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REVIEW ARTICLE

Obstetrics

Outcomes of interventions in neonatal sepsis: A systematic review of qualitative research

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Abstract

Background: While a systematic review exists detailing neonatal sepsis outcomes from clinical trials, there remains an absence of a qualitative systematic review capturing the perspectives of key stakeholders.

Objectives: Our aim is to identify outcomes from qualitative research on any intervention to prevent or improve the outcomes of neonatal sepsis that are important to parents, other family members, healthcare providers, policymakers, and researchers as a part of the development of a core outcome set (COS) for neonatal sepsis.

Search Strategy: A literature search was carried out using MEDLINE, EMBASE, CINAHL, and PsycInfo databases.

Selection Criteria: Publications describing qualitative data relating to neonatal sepsis outcomes were included.

Data Collection and Analysis: Drawing on the concepts of thematic synthesis, texts related to outcomes were coded and grouped. These outcomes were then mapped to the domain headings of an existing model.

Main Results: Out of 6777 records screened, six studies were included. Overall, 19 outcomes were extracted from the included studies. The most frequently reported outcomes were those in the domains related to parents, healthcare workers and individual organ systemas such as gastrointestinal system. The remaining outcomes were classified under the headings of general outcomes, miscellaneous outcomes, survival, and infection.

Conclusions: The outcomes identified in this review are different from those reported in neonatal sepsis clinical trials, thus highlighting the importance of incorporating

For affiliations refer to page 553.

qualitative studies into COS development to encapsulate all relevant stakeholders' perspectives.

KEYWORDS
core outcome set, infant, infectous disease, neonatal sepsis, newborn, qualitative research, qualitative systematic review

1 | INTRODUCTION

According to the global report on the epidemiology of sepsis, there are an estimated 1.3–3.9 million annual cases of neonatal sepsis worldwide, leading to 400000–700000 deaths.[1]

In high-income countries, the incidence of neonatal sepsis ranges between 1.3 and 1.6 per 1000 live births[2] and can reach 30% in extremely preterm newborns.[2–5] While the mortality rate varies between 10% and 18%[2,6,7] in high-income countries, it can increase up to 27% among neonates in low- and middle-income countries (LMICs).[8] In addition to increased mortality, neonatal sepsis increases the risk of long-term neurodevelopmental delay, neurodevelopmental abnormalities such as cerebral palsy and neurosensory deficiencies, impaired physical growth, and bronchopulmonary dysplasia.[9,10]

The lack of a consensus definition for neonatal sepsis hinders progress.[11] The variability in the definitions of neonatal sepsis used across studies leads to inconsistencies in study populations, which complicates the comparison and synthesis of research findings.[12] Furthermore, researchers often choose to report a diverse range of outcomes when evaluating the effectiveness of interventions for neonatal sepsis, which adds another layer of complexity to the synthesis of results across studies.[13]

The adoption of a core outcome set (COS) could help reduce this latter source of heterogeneity, facilitating more straightforward comparisons and meta-analyses.[14] A COS is the minimum set of outcomes that should be measured and reported in all clinical trials of a certain condition. They are suited for use in observational and experimental studies, in addition to clinical trials and audits.[15] Researchers are not restricted to reporting just those outcomes specified in the COS and can measure and report additional outcomes that are of relevance to their study.[14] Given the wide variation in outcomes reported in relation to the interventions for treating neonatal sepsis, the development of a COS in this space is warranted. As the outcomes that should be reported in neonatal sepsis studies have not yet been formalized, the standardization with a COS will bring crucial advantages.

Developing a COS involves (1) identifying potential outcomes and (2) prioritizing the outcomes for inclusion in the COS. During the development of a COS, a systematic review is useful in identifying a list of outcomes that researchers have deemed important to measure.[14] However, the outcomes identified in these reviews mostly reflect the viewpoints of researchers and clinicians, because clinical trials often do not report outcomes that are important for patients and families.[16–18] Yet the outcomes considered throughout the consensus process should reflect the opinions of all relevant stakeholders. Therefore, it has been recommended that COS developers should consider combining several methods to develop the initial list of outcomes presented to stakeholders for review and prioritization. For instance, data from patient interviews or analysis of qualitative research studies focusing on patients' opinions may be used to supplement outcomes from published clinical trials.[19]

