BMJ Open

Contemporary trends in global mortality of sepsis among young infants less than 90 days old: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Neonatal sepsis has a high mortality rate that varies across different populations. We aim to perform a contemporary global evidence synthesis to determine the case fatality rates of neonatal sepsis, in order to better delineate this public health urgency and inform strategies to reduce fatality in this high-risk population.

Methods and analysis We will search PubMed, Cochrane Central, Embase and Web of Science for articles in English language published between January 2010 and December 2019. All clinical trials and observational studies involving infants less than 90 days old with a clinical diagnosis of sepsis and reported case fatality rate will be included. Two independent reviewers will screen the studies and extract data on study variables chosen a priori. Quality of evidence and risk of bias will be assessed using Cochrane Collaboration's tool and ROBINS-I. Results will be synthesised qualitatively and pooled for meta-analysis.

Ethics and dissemination No formal ethical approval is required as there is no collection of primary data. This systematic review and meta-analysis will be disseminated through conference meetings and peer-reviewed publications.

PROSPERO registration number CRD42020164321.

Strengths and limitations of this study

► This review will synthesise the association and temporal trends between neonatal sepsis and death over the past decade.
► Analysis of subgroups will provide insights about mortality across gestation age, birth weight, timing of sepsis, setting where sepsis was acquired and geographical location.
► This protocol adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to ensure objectivity in literature search, data synthesis and reporting of outcomes.
► Heterogeneity across studies may exist due to differences in patient populations, settings and studies performed over a decade.
► The inclusion of only studies published in English may lead to a loss of data published in other languages.

INTRODUCTION

Neonatal sepsis accounts for more than 1.4 million deaths worldwide, with varying mortality in different geographical locations.[1–3] It is a systemic condition of bacterial, viral or fungal origin with an array of clinical manifestations.[4 5] Neonates exposed to these pathogens during the perinatal period are susceptible to invasive infections due to their relatively compromised immune system.[1] Despite recent advances in diagnostic, treatment and preventive strategies, neonatal sepsis is still a leading cause of death in this population, with 4 out of every 10 neonates with sepsis dying or experiencing significant morbidity.[2 6 7] Among these, premature neonates have the worst outcomes.[8]

Understanding worldwide mortality data on neonatal sepsis can provide valuable information to inform interventions in specific geographical locations. Mortality rates will differ due to the prevalence of pathogens, neonatal and maternal risk factors, and accessibility to quality perinatal care.[1 9–12] A systematic review by Liang *et al* evaluated 45 studies looking at the mortality from neonatal sepsis in 20 countries, but the setting was limited to developing countries.[9] Because of heterogeneity in the study population and the risk factors, they did not perform a meta-analysis.[9] Another systematic review and meta-analysis by Fleischmann-Struzek *et al* used population-based data to evaluate the mortality of neonatal sepsis in 12 high-income and middle-income countries but included the older paediatric population.[11] Given the heterogeneity of available data, as well as a lack of data from all low-income and most

middle-income countries, the authors mentioned that their estimate for the global burden of neonatal sepsis was considered exploratory.[11] Bakhuizen *et al* also carried out a meta-analysis of five studies involving 990 patients to evaluate mortality of neonatal sepsis.[12] However, it was limited to neonates with a gestation age of less than 34 weeks and/or with birth weight of less than 1500 g. Stronger conclusions could not be made due to limitation on available data.[12] Therefore, there are current gaps in knowledge about mortality across gestation ages, birth weight and geographical settings. These pieces of information would be necessary to give a better insight about the global burden of mortality following neonatal sepsis.

Classifications of neonatal sepsis are important because the likely causative agents differ between early-onset and late-onset sepsis.[4 13–16] Early-onset sepsis is due to transplacental or intrapartum transmission of pathogens from the mother and late-onset sepsis is due to postnatal acquisition of pathogens from community or nosocomial sources.[17 18] Group B streptococcus, *Escherichia coli* and *Listeria monocytogenes* are the pathogens frequently responsible for early-onset sepsis, with gram-negative pathogens featuring particularly in preterm infants.[19 20] Late-onset sepsis is most often attributable to coagulase negative staphylococci and *Staphylococcus aureus*, especially in the neonatal intensive care unit.[21 22] Herpes simplex virus and enterovirus are more commonly associated with late-onset sepsis, with invasive candidiasis as an emerging cause among neonates treated with broad spectrum antibiotics.[23–25] Moreover, there are variations in causative pathogens due to differences in geographical locations and settings.[26]

There has been a surge of advances and evolving trends in neonatal sepsis. Guidelines have been established for screening of group B streptococcus in pregnant women and administration of intrapartum antimicrobial prophylaxis to pregnant woman with group B streptococcus.[27 28] However, this practice can be difficult to implement in low-resource settings where the prevalence of screening is low and the follow-up of women who screen positive is incomplete.[29] There have been reports on novel preventive strategies such as the administration of fluconazole, lactoferrin, probiotics, anti-staphylococcal monoclonal antibodies, immunoglobulin and granulocyte-macrophage colony-stimulating factors, as well as breastfeeding and establishing measures to minimise healthcare-associated infections.[30] In addition, there have been new challenges in managing infections due to increasing antibiotic resistance among neonates.[31 32] While medical advancement is commensurate with reduced mortality, new infectious disease trends warrant close study.

