Author’s response to reviews

Title: Identifying risk factors for perinatal death at Tororo District Hospital, Uganda: a casecontrol study

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[Formatted responses to reviewers included with Cover Letter as a Supplementary Material]

Reviewer #1: Sarah Saleem

1. The best part of this effort is that data are coming from a non-academic rural hospital with limited resources makes this study important.

We appreciate the recognition of the unique contribution of this manuscript and for all of this review's thoughtful comments.

a. Some general comments are as follows;

1. “English language needs some strengthening, at some places rephrasing or correction of concepts is required.”
We have gone through the manuscript and improved the clarity of our phrasing throughout.

2. “For example in the introduction section in the very first line the definition of perinatal death is wrongly given;”

There are varied definitions of perinatal deaths in the literature. In the American Academy of Pediatrics' Clinical Report entitled Standard Terminology for Fetal, Infant, and Perinatal Deaths, there is acknowledgement of the differences between the WHO definition of stillbirths at or after 28 weeks gestation or neonatal deaths prior to 7 days of life and other definitions that expand out to stillbirths as early as 20 weeks gestation and neonatal deaths less than 28 days. At our study site, perinatal deaths are defined as stillbirths at or beyond 24 weeks and neonatal deaths less than 28 days, which we have clarified in the abstract (lines 34-35) and in the Methods section (lines 101-104). We have also noted the lack of data stratified by exact timing of perinatal death as a limitation (lines 246-248).

3. “for lines 77 to 78 more information is needed why facility levels are not responding;”

We also included more information about facility-level factors that vary by site "secondary to numerous factors ranging from access to specialists to antenatal care coverage" (lines 79-80)

4. “line 81 to 83 need rephrasing for clarity;

We have changed the text to the following (lines 81-84): “Local differences could theoretically result in distinct case mixes between rural and urban care settings, which are crucial to understand given that over three quarters of Uganda's population lives in rural locations."

5. “lines 87 to 88 need language correction.

We have modified the text as follows (lines 86-88): “In light of the limited data on perinatal deaths from rural hospitals, the goal of our study was to identify risk factors for perinatal death in one of Uganda’s rurally located district hospitals using routinely collected clinical data.”
b. Also recommendations do not match the data. Recommendation are addressing more of the additional analyses rather than the primary?

While we were not exactly sure what the reviewer meant by this comment, we revised our conclusions to clarify our primary recommendation to acknowledge the feasibility and importance of investigating local data to determine local trends in perinatal death to guide use of limited resources (lines 263-265, 277-278).

2. Abstract: t-test should be written correctly.

We have edited this (line 38) from "…exact, t, and Wilcoxon-Mann-Whitney rank sum tests" to "… exact, t-tests, and Wilcoxon-Mann-Whitney rank sum tests".

3. Results: it is mentioned that "rate of perinatal death prior to discharge was 35.5/1000 deliveries" this needs clarity in the write-up to show what authors are trying to present-- Prior to discharge and denominator is not clear, similarly the sentence-- fresh stillbirth and neonatal deaths were more associated with nulliparity ----- needs rephrasing

We have clarified that the perinatal death rate was calculated using "all deliveries at the institution" as the denominator (line 46).

4. Conclusion: needs complete revision

We modified the Conclusions to the following: "The rate of perinatal death at our rural hospital site was higher than national targets, and these deaths were associated with prematurity, low birth weight, breech presentation, multiple gestation, and cesarean delivery. This data and the approach can be utilized to acquire it can be leveraged to inform targeted interventions to reduce the rate of stillbirths and neonatal deaths in similar low resource settings." (lines 55-59).
5. Introduction: correct lines 65 to 68 and rephrase some as mentioned above

Given the variability of classification of perinatal death as noted above in response to comment 1a(2) above, we modified the language to state, "Perinatal deaths, defined as a composite of stillbirths and neonatal deaths, are unequally distributed globally..." (lines 65-66).