Where suitable publications are available, systematic reviews of qualitative studies may provide an alternative to primary qualitative research.[20] Systematic review of qualitative research has been used by researchers in the process of developing COSs in neonatal care,[21] type 2 diabetes,[22] chronic pelvic pain,[23] pelvic organ prolapse,[24] and bariatric surgery.[25]

A COS may be created to help with the decision of what to measure and how to measure it. This review focused solely on identifying outcomes from qualitative research on any intervention to prevent or improve the outcomes of neonatal sepsis that are important to parents, other family members, parent representatives, healthcare providers, policymakers, and researchers. The outcomes of this study will be merged with those noted in a recently published systematic review of the outcomes reported in neonatal sepsis clinical trials.[13] This combined list of outcomes will be presented in a subsequent Delphi survey, for key stakeholders to prioritize their importance, and the prioritized results will be discussed in consensus meeting which will lead to the development of a COS for neonatal sepsis.

2 | METHODS

The protocol of this systematic review was registered to the Prospective Register of Systematic Reviews (PROSPERO ID: CRD42022344485)[26] and details of the project were published elsewhere.[27] The study was conducted and reported in accordance with the guidelines of the ENTREQ statement[28] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[29]

The PerSPEcTiF framework was used to structure the description of our review question and inclusion criteria[30] as per qualitative review guidelines[31,32] (Table 1). Studies with a qualitative study design such as ethnography, grounded theory, and case study, those that used qualitative data-collection methods including observations, textual, or visual analysis, and mixed-method studies that included a

TABLE 1 The PerSPEcTiF question formulation framework.

Per	S	P	E	(C)	Ti	F
Perspective	Setting	Phenomenon of interest/ problem	Environment	Comparison (optional)	Time/timing	Findings
Parents, other family members, parent representatives, healthcare providers, policymakers, researchers	Any setting	The outcomes of treatments for neonatal sepsis that are important to parents, other family members, healthcare providers, policymakers, researchers	High, middle and low-income countries		Anytime following diagnosis of neonatal sepsis	All outcomes regarding phenomenon of interest

qualitative component (using qualitative methods of data collection and analysis and where participant experiences are reported separately) were included. As there is a lack of a consensus definition of neonatal sepsis, for this review, we included studies where the researchers used the term "neonatal sepsis." Abstracts, randomized controlled trials, clinical trials, intervention studies, cross-sectional studies, case–control studies, prospective and retrospective cohort studies, letters to the editor, conference proceedings, systematic reviews, and meta-analyses were excluded. There was no date restriction. Studies not written in English were excluded.

During our initial engagement with the literature, we noted the paucity of qualitative studies directly exploring the outcomes of neonatal sepsis interventions deemed important by parents, other family members, healthcare providers, and policymakers. We reviewed how other COS developers overcame similar issues and were informed by their work. Therefore, we decided that our review would also include qualitative studies exploring the experiences of parents, family members, healthcare workers (HCWs), and researchers during the management of neonatal sepsis. This paper presents a method for identifying outcomes referenced by stakeholders when asked about these experiences. This method has been employed in COS development by Gorst et al.[22] and Richardson et al.[33] We acknowledge that another approach could have been to undertake a qualitative study that focused specifically on the identification of outcomes by parents, other family members, healthcare providers, and policymakers.

A literature search was carried out using MEDLINE, EMBASE, CINAHL, and PsycInfo databases. Each database's complete search strategy is presented in Supporting Information S1.

In accordance with standard practice, the reference lists of pertinent research were hand-searched to uncover more relevant studies.[34–37] The findings of the literature search were transferred to Endnote.

Two reviewers (PET, LB) independently screened the titles, abstracts, and full texts in accordance with the eligibility requirements, and disagreements were settled by discussions with a third senior author (DD). All screening was conducted using the software platform Rayyan (Qatar Computing Research Institute (QCRI), Qatar Foundation, Doha, Qatar).

