Author’s response to reviews

Title: Cost-effectiveness of Introducing a Rotavirus Vaccine in Developing Countries: the Case of Mexico

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Author’s response to reviews: see over
Dr. Melissa Norton  
Editor-in-Chief  
BMC Infectious Diseases

Dear Dr. Norton:

Attached please find the first version of the revised manuscript entitled “Cost-effectiveness of Introducing a Rotavirus Vaccine in Developing Countries: the Case of Mexico,” MS: 1677367371726492, which we hereby resubmit for consideration by BMC Infectious Diseases. We really appreciate the reviewers’ comments to the above manuscript. Please, find enclosed to this letter a point-by-point answer to reviewers’ comments as well as a point-by-point description of the changes made to the manuscript.

We still believe that the BMC-ID is the ideal venue for publishing this manuscript. The need for high quality effectiveness and cost-effectiveness studies has been identified and the dissemination of our results through a highly respected journal, with broad distribution, will draw attention to the importance of improving child health through newly available public health interventions and will emphasize the key role of the cost-effectiveness evidence for decision-making.

Sincerely,

Atanacio Valencia-Mendoza
Author's response to reviews

Title: Cost-effectiveness of Introducing a Rotavirus Vaccine in Developing Countries: the case of Mexico

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Author's response to reviews: see over

Reviewer 1
The paper offers a limited description of the policy context for current rotavirus vaccine decisions, so its overall importance is somewhat unclear
We have clarified that many low- and middle-income countries are currently confronting the decision to include, or not, these new expensive vaccines in their national vaccination programs.

Changes in page 4 paragraph 2

The most important (compulsory) improvements are providing more clarity in describing how a child’s age by month was treated in the model and how the onset of vaccine benefits midway through infancy are handled by the model.
We expanded and clarified our initial description of how/why the model treats rotavirus incidence and vaccine effectiveness by month – but not understanding exactly what the reviewer wanted clarified, we may or may not have addressed his concerned.

Changes in page 7 paragraph 1

Second, and of equal (compulsory) importance are the need to check the robustness of results to alternative distributional assumptions and the need to actually present uncertainty intervals for costs and effects as well as the CE ratio
We are grateful for these very helpful suggestions and have incorporated them into the paper – see response to detailed comment below.

Specific Comments
Page 4 What is the current policy in Mexico regarding the rotavirus vaccine? CE results are one item in an adoption decision. What other concerns besides cost-effectiveness should policymakers bear in mind in deciding to adopt?
We have clarified current policy, as mentioned above and added a caveat to the discussion that makes it clear that the authors are not suggesting that CE is the only criterion for decision-making.
Page 20, paragraph 3.
Changes in page 20 paragraph 3

Page 5. å##â#|estimate the expected numberâ#|by month and ageâ#|â## [in what units?]
We have clarified that this always refers to a national estimate – i.e. total number of cases in the national cohort of children of that age.  

*Changes in page 7 paragraph 3*

Page 6 â## â#|according to the month of the year and the ageâ#|â## [in what units?]  
Same as above

Page 8 top line also ambiguous whether national data on diarrhoea incidence was by age in months for the first year of life or was stratified into mortality by age under 12 and age over 12 months.  
Have clarified that it is stratified by month of age under a year of age and by year from 1-5 using the curves from the IMSS.  
*Changes in page 8 paragraph 2*

Need to clarify. It is great that the model accounts for seasonal effects by â##monthâ##, but it is unclear whether the model accounts for child age in months or in years. Table 1 only shows age effects by year raising suspicion that age related changes in mortality are modeled year by year. However, for the first year of life, the model will be sensitive to age effects by month. This is because the earliest the vaccination schedule can be completed is 14 weeks. In fact the cost model assumes the vaccination schedule will parallel DPT schedule so children wonâ##t derive full protection until 6 months of age. Espinosa et al (1997) find that greater than 50% of Nicaraguan children show evidence of prior infection by age 2 monthsâ##before a rotavirus vaccine could have become effective. (Mexican case may not be so severe, but are there corresponding Mexican data?) Thus the model may overestimate the mortality reduction by assuming that 12 months of mortality exposure is reduced by the vaccine, when the child only derives 6-9 months of reduced mortality exposure.  
The model considers child age in months, precisely for the reasons the review cites. We have tried to ensure that this is unambiguous.  
*Changes in page 7 paragraph 1 and page 8 paragraph 2*

Page 8. Assumption of no antigenic shift though plausible is optimistic. Evidence on this will need 5-10 years.  
Agreed – but it seemed to us to not justify a whole discussion considering the rapidity with which the pharmaceutical manufacturers are expanding the subtypes covered by their vaccines. In 5-10 years we will be debating the introduction of an improved vaccine. Just in the last year we have gone from a monovalent to a pentavalent in the market. The government is making the decision about whether and how to vaccinate on an annual basis, thus it can reassess should significant antigenic shift occur.

