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: May 24, 2021
To: "Stephen Rulisa" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-861

RE: Manuscript Number ONG-21-861

Trend and causes of Maternal Mortality in Rwanda. Case study of University Teaching Hospital of Kigali

Dear Dr. Rulisa:

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 Jun 14, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Abstract
Objective: Objective could be succinctly stated without other introductory content in the 'objective' section of abstract.

Results: Would write 'mortality risk' or 'mortality rate' and not ratio, because the raw percentages were not ratios.

Introduction
Line 46 '...annual rate of reduction of 2.9 through the same time period.'
Do the authors mean 2.9% reduction per year?

Line 50 ' The United States of America, a high resource country, has documented an increase in maternal mortality from 9.8 in 2000 to 21.5 in 2017.'
Would cite CDC data which demonstrated 17.3 per 10,000 in 2017.
Would mention that risk is per 10,000 deliveries.
https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm

Line 55 'point of estimate of 542 (UI 498 to 649)'
Would cite denominators.
What does UI mean?

Methods
Was the entire delivery population at CHUK analyzed?

LIne 78-79 Was chi square test used for categorical variables?

Line 83-84 'Average number of maternal deaths was 7.17 ± 4.15, 6.50 ± 2.28 and 4.82 ± 1.33 mothers per month.'
Does ± represent SD, 95% CI, or some other estimate?

I would like to know more about the mortality reduction strategy in Rwanda - when was it initiated relative to when this data was collected.

I would like a few lines about CHUK - how many hospitals feed into it? Would high risk women deliver at CHUK and if so based on what criteria?

I don't understand the reason for the variation in monthly mortality - was this hypothesized a priori by the investigators?

Am presuming so since statistical tests were performed.

Would like some information (maybe one or two sentences) on how cause of death was reviewed and determined.

Results
FIgure 1 and Figure 2 were not included in my PDF file.

Table 2 - looks like obstetric volume went down 20% over 2 years - any specific reason for this?

Table 3 - Information in Table 3 is redundant given Table 4. Could combine.

Table 4 - Why would someone go to the ICU versus not go the ICU? This would be helpful in interpreting these findings. It makes sense that patients with stroke/hemorrhage/PE would be less likely to go to ICU if they experienced sudden death, but some
explanation in results would be helpful.

Table 5 - I don't really understand what comparisons are being made. Perhaps this is because I don't have the additional figure that the analysis is associated with.

Line 110-114 'We also observed a seasonal variation in number of maternal deaths showing an increase from November to March with a peak in January and lower numbers from May through September. This coincides with the known deployment of new medical student graduates to district hospitals where they increasingly become responsible for the management of critically ill pregnant women including their surgical interventions.'
This is interesting - is there any evidence of this type of finding/effect from other medical specialties in the hospital? Or from other hospitals in the region?

Line 116-119 - 'Despite a decline in maternal mortality ratio in Rwanda, the numbers are still far from the sustainable development goals (SDG) target of decreasing maternal deaths below 70 per 100 000 live births(5). The high number of maternal mortality ratio at the main referral hospital is consistent with other countries where majority of deaths occur centrally in the referral hospitals.'
This is a major question I had: as a referral hospital, to what degree are these deaths preventable based on optimal care at your hospital? What proportion of transfers are so ill that quality of care at CHUK is unlikely to change outcomes? Any thoughts to stratifying analysis based on women not transferred in?

The discussion section is generally pretty well written but could be edited to be better. It seems like the major findings of this study are that at your hospital half of deaths were due to sepsis and most deaths were referrals. The public health importance seems to be that the referral hospitals need to do better in terms of preventing infection, managing infection, managing sepsis, and referring patients who may benefit from care earlier.

For other obstetric centers in the region, is sepsis now the leading cause of death by a large margin? Are these findings in line or different from other findings in similar settings?