There is thus an urgent need at this time for a robust contemporary systematic review and meta-analysis on this topic. In this systematic review, we aim to appraise and summarise the association between neonatal sepsis and death over the past decade. In the meta-analysis, pooled estimates, along with the trends over time, of mortality and case fatality rates of neonatal sepsis will be reported.

METHODOLOGY
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines will be used to conduct this review.[33]

Eligibility criteria
The eligibility criteria for this systematic review and meta-analysis are as follows:

Inclusion criteria
► Population: Children less than 90 days old, regardless of gestation and birth weight. In term and post-term newborns, the neonatal period refers to the first 28 days of life, and in preterm newborns, the neonatal period for them is the day of birth, through the expected date of delivery plus 27 days.[34] Also, serious infections in this population can manifest beyond 28 days of life, including late-onset sepsis associated with group B streptococcus and *L. monocytogenes*.[21 22] Therefore, to present a complete picture of the disease burden, we choose to study young infants less than 90 days old. If a study includes both paediatric and adult populations, it will only be included if the data pertaining to the paediatric population (less than 90 days old) can be extracted.
► Exposure: Infection of bacterial, viral or fungal origin based on definition or diagnostic criteria for sepsis as determined by the study authors. We chose to include not only bacterial and fungal but also viral infections because young infants can become severely ill from viremic states.[4 5]
► Outcome: Case fatality rate.
► Design: Randomised controlled trial, cohort study or cross-sectional studies.
► Period: Date of publication between January 2010 and December 2019. We chose this date range with the intention to provide a robust update on a previously published systematic review.[11] This will also allow the team to focus on case fatality rates over the past decade in neonatal sepsis, given the changes in neonatal sepsis recognition and management.[35]

Exclusion criteria
► Studies with a primary focus on necrotising enterocolitis, respiratory distress syndrome without a primary sepsis study population, leukaemia or other malignancies.
► Studies with a sample size less than 50.
► Case reports, animal studies, laboratory studies, publication types of commentaries, letters, books, newsletters, fact sheets, guidelines or editorials.
► Published literature in non-English language.

Information sources
The literature search will cover the following electronic databases: PubMed, Cochrane Central, Excerpta Medica (Embase) and Web of Science. We also searched the following electronic registries for trial protocols to ensure that there are no completed or ongoing trials evaluating

the worldwide mortality of neonatal sepsis for both terms and preterm neonates: PROSPERO, ClinicalTrials.gov, International Standard Randomised Controlled Trial Number registry, WHO International Clinical Trials Registry Platform and European Union Clinical Trials Register.

Search strategy

The search strategy will be developed in consultation with research librarians experienced in systematic reviews and meta-analyses. The search will include all publications from January 2010 to December 2019. Medical Subject Headings (MeSH) are used for PubMed and Cochrane Central. Emtree terms are used for Embase. Topic terms are used for Web of Science. The terms will be exploded as appropriate and their synonyms will be included in the title, abstract and keyword searches.

The full search strategy can be found in online supplementary appendix 1–4. Strategic search terms include: Population—neonate, newborn, infant, baby; Exposure—sepsis, septicaemia, septic shock, pyaemia, endotoxaemia, blood poisoning; Outcome—mortality, fatality, death, demise, survival.

Study records

Covidence (V.1357.0, Melbourne, VIC, Australia) will be used to facilitate review of articles. After removing duplicates, the studies will be screened for relevance by title and abstract based on the patient, exposure and outcome (PEO) elements detailed above. This will be followed by a full text screening based on the eligibility criteria defined. Each article will be screened by two independent reviewers and any conflicts will be resolved by a third independent reviewer or by discussion. The reasons for excluding any article will be recorded.

Data items

Two independent reviewers will carry out data extraction using a standardised form consisting of study title, author(s), publication year, geographic origin, study design, enrolment period, sample size, source definitions of neonatal sepsis (clinically defined or culture confirmed), and classification of neonatal sepsis as early or late. Given the lack of consensus on the classification for early-onset versus late-onset sepsis, we will have two separate definitions for early-onset sepsis: less than 7 days and less than 72 hours—this will allow for a comprehensive analysis given current limitations in definitions.[17–22] We will also document the demographics (eg, gestational age, postnatal age, gender, birth weight), comorbidities, source of infection, causative organisms (ie, bacterial, fungal, parasitic or viral), community-acquired or hospital-acquired infection, blood markers (eg, white cell count, absolute neutrophil count, C-reactive protein, procalcitonin, lactate), number of deaths and time to mortality. Quantitative data will be used for meta-analysis and qualitative data will be used for systematic review.

