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Clinical prediction models to diagnose neonatal sepsis: a scoping review protocol

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ABSTRACT

Introduction: Neonatal sepsis is responsible for significant morbidity and mortality worldwide. Diagnosis is often difficult due to non-specific clinical features and unavailability of laboratory tests in many low and middle-income countries. Clinical prediction models have the potential to improve diagnostic accuracy and rationalise antibiotic usage in neonatal units, which may result in reduced antimicrobial resistance and improved neonatal outcomes. In this paper, we outline our scoping review protocol to map the literature concerning clinical prediction models to diagnose neonatal sepsis. We aim to provide an overview of existing models and evidence underlying their use and compare prediction models between high-income and low and middle-income countries.

Methods and analysis: The protocol was developed with reference to recommendations by the Joanna Briggs Institute. Searches will include six electronic databases (Ovid MEDLINE, Ovid Embase, Scopus, Web of Science, Global Index Medicus, and the Cochrane Library) supplemented by hand searching of reference lists and citation analysis on included studies. No time period restrictions will be applied but only studies published in English or Spanish will be included. Screening and data extraction will be performed independently by two reviewers, with a third reviewer used to resolve conflicts. The results will be reported by narrative synthesis in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines.

Ethics and dissemination: The nature of the scoping review methodology means that this study does not require ethical approval. Results will be disseminated through a peer-reviewed publication and conference presentations, as well as through engagement with peers and relevant stakeholders.

ARTICLE SUMMARY

Strengths and limitations of this study

- There have been few recent attempts to scope literature concerning clinical prediction models to diagnose neonatal sepsis across high-income and low and middle-income countries.
- The protocol was developed with reference to recommendations by the Joanna Briggs Institute and the review will be reported in line with the PRISMA-ScR guidelines.
- The search strategy includes six electronic databases, hand searching of reference lists and citation analysis on included studies.
- A limitation of the review is that we will only include non-grey literature published in English or Spanish and it is possible that studies relevant to non-English or non-Spanish speaking settings will not be included.

INTRODUCTION

Despite significant progress in global child health over the past two decades, there were 2.5 million neonatal deaths in 2018 with a global neonatal mortality rate of 18 deaths per 1,000 live births.[1] The vast majority of these deaths occur in low and middle-income countries and are most commonly due to prematurity (35%), intrapartum-related complications (24%) and neonatal sepsis (15%).[1] Neonatal sepsis has an estimated global incidence of 2,202 per 100,000 live births and a global case fatality rate of between 11-19%.[2] Moreover, it is a significant source of morbidity for survivors: complications including neurodevelopmental disorders, cerebral palsy and visual or hearing impairment may persist beyond the neonatal period.[3] Therefore, addressing neonatal sepsis as a preventable and treatable cause of neonatal morbidity and mortality is a global priority.

Neonatal sepsis is a clinical syndrome that results from systemic infection in the first month of life.[4] It is typically classified as early-onset sepsis (EOS, onset within the first 48-72 hours of life) or late-onset sepsis (LOS, onset after the first 48-72 hours of life) to reflect the differing microbiology of these two disease patterns.[5] EOS results from vertically-transmitted infection with pathogens obtained from the maternal genital tract shortly before or during birth.[6] Group B streptococcus (GBS) and *Escherichia coli* account for the majority of cases of EOS in high income settings, and risk factors for these infections include prematurity, low birth weight, prolonged rupture of membranes, maternal fever during labour and maternal rectovaginal colonisation with GBS.[6] In comparison, LOS occurs due to pathogens acquired through interaction with the home or hospital environment.[7] Coagulase-negative staphylococci (CONS) are the commonest organisms of LOS and other major pathogens include *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Pseudomonas* species, and fungal infection with *Candida* species.[7] It should be noted, however, that the exact microbiology of neonatal sepsis differs greatly across geographical regions and is liable to change over time.[8] Furthermore, the microbiology is difficult to determine in settings with limited or no access to reliable culture methods. There is increasing recognition that classification of neonatal sepsis as EOS or LOS is misplaced in low and middle-income countries (LMICs). In these settings, babies are exposed from birth to organisms typically associated with LOS due to poor infection, prevention and control practices such as hand hygiene, aseptic delivery and limited availability of GBS screening services in pregnancy.[9] In a systematic review of data from sub-Saharan Africa, *Staphylococcus aureus* (25%) and *Klebsiella* species (21%) were the most common causative organisms of neonatal sepsis.[10] Thus, in LMICs, it may be sensible to label all infections in facility-born neonates as hospital acquired, even if the infection presents within the first few days of life.[9]