Reviewer #2: 1) The study is a retrospective analysis of maternal mortalities occurring at the University Teaching Hospital of Kigali, Rwanda (CHUK) from 2017-2019.
2) According to the study, there were 217 maternal deaths occurring in the hospital from 2017-2019 out of 11,308 total maternal admissions (Lines 27-28). Assuming that a "maternal admission" would result in a live birth in most cases, the calculated maternal mortality rate for this single center is 1,919 per 100,000 live births in the three years studied. While the authors indicated that this calculated maternal mortality rate is "consistent with other countries where (the) majority of deaths occur centrally in the referral hospitals" (Lines 118-119), it is still of such magnitude that significant additional discussion (with comparative figures from other countries as cited) is clearly warranted.
3) The authors indicated that sepsis was the most common cause of maternal death in the study and later suggested that "puerperal and postoperative surgical site infections continue to be main causes of sepsis" (Lines 32-33; 132-133). Was the latter statement a general fact or what was actually discovered in the study? How was sepsis diagnosed or the cause of death attributed?
4) The authors cited "newly qualified yet inexperienced doctors" as a factor in the seasonal variation of maternal deaths (Lines 110-114; 144-145). What circumstances (other than timing) would lead the authors to this conclusion? Are there any other factors which may have contributed to this apparent phenomenon? What steps are being taken to mitigate this?
5) Although infection is a clear cause of maternal morbidity in the United States, it is rarely a cause of maternal mortality. Given the target audience, a brief overview of available antimicrobial therapies in smaller district hospitals as well as larger referral centers and how these therapies are typically utilized is necessary for context.
6) Commentary concerning a typical presentation and clinical course of a patient who died during the study period would be beneficial to assist the reader in gaining perspective on the root causes of infectious maternal mortality in Rwanda and what can be done to prevent it. For example, were most of these patients already suspected to be septic on presentation to the outlying "district" hospitals or did they deteriorate after transfer to CHUK? Were these patients already delivered or did they present with signs and/or symptoms of intrauterine infection or inflammation ("Triple I") prior to delivery?

Reviewer #3: Review of Manuscript ONG-21-861 "Trend and causes of maternal mortality in Rwanda. Case study of university teaching hospital of Kigali"

Rulisa and colleagues have submitted what they note is a secondary anlaysis of maternal mortality for the University Teaching Hospital of Kigali (CHUK) which per report is the largest referral hospital in Rwanda. The authors describe this as a cross sectional study although no STROBE checklist is included. Although they provide some information about historical trends in the discussion, placement of this information in the introduction may allow the reader to better evaluate the reported data and results. I have the following questions and comments.

Title - Consider adding the years in the title.

Précis - Consider noting the years of other adjustments as space allows.

Abstract - Eliminate lines 21-24 and just have the objective/purpose of the study.
Line 27 - Was there a primary analysis? What about IRB approval?
Line 30 - I suppose this is the age range in ( ), if so please confirm.

Introduction - Line 57 onward - Since the authors are evaluating outcomes in Rwanda, do they have historical information about maternal mortality in Rwanda rather than just referencing interventions to improve outcomes?

Methods - Line 76-78 - Was there previous knowledge about seasonal differences in maternal mortality? If so what is thought to drive this?

Results - Line 84-85 - You can just list the specific p values and allow the readers to note that there were no significant differences.
Line 88 - Again you do not need to state if there is statistical significance.
Line 89 - Do you have a way to quantify how they were "critically ill"?

Discussion - Line 100 - Some of this historical information needs to be in the introduction in order to help illustrate stability, improvement or worsening in this metric.
Line 112-4 - Has this been previously reported as the presumed reason?
Line 125-128 - Are the top causes of mortality remaining the same or changing?

Tables - Table 1 - Consider noting in the footnote that information was missing for the referring hospital and gravidity variables.

It seems like Table 1 and 2 can be combined with the Table 2 information at the top and then proceed with table 1 data. Alternatively, all of the table 2 data can be referenced in the manuscript which would allow it to be eliminated as a table.

Table 3 - Something happened with the line numbers which makes this a bit hard to read.

