

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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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:

obgyn@greenjournal.org.

Date: 10/04/2024
To: "Iona Munjal" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-24-1667

10/04/2024

RE: ONG-24-1667: Birth Outcomes from the MATISSE Maternal Vaccine Trial of Bivalent RSVpreF

Dear Dr. Munjal:

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. Due to the topic, they would like to fast-track the manuscript through the revision process.

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). Upload the tracked-changes version when you submit your revised manuscript.

Your submission will be maintained in active status for 7 days from the date of this letter. If we have not heard from you by 10/11/2024, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Please note the following:

As you revise the manuscript to address the reviewer's comments, please edit the text to ensure that it is concisely written to convey the main message. Additionally, please address the statistically significant (and worse) outcomes among the RSV recipients, which are not currently prominently cited or explained.

* 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.

* As of January 2024, only certain article types will appear in the print version of the journal. All accepted articles will continue to publish online. All articles will be indexed in PubMed as an official article of Obstetrics & Gynecology. Additional information is available in the Instructions for Authors (<https://journals.lww.com/greenjournal/Pages/InformationforAuthors.aspx#II>).

* Figures 1-4: Please upload as individual high quality figure files (jpeg or png) in Editorial Manger. The figure legends should remain in the main manuscript.

REVIEWER COMMENTS:

Reviewer #1:

The MATISSE study presents details of preterm birth outcomes associated with RSV preF vaccination. This report is needed given previously reported possible signal for preterm birth risk. Ultimately, I do find this study reassuring, but the way it is written is insufficiently transparent/balanced.

1. Precis: Are you powered for preterm birth-associated adverse outcomes? If not, this shouldn't be the highlight of the

Precis. Rather, you should focus on preterm birth frequency.

2. Abstract: could you clarify in the objective that, although the MATISSE trial found efficacy, there was also a preterm birth signal? This is really the basis for your current analysis.
3. Introduction, lines 45-49: Similar to comment 2, you need to be more straightforward here. There is a concern that there might be a signal for increased preterm birth with RSVpreF vaccination. Say this explicitly and then explain how this analysis can help us understand if the signal is real or concerning.
4. Methods: Please report a power analysis.
5. Results: Can you report statistical analysis (p-value, RR with 95% CI) for preterm birth categories (very or extremely preterm birth) between RSV vaccine and placebo groups overall? The way Table 1 portrays these frequencies doesn't make it easy to understand the difference as the preterm and term deliveries were first separated. Only preterm birth <37 weeks is clear.
6. Discussion, lines 272-273: Even post hoc analyses can include power calculations. More over, this is not just descriptive - you include many examples of analytic statistics.
7. Discussion, lines 277-278 and abstract conclusion: how have you defined "favorable benefit-risk"? I understand what you mean, but this was not a defined, tested hypothesis, and thus this conclusion is a reach.

Reviewer #2:

In this original manuscript, the authors describe "preterm-birth associated adverse outcomes" in vaccinated vs. placebo groups from the MATISSE trial. They describe no adverse signals of PTB, but there are some difference in specific countries and non-HICs which are understated throughout the manuscript. The study topic is of extreme importance given the new data on RSV vaccination and its benefits. However, this manuscript has some significant flaws. Many of the key details that are needed to determine the merit of the study are missing (see below). What the primary and secondary outcomes are is unclear. There is a host of stratified and secondary analysis of which analysis methods are not described. This article could use significant restructuring to clearly describe inclusion/exclusion, exposure, outcomes, how outcomes were ascertained, and analytic plan. The authors describe descriptive statistics - however comparisons between group are shown for some comparisons (which are unclear). The authors then describe that this study was limited by descriptive analysis. These significant flaws dampen the enthusiasm for this manuscript which needs significant reorganization and revision. Specific comments are outlined below.

Precis - the authors state there was "no increase in preterm birth-associated adverse outcomes" in the precis. I would consider revising this to PTB and its associated outcomes. It is hard to read the precise and understand what is a PTB-associated outcome without thinking neonatal adverse outcomes. In addition, the focus of this paper does not gauge risk-benefits of RSV vaccination and this qualifier should be omitted from the Precis.

Abstract: "severe medically attended RSV-associated lower respiratory tract illness" - is there a simpler way to describe this without a string of 6 descriptors of illness? I found this terminology very confusing to read.

- what is preterm-birth related epidemiology vs. outcomes?

Methods - was this a pre specified secondary analysis? What type of study this is is not provided

- It would be helpful in the methods to have some sense of the primary trial, # of patients in trial, and outcomes

- "adverse events of special interest" - is this secondary outcomes?

