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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%).

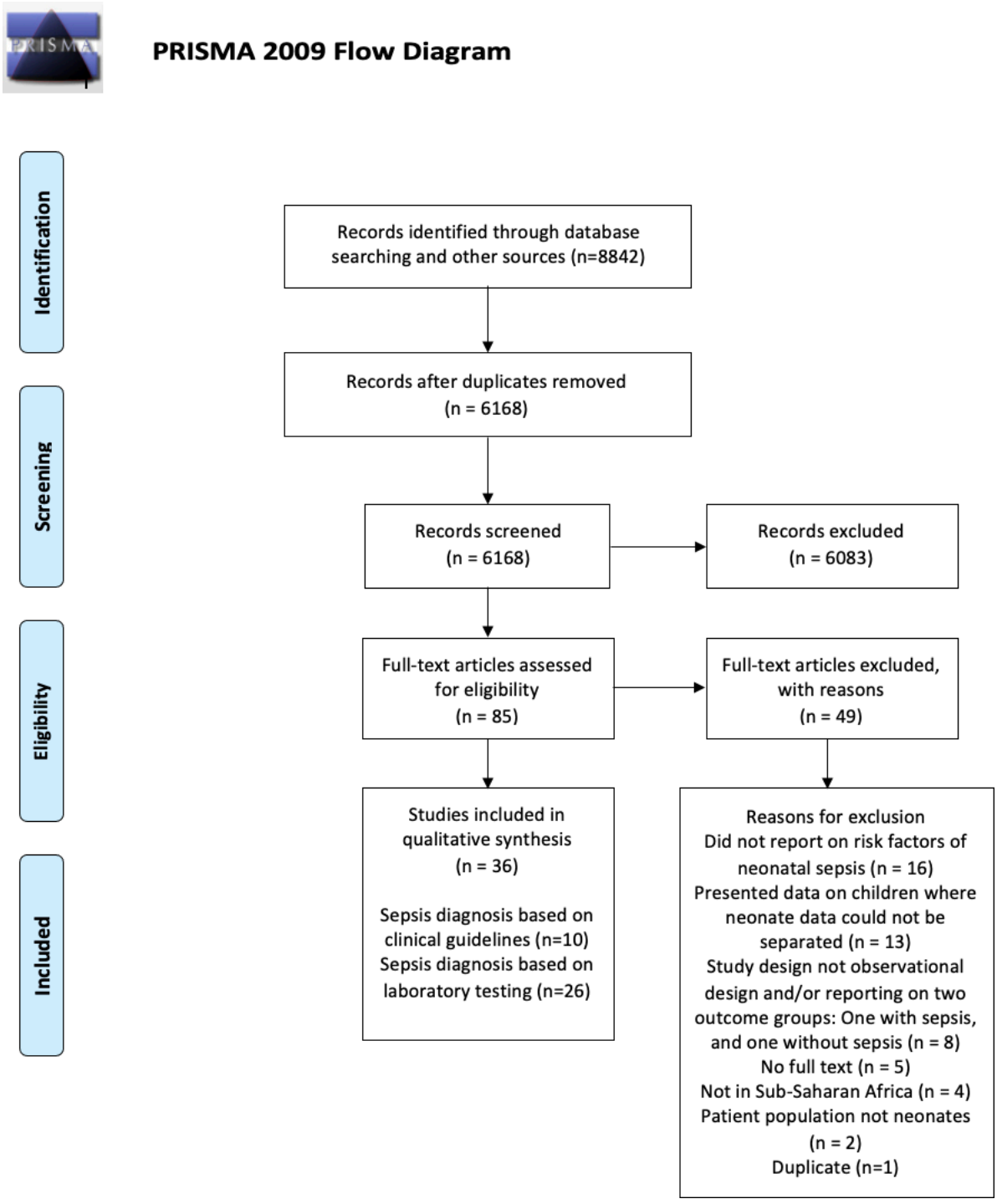

Figure 1 PRISMA 2009 flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