Diagnosis of neonatal sepsis is hindered by non-specific clinical features such as temperature instability, lethargy, poor feeding and respiratory distress, which often overlap with non-infectious diseases. The current gold standard method for diagnosing neonatal sepsis is identification of a pathogenic organism from a normally sterile site (e.g. blood or cerebrospinal fluid).[5] However, *clinical sepsis* (where the infant shows clinical features of sepsis despite negative blood cultures) is a recognised entity and may be more common than blood-culture proven sepsis, especially in the context of previous antibiotic exposure in the baby or mother.[11] When deciding to treat suspected cases of neonatal sepsis, there is a fine balance between failing to treat a serious infection and unnecessary use of antibiotics. Antimicrobial resistance is a growing global concern, with one estimate suggesting that 31% of annual sepsis-related neonatal deaths globally could be attributable to

antimicrobial resistance.[12] Furthermore, some reports have suggested that prolonged exposure to antibiotics are associated with negative neonatal outcomes such as death and necrotising enterocolitis.[13] Therefore, accurately identifying infants with neonatal sepsis is vital to guide optimal use of antibiotics, reduce antimicrobial resistance and improve neonatal outcomes.

Study rationale

Clinical prediction models are tools that combine multiple characteristics (or predictors) to estimate the probability of a diagnosis or prognostic outcome and they have gained increasing research attention in recent years.[14] Multiple prediction models exist to estimate the risk of neonatal sepsis based on a wide range of clinical features, risk factors and/or laboratory tests, for example the Kaiser Permanente neonatal sepsis risk calculator for EOS.[15] Clinical prediction models for neonatal sepsis have the potential to improve diagnostic accuracy and rationalise antibiotic usage in neonatal units. Models that do not include laboratory results as predictors are of particular importance in LMICs where basic laboratory tests are often unavailable and the initial care and clinical management of newborn infants may fall to lower cadre healthcare workers in remote settings with limited senior support. Some models used in LMICs have high sensitivity but low specificity for neonatal sepsis and result in overuse of antibiotics.[16]

A search to identify existing scoping reviews or systemic reviews of clinical prediction models to diagnose neonatal sepsis yielded three potentially relevant studies. Two reviews examined clinical prediction models for severe infections in children, however both excluded those targeting neonates.[17, 18] One review examined clinical prediction models for healthcare-associated bloodstream infections in neonates, but they excluded models developed for EOS and the searches are now relatively outdated in this rapidly evolving field.[19] Therefore, the present review will provide an important summary of existing clinical prediction models to diagnose neonatal sepsis to form a basis for future primary research or systematic reviews.

Study objectives

The aim of this scoping review is to map the literature concerning clinical prediction models to diagnose neonatal sepsis in high-income countries (HICs) and LMICs.

The specific objectives are:

- To provide an overview of existing clinical prediction models to diagnose neonatal sepsis.
- To determine the evidence underlying the use of clinical prediction models to diagnose neonatal sepsis.
- To compare clinical prediction models to diagnose neonatal sepsis between HICs and LMICs.
- To identify unanswered research questions surrounding clinical prediction models to diagnose neonatal sepsis, which may guide future primary research or systematic reviews.

METHODS AND ANALYSIS

The methods for this review were developed with reference to the scoping review guidelines provided by the Joanna Briggs Institute.[20] The major components of the review process are detailed in turn below.

Research question

Our review will be guided by the following specific research questions (Table 1).

Table 1. Research questions

1. What clinical prediction models exist to diagnose neonatal sepsis?	
2. What predictors are used in these models?	• Symptoms and signs • Risk factors • Laboratory tests
3. What is the evidence underlying the use of these models?	• Diagnostic accuracy • Success of implementation • Clinical efficacy
4. How do these models differ between HICs and LMICs?	• Number that exist • Predictors used • Evidence supporting use
5. What questions remain unanswered regarding clinical prediction models to diagnose neonatal sepsis?	

Inclusion criteria

The inclusion criteria (Table 2) were formulated according to the 'Population-Concept-Context (PCC)' framework recommended by the Joanna Briggs Institute.[20] As a scoping review is an iterative process, these may be amended as the review progresses and the extent of the literature becomes apparent.

Table 2. Inclusion criteria	
Population	• Human neonates (aged <28 days of life or hospitalised to a neonatal unit) being evaluated for neonatal sepsis (as defined by the individual studies). • Studies examining a range of patient ages will be included, providing sufficient data are available to examine findings for neonates in isolation.

Concept	• Studies that develop, validate or assess the impact of a clinical prediction model to diagnose neonatal sepsis.
	• Studies that report any of:
	  ○ modelling methods (including participants, predictors, outcomes and type of model);
	  ○ model performance (including sensitivity and specificity); or
	  ○ success of implementation (including acceptability and any changes to practice or outcomes).
	• Only internally and/or externally validated models will be included.
	• Studies evaluating prognostic models (e.g. to predict neonatal sepsis-related mortality or morbidity) will be excluded.