6. Methods: have the authors reviewed all the records or a sample size was calculated? How was stillbirth defined? what was the cutoff taken for the gestational age--give this upfront, as this comes late

We clarified that all records were reviewed for births between 1/2014 – 12/2014 (line 100), and therefore no sample size was calculated. We also clarified that demised fetuses at or beyond 24 weeks were classified as stillbirths (lines 101-102).

7. [Methods:] Controls should be defined properly-- infants with normal delivery outcomes does not say much -- if authors mean live birth ?normal vaginal delivery? APGAR? etc this should be mentioned clearly

We greatly appreciate this comment as the initial description of controls was vague. We have clarified that, "Control patients, collected in a 2:1 ratio, were the admissions immediately prior and immediately after the perinatal death case that had liveborn neonates who survived to discharge and was not discovered to have died within 28 days of delivery" (lines 112-114).

8. [Methods:] line 108 Fresh stillbirths were those with findings suggestive of death within hours of delivery?? this can be rephrased as "Fresh stillbirths were those where fetal death had occurred in the uterus less than 12 hours of birth and fetus had no signs of skin changes. etc.

We have clarified that "macerated stillbirths were those with findings suggestive of death greater than 8-24 hours prior to delivery (e.g. skin desquamation) whereas fresh stillbirths were those without such findings" (lines 110-111).
9. **Methods:** Was collinearity checked before modeling?

We have clarified that "collinearity was assessed for all predictor variables prior to application of these models to confirm that variance inflation factors were less than ten" (lines 136-137).

10. **Results:** Age should be described appropriately either as a continuous variable or in groups with percentage.

We have elected to report age as a continuous variable and removed references to extremes of age throughout the manuscript.

11. **Results:** Table 1 should give just a comparison of cases and controls with percentages only. Table 1 given is too busy and too many things are presented in one table, Suggest to combine variables with small numbers

We appreciate the reviewer's advice to simplify Table 1 and have removed the two following columns: "Unadjusted Odds Ratio (Confidence Interval)," and "P value for Multiple Regression." We did keep the column "Adjusted Odds Ratio (Confidence Interval)" since it reflects both the size and significance of the associations noted.

12. **Results:** don't see the reason for including fresh and macerated still birth analysis with such a scant data. a neat clean paper on perinatal death could suffice, if authors choose they may include a descriptive paragraph on this. same holds true for analysis on singleton and twin cases

We recognize the limited number of stillbirths, but we a priori wanted to investigate the differences between the subtypes of perinatal death and would like to maintain subgroup analysis. The distinction may have clinical relevance, as opportunities for intervention likely differ for each (e.g. pre-hospital care for macerated stillbirths, inpatient care for fresh stillbirths and neonatal deaths). We acknowledge that a more ideal analysis is of control pregnancies to the subtypes of perinatal death rather than among subtypes and have redone our analysis accordingly (Table 2). In an effort to incorporate the reviewer's recommendation to simply the analyses presented, we removed the analysis on twin cases.
13. [Discussion:] should emphasize on limited recourses, booked /unbooked cases/ rural facility-- quality of care to address fresh stillbirth, should be added.

We appreciate this advice and have more directly acknowledged the limitations faced by providers at the study site as well as other sites (lines 263-270).

14. [Discussion:] neonatal deaths should be written as early neonatal deaths;

As the terminology "early neonatal death" typically refers to those within first 7 days of life, we refrained from acting on this recommendation.

15. [Discussion:] conclusions should be revised completely.

We appreciate this advice and focused the conclusion on the fact that "we report that the rate of perinatal death in a non-academic rural hospital setting is higher than that based on regional reports and identified potential risk factors for adverse outcome, [and that these findings can be used to help prioritize interventions to improve perinatal outcomes in similar, low-resource settings” (lines 275-278).

