STUDY PROTOCOL

REVISED Burden, causes, and risk factors of perinatal mortality in Eastern Africa: a protocol for systematic review and meta-analysis

[version 2; peer review: 1 approved, 2 approved with reservations]

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Abstract

Background

Although global mortality rates in children under 5 years have decreased substantially in the last 30 years, there remain around 2.6 million stillbirths and 2.9 million neonatal deaths each year. The majority of these deaths occur in Africa and South Asia. To reduce perinatal deaths in East Africa, knowledge of the burden, but also the risk factors and causes of perinatal deaths are crucial. To the best of our knowledge, reviews have previously focused on the burden of perinatal deaths; here we aim to synthesize evidence on the burden, causes, and risk factors for perinatal mortality in East Africa.

Methods

We will conduct a systematic literature search in Medline, Web of Science, EMBASE, Global Health, SCOPUS, Cochrane Library, CINAHL, HINARI, African Index Medicus, African Journals Online (AJOL), and WHO African Regional Office (AFRO) Library. The study population includes all fetuses and newborns from ≥22 weeks of gestation (birth weight ≥500gm) to 7 days after birth, with reported causes or/and determinants as exposure, and perinatal mortality (stillbirths and/or early neonatal deaths) as an outcome. We will include studies from 2010 to 2022, and to facilitate the inclusion of up-to-date data, we will

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request recent data from ongoing surveillance in the region. To assess the quality of included studies, we will use the Joanna Briggs Institute quality assessment tool for observational and trial studies. We will analyze the data using STATA version 17 statistical software and assess heterogeneity and publication bias by Higgins' I2 and funnel plot, respectively.

Conclusions

This systematic review will search for published studies, and seek unpublished data, on the burden, causes, and risk factors of perinatal mortality in East Africa. Findings will be reported, and gaps in the evidence base identified, with recommendations, with the ultimate aim of reducing perinatal deaths.

Protocol registration

PROSPERO-CRD42021291719.

Keywords
Keywords: Perinatal mortality, stillbirths, early neonatal mortality, East Africa

CHAMPS

This article is included in the CHAMPS gateway.

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REVISED **Amendments from Version 1**

In this new version of our work, we have incorporated revisions guided by insightful feedback from our reviewers. We clarified the "significance, implication, and rationale of the study" within the Introduction to ensure a more explicit understanding. Additionally, we have provided more detailed explanations of our search strategy, eligibility criteria, language considerations, data collection methods, and our approach to assessing the risk of bias. Moreover, we have included a discussion of the outcomes from previously published meta-analyses and our methods for addressing challenges encountered during the analysis.

Any further responses from the reviewers can be found at the end of the article

Introduction

Despite the decline of global mortality rates in children under 5 years from 93 per 1000 live births in 1990 to 38 per 1000 live births in 2019, there are currently 2.6 million stillbirths and 2.9 million neonatal deaths each year[1–3]. The vast majority of these deaths occur in low- and middle-income countries, in Africa and South Asia[4]. More than three-quarters of all newborn deaths are from preventable and treatable conditions. The most common causes are prematurity, intrapartum-related deaths (including birth asphyxia) and neonatal infections[5,6].

The Every Newborn Action Plan (ENAP) was launched in 2014, which targets the reduction of the neonatal mortality rate (NMR) to 12 or fewer per 1,000 live births and stillbirths to 12 or fewer per 1,000 births in all countries by 2030[7]. However, Africa has the highest stillbirth rate, and the slowest improvement worldwide[8]. Thus, given current changes, it would take over 160 years for a pregnant woman in Africa to have the same chance of having an alive baby as a woman in high-income nations now[9]. Further, Africa has the slowest reduction rate of neonatal mortality and the highest neonatal mortality rate in the world, at 27 (25–32) deaths per 1,000 live births, followed by South Asia at 23 (21–26) deaths per 1,000 live births[10–12].

East Africa has particular challenges; a recent demographic and health surveys suggested that perinatal mortality in the region was one of the highest, with 34.5 deaths per 1000 births[13]. East Africa also has the weakest economy across Sub-Saharan Africa, and utilisation of reproductive health services (facility deliveries, skilled delivery assistance, and 4+ antenatal visits) in East and Central Africa is lower than in other areas of Sub-Saharan Africa[14,15]. Reducing perinatal mortality in this region is critical; counting the number of deaths precisely and consistently classifying causes and risk factors for perinatal mortality (one of the objectives of the Every Newborn Action Plan), is essential to inform effective interventions[7]. In addition, using consistent definitions and classification systems is important to interpret the causes of perinatal deaths[16,17].

Hence, in this systematic review, we aimed to describe the burden, causes and risk factors of perinatal mortality in East Africa, using the most up-to-date information, to determine progress in achieving the ENAP 2030 targets and direct policymakers allocate resources to the most effective interventions to prevent preventable perinatal deaths.

Research questions

This systematic review and meta-analysis will answer the following questions:

1. What is the overall perinatal mortality rate and how does this vary in different contexts (geographic location, study setting) in East Africa?

2. What are the causes of perinatal mortality in East Africa?

3. What are the risk factors for perinatal mortality in East Africa?

Methods

Protocols used for reporting and protocol registration

The design and implementation of this systematic review will adhere to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement[18] and reporting of findings will follow the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA-2020) updated guideline[19]. The protocol for this review was registered on PROSPERO (CRD42021291719).

Eligibility criteria

Studies for this systematic review and meta-analysis will be selected based on the criteria specified below.

