**Author’s response to reviews**

**Title:** Neonatal Near-Misses in Ghana: A Prospective, Observational, Multi-Center Study

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Responses to Reviewers:

Thank you for taking the time to go through our manuscript so carefully and providing such helpful feedback. As a result of the reviewers’ comments and our subsequent reassessment of the data, we have substantially revised the manuscript. We recognized that the true sample of interest was the babies for whom we had 28-day survival data, and it became clear that one of our sites had unacceptably high loss-to-follow-up. Thus in this revision, we have dropped the data from one of the three hospitals. (Two of our sites had 89% retention from enrollment, and the third had 22% retention, making it appear as if this one hospital had very few near-misses.)

As a result, the revised version of the manuscript includes two sites instead of three, and addresses the reviewers’ comments as follows:

Reviewer 1, Comment 1: This is a relevant study on neonatal Near Miss in developing countries. Since an instrument for neonatal near miss tracking is proposed, it is very important to assess its
validity. Some questions about the composition of the study population and the calculation of indicators of severe morbidity and neonatal mortality should be reviewed.

Response: Thank you, we have attempted to make this more clear in this revision.

R1, Comment 2) About the study population

The first step of the study was the revision of the admission ledgers at each site to identify newborns with complications by trained research assistants (Line 31 up to 33 of page 5). A total of 725 newborns were identified across the three sites as having experienced some type of complication at birth that might categorize them as a neonatal near miss.

Response: After removing the data from KBTH, there were 441 newborns identified with complications across the remaining two sites.

R1, Comment 3) 725 children were born at the three sites? If yes, the prevalence of "live births with complications" were about 8.6% (considering the number of live births of the three sites from April up to July 2015 (n = 8433). Or, this frequency included babies that were born at other hospital, but admitted to the neonatal units at KATH, CCTH, and KBTH? Did these babies have the same complications to be included in the study?

Response: 725 – which is now 441 – reflected the number of babies who were both born at the facility and came from outside the facility with complications to be admitted into the NICU. Complications were judged by what was recorded in the delivery ledger, with any baby indicated as needing medical attention or to be transferred to the NICU regarded as a complication.

R1, Comment 4) Which complications were considered at the first step of the study?

Response: As mentioned, complications were judged by what was recorded in the delivery ledger, which included the following specific complications: pre-term delivery, low birthweight (<2500g), Apgar scores <7 at 1 minute, birth asphyxia, congenital malformations. The delivery register also included less clear markers such as ‘complication’, or ‘transfer to NICU’ which were based on clinician judgment and we included in our enrollment criteria. We have revised the text to make this more clear.

R1, Comment 5) If babies admitted to the neonatal units at KATH, CCTH, and KBTH, regardless of where they were born, were recruited for participation (Lines 20 to 24 of page 5), but they don’t belong to the live birth cohort of each hospital. In general, neonatal near miss studies recruit children from the maternity where the birth occurred. How many children were in this situation? What kind of implication could the interpretation of the results considering that children born in other health facilities and transferred to hospitals were included in the study population?
Response: Thank you for this observation – and yes, it does make things a bit less clear to include those babies born outside the study facilities. However, in this setting, institutional neonatal mortality figures include any newborn &lt; 28 days (regardless of birth location) who dies in the facility. So including newborns admitted to the NICU from outside the facility in our assessment of near-misses makes the rate comparable to the institutional mortality rate. (Incidentally, 66% of the newborns enrolled were born within the study hospitals.)

R1, Comment 6) About the definition of neonatal near miss proposal using the NNMAT tool

Second step: the screening of "neonatal near-miss" (Classified as met any of the four NNMAT criteria), but, at that moment, they are being classified as life-threatening using the NNMAT criteria - 578 live births with complications). So, the prevalence of life-threatening was 79.7%. As expected, the prevalence at the second step increased. The next step is the survival up to 28 days of the delivery to classify babies as cases of neonatal near miss. I suggest that children classified as life-threatening by the NNMAT tool but not yet known about the occurrence of neonatal death, should be called as "life-threatening children" (not neonatal near miss cases). The text about these results is confusing (Linhas 25 a 37 da página 7).

Response: Thank you for this observation – you are absolutely correct, we were calling them near-misses before they had survived to 28 days. We have changed the language throughout the manuscript, referring to those newborns who screened positively ‘suspected near-misses’ until they reached 28 days, at which point they became ‘confirmed near misses’.

R1, Comment 7) The major question is: Why the validity (sensitivity and specificity) of the definition of neonatal near miss using the NNMAT tool wasn’t assessed? Although it is not the objective of the study assess the validity of the definition of neonatal near miss proposed, the justification of the study directs the reader to this question. There is a subgroup of children (456) with individual data of death (gold standard to neonatal near miss) that allows to do this analysis. I suggest the authors to assess the validity of neonatal near miss using the NNMAT tool.

