

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)*

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obgyn@greenjournal.org.

Date: Feb 12, 2021
To: "Timothy Wen" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-137

RE: Manuscript Number ONG-21-137

Influenza complicating delivery hospitalization and its association with severe maternal morbidity in the United States, 2000-2015

Dear Dr. Wen:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Mar 05, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: ONG 21-137

In the manuscript under review, Wen et al present a cross-sectional analysis of the Nationwide Inpatient Sample to evaluate the trends of an influenza diagnosis at delivery hospitalization and describe the associated maternal morbidity. They found that women with an influenza diagnosis at delivery were at an increased risk of SMM and obstetrical complications.

A few comments on the manuscript are as follows:

1. Precip - missing the word "at"
2. Abstract - no major issues
3. INTRODUCTION - No hypothesis is stated
4. Methods - How was a sample size calculated? What change in the rate of the primary outcome were the authors expecting to find?
5. Line 170 - What covariates are the authors referring to? All the covariates listed in lines 151-161 (20 in total)?
6. How were the cases of influenza diagnosed? Lab confirmed or suspected on clinical presentation?
7. The authors should add a line stating that STROBE guidelines were followed.
8. RESULTS - For Table 1, some measure of association would be useful to the reader. (i.e how much more likely was a vaginal delivery in the non-influenza group)
9. Line 204 - the sentence needs to be reworded to "delivery hospitalizations with an influenza diagnosis so no change" since the p value is >0.05 .
10. I would recommend condensing tables 2 and 3 into one table.
11. Line 222-225 how did the authors reach this conclusion? Did they base it on the fact that 95% CI did not overlap? What type of comparison was made?
12. DISCUSSION The main concerns with the use of administrative databases are the concerns for erroneous classification of diagnosis, which was acknowledged by the authors. Similar to this concern would be that this database only captured the most severe presentation of the disease, the one leading to admission and delivery due to disease severity. Many women presenting with minor symptoms at the moment of delivery are less likely to be tested, diagnosed and therefore included in the "cases". This form of potential misclassification bias should also be added to the limitations.
13. The authors are comparing 2 very different groups, especially when we look at the size of the study cohorts. Adding a propensity score analysis may further reduce the risk of confounding.

Reviewer #2:

Thank you for the opportunity to review and provide comments for this manuscript presents an analysis of data from the U.S. Nationwide Inpatient Sample (NIS), years 2000-2015, to characterize trends of an influenza diagnosis at delivery hospitalization and its association with severe maternal morbidity. The rationale for this analysis, methods, presentation of results, and conclusions are overall sound, and the authors should be commended for their thorough approach. Several major comments are outlined below:

- This analysis was limited to data through the third quarter of 2015, after which the NIS switched to use of ICD-10 codes. The authors should be aware that CDC has published an appendix which presents the SMM indicators and corresponding ICD-9-CM/ICD-10-CM/PCS codes during delivery hospitalization (<https://www.cdc.gov/reproductivehealth/maternalinfanthealth/smm/severe-morbidity-ICD.htm>). The overall associations and conclusions are well supported using the ICD-9-based data, but if feasible, the authors might consider updating their analysis with more recent years of data using ICD-10-based data, which might be more applicable for surveillance moving forward.
- It is unclear to this reviewer if the authors were able to make a distinction between influenza detected at delivery hospitalization vs a diagnosis code of influenza that carried over from infection earlier in the pregnancy. It could be made more explicit that the exposure in this analysis is an influenza diagnosis code from the inpatient delivery hospitalization administrative data rather than infection at delivery.
- The SMM indicators chosen by authors as "influenza SMM" also happen to be common outcomes for other severe conditions, and it is challenging to distinguish influenza from other possible contributors to the rise in SMM. It might be helpful to include the specific adjustment factors in the methods section and tables 3 and 4. Presenting the directed acyclic graph (DAG), might be helpful. As labeled, the figure might be misinterpreted as implying that influenza was the major contributor to the rise in influenza-related SMM over time.

Line-by-line comments below:

Line 25: "Women with influenza a delivery hospitalization..." to "Women with influenza AT delivery hospitalization".

Line 73: A conclusion statement was made on trend over time, however, data regarding trend over time was not presented in the results section of the abstract.

Line 154: Based on the results, the authors may have intended to say "income quartile" rather than ZIP code.

Line 191-195: The observations for differences in obstetric outcomes were not addressed in the discussion.

Line 198-199: Higher frequency of death was noted but was presented as "Those with an influenza diagnosis also had higher frequency of death (0.0% vs. 0.0%, $p < 0.01$),...".

Line 207-209: It might be helpful to the reader to understand which components of SMM contributed most to the dramatic increased rate observed by the authors.

Line 243-244: Influenza SMM indicators have other possible causes. Could other risk factors/etiologies be contributing to the rise?

Line 252-254: Could the increase in influenza diagnosis be due to increased recognition and documentation, especially after 2009-2010 when pregnancy was recognized as a risk factor for severe illness?

Line 279-281: The authors might have intended to say "cause" rather than "indication".

Line 292: missing punctuation

Tables 3 and 4: Strongly consider including in a footnote what factors were included in adjustment.