Table 4 - Can you add the N so we know how much information you may have as it does not appear to be all 217 patients - for instance under gravidity there is information about 146 patients. I would think there would be information about ICU care yes or no for all patients?

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

General: This report includes maternal deaths at a referral hospital. Most deaths were from outside community hospitals. Are there data re: the number of deaths not recorded? That is, deaths at an outside hospital that were not sent to the referral hospital? Could the variable death rates by season have been affected by differential referral rates by season?

Table 2: Should round the death rates to nearest 0.1% precision and include CIs for each year. Were the deaths per month normally distributed? If not, should cite as median (range or IQR). There is a typo of the SD during 2019. Should be 1.33, not 133.

Table 4: The %s should all be rounded to nearest integer %, not cited to nearest 0.1% precision.

Table 5: Were the distributions normal? If not, should use a non-parametric test and cite as median(range or IQR).

EDITOR 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. 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.

3. 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.

4. 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.

5. 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]."

6. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

7. 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.

8. 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%").

9. 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.

10. 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).

11. When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

Figures 1-2: Please upload as figure files on Editorial Manager.

12. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at https://wkauthorservices.editage.com/open-access/hybrid.html.

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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 Jun 14, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

Cover letter

RE: Manuscript Number ONG-21-861

Trend and causes of Maternal Mortality in Rwanda. Case study of University Teaching Hospital of Kigali from

Dear Editor,

Thank you for giving us the opportunity to review and address the comments of the reviewers. We have included in this cover letter all our responses in red and attach the manuscript with corrections in red. We hope the paper reads better and look forward to your final comments. Thank you

Professor Rulisa

REVIEWER COMMENTS:

Reviewer #1: Abstract
Objective: Objective could be succinctly stated without other introductory content in the 'objective' section of abstract. We have removed a significant portion of the objective stated as advised.

Results: Would write 'mortality risk' or 'mortality rate' and not ratio, because the raw percentages were not ratios. Corrected to mortality rates

Introduction
Line 46 '...annual rate of reduction of 2.9 through the same time period.'
Do the authors mean 2.9% reduction per year? Yes. Corrected

Line 50 ' The United States of America, a high resource country, has documented an increase in maternal mortality from 9.8 in 2000 to 21.5 in 2017.'
Would cite CDC data which demonstrated 17.3 per 10,000 in 2017.
Would mention that risk is per 10,000 deliveries.
https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm
We have substituted the reference but note the mortality ratio is per 100,000 live births
Line 55 'point of estimate of 542 (UI 498 to 649)'
Would cite denominators. DONE by adding per 100,000 live births
What does UI mean? Uncertainty index but we have removed it

Methods
Was the entire delivery population at CHUK analyzed? YES

LIne 78-79 Was chi square test used for categorical variables? YES

Line 83-84 'Average number of maternal deaths was 7.17 ± 4.15, 6.50 ± 2.28 and 4.82 ± 1.33 mothers per month.'
Does ± represent SD, 95% CI, or some other estimate? It is the SD

I would like to know more about the mortality reduction strategy in Rwanda - when was it initiated relative to when this data was collected. The work towards improvement in maternal care spanned over the three years (2017 to 2019) but was particularly intensified in 2019. The intervention was multipronged as it comprised national and local hospital interventions that included the introduction of a national ambulance system, over 90% national insurance coverage. Local interventions addressed improved communication with senior consultants with the creation of a whatsapp platform where emergencies were posted and reviewed, permanent presence of senior anesthesiologist who assisted with intensive care unit (ICU) transfer or managed patients within the maternity when ICU beds were unavailable, reduction in delays in respiratory support by providing an ICU machine in maternity.

I would like a few lines about CHUK - how many hospitals feed into it? Would high risk women deliver at

CHUK and if so based on what criteria? Yes. High risk women delivered at CHUK as it was one of three public referral hospitals. Criteria was based on acuity and unavailability of resources in referring hospital such as lak of intensive care beds or neonatal intensive care units. We have added a comment on this regard in the discussion section

I don't understand the reason for the variation in monthly mortality - was this hypothesized a priori by the investigators? Am presuming so since statistical tests were performed. We knew the trend of having less qualified doctors as recent graduants who take on immediate responsibilities in the smaller hospitals including surgical interventions and its impact on care but we were unaware of the impact on outcome. This was new discovery to us.

