Author's response to reviews

**Title:** Factors associated with uptake and series completion of the quadrivalent human papillomavirus vaccine in an Ontario cohort of Grade 8 girls

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**Author’s response to reviews:** see over
Response to Reviewers’ Comments and Suggestions

We thank the reviewers for their insightful comments and suggestions. We especially appreciated comments that helped us strengthen the rationale for this study and modify the terminology to better suit the journal’s audience. With respect to the latter, please note that the title of this manuscript was modified as a result. In all, we believe that our manuscript has been significantly improved by the changes we have made in response to the reviewers’ comments and suggestions. Below is a point-by-point description of how we have addressed these in our revised manuscript. As requested, the responses are followed by a list of authors’ contributions and competing interests.

Reviewer 1
*Since the original contribution of this paper is about its populational perspective and the use of administrative databases to assess factors related to health service utilization, I would have like to see, in the introduction section, a reason or an hypothesis about how this clinical information (such as past emergency visits or previous diagnoses) could influence vaccine uptake.

The introduction (lines 69-78) has been updated to provide justification for studying clinical information as potential predictors of HPV vaccine use.

*In the introduction section, reference 2 is unrelated to the topic.

The authors thank the reviewer for pointing out this mistake. We have replaced the original reference with the correct one.

Discretionary revisions

*Discussion section, end of 5th paragraph: need or needed?

This grammatical error has been corrected.

*Introduction section and results section: although it is mentioned that the decision to vaccinate is left to parents, the authors use the terms 'accept the HPV vaccine' or 'agreed to receive the first dose' when referring to girls.

We have clarified these statements (e.g., line 209) so that they refer to the parents rather than the girls.

Reviewer 2
*Thank you for the opportunity to review this manuscript. The paper describes factors associated with HPV vaccine initiation and dose completion in a cohort of Ontario girls. This is a well-written manuscript that makes use of a unique dataset that can link HPV vaccination behavior to receipt of other health care services, including other vaccines. The data distinguish this paper from many others that rely on self-report data to identify correlates of HPV vaccine coverage. However, it would be helpful to include a set of clearly stated hypotheses that drive the analysis of correlates of vaccination.

As previously mentioned, the introduction (lines 69-78) has been modified to provide justification for our analysis.

Introduction

*The authors note that higher HPV vaccine coverage is more cost-effective. Explain why, in what contexts, and in comparison to which other strategies.
Since the cost-effectiveness of this vaccine is not the focus of this paper, we did not elaborate on this issue. However, for the interested reader, we have added two references, one of which is Canadian-based and the other of which is a recent systematic review different cost-effective studies that have been done on the HPV vaccine.

*Briefly describe the sociodemographics and health care utilization of those living in KFL&A. Why is this a relevant region for study, and to which other areas might the findings be generalizable (or not)?

We had included information about the demographics of those living in KFL&A and the potential generalizability of our findings in the last paragraph of our discussion section. Based on the reviewer’s comment, we added quantitative details (e.g., median income) to allow for better assessment of generalizability to other jurisdictions (lines 365-368). In addition, we added a statement to the methods section (lines 149-151) indicating why we studied girls residing in KFL&A.

*What are the study hypotheses / research questions? Which factors would be expected to be associated with HPV vaccine initiation and completion in this region and why? Specifically, since this dataset allows for identification of health conditions and health care utilization, which of these were authors expecting to be associated with HPV vaccination and why?

As previously mentioned, the introduction (lines 69-78) has been modified to provide justification for our analysis.

Methods
*The term “non-adherers” suggests that those who have not completed the 3 dose vaccine series do not intend to do so. Please clarify how one can assess from the data if sufficient time has elapsed for completion of all three doses. Since some proportion of non-adherers have not yet had a chance to complete the series, another label for this group might be more appropriate.

We have clarified the extent of data we had to assess vaccine adherence in our methods (lines 102-103) and addressed the limitations associated with this in our discussion (lines 342-346).

*Other than their availability in the dataset, why were the covariates listed included?

This issue has been addressed in response to previous comments (lines 69-78). We also added further justification for the covariates selected to study medical history (lines 199-202)

Results
*This section is clearly written. Authors may wish to remind readers of the meaning of the income quintiles described in the text.

Because income quintiles have been described in the methods and the results tables 2 and 3, we opted not to include it here as well.