Reviewer #3:

This is a repeated cross-sectional analysis evaluating severe maternal morbidity among pregnant women at delivery who also have a diagnosis of influenza compared to women delivering without influenza. The manuscript is clear and well written. This is a large sample size allowing for the evaluation of fortunately rare outcomes like severe maternal morbidity. However, the cross-sectional design has significant limitations making it impossible to determine if the association found between severe maternal morbidity and influenza is due to influenza or a confounding characteristic associated with severe maternal morbidity as well as severe influenza.

Major comments:

- 1) Severe influenza is associated with preterm delivery, term labor and maybe a medical indication of induction of labor. Because the study design only includes influenza associated with the delivery hospitalization, the study population has a higher concentration of severe influenza than if we determined the obstetrical outcomes including those hospitalizations for

influenza for which delivery did not occur. Please note this in the limitations paragraph of the discussion.

2) I recommend statistically comparing the clinical characteristic in Table 1 between the no influenza group and the influenza group. Do you have any data on the obesity rates between groups? Please note in the limitations of the discussion that there are several confounding variables that are known to be associated with both severe maternal morbidity as well as severe influenza, therefore causation cannot be assessed.

Minor comments:

- 1) There is a typo in the Precis. An "a" that should be "at."
- 2) Abstract, results: If possible, for the low prevalence outcomes like maternal death, consider reporting cases in 10,000 women.
- 3) Methods, second paragraph: Please clarify why there was a change made in the way the NIS collected data between 2011 and 2012. What was the benefit to this change?
- 4) Results, 3rd paragraph: Consider reporting low prevalence outcomes like death in cases per 10,000 or 100,000 women to improve precision and clarity.
- 5) Discussion, 1st paragraph, last sentence: There is period missing at the end of this sentence. Perhaps consider including the specific obstetrical complications of interest.
- 6) Discussion: Consider putting "future research" paragraph after the strengths and limitations paragraphs.
- 7) Discussion: Consider adding unknown vaccination status of the population as a limitation and a consideration for future research.
- 8) Tables 3 and 4: Please list what factors the adjust analysis is adjusted for in the footnote of the table.

STATISTICS EDITOR COMMENTS:

General: As the Authors know, the NIS is a representative sample, rather than the entire US population. The Abstract and Tables show the entire US deliveries from 2000-2015, based on the sample. That distinction may be lost on the reader in the present version. Since the sample represents ~ 20% of the US population, the counts shown in Tables 1 and 2 are cited to the nearest integer, but that level of precision is not possible in a sample of ~ 1 in 5 births.

Table 2: The frequencies should all include CIs.

Table 3: The estimates of RR and aRR are correct, but the CIs are not, since they were based on extrapolation of the sample to the entire US population, which increases the sample size and consequently makes the CIs too narrow. For example the unadjusted analysis for SMM should have CIs that are ~ 0.47 units wide, rather than the cited value ~ 0.22. That is, based on actual sample sizes that were ~ 1/5 of the US population, the resulting CIs should be more than 2x as wide. Further, the actual counts for rare events, such as maternal death, are few and the aRRs may be over fitted.

Table 4: The conclusion that the SMM rates increase over time is more complicated than "the risk has increased over time". The risk increased during more severe influenza seasons, of which there were none from 2000-2005, one during 2006-2010 and two during 2011-2015. So, it is not that the SMM risk increased over time, but rather that it increased when there was a more severe influenza outbreak. If the years 2016-2020 had no severe influenza outbreaks, then I suspect the SMM rate would then be lower than in 2011-2015. Again, the CIs are incorrect.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

- A. OPT-IN: Yes, please publish my point-by-point response letter.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at <http://ong.editorialmanager.com>. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

5. Your study uses ICD-10 data, please make sure you do the following:

- a. State which ICD-10-CM/PCS codes or algorithms were used as Supplemental Digital Content.
- b. Use both the diagnosis and procedure codes.
- c. Verify the selected codes apply for all years of the study.
- d. Conduct sensitivity analyses using definitions based on alternative codes.
- e. For studies incorporating both ICD-9 and ICD-10-CM/PCS codes, the Discussion section should acknowledge there may be disruptions in observed rates related to the coding transition and that coding errors could contribute to limitations of the study. The limitations section should include the implications of using data not created or collected to answer a specific research question, including possible unmeasured confounding, misclassification bias, missing data, and changing participant eligibility over time.
- f. The journal does not require that the title include the name of the database, geographic region or dates, or use of database linkage, but this data should be included in the abstract.
- g. Include RECORD items 6.3 and 7.1, which relate to transparency about which codes, validation method, and linkage were used to identify participants and variables collected.

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions> and the gynecology data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

8. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

12. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%).

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist

is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

14. Please review examples of our current reference style at <http://ong.editorialmanager.com> (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources"). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found at the Clinical Guidance page at <https://www.acog.org/clinical> (click on "Clinical Guidance" at the top).

15. Figure 1: Please upload as a separate figure file on Editorial Manager and add tick marks along the x-axis.

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If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

16. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>),

and

* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Mar 05, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri D. Metz, MD
Associate Editor, Obstetrics

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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March 8, 2021

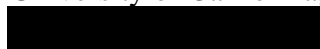
Dear Editors,

Thank you for the invitation to revise our manuscript, "Influenza complicating delivery hospitalization and its association with severe maternal morbidity in the United States, 2000-2015" (ONG 21-137) for consideration for publication in *Obstetrics and Gynecology*. We responded to the reviewers' and statistical editors' comments on a point-by-point basis at the end of this letter. One major change that we made was to include up to the most recent years of data (up to 2018) and have modified the number of variables in our analyses, at the direction of the Reviewers' comments. We believe that because of the revisions, the manuscript is substantially improved.

