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Risk factors for neonatal sepsis in Sub-Saharan Africa: a systematic review with meta-analysis

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ABSTRACT

Objectives To identify the risk factors for neonatal sepsis in Sub-Saharan Africa.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase, Web of Science, African Index Medicus and ClinicalTrials.gov were searched for observational studies from January 2010 to August 2020.

Setting Sub-Saharan Africa, at all levels of healthcare facilities.

Participants 'Neonates' (<28 days of age) at risk of developing either clinical and/or laboratory-dependent diagnosis of sepsis.

Outcome measures Identification of any risk factors for neonatal sepsis.

Results A total of 36 studies with 23 605 patients from secondary or tertiary level of care facilities in 10 countries were included. Six studies were rated as good quality, 8 as fair and 22 as poor. Four studies were omitted in the meta-analysis due to insufficient data. The significant risk factors were resuscitation (OR 2.70, 95% CI 1.36 to 5.35), low birth weight <1.5 kg (OR 3.37, 95% CI 1.59 to 7.13) and 1.5–2.5 kg (OR 1.36, 95% CI 1.01 to 1.83), low Apgar score at the first minute (OR 3.69, 95% CI 2.34 to 5.81) and fifth minute (OR 2.55, 95% CI 1.46 to 4.45), prematurity <37 weeks (OR 1.91, 95% CI 1.27 to 2.86), no crying at birth (OR 3.49, 95% CI 1.42 to 8.55), male sex (OR 1.30, 95% CI 1.01 to 1.67), prolonged labour (OR 1.57, 95% CI 1.08 to 2.27), premature rupture of membranes (OR 2.15, 95% CI 1.34 to 3.47), multiple digital vaginal examinations (OR 2.22, 95% CI 1.27 to 3.89), meconium-stained amniotic fluid (OR 2.72, 95% CI 1.58 to 4.69), intrapartum maternal fever (OR 2.28, 95% CI 1.18 to 4.39), foul-smelling vaginal discharge (OR 3.31, 95% CI 2.16 to 5.09) and low socioeconomic status (OR 1.93, 95% CI 1.11 to 3.35). We found considerable heterogeneity in the meta-analysis of 11 out of 15 identified risk factors.

Conclusion Multiple risk factors for neonatal sepsis in Sub-Saharan Africa were identified. We revealed risk factors not listed by the WHO guidelines. The included studies overall had high risk of bias and high heterogeneity and thus, additional research of high quality is needed.

PROSPERO registration number CRD42020191067.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review and meta-analysis has a high number of included studies (36) as well as a large sample size (23 605 neonates).
⇒ This systematic review has a broad search strategy, with a meta-analysis performed on 33 risk factors.
⇒ Heterogeneity in the study design of the included studies is a limitation.
⇒ The overall high risk of bias in the included studies is a limitation.

INTRODUCTION

The Millennium Development Goals from 1990 identified newborn health as a key priority for global development.[1] The global neonatal mortality rate has decreased by 37%, from 33 to 21 deaths per 1000 live births since then.[2] In 2016, the Sustainable Development Goals (SDGs) were announced.[3] SDG goal 3 aims to ensure healthy lives and promote well-being for all at all ages, and includes subtarget 3.2: by 2030, to end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births.[3] However, today a child born in Sub-Saharan Africa is still 10 times more likely to die in the first month compared with a child born in a high-income country.[4] In 2018, 2.5 million children died within the first 28 days of life globally.[4] In the same year, countries in Sub-Saharan Africa had the highest mortality, with 28 neonatal deaths per 1000 live births.[2 4]

The majority of the 2.5 million neonatal deaths in 2018 worldwide can be divided into three main causes, each contributing approximately one-third to neonatal deaths: infections, intrapartum asphyxia and preterm birth complications.[2 5] However, the causes of neonatal death vary among countries and regions.[5] In countries with high neonatal mortality, almost 50% of deaths are due to severe infection with sepsis, making sepsis a leading cause of admissions and deaths in neonatal units in low-income and middle-income countries (LMICs).[5 6] The

Sub-Saharan African region includes some of the highest rates of neonatal mortality due to neonatal sepsis, yet prevention strategies are and remain unsatisfactory.[7] Improved understanding of the underlying causes of neonatal sepsis is necessary to optimise prevention and management guidelines. Evidence from reviews of risk factors has been used globally to guide the development of management guidelines and prevention strategies for neonatal sepsis.[8] The WHO recommends prophylactic antibiotics to newborns within 48 hours after delivery if membranes ruptured >18 hours before delivery, the mother had fever >38°C before delivery or during labour, or the amniotic fluid was foul-smelling or purulent.[9] However, there might be discrepancies in the risk factors in different parts of the world. In a paper from 2020 on neonatal mortality, the authors conclude that there is a need to develop clinical guidelines for prevention and management of neonatal sepsis that are specific to the Sub-Saharan African context.[10]

Multiple studies aiming to identify the risk factors for neonatal sepsis have been performed in Sub-Saharan Africa during the last 10 years. With this systematic review and meta-analysis, we aim to provide quality evidence to identify the risk factors for neonatal sepsis in Sub-Saharan Africa. To the best of our knowledge, this is the first systematic review and meta-analysis to address neonatal risk factors for sepsis in the Sub-Saharan African context.

METHODS AND MATERIALS

This systematic review with meta-analysis has been reported in accordance with the 'Preferred Reporting Items for Systematic reviews and Meta-analysis' guidelines (online supplemental appendix 1).[11] A protocol (online supplemental appendix 2) was developed for our review in accordance with the 'Preferred Reporting Items for Systematic reviews and Meta-analysis protocols' guidelines.[12] It was registered on 12 July 2020 with the 'International prospective register of systematic reviews PROSPERO' (ID: CRD42020191067), which can be accessed on its website (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020191067).

Search strategy and selection criteria

A comprehensive search strategy including all possible risk factors for neonatal sepsis in Sub-Saharan Africa was developed in cooperation with subject experts and an information scientist. Free text and database-specific subject headings were included. Publication date was restricted to 1 January 2010–7 August 2020 and language was restricted to English. A search strategy was first developed for PubMed (online supplemental appendix 3) and subsequently adapted in other databases.

One author (CMB) searched PubMed, Embase, Web of Science (Clarivate Analytics) and African Index Medicus (accessed through the WHO) for published materials. ClinicalTrials.gov was searched for ongoing trials (grey literature). Additionally, the reference lists of the included studies were screened for potentially relevant studies. Systematic reviews and literature reviews were excluded from this systematic review, but the reference lists of these were screened as well. The authors of published abstracts were furthermore contacted to identify the full studies.

The following were the inclusion criteria:

- Neonates (<28 days of age) with sepsis,[4] that is, septicaemia/sepsis, pneumonia, meningitis, osteomyelitis, arthritis, urinary tract infections, malaria and candidiasis. Sepsis could be either clinical or laboratory-dependent diagnosis.
- Reported on one or more risk factor for neonatal sepsis.
- Observational prospective and/or retrospective analytical design, reporting on two outcome groups: one with sepsis and one without sepsis.
- For inclusion in the meta-analysis, studies had to present quantitative data on the two above-mentioned outcome groups and the risk factors had to be reported on in at least three studies or found to be significant factors in at least two studies.

Data extraction

One author (CMB) screened the studies in Covidence (www.covidence.com) in the title stage. Two authors independently performed abstract screening and full-text study selection, where both authors had to approve the inclusion of the study in the systematic review. Disagreements during full-text study selection were resolved by discussion and consensus was reached in the presence of senior authors (AP and SL). If needed data were missing (eg, full article or raw data for meta-analysis), the authors were contacted in order to obtain the data. A predesigned extraction tool, specific to this review, was developed in Excel. This tool included study identification, location, study period, setting, definition of a neonate, definition of early-onset and late-onset neonatal sepsis (EONS and LONS), study design, sample size associated with risk factors, risk factors examined (neonatal and/or maternal), and limitations in relation to our review's objective (eg, studies only examining risk factors for EONS). Only unadjusted/'raw' data were pooled in the meta-analysis.

Quality assessment

Two authors (CMB and CNS) independently performed quality assessment of the included studies using the National Heart, Lung, and Blood Institute's (NHLBI) 'Quality Assessment of Case-Control Studies' and 'Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies'.[13 14] If the study design was unclear/poorly reported but the study reported data with a comparison group, we classified the study design as either 'prospective' (data collected when the neonate was in the neonatal unit) or 'retrospective' (data collected after the neonate had been discharged from the neonatal unit). We assessed each study on its own based on the details reported and considered the concepts for minimising the risk of bias. Discrepancies were resolved by discussion and

consensus in the presence of senior authors (CHH, AP and SL) for all the above procedures. Covidence identified duplicate data and the duplicates were manually checked by CNS.

