Reviewer's report

Title: Evaluating human papillomavirus vaccination programs in Canada: should provincial healthcare pay for voluntary adult vaccination?

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Reviewer: Chris Bauch

Reviewer's report:

General

This manuscript develops a mathematical model of HPV vaccination that studies the effects of “catch-up” vaccination in adults. The model is of the classical deterministic compartmental type that allocates individuals into several mutually exclusive categories. The analysis indicates that HPV eradication would be possible with a programme that vaccinates children if efficacy, immunogenicity, and coverage were very high. However, surprisingly, vaccinating even a relatively modest proportion of adults would make eradication disproportionately easier to accomplish, and hence may make sense from the public health perspective. The paper is well-written, with relevant and up-to-date background research. Catch-up vaccination has not been approved, but this may help inform that decision-making process. Since vaccination programmes for HPV have recently been introduced in many provinces, I think this paper will be of significant interest to many researchers and should be accepted for publication in BMC Public Health, subject to revisions.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. I think the interpretation of the results needs to be rephrased. As currently written, the manuscript says that eradication of HPV is possible (and this presumably refers to all HPV types). However, since the vaccine only targets types 16/18 that cause 70% of cervical cancer cases (as the authors point out), and since cross-protection against other high-risk oncogenic types from this vaccine is limited, it is simply not possible to eradicate the other high-risk oncogenic types. At best, types 16/18 could be eliminated (but see also point #2 below). The manuscript needs to be revised in light of this distinction.

2. It might be difficult even to eradicate types 16/18. HPV is very prevalent and, in a situation of high Canadian vaccine coverage, would be constantly re-introduced from other populations with lower vaccine coverage. This should be discussed in the Discussion section.

3. The authors do an excellent job of discussing the strengths and limitations of the model in the Discussion section. I think it is important to discuss a few other...
limitations that would help readers understand the generalizability of the results: (1) the model does not include stochasticity, which would make eradication more likely due to the possibility of stochastic fade-out...deterministic models always over-predict the time to extinction and probability of extinction relative to their stochastic counterparts; (2) the model does not include age structure, which again can influence predictions significantly, since sexual-mixing patterns tend to be highly age-dependent, and since any type of heterogeneity tends to slow down transmission dynamics relative to the homogeneously-mixing case. The present model implicitly assumes that a 50-year-old man is as likely to have sex with a 25-year-old women as with a 50-year-old women, which changes both HPV transmission patterns as well as the impacts of vaccination, (3) the model does not include type structure (see also point #1 above) and in particular the possibility of replacement effects, ecological effects, and other types of type interactions that have been discussed in the HPV literature. I do not know whether factors (1) and (2) will qualitatively change the authors’ predictions, but they might, and hence these limitations should be discussed. Certainly, factor (3) changes the interpretation of the model (see Comment #1 above).

4. How do the model predictions depend on the parameter values used? I cannot be sure, since not all parameter values are listed (see comment #15 below). But, what if one were to assume a smaller differential in the man-to-woman versus woman-to-man transmission probabilities, for instance? Parameter values are always uncertain, and there should either be a univariate sensitivity analysis, or a discussion of the uncertainties in the Discussion.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Abstract: more details on the methodology should be given in the Methods section.

2. Page 2, start of third paragraph. Why do the authors suggest that vaccination is the best approach toward preventing cervical cancer? Innumerable cervical cancer cases have been prevented for decades using a simple, inexpensive technology: the Pap smear. The best approach to preventing cervical cancer is probably some combination of both approaches. I am sure the authors did not mean to say that screening is a worse strategy than vaccination (it may very well be, but this claim would have to be supported), but this should be clarified.

3. Page 2, second paragraph: both Merck and GSK vaccines are past the development stage. The Merck vaccine is already licensed in Canada and the GSK vaccine is up for a licensing decision in Canada. I would simply say there exist two types of vaccines.

4. Page 2, first paragraph: I think the authors mean “Without condoms, the probability of infection per sex act is 90%...”, not that the incidence is 90%... incidence is number of cases per population unit per unit time...

5. Page 3: a fifth limitation is that the vaccine is not against all HPV types.
6. Page 3: Please include a brief qualitative description of the model at the start of the Results section. Also, please define the parameters in Equation 1 right after the equation, so the reader does not have to go to the appendix to find out what they mean.

7. Page 3: I suggest using epsilon for efficacy, not immunogenicity.

8. Page 3: I was confused by the statement that “women are only in the sexually active pool for 4 years, after which they cannot be vaccinated and so are no longer under consideration”. Certainly, they can still transmit the virus after this 4 years even if they cannot be vaccinated, and will not this influence the model predictions?

9. Page 5, first full paragraph: the authors discuss logistic issues with adult vaccination, but in fact, a vaccination programme for adults could be simply and effectively implemented by offering free vaccines at STD clinics! This would target the subpopulation responsible for most of the transmission of sexually-transmitted infections, and would catch them at a time when they have just fully realized the folly of unprotected sex and are more likely to seek out vaccination. Of course, a model of targeted vaccination would require separate compartments for high-risk individuals.

10. Page 6, first full paragraph: I would further explain what is meant by saying that adult vaccination is more efficient than childhood vaccination, or use different terminology. In some sense it is less efficient because it requires expensive physician office visits and compliance rates can be low. School-based vaccination is the cheapest and most efficient form of vaccination in the conventional sense of the term. Also, even in the sense defined by the authors, the efficiency can vary according to other factors like coverage in the respective groups (the conclusion may be reversed if adult vaccination coverage were high and one were considering the incremental benefits of additional moderate childhood vaccination).

11. Page 7: Regarding the parameter for the “leaving rate of children”. Where do they go? I think this is really just a death rate?

12. Page 7, second full paragraph: since the model is not age-structured and therefore there is no ‘age’ to speak of (except child versus adult), I do not understand how the authors can make the simplifying assumption that women are only having sex with men of a similar age. Please clarify…

13. Page 8, model equations: what is I_M?

14. Page 8, model equations: note that the mu*M term appears twice.

15. I would suggest adding a table with parameter values used, and their literature sources, for the base case(s). At present, only the parameter values for Figure 2 are presented, in the Figure 2 caption. These types of tables are of immense help to both readers and authors, in my experience.

16. Everywhere: note that the Section numbers are missing in the text.
Discretionary Revisions (which the author can choose to ignore)

1. Page 5, first full paragraph again: I am uncomfortable with the recommendation that voluntary adult vaccination be introduced, based only on the results of this study. The model has many limitations, and in any case, it is the job of bodies like the National Advisory Committee on Immunization to issue recommendations, not us modelers! Our job is to provide the analysis and the information for them to use in their deliberations, in my opinion.

2. I don’t think the title is the best descriptor for the paper. The discussion of whether or not provincial healthcare in Canada should “pay” for vaccination implies to most readers of these types of journals that the analysis is an economic one (which it is not). When I first read the title, I assumed incorrectly it was an economic analysis. Also, I'm not sure how specific the model really is to Canada. I would imagine that the parameter values selected would apply to a broad number of populations, whereas a Canadian-specific model would have various details that are specific to the Canadian situation. I suggest revising the title.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.