Discussion
*HPV vaccine coverage was lower in this region than in other regions, but not truly “low,” as the authors write.

Although this might be true outside the context of a publicly funded program, we made this statement in the context that (1) the Ministry of Health and public health providers were aiming for vaccine coverage to exceed 80% and actual coverage was less than 60% and (2) this level of
coverage is considerably lower than that of other school-based vaccination programs offered in our region and elsewhere in Ontario (e.g., MMR, Hepatitis B) and represents the lowest known level of HPV vaccine coverage in Canada. As a result, we believe it is “low”.

*Please describe the “advertising black out” for those unfamiliar with the media conditions in Ontario prior to HPV vaccine introduction.
We thank the reviewer for reminding us that this terminology might be out of context for readers who are unfamiliar with the Ontario system. This issue has been clarified (lines 300-302).

*What is “validated exposure” data?
We appreciate the reminder that the terminology was out of context. In response, we have changed, “validated exposure data” to “validated HPV vaccination data” (line 333).

*Results related to health conditions are not mentioned in the Discussion. What did the authors expect to find and how did findings compare to these expectations?
We agree with the reviewers that we observed some potentially interesting trends in these results but were originally uncomfortable drawing attention to these given the small numbers on which they were based and resulting wide confidence interval. We had instead chosen to address these findings only briefly in the discussion. In response to the reviewer’s comment, we have dedicated an entire paragraph (lines 310-325) to addressing these findings, while maintaining the limitation of lack of statistical power and the need to replicate our findings in a larger cohort.

*What is the unique contribution of this paper to the large literature on correlates of HPV vaccination? (There are many more studies from the US that are not cited here.)
We had addressed the unique contribution of this paper in the discussion, but perhaps not strongly enough. In response, we have modified the discussion (line 326-333).

*The limitations section appropriately mentions the absence of data on why vaccine coverage is lower among girls in this region.

*The conclusions could be more specific about the factors associated with vaccine initiation and completion.
We have modified the conclusion to more explicitly reflect our findings.

Reviewer 3
*Starting pages 4 an 5, the immunization record system is misnamed (i.e., there should be no ‘ing’) and its purpose incompletely and inaccurately misrepresented (e.g., page 11 last paragraph), as it is used to support both ISDA and DNA legislative requirements. This is accurately reflected in the table ending page 24, but not in the text. See:
http://www.health.gov.on.ca/english/providers/program/pubhealth/oph_standards/ophs/progstds/
http://www.health.gov.on.ca/english/providers/program/pubhealth/oph_standards/ophs/ophsproto
cols
The authors thank the reviewer for pointing out the typo with respect to the name of the immunization database. Furthermore, we have clarified that the database was originally designed to capture “immunization mandated under the Immunization of School Pupils Act (1982)” and clarified IRIS’s role in capturing HPV vaccination data (lines 128-130).
also added one of the documents provided by the reviewer as a reference for the interested reader.

*The legislative requirements (use of term “mandatory”) of the ISPA are misrepresented; as well, the legislation is never named, nor are the specifics related to vaccines under the schedule under the Act. This is an important contextual piece for a reader unfamiliar with Ontario public health. Our response to the previous comment (i.e., clarifying role of IRIS and adding the reference) addresses this comment as well.

*I believe that both ‘grade’ and ‘class’ are variables in IRIS, and not merely date of birth. The authors should check whether these were not used in the analysis because they were incomplete, or whether these variables were not requested.

We had access to the complete contents of the KFL&A IRIS database. The only information required to enter vaccination data into IRIS is the child’s OHIP number (insurance coverage number), as well as the date and type of vaccination. As a result, other variables tend to be incomplete and inappropriate for use in research. While the variable ‘class’ is available in the ‘subject file’ of the database, it is not only incomplete but also represents a variable that changes over time. In other words, since class is only available at one time point per student, the information does not necessarily reflect the grade during which a girl is immunized against HPV. Unfortunately, grade at the time of individual immunizations is not available in the database. This has been clarified in the text (line 153).

Minor Essential Revisions

*With respect to the objectives, the term ‘factors associated with its use’ is somewhat misleading, as there was reliance on administrative data without attempts to establish factors by direct subject contact. We agree with the reviewer that our data sources did not capture all possible factors that could explain use of this vaccine (e.g., ethnicity). This point was previously described in terms of residual confounding in the discussion section. I would suggest using terms such as ‘correlates’ of use.

