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.
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Anja Poulsen (AP): Study design, revising protocol, data validation and interpretation, manuscript revision, supervision
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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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