Statistical analysis

For the meta-analysis, a forest plot was created according to a random effects model. We chose the random effects model over the fixed effects model because it accounts for variations between studies, which we expected due to significant differences in the methodology, design of the studies as well as the different healthcare resources.[15] ORs with 95% CIs were presented in the meta-analysis for dichotomous data (eg, sepsis vs no sepsis). The degree of heterogeneity across studies was determined using the I-test, with I^2 values of 25% or less, 25%–75% and 75% or greater representing low, moderate and high inconsistency, respectively. P<0.05 was considered statistically significant. All statistical calculations were performed with the assistance of a statistician using Review Manager (V.5.4.1; The Cochrane Collaboration).

Patient and public involvement

To our experience from different settings in Sub-Saharan Africa, it is an important issue for the quality of patient treatment to follow guidelines and therefore to have relevant, updated guidelines for health workers to follow. This is what the research question of this study is based on. As it is a systematic review, there are no direct study participants, but we will disseminate the results on international conferences and to WHO and other stakeholders.

RESULTS

A total of 6168 titles were screened after excluding 2674 duplicate records. Of these, 6083 were excluded based on screening of abstracts. The remaining 85 studies underwent full-text assessment for eligibility. Five of these were only available as an abstract online and we requested full text from the authors but only one author replied. Thirty-six full texts met the inclusion criteria of our review after discussion with senior authors and reaching consensus. Reasons for exclusion of 49 full-text records were other focus of study design (eg, not examining risk factors for sepsis) (n=8), wrong patient population/not neonates/no subgroup analysis (n=15), other outcomes/no risk factors studied (n=16), location not according to the protocol setting (eg, not in Sub-Saharan Africa or not in a hospital) (n=4), no full text (n=5) and duplicate (n=1). All included studies were published in peer-reviewed journals. The study selection process is illustrated in figure 1.

All the 36 included studies were of observational study design. Twenty-eight studies were prospective (five cohort, six case–control, eleven cross-sectional studies and six studies of unclear/mixed unspecified design), seven were retrospective (three case–control studies, three cross-sectional studies and one study of unspecified design) and one was combined prospective and retrospective. The total sample size was 23 605 neonates (range: 100[16]–8129[17 18]), and of these 4014 were diagnosed with sepsis. Ten studies reported the use of clinical guidelines for defining/diagnosing neonatal sepsis, while 26 studies required laboratory testing (eg, positive blood culture or haematological criteria) to establish the diagnosis of neonatal sepsis. All studies were conducted in secondary or tertiary level of care hospitals. The included studies were conducted in 10 different Sub-Saharan African countries, with majority of the studies conducted in Nigeria (n=10) and Ethiopia (n=10) (figure 2). The minimum study duration was 32 days[19] and the maximum was 7 years and 6 months.[20]

Some of the included studies had a narrowed approach; for example, some studies only examined one or a few risk factors, and some studies only examined a narrowed population (ie, babies born before arrival). There were variations in defining EONS and LONS, with EONS ranging from 48 hours to 7 days. The characteristics of the included studies are provided in table 1.

According to the the NHLBI quality assessment, 6 studies were rated as good, 8 were rated as fair and 22 were rated as poor (online supplemental appendix 4, table 1). No studies were excluded after quality assessment.

Risk factors were classified as neonatal, maternal or sociodemographic factors in our review. A total of 60 risk factors were reported. Twenty-seven studies examined both neonatal and maternal risk factors.

Meta-analysis

Thirty-two studies were included in the meta-analysis (n=22 731 neonates). For each risk factor, a meta-analysis with adjacent forest plot was performed (not shown). The number of studies and patients in the meta-analysis ranged from 3 studies and 832 patients to 21 studies with 14245 patients. The 33 examined risk factors are provided in table 2.

Four studies[6 20–22] did not provide sufficient data needed to conduct meta-analysis and we did not obtain these data after contacting the authors. These studies were therefore not included in the meta-analysis. Furthermore, some studies did not provide sufficient data for all of the examined risk factors in the studies.

The following neonatal risk factors were found significant[1]:

- Resuscitation at birth (12 studies and 3363 patients) increased the risk of sepsis (OR 2.70, 95% CI 1.36 to 5.35), but with a considerable I^2 (92%).
- Birth weight <1.5 kg (7 studies, 10 482 patients) increased the risk of sepsis (OR 3.37, 95% CI 1.59 to 7.13), but with a considerable I^2 (83%).
- Birth weight 1.5–2.5 kg (16 studies and 5151 patients) increased the risk of sepsis (OR 1.36, 95% CI 1.01 to 1.83), but with a considerable I^2 (76%).
- Low Apgar score at the first minute (7 studies and 2647 patients) increased the risk of sepsis (OR 3.69, 95% CI 2.34 to 5.81), but with a considerable I^2 (77%).

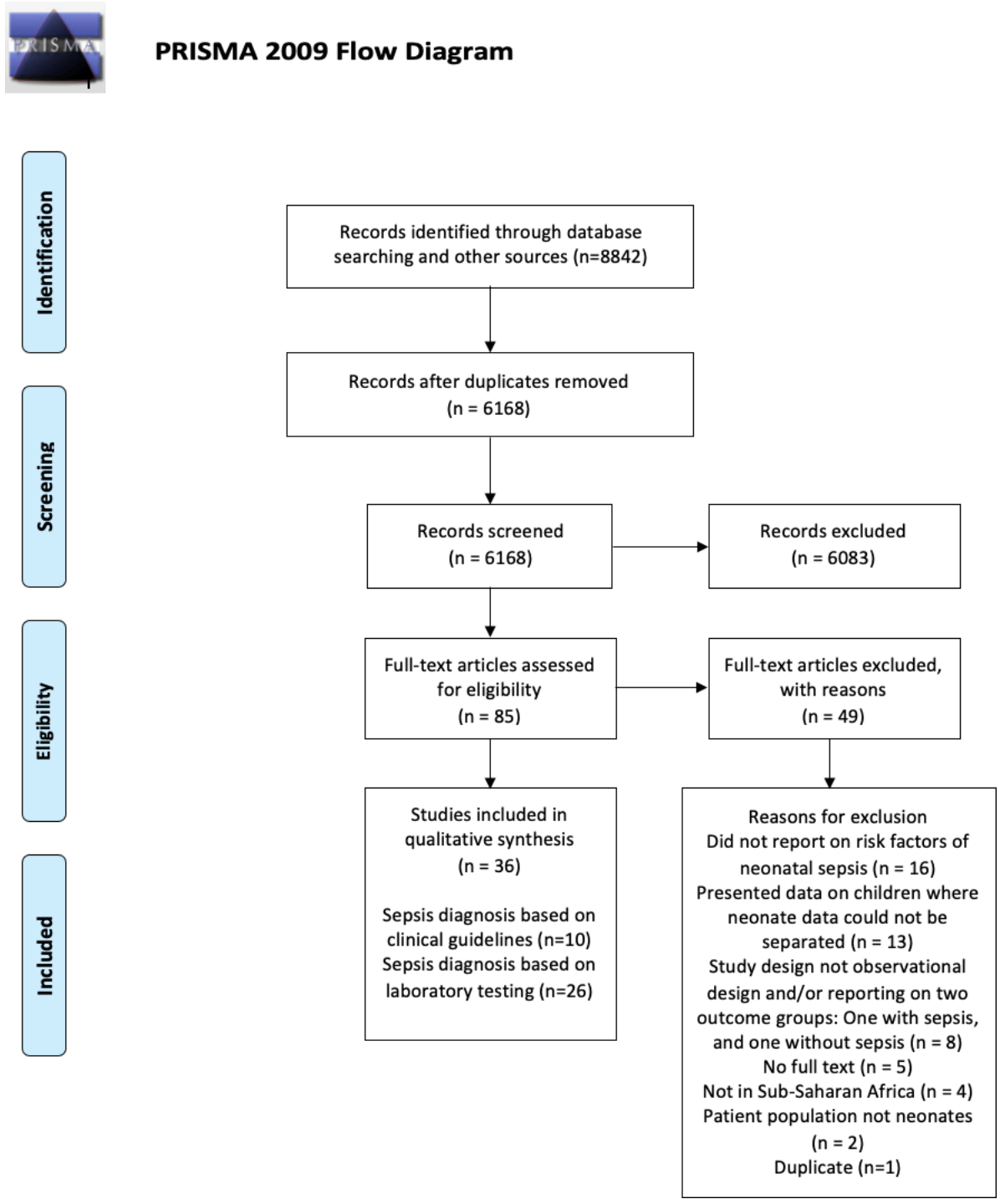

Figure 1 PRISMA 2009 flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

- Low Apgar score at the fifth minute (12 studies and 4185 patients) increased the risk of sepsis (OR 2.55, 95% CI 1.46 to 4.45), but with a considerable I^2 (90%).
- Prematurity <37 weeks (21 studies and 14 245 patients) increased the risk of sepsis (OR 1.91, 95% CI 1.27 to 2.86), but with a considerable I^2 (90%).
- No crying after birth (7 studies and 2772 patients) increased the risk of sepsis (OR 3.49, 95% CI 1.42 to 8.55), but with a considerable I^2 (92%).
- Male sex (18 studies and 4984 patients) increased the risk of sepsis (OR 1.30, 95% CI 1.01 to 1.67), but with a moderate I^2 (73%).