Would like some information (maybe one or two sentences) on how cause of death was reviewed and determined. Obstetric hemorrhage, strokes and left ventricular failure from hypertensive disorders and multiorgan failure from sepsis were the commonest causes of mortality and clinically diagnosed. They were often discussed during mortality reviews, sometimes in collaboration with anesthesia or other surgical disciplines to provide system improvement ideas. Included a comment / sentence in the discussion

Results
FIgure 1 and Figure 2 were not included in my PDF file. It was submitted

Table 2 - looks like obstetric volume went down 20% over 2 years - any specific reason for this? The national Human resource for health program was a 7 year training program that created residency program for specialists that included obstetricians and anesthesiologists. The government allocated these new graduates to the provincial hospitals and district hospitals who then were able to handle some of the previously referred patients.

Table 3 - Information in Table 3 is redundant given Table 4. Could combine. We still wanted to present as is. Table 3 simply demonstrates the percentage causes of mortality while table 4 shows what percentage of the conditions had ICU admissions. We would hope to leave the presentation as we described except if there is strong exception by the reviewer.

Table 4 - Why would someone go to the ICU versus not go the ICU? This would be helpful in interpreting these findings. It makes sense that patients with stroke/hemorrhage/PE would be less likely to go to ICU if they experienced sudden death, but some
explanation in results would be helpful. The problem centered on bed availability. The ICU was a 7-bed unit, significantly overutilized by neurosurgery and internal medicine. Their Patients occupied the beds for many days. Other tertiary institutions had similar bed occupancies challenges. Critically ill maternity patients therefore were often not admitted but were managed by the obstetricians and anesthesiologists in the recovery rooms of the maternity with limited nursing staff and expertise resources. Occasionally the intensive care consultant was consulted to assist with care.

Table 5 - I don't really understand what comparisons are being made. Perhaps this is because I don't have the additional figure that the analysis is associated with.

Line 110-114 'We also observed a seasonal variation in number of maternal deaths showing an increase from November to March with a peak in January and lower numbers from May through September. This coincides with the known deployment of new medical student graduates to district hospitals where they increasingly become responsible for the management of critically ill pregnant women including their surgical interventions.'
This is interesting - is there any evidence of this type of finding/effect from other medical specialties in the hospital? Or from other hospitals in the region?
(There are no available published data but, the experience from inter-departmental quality improvement meetings have highlighted the distribution of this effect in other emergency departments)

Line 116-119 - 'Despite a decline in maternal mortality ratio in Rwanda, the numbers are still far from the sustainable development goals (SDG) target of decreasing maternal deaths below 70 per 100 000 live births(5). The high number of maternal mortality ratio at the main referral hospital is consistent with other countries where majority of deaths occur centrally in the referral hospitals.'
This is a major question I had: as a referral hospital, to what degree are these deaths preventable based on optimal care at your hospital? What proportion of transfers are so ill that quality of care at CHUK is unlikely to change outcomes? Any thoughts to stratifying analysis based on women not transferred in? Many patients are transferred late. We do not have data on women not transferred and who were managed in the referring

hospitals. The most critically ill would have benefitted from timely intensive care admission but sometimes this was not offered due to unavailability.

The discussion section is generally pretty well written but could be edited to be better. It seems like the major findings of this study are that at your hospital half of deaths were due to sepsis and most deaths were referrals. The public health importance seems to be that the referral hospitals need to do better in terms of preventing infection, managing infection, managing sepsis, and referring patients who may benefit from care earlier. We think a significant number of maternal deaths can be avoided with improved surgical processes that reduce post surgical site infection that leads to sepsis. Earlier referrals will always be a solution but intensive care beds are still a significant resource deficiency.