We used a deductive approach to identify text that was relevant to the outcomes. It must be noted that none of the qualitative studies sought to determine outcomes; however, they did contain text that we could interpret as relevant to neonatal sepsis outcomes. The findings and discussion sections of the included papers served as the source of all such text, which contained quotes from participants about their experiences and opinions as well as the researchers' observations. Our approach to data extraction followed the methods described in the development of COS by Gorst et al.[22] and Richardson et al.[33]

One review author (PET) extracted the data using a pre-piloted data extraction form to obtain study characteristics from qualifying studies. A second review author (LB) double-checked the data extraction and verified that all relevant data were extracted. Author information, publication year, study design, number of participants, data collection and analysis methods, and the study findings that could be interpreted as relevant to neonatal sepsis outcomes were noted on the form. An example of the data extraction form is presented in Supporting Information S2.

Two reviewers (PET, LB) independently assessed the quality of the included studies using the Critical Appraisal Skills Programme (CASP) tool, *CASP Qualitative Studies Checklist*.[38] CASP is the most commonly used instrument for evaluating the quality of qualitative evidence syntheses relevant to health. It also has the support of the Cochrane Qualitative and Implementation Methods Group.[39] This assessment was used to aid us in assessing the methodological limitations of the included studies; it was not used as a tool to inform the exclusion of any studies nor did we use this assessment to categorize the level of evidence informing the outcomes we present. The findings of the review must be considered in the context of the methodological limitations of the included studies. This method and its application have been employed in other qualitative reviews that contribute to COS development.[22,33]

With reference to the concepts of thematic synthesis,[40] data related to outcomes of interventions in neonatal sepsis were coded line by line, with similar codes grouped to establish distinct, descriptive themes linked to therapeutic intervention outcomes in neonatal sepsis. The outcomes stated in the themes were examined and interpreted by two reviewers. These outcomes were then mapped to the domain headings of an existing model developed by Webbe et al., presenting a "Core outcomes in neonatology: development of a core outcome set for neonatal research."[41] The following domain headings guided the mapping: survival, respiratory, cardiovascular, gastrointestinal, neurological, genitourinary, skin, surgical, development (gross motor/fine motor/cognitive/special senses/speech and social), psychosocial, healthcare utilization, outcomes related to parents, outcomes related to HCWs, general outcomes, and miscellaneous. Where the outcomes noted in the qualitative data did not align with any of Webbe et al.'s domains, additional domains were developed.

3 | RESULTS

3.1 | Study characteristics

Out of 6777 records screened, six studies met the requirements for inclusion in the review (Figure 1). Studies included were published between 1998 and 2021. Two studies were conducted in India, one in the USA, one in Portugal, one in Australia, and one in Bangladesh.

The studies mainly used qualitative interviews for data collection (such as open-ended, tape-recorded interviews). Two studies also included focus group discussions Only one study used direct observation of the mother and the baby in the neonatal unit as the data collection method. There were 142 participants, with a 66.9% female rate. Parents and family members were the most frequent stakeholder group ($n=112$, 78.8%). The remaining participants were HCWs ($n=30$, 21.1%). Policymakers and researchers (the other stakeholder groups in our inclusion criteria) were not participants in any of the included studies.

3.2 | Quality appraisal of included studies

Quality appraisal of all the included studies is presented in Supporting Information S3. All studies had a clear statement of the research, appropriate methodology, and clear statements of the findings, and were valuable for our research question. Only one research design was considered inappropriate to address the study's aims. Recruitment strategies were not stated clearly in the three studies. Data-gathering to answer the research question was not clearly explained in the two studies. The relationship between the researcher and participants was not adequately considered in one study, and not enough information was given in three studies. Two studies did not mention ethical approval, and one study had unclear information about the ethical approval process. Data analysis was not sufficiently rigorous in one study, and one study did not provide clear information in relation to their methods of data analysis.