The following maternal risk factors were significant:

- Prolonged labour (11 studies and 11 190 patients) increased the risk of sepsis (OR 1.57, 95% CI 1.08 to 2.27), but with a moderate I^2 (73%).
- Premature rupture of membranes (PROM) (18 studies and 5620 patients) increased the risk of sepsis

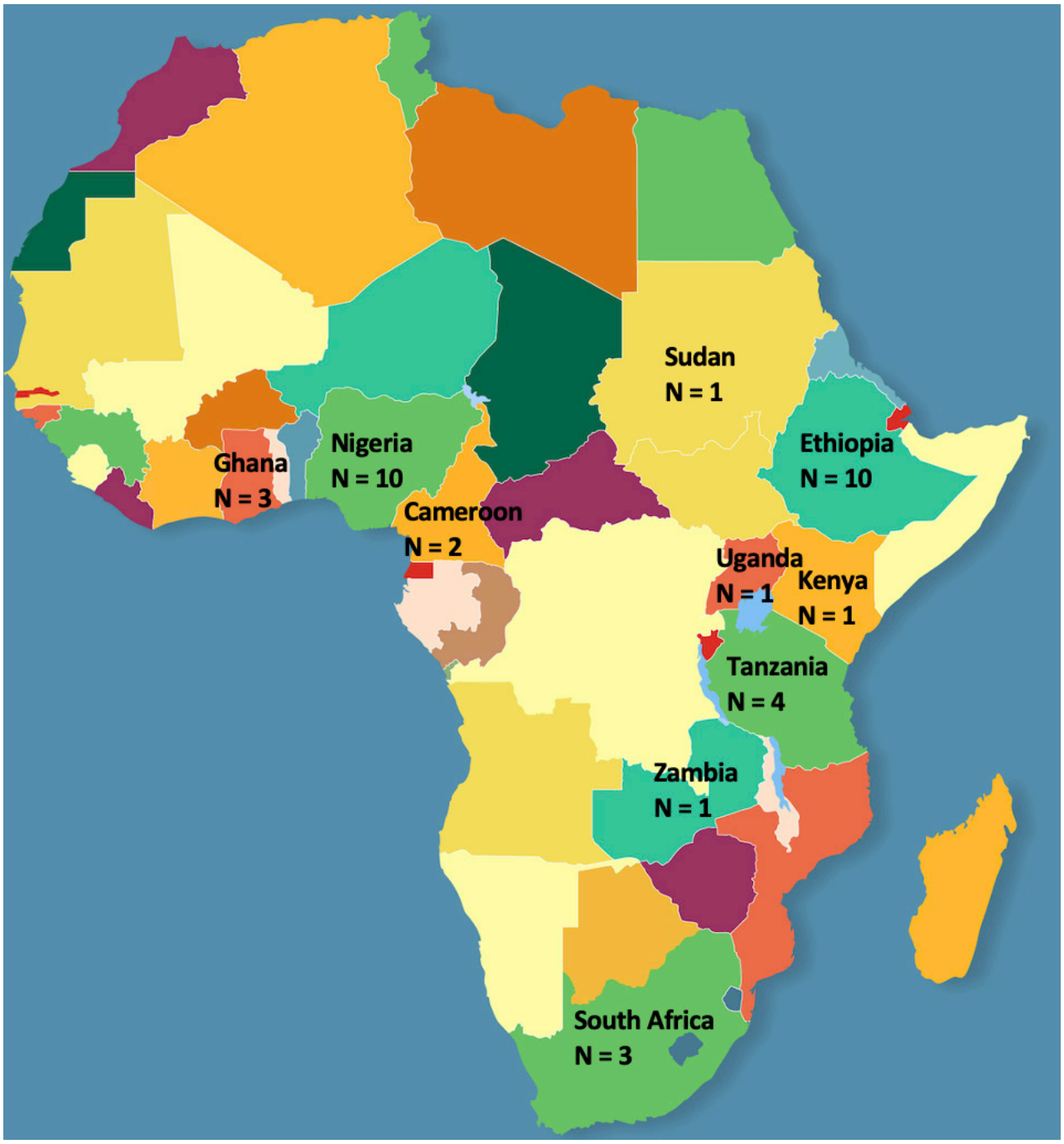

Figure 2 Location of the studies.

(OR 2.15, 95% CI 1.34 to 3.47), but with a considerable I^2 (88%).

- Multiple digital vaginal examinations (3 studies and 8684 patients) increased the risk of sepsis (OR 2.22, 95% CI 1.27 to 3.89), but with a considerable I^2 (79%).
- Meconium-stained amniotic fluid (8 studies and 10 108 patients) increased the risk of sepsis (OR 2.72, 95% CI 1.58 to 4.69), but with a considerable I^2 (84%).
- Intrapartum fever (10 studies and 2966 patients) increased the risk of sepsis (OR 2.28, 95% CI 1.18 to 4.39), but with a considerable I^2 (84%).
- Foul-smelling vaginal discharge (4 studies and 1318 patients) increased the risk of sepsis (OR 3.31, 95% CI 2.16 to 5.09), with no I^2 heterogeneity.

The following sociodemographic risk factor was significant:

- Low socioeconomic status (3 studies and 832 patients) increased the risk of sepsis (OR 1.93, 95% CI 1.11 to 3.35), but with a moderate I^2 (62%).

Table 1 Characteristics of the included studies

	Study identification	Location	Study period	Setting	Definition of neonate	Definition of EONS and LONS	Study design	Sample size associated with risk factors	Risk factors	Limitations	NHLBI score*
Neonatal sepsis: clinically diagnosed											
1	Masanja *et al*[25]	Tanzania: Kongwa and Mpwapwa District Hospitals and the Dodoma Regional Referral Hospital	May–July 2017	Secondary-level and tertiary-level hospitals	0–28 days	EONS: birth to 7 days of age.	Matched, prospective, case–control.	322 (105 cases and 217 controls).	Neonatal and maternal.	Only examines risk factors related to EONS.[21]	Good
2	Schrag *et al*[18]	South Africa: Chris Hani Baragwanath Hospital	1 April 2004–25 October 2007	Secondary-level and tertiary-level hospitals	0–28 days	EONS: birth to 2 days of age. LONS: 3–28 days of age.	Prospective cohort.	8129 (323 with sepsis).	Neonatal and maternal.		Fair
3	Shobowale *et al*[16]	Nigeria: Babcock University Teaching Hospital	August 2014–August 2015	Tertiary-level hospital	First 28 days of life	EONS: >3 days of age. LONS: older than 3 days.	Retrospective, cross-sectional study.	100 (34 with sepsis).	Neonatal and maternal.		Poor
4	Cutland *et al*[17]	South Africa: Chris Hani Baragwanath Hospital	April 2004–October 2007	Secondary-level and tertiary-level hospitals	0–28 days	EONS: within 3 days of life. LONS: between 4 and 28 days of life.	Prospective, cohort study.	8129 (324 with sepsis).	Maternal.	Only examines the association between maternal HIV infection and neonatal sepsis. Same cohort as used in Schrag *et al*.[18]	Good
5	Chiabi *et al*[21]	Cameroon: Yaounde Gynaeco-Obstetric and Pediatric Hospital	18 November 2008–18 May 2009	Tertiary-level hospital	0–28 days	EONS: birth to 7 days of age. LONS: 8–28 days of age.	Prospective study.	628 (218 with sepsis).	Neonatal and maternal.		Poor
6	Jabiri *et al*[19]	Tanzania: Two municipal referral hospitals	27 August–28 September 2015	Tertiary-level hospitals	≤28 days		Prospective, cross-sectional study.	220 (69 with sepsis).	Neonatal and maternal.		Poor
7	Subramaniam *et al*[26]	Cameroon: Three individual Cameroon Baptist Convention Health Services facilities	10 January–27 April 2017	Secondary-level hospitals	Not specified		Prospective, cohort study.	217 mothers giving birth to 219 babies. Of these, 10 were diagnosed with neonatal sepsis.	Maternal.	Only looking at the association between neonatal sepsis and maternal group B streptococcus anogenital colonisation.	Fair
8	Gudayu *et al*[27]	Ethiopia: University of Gondar Comprehensive Specialized Hospital	1 January–31 December 2017	Tertiary-level hospital	Not specified		Retrospective study.	504 (321 with sepsis).	Neonatal, maternal, role of the season.	EONS and LONS are not specified even though they investigate these as risk factors.	Poor
9	Woldu *et al*[28]	Ethiopia: Bishoftu General Hospital	15 October 2013–15 April 2014	Secondary-level hospital	0–28 days	EONS: 0–7 days. LONS: 7–28 days.	Prospective. cross-sectional study.	306 with sepsis.	Neonatal and maternal.		Poor
10	Getabelew *et al*[29]	Ethiopia: Shashemene Referral Hospital	5–30 February 2017	Tertiary-level hospital	0–28 days	EONS: 0–7 days. LONS: 7–28 days.	Cross-sectional study with retrospective document review.	244 (190 with sepsis).	Neonatal and maternal.		Poor