For other obstetric centers in the region, is sepsis now the leading cause of death by a large margin? Are these findings in line or different from other findings in similar settings? Yes, in Uganda and Tanzania (Northern and Eastern borders of Rwanda), infection have become the leading cause of mortality (cited in the paper).

Reviewer #2: 1) The study is a retrospective analysis of maternal mortalities occurring at the University Teaching Hospital of Kigali, Rwanda (CHUK) from 2017-2019.
2) According to the study, there were 217 maternal deaths occurring in the hospital from 2017-2019 out of 11,308 total maternal admissions (Lines 27-28). Assuming that a "maternal admission" would result in a live birth in most cases, the calculated maternal mortality rate for this single center is 1,919 per 100,000 live births in the three years studied. While the authors indicated that this calculated maternal mortality rate is "consistent with other countries where (the) majority of deaths occur centrally in the referral hospitals" (Lines 118-119), it is still of such magnitude that significant additional discussion (with comparative figures from other countries as cited) is clearly warranted. We did compare our data to other neighboring countries
3) The authors indicated that sepsis was the most common cause of maternal death in the study and later suggested that "puerperal and postoperative surgical site infections continue to be main causes of sepsis" (Lines 32-33; 132-133). Was the latter statement a general fact or what was actually discovered in the study? How was sepsis diagnosed or the cause of death attributed? This is a known complication of surgical process breakdown but the very root cause of the infection source is unknown and may be different in the different referring centers. A history of surgery, infection site and a deterioration of patient with obvious surgical site infection provides a clinical diagnosis of sepsis. Most patients died of multisystem failure.
4) The authors cited "newly qualified yet inexperienced doctors" as a factor in the seasonal variation of maternal deaths (Lines 110-114; 144-145). What circumstances (other than timing) would lead the authors to this conclusion? Are there any other factors which may have contributed to this apparent phenomenon? What steps are being taken to mitigate this? Every year, newly qualified doctors are dispersed to smaller hospitals and this trend has led to the observed phenomenon. The teaching hospitals has tried to incorporate better surgical training programs that include senior medical students being trained in practicing safer cesarean sections. Obstetric consultants also adopt specific hospitals where they mentor junior doctors on improved surgical skills.
5) Although infection is a clear cause of maternal morbidity in the United States, it is rarely a cause of maternal mortality. Given the target audience, a brief overview of available antimicrobial therapies in smaller district hospitals as well as larger referral centers and how these therapies are typically utilized is necessary for context. We really are comparing apples to oranges. The resources in the USA cannot even be compared to countries like Rwanda where there is a dearth of every available resource that leads to improved outcomes. There is simply a significant difference in expertise, high acuity bed availabilities, drugs, training, staff numbers, referral hospitals, diagnostic tools. Low resource countries have to also deal with ineffective drugs due to poor storage, poor transport systems and poor constitutions, often due to very poor-quality control. Many drugs have been discovered to be substandard yet in circulation. Added a comment in the discussion.
6) Commentary concerning a typical presentation and clinical course of a patient who died during the study period would be beneficial to assist the reader in gaining perspective on the root causes of infectious maternal mortality in Rwanda and what can be done to prevent it. For example, were most of these patients already suspected to be septic on presentation to the outlying "district" hospitals or did they deteriorate after transfer to CHUK? Were these patients already delivered or did they present with signs and/or symptoms of intrauterine infection or inflammation ("Triple I") prior to delivery? The majority of patients were relatively healthy prior to surgical intervention and evidence of infection appeared post cesarean section. District hospitals were able to diagnose infection and sepsis and promptly prescribed antibiotics. However, some patients inexplicably deteriorated and were transferred after several days of antibiotic therapy. Unfortunately, the transfers occurred after significant deterioration and the beginning of single or

multi system failures.

Reviewer #3: Review of Manuscript ONG-21-861 "Trend and causes of maternal mortality in Rwanda. Case study of university teaching hospital of Kigali"

Rulisa and colleagues have submitted what they note is a secondary anlaysis of maternal mortality for the University Teaching Hospital of Kigali (CHUK) which per report is the largest referral hospital in Rwanda. The authors describe this as a cross sectional study although no STROBE checklist is included. Although they provide some information about historical trends in the discussion, placement of this information in the introduction may allow the reader to better evaluate the reported data and results. I have the following questions and comments.