3.3 | Data categorization

Overall, 19 outcomes were extracted, using the methods described in previous paragraphs, from the included studies; six of these outcomes were unique to this review in that they could not be mapped to Webbe et al.'s framework.[41] Supporting Information S4 contains a complete list of the outcomes mapped into the Webbe

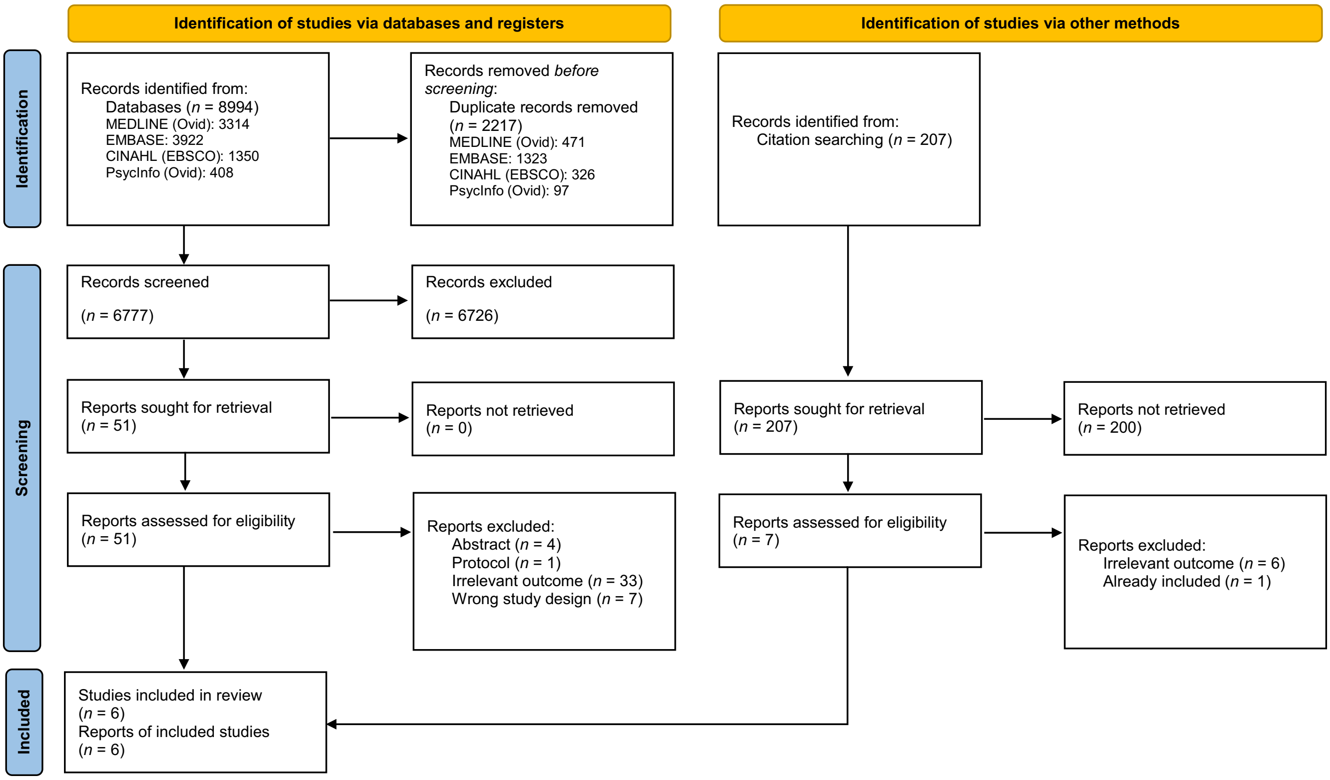

FIGURE 1 PRISMA 2020 flow diagram which includes searches of databases, registers and other sources. From Ref. [51]. For more information, visit: http://www.prisma-statement.org/.

et al. framework and displays the data extracted from each study separately. The findings of this review (identified outcomes from the qualitative studies) are presented in Figure 2.

The most frequently reported outcomes were related to the domain of outcomes related to parents (6 outcomes, 32%), individual organ systems (5 outcomes, 26%), and outcomes related to HCWs (4 outcomes, 22%). The remaining outcomes were classified under the headings of general outcomes (1 outcome, 5%) and miscellaneous outcomes (1 outcome, 5%), survival (1 outcome, 5%), and infection (1 outcome, 5%) (see Figure 2).