- 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

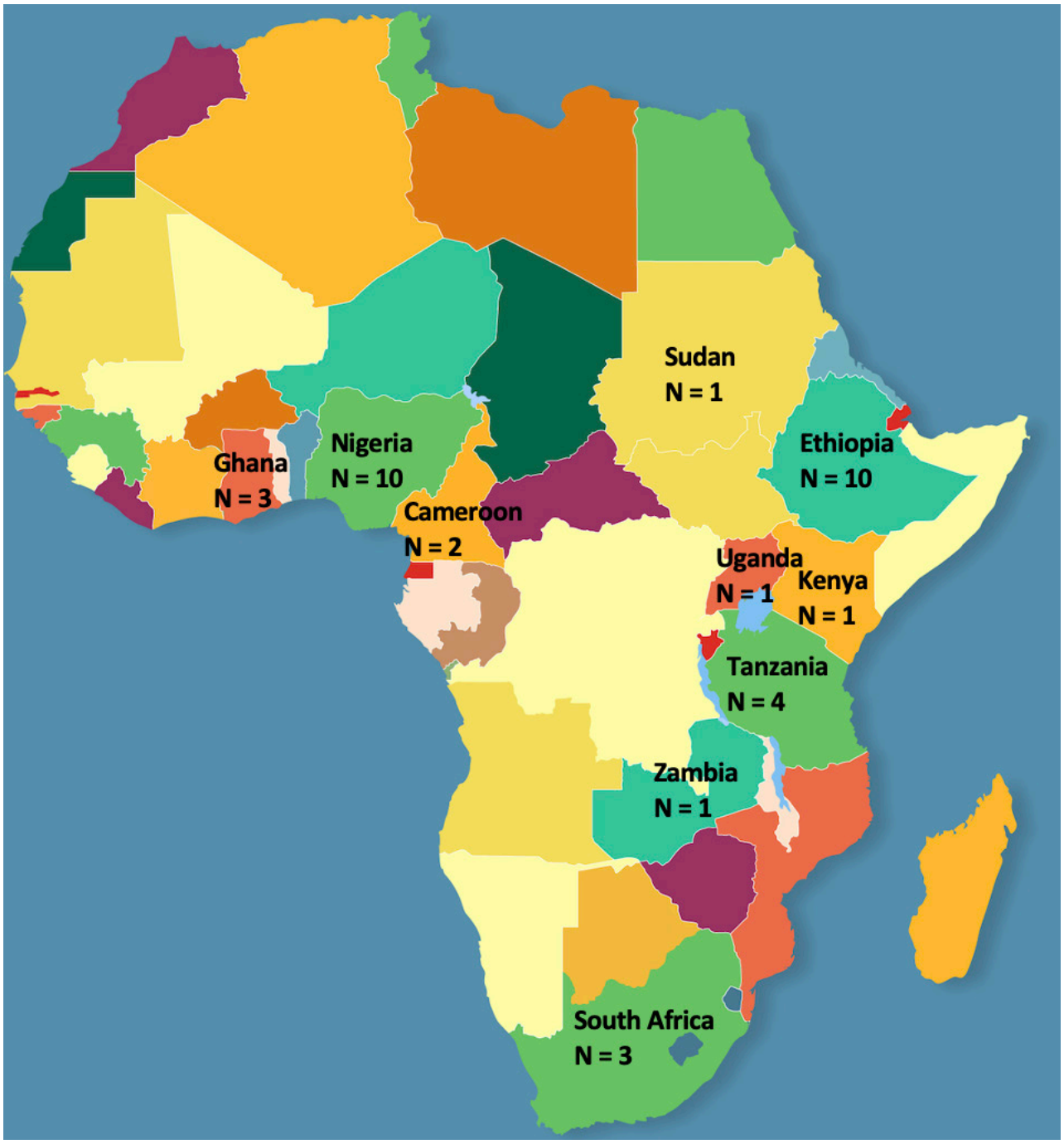

Figure 2 Location of the studies.

(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													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.

