

OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

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obgyn@greenjournal.org.

Date: 12/09/2022
To: "Fangjun Zhou" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-2010

RE: Manuscript Number ONG-22-2010

Association between influenza vaccination during pregnancy and infant influenza vaccination in a privately insured population

Dear Dr. Zhou:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 12/30/2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

1. Thank you for submitting this work to Obstetrics & Gynecology. If you choose to submit a revision, please be sure to respond adequately to reviewer #2's comments about general vaccine hesitancy and the importance of that driver versus just pushing obstetricians to work harder to get patient's vaccinated.

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

REVIEWER COMMENTS:

Reviewer #1:

This manuscript details an analysis of the association between influenza vaccination during pregnancy with subsequent infant influenza vaccination in a private insurance claims database. There is certainly a need for increased uptake of influenza vaccination in all people. However, how the authors define timing of pregnancy vaccination or the time at which the infant is first eligible for a two dose series of influenza vaccination is unclear. Moreover, this association is almost certainly confounded by vaccine hesitancy, which is impossible to assess in this type of dataset.

1. The precis should be briefer.
2. Abstract, conclusion, lines 36-39: this is a leap, not supported by your analysis.

3. Introduction, lines 49-51: although this is true, the population you are targeting here is by definition 6 months or greater, as this is the minimal age to receive influenza vaccine, so this statement is out of place. There are many studies demonstrating benefit of maternal vaccination in decreasing influenza incidence in the <6 month population that may be appropriate for the discussion.
4. Introduction, lines 64-65: as this study includes nonpregnant people, it is not really relevant to your background unless you contextualize it in some way, e.g. in the general population influenza vaccine falls short of goals and is perhaps even lower during pregnancy.
5. Introduction: I'm not clear what the evidence gap is for this analysis. It seems that evaluating this association is just assessing two outcomes that are influenced by vaccine hesitancy and then saying they are related. Vaccine hesitancy is a noted confounder, and presence or absence of receipt of influenza vaccine is unlikely to be causal of child vaccination uptake.
6. Methods, line 90: why did you limit to singletons?
7. Methods: it would be helpful to see a visual representation of your timeline and epochs. As written, it seems that some infants would have been eligible for their first vaccine in the spring of 2018 and some would be eligible in fall of 2018. Thus, when you focus on fall of 2018, it is unclear how to interpret the 1 versus 2 dose data. Infants who are getting their second season of influenza vaccine in the fall of 2018 would only be eligible for one dose. Also, if you include live births from September 2017 on, many of those who deliver in September may have done so prior to influenza vaccine availability. In many communities this is available in mid to late September. Thus, your ascertainment of vaccination during pregnancy would be flawed.
8. Methods: Similarly, how did you establish that vaccination occurred during pregnancy? Did you establish date ranges based on gestational age at delivery? It is certainly possible that the vaccine could have been received before or after pregnancy if you did not.
9. Methods: lines 117-122: can you include more detail of your statistical analysis, including descriptive analysis and comparisons?
10. Results: it would be helpful to visually demonstrate timing of deliveries and timing of vaccinations to better understand the proportion of people included who could have been affected by the ascertainment challenges discussed in comment 7.
11. Discussion, line 156-157: again, infants <6 months are not eligible for the influenza vaccine. More relevant is the benefit to these infants conferred directly by maternal vaccination during pregnancy.
12. Discussion, lines 159-174: you argue in this paragraph that OB providers need to educate and counsel patients about vaccines. However, you cite a study that shows that this does not affect attitudes about vaccines in the future when compared to receiving education at pediatric visits. Thus, the argument that prenatal education would increase infant vaccination seems unfounded.
13. Discussion, line 192: Another notable limitation is inability to generalize to those with public insurance.

Reviewer #2:

The authors objective was to examine the association between influenza vaccination during pregnancy and infant influenza vaccination. They conducted a retrospective analysis of beneficiaries aged 15-49 years who were continually privately insured from August 2017 to May 2019 and delivered singleton, live births from September 2017 through February 2018 and their infants. Influenza vaccination coverage was assessed for pregnant people during the 2017-18 influenza season and their infants during the 2018-19 season using the 2017-2019 MarketScan data. They found that there was a 35.7% higher in ≥ 1 dose coverage (adjusted risk ratio [ARR] 1.34 [95% CI: 1.33-1.36]) and a 45.8% higher in ≥ 2 dose coverage (ARR 1.43 [95% CI: 1.41-1.46]) for infants born to people who received influenza vaccination during pregnancy compared with infants born to people who did not. They suggest that interventions to increase influenza vaccination coverage among pregnant people may also increase infant influenza vaccination coverage.