3.4 | Domain 1: Outcomes related to parents

Parental outcomes were reported in five[42–46] out of six included studies. In total, six outcomes were reported. Two of them were unique to our review and were not a part of Webbe et al.'s framework. The most reported outcome was the "psychological wellbeing of the parents," which was reported by four out of five studies. It included emotional reactions such as feeling worried, shocked, angry, concerned, and distressed. "Support for parents" was reported in two studies comprising family, peer, and spiritual support. Mothers' and fathers' bonding with their babies and "parental involvement in care" during treatment were discussed in two studies. Three studies referred to "parental competence on care" and how their lack of understanding led to their inability to understand the significance of the treatment their baby received and the impact on the baby's well-being. The "economic burden" of neonatal sepsis on parents was discussed in one study.

3.5 | Domain 2: Outcomes related to HCWs

Four outcomes linked with HCWs were presented in three[43,45,46] of the six included studies, and three were unique to our review. The outcome "communication between parents and HCWs" was noted in three of the studies and had three associated concepts related to effective communication (with parents), non-effective communication (with parents), and parents' need for more information. Data in relation to the outcome of effective caring relationships with parents were noted in three studies. One study discussed the job satisfaction and well-being of the HCWs.

3.6 | Domain 3: Organ system outcomes

The gastrointestinal system accounted for the most frequently mentioned data in the organ systems domain,[42,46] followed by the respiratory[47] and neurological systems.[43] Two studies discussed breastfeeding outcomes, and one noted necrotizing enterocolitis. Tachypnea was noted in one study as important. The outcomes of seizures and quadriplegia were presented in one study. All the outcomes in this domain except quadriplegia were already included in Webbe et al.'s framework.

3.7 | Domain 4: Survival

Neonatal mortality was mentioned only in one study by HCWs.[45]

3.8 | Domain 4: Infection

One study (16.6%)[47] mentioned overprescribing antibiotics or increasing the regular antibiotic dose by doctors as a result of fearing the treatment may be unsuccessful.

3.9 | Domain 5: General outcomes

Three studies (50%)[43,44,46] discussed the normality after the discharge of neonates. Reported "normality" findings were "baby's normal behaviors," "baby's long-term wellbeing," and "gaining weight and becoming active."

3.10 | Domain 6: Miscellaneous

Two studies (33.3%)[43,46] involved comments about the body temperature of neonates. One study mentioned getting back to normal body temperature, and the other had a quote about persistent fever in neonates with sepsis.

4 | DISCUSSION

There are six studies in this qualitative systematic review. The data collection method most often used in these studies was the in-depth interview, and the most frequently reported outcomes were those related to parents. The quality appraisal we conducted highlighted that only two studies fulfilled all criteria; however, given the limited literature in this area, the focus of this review and how this review will contribute to the wider NESCOS (Neonatal Sepsis Core Outcome Set) project, we have not excluded any of the studies from this review. Most studies performed poorly in adequately reporting the relationship between the researcher and participants. Furthermore, two studies did not give any information about ethical approval. The findings presented in this review must be noted in the context of the methodological limitations of the studies included.

The most often reported outcome was related to parents' psychological well-being, which was mentioned in almost all included studies.[43–46] The responses provided by parents in the included studies noted that they felt worried and concerned about not knowing what would happen to their baby. Many parents highlighted that when they heard about their infant's diagnosis of sepsis, they were in shock because it was unexpected. As in previous qualitative systematic reviews for COS developments,[21–23] support during treatment was important for the patients. Similarly, our findings suggest the significance of the support given to the parents during treatment. Murty et al. presented