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Abstract - Eliminate lines 21-24 and just have the objective/purpose of the study. Done
Line 27 - Was there a primary analysis? What about IRB approval? IRB or ethics approval was obtained and stated
Line 30 - I suppose this is the age range in ( ), if so please confirm. YES

Introduction - Line 57 onward - Since the authors are evaluating outcomes in Rwanda, do they have historical information about maternal mortality in Rwanda rather than just referencing interventions to improve outcomes? Hogan MC, Foreman KJ, Naghavi M, Ahn SY, Wang MR, Makela SM, Lopez AD, Lozano R, Murray CJL. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. *Lancet (British edition)* 2010;**375**(9726):1609–23. This showed the national Rwanda maternal mortality to be 1071 per 100,000 live births in year 2000

Methods - Line 76-78 - Was there previous knowledge about seasonal differences in maternal mortality? If so what is thought to drive this? Newly dispersed doctors who graduated were immediately sent to lead smaller hospitals and part of their responsibilities was performing cesarean sections. The immediate increase in morbidity and mortality soon after their arrival is a contribution to this seasonal variable

Results - Line 84-85 - You can just list the specific p values and allow the readers to note that there were no significant differences. DONE
Line 88 - Again you do not need to state if there is statistical significance. DONE
Line 89 - Do you have a way to quantify how they were "critically ill"? We did not quantify this and could not retrospectively

Discussion - Line 100 - Some of this historical information needs to be in the introduction in order to help illustrate stability, improvement or worsening in this metric. Made some modification
Line 112-4 - Has this been previously reported as the presumed reason? No previous publication but, quality improvement meetings that analyze root cause of maternal death have hypothesized this reason and the association was also observed in our study
Line 125-128 - Are the top causes of mortality remaining the same or changing? The top causes have not changed but sepsis has superseded other causes as stakeholders have made significant effort to reduce the risk of mortality from Hypertensive diseases and hemorrhage

Tables - Table 1 - Consider noting in the footnote that information was missing for the referring hospital and gravidity variables. Done

It seems like Table 1 and 2 can be combined with the Table 2 information at the top and then proceed with table 1 data. Alternatively, all of the table 2 data can be referenced in the manuscript which would allow it to be eliminated as a table. We would still prefer a separation as table one speaks to demographics and table two to outcomes. It does seem to make for better presentation

Table 3 - Something happened with the line numbers which makes this a bit hard to read. Corrected

Table 4 - Can you add the N so we know how much information you may have as it does not appear to be all 217 patients - for instance under gravidity there is information about 146 patients. I would think there would be information about ICU care yes or no for all patients? We have added the N numbers. There is obviously some attrition in the numbers as it was retrospective and some data information were missing

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

General: This report includes maternal deaths at a referral hospital. Most deaths were from outside community hospitals. Are there data re: the number of deaths not recorded? That is, deaths at an outside hospital that were not sent to the referral hospital? Could the variable death rates by season have been affected by differential referral rates by season? Most deaths were women who died at the referral hospital (CHUK) after they were transferred from outside. There exist deaths that occurred outside the referral hospital (CHUK) but they were not included in this study because they have no medical record at CHUK.

Table 2: Should round the death rates to nearest 0.1% precision and include CIs for each year. Were the deaths per month normally distributed? If not, should cite as median (range or IQR). There is a typo of the SD during 2019. Should be 1.33, not 133. Death rates rounded to nearest 0.1%. This is a descriptive table that would not generate CIs. The typo error was corrected.

Table 4: The %s should all be rounded to nearest integer %, not cited to nearest 0.1% precision. Done

Table 5: Were the distributions normal? If not, should use a non-parametric test and cite as median(range or IQR). By plotting a frequency distribution, the distribution appeared normal distributed

Thank you