Author's response to reviews

Title: Invasive meningococcal disease epidemiology and control measures: a framework for evaluation

Authors:

Jamie J Caro (jcaro@caroresearch.com)
Jørgen Moller (jmoller@caroresearch.com)
Denis Getsios (dgetsios@caroresearch.com)
Laurent Coudeville (Laurent.Coudeville@sanofipasteur.com)
Wissam El-Hadi (wissam.el-hadi@sanofi-aventis.com)
Catherine Chevat (catherine.chevat@sanofipasteur.com)
Van Hung Nguyen (vanhung.nguyen@aventis.com)
Ingrid Caro (icaro@caroresearch.com)

Version: 2  Date: 29 November 2006

Author's response to reviews: see over
November 29, 2006

Annabel Phillips, PhD
Assistant Editor
BMC-series Journals
BioMed Central
Middlesex House
34-42 Cleveland Street
London W1T 4LB

Dear Dr. Phillips:

We would like to thank the reviewers for their insightful comments and assistance in improving our manuscript, entitled “Invasive meningococcal disease epidemiology and control measures: a framework for evaluation” (MS: 5513254931104146). We have taken the comments into consideration and modified the manuscript accordingly. Please find below, responses to the reviewers’ comments and a description of the changes made to the paper.

Reviewer: Adam Finn

General

Regarding the latter, there are important gaps in knowledge – notably about the efficacy and duration of protection both against invasive disease and against carriage of conjugate vaccines given to adolescents. However, as new data emerge on this, they can be fed into the model to produce revised outcomes.

Response: We agree that there are considerable gaps in knowledge. The goal of this work was to develop a practical tool to assess both the potential impact of vaccination on general incidence and outbreaks and to increase understanding of the factors that are important, particularly with respect to areas where data are limited or absent. We have expanded the rationale for the model in the introduction to make this point, and have added to the sensitivity analyses reported in the results.

Major Compulsory Revisions

I may have missed something, but was left feeling insufficiently clear precisely what the assumptions were that were fed into the model to produce the illustrative predictions shown in the figure on page 31 (figure 2) The legends says nothing. In particular what rate of uptake by 12 year olds is used and is this one that can realistically be expected to be achieved across the board in the USA based on success with current programs in adolescents?
Response: The coverage rate was 71%, and the results are presented for years after all people in the simulation between the ages of 12 and 100 have been vaccinated or were eligible for vaccination as part of a routine vaccination program. The coverage rate for routine vaccination has been added to the methods, as have the coverage rate assumptions behind the results presented. A figure has also been added showing incidence of disease over the first 100 years following implementation of vaccination. Results are stable after about 30 years. The legend for Figure 2 (cases by age at steady state, now Figure 4) has been changed. Finally, in the discussion section, we discuss coverage rate assumptions and their impact in greater detail.

Minor Essential Revisions

End page 2 start page 3 “aided by facilitated through…” Need to pick one verb for this sentence

Response: Corrected

Page 13 Analysis settings. What rate of uptake was assumed for routine immunization of layer olds (as opposed to immunization in response to outbreaks) in this illustration? Does the model assume this uptake rate is uniform or does it allow for variable uptake rates within and across communities?

Response: The coverage rate assumptions have been added to the text. The model assumes a constant coverage rate both within and across communities. This is not a serious limitation at steady state, but for results over time, variable uptake rates could be of interest. The model does not allow for differential uptake across communities but their impact could be assessed by running the model under various coverage rates and then weighting results across communities. The model does not consider migration from one community to another, so we cannot assess the effects of coverage rates in one community on the incidence of disease in another. This limitation is now described in the discussion.

Discretionary Revisions

Page 3 “That vaccine, however, has relatively poor efficacy in younger children, does not prevent carriage of the disease, and does not provide long-lasting protection”.

Although it is commonly stated, I believe it is not really know whether polysaccharide vaccines can impact on colonization. Certainly A and C polysaccharides can induce mucosal immune responses (Infection and Immunity 2000; 68: 2692-2697 and Infection 2001; 69: 4337-4341).

Response: We have modified this sentence to reflect this uncertainty.

Reviewer: Thomas Clark

Major Compulsory Revisions

Page 11, first paragraph under “Efficacy/Direct effects. I believe the authors are referring to reference 11 in the first sentence (Trotter et al. Lancet 2004;364:365-367).

Response: This has been corrected.