- A primary outcome is not defined

- Any statistical methods are not defined

Results - if this is evaluating preterm birth (although outcomes are not clear) why were infants included in this analysis? Preterm birth should be a maternal outcome

- line 19-21: the outcome is stated to be related to PTB. However, there is a lot of information on various infant related characteristics that are not pertinent to this analysis

- The authors describe a stratified analysis, which is not presented in the methods

Conclusions

- the authors describe that there was no increase in severe outcomes related to PTB. A) "severe outcomes" are not defined in the abstract" B) this is untrue given PTB was significantly higher in non-HICs or at least South Africa (the non-HICs are

not presented).

- The comment about RSV vaccination continues to have favorable benefit-risk is not the focus of this paper and is not shown in the data presented here.

Introduction:

- Line 47-49: Do the authors mean that outstanding questions were related to costs and any untoward effects on PTB? The authors describe recommendations for RSV Vaccination and then use the same term subsequently which is confusing

- Line 50-55: I believe these lines can be omitted as they are not related to the paper itself

- The introduction is missing an objective - what was the aim of this study? I think it is to describe rates of PTB and other related adverse outcomes in patients randomized to vaccination vs. placebo in the MATISSE trial. However, as written it is vague

- The introduction could use some additional details about MATISSE trial - number of patients, outcomes, where conducted

- Based on the introduction alone, why the description of HICs vs. LICs is unclear - does this apply to the MATISSE trial?

Methods:

- The actual dates of MATISSE should be provided

- Line 64: What are "no increased pregnancy complication risks" - this also seems very subjective

- "Line 66 - what is considered stable? And what conditions?

- Why is preterm birth/delivery considered both a maternal/neonatal outcome. This is unconventional

- how was developmental delay defined and assessed? The outcomes of MATISSE (are not described in the methods) but from the intro suggest outcomes at 180 days. This is < 1 year of life and thus assessing developmental delay is extremely challenging

- What SARS-Co-V2 test was used? Did this change during the study period?

- Who was included in this study - i.e. study population is not described

- The exposure groups (which I presume is vaccination vs. placebo) is not explicitly stated

- It is not stated what is the primary outcome nor secondary outcomes - or how these were ascertained

- Line 82-88: How outcomes are compared is unclear - the authors suggest "Preterm birth assessments" are presented descriptively. However, what is a preterm birth assessment is not defined

- Line 85: What are the birth outcome categories

No details on the stratified analysis by HIC or LIC is offered

- The type of analysis (secondary analysis, prespecified, etc.) is never described

Results

- Are the authors saying 7386 participated in the trial? Line 92 should be clarified

- The need for Line 95-98 is unclear

- Line 99-106: Some of this information - like term births is the converse of preterm births which I believe is the primary outcome.

- Outcomes should also include time from vaccination to delivery if we are looking at "preterm-birth" related outcomes

- The information on HICs/LICs seems randomly strewn amongst the language in this paper and the implications and rationale for this analysis are not provided

- Line 107: Are the safety concerns not part of the primary paper

- Line 108: "overall infant outcomes" - like what? This is vague and not specific. Depending on what the primary and secondary outcomes are - these rates should be described and presented early on. Not just summarized. New outcomes - APGAR scores, adverse events, etc are presented here but never mentioned in methods

- Is there an associated statistics for the late preterm comparisons between RSVpreF and placebo? Line 114
- No comparisons are offered or computed between low birthweight between groups.
- Were infant deaths not described in the primary trial? Perhaps for this study preterm infant deaths are more applicable
- Lines 121 to 127: What is the relationship of this data to the objective of the paper?
- Line 128: This analysis by GA at vaccination is never described in methods. But the authors seem to skim over increased PTB rate for vaccination at 28-32 weeks was significantly increased in the vaccination group.
- Why is this clumped in with income region? The PTB rate is significantly higher in the non-HICs but this is not mentioned in the abstract or acknowledged.
- What is a UMIC? Not spelled out. But also significantly increased risk of PTB that is unacknowledged
- Maternal characteristic subanalysis: This analysis is also not described in methods
- Line 155-157: This is very unclear as to the meaning of this sentence
- COVID-19 analysis did not evaluate whether there was an interaction between COVID, RSV vaccination, and PTB. It is unclear exactly what this analysis adds to the paper. It is also not detailed in the methods

Discussion

- Line 196-197: This is not part of the current original study to be the focus of the discussion.
- The first paragraph of the discussion focuses not on the primary outcomes in the paper but other tangential Secondary outcomes. While it acknowledges increased PTB rates in non-HICs this is not also described in the abstract
- There is no acknowledgement of increased PTB risk at lower GA of vaccine administration
- Perhaps the lower risk of PTB compared to national rates (which isn't described in the paper) is related to screening (which is not described) associated with a large-scale trial
- Line 272-273: This should be stated up front. But, subgroup analysis was performed.
- Line 277-278: This first sentence of the conclusion is not the objective of the study. I'm also not sure if the data supports line 279-281 given the higher rates of PTB in non_HICs and the lack of analysis to describe COVID and RSV interactions