Continued

Table 1 Continued

	Study identification	Location	Study period	Setting	Definition of neonate	Definition of EONS and LONS	Study design	Sample size associated with risk factors	Risk factors	Limitations	NHLBI score*
Neonatal sepsis (diagnosed by laboratory testing; eg, positive blood culture or haematological criteria)											
11	Silago *et al*[30]	Tanzania: Bugando Medical Centre	December 2018–July 2019	Secondary-level hospital	Not specified		Prospective, cross-sectional study.	200 (69 with sepsis).	Neonatal and maternal.	Only looking at sepsis caused by Gram-negative bacteria. Sample size consists of only 69 neonates.	Poor
12	Kabwe[31]	Zambia: University Teaching Hospital, Lusaka	October 2013–May 2014	Tertiary-level hospital	Not specified	EONS: positive culture in neonates aged ≤7 days. LONS: positive culture in neonates aged >7 days.	Prospective. cross-sectional study.	303 (113 with sepsis).	Neonatal and maternal.		Poor
13	Aiken *et al*[30]	Kenya: Kilifi District Hospital	16 April 2002–30 September 2009	Secondary-level hospital	≤28 days		Prospective, cohort study.	4668 (53 with nosocomial sepsis).	Neonatal.	Only examines hospital-acquired sepsis.	Fair
14	Kayange *et al*[32]	Tanzania: Bugando Medical Centre	March–November 2009	Secondary-level hospital	Not specified	EONS: disease occurring in ≤72 hours of age. LONS: disease occurring after more than 72 hours of age.	Prospective, cross-sectional study.	300 (149 with sepsis).	Neonatal and maternal.		Poor
15	Bassingthwaighte and Ballot[33]	South Africa: Charlotte Maxeke Johannesburg Academic Hospital	1 January 2011–31 January 2013	Tertiary-level hospital	Not specified	EONS: positive blood culture within 72 hours after birth. LONS: positive blood culture >72 hours after birth.	Matched, case–control, retrospective record review.	356; 178 cases (babies born before arrival) and 178 controls (babies born in hospital).	Born before arrival to hospital (neonatal?).	Only examines the risk of sepsis among babies born before arrival compared with babies born in the hospital.	Fair
16	Onalo *et al*[34]	Nigeria: Ahmadu Bello University Teaching Hospital	25 May 2004–31 May 2005	Tertiary-level hospital	0–28 days	EONS: sepsis within the first 48 hours of life.	Prospective study.	211 (75 with sepsis).			Poor
17	Ogunlesi *et al*[35]	Nigeria: Olabisi Onabanjo University Teaching Hospital	January 2006–December 2008	Tertiary-level hospital	0–28 days	EONS: positive blood culture drawn within the first 72 hours of life. LONS: positive blood culture drawn after 72 hours of life.	Prospective and retrospective observational study.	1050 (174 with sepsis).	Neonatal and maternal.		Poor

Continued

Table 1 Continued

	Study identification	Location	Study period	Setting	Definition of neonate	Definition of EONS and LONS	Study design	Sample size associated with risk factors	Risk factors	Limitations	NHLBI score*
18	Pius *et al*[36]	Nigeria: University of Maiduguri Teaching Hospital	1 January–31 December 2012	Tertiary-level hospital	0–28 days	EONS: first 72 hours of life. LONS: last 72 hours of life.	Prospective study.	110 (46 with sepsis).	Neonatal and maternal.		Poor
19	Shobowale *et al*[37]	Nigeria: Lagos University Teaching Hospital	Not specified	Tertiary-level hospital	0–28 days	EONS: first 7 days of life. LONS: after the seventh day of life.	Prospective, cohort study.	250 (85 with sepsis).	Neonatal.		Poor
20	Ekwochi *et al*[38]	Nigeria: Enugu State University Teaching Hospital	January 2013–December 2016	Tertiary-level hospital	First 28 days of life	EONS: first 72 hours of life. LONS: after 72 hours of life.	Matched, prospective, case–control study.	228 (57 cases and 171 controls).	Neonatal and maternal.		Fair
21	John *et al*[39]	Uganda: Kidera Health Center	January–August 2013	Secondary-level hospital	1–27		Prospective, cross-sectional study.	174 (38 with sepsis).	Neonatal and maternal.	Selection bias, since very sick newborns were transferred to district hospital.	Poor
22	Gebremedhin *et al*[40]	Ethiopia: public hospitals in Mekelle City	December 2014–June 2015	Secondary-level and tertiary-level hospitals	0–28	EONS: <7 days. LONS: 7–28 days.	Unmatched, prospective, case–control study.	324 (78 cases and 156 controls).	Neonatal and maternal.		Good
23	Alemu *et al*[41]	Ethiopia: Debre Markos Referral Hospital	1 February–30 March 2018	Tertiary-level hospital	0–28 days		Unmatched, prospective, case–control study.	246 (82 cases and 164 controls).	Neonatal and maternal.	Sepsis diagnosed by haematological criteria.	Good
24	Yismaw *et al*[42]	Ethiopia: University of Gondar Hospital	1 September–30 November 2017	Tertiary-level hospital	0–28 days		Prospective, cross-sectional study.	423 (47 with sepsis).	Neonatal and maternal.		Poor
25	Adatara *et al*[43]	Ghana: Trauma and Specialist Hospital, Winneba	January–December 2017	Tertiary level hospital	First 28 days of life	EONS: <7 days. LONS: 7–28 days.	Unmatched, retrospective, case–control study.	900 (103 cases and 797 controls).	Neonatal and maternal.	Some patients were only diagnosed based on clinical features.	Fair
26	Geyesus *et al*[44]	Ethiopia: University of Gondar Hospital	September 2015–May 2016	Tertiary-level hospital	0–28 days	EONS: confirmed infection in the blood or cerebrospinal fluid of patients younger than 3 days of life. LONS: onset of such infection between 3 and 28 days.	Prospective, cross-sectional study.	251 (117 with sepsis).	Neonatal and maternal.		Poor
27	Adatara *et al*[45]	Ghana: Trauma and Specialist Hospital, Winneba	January–December 2017	Tertiary-level hospital	First 28 days of life	EONS: <7 days. LONS: 7–28 days.	Retrospective, case–control study.	383 (67 cases and 316 controls).	Neonatal.		Fair

Continued

Table 1 Continued

	Study identification	Location	Study period	Setting	Definition of neonate	Definition of EONS and LONS	Study design	Sample size associated with risk factors	Risk factors	Limitations	NHLBI score*
28	Sorsa[46]	Ethiopia: Arsi University Teaching and Referral Hospital	April 2016–May 2017	Tertiary-level hospital	28 days of life or younger	EONS: first 6 days of life. LONS: 7–28 days of life.	Prospective, cross-sectional study.	303 (88 with sepsis).	Neonatal and maternal.		Poor
29	Kheir and Khair[6]	Sudan: Soba University Hospital	October 2011–February 2012	Tertiary-level hospital	First 28 days of life	Not specified.	Prospective study.	62 (38 with sepsis).	Maternal.	Small study population.	Poor
30	Onyedibe *et al*[47]	Nigeria: Jos University Teaching Hospital	Not specified	Tertiary-level hospital	First 28 days of life	Not specified.	Prospective, cross-sectional study.	218 (75 with sepsis).	Socioeconomic.	Only examines socioeconomic risk factors for neonatal sepsis.	Poor
31	Kpikpitse and Siakwa[48]	Ghana: St Elizabeth Hospital Asutifi	January 2011 and December 2013	Secondary-level hospital	Less than a month	Not specified.	Unmatched, prospective, case–control study.	196 (96 cases and 100 controls).	Neonatal and maternal.		Fair
32	Ogundare *et al*[49]	Nigeria: Wesley Guild Hospital	Conducted over 7 months, ended in March 2009	Tertiary-level hospital	0–28 days	EONS: positive blood culture drawn within the first 72 hours of life. LONS: positive blood culture drawn after 72 hours of life.	Prospective study.	360 (72 with neonatal sepsis).	Neonatal and maternal.		Good
33	West and Tabansi[50]	Nigeria: University of Port Harcourt Teaching Hospital	1 July–31 December 2007	Tertiary-level hospital	0–28 days	EONS: onset of illness within the first 72 hours of life. LONS: onset of illness after 72 hours of life.	Prospective study.	406 (169 with sepsis).	Neonatal and maternal.		Poor
34	Weldu *et al*[51]	Ethiopia: Ayder Comprehensive Specialized Hospital	March 2017–September 2018	Tertiary-level hospital	1–28 days	Not specified.	Prospective, cross-sectional study.	317 (116 with sepsis).	Neonatal and maternal.		Poor
35	Akalu *et al*[52]	Ethiopia: Debre Markos and Felege Hiwot Referral Hospitals	March–April 2018	Tertiary-level hospital	First 28 days after birth	Not specified.	Unmatched, prospective, case–control study.	231 neonates (77 cases and 154 controls).	Neonatal and maternal.		Good
36	Olorukooba *et al*[53]	Nigeria: Ahmadu Bello University Teaching Hospital	May 2017–May 2018	Tertiary-level hospital	First 28 days after birth	EONS: onset of symptoms 72 hours or less after birth. LONS: onset of symptoms more than 72 hours after birth.	Retrospective, cross-sectional study.	465 (175 with sepsis).	Neonatal and maternal.		Poor

*Quality assessment score from the NHLBI quality assessment tool (online supplemental Online supplemental appendix 4).
EONS, early-onset neonatal sepsis; LONS, late-onset neonatal sepsis; NHLBI, National Heart, Lung, and Blood Institute.