1. Can the authors elaborate more on why they chose the years 2017-2019, and not a longer time period?
2. Can the authors clarify how they linked the mother to the baby in this dataset?
3. Can the authors clarify whether infant vaccination under a father's insurance (if different from mother's) would have been captured?
4. What do the authors consider as next steps in further exploring the findings of this study?

5. Do the authors have any thoughts on how the pandemic experience may impact these findings?

STATISTICAL EDITOR COMMENTS:

As the Authors point out, there are limitations based on the population studied and on the database itself. However, this is important information documenting the correlation between maternal and infant influenza vaccination status, at least in this cohort with continuous private insurance.

Table 2: Should include the unadjusted RR with CIs to contrast with the aRRs. Should also list in footnote to Table all of the variables retained in the final aRR model.

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Sincerely,

Torri D. Metz, MD, MS
Deputy Editor-Elect, Obstetrics

The Editors of Obstetrics & Gynecology

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

EDITOR COMMENTS:

1. Thank you for submitting this work to Obstetrics & Gynecology. If you choose to submit a revision, please be sure to respond adequately to reviewer #2's comments about general vaccine hesitancy and the importance of that driver versus just pushing obstetricians to work harder to get patients vaccinated.

*We appreciate the opportunity to revise this manuscript for further consideration by Obstetrics & Gynecology. In addition to providing a robust response to the reviewer comment about the relationship of vaccine hesitancy to our findings, we have added a sentence to the conclusion to further highlight that it is the responsibility of **all** medical and public health professionals to reduce vaccine hesitancy and increase vaccination coverage among pregnant people (lines 257-261): "In addition, healthcare professionals, public health officials, and community groups should continue efforts to reduce misinformation about influenza vaccination and increase vaccine confidence among pregnant people to increase vaccination coverage and maximize protection from influenza infection for pregnant people and infants under 6 months."*

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at

https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

We have reviewed and edited the manuscript for consistency with the Revision Checklist.

REVIEWER COMMENTS:

Reviewer #1:

This manuscript details an analysis of the association between influenza vaccination during pregnancy with subsequent infant influenza vaccination in a private insurance claims database. There is certainly a need for increased uptake of influenza vaccination in all people. However, how the authors define timing of pregnancy vaccination or the time at which the infant is first eligible for a two dose series of influenza vaccination is unclear. Moreover, this association is almost certainly confounded by vaccine hesitancy, which is impossible to assess in this type of dataset.

1. The precis should be briefer.

We have shortened the précis; it now reads as follows: "Influenza vaccination receipt during pregnancy is associated with infant influenza vaccination in their first season eligible for vaccination."

2. Abstract, conclusion, lines 36-39: this is a leap, not supported by your analysis.

We respectfully disagree that this conclusion is unsupported by our findings. We use the word “may” to indicate uncertainty as our analysis does not demonstrate causality. We do agree with the reviewer’s implicit point, repeated below, that we have not adequately demonstrated how this association might be causal rather than a proxy for maternal vaccine hesitancy. We have made additional revisions to correct this, noted in our response to comment #5 below.

3. Introduction, lines 49-51: although this is true, the population you are targeting here is by definition 6 months or greater, as this is the minimal age to receive influenza vaccine, so this statement is out of place. There are many studies demonstrating benefit of maternal vaccination in decreasing influenza incidence in the <6 month population that may be appropriate for the discussion.

While the reviewer is correct that the infants included in this analysis are by definition at least 6 months of age, the purpose of this statement is to reinforce the importance of vaccination during pregnancy in order to protect infants too young to be vaccinated via transplacental transfer of antibodies. The efficacy of maternal vaccination in decreasing influenza infection in infants 6 months or older is not relevant to this analysis as these infants are best protected by direct vaccination. We have reordered the sentences in this section to clarify the purpose of including this information; now, the sentence about protection of young infants through maternal vaccination immediately follows the sentence about risk of influenza in infants under 6 months of age (lines 54-58).

4. Introduction, lines 64-65: as this study includes nonpregnant people, it is not really relevant to your background unless you contextualize it in some way, e.g. in the general population influenza vaccine falls short of goals and is perhaps even lower during pregnancy.