Inclusion and exclusion criteria

We will include both published and unpublished studies, that report perinatal mortality (stillbirth and/or early neonatal death), its causes and/or risk factors of perinatal mortality. No restrictions will be imposed on language of publication, sex, or ethnicity of participants. This study will include studies that have been conducted in East Africa and published between January, 2010 – December, 2022.

We will exclude studies which are reviews, or published outside of the study area and time period (before 2010 and after December, 2022). We will also exclude studies that focus on specific populations (e.g., high-risk mothers). Studies will be excluded if extracting data is not feasible after appropriate attempts to seek the full text and contact the corresponding author where needed. We will exclude studies that are limited in methodology (inappropriate statistical analysis or methods used to control confounders).

PECO search guide

Population: All births (both livebirths and stillbirths) with ≥500g/≥22 weeks of gestation and newborn deaths within the first week after birth (0–6 days)[20,21].

Exposure: Determinants or risk factors of perinatal mortality. The determinants or risk factors are characteristics or exposures that increase the likelihood of perinatal mortality. These may be related to distal, underlying, or proximal determinants.

Comparison: The reported reference group for each determinant or risk factor in each study (e.g., perinatal mortality in mothers with antenatal care versus mothers with no antenatal care).

Outcome: Perinatal mortality rate, which is defined as "the total number of deaths of a fetus with birth weight of 500 grams or more or a gestational age of 22 completed weeks of age or more until the 7th day after delivery per 1000 live birth"[22]. The other outcomes for this study are the causes and risk factors of perinatal mortality.

Study designs

All observational studies (cross-sectional, case-control, prospective cohort and retrospective studies) and community-based trials which reported the magnitude of perinatal mortality and/or its cause or risk factors will be included.

Study setting and time frame

Studies that have been conducted in East Africa, which encompasses the following countries; Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mauritius, Mozambique, Rwanda, Seychelles, Somalia, Somaliland, South Sudan, Sudan, Tanzania, Uganda, Zambia, and Zimbabwe according to United Nations[23] will be considered. Both community-based and facility-based studies will be used for this study. This study will be conducted from October 2022 to June 2024.

Years and language considered for study recruitment

All studies published from January 1, 2010, to December 31 2022 will be included in this study because it aims to examine up-to-date information regarding perinatal mortality and the advancements made towards attaining the 2030 goals, whilst ensuring sufficient years are assessed to maximize data included in the analysis.

All articles reported in any language will be considered for this study. After using software to translate, we will consult a specific language expert for translation for studies in a language, the authors do not speak.

Publication status

All studies that fulfill the eligibility criteria will be considered regardless of their publication status (published, and unpublished or grey literature). To access unpublished reports of likely high relevance and quality, up-to-date data will be requested from large surveillance studies, forming an investigator group.

Information sources

The databases searched to identify published research articles will be Medline, Web of Science, EMBASE, Global Health, SCOPUS, Cochrane Library, CINAHL, HINARI, African Index Medicus, African Journals Online (AJOL), and WHO African Regional Office (AFRO) Library. In addition to this, a manual search will be performed to retrieve unpublished studies and grey literature via Google Scholar, Google and institutional repositories of higher education institutions, which are found in East Africa and outside the region that have joint projects in East Africa. An investigator group from large studies with ongoing surveillance in the region will be requested from Child Health and Mortality Prevention Surveillance (CHAMPS) and Health and Demographic Surveillance sites (HDSS) to facilitate the inclusion of the most up-to-date data. Three CHAMPS networks in the region, namely Harar and Kersa, Ethiopia, Siaya and Kisumu, Kenya, and Manhiça, Mozambique[1], and HDSS from Ethiopia (Harar and Kersa, Dabat, Butajira, Arba Minch and Gilgel Gibe HDSS), Kenya (Nairobi, Kilifi, Mbita, Kombewa and Kisumu HDSS), Malawi (Blantyre, Karonga HDSS), Mozambique (Chokwe and Manhica HDSS), Tanzania (Magu, Rufiji, Bagamoyo, Ifakara, Korogwe, Moshi and Pemba HDSS), Uganda (Awach; Gulu, Iganga/Mayuge, Kyamulibwa, Rakai and Toro HDSS), Zambia (Lusaka HDSS)[24,25] will be asked to join the investigator group if they have appropriate data, which they are able to contribute.

Search strategy

We will search the electronic databases above, based on the following concepts: perinatal mortality (stillbirth and/or early neonatal mortality), causes of perinatal mortality, stillbirths or early neonatal mortality, risk factors for perinatal mortality, stillbirths or early neonatal mortality, study design (cross-sectional, case-control, cohort and community-based trial) and location and geographic setting (countries of Eastern Africa), and published covering the time period from January 1, 2010 to June 30, 2022.

The search will be conducted in appropriate search fields of electronic databases, and with sensitive searches that combine text words with indexing terms. Both free-text words (including spelling variants, synonyms, related terms, plurals, acronyms, truncations, wildcards, and proximity operators) and appropriate subject headings will be used. We will use Boolean operators 'AND' and 'OR' to connect and focus a search by combining subject headings and keywords.

Various combinations of the following key terms will be used to identify papers on the burden of perinatal mortality, its cause and determinants in Eastern Africa: 'perinatal mortality', 'perinatal death(s)', stillbirth(s), stillborn(s), 'fetal death(s)', 'fetal demise', 'fetal mortality', 'neonatal death(s)', 'infant mortality', and 'East Africa'. A summary of search strategy in Ovid Medline database is presented in Table 1, and we will report the search strategies with specific terms and Boolean operators used in each database in the systematic review result. We will also identify studies that were cited by others (descendent search strategy).