Context	• Studies from any country. • Studies from any healthcare setting (including neonatal unit, emergency department, outpatient or community setting).
Types of studies	• Randomised and quasi-randomised controlled trials, cohort studies, cross-sectional studies, case-control studies and guidelines. • Letters, comments and conference proceedings will be included if sufficient details are provided. • Studies published in English or Spanish. • Systematic reviews, meta-analyses and editorials will be excluded, but will be used to identify relevant primary literature.

Search strategy

The following databases will be searched: Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; Ovid Embase; Scopus; Web of Science; Global Index Medicus; and the Cochrane Library. Search terms were constructed to capture variations of “neonate”, “sepsis” and “prediction model” by examining the common text words and index terms of known relevant literature. These keywords were further expanded by including relevant potential synonyms. The search strategy for Ovid MEDLINE is detailed in Table 3 and a complete list of search strategies for each database can be found in the supplementary appendix. It is anticipated that additional keywords and index terms may be identified as the review progresses, and these will be incorporated into the search strategy and the searches will be rerun as applicable. To identify additional studies not found through the primary database searches, citation analysis will be performed on included studies using the citation analysis function of Scopus, Web of Science and Google Scholar. Furthermore, the

reference list of included studies will be hand searched. No time period or language restrictions will be applied to the search strategy, but studies will be manually limited to the English or Spanish language at the study selection stage. Searches will be updated prior to publication of our findings to ensure no recent studies are missed.

Table 3. Search strategy for Ovid MEDLINE	
1	exp Infant, Newborn/
2	(neonat* or newborn* or new born* or baby or babies or premature or preterm or infant* or low birth weight or LBW or VLBW or ELBW or NICU*).ti,ab,kw.
3	1 or 2
4	exp Sepsis/
5	(sepsis or septic* or bacter?emia).ti,ab,kw.
6	4 or 5
7	Decision Support Techniques/ or Neonatal Screening/
8	((predict* or diagnos* or screen* or identif* or manag*) adj5 (model* or rule* or scor* or tool* or algorithm* or decision tree* or pathway* or calculator*)).ti,ab,kw.
9	7 or 8
10	3 and 6 and 9

Evidence selection

All identified records will be imported into EndNote X9 (Clarivate Analytics, 2018) for bibliographic management and deduplication. First, titles and abstracts will be examined against the inclusion criteria (Table 2) to determine whether the study is potentially eligible for inclusion. Next, full texts of potentially eligible studies will be obtained and examined to confirm their eligibility. Relevant authors will be contacted to request full texts, if required. Record screening will be performed independently by two reviewers using the Rayyan web and mobile application.[21] Studies in Spanish will be translated to English and then considered for inclusion. Conflicts will be resolved by a third reviewer and discussion amongst the review team. The first database searches were performed in December 2019 (identifying 2,776 records after deduplication) and title and abstract screening is currently ongoing.

Data extraction

Data extraction will be performed independently by two reviewers. A draft data extraction form has been designed for this review and is shown in the supplementary appendix. This form was adapted from a template provided by the Joanna Briggs Institute[20] and will be further refined as the review progresses. Data to be extracted are based on the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement[22] and include study author(s), year of publication and name of the prediction model described; sources of data, number and characteristics of study participants; type of model, predictors used and defined outcome; and model performance or other evidence regarding the use of the model in clinical practice.

Analysis of the evidence and presentation of the results

The results of this review will be reported by narrative synthesis in line with the recommendations set out in the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).[23] The characteristics of several subgroups of clinical prediction models will be compared, including:

- Those that were developed and validated for use in HICs versus LMICs, as defined by the World Bank classification.[24]
- Those for diagnosing specific subgroups of neonatal sepsis (e.g. EOS versus LOS).
- Those based solely on clinical predictors versus those that require laboratory tests.

Data for quantitative outcomes such as model performance or measures of changes to clinical outcomes will not be pooled in a meta-analysis but, rather, general trends will be discussed. Furthermore, explicit risk of bias assessment will not be performed, as our aim is to report the extent of the current literature. It is hoped that this review can then act as a basis to determine important research questions for future primary research and systematic reviews or meta-analyses.

ETHICS AND DISSEMINATION

Since the scoping review methodology involves reviewing and collecting data from publicly available sources, this study does not require ethical approval. The results of this review will be disseminated through a peer-reviewed publication and/or conference presentation. Furthermore, we will engage with the stakeholders of our local and international projects to widen the dissemination of our findings. By identifying gaps in the literature, we hope that this review can form a basis for future primary research and systematic reviews or meta-analyses.

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AUTHORS' CONTRIBUTIONS

FF and MH conceived the idea for this review. SRN developed the research question, study methods and drafted the manuscript. FF, MH and MCB supervised the protocol design and continue to supervise the review process. GC also supervised the review process. All authors discussed the protocol design and critically edited and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable for this study design.