Table 2 Risk factors for neonatal sepsis reported in included studies and included in the meta-analysis

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	n
Neonatal risk factors																																					
Perinatal asphyxia	x									x						x	x																				6
Resuscitation at birth*	x					x																	x		x						x				x		12
Birth weight <1.5 kg*		x															x									x	x										7
Birth weight 1.5–2.5 kg*																										x		x			x			x			17
Age less than 3 days			x																																		3
Age less than 7 days										x																	x			x						x		7
LAS† at the first minute (<7)*																									x		x				x				x	x	7
LAS at the fifth minute (<7)*						x																x	x	x	x	x	x	x			x				x		13
Prematurity <37 weeks*		x	x			x		x								x							x			x		x			x						22
No crying after birth*																						x	x								x						7
Male sex*																																					21
Maternal risk factors																																					
Prolonged labour*†																x	x															x					11
PROM*	x				x	x								x		x	x	x				x	x	x	x			x								x	20
Maternal HIV	x																																				4
≥3 digital VE*	x	x																																			3
MSAF*		x												x													x	x			x				x		9
FSAF																															x		x				6
Increasing parity												x																										10
First birth		x																							x						x						4
Age <20 years						x																															8
Age >35 years																																					3
Intrapartum fever*																																					12
SVD																																					16
Caesarean section																																					17
Instrument-assisted birth																																					12
History of UTI/STI																																					9

Continued

Table 2 Continued

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	n
Foul-smelling VD*																								x							x						5
Sociodemographic risk factors																																					
Birth at home														x																							12
Lack of antenatal care																x					x														x		9
Low SE status*																	x	x																			3
Outborn‡															x					x																	7
Urban residence																														x							3
Low EL of the mother																																					4

Risk factors included in the table had to be investigated in at least three studies *or* found to have a significant association with neonatal sepsis in at least two studies.
The number of studies is the same as the number of studies in table 1.
n=total number of studies examining the risk factor.
x: significant association; : no significant association; no colour: not investigated.
*Risk factor with significant association in the meta-analysis.
†Labour lasting more than 9.5/14/24 hours.
‡Born outside tertiary hospital.
EL, education level; FSAF, foul-smelling amniotic fluid; LAS, low Apgar score; MSAF, meconium-stained amniotic fluid; PROM, premature rupture of membranes >12/18 hours; SE, socioeconomic; STI, sexually transmitted disease; SVD, spontaneous vaginal delivery; UTI, urinary tract infection; VD, vaginal discharge; VE, vaginal examination.

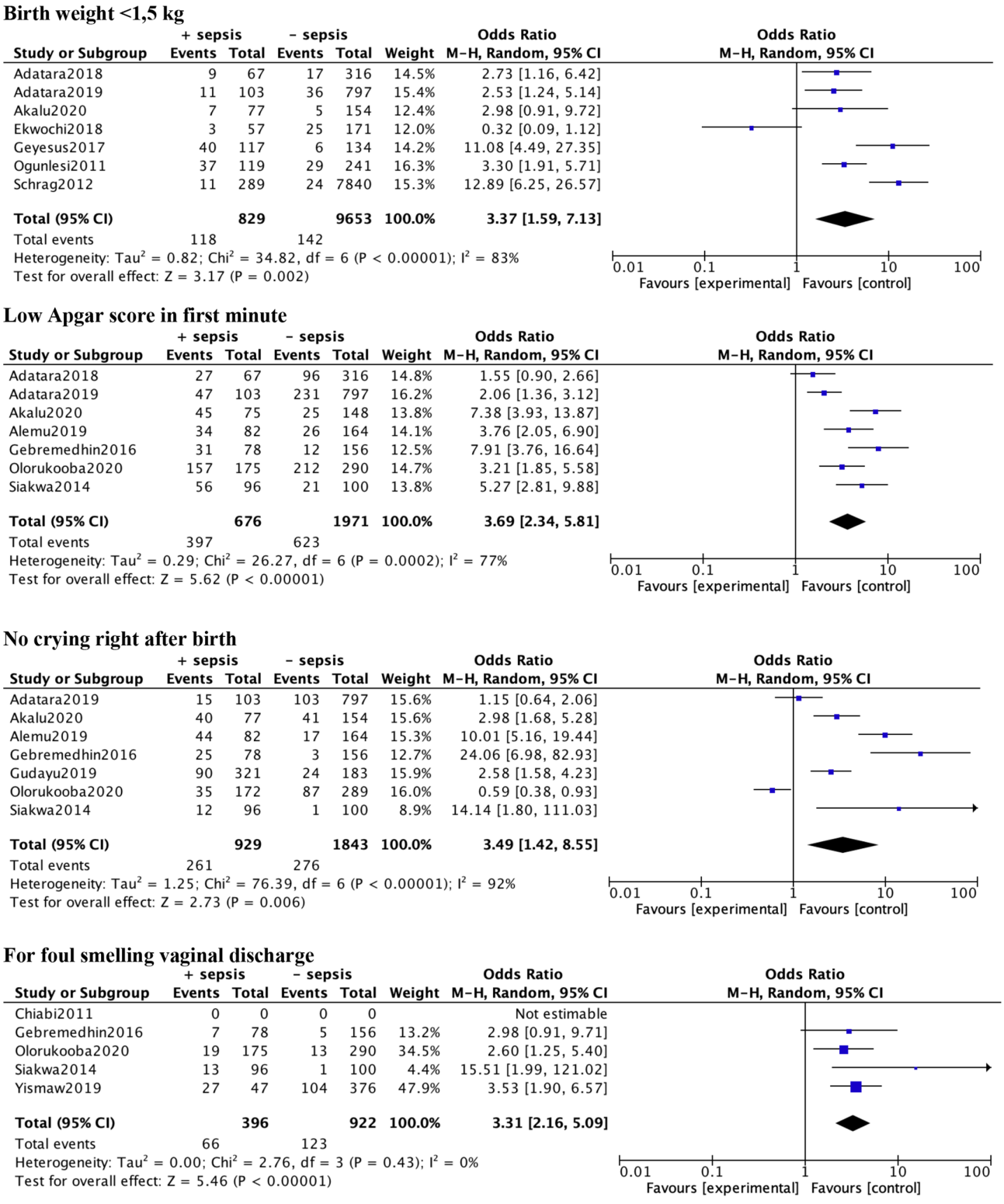

Figure 3 Meta-analysis and forest plots of the four risk factors with the highest OR for neonatal sepsis.

The meta-analysis and forest plots of the four risk factors with the highest OR for neonatal sepsis are provided in figure 3. The Mantel-Haenszel (M-H) formula was used for the analysis. We explored post-hoc for potential causes of heterogeneity via subgroup analyses in the meta-analysis with substantial heterogeneity (I^2 >75%), but country, design (retrospective vs prospective design), quality of study and publication year did not indicate a significant difference.

DISCUSSION

It is of importance to prevent neonatal sepsis in order to reduce neonatal mortality to at least as low as 12 per 1000

live births in 2030, as specified by the SDG. One step is to identify the risk factors for neonatal sepsis. In this systematic review and meta-analysis, we found that the significant risk factors for neonatal sepsis in Sub-Saharan Africa were resuscitation at birth, low birth weight (<1.5 kg and 1.5–2.5 kg), low Apgar score at the first and fifth minute, prematurity <37 weeks, no crying right after birth, male sex, prolonged labour, PROM, multiple digital vaginal examinations, meconium-stained amniotic fluid, intrapartum maternal fever, foul-smelling vaginal discharge and low socioeconomic status. Male sex was found to be a significant risk factor in the meta-analysis, even though only 1 of the 23 studies which examined the association found male sex to be a risk factor (table 2).