Review #2: Jillian Pintye, PhD

1. This is an interesting and well written article about an important topic, perinatal death in a rural Ugandan setting. The authors support that there are limited data on perinatal death from rural settings in Uganda, despite some previous studies from urban settings. The authors conducted a case-control study using maternity/birth registries to identify factors associated with stillbirth and perinatal death. The design is strong and the interpretation of results is sound. My primary recommendation is to tie the main findings to stronger implications supported with evidence-based recommendations cited with available literature.
We appreciate this review's thoughtful commentary on and constructive criticism of our manuscript.

a. For example, the authors report that breech presentation is associated with perinatal death and suggest that stronger training on intrapartum management is needed to prevent such deaths. More information on what that may look like in Uganda and whether there are recommended interventions or implementation strategies for improving intrapartum management would enhance the discussion and strengthen how this work fills an important gap.

We appreciate this advice and have included reference to "targeted audits of the perinatal deaths have been demonstrated to decrease such losses in a peri-urban setting in Kampala, Uganda" while highlighting that "[u]sing data such as those presented in our study could help focus the attention of such audits given the limited resources available to execute them" (lines 266-270).

b. My main critique is that the rationale for the analysis of macerated stillbirths vs fresh stillbirths and perinatal deaths is unclear. There were also no clear differences between the two groups. Combining fresh stillbirths and neonatal deaths could be obfuscating differences and I recommend comparing stillbirths (fresh and macerated) vs neonatal deaths or conducting separate analyses for each respective outcome vs controls to identify risk factors for each.

As noted in response to the preceding reviewer's comment 12, our rationale for analyzing macerated stillbirths distinct from fresh stillbirths and neonatal deaths was that the latter two categories of perinatal deaths theoretically occur more proximal to or often in the health care facility itself and thus plausibly could be more amenable to hospital-based intervention. We acknowledge that a more ideal analysis is of control pregnancies to the subtypes of perinatal death rather than among subtypes and have redone our analysis accordingly (Table 2).

2. Introduction

a. In the paragraph that starts with, "Uganda is among the top fifty countries with the highest burdens of perinatal deaths…", there are comparisons between Uganda and the U.S. It would be more informative to include targets for perinatal/neonatal deaths in Uganda. For example, does the government of Uganda have a goal of reducing perinatal mortality from its current rate of XX/1000 to XX/1000 by a specific year? What about progress on MDG/SDGs? This would be helpful to clarify the existing gap.
We appreciate the request to focus on more locally relevant data to Uganda such as country-wide targets rather than comparison to the US. We therefore have removed references to US statistics and included reference instead to WHO and UNICEF's "Every Newborn Action Plan, which...strives to promote progress in preventing such deaths across the globe and specifically to achieve 10 or fewer stillbirths among 1,000 total births and 10 or fewer newborn deaths among 1,000 live births by 2035" (lines 68-72).

b. Is there a citation available for this: "There are also notable differences between rural and urban populations with estimated 52% of deliveries in rural Uganda occurring in hospital settings as compared to close to 90% in urban areas"? How does this suggest a high likelihood of "case mixes"? Do the authors mean that the populations of mothers in urban vs. rural settings are different because urban mothers are more likely to deliver in hospitals? This is not clear as it is currently written. Please describe more fully.

In response to this feedback, we have included a citation for the rural versus urban composition of Uganda and included information about previous work understanding barriers to care for women in rural areas in order to shed more light on why we believe there could be distinct case mixes (lines 80-84).

3. Methods

a. It is unclear if only data from birth registers were used or if the study team actually interacted with human subjects seeking delivery services. Can this aspect of the design please be clarified in the being paragraph of the methods section? It is mentioned in the limitation sections of the discussion, but it is not clear in the methods section.

We did only utilize birth registry and clarified this in the Methods section (lines 106-107).

b. It is also unclear why the women were presenting at the health facility and to which unit. For example, were all controls coming in for normal vaginal deliveries?
We clarified that that, "Control patients, collected in a 2:1 ratio, were the admissions immediately prior and immediately after the perinatal death case that had liveborn neonates who survived to discharge and was not discovered to have died within 28 days of delivery" (lines 112-114).

c. Were all cases attending clinic for their obstetric issue? Adding more detail to the data collection procedures could clarify this (e.g., the entry before and after a stillbirth recorded in the maternity registry).

