Author's response to reviews

Title: Evidence of effective delivery of the human papillomavirus (HPV) vaccine through a publicly funded, school-based program: The Ontario Grade 8 HPV Vaccine Cohort Study

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Version: 2
Date: 1 August 2014

Author's response to reviews: see over
RESPONSE TO REVIEWERS’ COMMENTS AND SUGGESTIONS

We thank the reviewers for their insightful comments and suggestions. We believe our manuscript has been significantly improved by the changes we made in response to these reviews. Below is a description of how we addressed each issue in our revised manuscript.

Reviewer 1

Major Compulsory Revisions

http://www.ncbi.nlm.nih.gov/pubmed/24094062 - this paper should be cited and used as a comparison for the work detailed. By omitting this, you omit very important work, which is comparable to the present study. A number of statements will require amendment since they are clearly inaccurate. The uptake for all 3 doses in Scotland is higher (<90%) than detailed herein and was published prior to this manuscript - however, it could be revised to state that it's the first study to look at school-based vaccine compliance with respect to Gardasil. I think a more comprehensive literature review is required as important papers are missing.

We thank the reviewer for providing this reference. We have included it in the discussion with reference to the fact that Ontario should draw on the strategies implemented by other successful jurisdiction (such as Scotland) in order to increase overall HPV vaccine coverage in its population (page 15, end of second paragraph). As suggested, we amended our statement in the discussion to clarify that this is the first study to look at school-based vaccine compliance with respect to the quadrivalent HPV vaccine, and that we report one of the highest levels of series completion.

Minor Essential Revisions

Please include the following papers in your introduction:

We appreciate that the reviewer provided us with these important references, which we felt offered the greatest value when added to the discussion section of this manuscript. To incorporate the study by Neuzil et al., we added the reference and argument that “Although there is evidence suggesting receiving doses using alternative schedules does not have a major impact on immunogenicity,” the clinical implications of receiving doses outside of the indicated dosing intervals should nonetheless be further investigated (page 15). Furthermore, as the study by Schmidt et al. reported series completion levels of only 42% among females, we included it as additional support that our study (which reports closer to 90%) reports one of the highest levels of series completion that has been reported to date (page 13).

Methods - what is meant by 'generally requires parental consent' - as this is policy, surely girls cannot be vaccinated unless there is parental or guardian consent. Please clarify.
We see how this statement is confusing. We said, “generally requires parental consent” because we know that although parental consent is sought, ultimately it is up to the healthcare provider to determine whether the girl is mature enough to provide her own consent. The latter is not publicized, but reflects the reality of HPV vaccination in Ontario. Rather than explain this nuance, which adds unnecessary confusion and/or word count, we deleted this portion of the sentence, as it is not important to the overall message/aims of this study. Accordingly, the sentence now reads, “Approximately 84,000 girls are eligible for Ontario’s Grade 8 HPV vaccination program each year, but HPV vaccination is optional.” (page 6).

Please clarify whether $450 CAD is for one dose or 3 doses of vaccine.

We have clarified that this amount is for three doses of the vaccine (page 7).

Please check spelling of diphtheria on page 6.

Thank you. We have corrected the spelling error.

Discussion - presume 'series' and not 'serious'.

Thank you. We have corrected this oversight.

Please revise the discussion with respect to the Potts study mentioned above. How is adverse event monitoring maintained in Ontario for children who receive >3 doses of vaccine?

As mentioned above, we revised the discussion to include the study by Potts et al.

There is no adverse monitoring in place for children in Ontario who receive >3 doses of the vaccine. It is for that reason that we provided the recommendation that “the clinical impact of such potential medical errors must be investigated.” (page 14).

The H1N1 pandemic did not affect HPV vaccine uptake in Scotland – compare with your own data and explore why there may be differences.

We believe the reviewer is referring to our statement “Despite the promising results presented here, it is important to note that more than half of girls eligible for free HPV vaccination in the 2009/10 program year received their second dose later than recommended. These results are not surprising given the H1N1 outbreak and the corresponding immunization campaign that began in the fall of 2009 that was, understandably, prioritized over HPV vaccination programs.”

To clarify, that statement referred to a timing issue, not to decreased uptake; girls still received their second dose, just later than recommended. In fact, our findings seem to be consistent with those observed in Scotland, as evidenced by the paper by Sinka et al., which reported, “In Autumn 2009 (year 2), cases of pandemic H1N1 influenza [in Scotland] peaked between the scheduled first and second HPV dose. Vaccine uptake showed a temporary decline at this time, possibly related to sickness and absenteeism.” In that sense, both Ontario and Scotland were
similarly affected by the H1N1 pandemic in that there was no meaningful decline in overall use of the vaccine in 2009, but there were delays in administration of the second dose. In does however, seem the reason for the delays are different between these jurisdictions, as Sinka et al. report school absenteeism as a possible explanation, whereas we know in Ontario the HPV immunization clinics were delayed so that all available personnel resources could go toward the H1N1 immunization clinics. Therefore, we added a statement to the paragraph stating, “Another possible explanation for the delays in receipt may be increased school absenteeism due to illness during that time, as was believed to be the case in Scotland’s school-based program.”

Why in America where vaccine uptake is lower are they seeing positive benefits e.g. Kahn et al., 2012, Pediatrics, 130, p. 249? Discuss in context of your statement that lower uptake in Canada than expected may not see as much of an impact as expected.