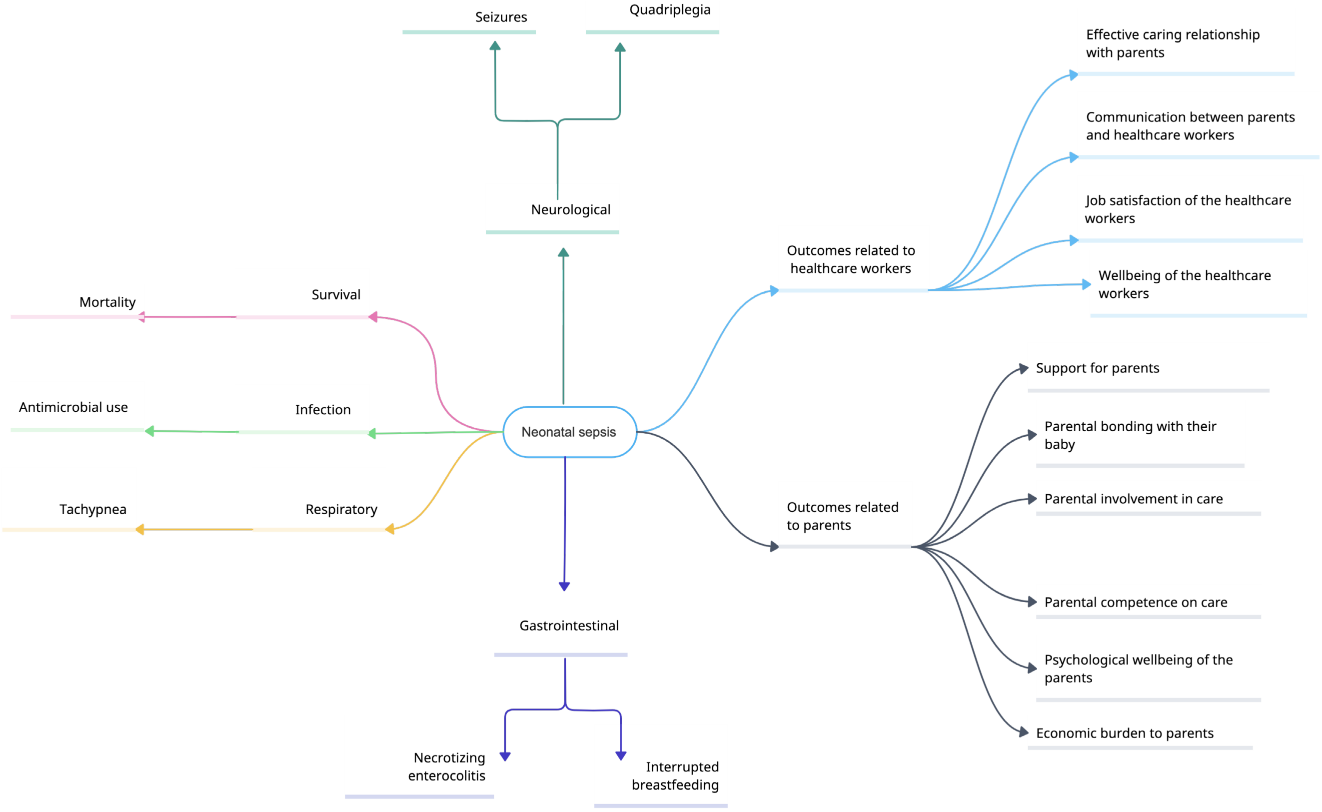

FIGURE 2 Identified outcomes from the qualitative studies.

examples of how parents valued social and spiritual support during the treatment of their babies with neonatal sepsis,[46] while Urbanovska et al. highlighted the importance of social support for the mothers to facilitate access to healthcare and social integration.[42]

The outcomes identified in this study vary from the findings of the systematic review of clinical trials,[13] which only included the following domains: morbidity, clinical outcome, neurodevelopment outcome, and pharmacology. The inclusion of the additional domains of "outcomes related to parents" and "outcomes related to healthcare workers" emphasizes the importance of ensuring a wide scope to include outcomes from all key stakeholders, contributing to the outcome list presented for prioritization during COS development. As in Webbe et al.'s study,[48] our findings show that the effects of diagnoses on everyday life are important to parents or family members. If the list of outcomes contributing to the Delphi rounds for COS development is derived solely from clinical trial reviews, this might unwittingly omit outcomes that are relevant and important to parents.

To expand the global relevance of COS, it is necessary to include participants from a broad range of geographic regions in its development. However, it is reported that only 16% of the published COS included participants from LMICs.[49] In our review, half of the included studies involved participants from LMICs, such as India and Bangladesh. Two out of three studies from LMICs reported on the psychological burden on the parents and the ineffective communication with HCWs.[44,46] The economic burden on parents associated with neonatal sepsis was noted in one study in this review, which was conducted in India.[46] As this is a unique finding of this review and only noted in one study, further exploration of this issue is necessary.

