| **Article details: 2020-0239** | |
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| Title | Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada: retrospective cohort study |
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| **Reviewer 1** | Tracy Morton |
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| General comments (author response in bold) | This is a retrospective cohort study examining the safety of maternal Tdap immunization in Ontario during a 5-year period from 2012 to 2017. The key conclusion is that maternal immunization is safe, with no evidence of harm in the seven maternal and infant outcomes specified. Additionally, within four outcomes, there was a statistically significant reduction in adjusted relative risk. It is the second of these results that suggests there are methodological concerns about this study.<br><br>Comment #1: ABSTRACT and INTRODUCTION are clear and explain the Canadian landscape of maternal pertussis immunization. The Introduction is supported with adequate citations. The rationale for the study is clear.<br>**No response required.**<br><br>Comment #2: METHODS<br>-Study Design, Data sources<br>The study population is clearly defined and Figure 1 complements the text. Exclusion criteria are explained and reasonable. However, it is not clear is why stillbirths (n = 628) were excluded, a key outcome suggested by the GAIA project (Global Alignment of Immunization Safety Assessment in Pregnancy). Please explain.<br>**Thank you for raising this issue – we fully agree that stillbirth is a priority outcome and when we designed this study as part of our original CIHR grant application, it was our intent to include stillbirth as an outcome. However, we initially had some challenges with identifying stillbirth records in the databases at ICES and had put that analysis on hold. After further consultation with colleagues and senior epidemiologists at ICES, we have been able to resolve this issue and now include stillbirth as an outcome in this revised manuscript.**<br>**Since we initially used a denominator of live births in our original *CMAJ* submission, we had to re- compute propensity scores using the new denominator of all births (live births + stillbirths) and this denominator was used for analyses of stillbirth, preterm birth and obstetrical outcomes. We continue to use live births as the denominator for the analyses of neonatal outcomes. To avoid confusion, we denote these as Cohort 1 (livebirths + stillbirths) and Cohort 2 (livebirths only) in the manuscript.**<br><br>Comment #3: METHODS<br>The databases used are adequately described in the text, supported by Supplemental Table A. The databases utilized describe several covariates |

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| | including ethnicity, rurality and geography of residence, income, social marginalization and health care utilization intensity. However, it is not clear in the Methods which important, key covariates are not available in these databases. Several are relevant to understanding the Results, and include maternal weight, smoking, drug, alcohol, and exercise habits. Though these covariates absent from the data sources are mentioned in the Interpretation, it would be helpful for the reader to understand these dataset limitations earlier in the course of reading the paper.<br>**Thank you for these comments. Due to the limitations of the data available in the ICES datasets, we were not able to include all possible confounders in our propensity score model, which may have resulted in residual confounding. Although our manuscript as originally submitted lacked specific data on maternal BMI, alcohol use, and smoking, our propensity score model did include pre-existing maternal health conditions (e.g., chronic hypertension, heart disease, diabetes), a multifaceted marginalization index, income quintile, and a prenatal care index (R-GINDEX), all of which may have served as useful proxies for the covariates mentioned by this Reviewer. For example, inadequate maternal use of prenatal care can be considered a proxy indicator for underlying low maternal propensity for health promotion activities and, in turn, poor health behaviour during pregnancy (e.g., smoking and alcohol use) (Shulman 2006, PMID: 17060479).**<br>**Nevertheless, we agree with that despite these proxy measures, the absence of specific data on maternal BMI, alcohol use, and smoking is important. Therefore, after further consulting the literature (Ray 2016, PMID: 27599330), we have included additional ICD-10-CA codes for obesity (E66) and tobacco/substance abuse (F10-F19; G312) in our revised propensity score model. Although these codes are likely to only capture the most severe forms of these conditions, we believe that their inclusion will help to further reduce potential residual confounding.**<br><br>Comment #4: METHODS<br>-Exposure and outcome measurement<br>Tdap immunization status was ascertained only by OHIP billings only, primarily G847, a relatively new code in the fee guide. 11,750 vaccinees were identified in this fashion, with an additional, possible 2845 recipients identified by an audit of G539 / G539 for parts of 9-months of the year. What deserves further discussion is an estimate of missed vaccinees, especially for readers outside of Ontario. For example, how are midwives billing for Tdap? What about providers on alternative payments, who may not bill in the same fashion? Can patients access vaccination directly through pharmacies? Are there mechanisms to receive immunizations through public health (in community health centres, for example) that are not captured in OHIP billing codes? Only 2% of women were vaccinated in Ontario during this timeframe - how does this compare to other provinces? If much different, it suggests this exposure ascertainment method may be missing a large and statistically meaningful group.<br>**In Ontario, physicians submit billing claims to the Ontario Health Insurance Plan (OHIP) for providing immunizations, which are captured in the OHIP database. Due to the lack of a centralized immunization registry in Ontario, administrative datasets such as OHIP are the only data source to access vaccine coverage across the province. As midwifery billings are not** |