The main/primary study findings have not been published elsewhere and everyone included on the author list have fulfilled criteria for authorship. We also OPT-IN for our point-by-point response letter. Thank you for your consideration. Please do not hesitate to contact me with questions.

Sincerely,

Timothy Wen, MD, MPH
Clinical Fellow
Division of Maternal Fetal Medicine
Department of Obstetrics, Gynecology, and Reproductive Sciences
University of California, San Francisco



Response to Reviewer/Editor Comments for: “Influenza complicating delivery hospitalization and its association with severe maternal morbidity in the United States, 2000-2015”

Reviewer #1

Comment #1:

Precis - missing the word "at"

Response:

Thank you for this comment. We have revised the Precis as recommended.

Comment #2:

INTRODUCTION - No hypothesis is stated

Response:

Thank you for this suggestion. We have added the following to the end of our INTRODUCTION paragraph:

“We hypothesized that pregnant women with influenza would be at higher risk of SMM at delivery hospitalization compared to those without influenza, and that this risk would be increased during more virulent influenza seasons.”

Comment #3:

How was a sample size calculated? What change in the rate of the primary outcome were the authors expecting to find?

Response:

Because this was a retrospective study and given the large sample size of a national administrative dataset, an a priori sample size was not calculated. We sought to leverage the significant sample size associated of a national administrative dataset to study relatively rare outcomes. The purpose of the study was to describe the contemporary epidemiology of delivery complications with influenza codes at delivery hospitalization.

In the Limitations section of the DISCUSSION, we have added: “Despite using a large national administrative dataset over 19 years, we may have been underpowered to assess relatively rare individual measures of SMM.”

Comment #4:

Line 170 - What covariates are the authors referring to? All the covariates listed in lines 151-161 (20 in total)?

Response:

Yes, these covariates were described in prior studies to be associated with the outcomes used in the study, and this analytical approach is consistent with prior analyses using the NIS by our group.

In the methods we have added: “Models included the following covariates: patient demographic (age, insurance type, median income quartile based on residential ZIP code, reported race/ethnicity), clinical (pre-gestational diabetes, asthma, obesity, and chronic hypertension), and obstetric (gestational diabetes, mode of delivery, placental abruption and/or antepartum hemorrhage, hypertensive diseases of pregnancy including preeclampsia and gestational hypertension, and multiple gestation), hospital characteristics (U.S. region, and hospital type), and year of hospitalization.”

Comment #5:

How were the cases of influenza diagnosed? Lab confirmed or suspected on clinical presentation?

Response:

Given we used administrative data with only billing codes, we were unable to identify specific diagnostic criteria for influenza. We revised the Limitations section in our DISCUSSION to more clearly define this:

“As a result, we were unable to ascertain gestational age at influenza diagnosis, initial treatment for influenza, influenza subtypes, severity of infection, vaccination status and diagnostic and confirmatory methods used.”

Comment #6:

The authors should add a line stating that STROBE guidelines were followed.

Response:

We have added the following to our METHODS section:

“We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cross sectional studies for this analysis.”

Comment #7:

For Table 1, some measure of association would be useful to the reader. (i.e how much more likely was a vaginal delivery in the non-influenza group)

Response:

Given the large sample size, we have not provided statistical tests for significance when comparing groups given that most if not all variables will be statistically significant even if not a clinically significant difference. Should the editors desire for p-values to be provided, we can do so.

Comment #8:

Line 204 - the sentence needs to be reworded to "delivery hospitalizations with an influenza diagnosis so no change" since the p value is >0.05.

Response:

We have now revised our RESULTS section as below:

“During the 19-year study time period, delivery hospitalizations with an influenza diagnosis code did not change from 23.7 to 23.8 per 10,000 deliveries (p=0.20), and the annual average percent change remained stable with a change in value of -0.6% (95% CI: -1.5%, 0.3%, p=0.20).”

Comment #9:

I would recommend condensing tables 2 and 3 into one table.

Response: We have combined both tables 2 and 3 into a single table 2.

Comment #10:

Line 222-225 how did the authors reach this conclusion? Did they base it on the fact that 95% CI did not overlap? What type of comparison was made?

Response:

We based this conclusion off of the non-overlapping 95% confidence intervals and also by the difference in magnitudes in the measure of association. We have added the text: “, as demonstrated by the differences in magnitude of the measures of association and non-overlapping confidence intervals”

Comment #11:

The main concerns with the use of administrative databases are the concerns for erroneous classification of diagnosis, which was acknowledged by the authors. Similar to this concern would be that this database only captured the most severe presentation of the disease, the one leading to admission and delivery due to disease severity. Many women presenting with minor symptoms at the moment of delivery are less likely to be tested, diagnosed and therefore included in the "cases". This form of potential misclassification bias should also be added to the limitations.

Response:

We agree with the Reviewer's concerns about the use of administrative data and the concerns for misclassification. We have made the following changes in our Limitations section of our DISCUSSION:

“As a result, we were unable to ascertain gestational age at influenza diagnosis, initial treatment for influenza, influenza subtypes, severity of infection, vaccination status and diagnostic and confirmatory methods used. We were also unable to assess for changes in diagnostic testing or changes in coding practice during the 19-year study period. Furthermore, the use of administrative data could have resulted in both under ascertainment and misclassification of influenza. It is possible our analysis may have captured only the most severe cases of influenza and that influenza diagnoses made earlier in pregnancy may not have been captured using delivery administrative data.”