The communication of HCWs with parents was prominent as an outcome in numerous included studies,[42,43,46] similar to earlier systematic reviews of qualitative studies for the development of COSs on neonatal care, chronic pelvic pain, and pelvic organ prolapse.[21,23,24] Parents noted that they had experienced effective communication with HCWs and suggested that they received the information they needed in relation to neonatal sepsis (e.g., care, treatments, the baby's well-being). The parents included in this review who had effective communication with HCWs declared that they felt reassured and well prepared to go through the treatment process.[43] Some parents stated that they were unable to fully understand the diagnosis of neonatal sepsis due to the usage of unexplained medical terminology by HCWs when speaking with them, which had a negative effect on their experiences. For the parents who felt that they were not informed in an appropriate manner, this had a negative impact on their experiences. In instances of poor communication, parents and families noted distress about their newborn's condition, treatment, and the cost of the treatment.[46]

4.1 | Strength and limitations

To our knowledge, this is the first review of qualitative studies to identify outcomes of interventions in neonatal sepsis that are important to parents, other family members, parent representatives, healthcare providers, policymakers, and researchers.

Our findings can be noted alongside the outcomes measured in clinical trials[13] and will increase the breadth of outcomes to go forward to the Delphi survey.[50] A strength of our review is that it includes studies from high- and low-income countries and across parent and healthcare provider groups. Thus, we could incorporate data from a wider range of stakeholders than a primary research study might have allowed. Furthermore, our comprehensive search strategy resulted in a thorough assessment of all aspects relevant to the opinions and perceptions of patients, family members, parent representatives, healthcare providers, and researchers.

Limitations of our review that we must acknowledge include the relatively small number and methodological limitations of the included studies. We also acknowledge that none of the included studies focused specifically on identifying important outcomes for parents and other key stakeholders. We are aware that undertaking a qualitative study that focused specifically on the identification of outcomes by parents, other family members, healthcare providers, and policymakers would be a more direct way to identify the outcomes and suggest this is a body of work that needs to be undertaken in this space. To conduct this review, we had to use methods to interpret outcomes in the findings of qualitative studies that include the experiences of parents, family members, parent representatives, and HCWs during the management of neonatal sepsis. Additionally, including only studies published in English might have been restrictive, potentially preventing the discovery and presentation of an even greater variety of cultural perspectives. Furthermore, although the aim of our review proposed a wide group of key stakeholders, we were not able to access qualitative studies focusing on the outcomes of treatments for neonatal sepsis that are important to policymakers and researchers. Finally we should point out that the identified outcomes might not be specific to neonatal sepsis alone. Outcomes such as psychological well-being of the parents and communication between parents and HCWs were already stated in the qualitative systematic review as the outcomes during and following neonatal care in a broader sense.[21] However, these outcomes will now be combined with those noted in a recently published systematic review of the outcomes reported in neonatal sepsis clinical trials[13] and prioritized by the key stakeholders via a Delphi survey and consensus meeting to inform the final COS.[22,33]

5 | CONCLUSIONS

This qualitative systematic review aimed to identify outcomes considered important to parents, family members, parent representatives, and healthcare providers. The patient, parent, and HCW-centered outcomes will complement the findings of a systematic review of outcomes included in clinical trials[13] within the methods of COS development. This study also highlights the lack of qualitative research identifying outcomes that are important to key stakeholders in addition to trialists. Given the outcomes identified in this review that were not noted in clinical trials, this work highlights the importance of incorporating qualitative studies into COS development to encapsulate all relevant stakeholders' perspectives.

AUTHOR CONTRIBUTIONS

PET, DD, JK, EM, and LB conceived and designed the qualitative systematic review. PET and LB conducted the screening, data extraction, quality assessment, and data synthesis. PET, LB, and DD wrote the paper. PET is the corresponding author and guarantor of this manuscript. As steering committee members of NESCOS (Neonatal Sepsis Core Outcome Set) project, MD, AB, DS, JLW, NK, KK, SHPS, LNB, EG, TS, MO, KM, FQ, and KB have inherently contributed to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. All authors critically revised the manuscript. All authors reviewed and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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