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# Magnitude and causes of sickle cell disease–related maternal mortality in sub-Saharan Africa: a systematic review and meta-analysis of proportions

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## ADMINISTRATIVE INFORMATION

**Support -** No Support.

**Review Stage at time of this submission -** Preliminary searches.

**Conflicts of interest -** None. The authors declare no conflicts of interest. The review receives no external funding and is conducted as part of an academic end-of-cycle dissertation (Travail de Fin de Cycle).

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 June 2026 and was last updated on 17 June 2026.

## INTRODUCTION

**Review question / Objective** This is a prevalence / proportion review; the CoCoPop framework (Condition – Context – Population) is used, as there is no intervention or comparator in the conventional sense.
Question: In sub-Saharan Africa (Context), among pregnant or peripartum women with sickle cell disease (Population), what is the magnitude of maternal mortality (Condition) — proportion of deaths / case fatality, and disease-specific maternal mortality ratio where available — and what are its immediate and contributory causes?
Primary objective: to estimate the pooled proportion (case fatality) of maternal deaths among pregnant/peripartum women with sickle cell disease in sub-Saharan Africa. Secondary objectives: to describe the distribution of immediate and contributory causes of death; to examine variation by genotype, country, type of facility and period; and, where data allow, to estimate the relative risk of maternal death compared with women without sickle cell disease.

**Rationale** Sickle cell disease is one of the most common inherited disorders, with the highest global burden in sub-Saharan Africa, where the majority of affected children are born. Pregnancy in women with sickle cell disease carries a high risk of complications and death (vaso-occlusive crises, acute chest syndrome, severe infections, worsening anaemia, pre-eclampsia, and thromboembolism), in addition to baseline obstetric risk. Global reviews (Oteng-Ntim et al., 2015; Boafor et al., 2016) have established a marked excess of maternal mortality, greater for the HbSS genotype and in low-income countries. However, these syntheses pool highly heterogeneous contexts, and the magnitude specific to sub-Saharan Africa remains poorly quantified, even though the region combines the highest disease prevalence with high maternal mortality. Local data come mainly from dispersed hospital cohorts that have never been pooled

specifically for the region. Producing a reliable regional estimate of this burden and of its causes is needed to inform specialised antenatal management, to size service needs (transfusion, infection prevention, monitoring), and to guide regional public-health priorities.

**Condition being studied** Maternal mortality associated with sickle cell disease during pregnancy, childbirth and the peripartum period (up to 42 days postpartum), in sub-Saharan Africa. Sickle cell disease refers to the major genotypes HbSS, HbSC and HbSβ-thalassaemia. The review focuses on the descriptive epidemiology of the mortality burden (proportion of deaths and causes), not on the evaluation of a specific intervention.

## METHODS

**Search strategy** The search combines four concept blocks — sickle cell disease, pregnancy / peripartum, maternal mortality, and sub-Saharan Africa — combining MeSH and free-text terms (OR within a block, AND between blocks). The mortality block deliberately keeps a broad term to preserve sensitivity, with restriction to maternal mortality applied at screening. The search runs from database inception to the search date and will be re-run before the final analysis. Main PubMed query (to be adapted to the syntax of each database):
("Anemia, Sickle Cell"[Mesh] OR "sickle cell"[tiab] OR drepanocyt*[tiab] OR "sickle cell disease"[tiab] OR "sickle cell anaemia"[tiab] OR "sickle cell anemia"[tiab] OR HbSS[tiab] OR HbSC[tiab]) AND ("Pregnancy"[Mesh] OR pregnan*[tiab] OR maternal[tiab] OR obstetric*[tiab] OR peripartum[tiab] OR postpartum[tiab]) AND ("Maternal Mortality"[Mesh] OR "maternal mortality"[tiab] OR "maternal death*"[tiab] OR "case fatality"[tiab] OR mortality[tiab]) AND ("Africa South of the Sahara"[Mesh] OR "sub-Saharan Africa"[tiab] OR Africa[tiab]).

**Participant or population** Pregnant or peripartum women (up to 42 days postpartum) with confirmed sickle cell disease (genotypes HbSS, HbSC, HbSβ-thalassaemia) living in sub-Saharan Africa.

**Intervention** Not applicable. This is a prevalence / proportion review and evaluates no intervention. The exposure of interest is sickle cell disease itself during pregnancy.

**Comparator** Not applicable for the primary (proportion) estimate. Optionally, where data allow, pregnant women without sickle cell disease will serve as a reference group to estimate a relative risk of maternal death.

**Study designs to be included** Observational studies reporting a denominator: prospective and retrospective cohorts; cross-sectional studies; hospital-based series with a defined population; registries; maternal death audits; and confidential enquiries into maternal mortality. Case reports, case series without a denominator, editorials, letters, opinion pieces and narrative reviews are excluded.

**Eligibility criteria** Inclusion: confirmed sickle cell disease (HbSS, HbSC, HbSβ-thal); study conducted in sub-Saharan Africa; a usable numerator (maternal deaths) and denominator (sickle cell pregnancies / deliveries) allowing a proportion to be computed.
Exclusion: sickle cell trait (HbAS) considered alone as cases; populations outside sub-Saharan Africa (unless data can be extracted separately); studies without a usable denominator; isolated case reports without a defined population.