STATISTICAL EDITOR COMMENTS:

Table 1, Fig 1A, Fig 4B: In Table 1, the count for Preterm RSVpref was 206, while elsewhere it was 207. Need to reconcile. If it actually was 206, then the estimates and CI bounds would change slightly, although the inferences would still hold.

lines 102-103: If one of the outcomes of interest was the rate of PTB, then the interval from vaccination to birth could be a biased comparison. Should instead compare the median (Range or IQR) of vaccination/placebo GA for the RSVpref vs placebo as a baseline, then the rates of PTB, then the interval from vaccination to delivery.

line 108-111, Fig 1A: Unclear what is meant by "comparable", but the RR for AEs within 1 month after birth was significantly higher for the RSV cohort. Also, this contradicts line 28.

Fig 4B: Some countries, notably Spain, Chile and Netherlands, each had relatively small counts and hence wide CIs. There is limited stats power to generalize the NS RRs for those examples.

Table 1: The rates of prior PTB were higher in the PTB (overall) than in the term (overall) which was statistically significant, but unsurprising. However, within those with PTB, there was a higher rate of prior PTB among the RSV compared to the placebo groups (4.9 vs 1.2%). This was not adjusted for in the analyses of subsequent PTB rates within the overall or by income strata or by country. Analysis is required (by either adjustment or sensitivity analysis by excluding those with prior hx of PTB), since pre-term birth rate is one of the key outcomes of interest and prior PTB affects the probability of that outcome. For example, were those with prior PTB non-randomly distributed by Income group or by country?

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Sincerely,

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.

Jason D. Wright, MD
Editor-in-Chief
Obstetrics & Gynecology

RE: ONG-24-1667

Dear Dr Wright,

On behalf of my coauthors, I am pleased to resubmit our manuscript titled: "Birth Outcomes from the Matisse Maternal Vaccine Trial of Bivalent RSVpreF" for potential publication in *Obstetrics & Gynecology*.

We have responded to the reviewers' and statistical editor's comments in a point-by-point manner and have provided both a clean and tracked changes version of the manuscript. To adequately address the reviewer and statistical editor comments, we have exceeded the recommended word count limit by <10%.

We believe these changes have strengthened the manuscript and we look forward to your decision regarding publication of our work.

Kind regards,

Iona Munjal, MD
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401 N Middletown Road, Pearl River, NY 10965, USA
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REVIEWER COMMENTS:

Reviewer #1:

The MATISSE study presents details of preterm birth outcomes associated with RSV preF vaccination. This report is needed given previously reported possible signal for preterm birth risk. Ultimately, I do find this study reassuring, but the way it is written is insufficiently transparent/balanced.

1. **Precis:** Are you powered for preterm birth-associated adverse outcomes? If not, this shouldn't be the highlight of the Precis. Rather, you should focus on preterm birth frequency.

Response: We have rephrased the precis based on this and another comment. It now states: "No increases in overall preterm birth frequency and associated outcomes were observed with maternal RSVpreF vaccination, supporting an overall favorable safety profile."

2. **Abstract:** could you clarify in the objective that, although the MATISSE trial found efficacy, there was also a preterm birth signal? This is really the basis for your current analysis.

Response: We have revised the objective of the abstract as follows (lines 6–9): "Maternal RSVpreF vaccination is licensed globally with varying recommendations for gestational age (GA) at administration. Consideration for these recommendations included preterm births observed during the study for which available trial data were insufficient to verify/exclude causal links with RSVpreF."

3. **Introduction, lines 45-49:** Similar to comment 2, you need to be more straightforward here. There is a concern that there might be a signal for increased preterm birth with RSVpreF vaccination. Say this explicitly and then explain how this analysis can help us understand if the signal is real or concerning.

Response: We have revised this sentence in the introduction as follows (lines 46–49): "A consideration for these recommendations was concern regarding preterm births occurring among infant participants during the study for which available trial data were insufficient to verify or exclude causal links with RSVpreF vaccination."

We have revised the final sentence of the introduction to more clearly explain the importance of this analysis as follows (lines 56–59): "To further study preterm births and associated outcomes that occurred in the trial, this descriptive analysis from MATISSE considers preterm birth-related epidemiology and overall infant and preterm infant outcomes using entire trial data after study completion in October 2023."

4. **Methods:** Please report a power analysis.

Response: We have included within the manuscript that this post hoc analysis was not powered to assess differences between groups, based on the modest numerical difference observed. It is acknowledged that retrospective power analyses are difficult to interpret (eg, Zhang Y, Hedo R, Rivera A, Rull R, Richardson S, Tu XM. Post hoc power analysis: is it an informative and meaningful analysis? Gen Psychiatr. 2019 Aug 8;32(4):e100069)

A phase 2 study of the vaccine also showed an imbalance in premature births (6 cases vs 3 cases, unpublished data). If a 2-fold increase in preterm births had been the basis of the power calculation, the power of the present study is >99%. Since such a magnitude of difference did not occur, we can safely rule out a 2-fold increase. Similarly, if a 1.5-fold increase had been posited, the study has 99% power to detect that. Smaller differences such as the observed difference are better evaluated in post-approval surveillance studies, which are ongoing for the vaccine.