Our findings are to some extent in line with a literature review from 2009 on the risk factors for maternal sepsis and EONS in Sub-Saharan Africa, where the most common risk factors for EONS were identified as prematurity, PROM, maternal fever, low birth weight and difficulties at delivery (obstructed labour or birth asphyxia).[7] Our review and meta-analysis furthermore identified resuscitation at birth, low Apgar score at the first and fifth minute, no crying right after birth, male sex, prolonged labour, multiple digital vaginal examinations, meconium-stained amniotic fluid, foul-smelling vaginal discharge and low socioeconomic status as risk factors. However, we did not find birth asphyxia to be a risk factor. The review from 2009 examined the risk factors for EONS only, whereas our review and meta-analysis examined the risk factors for both EONS and LONS. EONS is more likely to reflect vertically acquired infections from the maternal genital tract and consequently has a different aetiology than LONS, different risk factors and potentially different means of prevention.[7] Not all the included studies in our review and meta-analysis differentiate between EONS and LONS and there is no universal consensus on the definitions.

When comparing our findings with a systematic review and meta-analysis of risk factors for neonatal sepsis in India from 2019, we also find that these are to some extent in line. The review from India found that male gender, outborn admission, need for artificial ventilation, birth weight, delivery <37 weeks of gestation and PROM were risk factors for neonatal sepsis.[8] Our review and meta-analysis furthermore identified low Apgar score at the first and fifth minute, no crying right after birth, prolonged labour, multiple digital vaginal examinations, meconium-stained amniotic fluid, intrapartum maternal fever, foul-smelling vaginal discharge and low socioeconomic status as risk factors. In our meta-analysis we did not find outborn admission to be a risk factor. The differences between our findings and the findings from India could indicate different risk factors in the two settings, but it could also partly be due to structural differences in the studies included. The Indian review included 13 studies with the diagnosis of neonatal sepsis based on laboratory testing, whereas our review included 36 studies, with 26 studies based on a laboratory-dependent diagnosis of neonatal sepsis and the remaining 10 studies based on clinical diagnosis. Data from studies that used clinical criteria exclusively to diagnose neonatal sepsis were included in our review and meta-analysis due to the fact that not all hospitals in Sub-Saharan Africa have access to validate the sepsis diagnosis with laboratory testing. Furthermore, the studies from the Indian review were solely from hospitals in urban settings, whereas the studies included in this review were conducted at both rural and urban hospitals. Risk factors for neonatal sepsis might be different in urban and rural settings.

Our findings add multiple risk factors to the risk factors identified in the WHO's universal guidelines. In our meta-analysis we identify resuscitation at birth, low birth weight (<1.5 kg and 1.5–2.5 kg), low Apgar score at the first and fifth minute, prematurity <37 weeks, no crying right after birth, male sex, prolonged labour, multiple digital vaginal examinations, meconium-stained amniotic fluid and low socioeconomic status as significant risk factors for neonatal sepsis, none of which are mentioned in the WHO guidelines. However, further research is needed to confirm our findings and they do not necessarily imply expansion of the WHO criteria for prophylactic antibiotics. That is, in our meta-analysis, male sex is a risk factor, but we do not suggest treating all male children with prophylactic antibiotics. If more risk factors were to be treated with prophylactic antibiotics, the risk of overtreatment should be kept in mind since it could lead to high medical cost and use of resources and increased antibiotic resistance.[23] Alternative preventive strategies, such as in-hospital observation of the newborn and measurement of C-reactive protein (CRP), are used in high-income countries and could be feasible in some LMICs but also challenging, for example, due to lack of resources. Future research should focus on identifying the risk factors qualifying for preventive measures.

This systematic review and meta-analysis has several strengths and limitations. The broad search strategy and the combination of global and regional databases reduced the risk of missing relevant regional studies and ensured that the evidence in this review was derived from different countries and different hospital settings. The relatively high number of included studies is a strength. However, the geographics of the included studies make our findings not necessarily generalisable; Ethiopia and Nigeria together accounted for more than 50% of the included studies and many Sub-Saharan countries are not represented in this review. Furthermore, the countries in Sub-Saharan Africa differ in the level of hospital expertise, hygiene and medical tools, as well as in climate, diseases and bacteria, limiting the generalisability of the review findings. Another limitation is that the studies were heterogeneous; some were based on a clinical diagnosis of sepsis, some laboratory-dependent, some only examined limited populations, some were retrospective and some were prospective. The studies were also heterogeneous in regard to which risk factors to investigate (table 2). This heterogeneity makes them

not perfectly comparable and is thus a limitation. The English language restriction is also a possible risk of bias and is a limitation. Africa has 29 francophone countries and it could be presumed that we could have missed relevant studies written in French. However, a quick search in PubMed with language restricted to French showed 105 studies, of which none was relevant to this review based on their English abstracts. The greatest limitation of this systematic review and meta-analysis is the overall poor quality of the included studies. The study designs used for risk factor analysis (eg, cross-sectional studies) differ from experimental designs and are more prone to bias.[24] Furthermore, multiple studies found some factors to be significant risk factors for neonatal sepsis, but when looking at the data, we found that the factors were protecting factors. Despite email correspondence with the authors, agreement was not obtained.

This systematic review and meta-analysis found multiple risk factors for neonatal sepsis in Sub-Saharan Africa, many of which are not on the WHO's recommendations for prophylactic antibiotics. It has previously been emphasised that there is a need to develop clinical guidelines for prevention and treatment of neonatal sepsis that are specific to the Sub-Saharan African context[10] and our review supports this notion. However, even though there are already multiple studies on risk factors for neonatal sepsis in Sub-Saharan Africa, there is a need for research of higher quality in the future as well as research in different settings in order to make presumptions, generalise on the topic or make multinational recommendations for clinical practice. National guidelines for Sub-Saharan African countries might also be beneficial due to differences in risk factors and bacterial agents among the countries. If new guidelines are to be developed, the challenges to implementation and resources should be kept in mind. There are still too many preventable neonatal deaths in LMICs, but with new preventive guidelines it might be possible to save thousands of lives.

Contributors CMB: Development of the protocol and search strategy, screening of studies, performance of quality assessment, development of all sections of the manuscript, development of the tables, performance of meta-analysis. Guarantor. CNS: Development of protocol, screening of studies, performance of quality assessment. SL, AP: Development of protocol, screening of studies, development of the tables, development of all sections of the manuscript. CHH: Development of protocol, development of the Introduction section. UN, JSB: Development of the results and discussion sections, performance of meta-analysis.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page no. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Appendix 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4+7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4+15
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4+16
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4+5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7
Study characteristics	17	Cite each included study and present its characteristics.	9-14
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	14-15
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Appendix 4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	15-16
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	16
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Appendix 4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	14-15
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	19-21
	23b	Discuss any limitations of the evidence included in the review.	20
	23c	Discuss any limitations of the review processes used.	20
	23d	Discuss implications of the results for practice, policy, and future research.	20-21
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2+3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2+3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	2+5
Competing interests	26	Declare any competing interests of review authors.	2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Prospero, appendix 2, appendix 3

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Risk factors of neonatal sepsis in Sub-Saharan Africa: a protocol for a systematic review

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Administrative information

Registration

When completed, this protocol will be registered in PROSPERO, an International prospective register of systematic reviews [1].

Authors

Christine Manich Bech (CB): Study design, drafting protocol, data collection, management, analysis and interpretation and drafting manuscript.
Christina Nadia Christofferson (CC): Study design, protocol revision, data collection, management, analysis and interpretation and manuscript revision.
Charlotte Holm-Hansen (CH):
Anja Poulsen (AP): Study design, revising protocol, data validation and interpretation, manuscript revision, supervision
Stine Lund (SL): Study design, revising protocol, data interpretation, manuscript revision, supervision

Amendments

This is the first draft of the protocol.

Introduction

Rationale

Globally 2.9 million children die within the first 28 days of life every year. Recent data of neonatal mortality show that countries in Sub-Saharan Africa had the highest mortality with 28 neonatal deaths per 1,000 live births in 2018 [2, 3]. Since 1990, the global neonatal mortality rate has decreased by 37%, from 33 to 21 deaths per 1,000 livebirths, but this reduction is lacking behind compared to a reduction greater than 50% for mortality rates among children aged 1–59 months [2]. Today a child born in Sub-Saharan Africa is still 10 times more likely to die in the first month than a child born in a high-income country [3].

The majority of the 2.9 million annual neonatal deaths worldwide can be divided into three main causes, which contributes to approximately one third each: Infections, intrapartum asphyxia and preterm birth complications [2, 4]. However, the distribution of causes in neonatal death varies between countries, correlating with the degree of neonatal mortality, and in very high-mortality countries almost 50% of the deaths are due to severe infection with sepsis [4]. There is to our knowledge until now no systematic review done on risk factors of neonatal sepsis in Sub-Saharan Africa. In 2019, Murthy et al. conducted a systematic review on risk factors of neonatal sepsis in India, but it is uncertain, if the risk factors are the same in the two different settings [5].