Study records

Data management

Articles will be searched using different electronic databases and imported to EndNote software version X20 using each of the databases' citation manager to facilitate review process and exclusion of duplicated studies.

Selection of studies

After importing studies to Endnote X20, duplicates will be excluded. Titles and abstracts of remaining studies will be screened by Y.A.A., and N.A then abstracts of selected studies will be exported to Covidence review management software for full-text screening[26]. Full-text articles will be independently

Table 1. Summary of search strategy in Ovid Medline electronic database.

Component	Search terms
1	Perinatal Mortality/ or stillbirth/ or fetal death/ or infant mortality/
2	((perinat* or f?etal or f?etus* or infant* or neonat*) adj5 (death* or mortalit* or demise)).mp.
3	(stillbirt* or stillborn* or adverse birth outcome* or pregnancy outcome* or perinatal outcome*).mp.
4	**1 Or 2 OR 3**
5	exp Africa, Eastern/
6	(eastern Africa or Burundi or Comoros or Djibouti or Kenya or Madagascar or Malawi or Mauritius or Mozambique or Rwanda or Seychelles or Somalia or Somaliland or South Sudan or Tanzania or Uganda or Zambia or Zimbabwe).mp.
7	**5 OR 6**
8	**4 and 7**
9	**limit 8 to yr="2010 – 2022"**

screened by two investigators (Y.A.A. and N.A), and when there is uncertainty, a third reviewer (L.A.P or A.C.S) will make a final decision. The total number of studies identified, screened, eligible and included in the study will be described, and the reason for exclusion at each stage of the study selection process will be explained. A single failed eligibility criterion is sufficient for a study to be excluded from a review. Results from comparable groups of studies will be combined into a statistical meta-analysis using STATA-17 software[27].

Data collection process

Required information for the systematic review will be extracted and summarized using the Joanna Briggs Institute and Cochrane data extraction template. Information on the title, author, publication year, study design, study setting (rural vs. urban), study type (community-based vs. hospital-based), sample size, study participants, study period, sampling methods, and outcome of interest (definition of outcomes) will be extracted. When we extract data regarding perinatal mortality rate, we will note the denominator used by studies (live births or total births) and we will also collect the stillbirth and early neonatal death rates separately. Furthermore, we will extract the time of death for stillbirths; antepartum or intrapartum (fresh or macerated) if reported. In addition to this, we will look at the ascertainment of causes and risk factors in each study and the classification system will be recorded where available. The measures of association (odds ratio or relative risk with their respective confidence intervals) for each risk factor will be extracted and included in meta-analyses where feasible.

Data items

Perinatal mortality rate: is the sum of stillbirths and deaths in the first week of life (0–6 days) per 1000 total birth (both live and stillbirths)[21].

Stillbirth rate: is fetal death at ≥500g/≥22 weeks gestation, or ≥1000g /≥28 weeks gestation by WHO for general statistics and international comparison respectively per 1000 total births[20]. We consider a broad definition to look at the variation of definitions across different studies; however, in our meta-analysis we will only consider studies with similar definition (≥1000g /≥28 weeks gestation).

Early neonatal mortality: deaths among live births during the first week (0–6 days) of life[28].

Causes of perinatal mortality: are any condition/s with a reasonable mechanism likely to lead to the death of the fetus or early neonate and it is classified as the underlying cause, immediate cause, and main maternal cause)[29,30].

ICD-PM: is the WHO application of ICD-10 to deaths during the perinatal period, which provides a standardized system for classifying perinatal mortality based on time of death as antepartum (before the onset of labor), intrapartum (during labor but before delivery) or neonatal (the first week after delivery), and it also links the contributing maternal condition, if any, with perinatal death[29].

Determinants or risk factors: are characteristics associated with, but not obviously causal for, stillbirths or early neonatal deaths, such as advanced maternal age[31]. (Figure 1)

Outcomes and prioritization

The perinatal mortality rate will be the primary outcome measure; it is calculated by dividing the number of fetal deaths after 22 weeks of gestation or weighing more than 500g and neonatal deaths in the first week after delivery by the total number of births (stillbirths and live births) that have been included in the study (sample size)[7,21]. The second outcome