5. Results: Can you report statistical analysis (p-value, RR with 95% CI) for preterm birth categories (very or extremely preterm birth) between RSV vaccine and placebo groups overall? The way Table 1 portrays these frequencies doesn't make it easy to understand the difference as the preterm and term deliveries were first separated. Only preterm birth <37 weeks is clear.

Response: A RR and 95% CI for very or extremely early preterm birth has been added (line 132).

6. Discussion, lines 272-273: Even post hoc analyses can include power calculations. More over, this is not just descriptive - you include many examples of analytic statistics.

Response: Please see our response to item 4 above.

7. Discussion, lines 277-278 and abstract conclusion: how have you defined "favorable benefit-risk"? I understand what you mean, but this was not a defined, tested hypothesis, and thus this conclusion is a reach.

Response: We have omitted these statements from the abstract. We feel that based on the totality of the data presented in the initial publication of the primary analysis as well as the post hoc analysis of infant outcomes overall and in those who were born preterm, this sentence is sufficiently supported. However, we have revised this sentence to avoid the term benefit-risk as follows (lines 298–300): “In conclusion, this analysis continues to support the overall favorable safety profile of maternal vaccination with RSVpreF.”

Reviewer #2:

In this original manuscript, the authors describe "preterm-birth associated adverse outcomes" in vaccinated vs. placebo groups from the MATISSE trial. They describe no adverse signals of PTB, but there are some difference in specific countries and non-HICs which are understated throughout the manuscript. The study topic is of extreme importance given the new data on RSV vaccination and its benefits. However, this manuscript has some significant flaws. Many of the key details that are needed to determine the merit of the study are missing (see below). What the primary and secondary outcomes are is unclear. There is a host of stratified and secondary analysis of which analysis methods are not described. This article could use significant restructuring to clearly describe inclusion/exclusion, exposure, outcomes, how outcomes were ascertained, and analytic plan. The authors describe descriptive statistics - however comparisons between group are shown for some comparisons (which are unclear). The authors then describe that this study was limited by descriptive analysis. These significant flaws dampen the enthusiasm for this manuscript which needs significant reorganization and revision. Specific comments are outlined below.

Precis - the authors state there was "no increase in preterm birth-associated adverse outcomes" in the precis. I would consider revising this to PTB and its associated outcomes. It is hard to read the precise and understand what is a PTB-associated outcome without thinking neonatal adverse outcomes. In addition, the focus of this paper does not gauge risk-benefits of RSV vaccination and this qualifier should be omitted from the Precis.

Response: We have rephrased the precis based on this and an earlier comment. It now states: “No increases in overall preterm birth frequency and associated outcomes were observed with maternal RSVpreF vaccination, supporting an overall favorable safety profile.”

Abstract: "severe medically attended RSV-associated lower respiratory tract illness" - is there a simpler way to describe this without a string of 6 descriptors of illness? I found this terminology very confusing to read.

Response: We have simplified the terminology in the abstract as follows (lines 2–6): “In the MATISSE trial, maternal vaccination with bivalent respiratory syncytial virus prefusion F protein-based (RSVpreF) vaccine was effective at preventing severe RSV-associated illness requiring medical attention in infants through 90 and 180 days after birth.

- what is preterm-birth related epidemiology vs. outcomes?

Response: For clarity, we have revised the sentence as follows (lines 9–11): “Therefore, this descriptive post hoc analysis from MATISSE describes preterm birth frequency and infant outcomes overall and among preterm infants.”

Methods - was this a pre specified secondary analysis? What type of study this is is not provided

Response: The design of MATISSE including that it was a phase 3, double-blind, randomized, placebo-controlled trial is provided in the opening sentence of the methods. We have clarified that this is a post hoc analysis as follows (lines 91–94): “Preterm birth (ie, <37 weeks GA) and overall infant and preterm infant outcomes (ie, low birthweight, SAE-related hospitalization, AEs within 1 month of birth, low APGAR score, death within 24 months of birth) described in this post hoc analysis are presented descriptively, using categorical variables and Clopper-Pearson 95% CIs

- It would be helpful in the methods to have some sense of the primary trial, # of patients in trial, and outcomes

Response: We have provided this clarification in the methods as follows (lines 62–65): “Briefly, MATISSE was a phase 3, double-blind, randomized, placebo-controlled efficacy trial conducted in over 7000 participants in 18 countries over 4 RSV seasons (2 per hemisphere) during the COVID-19 pandemic”.

- "adverse events of special interest" - is this secondary outcomes?

