Author's response to reviews

Title: Is expanding HPV vaccination programs to include school-aged boys likely to be value-for-money? A cost-utility analysis in a country with an existing school-girl program

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Version: 3
Date: 25 February 2014

Author's response to reviews: see over
Dear Nathaniel Nazarenno,

Thank you very much for the opportunity to upgrade various aspects of this manuscript. We responded to your editorial comments and those by the reviewers, point by point, in the text below.

Editor's comment:

"The reviewers have raised some serious concerns regarding the manuscript, the implementation of the model and the conclusions drawn. In particular the authors need to do more to show that the adaptation of the Canadian model to the New Zealand context is valid. I agree with Johannes Berkhof that the main conclusion drawn, that male vaccination is not cost-effective in New Zealand, is too strong given the limitations of the modelling approach and the fact that non-cervical cancers and MSM have been ignored."

Our response: It is important to clarify that we actually did include a number of the non-cervical cancers associated with the highest burden of disease in our model (e.g. anal and oropharyngeal cancers). As noted in the paper, vaginal and penile cancers were excluded due to their small contribution to the HPV16/18-related cancer burden (<3%). Likewise RRP represents a small contribution to HPV-related disease.

While the HPV reduction estimates for our model were derived from Brisson et al.'s heterosexual model, we used population data (which includes men-who-have-sex-with-men [MSM]) on cancer and genital warts incidences as baseline model inputs. What we cannot do in the NZ setting, and do not pretend to do, is to fully model MSM separately and specifically; neither have most other models of male HPV vaccination. However, we did conduct a scenario analysis which removed the herd immunity cancer (i.e. anal and oropharyngeal) reduction benefits for males in the girls-only vaccination program (1G). We then compared these results with the benefits of adding boys to the vaccination program (1G+B) and included MSM-attributable warts and cancers in the disease incidence data that populates the model. That is, we compared [1G without any anal and oropharyngeal cancer benefits for males] with the 1G+B as per the main analysis. The results from this extreme scenario analysis (as it assumes all male and anal and oropharyngeal cancer among boys is due to homosexual contact among MSM) led to an ICER of $80,000, which is still far above a threshold willingness-to-pay of $45,000 per HALY gained (using the GDP per capita threshold). This scenario analysis is now included at the bottom on Table 4 (which could be moved to the text, if the Editor or production team prefers).

It is important to not lose sight of the fact that the infectious disease modelling is just one component of this cost-effectiveness analysis. Please note that other researchers have used a similar population model approach to answer similar research questions to ours (Chesson, H., et al., The cost-effectiveness of male HPV vaccination in the United States. Vaccine, 2011. 29(46): p. 8443-8450).

In our Supplementary materials (Supplementary Figure 1), we now provide a ‘tornado plot’ to show what input parameter uncertainty (e.g. the uncertainty about future HPV prevalence reduction) contributes the most uncertainty in the model outputs of interest – namely the ICER comparing interventions ‘1G+B’ to ‘1G’ (adding boys vaccination
to the current girls-only program). The concerns related to our use of a population model and relying on estimates from the Canadian HPV transmission model translate to this input parameter: marginal gain in HPV reduction by adding boys to a girls-only vaccination program. Even if we assume the most favorable HPV reduction for adding boys (i.e. the 97.5\textsuperscript{th} percentile about the uncertainty distribution of HPV prevalence reduction), the ICER still remains >$75,000 for adding boys to the current girls-only program. We note that we have specified ‘generous’ uncertainty about this HPV prevalence reduction. Thus, it is reasonable to be fairly confident that uncertainty about the marginal impact on HPV prevalence from vaccinating boys (over and above girls), due to underlying uncertainty in transferring Brisson et al parameters derived in Canada to New Zealand, does not seriously challenge the conclusion that vaccinating boys is unlikely to be cost-effective in the New Zealand setting (other variables held constant). In addition, please refer to our responses below related to the comparability of sexual behavior between Canada and NZ.

Nevertheless, we now provide modifications to the text in the discussion and conclusion to better justify the case being made (while also emphasizing that the threshold around cost-effectiveness is that for New Zealand – and other countries could apply different thresholds). We also strengthen the conclusion around these results favoring greater policy-maker attention to first improve HPV coverage for girls (at least in countries with relatively low coverage as in New Zealand).

Reviewer 1 Comments:
The authors present a model-based cost-effectiveness evaluation of the incremental cost-effectiveness of including boy in an HPV vaccination programme. Such an extension is found not to be cost-effective unless the vaccine price is substantially below current HPV vaccine prices in New Zealand (and indeed anywhere in the world).