Supplementary appendix

CONTENTS

1. SEARCH STRATEGIES FOR EACH DATABASE

Ovid MEDLINE

1	exp Infant, Newborn/
2	(neonat* or newborn* or new born* or baby or babies or premature or preterm or infant* or low birth weight or LBW or VLBW or ELBW or NICU*).ti,ab,kw.
3	1 or 2
4	exp Sepsis/
5	(sepsis or septic* or bacter?emia).ti,ab,kw.
6	4 or 5
7	Decision Support Techniques/ or Neonatal Screening/
8	((predict* or diagnos* or screen* or identif* or manag*) adj5 (model* or rule* or scor* or tool* or algorithm* or decision tree* or pathway* or calculator*)).ti,ab,kw.
9	7 or 8
10	3 and 6 and 9

Ovid Embase

1	newborn/
2	(neonat* or newborn* or new born* or baby or babies or premature or preterm or infant* or low birth weight or LBW or VLBW or ELBW or NICU*).ti,ab,kw.
3	1 or 2
4	exp sepsis/
5	(sepsis or septic* or bacter?emia).ti,ab,kw.
6	4 or 5
7	exp decision support system/ or newborn screening/
8	((predict* or diagnos* or screen* or identif* or manag*) adj5 (model* or rule* or scor* or tool* or algorithm* or decision tree* or pathway* or calculator*)).ti,ab,kw.
9	7 or 8
10	3 and 6 and 9

Scopus

TITLE-ABS-KEY((neonat* OR newborn* OR "new born*" OR baby OR babies OR premature OR preterm OR infant* OR "low birth weight" OR lbw OR vlbw OR elbw OR nicu*) AND (sepsis OR septic* OR bacter?emia) AND ((predict* OR diagnos* OR screen* OR identif* or manag*) W/5 (model* OR rule* OR scor* OR tool* OR algorithm* OR "decision tree*" OR pathway* OR calculator*)))

Web of Science

TS=((neonat* OR newborn* OR "new born*" OR baby OR babies OR premature OR preterm OR infant* OR "low birth weight" OR lbw OR vlbw OR elbw OR nicu*) AND (sepsis OR septic* OR bacter$emia) AND ((predict* OR diagnos* OR screen* OR identif* or manag*) NEAR/5 (model* OR rule* OR scor* OR tool* OR algorithm* OR "decision tree*" OR pathway* OR calculator*)))

Globus Index Medicus

((mh:("Infant, Newborn")) OR (tw:(neonat* OR newborn* OR "new born*" OR baby OR babies OR premature OR preterm OR infant* OR "low birth weight" OR lbw OR vlbw OR elbw OR nicu*))) AND ((mh:("Sepsis")) OR (tw:(sepsis OR septic* OR bacter*emia))) AND ((mh:("Decision Support Systems, Clinical" OR "Neonatal Screening")) OR (tw:(model* OR rule* OR scor* OR tool* OR algorithm* OR "decision tree*" OR pathway* OR calculator*)))

Cochrane Library

1	MeSH descriptor: [Infant, Newborn] explode all trees
2	(neonat* or newborn* or "new born*" or baby or babies or premature or preterm or infant* or "low birth weight" or LBW or VLBW or ELBW or NICU*):ti,ab,kw
3	#1 or #2
4	MeSH descriptor: [Sepsis] explode all trees
5	(sepsis or septic* or bacter*emia):ti,ab,kw
6	#4 or #5
7	MeSH descriptor: [Decision Support Systems, Clinical] explode all trees
8	MeSH descriptor: [Neonatal Screening] explode all trees
9	((predict* or diagnos* or screen* or identif* or manag* or estimat*) NEAR/5 (model* or rule* or scor* or tool* or algorithm* or "decision tree*" or pathway* or calculator*)):ti,ab,kw
10	#7 or #8 or #9
11	#3 and #6 and #10

2. DRAFT DATA EXTRACTION FORM

Study Details and Characteristics		
Study ID (Author, year)		
Source of data (e.g. RCT)		
Country		
Context (e.g. NICU)		
Participants	Number	
	Characteristics	
Objectives		
Study Results		
Name of prediction model		
Type of model		
Outcome definition		
Predictors used	Symptoms and signs	
	Risk factors	
	Laboratory tests	
Underlying evidence	Model performance (e.g. specificity and sensitivity)	
	Acceptability	
	Mortality	
	Antibiotic prescriptions	
	Other evidence	

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ABSTRACT

Introduction: Neonatal sepsis is responsible for significant morbidity and mortality worldwide. Diagnosis is often difficult due to non-specific clinical features and unavailability of laboratory tests in many low and middle-income countries. Clinical prediction models have the potential to improve diagnostic accuracy and rationalise antibiotic usage in neonatal units, which may result in reduced antimicrobial resistance and improved neonatal outcomes. In this paper, we outline our scoping review protocol to map the literature concerning clinical prediction models to diagnose neonatal sepsis. We aim to provide an overview of existing models and evidence underlying their use and compare prediction models between high-income and low and middle-income countries.