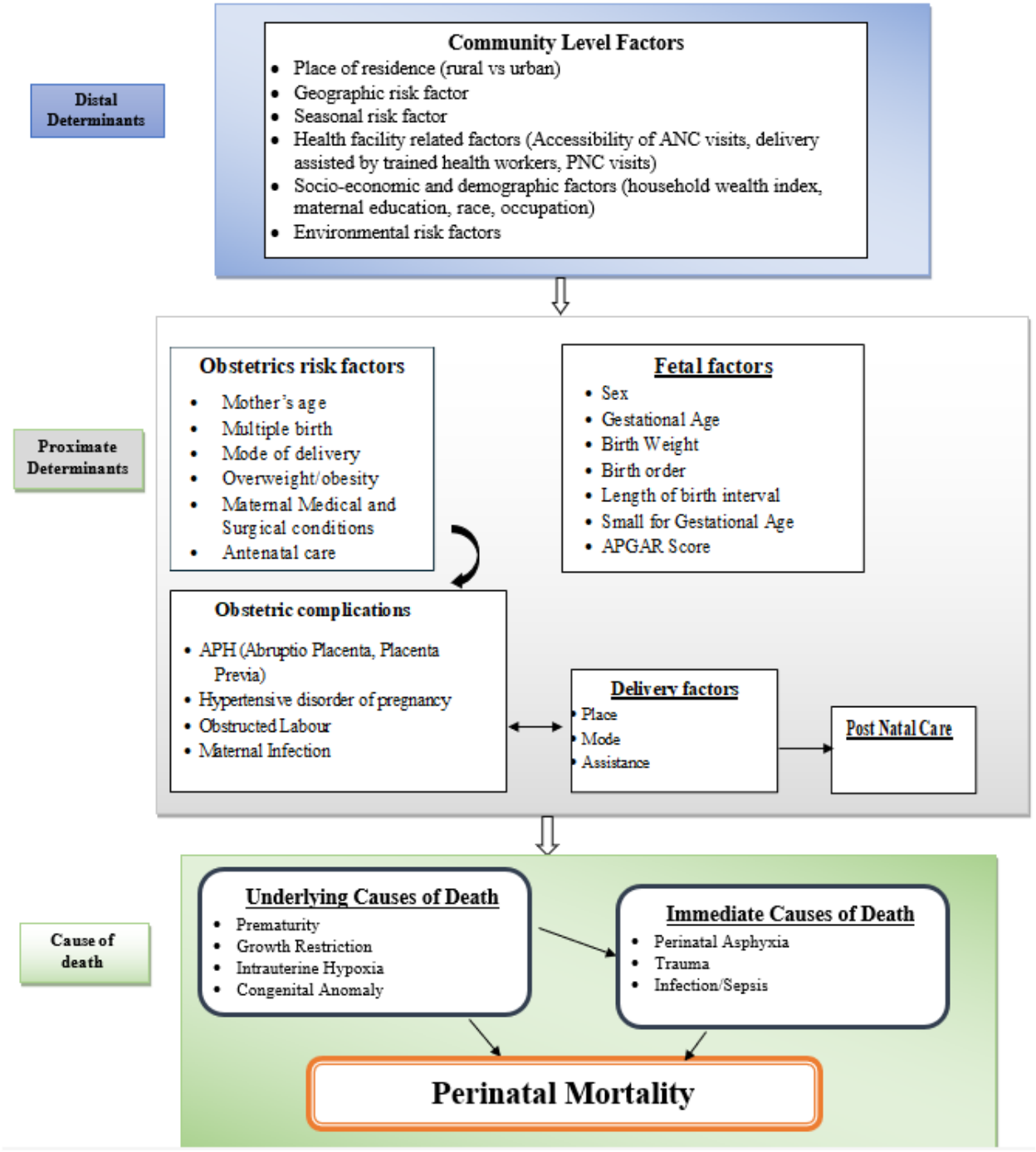

Figure 1. Conceptual framework for causes and risk factors of perinatal mortality, adapted and modified from Mosley and Chen[32].

is the determinants (risk factors) that are associated with perinatal mortality among the study subjects; factors associated with perinatal mortality will be socio-demographic and economic factors, maternal factors, fetal factors, health service-related factors, and environmental factors. The third outcome measure of the study will be the causes of perinatal mortality, which can be classified as the underlying cause (perinatal asphyxia or hypoxia, infection or sepsis, preterm

birth complications, congenital anomalies), immediate cause (perinatal asphyxia or hypoxia, infection or sepsis, preterm birth complication, and birth trauma), and main maternal factors (complications of placenta, cord or membranes and maternal medical or surgical conditions, mainly associated with hypertensive disorder of pregnancy) of death[1,33] (Figure 1). Furthermore, if any other classification systems were utilized in the included studies, we will also attempt to synthesize them.

Critical appraisal of individual studies

We will assess the methodological quality of included studies using the Joanna Briggs Institute quality assessment tool for observational and trial studies[34]. The Joanna Briggs Institute critical appraisal tool for cross-sectional, case-control and cohort studies comprises 8, 10 and 11 questions, respectively. The tool supports an assessment of sample representativeness of the target population, participant recruitment, adequacy of the sample size, detailed description of the study subjects and study setting, appropriate method of the statistical analysis, objective criteria in the measurement of the outcome variable and identification of subpopulation, reliability, and identification of confounding variables[35].

Each item for each study will be judged as Yes (1) and No (0). When the information provided is not adequate to make a judgment for a specific item, we will grade that item with a 'No' (0). Each study will be graded depending on the number of items judged 'Yes' (1) as low-risk bias (≥ 7), medium-risk bias (5 to 6), or high-risk bias (≤ 4) for cross-sectional studies, low-risk (≥8), medium-risk (5 to 7) and high-risk (< 5) for case-control studies, and low-risk (≥ 9), medium-risk (6 to 8) or high-risk (≤ 5) for cohort studies, and trials will be treated as cohort studies. We will conduct a sensitivity analysis to investigate how variations in the inclusion and exclusion of high-risk bias studies can affect the overall results after assessing the Risk of Bias In Non-randomized Studies - of Exposure (ROBINS-E)[36].

Data synthesis

The study selection processes will be summarized using a PRISMA flow diagram, and for studies which are excluded the reason will be described and explained[18]. A narrative synthesis will be used to summarize all studies included in the study and characteristics like study population, cause of perinatal mortality, and identified risk factors will be summarized in a descriptive table.

Meta-analysis

If appropriate perinatal mortality rates from different studies with a common definition of perinatal mortality will be pooled together to provide a single summary (pooled perinatal mortality rate) estimate using STATA-17 software. Further, we will calculate the pooled risk ratio for the risk factors of perinatal mortality using the random effect model as it assumes that the observed variation of effect size is because of real differences[37]. The syntax "metaforestplot" will be used to generate forest plots with their corresponding weights, as well as the pooled rate across studies and its corresponding 95% Confidence Intervals (Cl).