We recognize the importance of understanding the antenatal care received by patients, but unfortunately this data was not available in the birth registry. Based on nationally available data, less than half of women in rural Uganda have at least 4 antenatal visits (Reference 7). We can include this information in the manuscript if desired.

d. Information on data collection procedures should be specified. For example, how did the study team digitize the data? Did mobile data teams abstract the data on site and hand enter the data into an electronic system?

We have clarified that the data used for this study was obtained "by audit of anonymous data from all birth register.. [that] had been collected through abstraction and digitized by author ND for quality improvement purposes" with approval of the hospital administration (lines 102 – 103).

e. Is there any information available on approximate timing of death and the death-to-delivery interval for the stillbirths?

Unfortunately, there is not data available on timing of stillbirths beyond the subjective assessment of the fresh versus macerated appearance of the fetus nor is there readily available on the exact time of the neonatal death, which highlights a limitation of the current birth registries. We agree that this is important data that would need to be obtained through improved record keeping and/or a prospective study of stillbirth in this setting.
f. Please operationally define a "normal delivery outcome" in the methods. Was this just a live birth?

As noted above in response to comment 7 for the preceding reviewer and to comment 3b, "[c]ontrol patients… were the admissions immediately prior and immediately after the perinatal death case that had liveborn neonates who survived to discharge and was not discovered to have died within 28 days of delivery" (lines 112-114).

g. What happened if 2 cases were consecutively admitted? Was only one case included in your study?

This did not occur, but the plan if the scenario of 2 consecutive cases had been encountered was to use the 2 preceding and 2 subsequent deliveries that resulted livebirths of neonates who survived to discharge.

h. How was gestational age determined? This is important both for staging the primary perinatal death outcomes but also the cofactor of prematurity. Was this information abstracted from maternal health cards? How is gestational age typically determined in this setting (e.g., LMP, fundal height, etc)?

We agree that gestational age is a critical variable in our study. As is true for many low resource settings, the ability to determine gestational age is complicated by limited access to care and ultrasounds. For our study, we utilized the designation of preterm versus term birth that was noted by the birth attendant charting on behalf of patients, who ascertain "[g]estational age… using patient reported dating and use of a pregnancy wheel" (lines 100-101).

i. It could be more clear to just say "≥4 births" instead of using "Grand multiparity", particularly in the abstract where grand multiparity is not defined.

We have modified references to grand multiparity throughout the manuscript to be consistent with the reviewer's recommendation.
j. Please operationally define how "perinatal mortality" was included in regression models (ie, any case defining outcome—stillbirth or neonatal death).

We have modified the language to start explicitly that the models were looking at "the outcome of either stillbirth or neonatal death as well as with each subtype of perinatal death" as the outcomes of interest (line 134-135).

k. A lot of outcomes/variables included in the models are likely collinear or on the casual pathway to one another, rather than independent exposures/outcomes. This could also explain some of the unusual/imprecise estimates with wide confidence intervals. For example, preterm birth is on the casual pathway to perinatal and neonatal death. Twin birth and prematurity are collinear. There should be a rationale inserted for why the authors chose to assess this set of variables as independent predictors for their outcome(s) and how potential collinearity was handled.

As noted in response to the other reviewer's comment 9, we have clarified that "[c]ollinearity was assessed for all predictor variables prior to application of these models to confirm that variance inflation factors were less than ten" (lines 136-137).

4. Results

a. It would be helpful to know how many potential cases/controls were excluded due to missingness, incomplete entries, etc. Using routine data, it is hard to believe that every case was able to be used with no incomplete data out of the &gt;5000 entries.

