thus indirectly protecting unvaccinated individuals (including older kids and adults) as well as vaccinated children who did not respond well to vaccination. This effect could be extremely important, as suggested from preliminary data from the US, where 30-60% vaccine coverage in kids under 13 months of age produced in a dramatic decrease in rotavirus transmission (MMWR June 27, 2008). I wonder if the authors could take this herd effect into account in their model, as this would work in favor of the vaccination program. If this effect cannot be taken into account, this has to be at least stated as a major limitation of the model.
We fully agree that examining any potential herd immunity effects is crucial in evaluating any vaccination programs. However, as is widely known, a static model like ours cannot take into account herd immunity effects within the model. Clearly recognizing this as a limitation, we made the following statement in the Discussion section in the original manuscript.

Page 15 (Lines 351-353): “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.”

4) Why isn’t there a range of estimates considered for age-specific rotavirus mortality rates (table 1)?

We apologize for the missing ranges of the parameter estimates that were used in one-way sensitivity analyses. We have provided ranges for the estimates in Table 1 in the revised manuscript. As for the reason that these age-specific estimates were not varied for the probabilistic sensitivity analysis, please refer to our responses to the Reviewer 1 comments #2 on pages 2-3.