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.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Jan 18, 2022
To: "Ayodeji Sanusi" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-2413

RE: Manuscript Number ONG-21-2413

Timing of adjunctive azithromycin at non-elective cesarean delivery and post-cesarean infection

Dear Dr. Sanusi:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

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 Feb 08, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Obstetrics and Gynecology
Manuscript # ONG-21-2413
"Timing of adjunctive azithromycin at non-elective cesarean delivery and post-cesarean infection"

GENERAL

The submitted manuscript is a secondary analysis of a previously conducted randomized controlled trial describing specific timing of adjunctive prophylactic azithromycin administration at time of cesarean delivery (Tita 2016).

1. The abstract states that risks of the primary outcome were significantly lower for patients receiving azithromycin within 60 minutes of incision, followed by (Line 46) "Risks were also lower, but not statistically significant in the group receiving >60 minutes prior to incision…" One cannot state conclusively that the risks were lower in this subgroup as statistical significance was not achieved. See also Lines 186-187 and consider revision.
2. Consequently, consider revising to the conclusion to mirror the study findings that "administration of azithromycin within 60 minutes of incision for cesarean delivery reduced the primary studied outcome".
3. Please include the data regarding timing of azithromycin administration following skin incision, as this is not presented in either the text or Table 2 (i.e., the manuscript lists only "after skin incision")? Did all occur within 60 minutes? (Lines 168-169 would suggest some patients were treated >60 minutes post-incision)
4. Did any of the patients included in the study experience postpartum hemorrhage and/or require repeat dosing of prophylactic antibiotics?
5. (Line 102) Recognizing the criteria for original study inclusion/exclusion are described in the original manuscript, for clarity consider briefly summarizing for the reader.
6. Consider incorporating a review of azithromycin and cefazolin pharmacokinetics in the Discussion section, along with typical antibiotic susceptibilities of common organisms implicated in the pathogenesis of postpartum endomyometritis and wound infections.

Reviewer #2:

Summary of submission:
This is a secondary analysis of data arising from a multi-center RCT of adjunctive azithromycin compared to placebo among women with singletons undergoing unscheduled cesarean delivery; this analysis investigates whether there exists an association between timing of initiation of study drug and composite post-operative infection risk.

Precis:
This is a well-written summary of study findings.

Abstract:
Summarizes study objective, design, results and conclusions effectively.

Line 26: In the introduction, maternal and neonatal infectious morbidity are identified as overarching outcomes of interest; however, in the abstract, only maternal infectious morbidity is stated.

Line 34: Similarly, in the study design section, "other maternal infections" is stated as a component of the composite outcome, while neonatal infectious morbidity is not mentioned.
Neonatal morbidity is not addressed in the results or conclusion either. Consider more clearly stating in the abstract whether or not neonatal infectious outcomes were analyzed and ensure that the abstract is consistent with the body of the manuscript in this way.

Intro:
The objective is clearly stated "our primary objective was to evaluate the association between timing of adjunctive azithromycin administration for prophylaxis at non-elective cesarean delivery and maternal and neonatal infectious morbidity."
Is there a hypothesis?

Methods:
The approach to this secondary analysis was thoroughly and clearly explained.

Line 122: Consider elaborating on how the trained research staff ascertained the outcomes of interest - by chart review? ICD coding? Patient interview? Survey? While these details are elucidated in the parent manuscript, it would be helpful to have this component of the study design re-explained in the present manuscript.

Results:
The results are well-organized. The tables are easy to follow and contain all pertain information needed to understand outcomes.

Discussion

The discussion is a thoughtful reflection on the findings of this study. Strengths and limitations are identified. Consider commenting on the following in terms of additional limitations: would the manner in which the trained research staff ascertained the outcomes of interest introduce any bias? For example, does the three month follow up phone call conducted by trained researchers introduce any element of recall bias? Without looking at the parent manuscript, it is not clear what outcome data was collected from the three month phone call.