Methods and analysis: The protocol was developed with reference to recommendations by the Joanna Briggs Institute. Searches will include six electronic databases (Ovid MEDLINE, Ovid Embase, Scopus, Web of Science, Global Index Medicus, and the Cochrane Library) supplemented by hand searching of reference lists and citation analysis on included studies. No time period restrictions will be applied but only studies published in English or Spanish will be included. Screening and data extraction will be performed independently by two reviewers, with a third reviewer used to resolve conflicts. The results will be reported by narrative synthesis in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines.

Ethics and dissemination: The nature of the scoping review methodology means that this study does not require ethical approval. Results will be disseminated through a peer-reviewed publication and conference presentations, as well as through engagement with peers and relevant stakeholders.

ARTICLE SUMMARY

Strengths and limitations of this study

- There have been few recent attempts to scope literature concerning clinical prediction models to diagnose neonatal sepsis across high-income and low and middle-income countries.
- The protocol was developed with reference to recommendations by the Joanna Briggs Institute and the review will be reported in line with the PRISMA-ScR guidelines.
- The search strategy includes six electronic databases, hand searching of reference lists and citation analysis on included studies.
- A limitation of the review is that we will only include non-grey literature published in English or Spanish and it is possible that studies relevant to non-English or non-Spanish speaking settings will not be included.

INTRODUCTION

Despite significant progress in global child health over the past two decades, there were 2.5 million neonatal deaths in 2018 with a global neonatal mortality rate of 18 deaths per 1,000 live births.[1] The vast majority of these deaths occur in low and middle-income countries and are most commonly due to prematurity (35%), intrapartum-related complications (24%) and neonatal sepsis (15%).[1] Neonatal sepsis has an estimated global incidence of 2,202 per 100,000 live births and a global case fatality rate of between 11-19%.[2] Moreover, it is a significant source of morbidity for survivors: complications including neurodevelopmental disorders, cerebral palsy and visual or hearing impairment may persist beyond the neonatal period.[3] Therefore, addressing neonatal sepsis as a preventable and treatable cause of neonatal morbidity and mortality is a global priority.

Neonatal sepsis is a clinical syndrome that results from systemic infection in the first month of life.[4] It is typically classified as early-onset sepsis (EOS, onset within the first 48-72 hours of life) or late-onset sepsis (LOS, onset after the first 48-72 hours of life) to reflect the differing microbiology of these two disease patterns.[5] EOS results from vertically-transmitted infection with pathogens obtained from the maternal genital tract shortly before or during birth.[6] Group B streptococcus (GBS) and *Escherichia coli* account for the majority of cases of EOS in high income settings, and risk factors for these infections include prematurity, low birth weight, prolonged rupture of membranes, maternal fever during labour and maternal rectovaginal colonisation with GBS.[6] In comparison, LOS occurs due to pathogens acquired through interaction with the home or hospital environment.[7] Coagulase-negative staphylococci (CONS) are the commonest organisms of LOS and other major pathogens include *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Pseudomonas* species, and fungal infection with *Candida* species.[7] It should be noted, however, that the exact microbiology of neonatal sepsis differs greatly across geographical regions and is liable to change over time.[8] Furthermore, the microbiology is difficult to determine in settings with limited or no access to reliable culture methods. There is increasing recognition that classification of neonatal sepsis as EOS or LOS is misplaced in low and middle-income countries (LMICs). In these settings, babies are exposed from birth to organisms typically associated with LOS due to poor infection prevention and control practices such as hand hygiene, aseptic delivery and limited availability of GBS screening services in pregnancy.[9] In a systematic review of data from sub-Saharan Africa, *Staphylococcus aureus* (25%) and *Klebsiella* species (21%) were the most common causative organisms of neonatal sepsis.[10] Thus, in LMICs, it may be sensible to label all infections in facility-born neonates as hospital acquired, even if the infection presents within the first few days of life.[9]

Diagnosis of neonatal sepsis is hindered by non-specific clinical features such as temperature instability, lethargy, poor feeding and respiratory distress, which often overlap with non-infectious diseases. The current gold standard method for diagnosing neonatal sepsis is identification of a pathogenic organism from a normally sterile site (e.g. blood or cerebrospinal fluid).[5] However, *clinical sepsis* (where the infant shows clinical features of sepsis despite negative blood cultures) is a recognised entity and may be more common than blood-culture proven sepsis, especially in the context of previous antibiotic exposure in the baby or mother.[11] When deciding to treat suspected cases of neonatal sepsis, there is a fine balance between failing to treat a serious infection and unnecessary use of antibiotics. Antimicrobial resistance is a growing global concern, with one estimate suggesting that 31% of annual sepsis-related neonatal deaths globally could be attributable to

antimicrobial resistance.[12] Furthermore, some reports have suggested that prolonged exposure to antibiotics is associated with negative neonatal outcomes such as death and necrotising enterocolitis.[13] Therefore, accurately identifying infants with neonatal sepsis is vital to guide optimal use of antibiotics, reduce antimicrobial resistance and improve neonatal outcomes.