CDC reports maternal influenza vaccination data consistent with the recommendation of the Advisory Committee on Immunization Practices for people who are or could become pregnant during influenza season to be vaccinated. Observational studies of infant protection conferred by maternal influenza vaccination have also used in-season vaccination, regardless of timing, as a primary predictive variable (for example, Thompson et al., Clin Infect Dis. 2014;58(4):449–57). The reviewer’s point that the proportion of panelists vaccinated during pregnancy is even lower is well taken; however, given that the 61% vaccination coverage cited here is both demonstrably suboptimal and well below the coverage for children under 24 months, we believe the cited report is an acceptable reference for this point.

5. Introduction: I’m not clear what the evidence gap is for this analysis. It seems that evaluating this association is just assessing two outcomes that are influenced by vaccine hesitancy and then saying they are related. Vaccine hesitancy is a noted confounder, and presence or absence of receipt of influenza vaccine is unlikely to be causal of child vaccination uptake.

Maternal influenza vaccination in the ‘post-COVID’ era is notably lower than the already suboptimal vaccination coverage levels observed prior to 2020. Given the timing and severity of the 2022-23 influenza season thus far, inadequate maternal influenza vaccination could lead to a substantial uptick in adverse pregnancy outcomes and influenza-associated morbidity and

mortality among pregnant people and their infants under 6 months of age. A major impetus for conducting this analysis and publishing the results is to provide an urgent, data-driven call to action to increase influenza vaccination during pregnancy.

We agree with the reviewer that vaccine hesitancy is an important consideration in this study. However, the observed correlation between maternal and infant vaccination might also be driven by maternal resources, provider access, or other patient characteristics. If maternal and infant vaccination were both influenced solely by parental vaccine hesitancy, one would expect vaccination coverage levels in the two populations to be similar; however, as noted in lines 72-74, childhood influenza vaccination in the youngest age group is nearly 20 percentage points higher than maternal vaccination. One potential hypothesis explaining this discrepancy would be that pediatricians provide substantial information about the importance of influenza vaccination to new parents, who take action to vaccinate their infants based on the recommendation of their trusted healthcare provider – hence, the higher vaccination coverage of young children compared with pregnant people. Because pregnancy is well-documented as a period in which people are motivated to change their health behaviors, receiving information on the importance of influenza vaccination for infants, and for themselves, directly from a trusted prenatal care provider might increase influenza vaccination coverage in both populations. By identifying the association between maternal vaccination patterns during pregnancy and infant vaccination uptake, we highlight a potential opportunity for healthcare professionals seeing pregnant patients to discuss and address barriers to vaccination, including any vaccine hesitancy.

In order to clarify the nature of the hypothesis being explored in this analysis, we re-ordered the sentences in the introduction and modified the final sentence to read as follows (lines 85-90): “We hypothesized that more recent data from a large national sample would corroborate the trends observed elsewhere and demonstrate an association between influenza vaccination received during pregnancy and infant influenza vaccination among privately-insured people in the United States.” We also added a sentence and citation specifically referencing pregnancy as a period for motivated behavior change (lines 74-77): “Pregnancy is widely understood to be a period when people are motivated to change their health behaviors; people who receive information about vaccination during pregnancy may use this information to make vaccination decisions both for themselves and for their newborns.”

6. Methods, line 90: why did you limit to singletons?

Inclusion of only singleton births reduces the possibility of error in analysis and simplifies interpretation. As approximately 97% of births are singletons, we believe the exclusion of multiple births has a limited effect on the validity of our findings. We have added an explanation for this decision to the Methods at lines 106-107.

7. Methods: it would be helpful to see a visual representation of your timeline and epochs. As written, it seems that some infants would have been eligible for their first vaccine in the spring of 2018 and some would be eligible in fall of 2018. Thus, when you focus on fall of 2018, it is unclear how to interpret the 1 versus 2 dose data. Infants who are getting their second season of influenza vaccine in the fall of 2018 would only be eligible for one dose. Also, if you include live births from September 2017 on, many of those who deliver in September may have done so

prior to influenza vaccine availability. In many communities this is available in mid to late September. Thus, your ascertainment of vaccination during pregnancy would be flawed.