Comment #12:

The authors are comparing 2 very different groups, especially when we look at the size of the study cohorts. Adding a propensity score analysis may further reduce the risk of confounding.

Response:

Given that the exposure of interest is a disease state rather than a treatment or intervention, we believe propensity matching would not be an appropriate approach given influenza is not a treatment that a provider chooses. Though we were able to adjust for many clinical, demographic, and obstetrical covariates due to a large sample size (without concern for overfitting the model), residual confounding is still possible. We have added to the Limitations section of our DISCUSSION:

“While we attempted to adjust for multiple confounding socio-demographic, clinical, and obstetric factors (which was possible given the large sample size), residual confounding is still possible.”

Reviewer #2

Comment #1:

This analysis was limited to data through the third quarter of 2015, after which the NIS switched to use of ICD-10 codes. The authors should be aware that CDC has published an appendix which presents the SMM indicators and corresponding ICD-9-CM/ICD-10-CM/PCS codes during delivery hospitalization (https://urldefense.proofpoint.com/v2/url?u=https-3A__www.cdc.gov_reproductivehealth_maternalinfanthealth_smm_severe-2Dmorbidity-2DICD.htm&d=DwIGaQ&c=iORugZls2LIYyCAZRB3XLg&r=tIe4oGY4yI0XNgP6f9Qnt3vfLKJWjyX5KfwMUet_O10&m=PFO-XYqiHnIjY81zJSGsWduc2SlqE_mJRdMpDmUyni4&s=VW6hBiR1ZGHezMQ3mXGk_GxJT-ZOnYBq1ufnJw7kJcM&e=). The overall associations and conclusions are well supported using the ICD-9-based data, but if feasible, the authors might consider updating their analysis with more recent years of data using ICD-10-based data, which might be more applicable for surveillance moving forward.

Response:

While the ICD-10 codes have not been well validated for these conditions, we have recently identified ICD-10 General Equivalence Mappings (GEM) that were developed by AHRQ and other organizations. We have now utilized these GEM models to convert our ICD-9 codes to ICD-10 codes. Hence, the updated analysis uses data through 2018.

We have added in the METHODS: “The primary exposure was an influenza diagnosis code present at delivery hospitalization, which was identified using ICD-9-CM and ICD-10-CM codes. ICD-9-CM codes were identified from prior research and translated to ICD-10-CM codes via the publicly available General Equivalence Mappings SAS programming (Cary, NC) provided by the Centers for Medicare and Medicaid Services and National Center for Health Statistics. (citations in text)”

Comment #2:

It is unclear to this reviewer if the authors were able to make a distinction between influenza detected at delivery hospitalization vs a diagnosis code of influenza that carried over from infection earlier in the pregnancy. It could be made more explicit that the exposure in this analysis is an influenza diagnosis code from the inpatient delivery hospitalization administrative data rather than infection at delivery.

Response:

We agree with the Reviewer’s point and note that we are unable to distinguish between influenza detected at a delivery hospitalization versus a prior infection. We do acknowledge the Reviewer’s point in our Limitations section. Throughout the paper now we state that “influenza diagnosis documented at delivery hospitalization” and justify in the METHODS that “An influenza diagnosis could have been made at the time of delivery hospitalization or earlier in pregnancy, which is not possible to ascertain when using administrative data at the time of delivery hospitalization.”

Comment #3:

The SMM indicators chosen by authors as “influenza SMM” also happen to be common outcomes for other severe conditions, and it is challenging to distinguish influenza from other possible contributors to the rise in SMM. It might be helpful to include the specific adjustment factors in the methods section and tables 3 and 4. Presenting the directed acyclic graph (DAG), might be helpful. As labeled, the figure might be misinterpreted as implying that influenza was the major contributor to the rise in influenza-related SMM over time.

Response:

We have added the following Limitation to our DISCUSSION: “Additionally, many measures of SMM may not be a result of influenza, but rather due to other common medical and obstetrical complications during delivery hospitalization. Influenza may be a confounder and not a causal risk factor in identifying patients at higher risk of SMM. Finally, while we were able to demonstrate an association between influenza and SMM at the delivery hospitalization, influenza may not have been the primary cause of SMM.”

In the statistical analysis section of our METHODS, we have added a sentence describing the covariates included in the multivariable model:

“Models included the following covariates: patient demographic (age, insurance type, median income quartile based on residential ZIP code, reported race/ethnicity), clinical (pre-gestational diabetes, asthma, obesity, and chronic hypertension), and obstetric (gestational diabetes, mode of delivery, placental abruption and/or antepartum hemorrhage, hypertensive diseases of pregnancy including preeclampsia and gestational hypertension, and multiple gestation), hospital characteristics (U.S. region, and hospital type), and year of hospitalization.”

Comment #4:

Line 25: "Women with influenza a delivery hospitalization..." to "Women with influenza AT delivery hospitalization".

Response:

We have made the correction as recommended.

Comment #5:

Line 73: A conclusion statement was made on trend over time, however, data regarding trend over time was not presented in the results section of the abstract.

