Reviewer's report

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

Version: 1 Date: 27 March 2008

Reviewer: Lone Simonsen

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This is a clever and carefully done modeling study of the likely cost benefits of a National rotavirus vaccine program in Mexico. This reviewer very much likes the demographic modeling approach, taking a cohort of 2 million kids through the first 5 years of life, with and without a vaccination program in place. The model nicely takes into account the profound winter seasonality of rotavirus epidemics in Mexico, by modeling calendar months and birth cohorts. Finally, the health economics analysis is sophisticated and the modeling approach far more advanced than cost benefit studies done for other countries including the United States. The authors include corporate sector with a clear interest in the outcome of such a cost-benefit study, however this is clearly indicated and the other authors are government researchers with international standing as experts in health economics.

This well written and well conceived paper concerning model data for an important and timely public health decision about rotavirus vaccine introduction in Mexico definitely deserves publication in a good journal in my opinion. However, I have important concerns about some of the epidemiological parameters chosen – especially for the mortality outcome. The vaccine preventable burden of mortality seems overestimated and this needs to be addressed because the conclusion of cost effectiveness of a national program strongly bear on mortality data assumptions. Below is a list of major and minor concerns:

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.

2. Background, page 3. The authors cites one “global” reference that 20% of all diarrheal deaths are from diarrhea {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 rota (would correspond to a ~40% elevation in winter rates over summer rates).

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 months of age. http://www.ncbi.nlm.nih.gov/pubmed/17357047?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RVDocSum

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).

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).

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 diarrhea 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?

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.

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.

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?