Objective

The aim of this systematic review is to identify and assess the evidence on risk factors of neonatal sepsis in Sub-Saharan Africa.

Review question

What are the main risk factors of neonatal sepsis in Sub-Saharan Africa?

Methods

This protocol is developed in accordance with "Preferred Reporting Items for Systematic reviews and Meta-analysis Protocols (PRISMA-P)", PICO guidelines and the book *Finding What Works in Health Care: Standards for Systematic Reviews* [6-8].

Eligibility criteria

Type of participants: We will use WHO's definition of neonates as infants under 28 days of age [9]. We are also going to include studies on children "up to 28 days of age". It is not necessary for the studies to have the exact definition on neonates in order to be included in the systematic review. If a study states the study population as "neonates" or "newborns", and if it is not in the study defined differently than above, they will be included. We will also include studies with a study population of "infants" or "under-five" or "child/children" specified, but only if the study include a note/section/subgroup of neonatal age group.

Type of disease: The term neonatal sepsis is used to designate a systemic condition of bacterial, viral, or fungal (yeast) origin that is associated with haemodynamic changes and other clinical manifestations and results in substantial morbidity and mortality [10]. There is until today no consensus definition of neonatal sepsis [10, 11]. In high income countries it is golden standard to take a blood culture from a neonate with sign of sepsis in order to identify and characterize the antibiotic sensitivities of the cultured pathogens [12]. Not all rural hospitals in Sub-Saharan Africa have access to validate the sepsis diagnose with microbiology testing. Therefore, we will include studies regarding clinically diagnosed neonatal sepsis. The signs of clinically diagnosed neonatal sepsis are many and diverse, and so are the possible primary infections leading to systemic infection (sepsis) [10]. We have considered studies conducted on neonatal sepsis for our review, which included the following systemic infections: neonatal septicaemia/sepsis, pneumonia, meningitis, osteomyelitis, arthritis and urinary tract infections.

Type of setting: We will include studies conducted in hospitals in Sub-Saharan Africa.

Outcome of our review: The outcome of our review is risk factors of neonatal sepsis. Studies in neonates, which reports on risk factors of sepsis (one risk factor or more) are eligible for inclusion.

Report characteristics: Studies dating back to year 2010 until now (June 2020) will be included. The reason for this time span is the before mentioned decrease in neonatal deaths. The significant decrease in neonatal deaths can be assumed to correlate with a change in risk factors associated with neonatal death, and thus a change in risk factors associated with neonatal sepsis. We want to examine the current risk factors of neonatal sepsis in Sub-Saharan Africa.

We will search for grey literature; thus, the studies do not need to be published to be eligible for inclusion. We will only include articles/study reports written in English.

Information source

We will search for literature in the databases PubMed, Embase, ISI Web of Science. We will furthermore look for grey literature in the form of not published material at clinicaltrials.gov as well as by going through the references of the articles found in our search. If we find it necessary, we will contact study authors in an attempt to obtain missing information or gain clarity of information on methodology (e.g case definition and study setting) and outcomes. If the author's reply is inadequate or we do not receive a reply, we will exclude that study from the review.

Search Strategy

A search strategy including all possible risk factors for neonatal sepsis in Sub-Saharan Africa was developed after looking at the search strategy for the systematic review of risk factors of neonatal sepsis in India performed by Murthy et al. [5] and in consultation with information scientist and subject experts. A time restriction was applied from January 2010 until December 2020 and a language restriction was applied with english as the language. A search strategy was first developed for PubMed and subsequently adapted for the other databases. The search strategy for PubMed is shown below.

Search in Pubmed/medline the 04th of June 2020	**Search word**	**Number of hits**
Neonatal	((((("Infant, Newborn"[Mesh]) OR "Neonatology"[Mesh])) OR ((infant*[Text Word] OR newborn*[Text Word] OR neonate*[Text Word] OR neonatal*[Text Word] OR toddler*[Text Word] OR baby[Text Word] OR babies[Text Word] OR paediatric[Text Word] OR pediatric[Text Word]))))	
Sepsis	AND ((((((((((("Sepsis"[Mesh]) OR "Meningitis"[Mesh]) OR "Encephalitis"[Mesh]) OR "Arthritis"[Mesh]) OR "Osteomyelitis"[Mesh]) OR "Urinary Tract Infections"[Mesh])) OR ((septicaemia[Text Word] OR	

	sepsis[Text Word] OR septicemia[Text Word] OR pneumoni*[Text Word] OR meningitis[Text Word] OR meningoencephalitis[Text Word] OR encephalitis[Text Word] OR bone infection*[Text Word] OR arthritis[Text Word] OR osteomyelitis[Text Word] OR urinary tract infection*[Text Word] OR urethritis[Text Word] OR cystitis[Text Word] OR bacteriuria[Text Word] OR bacteremia[Text Word] OR pyogen*[Text Word] OR epididymitis[Text Word] OR prostatits[Text Word] OR "vesicoureteral reflux"[Text Word] OR pyuria[Text Word] OR trigonitis[Text Word] OR pyelonephritis[Text Word] OR pyonephrosis[Text Word] OR hydronephrosis[Text Word] OR urinary infection*[Text Word] OR "lung infection"[Text Word] OR respiratory tract infection*[Text Word] OR blood infection*[Text Word] OR brain infection*[Text Word] OR joint infection*[Text Word] OR malaria[Text Word]))))	
Risk factors	((((((("Risk"[Mesh]) OR "Causality"[Mesh]) OR "Association"[Mesh])) OR (("Risk" OR "Causality" OR "Association" OR determinant* OR predictor* OR causal OR association OR "odds ratio"))) OR "Odds Ratio"[Mesh]))	
Sub-Saharan Africa	AND ((("Africa South of the Sahara"[Mesh]) OR ((Cameroon[Text Word] OR “Central African Republic”[Text Word] OR Chad[Text Word] OR Congo[Text Word] OR ”Democratic Republic of the Congo”[Text Word] OR ”Equatorial Guinea”[Text Word] OR Gabon[Text Word] OR ”Sao Tome”[Text Word] OR Burundi[Text Word] OR Djibouti[Text Word] OR Eritrea[Text Word] OR Ethiopia[Text Word] OR Kenya[Text Word] OR Rwanda[Text Word] OR	

	Somalia[Text Word] OR Sudan[Text Word] OR Tanzania[Text Word] OR Uganda[Text Word] OR Angola[Text Word] OR Botswana[Text Word] OR Eswatini[Text Word] OR Lesotho[Text Word] OR Malawi[Text Word] OR Mozambique[Text Word] OR Namibia[Text Word] OR "South Africa"[Text Word] OR Zambia[Text Word] OR Zimbabwe[Text Word] OR Benin[Text Word] OR "Burkina Faso"[Text Word] OR "Cabo Verde"[Text Word] OR "Cote d'Ivoire"[Text Word] OR Gambia[Text Word] OR Ghana[Text Word] OR Guinea[Text Word] OR "Guinea-Bissau"[Text Word] OR Liberia[Text Word] OR Mali[Text Word] OR Mauritania[Text Word] OR Niger[Text Word] OR Nigeria[Text Word] OR Senegal[Text Word] OR "Sierra Leone"[Text Word] OR Togo[Text Word])))) OR (("Africa South of the Sahara"[Text Word] OR "sub-saharan africa"[Text Word]))))	

Filters:
Publication date: from 2010/01/01 to current date (04/06/2020)
Language: English

Study records

We will use the program Covidence to manage our data and the program endnote to store our references throughout the review. The selection process will be done by two independent reviewers, who will be screening the literature and reviewing each study eligibility independently. We will make a flow chart of the selection process.

Data items

We will extract data on study ID, characteristics of studies, methodology, definitions, type of sepsis, whether the sepsis diagnosis is validated by microbiology, risk factors and outcomes. These data will be provided for each included study in a table. We will also to the best of our ability assess whether there is a risk of bias in the individual studies. If we find one, this will also be included in the table. Risk of bias can be in the outcome level as well as the study level. We are aware, that there is always a risk of bias.

Outcome and prioritization

Data will be sought for outcomes in terms of risk factors of neonatal sepsis. Neonatal sepsis can be diagnosed with the use of microbiology (e.g. finding bacteria in blood) or by a clinical diagnosis by a physician. Risk factors can be both maternal risk factors and neonatal risk factors of neonatal sepsis.

Data synthesis

The characteristics of studies, risk factor profile of included studies, summary of findings of risk factors and quality assessment will be outlined in tables, along with a concise textual reporting. There will not be made a meta-analysis.