Line 200: Along similar lines, while there exist guidelines for redosing standard antibiotics used for infection prophylaxis at time of cesarean section, the guidance on redosing azithromycin is limited and another avenue arguably worthy of study.

Reviewer #3:

This is a well written manuscript. The authors perform a secondary analysis of the CSOAP trial to investigate the impact that timing of azithromycin administration has on SSI reduction.

Abstract: Succinct and well written. I would prefer that the timing of antibiotic administration be listed in chronologic order and mirror the tables: after skin, 0-30, 30-60, >60. (True for abstract and throughout the manuscript)

Introduction: The first paragraph provides a lovely overview of SSI, but could be more focused on why the timing of antibiotic administration is important. Additionally, I think a justification of why we need specifically to look at timing of azithromycin prophylaxis is important.

Methods: While I appreciate that the details of CSOAP were previously published, readers would appreciate a brief overview. Specifically, the authors need to state when the protocol specified that azithromycin was intended to be started. Was azithromycin timing classified by the start time or end time of the infusion? I presume that it was the start time, but as azithromycin is a one hour infusion I think it is worth stating.

Results: In Table 1, what does standard prophylactic antibiotic referring to? That a patient received any standard prophylactic antibiotic? Or that they received cefazolin as their standard prophylactic antibiotic?

Discussion: Appropriate and fitting. May benefit by comparing to current recommendations on timing of antibiotic prophylaxis.

Throughout the manuscript, you reference elective or non-elective cesareans when I think you mean laboring or unscheduled cesareans.

STATISTICS EDITOR COMMENTS:

Lines 46-47, 150-153: The RR was not different from the null, regardless of its nominal value. Should just state that the RR was NS different from its referent for the subset with azithromycin >60mins pre skin incision. There is no "direction of the effect", it was bounded by 0.10 to 3.36, ie, plausibly protective or plausibly harmful vs its referent.

Table 2 and General: While it is true that there is no statistical difference in RR among the 4 time periods shown, the issue is whether there was sufficient statistical power to generalize that conclusion. Esp for the > 60mins pre-incision category, the counts are relatively small for the primary composite maternal outcome and the resultant CIs are wide, such that the RR (0.59 with CIs = 0.10-3.36) are not different from the null. So, it would seem imprudent to generalize from these data that there is no difference in outcomes for all the times cited. In addition to the RRs, should include CIs for the rates of the primary composite outcome for both azithromycin and placebo groups for each time point.

Table 3: Similar to Table 2, but exacerbated by the smaller differences in crude rates for azithromycin vs placebo, each of the RRs have CIs that include the null. That is, no association. It seems even more fraught than for the maternal comparisons by time point to conclude that the timing of antibiotics has no association with the composite neonatal outcome. Again, should include CIs for the crude rates for the azithromycin and placebo groups for each time point.

EDITOR COMMENTS:

Please remove all causal language as what you are reporting are associations.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

4. 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.

5. 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.

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 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, 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).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

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; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 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 references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and 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.

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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 as a Microsoft Word document. 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 Feb 08, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
Dwight J. Rouse, MD
Deputy Editor, Obstetrics

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

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February 7, 2021

The Editors

Dear Editors:

On behalf of my co-authors, I am pleased to resubmit our revised manuscript, "**Timing of adjunctive azithromycin at unscheduled cesarean delivery and post-cesarean infection**" for consideration for publication in *Obstetrics & Gynecology*. Each author participated actively in researching the subject, drafting sections of the manuscript, editing, and approving the final submitted version.

As the lead author, I affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted, that any discrepancies from the study as planned have been explained and the manuscript is not currently under review by another journal. The authors report no conflicts of interest. Institutional Board Review approval was obtained at all sites for the primary study. This study was presented at the 41st Annual Pregnancy Meeting of the Society for Maternal Fetal Medicine. January 25-30, 2021 (Abstract #1103). The original trial is registered at www.clinicaltrials.gov, NCT01235546.