We appreciate the reviewer's suggestion to provide a timeline in order to facilitate interpretation of the data. We have included this timeline as a new figure (Figure 1). We agree with the reviewer that there may be some uncertainty in the proportion of infants in our sample who were due for one versus two doses of influenza vaccine when vaccinated. However, our findings are consistent for both one- and two-dose coverage, so this uncertainty does not change our interpretation of the analytic findings. In addition, as Figure 1 illustrates, only a small proportion of infants in our sample (i.e. those deliveries occurring from approximately September 1-October 1, 2017) would be age-eligible for influenza in the 2017-2018 rather than the 2018-2019 influenza season. Previous analyses of pediatric influenza vaccination suggest very little vaccination occurs in or after March of any given influenza season (see for example <https://www.cdc.gov/flu/fluview/coverage-1516estimates.htm#data>); therefore, it is likely that close to 100% of infants in our sample were eligible for two doses in the season of interest. Regarding ascertainment of vaccination during pregnancy, it is true that a person delivering in early September may not be able to receive that season's influenza vaccine, although influenza vaccines are increasingly available in August in many parts of the country. However, we believe that the relatively small proportion of births occurring in this time period limits the effect of this factor on our findings.

8. Methods: Similarly, how did you establish that vaccination occurred during pregnancy? Did you establish date ranges based on gestational age at delivery? It is certainly possible that the vaccine could have been received before or after pregnancy if you did not.

We did not rely on gestational age for this analysis since only the date of delivery was available in the data source. We limited our analysis to births during a six-month period during the 2017-2018 influenza season and searched for influenza vaccination claims between August 1, 2017 and the recorded delivery date. Therefore, with the exception of extremely premature deliveries, all vaccination claims included in our analysis would have by definition occurred during pregnancy.

9. Methods: lines 117-122: can you include more detail of your statistical analysis, including descriptive analysis and comparisons?

We have included the requested information in the Methods section at lines 136-137, lines 140-142, and lines 145-147.

10. Results: it would be helpful to visually demonstrate timing of deliveries and timing of vaccinations to better understand the proportion of people included who could have been affected by the ascertainment challenges discussed in comment 7.

Agreed; see response to comment #7 above.

11. Discussion, line 156-157: again, infants <6 months are not eligible for the influenza vaccine. More relevant is the benefit to these infants conferred directly by maternal vaccination during pregnancy.

To clarify, this line refers to infants aged 6 months and older, who are at increased risk for influenza-associated hospitalization and death relative to older children. We agree with the reviewer that it is important to emphasize the direct protection vaccination during pregnancy can provide to the youngest infants. We have edited the sentence to read as follows (lines 182-186): “Increasing uptake of influenza vaccination during pregnancy would provide greater protection against influenza-associated morbidity and mortality for infants too young to be vaccinated and may contribute to increased influenza vaccination of infants aged six months and older who remain vulnerable to hospitalization and death from influenza infection relative to older children.”

12. Discussion, lines 159-174: you argue in this paragraph that OB providers need to educate and counsel patients about vaccines. However, you cite a study that shows that this does not affect attitudes about vaccines in the future when compared to receiving education at pediatric visits. Thus, the argument that prenatal education would increase infant vaccination seems unfounded.

We believe the reviewer is referencing Vannice et al, which concluded that maternal attitudes toward infant vaccination were similar whether women received information about infant immunization at a prenatal visit, at an early infant wellness visit, or at the two-month well check (i.e. the first vaccination visit). While this is correct, the authors also found that one-third of study participants reported a preference for receiving this information at a prenatal visit, suggesting a substantial role of OB providers in vaccine education. We have edited the sentence discussing Vannice et al to emphasize this finding (lines 192-195): “One study found similar attitudes toward childhood vaccination among women who received vaccine information during their pregnancy and at the first infant immunization visit, but 34% of study participants indicated a preference for receiving the information at a prenatal visit”. In addition, we have cited several other studies indicating that decision-making about infant vaccinations occurs prior to delivery, putting OB providers in a unique position to ensure that pregnant people are making these decisions based on accurate information from a trusted healthcare provider. Related to the reviewer’s earlier point about vaccine hesitancy, Glanz et al found that parents who ultimately delayed or refused vaccinations were more likely than those who accepted vaccinations for their infant to report thinking about vaccination decisions during pregnancy, underscoring the particular importance of vaccine education during pregnancy as a means to address vaccine hesitancy leading to vaccine refusal. We have highlighted this finding in the discussion as follows (lines 211-216): “One study found that parents who ultimately delayed or refused vaccination were more likely than vaccine-accepting parents to report thinking about infant vaccination during pregnancy and repeatedly re-evaluating this decision, suggesting that vaccination counseling by prenatal care providers may be particularly important in reducing vaccine hesitancy.”