Heterogeneity test

To examine the magnitude of the variation between studies statistical heterogeneity test will be assessed by Higgins' I^2. The I^2 test measures level of statistical heterogeneity between studies; the values of <25 %, 25–50 %, 50–75 % and >75% are to mean very low, low, medium and high heterogeneity respectively[38]. Since heterogeneity is expected in this study because of the differences in perinatal mortality rate across different settings, random effect model will be used. If heterogeneity is significant (I^2>50%), sub-group analysis, meta-regression or meta-analysis will be conducted to investigate sources of heterogeneity and if meta-analysis is not possible, a narrative synthesis will be conducted.

Subgroup and sensitivity analysis

Sub-group analysis will be conducted based on study design, study type (community-based or facility-based), publication status (published or unpublished), study setting (rural vs. urban), geographic stratification, publication year, and study quality score (low or high score).

Sensitivity analysis will be performed to assess the robustness of a pooled estimate. We will use the single study omission analysis to test the robustness of a pooled estimate, and a study will be considered to have no influence on the pooled prevalence if the pooled estimate without it lies within the 95% confidence limits of the overall pooled prevalence. Sensitivity analysis will also be done using a risk of bias assessment result to ensure the robustness of the conclusion[39,40]. Furthermore, although most countries use the definition of perinatal mortality for international comparison, which is fetal deaths after 28 weeks of gestation or weighing more than 1000g till 7th day after birth, in the primary analysis we will try to capture studies that were done using the WHO definition for general statistics (≥500g or ≥22 weeks of gestation). Then, the analysis will be repeated using the perinatal mortality definition for international comparison.

Publication bias

We will inspect funnel plots subjectively and Egger's test objectively to assess publication bias. Evidence of publishing bias will be suggested by an asymmetrical funnel plot and a p-value < 0.1[41,42].

Discussion and conclusion

Although there is no specific systematic review and meta-analysis in Eastern Africa, a meta-analysis of demographic and health surveys in Sub-Saharan Africa indicated that the pooled perinatal mortality in East Africa was 34.5 (95% CI: 32.2, 36.8) per 1000 births[11]. However, the data from demographic and health surveys suffered from underreporting as data is collected retrospectively (deaths happening in the past five years). Another study conducted in Sub-Saharan Africa reported that perinatal mortality in East Africa was 49.88 (28.60, 71.18) per 1000 births and low birth weight, primiparity, history of perinatal loss, multiple gestation, preterm birth, and birth interval <2 years were identified as determinants of perinatal mortality[19]. Although it is crucial to consider studies that report only stillbirths or early neonatal

deaths, this study did not consider specific studies on either stillbirths or early neonatal deaths. Therefore, this review will consider all studies in perinatal mortality, including those that report only stillbirths and early neonatal death, and the analysis will be done accordingly. Further, this study will shed light on the causes of perinatal mortality, including whether studies use a recently introduced unified classification system (ICD-PM).

This review will provide up-to-date evidence on the burden, causes, and risk factors of perinatal mortality in East Africa. Published data and unpublished reports will be included, and estimates of the burden, causes and risk factors will be compared according to geographic location, study type, and study setting. The review will provide more information on this key topic, identify gaps and make recommendations, with the aim of informing interventions to prevent perinatal deaths. The findings of the study will be shared with the participating surveillance sites, and disseminated through national and international conferences, and peer-reviewed publication.

Study status

We have developed search strategies and data extraction tools, and the collection and screening of published articles began in August 2022. Data collection from Investigator groups for unpublished reports and overall analysis will be completed by May and June 2024, respectively.

Data availability

No data are associated with this article.

Reporting guidelines

figshare: PRISMA-P checklist for 'Burden, causes, and risk factors of perinatal mortality in Eastern Africa; a protocol for systematic review and meta-analysis', https://doi.org/10.6084/m9.figshare.20627859[43]

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Open Peer Review

Current Peer Review Status: ? ✔ ?

Version 2

Reviewer Report 18 July 2024

https://doi.org/10.21956/gatesopenres.17085.r37376

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Kim J. C Verschueren
Utrecht University, Utrecht, The Netherlands

Thank you for the opportunity to review this protocol for an important systematic review. I strongly encourage that this review is conducted, with the recommendations of some minor revisions. It is great that the authors will report articles in all languages (as there may be several in French, Arabic or Swahili).

1. Objective should be to synthesize evidence on the prevalence, timing (antepartum, intrapartum, unknown), causes, risk factors of perinatal deaths in East-Africa. "The burden" is too general (and difficult to assess as this goes beyond the deaths). Consider to also include 'lessons learned' or 'recommendations' described in literature.
2. In background the authors mention ENAP goal of 12/1000 by 2030; the action plan itself mentions 10/1000 for each by 2035, please review.
3. Consider including neonatal deaths until 28 days as some studies define perinatal mortality including late neonatal deaths as well.
4. Why did the authors decide to include studies until 2022 and not until 2024? This should be updated. Please clarify why 2010 was chosen as the starting point.
5. Causes are classified with different classification systems; it is not clear how the authors will assess the causes and reclassify them. Why did the authors choose the classification system from Mosley and Chen (2003) and not the WHO-validated ICD-PM classification? (while they do mention it under data items?). I would suggest them, considering that they have to reclassify anyway, to use the latter.
6. Consider describing not only the relative risk or odds ratio, but also the absolute risk, as this can be clinically more relative.
7. Perinatal death rate has denominator 'total births' (not live births).
8. Please include mode of delivery in your review, as every cesarean performed on a baby who dies, should be considered a CS too much (considering the risks a previous CS scar carries in future pregnancies), as well as the under-utilisation of ventouse (which may save some babies as it is quicker, and reduce many CS).
9. I recommend the authors not to look too much into 'risk factors / medical determinants' of perinatal deaths, as they are well known and vary not very much between contexts. Many