Study rationale

Clinical prediction models are tools that combine multiple characteristics (or predictors) to estimate the probability of a diagnosis or prognostic outcome and they have gained increasing research attention in recent years.[14] Multiple prediction models exist to estimate the risk of neonatal sepsis based on a wide range of clinical features, risk factors and/or laboratory tests, for example the Kaiser Permanente neonatal sepsis risk calculator for EOS.[15] Clinical prediction models for neonatal sepsis have the potential to improve diagnostic accuracy and rationalise antibiotic usage in neonatal units. Models that do not include laboratory results as predictors are of particular importance in LMICs where basic laboratory tests are often unavailable and the initial care and clinical management of newborn infants may fall to lower cadre healthcare workers in remote settings with limited senior support. Some models used in LMICs have high sensitivity but low specificity for neonatal sepsis and result in overuse of antibiotics.[16]

A search to identify existing scoping reviews or systemic reviews of clinical prediction models to diagnose neonatal sepsis yielded three potentially relevant studies. Two reviews examined clinical prediction models for severe infections in children, however both excluded those targeting neonates.[17, 18] One review examined clinical prediction models for healthcare-associated bloodstream infections in neonates, but they excluded models developed for EOS and the searches are now relatively outdated in this rapidly evolving field.[19] Therefore, the present review will provide an important summary of existing clinical prediction models to diagnose neonatal sepsis to form a basis for future primary research or systematic reviews.

Study objectives

The aim of this scoping review is to map the literature concerning clinical prediction models to diagnose neonatal sepsis in high-income countries (HICs) and LMICs.

The specific objectives are:

- To provide an overview of existing clinical prediction models to diagnose neonatal sepsis.
- To determine the evidence underlying the use of clinical prediction models to diagnose neonatal sepsis.
- To compare clinical prediction models to diagnose neonatal sepsis between HICs and LMICs.
- To identify unanswered research questions surrounding clinical prediction models to diagnose neonatal sepsis, which may guide future primary research or systematic reviews.

METHODS AND ANALYSIS

The methods for this review were developed with reference to the scoping review guidelines provided by the Joanna Briggs Institute.[20] The major components of the review process are detailed in turn below.

Research question

Our review will be guided by the following specific research questions (Table 1).

Table 1. Research questions

1. What clinical prediction models exist to diagnose neonatal sepsis?	
2. What modelling methods are used to derive these models?	
3. What predictors are used in these models?	• Symptoms and signs • Risk factors • Laboratory tests
4. What is the evidence underlying the use of these models?	• Type of studies • Diagnostic accuracy • Success of implementation • Clinical efficacy
5. How do these models differ between HICs and LMICs?	• Number that exist • Predictors used • Evidence supporting use
6. What questions remain unanswered regarding clinical prediction models to diagnose neonatal sepsis?	

Inclusion criteria

The inclusion criteria (Table 2) were formulated according to the 'Population-Concept-Context (PCC)' framework recommended by the Joanna Briggs Institute.[20] As a scoping review is an iterative process, these may be amended as the review progresses and the extent of the literature becomes apparent.

Table 2. Inclusion criteria	
Population	• Human neonates (aged <28 days of life or hospitalised to a neonatal unit) being evaluated for neonatal sepsis (as defined by the individual studies). • Studies examining a range of patient ages will be included, providing sufficient data are available to examine findings for neonates in isolation.

Concept	• Studies that develop, validate or assess the impact of a clinical prediction model to diagnose neonatal sepsis.
	• Studies that report any of:
	  ○ modelling methods (including participants, predictors, outcomes and type of model);
	  ○ model performance (including sensitivity and specificity); or
	  ○ success of implementation (including acceptability and any changes to practice or outcomes).
	• Only internally and/or externally validated models will be included.
	• Management algorithms, decision rules or prediction models based on expert opinion will not be included, unless validated in a subsequent study.
	• Studies evaluating prognostic models (e.g. to predict neonatal sepsis-related mortality or morbidity) will be excluded.