Outcomes and prioritisation

The primary outcome of our study is the case fatality rate which is based on the number of deaths within the study population as reported by the study authors. The case fatality rate will be reported by specific timeframes of (1) within 24 hours, (2) 24 hours to less than 7 days and (3) 7 to 30 days from diagnosis of sepsis to occurrence of death. The studies that use numerical tests to measure the case fatality rate will contribute to the meta-analysis, where case fatality rates will be calculated and compared across the following subgroups: gestation age (term vs preterm), birth weight (low birth weight, very low birth weight and extremely low birth weight), early-onset versus late-onset sepsis, community-acquired versus hospital-acquired sepsis and by country's gross national income.[36 37] Young infants 28 days old or less will be presented and analysed on their own as part of a sensitivity analysis in the systematic review and meta-analysis respectively. We will also seek to exclude viral and fungal infections in a sensitivity analysis. The remaining studies will be reviewed systematically and described.

Risk of bias individual studies

By using the Cochrane Collaboration's tool and ROBINS-I for randomised and non-randomised studies respectively, we will assess each study for selection bias, performance bias, detection bias, attrition bias and reporting bias by assigning a rating of low, high or unclear risk of bias and evaluating the overall strength of the evidence provided by the study.[38 39]

Data synthesis

Case fatality rates will be calculated for each individual study and presented in forest plots to illustrate the overall effect. Standardised mean differences will be used as the effect measure. This will be determined by a random-effects approach using the DerSimonian and Laird method.[40]

The original authors will be contacted for missing data. Otherwise, the study will be excluded from meta-analysis but not the systematic review. The systematic review will include a table for the findings of each study and a narrative based on synthesis of this information.

Software to be used

The software Stata (V.16.0, College Station, Texas, USA) will be used for this meta-analysis.

Meta-bias

We will assess for publication bias, systematic difference between higher and lower precision studies, as well as any false effects due to poor methodology of the individual studies using a Funnel plot.

Patient and public involvement

This protocol is developed without patient and public involvement as this is not an interventional study and does not involve patient enrolment. Patients are not invited to comment on the study design and were not

consulted to develop patient relevant outcomes or interpret the results. Patients are not invited to contribute to the writing or editing of this document for readability or accuracy.

DISCUSSION

Neonatal sepsis is the most common diagnosis in neonatal intensive care units.[14 22 41] Despite improvements in the standard of medical care and advances in management strategies, the incidence and mortality rate of neonatal sepsis remains high.[42] In this systematic review and meta-analysis based on both population and hospital-based studies, we will describe patients' comorbidities, sources of infection and causative organisms of neonatal sepsis, as well as stratify the pool estimates by gestation age, birth weight, onset of sepsis, causative organism, place where infection was acquired and gross national income,[36 37] in order to identify the predictors of mortality and the factors associated with case fatality in neonatal sepsis. As there are no completed or ongoing trials with this focus, in undertaking this task, we will be able to contribute to a more complete knowledge-based research about the impact of neonatal sepsis, thus facilitating future research and developments to improve care and outcomes for this high-risk population.

Limitations

There is a lack of consensus-based definitions for neonatal sepsis, unlike in paediatric and adult sepsis.[43] The neonate's developmental stage and the associated aberrations in host immune response further preclude drawing references from paediatric or adult definitions of sepsis for use in this unique population. Neonatal and young infant sepsis is further compounded by the lack of comprehensive diagnostic testing, particularly in low-resource settings. On one hand, sepsis may not be diagnosed or recognised as a cause of death of those with severe illness, leading to a lower than actual incidence and case fatality rates. On the other hand, deaths may be assumed as sepsis, leading to false labelling and higher than actual incidence and case fatality rates. To address this, we decided to include all studies with sepsis as defined by the authors. However, as a quality measure, we will document if the study team adopted the sepsis definition by Goldstein *et al* which is a systemic inflammatory response syndrome (SIRS) in the presence of or as a result of a suspected or proven infection.[35] This definition is relevant and practical to use as age-specific references ranges for vital signs and laboratory variables of SIRS in the neonatal population are clearly stated. Similarly, there is a lack of consensus-based definitions for early-onset and late-onset sepsis.[44] To handle this data, we will have two separate definitions for early-onset sepsis: less than 7 days and less than 72 hours – this will allow for a comprehensive analysis given current limitations in definitions.

Although using MeSH, Emtree and Topic terms in our search strategy in the various search engines provides a systematic and standardised way of identifying studies in the respective databases, studies may be missed if they were not indexed under the terms used. To address this, we will hand search other systematic reviews and meta-analyses for relevant publications which may have been omitted by the search strategy. Also, the databases are not exhaustive and included only studies published in English language.

Furthermore, by including different study designs in our systematic review and meta-analysis, we anticipate a variable quality of evidence. Mortality in this age group is heavily confounded by other factors which we hope to mitigate by stratifying the following: gestation age, birth weight, early-onset versus late-onset sepsis, community-acquired versus hospital-acquired sepsis and gross national income.[36 37]

This systematic review and meta-analysis of neonatal sepsis and the associated case fatality rate will provide insights about the global healthcare burden of neonatal sepsis. Ultimately, the knowledge gained will provide an update on regions with high fatality rates and facilitate a better understanding of this high-risk population.

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