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| | **captured in the OHIP database at ICES, women with a home birth, whose antenatal care was provided entirely by a midwife would not have been captured in our study. Those with a hospital birth under the care of a midwife would have been included in the eligible study population, but we would not have been able to ascertain an immunization administered by a midwife since it would not have been recorded in the OHIP database.**<br>**Midwives typically refer to practice guidelines from the Society for Obstetricians and Gynaecologists of Canada (SOGC) for information regarding maternal vaccination, as specific midwifery guidelines on vaccination do not currently exist (personal communication: Dr. Liz Darling, Assistant Dean of Midwifery at McMaster University, May 24, 2020).**<br>**Considering that our study time period was prior to the Canadian Tdap recommendation release and SOGC guidelines on maternal Tdap vaccination, the number of pregnant women who received Tdap vaccination from their midwife, or from any other health care professionals not captured within OHIP billings (e.g., pharmacists), is likely low to non- existent.**<br>**Further, according to a Public Health Ontario technical report published in response to the 2018 NACI recommendation, administering Tdap vaccination to pregnant women is outside the scope of practice for pharmacists and midwives. The Association of Ontario Midwives (AOM) similarly report that Tdap vaccination in pregnancy is outside midwifery scope of practice, necessitating a referral to a physician (https://www.ontariomidwives.ca/vaccinations-pregnancy).**<br>**As this is the first Canadian study to assess Tdap vaccination in pregnancy, we have no Canadian estimates of Tdap coverage to compare to. Although the overall rate of Tdap vaccination across the study time period was close to 2%, coverage actually increased 10-fold from 0.4% in fiscal year 2011-12 to almost 4% in fiscal years 2015-16 and 2016-17. These low estimates were expected, given that our study period was prior to the official NACI recommendation in Canada. According to a US cohort study, maternal Tdap vaccination coverage increased from <1% in 2009 to 28% in 2013, and reached over 50% by 2015 (Kerr 2017, PMID: 29049273). This increase in US Tdap vaccine coverage reflects the implementation of recommendations in 2011, and we are likely to observe increasing uptake in Canada in the coming years.**<br><br>Comment #5: METHODS<br>The outcomes chosen are clinically important, clearly defined, and were identified in prior studies as possibly linked to pertussis. The inclusion of the NAO Index is very useful. Again, the question is why stillbirth was excluded?<br>**Thank you for this comment. Please see our earlier explanation concerning stillbirth (Reviewer #2, Comment #2).**<br><br>Comment #6: Statistical analyses<br>The matching process is well explained and Table 1 is vital to understanding the process. It would be helpful for the reader to have highlighted in this Table which key covariates are not available (see above). As previously mentioned, some of these (such as smoking and very high BMI) are more strongly linked to adverse maternal and infant morbidity than anything else in this table.<br>**Thank you for this comment. Please see our earlier explanation concerning** |

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| | **this issue (Reviewer #2, Comment #3).**<br><br>Comment #7: The first two of the additional Sensitivity analyses are clear and well explained. The last is unclear. Please define and explain 'inverse probability of treatment weights' and how it improves the validity of the results. It needs more than a citation.<br>**Thank you for this suggestion. We have provided additional explanation concerning the inverse probability of treatment weighted analyses in the manuscript, since we now use this propensity score method to adjust for confounding; please see our earlier response to Reviewer #1 (Comment #7) on this issue. We have also added a detailed explanation of propensity score adjustment using inverse probability of treatment weights within the supplementary methods (eAppendix 2).**<br><br>Comment #8: RESULTS<br>This Reviewer did not assess the accuracy and validity of the statistical methods employed, and it is assumed this was done correctly. For example, it is assumed the choice to use Cox and log-binomial regression techniques for the outcomes described are correct. This stems from the Reviewer's lack of statistical sophistication. That stated, the results, as presented, are clear and understandable.<br>**Thank you for these comments about the statistical methods we employed in our study. We were careful to follow recommended approaches for analysis of time-dependent exposure and time-dependent outcomes in studies of immunization during pregnancy (Hutcheon 2016, PMID: 27449413; Savitz 2015, PMID: 26319740) and for directly estimating risk ratios using log-binomial regression (Knol 2012, PMID: 22158397).**<br><br>Comment #9: INTERPRETATION<br>Key results were that no harms were identified in any of the chosen health outcomes. However, there are four outcomes with statistically reduced aRR in pregnancies receiving Tdap: SGA (aRR 0.91), NICU admissions (0.84), neonatal morbidity (0.79) and gestational hypertension (0.82). This is addressed with: "Given known biases in observational studies on immunization, we also cannot rule out the possibility of residual confounding inducing a healthy vaccinee bias."<br><br>What is germane here is the absence within the employed databases of several important covariants, without which matching is much less valid. It is in the last paragraph of the Interpretation that it is disclosed that no information was available for maternal body weight, smoking, drug and alcohol consumption. This is highly pertinent to the results, as there is little biological plausibility that Tdap immunization would have such salutary benefit on both mother and child. Nor have these broad benefits been reported in other similar, large cohort studies (several being cited, from the US, UK and New Zealand). A key revision should be highlighting these methodological concerns earlier in the paper.<br>**Thank you for this comment. Please see our earlier explanations concerning this issue (Author response #2 to the Editorial Board and Author response #3 to Reviewer #2). As discussed in these earlier responses, we have included an additional sensitivity analysis to quantitatively assess potential residual confounding bias on our observed estimates (eAppendix 3) and we** |

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| | **have also revised our propensity score model to include ICD-10-CA codes for obesity and tobacco/substance abuse.**<br>**Further, we have revised the methods and discussion of the paper to include mention of these limitations.**<br><br>Comment #10: CONCLUSION<br>No changes suggested.<br>**No response required.**<br><br>Comment #11: Summary<br>This is a useful paper of broad interest to Canadian clinicians. The strengths of the study are well described by the authors in the Interpretation. The evidentiary strength of the main finding that Tdap immunization is safe is fair, and adds to the large and growing body of evidence about the safety and efficacy of this important vaccine. As long as the methodological limitations are clearly defined throughout the paper, the data showing reduced risks across outcomes with Tdap immunization will become easier to interpret and possibly, hypothesis generating, particularly when post-NACI 2018 data become available.<br>**Thank you for these comments – we appreciate the recognition of the importance of this topic.** |