important variables will also likely not be available, which can be absolutely contributing (for example maternal malnutrition, severe anaemia, malaria during pregnancy, etc). It is important to find out and explain why the high perinatal death rate is high in this context: referral system (primary to secondary), referral criteria for high-risk, maternity waiting home, quality of ANC (not just number), quality of 'skilled birth attendant', number of birth attendants per number of births per day, availability of medication/tests during ANC, presence of medical specialist / hospital in case of complications, access and infrastructure, number of women with previous CS and % of VBACs (at higher risk in subseq pregnancy), the manner of fetal monitoring, the possibility to perform ventouse, etc etc) and to develop clear recommendations which interventions are likely the most helpful to reduce perinatal deaths - and these are not similar to the risks (we cannot prevent births from primiparas, nor multiple gestation, but we can improve the management). It is for this reason that we recommend and strongly encourage the authors to go beyond the numbers to really make impact !

All the best to the authors.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Maternal mortality and near miss, and perinatal mortality in low- and middle-income settings. Cesarean sections in LMIC.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 19 June 2024

https://doi.org/10.21956/gatesopenres.17085.r36767

Anna Akselsson

Sophiahemmet University, Stockholm, Sweden

The revisions are appropriate.

Is the rationale for, and objectives of, the study clearly described?
Not applicable

Is the study design appropriate for the research question?
Not applicable

Are sufficient details of the methods provided to allow replication by others?
Not applicable

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Stillbirth, fetal movements, antenatal care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 25 August 2023

https://doi.org/10.21956/gatesopenres.15208.r34567

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Anna Akselsson
[1] Sophiahemmet University, Stockholm, Sweden
[2] Sophiahemmet University, Stockholm, Sweden

Thank you for giving me the opportunity to review this study protocol. It is important that this type of study is focusing on a low resource setting in where most of the worlds perinatal mortality occur. The authors aim to address the burden, causes, and risk factors of perinatal mortality in East Africa and are planning to include both unpublished and published data. The protocol is well written and address an important topic. Thank you for conducting this study.

I have some concerns that follow below.

Introduction: Well written and includes the most important information. However, research question nr 1 is contradictory to one of the exclusion criteria. The sentence “We will also exclude studies that focus on specific populations (e.g., high-risk mothers).” in exclusion criteria versus “What is the overall perinatal mortality rate and how does this vary in different contexts (geographic location, study setting) in East Africa?”.

Question: Can you be more specific in exclusion criteria of when to exclude specific populations?

Methods: Clearly written and structured well. I miss information about how you obtain unpublished data and how you will handle missing values in the dataset, are you planning to handle missing values by imputation? I guess a lot of studies from East Africa will have many missing values to consider. A lot of potential risk factors and confounders may not be available in the studies you include. Will you publish a statistical analysis plan later on describing this matter?

Question: How will you obtain unpublished data and how are you planning on handle missing data?
Figure 1 is good and clarifies the process, “Ante Natal Care” should be “Antenatal care”

Question: In figure 1, can you check the spelling and change where necessary?

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Stillbirth, fetal movements, antenatal care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 14 Apr 2024

Yohanis Alemeshet

Thanks very much for reviewing our paper. Our responses to the specific points are discussed in the following bullet points.

Introduction: Well written and includes the most important information. However, research question nr 1 is contradictory to one of the exclusion criteria. The sentence "We will also exclude studies that focus on specific populations (e.g., high-risk mothers)." in exclusion criteria versus "What is the overall perinatal mortality rate and how does this vary in different contexts (geographic location, study setting) in East Africa?".
Question: Can you be more specific in exclusion criteria of when to exclude specific populations?

- Thank you for your comment and question. We plan to exclude studies that were conducted on specific populations, for instance, high-risk mothers, that don't reflect the population, and frequently lack a population denominator. However, if studies report the population denominator (vs the facility denominator) or report the effect size after comparing with low-risk mothers, we will not exclude them.

Methods: Clearly written and structured well. I miss information about how you obtain unpublished data and how you will handle missing values in the dataset, are you planning to handle missing values by imputation? I guess a lot of studies from East Africa will have many missing values to consider. A lot of potential risk factors and confounders may not be available in the studies you include. Will you publish a statistical analysis plan later on describing this matter?
Question: How will you obtain unpublished data and how are you planning on handle missing data?

- We will try to get unpublished internal reports and/or aggregate data from HDSS sites to complement published sources, using our connections to investigators in the region.
- We will assess the missing data and then consider the strategies for handling it, including consideration of imputation, if appropriate. We have incorporated this into the meta-analysis section. *"For unpublished data from the internal reports/ aggregate data from HDSS sites, We will assess the gaps in the data and deliberate on effective strategies to manage them. This may encompass the possibility of imputation, if appropriate."*

Figure 1 is good and clarifies the process, "Ante Natal Care" should be "Antenatal care"
Question: In figure 1, can you check the spelling and change where necessary?
Thank you for this. Now, "Ante Natal Care" has been corrected into "Antenatal care.