I have made changes to the manuscript based on the reviewer and editors' comments and these are detailed below. Thank you for considering our manuscript. If you have any additional questions about the manuscript, I will be serving as the corresponding author. We look forward to hearing back from you.

Sincerely,

Ayodeji A Sanusi, MD

REVIEWER COMMENTS:

Reviewer #1:

Obstetrics and Gynecology
Manuscript # ONG-21-2413
"Timing of adjunctive azithromycin at non-elective cesarean delivery and post-cesarean infection"

1. The abstract states that risks of the primary outcome were significantly lower for patients receiving azithromycin within 60 minutes of incision, followed by (Line 46) "Risks were also lower, but not statistically significant in the group receiving >60 minutes prior to incision…" One cannot state conclusively that the risks were lower in this subgroup as statistical significance was not achieved. See also Lines 186-187 and consider revision.

Response:
Revised to state 'Risks were not significantly different in patients receiving azithromycin >60mins before skin incision (0.59 [0.10-3.36]).'

Revised to state 'Therefore, the protective association of adjunctive azithromycin in patients receiving azithromycin within 60minutes prior to, or after skin incision is not unexpected.'

Line change:
Lines 151-152, 426-428

2. Consequently, consider revising to the conclusion to mirror the study findings that "administration of azithromycin within 60 minutes of incision for cesarean delivery reduced the primary studied outcome".

Response:
Revised to 'Adjunctive azithromycin administration within 60 minutes prior to or after skin incision is associated with reduced risks of maternal composite post-operative infection in unscheduled cesarean deliveries.'

Line change:
157-159

3. Please include the data regarding timing of azithromycin administration following skin incision, as this is not presented in either the text or Table 2 (i.e., the manuscript lists only "after skin incision")? Did all occur within 60 minutes? (Lines 168-169 would suggest some patients were treated >60 minutes post-incision)

Response:
'Given more than 60 minutes' was a typographical error and subsequently revised to 'The findings generally show reductions in infectious morbidity, although not statistically significant for the primary

composite when azithromycin was given more than 60 minutes **before** skin incision, or for endometritis when administered within 30 minutes of skin incision,'

We have also included the data on the number of patients who received antibiotics more than one hour after skin incision. We combined this group with other participants treated within one hour after the skin incision for statistical power.

Line change:
263-264, 317-318, 359-361

4. Did any of the patients included in the study experience postpartum hemorrhage and/or require repeat dosing of prophylactic antibiotics?

Response:
We have included information on the redosing azithromycin and the number of patients (3) who experienced postpartum hemorrhage.

Line change:
275-277, 466-469

5. (Line 102) Recognizing the criteria for original study inclusion/exclusion are described in the original manuscript, for clarity consider briefly summarizing for the reader.

Response:
We have updated and summarized the original study's inclusion and exclusion criteria.

Line change:
256-262

6. Consider incorporating a review of azithromycin and cefazolin pharmacokinetics in the Discussion section, along with typical antibiotic susceptibilities of common organisms implicated in the pathogenesis of postpartum endomyometritis and wound infections.

Response:
We have included a review of Azithromycin and Cefazolin's pharmacokinetics along with typical antibiotic susceptibilities of microorganisms

Line change:
366-398

Reviewer #2:

1. Line 26: In the introduction, maternal and neonatal infectious morbidity are identified as overarching outcomes of interest; however, in the abstract, only maternal infectious morbidity is stated.

Response:
We have updated the abstract to reflect both maternal and neonatal morbidity

Line change:
Line 70-71

2. Line 34: Similarly, in the study design section, "other maternal infections" is stated as a component of the composite outcome, while neonatal infectious morbidity is not mentioned.
Neonatal morbidity is not addressed in the results or conclusion either. Consider more clearly stating in the abstract whether or not neonatal infectious outcomes were analyzed and ensure that the abstract is consistent with the body of the manuscript in this way.

Response:
We have updated the study design to include composite neonatal morbidity, NICU admission and neonatal sepsis as secondary outcomes.
We have also indicated in the results the results for neonatal outcomes.