Same paragraph. The description of extrapolating waning efficacy is not clear. The reference above only includes two data points, efficacy at less than one year and at greater than one year. Are these the data from which the authors extrapolate? Did they receive additional data from the authors? If possible, a
curve could be included, so that the reader could at least be intuitively convinced that the exponential function is an appropriate one. This is not necessarily intuitive in the data, or accepted as a function of waning efficacy, so additional information or a reference would help. This has implications in how long the model is iterated. Over time, it may be quite susceptible to variations in waning immunity, which I believe the authors should also address.

Response: The text describing direct and indirect effectiveness of the vaccine and assumptions on waning efficacy has been re-written and a Figure illustrating waning efficacy using an exponential function has been added. We selected an exponential function as this is consistent with prevailing assumptions on waning of vaccine efficacy. For example, it has been used by Trotter et al.[reference 20 in the manuscript] in their recent model on use of a C meningococcal vaccine in the UK. We have also clarified that the sensitivity analyses of vaccine effectiveness refer to the rate of waning assumed in the model. Finally, in the conclusion, we highlight the fact that the actual effectiveness of the vaccine over the long-term is uncertain.

Similarly, the authors discuss that the results of the model can be presented over any time horizon, but I do not see in the paper the time horizon of the results presented.

Response: We have added a figure showing the change in incidence over time, and in the last section of the methods, clarified the explanation of the time horizon over which the steady state results are presented.

Minor Essential Revisions

Last paragraph on page 3, as written, "...does not prevent carriage of the disease..." should be "does not prevent carriage of the bacteria...."

Response: We have made this change.

Similarly, in the next sentence, "conjugate vaccine are available that may (or "are expected") offer better effectiveness."

Response: We have made this change.

Next sentence, "...may also protect against carriage of meningococci."

Response: We have made this change.

Page 10, second paragraph, the authors describe the "resulting risks" of infection during high incidence periods, including "87.5 for serogroup B." Is this a relative risk, or 87.5 times the baseline risk? Please clarify.

Response: The text has been modified. The age-specific baseline risk of infection for serogroup B is multiplied by a factor of 87.5

Reviewer: Sally Blower
Major Compulsory Revisions

The authors have developed an extremely complex model – could they achieve similar results (as those they present in the paper) with a much simpler stochastic model? Therefore can they justify the complexity of the model that they have developed?

Response: We believe that simpler models cannot adequately address herd immunity and the impact of vaccination on the frequency of outbreaks. Even fairly complex dynamic disease transmission models, which do account for herd immunity, do not account for changes in the size or frequency of outbreaks, an element especially important in meningococcal disease. We have modified the introduction to expand on the rationale for the type of model developed.

The authors mention, in passing, previous modeling work, but these previous studies are not discussed. The authors should explain (briefly) the structure of the previous models, and the results that were found from analyzing these models. Thus it can be ascertained as to whether the question posed by the authors is new and as to whether their results differ from, or are similar to, results from previous studies.

Response: We have modified the text to point out that, to our knowledge, this is the only model that directly models herd immunity, the occurrence of outbreaks, and the effects of vaccination, and that previous work has shown that oversimplified models can lead to misleading results. We also note the strengths of some of the more sophisticated models, which support the belief that including herd immunity and outbreaks is important in this disease area.

Whenever the authors mention % they should also report the results in absolute numbers.

Response: We have added the absolute numbers.

A major concern is that the authors present an extremely detailed model, but present only a few results. I would suggest that substantially more results are presented in the manuscript.

Response: We have expanded the results presented in the manuscript, although the emphasis of the manuscript was to describe the framework for analyses, not on specific results.

Although the authors do not present a cost-effectiveness analysis they should comment on whether it is likely that such a vaccination approach is likely to be cost-effective. For example, they could present an analysis of cases averted per vaccinated case.

Response: We have added the number needed to vaccinate to avoid one case of meningococcal disease. Given the complexity of the model a more detailed sensitivity analysis should be presented.

Response: We have expanded the sensitivity analyses but we limit them to those that could lead to a meaningful change in cases and outbreaks averted.

I am unclear as to what the authors mean by “a linear relation is assumed between direct vaccine protection in the community and the extent of herd immunity” – the authors should clarify this point and discuss the potential consequences of relaxing this assumption.

Response: The discussion section has been modified to better explain this assumption.
Thank you for your consideration of this manuscript. We look forward to hearing from you soon.

Sincerely,

J. Jaime Caro, MDCM, FRCPC, FACP