Response: AESIs were primary safety endpoints. This has been clarified in the manuscript (line 84).

- A primary outcome is not defined

Response: We have outlined the primary efficacy and safety outcomes of the trial within the methods (lines 65–68).

- Any statistical methods are not defined

Response: Statistical methods in this post hoc descriptive analysis are outlined in the last paragraph of the methods (lines 91–97).

Results - if this is evaluating preterm birth (although outcomes are not clear) why were infants included in this analysis? Preterm birth should be a maternal outcome

Response: We have endeavored to refer to preterm births when referring to maternal outcomes and preterm births when referring to infant outcomes. The objectives of the manuscript have been further clarified to stipulate that the goals of this descriptive analysis were to assess the epidemiology of preterm births and overall infant and preterm infant outcomes using the entire trial data (lines 56–59).

- line 19-21: the outcome is stated to be related to PTB. However, there is a lot of information on various infant related characteristics that are not pertinent to this analysis

Response: We have revised the objectives in the final paragraph of the introduction to describe the objectives of this analysis as follows (lines 56–59): “To further study the occurrence of preterm births and associated outcomes that occurred in the trial, this descriptive analysis from MATISSE considers preterm birth-related epidemiology and overall infant and preterm infant outcomes using entire trial data after study completion in October 2023.”

We have also clarified in the last paragraph of the methods that preterm birth assessments and overall infant and preterm infant outcomes are described in this post hoc analysis (lines 91–94).

- The authors describe a stratified analysis, which is not presented in the methods

Response: We have revised the methods to note that outcomes were stratified by income categories (lines 100–103).

Conclusions

- the authors describe that there was no increase in severe outcomes related to PTB. A) "severe outcomes" are not defined in the abstract" B) this is untrue given PTB was significantly higher in non-HICs or at least South Africa (the non-HICs are not presented).

Response: We have rephrased the abstract Conclusion (lines 28–29) as follows: “No overall increase in clinically significant infant outcomes related to preterm births was observed with maternal RSVpreF vaccination”.

- The comment about RSV vaccination continues to have favorable benefit-risk is not the focus of this paper and is not shown in the data presented here.

Response: We have revised this sentence (please see response to Reviewer #1, Question 7 above).

Introduction:

- Line 47-49: Do the authors mean that outstanding questions were related to costs and any untoward effects on PTB? The authors describe recommendations for RSV Vaccination and then use the same term subsequently which is confusing

Response: We have revised this sentence to remove mention of cost effectiveness as follows (lines 46–49): “A consideration for these recommendations was concern regarding preterm births occurring among infant participants during the study for which available trial data were insufficient to verify or exclude causal links with RSVpreF vaccination.”

- Line 50-55: I believe these lines can be omitted as they are not related to the paper itself

Response: We respectfully would prefer to keep this paragraph on preterm birth rates in non-HICs and risk factors in the manuscript. We feel this context is important as this paper may be read by a wide audience including a variety of providers who might provide care to infants and pregnant individuals.

- The introduction is missing an objective - what was the aim of this study? I think it is to describe rates of PTB and other related adverse outcomes in patients randomized to vaccination vs. placebo in the MATISSE trial. However, as written it is vague

Response: We have revised the objectives in the final paragraph of the Introduction to describe the objectives of this analysis as follows (lines 56–59): “To further study preterm births and associated associated outcomes that occurred in the trial, this descriptive analysis from MATISSE considers preterm birth-related epidemiology and overall infant and preterm infant outcomes using entire trial data after study completion in October 2023.”

- The introduction could use some additional details about MATISSE trial - number of patients, outcomes, where conducted

Response: We have included details regarding MATISSE in the first paragraph of the methods (lines 62–68).

- Based on the introduction alone, why the description of HICs vs. LICs is unclear - does this apply to the MATISSE trial?

Response: This post hoc assessment stratifying results by HICs versus non-HICs was driven by the clear difference in baseline preterm birth rates in different geographical regions. This was a natural categorization to investigate whether there were differences in the benefit-risk assessment.

Methods:

- The actual dates of MATISSE should be provided

Response: The dates of the MATISSE trial are provided on line 107.

- Line 64: What are "no increased pregnancy complication risks" - this also seems very subjective

Response: Consistent with most clinical investigational studies, investigators were given some leeway in managing their patients. This also better reflects real-world clinical practice.

- "Line 66 - what is considered stable? And what conditions?"

Response: This has been clarified as follows (lines 71–76): "Maternal participants with underlying stable conditions before enrollment were included (eg, treated hyperthyroidism or hypothyroidism and controlled disorders of glucose intolerance antedating pregnancy or occurring during pregnancy if uncontrolled at the time of consent)."