**Information sources** • Free bibliographic databases (searched systematically): MEDLINE (via PubMed); LILACS; Global Index Medicus / African Index Medicus. • Grey literature: the WHO institutional repository (IRIS, iris.who.int); confidential enquiry reports / maternal death audits; theses. • Citation chasing in PubMed ("Cited by") from pivotal reviews, and reference lists of included
studies. • Hand-searching of the reference lists of included
studies. Subscription databases (Embase, CINAHL) will be searched only if access is available through the university library or HINARI / Research4Life; otherwise their non-searching will be reported as alimitation.

**Main outcome(s)** Pooled proportion of maternal deaths (case fatality) among pregnant / peripartum women with sickle cell disease, with 95% confidence interval. The disease-specific maternal mortality ratio (deaths per 100,000 live births) will be reported where available. Effect measure: proportion, stabilised by the Freeman–Tukey double-arcsine transformation before pooling and back-transformed for presentation.

**Additional outcome(s)** • Distribution of immediate and contributory causes of death (severe anaemia, acute chest syndrome, sepsis / infection, pre-eclampsia / eclampsia, haemorrhage, thromboembolism, vaso-occlusive crisis,
etc.). • Timing of death (antepartum, intrapartum,

postpartum). • Mortality by genotype (HbSS vs HbSC). • Where available, relative risk of maternal death versus women without sickle celldisease.

**Data management** Records will be imported into Rayyan for de-duplication and screening. Selection will proceed in two stages (title/abstract, then full text), each performed independently and blinded by two reviewers; disagreements will be resolved by discussion or a third reviewer, and inter-reviewer agreement estimated (kappa). Data will be extracted on a piloted standardised Excel form by two independent reviewers, capturing numerator, denominator, genotype, causes of death, timing, period, facility type and management programme. The selection flow will follow the PRISMA 2020 flow diagram.

**Quality assessment / Risk of bias analysis** Methodological quality will be assessed independently by two reviewers using the Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data (Munn et al., 2015), which addresses sampling and setting, representativeness, sample size, reliable identification of sickle cell disease, standardised measurement of the outcome (death), adequacy of the denominator, and statistical analysis. Disagreements will be resolved by a third reviewer; judgements will inform interpretation and sensitivity analyses.

**Strategy of data synthesis** If clinical relevance and heterogeneity allow, a random-effects meta-analysis of proportions will be performed in R (package meta, function metaprop; metafor), with proportion forest plots; pooled estimates will be back-transformed for presentation. Proportions will be stabilised using the Freeman–Tukey double-arcsine transformation (logit transformation in sensitivity analysis). Heterogeneity will be quantified using $I^2$ and $\tau^2$ and explored through subgroup analyses and, where the number of studies allows, meta-regression (publication year, genotype mix, methodological quality). Causes of death will be synthesised as proportions (share of each cause among deaths) and narratively. Where meta-analysis is not appropriate (high heterogeneity or insufficient data), a structured synthesis without meta-analysis (SWiM) will be conducted. Publication / small-study bias will be explored with caution, as funnel plots are unreliable for proportions (Barker et al., 2021).

**Subgroup analysis** • By genotype (HbSS vs HbSC).
• By country / region of sub-Saharan Africa.
• By type of facility (referral / tertiary vs general facility). • By period (before vs after 2010).
• By presence or absence of a specialised antenatal managementprogramme.

**Sensitivity analysis** Robustness will be tested by: excluding studies at high risk of bias; comparing the Freeman–Tukey and logit transformations; and comparing fixed-effect and random-effects models. The influence of individual studies on the pooled estimate will be examined through leave-one-out analysis where feasible.

**Language restriction** English and French only.

**Country(ies) involved** Democratic Republic of the Congo.

**Other relevant information** The final report will follow PRISMA 2020; the search will be reported according to PRISMA-S. The meta-analysis of proportions will follow established methodological guidance (Munn et al., 2015; Barendregt et al., 2013; Barker et al., 2021; Nyaga et al., 2014). The review differs from existing global reviews (Oteng-Ntim 2015; Boafor 2016) by its exclusive focus on sub-Saharan Africa and a single outcome (maternal mortality and its causes). Limitations to be acknowledged include the restriction to French and English publications (risk of language bias), the reliance on hospital-based data (limited generalisability), and the possible non-searching of subscription databases. Anchor references for search validation: Oteng-Ntim E, et al. Blood. 2015;125(21):3316-3325; Boafor TK, et al. BJOG. 2016;123(5):691-698; Rahimy MC, et al. Blood. 2000;96(5):1685-1689; Munn Z, et al. Int J Evid Based Healthc. 2015;13(3):147-153.

**Keywords** Sickle cell disease; pregnancy; maternal mortality; case fatality; causes of death; sub-Saharan Africa; meta-analysis of proportions; systematic review.

**Dissemination plans** End-of-cycle dissertation (Travail de Fin de Cycle); academic presentation; possible submission to a peer-reviewed journal; feedback to national maternal-health and sickle cell disease control programmes and to health actors in Kongo Central.

**Contributions of each author**
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