Major compulsory revisions
1. The core of the analysis is based on imputing the reduction in HPV prevalence from a transmission dynamic Canadian model to the current Markov model, interpolating between results at different coverage levels presented in the Canadian paper.
   (i) Could more be done to convince readers that the two populations are similar enough to do this kind of imputation – e.g. comparing HPV prevalence, cervical cancer incidence and/or sexual behaviour in the two settings?

Our response: We suspect that a direct head to head comparison of cervical cancer rates between Canada and New Zealand is of limited value – since the vast majority of plausible causal pathways will have HPV as a necessary component cause (i.e., as per Rothman causal pies). The incidence of cancers will vary between countries, due to a suite of factors (including smoking prevalence and use of screening programs). Indeed, specifically for cervical cancer incidence, screening is a major influence. Although New Zealand and Canada recommendations are similar (e.g. 3-yearly screening), Canadian screening is organized at a provincial level and the timing of the establishment of these programs, recommendations and coverage rates vary between provinces.
While data on adolescent sexual behavior are sparse, age of sexual debut are similar between Canada and NZ. A longitudinal cohort in NZ indicates that roughly 30% of participants were sexually active before the age of 16 years (Ramrakha S, Bell ML, Paul C, Dickson N, Moffitt TE, Caspi A, Childhood Behavior Problems Linked to Sexual Risk Taking in Young Adulthood: A Birth Cohort Study, Journal of the American Academy of Child & Adolescent Psychiatry, Volume 46, Issue 10, October 2007, Pages 1272-1279). In comparison, a study in Canada indicated that about 40% of 16-year-olds had sexual intercourse (Boyce, W. Sexual Health of Canadian Youth: Findings from the Canadian Youth, Sexual Health and HIV/AIDS Study. Canadian Journal Of Human Sexuality 2006 ,15(2), 59). Indeed, other research has concluded that timing and levels of sexual activity are quite similar across many wealthy countries (Darroch JE, Frost JJ, Singh S, Teenage Sexual and Reproductive Behavior in Developed Countries, Guttmacher Institute, 2001).

Likewise, incidence of genital warts peak in the same age groups in both countries. Over 50% (1252/2469) of the reported cases of genital warts in New Zealand in 2011 were those aged less than 25 years (The Institute of Environmental Science and Research Ltd., Sexually Transmitted Infections in New Zealand: Annual Surveillance Report 2011, Porirua, New Zealand). In Canada, 2006 data showed that the incidence of genital warts was greatest in women under 25 years (3.4/1000 population aged 20-24 years), followed by and 3.0/population among men aged 25-29 years (Marra F, Ogilvie G, Colley L et al. Epidemiology and costs associated with genital warts in Canada. Sex Transm Infect. 2009 04;85:111-5).

Again, it is important to remember that our input parameter uncertainty analysis (i.e. the tornado plot in the supplementary materials) indicates that the ICER for the marginal gain in HPV reduction by adding boys to a girls-only vaccination program, is not lower than $75,000, even with specified ‘generous’ uncertainty about this HPV seroprevalence reduction. It is reasonable to be fairly confident that uncertainty about the marginal impact on HPV seroprevalence does not seriously challenge the conclusion that vaccinating boys is unlikely to be cost-effective in the New Zealand setting (other variables held constant).

(ii) Another problem with this is not the change in setting but the move from a population model to a cohort model. This necessitates taking predicted long-term HPV prevalence (i.e. 70 years after vaccination begins; page 8 of the manuscript in submission to Vaccine) from the Canadian model and assuming that this equilibrium applies to the first (and only) vaccinated cohort in the New Zealand model. It isn’t clear that this is valid since the Brisson paper indicates that it takes 20-30 years for HPV prevalence to reach a steady state. The authors argue that this is less important because the cohort has decades before cancer onset, but actually it is the time to HPV acquisition rather than cancer onset that matters, and the peak years of HPV acquisition are likely to be around 10-15 years after vaccination. Hence the first vaccinated cohort may have a very different risk of HPV acquisition from the cohort vaccinated 70 years after the programme starts. It isn’t clear how this would change results: the indirect benefit of vaccination would decrease if the steady state assumption is not used, but this would have two effects in opposite directions: (i) female vaccination would have less impact on disease in males, so male vaccination may look more attractive, (ii) male vaccination would have less impact on disease in general, so male vaccination may look less attractive.
Our response: It is true that the Brisson paper indicates that it takes 20-30 years for HPV prevalence to reach a steady state. However, the largest reductions in HPV prevalence occur in the first few years (see Smith 2011, Smith 2007). For example, in Smith 2007, HPV incidence was predicted to drop by 50% within a few years of the vaccination program.