Page 10. Are the PRV efficacy estimates different for children of different ages. Efficacy is presumably 0 for children below 2 months?  
Correct – efficacy is 0 prior to the first dose and increases with subsequent doses. However, we have no data on how the efficacy of the first dose might vary with age of application. In other words, the model uses the data from the clinical trials on protection conferred by the first dose at 2 months regardless of the age at which the child receives the first dose. As per the suggestion of the other reviewer we have added a scenario in which first dose is delayed till 6 months (max permitted). If the immunogenicity of the vaccine is greater at 6 months than it is at 2 months, then the 6 months estimate is conservative; if less immunogenic, then it is optimistic.

Given the history of the Glaxo vaccine, paper should state and support the assumption that vaccine related morbidity and mortality are negligible.
We have included a statement to this effect.

*Changes in page 20 paragraph 1*

Page 10. â##â#|â## Give more detail so readers can ascertain whether mortality reductions in the first year of life were pro-rated by the proportion of the first year spent unprotected. As per the comment above, the calculations were done monthly during the first year of life and thus the benefits are automatically pro-rated.

*Changes in page 7 paragraph 1*

Page 11. Equation formatting and choice of notation could be made more attractive using subscripts like Epp and NPP etc.

Done

Page 13. Paper should flag the assumption that infants who die of rotavirus would have otherwise lived lives of normal length. Some might hold the belief that children who die of rotavirus may be more likely to suffer from other chronic diseases that shorten life expectancy. Indeed, many vaccine programs used to be built around the assumption that those at high risk of complications can be targeted ex ante and the vaccine could be targeted. Authors may want to address the ability of their model to address the cost effectiveness of a rotavirus vaccine targeting program.

*Added to the discussion.*

*Changes in page 20 paragraph 2*

Page 16. Describe the upper and lower bounds of what emerged for deaths averted, life years saved and costs from the probabilistic sensitivity analysis. Not enough to present just Figure 4 and be done with tell readers all they need to know.

Done. *see Table 4 and the results section*

Conclusion: Since the premise of the paper is that other countries can learn from a model for Mexico, paper should give guidance regarding the limits of extrapolation of CE estimates. What should be similar about another countryâ##s diarrhea prevalence, overall child health, and medical costs before the Mexican results would be relevant? What differences would be most important in making an extrapolation.

Inserted in the discussion.

*Changes in page 22 paragraph 2*

Table 3 needs to display the units for any epidemiological rates, (e.g. events per 100,000 infants age xx) or (Percent) or (Pesos in 2007)

Done

Table 4 It is unconventional to model the distributions for probabilities as being uniformly distributed or as truncated normal. (Briggs, 2000). These are typically taken to be beta distributions with medians set as per table 3 and 5th and 95th %iles as per table 3. Exponential distribution for hospital day costs is correct. It would be important to test conclusions from current distributional assumptions against better assumptions. If results are very robust to alternative distributional assumptions AND authors can somehow defend current distributional assumptions then unconventionality would be tolerable. Sources of these distributional assumptions may not be available, so they need to be justified based on Bayesian priors for what best reflects the worldâ##s state of knowledge.
We have accepted (with thanks) the suggestions for revised distributions and also reconsidered ones that he did not mention (for example we replaced the uniform distribution for cost per medical visits with a Gamma distribution).

*See tables 4 and 5 and Figure 4.*

Table 5. Since @risk was used. Table 5 can and should present the uncertainty interval (5th and 95th %ile) emerging from the 100,000 iterations studied. Intervals should be presented for both the numerator (costs) and denominator (effects).

Done

Figure 4 is oddly normal. Cost effectiveness ratios aren’t always distributed normally especially when the denominator has a significant density over zero. Given that the CE ratio is normal, it can be fully summarized by mean and SD and the histogram is unnecessary. That is the beauty of normal distributions. So can eliminate Figure 4.