Line change:
78-80, 154-155

3. Intro:
The objective is clearly stated "our primary objective was to evaluate the association between timing of adjunctive azithromycin administration for prophylaxis at non-elective cesarean delivery and maternal and neonatal infectious morbidity."
Is there a hypothesis?

Response:
We have updated the introduction to include our hypothesis.
‘Our hypothesis was that azithromycin when administered as soon as possible after cesarean incision or within one hour prior to skin incision would be associated with a reduction in post cesarean infections.’

Line change:
233-235

4. Line 122: Consider elaborating on how the trained research staff ascertained the outcomes of interest - by chart review? ICD coding? Patient interview? Survey? While these details are elucidated in the parent manuscript, it would be helpful to have this component of the study design re-explained in the present manuscript.

Response:
We have provided additional details on outcomes ascertainment in the methods sections.

'The primary outcome and its components were ascertained through central adjudication by investigators unaware of treatment assignments. Other maternal and infant outcomes were ascertained by trained research staff through review of the electronic medical records and direct questioning in person or by telephone. At the six-week postpartum visit (in-person or by telephone) and at a three-month telephone follow up, participants were asked about infant deaths and adverse events which were verified through medical records. All outcomes are defined in detail in the primary report'

Line change:
293-302

5. Discussion
The discussion is a thoughtful reflection on the findings of this study. Strengths and limitations are identified. Consider commenting on the following in terms of additional limitations: would the manner in which the trained research staff ascertained the outcomes of interest introduce any bias? For example, does the three month follow up phone call conducted by trained researchers introduce any element of recall bias? Without looking at the parent manuscript, it is not clear what outcome data was collected from the three month phone call.

Response:
We have provided the information on what outcome data were collected from the three-month phone call – these were adverse events and infant deaths.

We believe the risk of recall bias from follow up telephone visits are low, as all reported outcomes were also verified with electronic medical records, ana have update the manuscript to reflect these. We also provided information on central adjudication for the primary outcome.

Line change:
293-299, 441-443

6. Line 200: Along similar lines, while there exist guidelines for redosing standard antibiotics used for infection prophylaxis at time of cesarean section, the guidance on redosing azithromycin is limited and another avenue arguably worthy of study.

Response:
We have updated the manuscript to include azithromycin redosing as avenues worthy of potential future studies
‘Further studies are needed to determine whether re-administration of azithromycin would have additional benefits, if initially administered more than one hour from skin incision, in prolonged cesarean deliveries or in those complicated by excessive blood loss’

Line change:
472-475

Reviewer #3:

1. Abstract: Succinct and well written. I would prefer that the timing of antibiotic administration be listed in chronologic order and mirror the tables: after skin, 0-30, 30-60, >60. (True for abstract and throughout the manuscript)

Response:
We have updated all the tables, abstract and body of the manuscript to reflect chronological order of antibiotic administration- after skin incision, 0-30, 30-60 and >60mintes prior to skin incision

Line change:
85, 150, 264, 318, 329, Tables

2. Introduction: The first paragraph provides a lovely overview of SSI, but could be more focused on why the timing of antibiotic administration is important. Additionally, I think a justification of why we need specifically to look at timing of azithromycin prophylaxis is important.

Response:
We have updated the introductory paragraph to include the importance of timing of antibiotic prophylaxis- specifically with standard prophylaxis, timing of administration is associated with post-cesarean infection risk and there is limited data on azithromycin timing for prophylaxis.

Line change:
203-207

3. Methods: While I appreciate that the details of CSOAP were previously published, readers would appreciate a brief overview. Specifically, the authors need to state when the protocol specified that azithromycin was intended to be started. Was azithromycin timing classified by the start time or end time of the infusion? I presume that it was the start time, but as azithromycin is a one hour infusion I think it is worth stating.