Also, thank you to the referee; Yes, we should talk more in terms of time to HPV exposure/acquisition, than to cancer incidence. Still, we stand by the general robustness of our modelling. Our model estimates likely health impacts, cost and cost-effectiveness for cohorts of 12 year olds one to three decades into the future after the first cohort is vaccinated. We stand by this as the baseline model for the following reasons, which we now outline in the Discussion section of the manuscript:

- It does model equilibrium
- Even for the first cohort vaccinated, they will still enjoy:
  - the benefits of direct immunity (i.e. the majority of the benefit from 16/18 as herd immunity is less notable, and much of benefit from 6/11 which has greater herd immunity)
  - the benefit of herd immunity from vaccination of their immediate age contemporaries and vaccination of younger cohorts (although it will be less herd immunity than in the future/equilibrium due to less herd immunity, and increased circulating HPV, for sexual contacts with older cohorts)
  - the benefit of some herd immunity from some older cohorts included in the catch-up program (girls up to nine years older than the modelled cohorts i.e., born in 1990 or later were offered vaccination with achieved three-dose coverage in the range 37-54%), although this will be less than that achieved at equilibrium
  - a ‘lead time’ benefit, i.e. by being vaccinated at age 12 and assuming modal age of debutant sexual activity of (say) 15-18, and maximum period of multiple sexual partners from (say) 16 to 30, then the actual HPV DNA prevalence the first 12 year old cohort will be exposed to is already starting to benefit from herd immunity.

(iii) Have the authors tried contacting the Brisson group for the full posterior probability distributions from their model? This would produce a more robust fit than fitting separate functions to the median and endpoints of the uncertainty interval.

Our response: Yes, we contacted the Brisson group (and have met personally with Mark Brisson at a conference). Unfortunately he reported that they were unable to process such a request due to staff changeover and difficulty this caused for relevant data retrieval.

2. Given that the conclusion of the article is that male vaccination is unlikely to be cost-effective, it doesn’t seem appropriate to make assumptions that bias the results against male vaccination eg. ignoring vaginal and penile cancers, RRPs and MSMs. Even if little data are available, some simple assumptions could be made (eg. rescaling figures on disease burden from other countries, assuming no herd immunity from female vaccination in MSMs).
**Our response:** Please see our response to the Editor above.

3. On page 6, it is mentioned that lack of local data prevented building a dynamic model. What kind of data these that were lacking?

**Our response:** Unfortunately, New Zealand (like a number of other developed countries) has not funded sexual health surveys. Therefore sexual behavior parameters are not precisely known for this country and have to be inferred from levels of teenage fertility, abortion service data, and prevalence of sexually transmitted infections. Nevertheless, such behaviors are reasonably similar to those for Canada (see the response to Reviewer 1, Major compulsory revisions #1 above for more detail).

**Minor compulsory revisions**

1. For the benefit of international readers, it would be helpful to know the threshold in New Zealand for deciding whether an intervention is cost-effective (even if only an informal, approximate guess can be made).

   **Our response:** In the text, we note, “Because there is no universally accepted threshold in New Zealand for describing interventions as being “cost-effective” or not, we relied on the WHO definition (work by “WHO Choice”) and used a nominal GDP per capita of NZ$45,000 in 2011 (US$29,600) as being such a threshold.” This threshold is also in the Abstract so as to help put the results in context.

2. On page 14, it should be made clear that this is the incremental amount per 12-year old girl in the relevant age cohort not per vaccinated girl (if this is indeed the case).

   **Our response:** The total costs and HALYs presented in Table 3 (on page 14) are for each individual 12-year-old in the cohort (regardless of gender or vaccination status). But to make this clearer we have added extra wording to the table (i.e. that HALYs gained are regardless of vaccination status).

3. It would be useful to present the threshold price (purchase + administration) at which the different options will become cost-effective. This could include the possibility that vaccines can be purchased under a national tender for males at a cheaper price compared to for females.