Response:

We have made the following changes in the Results section of our ABSTRACT to answer the Reviewer's comment: "During the study time period, the rate of SMM was higher with an influenza diagnosis (86 to 410 cases per 10,000 delivery hospitalizations) compared to without (53 to 70 cases per 10,000 delivery hospitalizations). SMM increased over the study period for deliveries with and without an influenza diagnosis code, but the increase was larger in the presence of influenza ($p<0.01$)."

Comment #6:

Line 154: Based on the results, the authors may have intended to say "income quartile" rather than ZIP code.

Response:

We have changed this in our methods to the more accurate title for the variable:

"Demographic factors included maternal age (15-17, 18-24, 25-29, 30-34, 35-39, 40-54 years old), payer type (Medicare, Medicaid, private, self-pay, no charge, other), median income quartile based on ZIP code (quartiles 1(low) to 4 (high)), and maternal race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other, Unknown)."

Comment #7:

Line 191-195: The observations for differences in obstetric outcomes were not addressed in the discussion.

Response:

We have added the following to the discussion: "We also found that influenza was associated with an increased risk of both preterm birth as well as hypertensive disorders of pregnancy." The paragraph then compared this finding to prior studies that have assessed the association between influenza in pregnancy and obstetrical outcomes.

Comment #8:

Line 198-199: Higher frequency of death was noted but was presented as "Those with an influenza diagnosis also had higher frequency of death (0.0% vs. 0.0%, $p<0.01$),..."

Response:

We have made the following changes in our RESULTS section:

"Those with an influenza diagnosis code also had higher frequency of death (0.004% vs. 0.04%, $p<0.01$), and influenza-related complications, including sepsis and shock (0.3% vs. 0.0%, $p<0.01$), mechanical intubation and ventilation (0.17% vs. 0.01%, $p<0.01$), and acute respiratory distress syndrome (0.6% vs. 0.1%, $p<0.01$). They also had a higher frequency of preterm birth (11.7% vs. 6.6%, $p<0.01$) and hypertensive diseases of pregnancy (13.2% vs. 7.7%, $p<0.01$)."

Comment #9:

Line 207-209: It might be helpful to the reader to understand which components of SMM contributed most to the dramatic increased rate observed by the authors.

Response: We have added an additional appendix table where we tabulate the frequency of each SMM component outcome overall and by influenza status (Supplemental Table 5).

Comment #10:

Line 243-244: Influenza SMM indicators have other possible causes. Could other risk factors/etiologies be contributing to the rise?

Response: We have added the following to our DISCUSSION section:

“It is possible that other factors other than influenza may have contributed to the rise SMM over time, including increasing maternal age and chronic comorbid conditions, which may have also increased the severity of influenza.”

Comment #11:

Line 252-254: Could the increase in influenza diagnosis be due to increased recognition and documentation, especially after 2009-2010 when pregnancy was recognized as a risk factor for severe illness?

Response:

Our findings actually showed a relatively stable prevalence of delivery hospitalizations with influenza diagnosis codes. In the limitations section we do address the fact that documentation and abstraction of influenza may have changed over time.

Comment #12:

Line 279-281: The authors might have intended to say "cause" rather than "indication".

Response:

We have made this correction in our revised draft.

Comment #13:

Line 292: missing punctuation

Response:

We have made this correction in our revised draft.

Comment #14:

Tables 3 and 4: Strongly consider including in a footnote what factors were included in adjustment.

Response:

We have made a footnote to include what factors are included in the adjusted model.

Reviewer #3

Comment #1

Severe influenza is associated with preterm delivery, term labor and maybe a medical indication of induction of labor. Because the study design only includes influenza associated with the delivery hospitalization, the study population has a higher concentration of severe influenza than if we determined the obstetrical outcomes including those hospitalizations for influenza for which delivery did not occur. Please note this in the limitations paragraph of the discussion.

Response: We added the following sentence to address this comment in the Limitations section of our DISCUSSION section:

“If most influenza diagnoses documented at the time of delivery hospitalization were diagnosed rather than documented at that time, it is possible our analysis may have captured the most severe cases of influenza. Further data are needed with regards to the impact of influenza during pregnancy as part of both routine and emergency antepartum care.”

Comment #2:

I recommend statistically comparing the clinical characteristic in Table 1 between the no influenza group and the influenza group. Do you have any data on the obesity rates between groups? Please note in the limitations of the discussion that there are several confounding variables that are known to be associated with both severe maternal morbidity as well as severe influenza, therefore causation cannot be assessed.

Response:

Given the large sample size, we chose to not provide statistical tests for significance when comparing groups given that most if not all variables will be statistically significant even if not a clinically significant difference. Should the editors desire for p-values to be provided, we can do so. We also have added information regarding obesity. We have also acknowledged that causation cannot be assessed in our analysis in the DISCUSSION section:

“While we attempted to adjust for multiple confounding socio-demographic, clinical, and obstetric factors (which was possible given the large sample size), residual confounding is still possible. Despite using a large national administrative dataset over 19 years, we may have been underpowered to assess relatively rare individual measures of SMM.”

We have also added: “Influenza may not be a causal risk factor but may identify patients at higher risk of SMM.”

Comment #3:

There is a typo in the Precis. An "a" that should be "at."

Response:

We have made the revision in the revised manuscript.