Context	• Studies from any country. • Studies from any healthcare setting (including neonatal unit, emergency department, outpatient or community setting).
Types of studies	• Randomised and quasi-randomised controlled trials, cohort studies, cross-sectional studies, case-control studies and guidelines. • Letters, comments and conference proceedings will be included if sufficient details are provided. • Studies published in English or Spanish. • Systematic reviews, meta-analyses and editorials will be excluded, but will be used to identify relevant primary literature.

Search strategy

The following databases will be searched: Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; Ovid Embase; Scopus; Web of Science; Global Index Medicus; and the Cochrane Library. Search terms were constructed to capture variations of “neonate”, “sepsis” and “prediction model” by examining the common text words and index terms of known relevant literature. These keywords were further expanded by including relevant potential synonyms. The search strategy for Ovid MEDLINE is detailed in Table 3 and a complete list of search strategies for each database can be found in the supplementary appendix. It is anticipated that additional keywords and index terms may be identified as the review progresses, and these will be incorporated into the

search strategy and the searches will be rerun as applicable. To identify additional studies not found through the primary database searches, citation analysis will be performed on included studies using the citation analysis function of Scopus, Web of Science and Google Scholar. Furthermore, the reference list of included studies will be hand searched. No time period or language restrictions will be applied to the search strategy, but studies will be manually limited to the English or Spanish language at the study selection stage to reflect the languages spoken by the review team. Searches will be updated prior to publication of our findings to ensure no recent studies are missed.

Table 3. Search strategy for Ovid MEDLINE

1	exp Infant, Newborn/
2	(neonat* or newborn* or new born* or baby or babies or premature or preterm or infant* or low birth weight or LBW or VLBW or ELBW or NICU*).ti,ab,kw.
3	1 or 2
4	exp Sepsis/
5	(sepsis or septic* or bacter?emia).ti,ab,kw.
6	4 or 5
7	Decision Support Techniques/ or Neonatal Screening/
8	((predict* or diagnos* or screen* or identif* or manag*) adj5 (model* or rule* or scor* or tool* or algorithm* or decision tree* or pathway* or calculator*)).ti,ab,kw.
9	7 or 8
10	3 and 6 and 9

Evidence selection

All identified records will be imported into EndNote X9 (Clarivate Analytics, 2018) for bibliographic management and deduplication. First, titles and abstracts will be examined against the inclusion criteria (Table 2) to determine whether the study is potentially eligible for inclusion. Next, full texts of potentially eligible studies will be obtained and examined to confirm their eligibility. Relevant authors will be contacted to request full texts, if required. Record screening will be performed independently by two reviewers using the Rayyan web and mobile application.[21] Studies in Spanish will be translated to English by MCB and then considered for inclusion. Conflicts will be resolved by a third reviewer and discussion amongst the review team. The first database searches were performed in December 2019 (identifying 2,776 records after deduplication) and title and abstract screening is currently ongoing.

Data extraction

Data extraction will be performed independently by two reviewers. A draft data extraction form has been designed for this review and is shown in the supplementary appendix. This form was adapted from a template provided by the Joanna Briggs Institute[20] and will be further refined as the review progresses. Data to be extracted are based on the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement[22] and include study author(s), year of publication and name of the prediction model described; sources of data, number and

characteristics of study participants; type of model, predictors used and defined outcome; and model performance or other evidence regarding the use of the model in clinical practice.

Analysis of the evidence and presentation of the results

The results of this review will be reported by narrative synthesis in line with the recommendations set out in the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).[23] The characteristics of several subgroups of clinical prediction models will be compared, including:

- Those that were developed and validated for use in HICs versus LMICs, as defined by the World Bank classification.[24]
- Those for diagnosing specific subgroups of neonatal sepsis (e.g. EOS versus LOS).
- Those based solely on clinical predictors versus those that require laboratory tests.
- Those that specifically consider the management of neonates born to mothers with chorioamnionitis.
- Those using different outcome definitions for neonatal sepsis (such as those defining sepsis as a positive blood culture versus those that also include 'clinical sepsis').

Data for quantitative outcomes such as model performance or measures of changes to clinical outcomes will not be pooled in a meta-analysis but, rather, general trends will be discussed. Furthermore, explicit risk of bias assessment will not be performed, as our aim is to report the extent of the current literature. It is hoped that this review can then act as a basis to determine important research questions for future primary research and systematic reviews or meta-analyses.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

ETHICS AND DISSEMINATION

Since the scoping review methodology involves reviewing and collecting data from publicly available sources, this study does not require ethical approval. The results of this review will be disseminated through a peer-reviewed publication and/or conference presentation. Furthermore, we will engage with the stakeholders of our local and international projects to widen the dissemination of our findings. By identifying gaps in the literature, we hope that this review can form a basis for future primary research and systematic reviews or meta-analyses.