Competing Interests: No competing interests were disclosed.

Reviewer Report 20 July 2023

https://doi.org/10.21956/gatesopenres.15208.r33334

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Vivek V Shukla
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The current study aims "to synthesize evidence on the burden, causes, and risk factors for perinatal mortality in East Africa." The study's authors are commended for their work; I have a few suggestions for consideration to improve the manuscript and the overall research.

Title: The title of the meta-analysis is clear and concise, providing a good overview of the study's focus.

Abstract: The abstract summarizes the study objectives, methods, and expected outcomes. However, it lacks specific details regarding the population, interventions, comparisons, and outcomes (PECO) framework, which are essential for understanding the scope of the study.

Introduction: The introduction could benefit from providing more information on perinatal mortality in East Africa. For instance, it would be helpful to include statistics or prevalence rates of perinatal mortality in the region to emphasize the significance of the problem. Additionally, discussing the socioeconomic and healthcare factors specific to East Africa that may contribute to perinatal mortality rates would provide context and enhance the reader's understanding.

Significance and implications: The introduction could provide a statement on the importance of the study and the potential impact on research and practice. It would be beneficial to highlight how the meta-analysis results can contribute to improving perinatal health outcomes in East Africa, inform policy decisions, or guide future research directions.

Rationale for the study: The introduction lacks a clear and concise statement of the research gap or rationale for conducting the meta-analysis. It is important to explicitly state why a meta-analysis is needed for the specific region "East Africa" and how it will contribute to the existing body of knowledge.

Methods:

Search Strategy: The comprehensive search strategy includes multiple databases and sources to ensure broad coverage of relevant studies. Specific search terms and Boolean operators are helpful in enhancing transparency and reproducibility.

Eligibility Criteria: The inclusion and exclusion criteria are well-defined, specifying the types of studies, population, interventions, comparisons, and outcomes of interest. Eligibility criteria are clearly described, including the inclusion of both published and unpublished studies. However, it would be helpful to provide a justification for the selected time frame (January 2010 to June 2022) and discuss potential limitations or biases that might arise from excluding studies published before 2010 or after June 2022.

Language Consideration: It is mentioned that articles reported in any language will be considered, but it would be helpful to mention whether language translation services will be used and the process of extraction for such studies.

Data Collection: The data extraction process is adequately described, mentioning the key information to be collected. However, the title and abstract screen by a single investigator is sub-optimal. Adding a second reviewer to screen and a third to resolve conflicts would be a better approach.

Definitions: Stillbirths defined as "fetal death at ≥500g/≥22 weeks gestation or ≥1000g /≥28 weeks gestation" is confusing. How do the authors plan to ensure comparability across studies?

The critical appraisal plan is robust.

Risk of Bias Assessment: The protocol mentions using the Joanna Briggs Institute quality assessment tool for observational and trial studies. Please clarify how the risk of bias will be evaluated and incorporated into the analysis. Will there be any secondary analyses with studies that have been identified as having a low risk of bias? Consider conducting a sensitivity analysis to explore the impact of different inclusion criteria or the exclusion of specific studies on the overall findings.

Results: A descriptive paragraph elaborating the expected results would be helpful for readers.

Discussion: I suggest presenting the findings of the published meta-analysis on the subject. What factors did they identify, their impact, and how would the proposed analyses add to the existing literature and its likely impact? I would also add a section on limitations and how the authors have tried to address the limitations.

Overall, this proposal is of significant importance, featuring commendable writing, and tackling a crucial research topic.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Perinatal Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 14 Apr 2024

Yohanis Alemeshet

Thank you very much for reviewing our paper. Our responses to the specific points are discussed in the bullet points following the raised comments/questions.

Abstract: The abstract summarises the study objectives, methods, and expected outcomes. However, it lacks specific details regarding the population, interventions, comparisons, and outcomes (PECO) framework, which are essential for understanding the scope of the study.

- Thank you for this comment. Specific details of the population, exposure comparisons and outcomes are now included in the abstract. *"The study population includes all fetuses and newborns from* ≥22 weeks of gestation (birth weight ≥500gm) to 7 days after birth, with reported causes or/and determinants as exposure and perinatal mortality (stillbirths and/or early neonatal deaths) as an outcome.

Introduction: The introduction could benefit from providing more information on perinatal mortality in East Africa. For instance, it would be helpful to include statistics or prevalence rates of perinatal mortality in the region to emphasise the significance of the problem. Additionally, discussing the socioeconomic and healthcare factors specific to East Africa that may contribute to perinatal mortality rates would provide context and enhance the reader's understanding.

- In the second paragraph, we have incorporated more information specific to East Africa, including some statistics and relevant factors like socioeconomic and healthcare factors specific to the region.

Significance and implications: The introduction could provide a statement on the importance of the study and the potential impact on research and practice. It would be beneficial to highlight how the meta-analysis results can contribute to improving perinatal health outcomes in East Africa, inform policy decisions, or guide future research directions.

- At the end of the introduction, the following statements are added to indicate the significance and implication of this study: **"***Hence, in this systematic review, we aimed to describe the burden, causes and risk factors of perinatal mortality in East Africa, using the most up-to-date information, to determine progress in achieving the ENAP 2030 targets and direct policymakers to allocate resources to the likely most effective interventions to prevent preventable perinatal deaths.*"

Rationale for the study: The introduction lacks a clear and concise statement of the research gap or rationale for conducting the meta-analysis. It is important to explicitly state why a meta-analysis is needed for the specific region "East Africa" and how it will contribute to the existing body of knowledge.