Comment #4:

Abstract, results: If possible, for the low prevalence outcomes like maternal death, consider reporting cases in 10,000 women.

Response:

To remain within the bounds of the character count for the abstract and for uniformity, we have maintained this description of frequency. Our tables demonstrate the rates of rare events in cases per 10,000 delivery hospitalizations.

Comment #5:

Methods, second paragraph: Please clarify why there was a change made in the way the NIS collected data between 2011 and 2012. What was the benefit to this change?

Response:

The Healthcare Cost and Utilization Project embarked on a methodological redesign of the NIS starting in 2012 to include a sample of discharge records from all HCUP hospitals (as opposed to all discharge records from a sampling of hospitals) and revisions to the definition of discharge. These changes resulted in sampling error reductions and produced improved national estimates compared to prior NIS iterations. Full description of the redesign can be found here: <https://www.hcup-us.ahrq.gov/db/nation/nis/reports/NISRedesignFinalReport040914.pdf>

Comment #6:

Results, 3rd paragraph: Consider reporting low prevalence outcomes like death in cases per 10,000 or 100,000 women to improve precision and clarity.

Response:

In the RESULTS section, we now report outcomes as cases per 10,000 delivery hospitalizations.

Comment #7:

Discussion, 1st paragraph, last sentence: There is period missing at the end of this sentence. Perhaps consider including the specific obstetrical complications of interest.

Response:

Yes, we have added “including preterm birth and hypertensive disorders of pregnancy.”

Comment #8:

Discussion: Consider putting "future research" paragraph after the strengths and limitations paragraphs.

Response:

Yes, as requested we have moved this paragraph to be after the strengths and limitations.

Comment #9:

Discussion: Consider adding unknown vaccination status of the population as a limitation and a consideration for future research.

Response:

We have added the following to the Limitations of our DISCUSSION section.

Comment #10:

Tables 3 and 4: Please list what factors the adjust analysis is adjusted for in the footnote of the table.

Response:

We have now included footnotes for these tables to account for what factors we used in our adjusted analysis, and have added a sentence to the methods section to highlight variables that were adjusted for in all models.

Statistical Editor**Comment #1:**

General: As the Authors know, the NIS is a representative sample, rather than the entire US population. The Abstract and Tables show the entire US deliveries from 2000-2015, based on the sample. That distinction may be lost on the reader in the present version. Since the sample represents ~ 20% of the US population, the counts shown in Tables 1 and 2 are cited to the nearest integer, but that level of precision is not possible in a sample of ~ 1 in 5 births.

Response:

In the methods we have added: “National estimates were created using the weights included in NIS. Because weights can lead to non-integer estimates of subjects, we rounded the number of subjects to the nearest integer.”

Comment #2:

Table 2: The frequencies should all include CIs.

Response:

Yes, we have added 95% CIs for frequencies in table 2.

Comment #3:

Table 3: The estimates of RR and aRR are correct, but the CIs are not, since they were based on extrapolation of the sample to the entire US population, which increases the sample size and consequently makes the CIs too narrow. For example the unadjusted analysis for SMM should have CIs that are ~ 0.47 units wide, rather than the cited value ~ 0.22. That is, based on actual sample sizes that were ~ 1/5 of the US population, the resulting CIs should be more than 2x as wide. Further, the actual counts for rare events, such as maternal death, are few and the aRRs may be over fitted.

Response:

We have also calculated unweighted models with RR and aRR with 95% CIs for tables 2 and 3, and have included them as a supplemental set of tables. We have added the following to the METHODS: "The NIS contains population weights for calculating national estimates, which have been utilized across population-based analyses. (citations in text) These nationally representative weights in the NIS were applied for this analysis. Because weights can lead to non-integer estimates of subjects, we rounded the number of subjects to the nearest integer. Because of the possibility that weights could overestimate confidence intervals we repeated analyses with unweighted data and present risk estimates as supplemental data."

We also added the following to the RESULTS:

"Overall, the rate of SMM excluding transfusion was over three times higher among women with an influenza diagnosis code at delivery hospitalization compared to those without an influenza diagnosis code (226 per 10,000 deliveries vs. 68 per 10,000 deliveries) (Table 2, unweighted data Supplemental Table 1, individual diagnoses Supplemental Table 5)."

"In adjusted analyses, women with an influenza diagnosis codes at delivery hospitalization were at an increased risk of SMM compared to those without (aRR: 2.24, 95% CI: 2.17, 2.31) (Table 2, unweighted data Supplemental Table 1)."

"In secondary analyses, the association between the presence of influenza diagnosis codes and SMM was higher during the 2014-2015 (aRR: 2.78, 95% CI: 2.44, 3.16) and 2017-2018 (aRR: 3.60, 95% CI: 3.21, 4.04) influenza seasons, but not during the 2009-2010 (i.e., H1N1) nor the 2012-2013 influenza seasons, compared to the overall primary analysis (aRR: 2.24, 95% CI: 2.17, 2.31) (Table 3, unweighted data Supplemental Table 2), as demonstrated by the differences in magnitude of the measures of association and non-overlapping confidence intervals."

Comment #4:

Table 4: The conclusion that the SMM rates increase over time is more complicated than "the risk has increased over time". The risk increased during more severe influenza seasons, of which there were none from 2000-2005, one during 2006-2010 and two during 2011-2015. So, it is not that the SMM risk increased over time, but rather that it increased when there was a more severe influenza outbreak. If the years 2016-2020 had no severe influenza outbreaks, then I suspect the SMM rate would then be lower than in 2011-2015. Again, the CIs are incorrect.