We thank the reviewer for her comment, but believe the term “correlates” does not accurately reflect our measure. However, if the reviewer’s comment reflects different use of terms in different fields, we would consider adjusting our terminology accordingly. However, in epidemiology, the term ‘correlates’ tends to be used when temporality is either absent or cannot be established (i.e., when measuring a correlation), and association is used when temporality can be established (i.e., when the value of one factor is dependent on the value of another factor). Since our design ensures temporality (i.e., factors studied precede vaccination), we believe the term “association” is more accurate.

*It would be useful in the study design section to outline why this design was chosen, e.g., why KFLA, whether the option of choosing a larger health unit or several of different types, or alternately a random sample of girls from the provincial IRIS data base that could have been linked to the same data sets and provided representative results for the Ontario population were considered.
Unfortunately, there is no provincial holding of the IRIS databases; each of the 36 health units is responsible for maintaining their own individual IRIS database. We have clarified the reasons for utilizing the KFL&A dataset in the manuscript based on a previous reviewer’s comment (lines 149-151).

*Terminology of ‘adherers’ and ‘non-adherers’ for those who completed the series and those who partially completed the series is less clear than using ‘series completion’ and perhaps terms such as ‘partial series completion – 1 dose’ and ‘partial series completion – 2 doses’.

We agree with the reviewer. The term “adherence” has been changed to “series completion” and “adherers” and “non-adherers” to “completers” and “non-completers”, respectively. In addition, we have indicated the number of doses (1 or 2) received.

* It would be useful if the authors could comment on whether neighbourhood incomes have been shown in Ontario or in this district to correlate with individual household incomes. It’s my understanding that in some areas, there is poor correlation.

The authors thank the reviewer for this important oversight. This issue has now been addressed in the discussion (lines 350-351).

*Similarly, are there validations available to indicate that health encounter data based on physician billings and hospital separations as used in this study are ‘indicators of health status’, as stated on the bottom of page 7? As well, with a larger proportion of the population accessing non-medical health services, this should be cited as a limitation of the data sources used or otherwise commented upon. Elsewhere in the paper the authors state that assembly of data from the administrative data bases constitutes the subject’s ‘medical history’. If this has been validated against a more complete set of records, this would be worth pointing out.

We have clarified in the methods section (line 117) that OHIP claims are not restricted to physicians and may include other types of service providers. In addition, as recommended by the reviewer, we acknowledged this as a limitation in the discussion (lines 348-349).

*Top of page 8: medical conditions of interest appear to have been focused on autoimmune disease and immune mediated disease, but no reason for this is stated nor is this grouping commented upon in the results section. If this was a focus of analysis it would be worth stating why, and providing specific results. As well, it would be worthwhile providing some additional explanation as to why and how these and other medical encounter data were expected to be associated with HPV vaccination. What was the hypothesis being explored here, especially in reference to the large number of diagnostic medical codes that were each analyzed for associations? The risk in such a ‘broad spectrum’ analysis is finding spurious associations, and I wonder if the authors had a hypothesis that they were testing here. It’s not clear.

We have further elucidated the rationale for these categories in the methods section (lines 199-202).

*In ‘Results’, 2nd sentence, specify the percent of the Ontario population studied i.e., 1.36%. In final sentence in same paragraph, should read: “based on our assumptions these girls were between 12.7 and 13.6 years…. as this was an artefact of the definition of the cohort, and not true assessment of age at the time of grade 8 entry, as is discussed in the final section of the paper.
We have specified the percent studied. Our assumption about age had been addressed at the beginning of the paragraph (“based on birth year”), however, we have adjusted the final sentence of that paragraph to more closely reflect our methods.

*Page 9, paragraph starting ‘After adjustment’, should read “with MMR” rather than “against MMR” as this is a vaccine name. Similarly, ‘vaccines’ needs to be inserted before ‘and were even more likely’.  
We thank the reviewer for pointing out this technical error. This statement has been revised (line 237) as have similarly errors (line 206, line 263).