- Why is preterm birth/delivery considered both a maternal/neonatal outcome. This is unconventional

Response: We have endeavored to refer to preterm deliveries when referring to maternal outcomes and preterm births when referring to infant outcomes. In this type of clinical trial, the maternal participants are followed separately and independently of their infants, which are also participants; therefore, each have independent outcomes.

- how was developmental delay defined and assessed? The outcomes of MATISSE (are not described in the methods) but from the intro suggest outcomes at 180 days. This is < 1 year of life and thus assessing developmental delay is extremely challenging

Response: Developmental delay was to be assessed by clinical expertise using local guidelines and standards of care and must have been assessed for seriousness and reported accordingly. The specific term (eg, fine motor delay or speech delay) associated with developmental delay was to be provided. In the final analysis of the trial, which we hope to soon publish, this outcome was reported for up to 2 years.

- What SARS-CoV-2 test was used? Did this change during the study period?

Response: Because of the rapidly changing situation during the pandemic and the number of sites and countries included in the trial, a wide range of SARS-CoV-2 tests could have been used.

- Who was included in this study - i.e. study population is not described

Response: The study populations of maternal participants and their infants are described in the methods (lines 69–76).

- The exposure groups (which I presume is vaccination vs. placebo) is not explicitly stated

Response: The exposure groups, which are RSVpreF or placebo, are described in the methods (lines 80–81).

- It is not stated what is the primary outcome nor secondary outcomes - or how these were ascertained

Response: We have included clarification on the primary efficacy outcomes and the primary safety outcomes, which were reported previously (lines 65–68).

- Line 82-88: How outcomes are compared is unclear - the authors suggest "Preterm birth assessments" are presented descriptively. However, what is a preterm birth assessment is not defined

Response: We have clarified this and the sentence now states (lines 91–94): "Preterm birth (ie, <37 weeks GA) and overall infant and preterm infant outcomes (low birth weight, SAE-related hospitalization, AEs within 1 month of birth, low APGAR score, death within 24 months of birth) described in this post hoc analysis are presented descriptively..."

- Line 85: What are the birth outcome categories

Response: These are low birth weight, SAE-related hospitalization, AEs within 1 month of birth, low APGAR score, death within 24 months of birth. These have been added to the methods as described in the previous query.

No details on the stratified analysis by HIC or LIC is offered

Response: We have clarified in the last paragraph of the methods that this was stratified by World Bank income subcategories (lines 100–103).

- The type of analysis (secondary analysis, prespecified, etc.) is never described

Response: We have clarified that this is a post hoc analysis that is presented descriptively (lines 91–94).

Results

- Are the authors saying 7386 participated in the trial? Line 92 should be clarified

Response: This has been revised as follows (lines 107–108): "From June 17, 2020–October 27, 2022, 7386 pregnant individuals participated in the trial and received RSVpreF (n=3698) or placebo (n=3688; Appendix 3)."

- The need for Line 95-98 is unclear

Response: This sentence on the percentages of participants with first trimester dating ultrasounds in HICs versus non-HICs was provided because gestational dating varies owing to wide geographic variability regarding when these ultrasounds are performed. The relevance of this result is stipulated in the discussion as first-trimester dating ultrasounds, which were performed more frequently in HICs than non-HICs, can provide more reliable gestational age estimates than second-trimester dating ultrasounds, which were used in about half of non-HICs assessments.

- Line 99-106: Some of this information - like term births is the converse of preterm births which I believe is the primary outcome.

Response: We have revised the objectives of the manuscript to include overall infant outcomes as well as those born at term and preterm. We feel to provide context on the birth outcomes from the trial, both overall and in infants born preterm, it is important to also provide these assessments of outcomes in infants overall and those who were born at term.

- Outcomes should also include time from vaccination to delivery if we are looking at "preterm-birth" related outcomes

Response: Outcomes stratified from time from vaccination to delivery are provided in Table 1.

- The information on HICs/LICs seems randomly strewn amongst the language in this paper and the implications and rationale for this analysis are not provided

Response: This post hoc assessment stratifying results by HICs versus non-HICs was driven by the clear difference in preterm birth rates in different geographical regions. This was a natural categorization to consider whether there were differences in the benefit-risk assessment.

- Line 107: Are the safety concerns not part of the primary paper

Response: The safety concerns were part of the primary analysis, and part of the final report of the trial that included up to 2 years safety follow-up of infants through study completion and which we hope to publish as a companion manuscript to this current manuscript.

- Line 108: "overall infant outcomes" - like what? This is vague and not specific. Depending on what the primary and secondary outcomes are - these rates should be described and presented early on. Not just summarized. New outcomes - APGAR scores, adverse events, etc are presented here but never mentioned in methods

Response: Infant outcomes (ie, low birth weight, SAE-related hospitalization, AEs within 1 month of birth, low APGAR score, death within 24 months of birth) are now described in the methods (lines 91–93).