13. Discussion, line 192: Another notable limitation is inability to generalize to those with public insurance.

We agree with the reviewer and have added the following text to the limitations section (lines 238-239): “Finally, our findings may not be generalizable to people who are publicly insured or uninsured during pregnancy.”

Reviewer #2:

The authors objective was to examine the association between influenza vaccination during pregnancy and infant influenza vaccination. They conducted a retrospective analysis of beneficiaries aged 15-49 years who were continually privately insured from August 2017 to May 2019 and delivered singleton, live births from September 2017 through February 2018 and their infants. Influenza vaccination coverage was assessed for pregnant people during the 2017-18 influenza season and their infants during the 2018-19 season using the 2017-2019 MarketScan data. They found that there was a 35.7% higher in ≥ 1 dose coverage (adjusted risk ratio [ARR] 1.34 [95% CI: 1.33-1.36]) and a 45.8% higher in ≥ 2 dose coverage (ARR 1.43 [95% CI: 1.41-1.46]) for infants born to people who received influenza vaccination during pregnancy compared with infants born to people who did not. They suggest that interventions to increase influenza vaccination coverage among pregnant people may also increase infant influenza vaccination coverage.

1. Can the authors elaborate more on why they chose the years 2017-2019, and not a longer time period?

We appreciate the reviewer’s request to clarify this decision. The COVID-19 pandemic has had widely-documented effects on receipt of all types of non-emergency medical care across all age groups and among both general medical and specialty providers. In order to avoid confounding caused by the effects of the COVID-19 pandemic, we elected to look at the two influenza seasons immediately prior to the one in which the pandemic began, which provided a sufficient sample for our analysis. This is noted in the Methods (lines 95-96). The reason we did not include more influenza seasons prior to 2017 is because influenza vaccination coverage among pregnant people is regrettably fairly static and we did not feel that additional years of data were likely to change the conclusions of the study.

2. Can the authors clarify how they linked the mother to the baby in this dataset?

Thank you for this question; we have clarified this linkage in the Methods section as follows (lines 107-108): “Birthing parents and the infants were linked through family ID and birth year from the same insurance plan.”

3. Can the authors clarify whether infant vaccination under a father's insurance (if different from mother's) would have been captured?

As noted in the response to comment #2 above, birthing parents and infants were linked via a shared family ID associated with the payor. If the birthing parent and an infant’s other parent had different insurance plans, it is possible that an infant vaccinated under the other parent’s insurance plan would not be identified as vaccinated in our analysis. We believe this would be a

rare occurrence; however, we have noted this possibility in the limitations sections as follows (lines 235-238): “Infant influenza vaccination might also be underestimated if the infant was vaccinated under a different insurance plan than the one that covered the birthing parent as these plans would not share the family ID used to link infants to parents in our analysis.”

4. What do the authors consider as next steps in further exploring the findings of this study?

Thank you for this question. One additional avenue of research related to the findings of this study would be a similar analysis in the intra- and post-pandemic periods once data are available, consistent with the reviewer’s observation in comment #5 that the pandemic may have impacted this relationship. We would also like to conduct a similar analysis examining how receipt of maternal Tdap vaccination may influence uptake of other infant vaccines, since Tdap is generally more acceptable to pregnant persons and is administered later in pregnancy than influenza vaccine so may have a different effect on how birthing parents decide to vaccinate their young infants because of the proximity of the vaccine administration to delivery.

5. Do the authors have any thoughts on how the pandemic experience may impact these findings?

We appreciate the reviewer bringing up this question. As noted in the conclusion (lines 244-247), influenza vaccination coverage among pregnant people appears to be lower in the early part of the current influenza season, which we believe is likely linked to changes in preventive care-seeking and routine vaccination behavior as a result of the COVID-19 pandemic. We have outlined this further in the conclusions as follows (lines 243-244): “The COVID-19 pandemic resulted in substantial reductions in utilization of preventive care, including routine vaccination among adults.”

STATISTICAL EDITOR COMMENTS:

As the Authors point out, there are limitations based on the population studied and on the database itself. However, this is important information documenting the correlation between maternal and infant influenza vaccination status, at least in this cohort with continuous private insurance.

Table 2: Should include the unadjusted RR with CIs to contrast with the aRRs. Should also list in footnote to Table all of the variables retained in the final aRR model.

We agree and have made this change to Table 2 and clarified the footnote regarding the composition of the final adjusted model.