*Top of page 10 discussion about urban/ rural: was there any attempt to correlate income to rurality as the results of this analysis appear to go in the opposite direction to income. This could be examined in logistic regression with multiple variables.  
We thank the reviewer for this suggestion. The results of the logistic regression were those of a multivariable regression, in which rurality and income were considered simultaneously. We also considered including an interaction term, but unfortunately the size of these two strata (i.e., non-completers and rurality) was too small to ensure sufficient statistical power.

*In last sentence of top paragraph, replace ‘from individual’ with ‘with ‘three types of’
This sentence has been modified (line 250).

*Bottom of page 10, suggest delete ‘where a girl need only be present to receive the vaccine’ as this is clearly not the only factor (i.e., presence in school) for HPV immunization.  
We have revised the paragraph, removing the wording from its original position (line 265) and placing it where we feel it is more accurate (line 278).

*Same paragraph and thought, it would be important to consider both intentional and unintentional non completion. While the variables examined may not have been sufficient to examine this, although these may be recorded in IRIS, the authors assume that non-completion for the series is unintentional because of lack of access to services. Given that our statement about potential lack of access was in the discussion section of our manuscript, we were merely hypothesising vis-à-vis possible explications for our findings especially in light of the evidence regarding school absenteeism and SES.

Hepatitis B vaccine was also assessed and is given in a series; was non completion of the hepatitis B vaccine series similarly correlated with income quintiles? Are data available from the school boards in KFLA or Ministry of Education related to school attendance by the correlates examined in this study in order to make the conclusions that the authors make?
Since Hepatitis B was not the focus of this study, we did not study its association within income quintiles.  
Unfortunately, records of school attendance at the individual-level are not available to researchers.

*Page 11, last paragraph: surveys have included both parental and girls’ attitudes.  
We feel parental surveys are more relevant to our study since the decision to vaccinate with the HPV vaccine is predominantly left to parents and guardians.
*Page 12, 3rd paragraph: suggest use of ‘correlates’ over ‘clinical predictors’ (which also appears on page 13) as the latter term is quite unclear in this context given that data used were entirely from administrative data bases. Sentence ‘While it also benefits from validated exposure data’ is unclear. In the final section of this paragraph, reference to errors based on assumptions of age and grade attendance; this can be quantified with data available from the school board(s) and/or Ministry of Education.

The first two points made by the reviewer have been previously addressed. As for the verification of age and grade, individual-level data is not available from the Ministry of Health.

*Top of page 13, second line, should read not ‘not born’ but …‘resided in Ontario throughout their lifetime’. We thank the reviewer this comment. The appropriate change has been made (line 248).

*In Conclusion suggest ‘will likely have’ can be substituted with ‘has’. We believe that since the potential health benefits and cost-effectiveness occur subsequent to vaccine acceptance, use of the future tense (“will likely have”) is more appropriate than present tense (“has”), especially since we don’t yet know if the latter is true. In 2nd sentence, replace ‘influence’ with ‘correlate with’ as influence suggests a causal relationship and this cannot be ascertained using the study design. In light of this comment, we have replaced “influenced” with “associated with” as this more accurately reflects our methods.

*The contact information for the first author appears to be a personal home address; this is not ideal and perhaps the contact should be an author (second or last) with a work address where follow up can be obtained if contact is established at future date. The address has been changed (line 22).

Discretionary Revisions

*Suggest that tables asterisk or otherwise flag (with S.S. for instance) significant ORs Tables 1, 2, and 3 have been modified accordingly.

*Figure 1 is not necessary as the numbers are provided in the text; as well, it’s displayed as a ‘flow diagram’ which is likely not appropriate given what’s being presented, i.e., that the group of girls assessed were about 1% of the Ontario population. We defer to the editor(s) for this decision.

*Regarding the titles of both a table and figure ‘patterns of use’ it would be clearer to state that these were HPV vaccine initiation and series completion rates.
We defer to the editor(s) for this decision.

Authors’ Contributions
Substantial contributions to conception and design: LM Smith, LE Levesque, P Brassard, J Kwong, S Deeks, A Ellis
Data acquisition: LM Smith & LE Levesque
Analysis and interpretation of data: LM Smith, LE Levesque, P Brassard
Draft of article: LM Smith
Critical revision for intellectual content: LM Smith, LE Levesque, P Brassard, J Kwong, S Deeks, A Ellis

Competing Interests
The authors have no competing interests to declare.