We appreciate this input and therefore have added that "[t]here were 46 weeks of birth register data available… and upwards of 90% was legible" as determined by reviewing the calendar dates of the births included and illegible control pregnancy data proximal to the case pregnancy data (lines 148-149).
b. The analysis for comparing cases with fresh stillbirths and neonatal deaths to macerated stillbirths is confusing and not described in the methods. If you wanted to assess whether there are differences in factors associated with fresh stillbirth/neonatal deaths vs macerated stillbirths, the appropriate analysis would be to run 2 separate models: one with controls vs macerated stillbirths (no other outcome included) and then a separate model with controls vs fresh stillbirth/neonatal deaths. One could also argue that the more appropriate comparison would be combing macerated/fresh stillbirth into one outcome (instead of fresh stillbirth/neonatal death) as the casual pathways are likely more similar.

As noted in response to the preceding reviewer's comment 13 as well as this reviewer's comment 1, we agree that comparison of stillbirths and neonatal deaths (rather than macerated stillbirths compared to fresh stillbirths and neonatal deaths) is very appropriate and have modified our analysis and manuscript accordingly throughout.

5. Discussion

a. It would be more convention to report that prematurity, breech, and twin gestation had the "strongest association" rather than "most significant".

We have modified the language to "has the strongest associations" as suggested (line 201).

b. It would also be helpful to try and explicit state what gaps these data fill. It is already known that prematurity, breech presentation, and twin gestation are association with adverse perinatal outcomes. How will confirming this information in this rural setting fill any gap or advance programs?

We appreciate the reviewer's request for making the link between our findings and holes filled in the literature. As noted in response to the preceding reviewer's comment 1b, we revised our conclusions to acknowledge the importance of investigating local data to determine local trends in perinatal death that can then be utilized to conceptualize and implement customized interventions (lines 266-270).

c. It seems that "17/2019 12:29:00 PM" was added to the end of a paragraph in error?
We are unaware of how this appeared in the uploaded version, but we confirmed that this typo is not present in our revised manuscript.

d. The authors state, "..we are the first group to analyze risk factors based on the type of perinatal death: stillbirth (macerated or fresh) and neonatal death". Do you mean in the specific setting of Tororo? Other studies in African settings have looked at these outcomes separately with robust prospective designs. One example from a rural setting is Warr AJ et al Sexually transmitted infections during pregnancy and subsequent risk of stillbirth and infant mortality in Kenya: a prospective study. Sexually Transmitted Infections 2019 PMCID: PMC6525108. There are other examples too. Please clarify this statement and contextualize within the broader literature which has examined this research question (ie, predictors of stillbirth and neonatal death in similar populations).

Our initial statement was in reference to not identifying publications on differing association of risk factors for each subtype of perinatal death in Uganda, but we removed this referenced sentence to avoid confusion.

e. Please cite studies that support, "...increased training on intrapartum management and vaginal delivery of breech presentation may improve outcomes" is an evidence-based intervention. For example, the PRONTO studies.

We have included references to studies on doing more detailed audits as the more appropriate next step to understand what interventions are needed (lines 266-270).

f. The authors note that HIV prevalence was low in their study population. What about info on other MCH indicators? For example, syphilis results from pregnancy?

We acknowledge the value of including more robust mother-child indicators, however we were limited in the data that was available in the birth register. If desired, we can request hospital-wide data on such indicators, but we would not be able to obtain patient-level data.
Discussion: A major strength of this paper is that routine programmatic data were used to answer a question linked to the local context with potentially direct implications for practice. I think it would be beneficial to raise this, given the move in the field towards strategic use of programmatic data to answer implementation science questions tailored to the context. It sounds like the field team may not have encountered much missingness which is also a strength to be noted. Using routine registries for such surveillance studies is exactly the direction we should be going in and it would be helpful to include a couple of sentences on this since it is a unique and important aspect of this paper.

We appreciate this reviewer's recognition of our desire to leverage locally available and relevant data to guide care decisions, and we have strived to include more discussion of this in the discussion (lines 265-278).