- Is there an associated statistics for the late preterm comparisons between RSVpreF and placebo? Line 114

Response: The authors feel that an analysis of the births 34–<37 weeks would be difficult to interpret, as it ignores preterm births occurring earlier than 34 weeks. Therefore, we believe analyses of preterm births up to specific GA limits are more meaningful (eg, all births; <37 weeks GA, <32 weeks GA).

- No comparisons are offered or computed between low birthweight between groups.

Response: This comparison is provided in Figure 2.

- Were infant deaths not described in the primary trial? Perhaps for this study preterm infant deaths are more applicable

Response: Infant deaths were described in the primary analysis. However, we have included this information based on the final data and for infants overall and those born preterm specifically to better ascertain the safety profile of maternal vaccination with RSVpreF on infant outcomes. Notably, this information is important in the context of the recently reported phase 3 trial of a monovalent RSV prefusion F subunit vaccine candidate, RSVpreF3, which was terminated early because of imbalances in neonatal deaths (attributed to prematurity) between vaccine and placebo groups (as described in the discussion).

- Lines 121 to 127: What is the relationship of this data to the objective of the paper?

Response: Please see our previous response. We have also clarified that objectives of this assessment include consideration of infant outcomes overall and in infants born preterm.

- Line 128: This analysis by GA at vaccination is never described in methods. But the authors seem to skim over increased PTB rate for vaccination at 28-32 weeks was significantly increased in the vaccination group.

Response: We have added “by GA at vaccination” to the methods (line 96). We included the relative risk of preterm birth for vaccination given at 28–<32 weeks GA both in text (lines 150–151) in the results and within Figure 3.

- Why is this clumped in with income region? The PTB rate is significantly higher in the non-HICs but this is not mentioned in the abstract or acknowledged.

Response: The significantly higher preterm birth rate is described in the abstract (lines 24–27) as well as in the discussion (lines 222–225). As mentioned previously, this post hoc assessment stratifying results by HICs versus non-HICs was driven by the clear difference in preterm birth rates in different geographical regions. This was a natural categorization to consider whether there were differences in the benefit-risk assessment.

- What is a UMIC? Not spelled out. But also significantly increased risk of PTB that is unacknowledged

Response: UMIC has been defined as upper-middle-income country at first mention (line 102). For the assessments stratified by HIC and non-HIC, UMIC, low-income country (LIC), and lower-middle income country (LMIC) are included within the non-HIC groupings particularly because of the small numbers in LICs and LMICs limiting meaningful assessments.

- Maternal characteristic subanalysis: This analysis is also not described in methods

Response: We have added the following to the methods (lines 97–100): “Preterm delivery rates among pregnant individuals were assessed by demographic characteristics and medical history including number of previous pregnancies, smoking/alcohol use, anemia, genitourinary infections, diabetes, hypertension and vaccination status.”

- Line 155-157: This is very unclear as to the meaning of this sentence

Response: This has been revised as follows (lines 174–181): “Potential indications for preterm delivery among maternal participants, including maternal/fetal indications and pregnancy complications (Medical Dictionary of Regulatory Activities [MedDRA] terms of cholestasis of pregnancy, diabetes mellitus, gestational diabetes, anemia, amniotic cavity infection, fetal growth restriction, placental insufficiency, premature placental separation, threatened uterine rupture), were overall similar between study groups (Appendix 10).”

- COVID-19 analysis did not evaluate whether there was an interaction between COVID, RSV vaccination, and PTB. It is unclear exactly what this analysis adds to the paper. It is also not detailed in the methods

Response: The rates of seroconversion were low, so a stratified analysis could not be done. However, we feel it is prudent to note potential contributory ecological factors such as the COVID-19 pandemic. The relevance of these results are noted in the discussion. Specifically, we emphasize that no firm conclusions may be drawn regarding associations between maternal COVID-19 and observed RSVpreF preterm deliveries, given the rapidly changing COVID-19 pandemic landscape during MATISSE. In the absence of

large future SARS-CoV-2 waves with naive populations, these conditions are unlikely to be replicated. The COVID-19 assessments were included as AESIs as described in the methods (lines 84–88).

Discussion

- Line 196-197: This is not part of the current original study to be the focus of the discussion.

Response: We respectively feel that overall infant outcomes are germane to the discussion to provide context regarding preterm birth epidemiology and outcomes among term and preterm infants. We have revised the objectives of the manuscript within the introduction to further emphasize the importance of infant outcomes to this assessment.

- The first paragraph of the discussion focuses not on the primary outcomes in the paper but other tangential Secondary outcomes. While it acknowledges increased PTB rates in non-HICs this is not also described in the abstract

Response: Please refer to our previous response above including the revision of the objectives of the manuscript to describe outcomes in infants. Preterm birth rates in non-HICs are described in the abstract (lines 24–27).