We believe the reviewer is referring to our statement: “Unfortunately, despite high HPV vaccine series completion and compliance, such low coverage suggests this vaccination program may have a considerably smaller impact on population health than anticipated.” We would like to highlight that this sentence does not refer to vaccine efficacy, rather to program effectiveness (i.e., the population-level impact of the vaccination program). We have no reason to believe coverage will impact efficacy of the vaccine and certainly did not mean to imply otherwise. Indeed, the study by Kahn et al. (and other similar studies) reports on vaccine efficacy/effectiveness; as such, vaccine coverage would have no impact on these estimates. Since we believe our initial statement clearly indicated we were referring to program effectiveness and population-level impact, we have not altered the text. However, please let us know if we have misunderstood the reviewer’s comment in any way, and we would be happy to rectify the discussion accordingly.

Figures 2 and 3 - please use hatched bars vs. solid bars since it is hard to compare the different variables.

We regret that these figures were unclear. We have modified them as requested.

Please note that, based a couple of the comments above, we were concerned the distinction between series completion (which is based on receipt of all three doses) and compliance (which is based on proper timing of each dose) was not entirely clear to the reviewer. To avoid future confusion, we changed some of the language from “compliance” to “on-time dosing”.

Reviewer 2

Major compulsory revisions

1. Data is available on only 21 health units in Ontario, out of a possible 36. Please provide details of how these 21 included areas (40% of eligible girls in Ontario) contrast with the 15 health units not included (the remaining 60%). How representative are the 40%? Ontario is a vast province - geographically where are the 21 units located? Are there differences between included and non-included health units in terms of socio-economics, geographical distance to deliver vaccine supplies, cultural composition, or urban/rural/remote characteristics etc. that would allow a better understanding of the included population?

We thank the reviewer for pointing out this omission. We have included a figure (Figure 1) indicating the location and name of all health units that were included and excluded from the analyses. This figure is referenced on page 12. We also indicated that “geographically, [these girls] were representative of all girls eligible for publicly funded qHPV vaccination in Ontario” (page 12) to indicate the regions included represent socially divers populations of both urban and rural areas within Ontario. In addition, we added a statement indicating, “Although all 36 health units were recruited for this study at the same time, due to various administrative delays, the data for the remaining 15 health units were not yet available” (page 7-8) to clarify that inclusion/exclusion was simply a result of time constraints.

2. Please provide information on how health units relate to school areas/educational regions in Ontario. Given the HPV vaccine does were delivered through schools, it would be useful to know if possible whether the factors related to lower levels of compliance with the timing of doses, or differences in uptake, were related to school regions.

We respectfully disagree that adding information on school areas would improve this paper. In particular, since health units (not schools) administer the program and deliver the vaccine, we believe it is the pertinent unit of discussion in this paper. We do, however, completely agree that it would be useful to identify the predictors of series initiation, completion, and on-time dosing; however, these questions are well beyond the scope of this study.

3. Demographic data is used to describe baseline characteristics of the girls who were vaccinated, but are not used to illuminate which of these demographic factors - if any - are associated with high coverage and compliance with dosing timing.

As stated above, we completely agree that a study on the predictors of HPV vaccine use is of great interest; however, it is a completely different research question and is beyond the scope of this study. In fact, we have a study on individual- and regional-level predictors of HPV vaccine uptake that is currently also under peer review at BMC Public Health. A similar study on predictors of series completion and on-dose timing is also underway. However, based on the reviewer’s comment, we have added a statement to the discussion to highlight the importance of these study questions: “Nevertheless, the predictors of both series completion and on-time dosing should be investigated to further improve proper receipt of this vaccine.” (page 14).

We thank the reviewer for providing this reference. We have added it, as well as its partner paper (Potts et al. 2013, provided by Reviewer 1) to the discussion section of this manuscript to suggest that Ontario should draw on the strategies implemented by other successful jurisdictions (such as Scotland) in order to increase overall HPV vaccine coverage in its population (page 15, top). We have also cited it in references to Scotland’s experience with the H1N1 outbreak (page 15, bottom).

Minor essential revisions

1. Please provide further details of the approvals required to link databases of patient-sensitive data. Although ethics approvals were obtained from Queen’s University Health Sciences Ethics Board and Sunnybrook Health Sciences Centre’s Ethics Review Board, what approvals were in place to cover linkage of the databases?

As suggested, we added the following statement to the description of data sources, when the notion of data transfers & linkage is first introduced: “In Ontario, the transfer, linkage, and encryption of health data is permitted under section 45.1 of the Personal Health Information Protection Act (2004) and was executed under data sharing agreements between each participating health unit and ICES.”

Discretionary revisions

1. It would be a far stronger paper if the authors made use of the demographic data they have available to describe the approx. 50% of girls within their study sample who did NOT initiate HPV vaccination during the study period, and compare their characteristics with those of the HPV vaccine cohort. Maybe this is another paper, but it would be good to have a better understanding of which girls are taking up the vaccine and which are not.

We agree with the reviewer that this is an interesting concept. However, as the reviewer acknowledges, this is outside the scope of this manuscript and is indeed “another paper”. As previously mentioned, our study on that very topic is currently under peer review at BMC Public Health.

2. The authors have raised an issue of some importance (a concern that timely delivery of three dose HPV vaccine has decreased over time, particularly in a year where there are competing vaccination schedules). Clearer recommendations could be provided as to potential approaches to deal with this. This could include research and policy recommendations to better understand and to strengthen the processes that impact timely
We believe our statement in the discussion (page 15) provided a clear research recommendation: “the clinical implications of receiving doses outside of the recommended dosing intervals should be further investigated.” We do not believe we are in the position to make specific policy recommendations before this type of research is done. However, in the following paragraph we added a statement advising policy makers in Ontario to look to other successful programs (such as Scotland’s) for strategies on how to improve overall HPV vaccine program delivery.