Smith et al. have extended an existing model of seasonal transmission of viruses like respiratory syncytial virus (RSV) to include protection by vaccinations that are currently under development. The authors determine the strength and frequency of vaccination that will control but not eradicate RSV. The vaccine waning rate is highlighted as a critical factor, more important than coverage for reduction of RSV prevalence. In other words, duration of protection will be critical for protection of the population.

The authors describe current efforts at vaccine development as "focused on the development of particle-based and subunit vaccines (p.2, ¾ 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.

AH: This is a bit picky, but okay! We could change 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

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.

AH: This comment relates to the comment directly below, and also to the first comment by reviewer 2. It is a bit problematic – there are a number of issues with vaccinating newborn children, and a vaccine would not be given immediately at birth even if this was a likely strategy. My suggestion is that we change our focus to maternal vaccination, as this would have the same modelling outcome.

"…a vaccine strategy for RSV where a fixed proportion of individuals entering the model are temporarily immune to infection. This reflects the situation where pregnant women are vaccinated in the third trimester of pregnancy, generating protective maternal antibodies that are transferred transplacentally to the unborn infant, conferring protection from RSV infection in the first few months of life."

It's important to note that there is some (poorly understood) existing level of maternal antibodies that protect some unknown proportion of infants from RSV in their first few months of life (perhaps up to three months). Some other models have accounted for this existing protection, so it would be a limitation in our modelling approach.

Vaccination of infants as soon as they are born is seldom successful for any pathogen because the infant's 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.

Note that we are actually doing both: the first (non-impulsive) model is the first, but the second model considers the latter.

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 1960's 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.

AH: I agree that this is a bit tricky as a vaccine is unlikely to provide protection for a longer duration than 6 to 8 months.

RS?: Rerun simulations for 2 years, with 10 as optimistic scenario (i.e., not 70 years). So \omega=0.5 as a baseline.

--> Better results. r=0 --> 7%, r=0.5 --> 2%, r=0.75 --> 0%

p.1, author list. Why is Robert J. Smith followed by a "?" ?

AH: I'm sure you will be happy to explain

p.18, l.10. vaccination-induced

AH: Yes, fine to change.

p.18, l.20.outcome than coverage

AH: Yes, fine to change.

The manuscript submitted by Smith, Hogan, and Mercer, the authors propose a new dynamic mathematical model to test the effect of a putative new RSV vaccine on disease burden. The authors find that using their model, vaccine duration is more important than vaccine coverage.

Considering the significant effort being put forth in RSV vaccine development currently, the research questions examined in this manuscript is extremely important and relevant. The authors use an innovated approach to address the question of potential vaccine efficacy in a way that is not biased towards the actual vaccine. The conclusions from this model indicate that vaccine coverage would not be as important as duration of vaccine efficacy. In design of this model, like any other mathematical model, the authors had to make some assumptions, which may or may not be true or relevant when an actual vaccine is introduced. As is such, the authors need to address these assumptions, along with some other details as listed below.

There are some issues that the authors need to address.

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.

AH: See response to reviewer 1 comment above.

Note that we are examining both.

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.

RS?: Reduce \omega as per above.

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.

RS?: Define waning and note this in discussion. Not as important now?

The authors should cite other, already licensed vaccines that are in use where duration is more important than vaccine coverage.

Pertussis

http://journals.lww.com/pidj/fulltext/2005/05001/duration_against_pertussis_after.11.aspx?trendmd-shared=0

http://jid.oxfordjournals.org/content/186/3/415.short

HPV

http://jid.oxfordjournals.org/content/204/3/372.short (?)

https://www.researchgate.net/profile/Elamin_Elbasha/publication/6435961_Model_for_Assessing_Human_Papillomavirus_Vaccination_Strategies/links/02e7e5187abe5cb062000000.pdf (Page 33)

http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0030138

(Not as important now?)

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.

AH: This is a good point and worth mentioning in the discussion section. Our model is a general model that is not applied to a specific population, and different populations have very different hospitalization rates for RSV, therefore we did not incorporate this endpoint in our research, but our models could certainly be extended to estimate the reduction in RSV hospitalizations for specific regions. I've included something along these lines in the discussion section but it needs a some wordsmithing!