- The rationale for conducting this study in East Africa is now more clearly indicated in the second paragraph by adding the following statement – *". . . Perinatal mortality in the region was one of the highest, with 34.5 deaths per 1000 births [1]. East Africa also has*

the weakest economy across Sub-Saharan Africa, and utilisation of reproductive health services (facility deliveries, skilled delivery assistance, and 4+ antenatal visits) in East and Central Africa is lower than in other areas of Sub-Saharan Africa [2,3]. Reducing perinatal mortality in this region is critical; counting the number of deaths precisely and consistently classifying causes and risk factors for perinatal mortality (one of the objectives of the Every Newborn Action Plan), is essential to inform effective interventions [4]."

Methods: Search Strategy: The comprehensive search strategy includes multiple databases and sources to ensure broad coverage of relevant studies. Specific search terms and Boolean operators are helpful in enhancing transparency and reproducibility.

- Thank you for this comment. The specific search terms and Boolean operators used in Medline were included in the protocol, and to enhance transparency and reproducibility, we will also report the search strategies with specific terms and Boolean operators used in each database when we submit the systematic review results. We have also stated this in the protocol under the search strategy section.

Eligibility Criteria: The inclusion and exclusion criteria are well-defined, specifying the types of studies, population, interventions, comparisons, and outcomes of interest. Eligibility criteria are clearly described, including the inclusion of both published and unpublished studies. However, it would be helpful to provide a justification for the selected time frame (January 2010 to June 2022) and discuss potential limitations or biases that might arise from excluding studies published before 2010 or after June 2022.

- We decided to consider the timeframe from 2010 until the end of 2022, because the aim of this study is to review the up-to-date information in perinatal mortality, and to ensure that we use sufficient data. Therefore, the following statement is added under the sub-title Years and language considered for study recruitment *". . . because it aims to examine up-to-date information regarding perinatal mortality and the advancements made towards attaining the 2030 goals, whilst ensuring sufficient years are assessed to maximize data included in the analysis."*

Language Consideration: It is mentioned that articles reported in any language will be considered, but it would be helpful to mention whether language translation services will be used and the process of extraction for such studies.

- We plan to consult a specific language expert to translate other languages that authors do not speak, and we will also use language translation softwares.

Data Collection: The data extraction process is adequately described, mentioning the key information to be collected. However, the title and abstract screen by a single investigator is sub-optimal. Adding a second reviewer to screen and a third to resolve conflicts would be a better approach.

- Thank you for this, We have corrected this as "*Titles and abstracts of remaining studies will be screened by Y.A.A., and N.A*"

Definitions: Stillbirths defined as "fetal death at ≥500g/≥22 weeks gestation or ≥1000g /≥28 weeks gestation" is confusing. How do the authors plan to ensure comparability across studies?

- We are considering this broad definition to look at the variation of definitions across different studies; however, in our meta-analysis, we will only consider studies with similar definitions (≥1000g /≥28 weeks gestation).

The critical appraisal plan is robust.

Risk of Bias Assessment: The protocol mentions using the Joanna Briggs Institute quality assessment tool for observational and trial studies. Please clarify how the risk of bias will be evaluated and incorporated into the analysis. Will there be any secondary analyses with studies that have been identified as having a low risk of bias? Consider conducting a sensitivity analysis to explore the impact of different inclusion criteria or the exclusion of specific studies on the overall findings.

- Thank you for this, in order to check the risk of bias we will use the Risk Of Bias In non-randomized Studies – of Exposure (ROBINS-E), and we will consider a sensitivity analysis to investigate how variations in the inclusion and exclusion of high-risk bias studies can affect the overall. A statement describing this is added under the critical appraisal of individual studies section.

Results: A descriptive paragraph elaborating the expected results would be helpful for readers.

Discussion: I suggest presenting the findings of the published meta-analysis on the subject. What factors did they identify, their impact, and how would the proposed analyses add to the existing literature and its likely impact? I would also add a section on limitations and how the authors have tried to address the limitations.

- We tried to consider both the expected outcome and discussion under the Discussion and Conclusion section added the following paragraph *"Evidence shows that East Africa has the weakest economy across Sub-Saharan Africa, and utilisation of reproductive health services (facility deliveries, skilled delivery assistance, and 4+ antenatal visits) in East and Central Africa is lower than in other areas of Sub-Saharan Africa.*
- *Although there is no specific systematic review and meta-analysis in Eastern Africa, a meta-analysis of demographic and health surveys in Sub-Saharan Africa indicated that the pooled perinatal mortality in East Africa was 34.5 (95% CI: 32.2, 36.8) per 1000 births. However, the data from demographic and health surveys suffered from underreporting as data is collected retrospectively (deaths happening in the past five years). Another study conducted in Sub-Saharan Africa reported that perinatal mortality in East Africa was 49.88 (28.60, 71.18) per 1000 births and low birth weight, primiparity, history of perinatal loss, multiple gestation, preterm birth, and birth interval <2 years were identified as determinants of perinatal mortality 4. Although it is crucial to consider studies that report only stillbirths or early neonatal deaths, this study did not consider specific studies on either stillbirths or early neonatal deaths. Therefore, this review will consider all studies in perinatal mortality, including stillbirths and early neonatal death-only studies, and the analysis will be done accordingly. Further, this study will shed light on the causes of perinatal mortality, including whether studies use a recently introduced unified classification system (ICD-PM)."*

Competing Interests: No competing interests were disclosed.