Response: We have now provided a supplemental table for table 3 with unweighted models. We have also changed the statement "the risk has increased over time" to "the risk has increased with more severe influenza seasons over time."

Date: Mar 19, 2021
To: "Timothy Wen" timothy.wen2@ucsf.edu
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-137R1

RE: Manuscript Number ONG-21-137R1

Influenza complicating delivery hospitalization and its association with severe maternal morbidity in the United States, 2000-2018

Dear Dr. Wen:

Thank you for submitting a revision of your manuscript. The editors reviewed the revision, and we are concerned that you may not have understood the concerns from the statistical editor regarding the NIS database. His comments regarding the revisions that need to be made in order for us to consider this manuscript for publication, along with the Word document version of the manuscript you should be editing, will be sent in a follow-up email by Emily Fernandez. We look forward to receiving a revision addressing these comments in a point-by-point fashion.

Sincerely,
 Torri

Torri Metz, MD
 Associate Editor, Obstetrics
 Obstetrics and Gynecology

You should be editing the version of the manuscript emailed to you. Please provide a point-by-point response to the following. Make your edits to the attached version of your manuscript, do not "accept all" changes, do not "resolve" comments, and keep "track changes" on. This is important. Once finished addressing editors' concerns and comments, you will upload your updated Word document in Editorial Manager.

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Apr 02, 2021, we will assume you wish to withdraw the manuscript from further consideration.

PLEASE ADDRESS THE FOLLOWING:

1. The following co-author will need to complete our electronic Copyright Transfer Agreement, which was sent to them by email through Editorial Manager. Please note their email address and make sure they are correct. Once the form is complete, please add their disclosures to the "Financial Disclosure" section: Mary Norton (mary.norton@ucsf.edu)
2. Please provide a completed STROBE checklist. The checklist is available at <http://ong.editorialmanager.com>.
3. The abstract is about 87 words over the recommended limit. Please shorten.
4. Please be sure these data (74.7) are stated in the body of your paper, tables, or figures. Statements and data that appear in the Abstract must also appear in the body text for consistency.
5. Table 2 just says "zero" for both of these numbers. Do you want to add the numbers in the abstract to the table to make them consistent?
6. Table 2 says 0.0% and 0.2%, respectively. Please make these consistent between the abstract and text.
7. "SMM" was spelled out according to how it's stated in the abstract: "severe maternal morbidity." Is this correct?
8. Be sure to explain why race was collected.
9. Does the phrase in parentheses here have the correct punctuation? What are you showing in Appendix 1 vs Appendix 2?
10. Is the semicolon correctly added here?
11. Is the semicolon correctly added here?

12. References: Provide the accessed date in reference 33 (month, day, year). Also provide the month and day of the Accessed date in references 12, 17-20, 22-27, 32, 35, and 49.

STATISTICS EDITOR COMMENTS:

I think that my comments re: precision may have been misinterpreted. While I completely agree that the NIS methodology should not be used to extrapolate counts to a decimal fraction of an individual, it also cannot be used to estimate counts to the nearest 1 part per 3 million, as was done in Table 1 for annual counts of non-influenza deliveries. After all, extrapolated counts should be rounded to the nearest 5 and it should be made clear to readers not familiar with NIS that supplemental Table 1 (which should be in main text), represents the actual survey counts. Similarly, the both the unadjusted and adjusted RRs presented in Table 1 are based on the extrapolated counts, which results in narrower CIs than those calculated using the crude data. That is, the estimates presented in the main text and the present Tables are narrower than is possible from the data. If the Authors want to adjust (but not inflate x5) the crude counts to allow for better US national population and then use those for estimation of RR and aRR, that would be OK. The present approach both makes the crude counts more representative (which is good), but inflates the counts which in turn makes the CIs too narrow. While this difference may seem moot for many of the secondary outcomes with relatively large counts, it has increasing importance for rarer outcomes (note the difference in CIs for maternal death when comparing the actual count of N = 15 vs the weighted count of N=73).

If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

- * A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and
- * A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Apr 02, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri D. Metz, MD
Associate Editor, Obstetrics

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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.



University of California
San Francisco

Division of Maternal-Fetal
Medicine

Department of Obstetrics,
Gynecology and
Reproductive Sciences

March 31, 2021

Dear Editors,

Thank you for the invitation to revise our manuscript, "Influenza complicating delivery hospitalization and its association with severe maternal morbidity in the United States, 2000-2015" (ONG 21-137 R1) for consideration for publication in *Obstetrics and Gynecology*. We responded to the editors' and statistical editors' comments on a point-by-point basis at the end of this letter. To respond to the Statistical Editor's comments, we have replaced our unadjusted and adjusted analyses with unweighted data and have placed our analyses involving weighted data in the appendices.

Thank you for your consideration. Please do not hesitate to contact me with questions.