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AUTHORS' CONTRIBUTIONS

FF and MH conceived the idea for this review. SRN developed the research question, study methods and drafted the manuscript. FF, MH, GC and MCB supervised the protocol design and continue to supervise the review process. SRN, DM and HG piloted the protocol and continue to screen records for inclusion. All authors discussed the protocol design and critically edited and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable for this study design.

Supplementary appendix

CONTENTS

1. SEARCH STRATEGIES FOR EACH DATABASE

Ovid MEDLINE

1	exp Infant, Newborn/
2	(neonat* or newborn* or new born* or baby or babies or premature or preterm or infant* or low birth weight or LBW or VLBW or ELBW or NICU*).ti,ab,kw.
3	1 or 2
4	exp Sepsis/
5	(sepsis or septic* or bacter?emia).ti,ab,kw.
6	4 or 5
7	Decision Support Techniques/ or Neonatal Screening/
8	((predict* or diagnos* or screen* or identif* or manag*) adj5 (model* or rule* or scor* or tool* or algorithm* or decision tree* or pathway* or calculator*)).ti,ab,kw.
9	7 or 8
10	3 and 6 and 9

Ovid Embase

1	newborn/
2	(neonat* or newborn* or new born* or baby or babies or premature or preterm or infant* or low birth weight or LBW or VLBW or ELBW or NICU*).ti,ab,kw.
3	1 or 2
4	exp sepsis/
5	(sepsis or septic* or bacter?emia).ti,ab,kw.
6	4 or 5
7	exp decision support system/ or newborn screening/
8	((predict* or diagnos* or screen* or identif* or manag*) adj5 (model* or rule* or scor* or tool* or algorithm* or decision tree* or pathway* or calculator*)).ti,ab,kw.
9	7 or 8
10	3 and 6 and 9

Scopus

TITLE-ABS-KEY((neonat* OR newborn* OR "new born*" OR baby OR babies OR premature OR preterm OR infant* OR "low birth weight" OR lbw OR vlbw OR elbw OR nicu*) AND (sepsis OR septic* OR bacter?emia) AND ((predict* OR diagnos* OR screen* OR identif* or manag*) W/5 (model* OR rule* OR scor* OR tool* OR algorithm* OR "decision tree*" OR pathway* OR calculator*)))

Web of Science

TS=((neonat* OR newborn* OR "new born*" OR baby OR babies OR premature OR preterm OR infant* OR "low birth weight" OR lbw OR vlbw OR elbw OR nicu*) AND (sepsis OR septic* OR bacter$emia) AND ((predict* OR diagnos* OR screen* OR identif* or manag*) NEAR/5 (model* OR rule* OR scor* OR tool* OR algorithm* OR "decision tree*" OR pathway* OR calculator*)))

Globus Index Medicus

((mh:("Infant, Newborn")) OR (tw:(neonat* OR newborn* OR "new born*" OR baby OR babies OR premature OR preterm OR infant* OR "low birth weight" OR lbw OR vlbw OR elbw OR nicu*))) AND ((mh:("Sepsis")) OR (tw:(sepsis OR septic* OR bacter*emia))) AND ((mh:("Decision Support Systems, Clinical" OR "Neonatal Screening")) OR (tw:(model* OR rule* OR scor* OR tool* OR algorithm* OR "decision tree*" OR pathway* OR calculator*)))

Cochrane Library

1	MeSH descriptor: [Infant, Newborn] explode all trees
2	(neonat* or newborn* or "new born*" or baby or babies or premature or preterm or infant* or "low birth weight" or LBW or VLBW or ELBW or NICU*):ti,ab,kw
3	#1 or #2
4	MeSH descriptor: [Sepsis] explode all trees
5	(sepsis or septic* or bacter*emia):ti,ab,kw
6	#4 or #5
7	MeSH descriptor: [Decision Support Systems, Clinical] explode all trees
8	MeSH descriptor: [Neonatal Screening] explode all trees
9	((predict* or diagnos* or screen* or identif* or manag* or estimat*) NEAR/5 (model* or rule* or scor* or tool* or algorithm* or "decision tree*" or pathway* or calculator*)):ti,ab,kw
10	#7 or #8 or #9
11	#3 and #6 and #10

2. DRAFT DATA EXTRACTION FORM

Study Details and Characteristics		
Study ID (Author, year)		
Source of data (e.g. RCT)		
Country		
Context (e.g. NICU)		
Participants	Number	
	Characteristics	
Objectives		
Study Results		
Name of prediction model		
Type of model		
Outcome definition		
Predictors used	Symptoms and signs	
	Risk factors	
	Laboratory tests	
Underlying evidence	Model performance (e.g. specificity and sensitivity)	
	Acceptability	
	Mortality	
	Antibiotic prescriptions	
	Other evidence	