Revised Figure 4 is less normal – reflecting the changes in the assumed distributions.
Reviewer 2

Major Comments
1. Abstract and Discussion p. 15. The finding that ~5,000 hospitalizations and ~600 deaths can be prevented during childhood with a vaccine program suggests that a case fatality ratio of over 1 in 10 children hospitalized with diarrhea die. This seems very high, and is certainly not the case in the neighboring U.S., where the seasonal burden of ~50,000 hosp and ~20-40 deaths are consistent with a CF ratio of 1 in 100 or lower. Thus, I am concerned that this important case fatality parameter is overestimated; the sensitivity analysis of 50% to 200% is likely far too narrow in the lower range.

Mortality considered in our analysis includes that reported by the INEGI (National Institute of Statistics Geography and Informatics) which also includes the deaths occurring outside the health system. So, strictly speaking we don’t have complete information to calculate a case fatality rate since we are missing all non-fatal cases that occur outside the health systems. In the denominator of your calculation you are mixing deaths occurring outside and inside the system while in the denominator you only have hospitalizations.

According to the 2006 National Health and Nutrition Survey, 22% of the Mexican population still lives in rural areas with poor access to health care. Population in rural areas and some urban population with high degree marginalization are not well informed to do an adequate home based management of diarrhea for children.

The statement in the paper is as follow: “Given the perspective adopted in this study, the model does not distinguish between children who do not become ill with rotavirus diarrhoea and those who become ill and do not use healthcare services (unless they die)” Page 6 paragraph 3.

2. Background, page 3. The authors cites one “global” reference that 20% of all diarrheal deaths are from diarrhoea (ref 4). While this may be true globally, Mexico is a middle income country and so may be more like the US where there is not even winter seasonality in all-cause diarrhea. This important parameter assumption should therefore be tested in Mexico national mortality data – is there winter seasonality in all-cause mortality consistent with an attribution of 20% of annual deaths to rotavirus (would correspond to a ~40% elevation in winter rates over summer rates).

The differences in hospitalization and death rates due to diarrhea among children under 5 in the winter and summer has been well documented in the United States and Mexico. The recent estimates of 55 – 70,000 hospitalizations due to rotavirus in the US are based on the Winter Residual Method. This method compares the number of hospitalizations due to diarrhea in the winter and summer to determine the burden attributable to rotavirus (Charles et al., 2006; Malek et al., 2006; Fischer et al., 2007). Both Villa et al. 1999 and Velazquez et al. 2004 describe how improvements in the water supply after the cholera epidemic in Mexico reduced the mortality rate due to diarrhea among children in the summer more dramatically than in the winter. They attributed this to the prevalence of rotavirus in the winter which is less affected by improvements in sanitary conditions compared to diarrhea from bacteria. The assumption that 20% of diarrheal deaths in children under 5 is conservative. Velazquez found that from 1996 to 2002, 62 -68% of severe diarrhea episodes occurring during the fall-winter season were rotavirus-positive compared to 6 -12 % in the spring summer season. More recently both Merck and Glaxo Smith Kline reported reductions in hospitalizations for all cause diarrhea of close to 60% (Vesikari et al, 2006; Ruiz-Palacios et al., 2006).
3. Methods, page 8. The authors state there are no literature that further breaks down rotavirus burden by age. This is not true. A recent study by Fischer et al studies a large subset of US hospitalizations and breaks data down to moths of age.


Even though these data are not for Mexico, the age pattern from these US data should clearly be proportionally incorporate into the Mexico model (similar to other aspects of the model handled this way by the authors). The reasons this is important is that a considerable proportion of disease burden occurs in the first 3 months of life – so likely not preventable with a vaccine with a 2-4-6 month schedule. Taking this infant burden variability into account will therefore lead to lower cost-effectiveness and so should be included for a prudent estimate (I am assuming the demographic model is actually not modeling 1-month age cohorts of children; if not, then this important epidemiological fact of age patterns and early-month-non-preventable disease burden in the first year of life should at a minimum be included in the sensitivity analysis).

This is a typographical error. That we wanted to state is that there is no literature for Mexico that further breaks down rotavirus burden by age. Soon after we describe the method used to distribute the diarrhea events (outpatients, hospitalizations and deaths) across age by month based on IMSS’ data and how the proportion attributed to rotavirus per month is based on papers from France and Canada. Finally, we are in fact considering in our analysis age-specific total diarrhea and age-specific proportion due to rotavirus.

