Unexpected infection spikes in a model of Respiratory Syncytial Virus vaccination

Dear Dr. Yang,

We thank the Editor and Reviewers for their time and consideration of our manuscript on RSV vaccination. We have done everything the reviewers requested. Here is a point-by-point response to the reviewers.

Reviewer 1

General This reviewer had four major comments and three minor comments.
Response: We have done everything this reviewer suggested. Changes due to this reviewer are in blue.

Comment (1) The authors describe current efforts at vaccine development as "focused on the development of particle-based and subunit vaccines (p.2, 3/4 down)". They do not mention, or consider, the continuing work on live attenuated vaccines or vectored vaccines both of which are supported by multiple large pharma companies.
Response: Good point. We have changed this sentence to: "focused on the development of particle-based, subunit and vectored vaccines. Live-attenuated vaccines are also undergoing phase 1 trials." This is based on the summary at `http://www.path.org/vaccineresources/files/RSV-snapshot-December2016.pdf` (Page 2)

Comment (2) The authors consider (p.3, middle) "a vaccine strategy for RSV where a fixed proportion of individuals entering the model are temporarily immune to infection. This reflects the situation where newborn children are vaccinated at birth." They do not mention, or consider, that the main vaccine strategy now being pursued for the youngest infants is not direct immunization, but is instead maternal immunization. Vaccination occurring during the third trimester generates antibodies in the mother that are transferred transplacentally to the infant, resulting in higher antibody titers in the infant at birth. The thought is that the higher antibody titers should protect the infant for approximately two months longer. Pre-formed antibodies decay with time, and by 6 months maternal antibodies are no longer detectable in an infant.

Response: This is an excellent point, so we have changed the focus in this section to maternal vaccination and discussed this in some detail. Happily, by doing so, the results are unchanged from a mathematical perspective. (Pages 3, 7, 16, 17)

Comment (3) Vaccination of infants as soon as they are born is seldom successful for any pathogen because the infants immune system is immature. It is not currently being contemplated for RSV. However, MedImmune (owner of the prophylactic monoclonal antibody that is currently used for "at risk" infants to protect them against RSV) has developed a more potent RSV-neutralizing monoclonal antibody with increased stability that could be given at birth to protect infants for their first 6 months. This approach would avoid the uncertainties of individual maternal responses to RSV and the problem of premature birth which could result in incomplete transfer of the antibodies elicited by a maternal vaccine, depending on the time of vaccination relative to birth.
In general, the thinking in the field is that there will be two vaccines for RSV, one to protect infants during their first 6 months, and another to protect them from 6 months on. I realize that there may be too many variables for the authors to consider in one report, but they could choose one of these strategies and model that. Maternal vaccination before birth would seem to be the most important to study now since it is being pursued aggressively by the NIH and two big pharma companies and several smaller companies, and is being supported by the Bill and Melinda Gates Foundation. The MedImmune stabilized monoclonal antibody approach could be included as generally equivalent.
Response: This brings up a point that we realise was not clear: we are actually considering both options. The nonimpulsive model considers pre-infection vaccination only, while the impulsive model considers subsequent vaccination. We have added emphasis in several places to make this clear. (Pages 3, 7, 11, 16, 17)

Comment (4) But the protection of any of these approaches would cover only the first 6 months of life. Thereafter, immunization of the child with another vaccine would be needed to induce active immunity and a recall response that would provide future, more rapid protection upon infection. Right now, live attenuated or vectored (adenovirus) vaccines are the front runners, but direct immunization with a subunit vaccine might eventually be considered. A subunit vaccine has not been considered largely because of the initial formalin-inactivated vaccine trial in the 1960s resulted in much more severe disease following the first community acquired infection in the vaccinees.
While modeling a 10-year protective vaccine and a lifetime-protective vaccine can be done, even infection with the wild-type virus does not provide 10-year protection, so it is difficult to see how a long-term protective vaccine could be generated. Nevertheless, it is a laudable goal.
Response: This is a helpful observation. We have decided to change our focus away from long-lasting vaccines and instead mostly focus on short-term durations, as the

reviewer suggests. We have mostly restricted ourselves to vaccines lasting six months (corresponding to $\omega = 2$) and have instead moved the focus to vaccine coverage via the proportion of individuals who are vaccinated (r). We re-ran all our simulations and have thus updated all figures. The results are actually stronger with this new focus, so we are grateful to the reviewer for raising this. (Pages 12, 13, 14)

Comment (5) p.1, author list. Why is Robert J. Smith followed by a ? ?
Response: It is part of the author's name. See, for example:
`http://mysite.science.uottawa.ca/rsmith43/MDRHIV.pdf`

Comment (6) p.18, l.10. vaccination-induced
Response: Fixed (Page 16)

Comment (7) p.18, l.20.outcome than coverage
Response: We agree, although this sentence has now been deleted, so it no longer applies.

Reviewer 2

General This reviewer noted that the research questions examined in our manuscript are extremely important and relevant and that we use an innovative approach to address the question of potential vaccine efficacy. This reviewer had five major comments.
Response: We have done everything this reviewer suggested. Changes due to this reviewer are in red.

Comment (1) The authors base the model on the assumption that infants will be given the vaccine at birth. While this is true for a few vaccines, most are not given at birth. Additionally, the most advanced vaccines in development are not being targeted to infants. They are primarily targeting the elderly, and pregnant mothers to protect newborns. The authors need to address the fact that their assumption is very unlikely, or even false more than they have as the manuscript stands.
Response: This is a good point that was also raised by Reviewer #1. See our response to Comments (2) and (3) above. Note in particular that we are actually considering both and have made that more clear. (Pages 3, 12, 16, 17, in blue.)

Comment (2) The authors conclude that vaccine duration would be more important than vaccine coverage. They recommend that vaccine be tested for duration before approval. The authors need to discuss how the practicality of studying long term immunity is very challenging, especially regarding the time frames they test. Obviously 70, or even 10 years would be impossible to test during a clinical trial before licensure.

Response: This point was also raised by Reviewer #1. We have changed the focus to short-term durations and re-run our simulations. See our response to Comment (4) above. (Pages 12, 13, 14, in blue.)

Comment (3) Vaccine duration is a somewhat vague term, especially since the correlates of immunity have not been fully defined for RSV, and natural infection does not necessarily confer protection from reinfection.
Response: This isn't as important now, although we will note that it is a well-defined term mathematically, even if that is an approximation to a more fuzzy concept in reality. We have added a definition. (Pages 3–4)

Comment (4) The authors should cite other, already licensed vaccines that are in use where duration is more important than vaccine coverage.
Response: We have changed the focus away from this, although we did find that this is true for both pertussis and HPV.

Comment (5) The endpoints of most RSV clinical trials are not sterilizing immunity, but a reduction in RSV-associated hospitalizations. The authors should consider incorporating this endpoint into their model or at least discuss this point.
Response: This is a good point that is worth mentioning. We have added a paragraph to the discussion addressing this. (Page 17)

In summary, we feel that these revisions have addressed all the points raised by the reviewers and hope that the manuscript is now acceptable.

Yours sincerely,

Alexandra Hogan, Geoffry Mercer and Robert Smith?