Sincerely,

Timothy Wen, MD, MPH
Clinical Fellow
Division of Maternal Fetal Medicine
Department of Obstetrics, Gynecology, and Reproductive Sciences
University of California, San Francisco
timothy.wen2@ucsf.edu



Response to Editor Comments for: “Influenza complicating delivery hospitalization and its association with severe maternal morbidity in the United States, 2000-2018”

Editor

Comment #1:

1. The following co-author will need to complete our electronic Copyright Transfer Agreement, which was sent to them by email through Editorial Manager. Please note their email address and make sure they are correct. Once the form is complete, please add their disclosures to the “Financial Disclosure” section: Mary Norton (mary.norton@ucsf.edu)

Response:

The email address for Dr. Norton is correct. We have reached out to Dr. Norton and also have requested that the Editorial Manager resend this to her. We will follow up with Dr. Norton.

Comment #2:

2. Please provide a completed STROBE checklist. The checklist is available at [https://urldefense.com/v3/_http://ong.editorialmanager.com_!!LQC6Cpwp!89PSrWreOLFOHXfTe1T5Xw-TahlhpiPQU2xnfxe_ULeFB--QE8rrGLnZsA-Z_wVII5MR\\$](https://urldefense.com/v3/_http://ong.editorialmanager.com_!!LQC6Cpwp!89PSrWreOLFOHXfTe1T5Xw-TahlhpiPQU2xnfxe_ULeFB--QE8rrGLnZsA-Z_wVII5MR$).

Response:

We have completed this checklist and have attached it our submission.

Comment #3:

3. The abstract is about 87 words over the recommended limit. Please shorten.

Response:

We have shortened the abstract to the word count. Please refer to the tracked changes copy.

Comment #4:

4. Please be sure these data (74.7) are stated in the body of your paper, tables, or figures. Statements and data that appear in the Abstract must also appear in the body text for consistency.

Response:

We have reviewed the manuscript and ensured that 74.7 million is consistent throughout the manuscript.

Comment #5:

5. Table 2 just says “zero” for both of these numbers. Do you want to add the numbers in the abstract to the table to make them consistent?

Response:

Thank you for this comment. In our attempt to shorten our abstract, we have removed these numbers.

Comment #6

6. Table 2 says 0.0% and 0.2%, respectively. Please make these consistent between the abstract and text.

Response:

We have removed this from the abstract to reach the word count.

Comment #7:

7. “SMM” was spelled out according to how it’s stated in the abstract: “severe maternal morbidity.” Is

this correct?

Response:

Yes

Comment #8:

8. Be sure to explain why race was collected.

Response:

Thank you for this point. We have now included the following sentence in our METHODS section:

“Race and ethnicity data were included in the NIS and included in analysis based on prior work in assessing disparities and severe maternal morbidity.(citations in text)”

Comment #9:

9. Does the phrase in parentheses here have the correct punctuation? What are you showing in Appendix 1 vs Appendix 2?

Response:

Table 2 now refers to the unweighted data. The weighted data version of Table 2 is represented in Appendix 1. The individual diagnoses of SMM (weighted) refers to Appendix 2.

The lengthier version should read: “(Table 2. For weighted data, please refer to Appendix 1. Individual SMM diagnoses (weighted), please refer to Appendix 2).” We will defer to the editorial staff with regards to the wording.

Comment #10:

10. Is the semicolon correctly added here?

Response:

The semicolon should be removed. This should read: “...(Table 2. For weighted data, please refer to Appendix 1).”

Comment #11:

11. Is the semicolon correctly added here?

Response:

The semicolon should be removed. This should read: “...(Table 3. For weighted data analysis, please refer to Appendix 3).”

Comment #12:

12. References: Provide the accessed date in reference 33 (month, day, year). Also provide the month and day of the Accessed date in references 12, 17-20, 22-27, 32, 35, and 49.

Response:

We have now added access dates to these references. Reference 27 and 49 are manuscript articles and we do not believe needs an Accessed date (but we can provide if necessary).

Statistics Editor

Comment #1:

I think that my comments re: precision may have been misinterpreted. While I completely agree that the NIS methodology should not be used to extrapolate counts to a decimal fraction of an individual, it also cannot be used to estimate counts to the nearest 1 part per 3 million, as was done in Table 1 for annual counts of non-influenza deliveries. After all, extrapolated counts should be rounded to the nearest 5 and

it should be made clear to readers not familiar with NIS that supplemental Table 1 (which should be in main text), represents the actual survey counts. Similarly, the both the unadjusted and adjusted RRs presented in Table 1 are based on the extrapolated counts, which results in narrower CIs than those calculated using the crude data. That is, the estimates presented in the main text and the present Tables are narrower than is possible from the data. If the Authors want to adjust (but not inflate x5) the crude counts to allow for better US national population and then use those for estimation of RR and aRR, that would be OK. The present approach both makes the crude counts more representative (which is good), but inflates the counts which in turn makes the CIs too narrow. While this difference may seem moot for many of the secondary outcomes with relatively large counts, it has increasing importance for rarer outcomes (note the difference in CIs for maternal death when comparing the actual count of N = 15 vs the weighted count of N=73).

Response:

We have now updated our analyses to focus primarily on the unweighted data as to avoid narrowing the confidence intervals. We added the following sentence to our METHODS section:

“Because of the possibility that employing population weights could overestimate confidence intervals, our primary analyses are presented using unweighted data. We repeated analyses with weighted data and presented risk estimates as supplemental data.”

To be consistent with presentation of results, we have also rearranged our tables such that the weighted analysis is now presented in the Appendices and the unweighted analysis is presented in the primary results analysis. The numbers have been updated to reflect this.