- There is no acknowledgement of increased PTB risk at lower GA of vaccine administration

Response: As shown in Figure 3 of the manuscript, which describes preterm births in infants by GA at vaccination, no increased risk of preterm births at lower GA of vaccine administration was observed. The second paragraph of the discussion (lines 226–230) accurately describes this finding.

- Perhaps the lower risk of PTB compared to national rates (which isn't described in the paper) is related to screening (which is not described) associated with a large-scale trial

Response: We thank the reviewer for this insight and have added the potential effect of screening on this lower risk of preterm birth between what was observed in MATISSE versus national rates as follows (lines 234–236): “Eligibility criteria for study entry limiting participants with preterm birth risk factors and enhanced screening associated with conduct of a large clinical trial likely contributed to this finding.”

- Line 272-273: This should be stated up front. But, subgroup analysis was performed.

Response: For clarity, we have omitted “or for further analysis of subgroups” from the limitations. We have revised the first sentence of the discussion to include clarification that this was a post hoc analysis (line 216).

- Line 277-278: This first sentence of the conclusion is not the objective of the study. I'm also not sure if the data supports line 279-281 given the higher rates of PTB in non_HICs and the lack of analysis to describe COVID and RSV interactions

Response: The concluding paragraph has been revised to remove mention of efficacy outcomes and instead describes the overall favorable safety profile of maternal vaccination with RSVpreF (lines 298–304). The limitations including that all potential confounding risk factors for preterm delivery may not have been captured in all maternal participants, and COVID-19 rates were likely underestimated due to passive reporting and inability to assess reinfections are described in the preceding paragraph. The intention of the remainder of the concluding paragraph of the discussion was to put this analysis in the context of future pharmacovigilance activities to supplement our assessment and that of other groups.

STATISTICAL EDITOR COMMENTS:

Table 1, Fig 1A, Fig 4B: In Table 1, the count for Preterm RSVpref was 206, while elsewhere it was 207. Need to reconcile. If it actually was 206, then the estimates and CI bounds would change slightly, although the inferences would still hold.

Response: There was a set of preterm twins whose mother received RSVpref. Table 1 describes maternal outcomes (ie, 206 preterm births in the RSVpref group). This has been clarified as a footnote to Table 1. In contrast Figure 1A and Figure 4B describe infant outcomes, so there were 207 infants in this group including the set of twins.

lines 102-103: If one of the outcomes of interest was the rate of PTB, then the interval from vaccination to birth could be a biased comparison. Should instead compare the median (Range or IQR) of vaccination/placebo GA for the RSVpref vs placebo as a baseline, then the rates of PTB, then the interval from vaccination to delivery.

Response: The summaries of vaccination – delivery interval in Appendix 6 are for the whole study, regardless of whether the delivery was premature or not, and so are not biased. Mean, median, and range are presented. It is acknowledged that the summaries of interval in Table 1 when presented for preterm and term deliveries separately are biased. Overall, infant births were not noted to occur closer to administration for RSVpref versus placebo.

line 108-111, Fig 1A: Unclear what is meant by "comparable", but the RR for AEs within 1 month after birth was significantly higher for the RSV cohort. Also, this contradicts line 28.

Response: We agree with this assessment and the sentence has been revised as follows (lines 124–127): “Rates of preterm births and low birthweight, low APGAR scores, and serious adverse event (SAE)-related hospitalization in the neonatal period were comparable between infants whose mothers received RSVpref or placebo (Figure 1A).” The first line of the conclusion section of the abstract refers to clinically significant outcomes, which does not include AEs occurring within 1 month after birth.

Fig 4B: Some countries, notably Spain, Chile and Netherlands, each had relatively small counts and hence wide CIs. There is limited stats power to generalize the NS RRs for those examples.

Response: In the interests of transparency and presenting the totality of data, we respectively request that data for Spain, Chile, and the Netherlands be maintained in the manuscript. The wide confidence intervals are consistent with the small sample sizes, which are also presented within the table associated with the figure.

Table 1: The rates of prior PTB were higher in the PTB (overall) than in the term (overall) which was statistically significant, but unsurprising. However, within those with PTB, there was a higher rate of prior PTB among the RSV compared to the placebo groups (4.9 vs 1.2%). This was not adjusted for in the analyses of subsequent PTB rates within the overall or by income strata or by country. Analysis is required (by either adjustment or sensitivity analysis by excluding those with prior hx of PTB), since pre-term birth rate is one of the key outcomes of interest and prior PTB affects the probability of that outcome. For example, were those with prior PTB non-randomly distributed by Income group or by country?

Response: The number of subjects in the study with a history of preterm birth was small, limiting the ability to draw conclusions. We have added the following to the manuscript to clarify (lines 165–167): “When those with a history of preterm birth were excluded, the imbalance in the rates of preterm birth in the study was virtually unchanged (RSVpref, 5.4%; placebo, 4.7%; RR=1.15; 95% CI 0.94–1.40).”