Quality assessment

Two authors (CB and CC) will independently perform quality assessment of included studies using the National Heart, Lung and Blood Institute's (NHLBI) "Quality Assessment of Case-Control Studies" and "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" [13, 14]. The outcome of these quality assessments will be provided in results and also discussed in our review. Discrepancies, if they arise, will be resolved by discussion and consensus in the presence of senior authors (CH, AP and SL) for all the above procedures.

Timetable for conducting the systematic review

We expect to finish the systematic review by November 1st 2020.

Conflict of Interest

None.

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14. National Heart, L.a.B.I., *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.* https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

Search in Pubmed/Medline 7th of august 2020	**Search word**
Neonatal	((((("Infant, Newborn"[Mesh]) OR "Neonatology"[Mesh])) OR ((infant*[Text Word] OR newborn*[Text Word] OR neonate*[Text Word] OR neonatal*[Text Word] OR toddler*[Text Word] OR baby[Text Word] OR babies[Text Word] OR paediatric[Text Word] OR pediatric[Text Word]))))
Sepsis	AND ((((((((((("Sepsis"[Mesh]) OR "Meningitis"[Mesh]) OR "Encephalitis"[Mesh]) OR "Arthritis"[Mesh]) OR "Osteomyelitis"[Mesh]) OR "Urinary Tract Infections"[Mesh])) OR ((septicaemia[Text Word] OR sepsis[Text Word] OR septicemia[Text Word] OR pneumoni*[Text Word] OR meningitis[Text Word] OR meningoencephalitis[Text Word] OR encephalitis[Text Word] OR bone infection*[Text Word] OR arthritis[Text Word] OR osteomyelitis[Text Word] OR urinary tract infection*[Text Word] OR urethritis[Text Word] OR cystitis[Text Word] OR bacteriuria[Text Word] OR bacteremia[Text Word] OR pyogen*[Text Word] OR epididymitis[Text Word] OR prostatits[Text Word] OR "vesicoureteral reflux"[Text Word] OR pyuria[Text Word] OR trigonitis[Text Word] OR pyelonephritis[Text Word] OR pyonephrosis[Text Word] OR hydronephrosis[Text Word] OR urinary infection*[Text Word] OR "lung infection"[Text Word] OR respiratory tract infection*[Text Word] OR blood infection*[Text Word] OR brain infection*[Text Word] OR joint infection*[Text Word] OR malaria[Text Word]))))
Risk factors	((((((("Risk"[Mesh]) OR "Causality"[Mesh]) OR "Association"[Mesh])) OR (("Risk" OR "Causality" OR "Association" OR determinant* OR predictor* OR causal OR association OR "odds ratio"))) OR "Odds Ratio"[Mesh]))
Sub-Saharan Africa	AND ((("Africa South of the Sahara"[Mesh]) OR ((Cameroon[Text Word] OR "Central African Republic"[Text Word] OR Chad[Text Word] OR Congo[Text Word] OR "Democratic Republic of the Congo"[Text Word] OR "Equatorial Guinea"[Text Word] OR Gabon[Text Word] OR "Sao Tome"[Text Word] OR Burundi[Text Word] OR Djibouti[Text Word] OR Eritrea[Text Word] OR Ethiopia[Text Word] OR Kenya[Text Word] OR Rwanda[Text Word] OR Somalia[Text Word] OR Sudan[Text Word] OR Tanzania[Text Word] OR Uganda[Text Word] OR Angola[Text Word] OR Botswana[Text Word] OR Eswatini[Text Word] OR Lesotho[Text Word] OR Malawi[Text Word] OR Mozambique[Text Word] OR Namibia[Text Word] OR "South Africa"[Text Word] OR Zambia[Text Word] OR Zimbabwe[Text Word] OR Benin[Text Word] OR "Burkina Faso"[Text Word] OR "Cabo Verde"[Text Word] OR "Cote d'Ivoire"[Text Word] OR Gambia[Text Word] OR Ghana[Text Word] OR Guinea[Text Word] OR "Guinea-Bissau"[Text Word] OR Liberia[Text Word] OR Mali[Text Word] OR Mauritania[Text Word] OR Niger[Text Word] OR Nigeria[Text Word] OR Senegal[Text Word] OR "Sierra Leone"[Text Word] OR Togo[Text Word]))) OR (("Africa South of the Sahara"[Text Word] OR "sub-saharan africa"[Text Word]))))

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Language: English

Appendix 4, table 1 – Quality assessment

Quality assessment tool for Observational Cohort and Cross-Sectional Studies (tool from National Heart, Lung and Blood Institute (NHLBI)) (1)

Study number*	2	3	4	5	6	7	8	9	10	11	12	13	14	16	17	18	19
1. Was the research question or objective in this paper clearly stated?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
2. Was the study population clearly specified and defined?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
3. Was the participation rate of eligible persons at least 50%?	cd**	cd	cd	cd	cd	no	cd	cd	yes	yes	cd	yes	cd	yes	yes	cd	cd
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	cd
5. Was a sample size justification, power description, or variance and effect estimates provided?	no	yes	no	no	no	yes	yes	yes	yes	yes	no	yes	yes	no	no	no	yes
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	yes	cd	yes	yes	cd	cd	no	cd	no	yes	yes	yes	yes	yes	cd	yes	yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	na	na	na	na	na	na	na	na	na	na	na	na	na	na	n	na	na
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	cd	yes	yes	yes	No	yes	yes
10. Was the exposure(s) assessed more than once over time?	no	no	no	no	no	no	no	no	no	no	cd	no	no	no	no	no	no
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	yes	yes	yes	yes	yes	yes	no	no	yes	yes	yes	yes	yes	yes	yes	yes	yes
12. Were the outcome assessors blinded to the exposure status of participants?	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no
13. Was loss to follow-up after baseline 20% or less?	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	yes	no	yes	no	yes	no	yes	yes	yes	yes	yes	yes	yes	no	yes	no	yes
Overall quality (good, fair or poor)	fair	poor	good	poor	poor	fair	poor	poor	poor	poor	poor	fair	poor	poor	poor	poor	poor

* Study number is connected to the numbers given to the studies in table 1.
** cd = cannot determine

Quality assessment tool for Observational Cohort and Cross-Sectional Studies (tool from National Heart, Lung and Blood Institute (NHLBI)) (2)

Study number*	21	24	26	28	29	30	32	33	34	36
1. Was the research question or objective in this paper clearly stated?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
2. Was the study population clearly specified and defined?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
3. Was the participation rate of eligible persons at least 50%?	yes	yes	cd	Yes	yes	cd	yes	yes	cd	yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	yes	yes	yes	yes	yes	cd	yes	yes	yes	yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	yes	yes	no	yes	no	no	no	no	yes	Yes
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	yes	cd	cd	cd	yes	yes	yes	yes	yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	yes	yes	yes	yes	yes	yes	yes	yes	yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	na	na	na	na	na	na	na	na	na	Na
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	yes	yes	yes	yes	yes	yes	yes	yes	yes	Yes
10. Was the exposure(s) assessed more than once over time?	no	no	no	no	no	no	no	no	no	no
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
12. Were the outcome assessors blinded to the exposure status of participants?	no	no	no	no	no	no	no	no	no	no
13. Was loss to follow-up after baseline 20% or less?	na	na	na	na	na	na	na	na	na	na
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	yes	yes	yes	yes	no	no	yes	no	yes	yes
Overall quality (good, fair or poor)	poor	poor	poor	poor	poor	poor	good	poor	poor	poor

* Study number is connected to the numbers given to the studies in table 1.
** cd = cannot determine

Quality assesment of Case-Control Studies (tool from National Heart, Lung and Blood Institute (NHLBI))

Study number*	1	15	20	22	23	25	27	31	35
1. Was the research question or objective in this paper clearly stated and appropriate?	yes	yes	yes	yes	yes	yes	yes	yes	yes
2. Was the study population clearly specified and defined?	yes	yes	yes	yes	yes	yes	yes	yes	yes
3. Did the authors include a sample size justification?	yes	no	cd	yes	yes	no	no	no	yes
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	yes	yes	yes	yes	yes	yes	yes	yes	yes
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	yes	yes	yes	yes	yes	no	no	yes	yes
6. Were the cases clearly defined and differentiated from controls?	yes	yes	yes	yes	yes	yes	yes	yes	yes
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	yes	cd	no	yes	na	na	na	cd	na
8. Was there use of concurrent controls?	yes	yes	yes	yes	yes	yes	yes	yes	yes
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	yes	yes	yes	yes	yes	yes	yes	yes	yes
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	yes	yes	yes	yes	yes	yes	yes	yes	yes
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	yes	no	No	No	no	no	no	no	no
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	yes	yes	No	yes	yes	yes	yes	no	yes
Overall quality (good, fair or poor)	good	fair	fair	good	good	fair	fair	fair	good

*CD, cannot determine; NA, not applicable; NR, not reported

* Study number is connected to the numbers given to the studies in table 1.
** cd = cannot determine