Changes in page 8 paragraph 2

4. Vaccine effectiveness model assumptions – it is not clear from the paper when the model has the cohort children get the first doses. Specifically, does the model assume a normal distribution around 2 months of age? Or, is a proportion of children assigned to be “late vaccines” due to delay in first well visit or due to missed opportunity at first well visit? This is important for the reason of profound age variability in disease burden during the first year of life – which exactly overlaps the vaccine age window of 2-6 months (Fischer et al, 2007).

In the model we assumed a coverage rate of the vaccine and assumed that the children getting the vaccine will receive the three doses exactly at 2, 4 and 6 months of age. This certainly overestimated the value of the vaccine. As per the suggestion of the reviewer we have added the results of a scenario in which first dose is delayed till 6 months (max permitted).

Changes in page 11 paragraph 1 and page 17 paragraph 2

5. Table 1 and Table 2 all-cause diarrhea morbidity and mortality burden assumptions. Why take mortality data from 2002? Seems this would bias the study towards cost-effectiveness because Mexico has seriously reduced its all-cause diarrheal mortality burden over the recent decade due to introduction of municipal water. While rotavirus burden is probably not reduced with cleaner drinking water (mostly a reduction in bacterial diarrhea burden), a reduction would greatly affect the model because it assigns a proportion of 20% of these all-cause deaths to rotavirus.

At a minimum, the authors need to explain the rational for choosing 2002 burden data for a 2006 cost estimate. Are no mortality data available for Mexico for more recent years? Wouldn’t it be better to match the table 1 data with Table 2 data, by taking them all from IMSS 2005?

The reviewer is correct that we have access to all-cause diarrhea mortality from 2006, but the most recent data on rotavirus-specific morbidity are from 2002 (see paragraph 2 in page 9). Because, as the reviewer observes, all-cause diarrhea mortality has fallen between 2002 and 2006 (although the dramatic fall in diarrhea mortality occurred in the 80s and 90s with the effective expansion of the ORS program), disproportionately due to reduction in deaths due to bacterial pathogens, we felt that it would be preferred to use 2002 estimates in both the numerator and denominator. As we have no information on how rotavirus morbidity/mortality may have changed 2002 to the present, we assume
that is has remained constant. That may slightly overestimate the benefit of vaccination if health service access has marginally improved over that period and we reflect that now in the discussion. 9, 2

With respect to use of the IMSS data to update the 2002 data there are two important problems. First, they are not etiology-specific. Second, they are highly unrepresentative of the national population, as they are largely limited to the population from the top half of the income distribution.

6. The authors do not discuss the implications of their findings of diarrheal mortality being a major driver of cost-effectiveness of a rotavirus vaccination program. Are there other competing interventions that may be more cost-effective (for example, oral rehydration therapy? Education of mothers to seek supportive diarrhea care for infants? ). It would be nice if this paper closed with a broader perspective than vaccination - since this is an analysis done for the National Institute of Public Health and so it is in the context of a broader public health evaluation of solutions for reducing burden of diarrheal disease than just vaccines. Likewise, I believe (for all the reasons listed above) that a reconsideration of the very high assumptions of preventable diarrheal mortality would result in a more robust cost-benefit analysis.

We are grateful for these very helpful suggestions and have incorporated them into the paper

Changes in page 22 paragraphs 1 and 2

Minor comments

Page 7. Authors point out that timing of vaccination (well visits or campaigns) are important for understanding vaccine benefits. It should be pointed out that the assumptions in this Mexico study is the "optimal" well visit scenario. Also, I am assuming the authors are expecting 2-4-6 months schedule, but this is not adequately clear from the paper. Please clarify.

The reviewer correctly points out that the model currently estimates a best-case scenario in which children receive their vaccinations at the manufacturer-recommended ages. We designed the model to be able to model different likely benefits as the age of vaccination varies from the ideal. However, we do not yet have access to the data from the scale-up of rotavirus vaccination in Mexico that would enable anything more than speculative description of what the real distribution of age at vaccination is. What we have done to respond to the reviewer is to include in the discussion a worst-case estimate, in which a child received his first dose at the latest recommended age, 6 months. Estimation of how much worse than ideal the program is in Mexico will have to wait for a subsequent paper.

Changes in page 11 paragraph 1 and page 17 paragraph 2

Methods section is very long.....could the equations be placed in a technical appendix perhaps, leaving space in the main paper methods section for the principles behind each analysis element?Cambiar la ecuación a un appendix