Response:
We updated the manuscript to include a brief overview of the inclusion and exclusion criteria, classification of azithromycin timing (by start time when the infusion was connected to the patient) and additional details on outcome ascertainment

Line change:
256-262, 267-268, 293-299

4. Results: In Table 1, what does standard prophylactic antibiotic referring to? That a patient received any standard prophylactic antibiotic? Or that they received cefazolin as their standard prophylactic antibiotic?

Response:
We have updated the table foot note to define ‘standard antibiotic prophylactic and reference the methods section to clarify that standard prophylactic antibiotic was mostly with a first-generation cephalosporin (cefazolin), that administered over a five-minute period as an intravenous push, followed by the study drug (azithromycin or placebo)

Line change:
272-274, Table 1 footnote

5. Discussion: Appropriate and fitting. May benefit by comparing to current recommendations on timing of antibiotic prophylaxis.

Response:
We updated the discussion to include comparisons to current recommendations on antibiotic prophylaxis timing:
‘It is surprising that despite the longer half-life, there was no benefit > 60 minutes prior to skin incision. However, these findings fall in line with current ACOG recommendations to administer prophylactic antibiotics within 1 hour before skin incision.’

Line change:
428-431

6. Throughout the manuscript, you reference elective or non-elective cesareans when I think you mean laboring or unscheduled cesareans.

Response:
We updated the manuscript to reflect non-elective cesareans as ‘unscheduled cesareans’

Line change:
1, 60,70,75,159,232, 257,424, Tables 1,2 & 3 headings

STATISTICS EDITOR COMMENTS:

1.Lines 46-47, 150-153: The RR was not different from the null, regardless of its nominal value. Should just state that the RR was NS different from its referent for the subset with azithromycin >60mins pre skin incision. There is no "direction of the effect", it was bounded by 0.10 to 3.36, ie, plausibly protective or plausibly harmful vs its referent.

Response:
Revised to state 'Risks were not significantly different in patients receiving azithromycin >60mins before skin incision (0.59 [0.10-3.36]).'

Revised to state 'Therefore, the protective association of adjunctive azithromycin in patients receiving azithromycin within 60minutes prior to, or after skin incision is not unexpected.'

Line change:
Lines 151-152, 426-428

2. Table 2 and General: While it is true that there is no statistical difference in RR among the 4 time periods shown, the issue is whether there was sufficient statistical power to generalize that conclusion. Esp for the > 60mins pre-incision category, the counts are relatively small for the primary composite maternal outcome and the resultant CIs are wide, such that the RR (0.59 with CIs = 0.10-3.36) are not different from the null. So, it would seem imprudent to generalize from these data that there is no difference in outcomes for all the times cited. In addition to the RRs, should include CIs for the rates of the primary composite outcome for both azithromycin and placebo groups for each time point.

Response:
We have included the confidence intervals for the rates of all outcomes in the table 2 and updated the conclusions on the test of interaction to reflect that the Breslow-Day test for homogeneity did not suggest any significant differences in maternal and neonatal outcomes between the antibiotic timing groups.

Line change:
Table 2, Line 82,353

3. Table 3: Similar to Table 2, but exacerbated by the smaller differences in crude rates for azithromycin vs placebo, each of the RRs have CIs that include the null. That is, no association. It seems even more fraught than for the maternal comparisons by time point to conclude that the timing of antibiotics has no association with the composite neonatal outcome. Again, should include CIs for the crude rates for the azithromycin and placebo groups for each time point.

Response:
We have included the confidence intervals for the rates of all outcomes in the table 3 and updated the conclusions on the test of interaction to reflect that the Breslow-Day test for homogeneity did not suggest

any significant differences in maternal and neonatal outcomes between the antibiotic timing groups.

Line change:
Table 3, Line 82,353

EDITOR COMMENTS:

1. Please remove all causal language as what you are reporting are associations.

Response:
We have updated the manuscript to reflect associations and avoided the use of words to imply causation (such as effects)

Line changes:
80,82,207,231, 234,307,426,432,464,466, 470,475