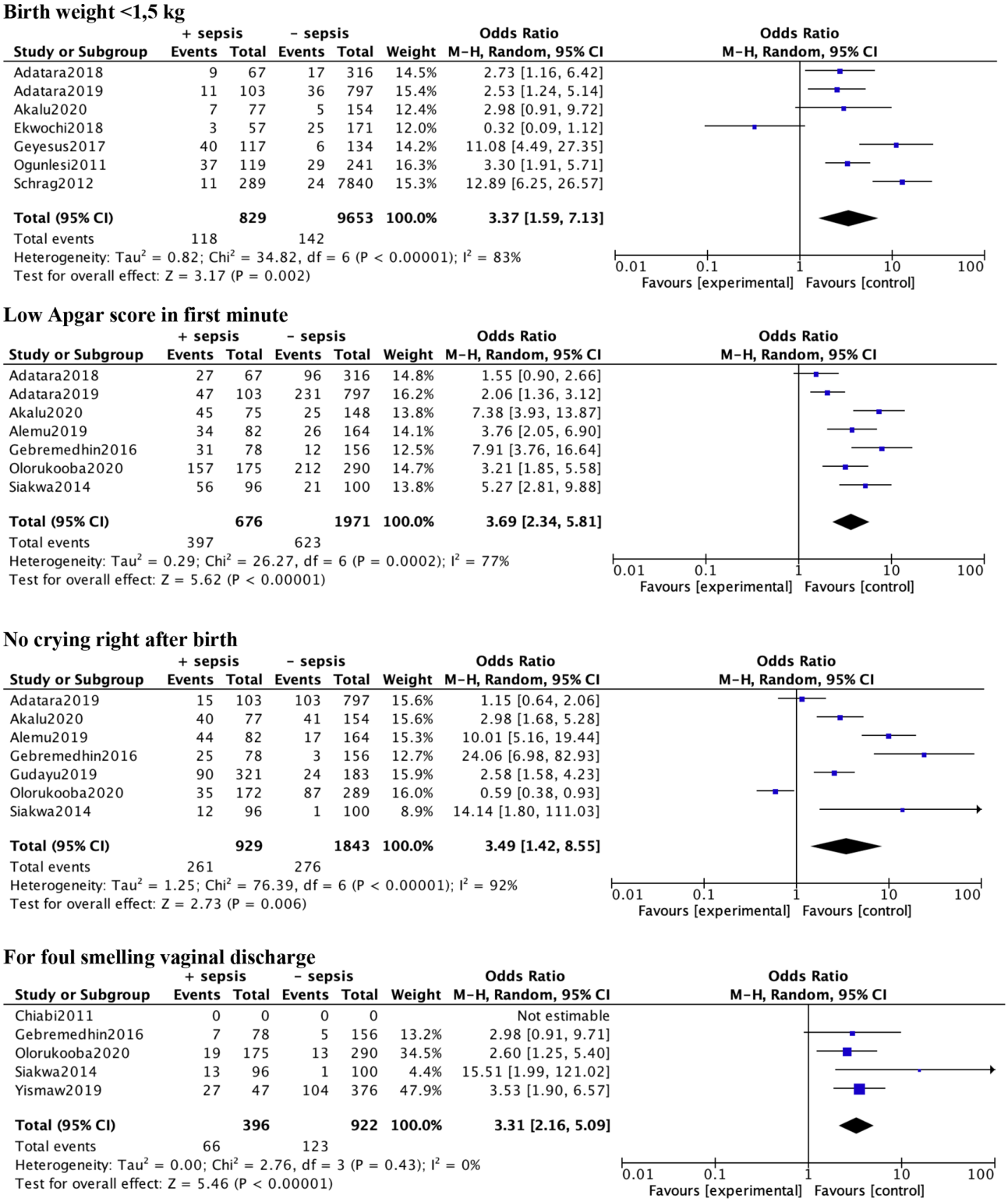

Figure 3 Meta-analysis and forest plots of the four risk factors with the highest OR for neonatal sepsis.

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.

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