Response: Thank you for this suggestion, and we have added analysis around the positive predictive value and the negative predictive value of the NNMAT. The challenge with such an assessment is that it assumes that if the near-miss tool predicts death very well, then it is a good tool. (Death being the gold standard.) However, a near-miss tool should NOT perfectly predict death, hence our inclusion of negative predictive value.

R1 Comment 8) About the indicators of neonatal severe morbidity and mortality (third objective of the study)

Data from table 2:

725 children with complications were recruited for the study.
578 live births with complications were classified as "life-threatening children" using the NNMAT criteria.

456 babies for whom neonatal death data were available and it was possible to classify them according to neonatal near miss. 310 of them were classified as neonatal near miss case (table 3).

Response: Yes, thank you for articulating the numbers in this way. It clarifies that there is a distinction between suspected near misses and true / confirmed near-misses

R1 Comment 9) Data from table 3:

The neonatal near miss rate (not ratio) considered 578 children with life-threatening conditions according to NNMAT criteria (without complete individual death information) as near miss cases. The neonatal near miss rate per 1000 live births was 68.5. It's important to consider that there aren't individual near miss (according to NNMAT criteria) and death data for all 8433 live births. The study population recruited for the study is 725 children with complications (not all live births of the three sites).

Response: Thank you for this, and we have added language to the limitations section of the discussion to address this issue. We recognize that we do not have complete data on all live births during the study period, however we do have the ‘institutional neonatal mortality rate’ that reflects newborns who died in the study hospitals, regardless of where they were born. While this is not a perfect measure of neonatal mortality, it does allow for crude comparison of the number of babies who die (relative to the number of live births) compared to those who suffer a near-miss.

R1 Comment 10)

C.1) Considering only children classified as "life-threatening children" using the NNMAT criteria who had individual follow-up data for neonatal death classification, the real number of neonatal near miss cases is 310 (table 2). The sample consists of 725 children with complications (not all live births) and only 456 children have individual neonatal death data available).

Response: Thank you – we have adjusted the neonatal near-miss number to reflect 310 true near-miss cases. We have also added Figure 1 to make this process of classification more clear.

R1 Comment 11)

D.1) Methods

Line 13 up to 35 of page 4 (just to check the numbers): KATH 12,000 and KBTH have approximately the same frequency of deliveries annually (11,000)?
Response: Yes, this is correct.

R1 Comment 12)

Line 49 of page 5: Key variables: The category "don't know" was accounted as "no" or the record was excluded from the analyses? If these categories were added, what kind of implication would result? Differentiated misclassification bias?

Response: This is an excellent question. We classified newborns based on a ‘yes’ response to any of the items. Thus a ‘don’t know’ on an individual item was effectively treated as a ‘no’. We made this methodological decision to allow for different settings where different interventions and investigations were readily available (e.g. perhaps no blood test had been done yet, so the provider wouldn’t know hematocrit or hemoglobin levels.) This does have implications for potential underestimation of near-misses in settings where communication between providers is poor, if certain interventions or investigations are not available, or where test results take a long time to come back. We have added language to the discussion to address this issue.

R1 Comment 13)

D.2) Results Tables

* The * at number 725 does not have the corresponding explanation in the footer of table 2.

Response: Thank you, this has been removed.

R1 Comment 14)

* Lines 32 and 33 of table 4: Birthweight &lt; 1800g ou &lt; 1750g (methods)?

Response: Thank you for identifying this inconsistency. The correct weight is 1800g.

R1 Comment 15)

D.3) Discussion

The lines 48 of page 8 up to 12 of page 9 should be rewritten. The authors mentioned a study that compare cut off points of the pragmatic criteria of different definitions of neonatal near miss. They must consider that in this paper (reference 3), the authors said "Periodic studies could apply a more complete definition, based on the literature on the subject and considering the availability of more technology in the care. When qualified information can be obtained on criteria other than the pragmatic ones, we recommend the incorporation of clinical, laboratory, and management criteria".
Response: Thank you – we have adjusted the language accordingly.

Reviewer 2, Comment 1: I would like to compliment the authors on a well written paper and their work on an important topic in global newborn health. I have only minor suggestions:

Response: Thank you for this, and thank you for taking the time to review the manuscript.

R2 Comment 2)

1. Please define "major congenital abnormality" and if possible, list the most common types of anomalies seen in these sites.

Response: Thank you. We defined major congenital abnormality as any congenital abnormality requiring surgical repair, including such things as gastroschisis, hydrocephalus, gut malrotation, duodenal artresia, tracheoesophageal fistulae, congenital heart defects, and others.

R2 Comment 3)

2. In Table 2, the overarching title of columns 3-5 should be "Indicators among 456 babies for whom survival data for the neonatal period were available"

Response: Thank you. We have adjusted Table 2 headings based on the revised analysis.