   **Our response:** Such a threshold analysis is now included as Figure 4. We also already include a variety of cost scenarios related to halving vaccine price, using the GAVI price and using a lower administrative cost (based on alternative NZ costing data). So for adding the vaccination of boys to the intensified program for girls, this particular intervention would only become cost-effective using the NZ threshold of GDP per capita ($45,000) when vaccine/administration is $104 or lower per dose (Figure 4) and in the scenario for $NZ 1 dose combined with low delivery costs at $19 per dose (Table 3).
Reviewer 2 Comments:

Major Compulsory Revisions
1. The main conclusion of the analysis (male HPV vaccination is not cost-effective) is much too strong given the weak level of evidence provided by a model. The model presented by the authors, in particular, has some shortcomings that are not easily resolved and therefore the conclusion should be toned down. Shortcomings are:
   a. The evidence against male vaccination is mainly based on a Canadian transmission model. According to the Canadian model (Table 1), vaccinating girls gives nearly equal protection for females and males, regardless the level of coverage among girls (1G and 2G). A direct consequence of this prediction is that vaccinating boys hardly provides any additional protection; they are already indirectly protected. However, it is well known that the level of herd immunity strongly depends on the sexual heterogeneity which may be different in Canada and NZ.

   Our response: It is unclear what is meant by ‘the sexual heterogeneity which may be different in Canada and NZ’. If this means heterogeneity in number of partners and age at debut between males and females, the data are sparse – but we identified some parallel indicators of sexual behaviors in the response to Reviewer 1 (and parallels found in many Western countries).

   Since these populations are probably fairly similar, it seems unlikely that our conclusions would change. Still, we modified some of the text in the abstract, discussion and conclusion to provide more explanation and context around the cost-effectiveness issue for the New Zealand setting.

Furthermore, different transmission models may predict different levels of herd immunity in particular when the vaccine uptake among girls is low; compare for instance the Canadian model with an early model by Garnett and colleagues in which the impact of vaccinating girls on the HPV prevalence in males was low if the uptake among girls was low.


   However, importantly, results will differ between models due to different model structure, parameterization of the model, etc.

b. Oropharyngeal cancer and in particular anal cancer are more prevalent in MSM than in the heterosexual population. The former group is not included in the model which may lead to an underestimation of the impact of male vaccination.

   Our response: Please see response above to the Editor.
2. The model description is very limited. A complete list of Markov transition parameters, utility measures, survival probabilities etc. etc. should be added to the Supplementary material. It should also be shown that the model is calibrated to current NZ registry data.

*Our response:* Please note that details of model parameters were included in a detailed Supplementary Table 1. The cancer input rates were those predicted for 2011 (and projected to 2026 for cervical and oropharyngeal) based on regressions on New Zealand Cancer Registry data (Blakely, Costilla et al. 2012). Therefore, when the model was run without intervention effects, the model produced the same disease data as the input dataset.

We also included a diagram of the model structure as Figure 1.

3. Vaccine prices decrease rapidly. The cost paid per dose in the NZ program is much higher than in several European countries with comparable GDP per capita levels. The administrative costs ($141 per dose) are five to tenfold higher than in other countries with an immunization program and deserves explanation. At much lower cost level for both vaccine + administration, the picture will look different. The authors consider administration costs of NZ $19 (per dose?) as very low but for other countries such figures have been reported.

*Our response:* We have added text in the discussion around study limitations to explain that our costing data were based on official Ministry of Health data which include funding to cover program management (a component which doesn’t seem to typically be included in the ‘administration costs’ of other studies). Nevertheless, we did explore lower costs in a number of scenario analyses (for both administration costs and vaccine prices and performed a threshold analysis – as thoughtfully suggested by a Reviewer). For example, we explored vaccine cost as low as $1/dose and administration costs as low at $19/dose. We also now note the change in purchase arrangements from the Ministry to a state-owned organization (Pharmac) that will probably negotiate much better prices in the future.

4. To compare HPV male vaccination with interventions in tobacco control, alcohol control and diet (policy implications) is somewhat tendentious. It is not the idea of gender inequality in health that worries policy makers but the idea of gender inequality in offering health prevention measures. Furthermore, some policy makers think that uptake among girls will be higher in a gender-neutral program than in a female-only program.

*Our response:* Thank you for this thoughtful comment. We have now dropped this comparison and expanded other aspects of the discussion (e.g. the focus on improving vaccination for girls first, and explaining the spillover benefits for boys from this approach).

5. The authors claim that the study fills a gap in the knowledge base for NZ which might come under public pressure to "follow Australia". I got the impression the cervical cancer disease model is essentially an Australian model so it seems that the current article also serves as a knowledge base for Australia that should rethink their male vaccination policy. Either the authors leave out the NZ – AUS comparison or better explain the main reason for Australia to adopt male vaccination.
**Our response:** We have now removed the comparison with Australia in the paper.

**Final comments:** We thank the editor and the reviewers for thoughtful comments that have helped us to further improve the manuscript through clarification and justification.