BMJ Open

Predicting late-onset sepsis by routine neonatal screening for colonization by gram-negative bacteria in neonates at intensive care units: protocol for a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014986
Article Type:	Protocol
Date Submitted by the Author:	03-Nov-2016
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	Systematic review, Protocol, Prognostic accuracy, neonatal sepsis, screening

Protocol

Predicting late-onset sepsis by routine neonatal screening for colonization by gram-negative bacteria in neonates at intensive care units: protocol for a systematic review

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ABSTRACT

Introduction: Hospitals conduct extensive screening procedures to assess colonization of the body surface of neonates by gram-negative bacteria to avoid complications like sepsis. However, the benefits of these procedures are controversially discussed. So far, no systematic review investigated the value of routine screening for colonization by gram-negative bacteria in neonates for sepsis prediction.

Methods and analysis: We will conduct a systematic review, considering studies of any design that include infants up to an age of 12 months. We will search MEDLINE and EMBASE (inception to 2016), check reference lists and search grey literature. Screening of titles, abstracts and full-texts will be conducted by two independent reviewers. We will extract data on study characteristics and study results. Risk of bias will be assessed using QUADAS-2 and QUIPS. Subgroup analyses are planned according to characteristics of studies, participants, index tests and outcome. For quantitative data synthesis on prognostic accuracy, sensitivity and specificity of screening to detect sepsis will be calculated. If sufficient data are available, we will calculate summary estimates using hierarchical summary receiver operating characteristics and bivariate models. Applying a risk factor approach, pooled summary estimates will be calculated as relative risk or odds ratio, using fixed-effects and random-effects models. I-squared will be used to assess heterogeneity. All calculations will be performed in Stata 14.1 (College Station, Texas, USA). The results will be used to calculate positive and negative predictive value and number needed to screen to prevent one case of sepsis. GRADE will be used to assess certainty in the evidence. The protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline.

Ethics and dissemination: This study will not require ethical approval since it is not carried out in humans. The systematic review will be published in an open-access peer-reviewed journal.

Prospero registration number: 42016036664

Strengths and limitations of this study

- This systematic review will provide a comprehensive overview on the available evidence regarding the value of routine screening for colonization by gram-negative bacteria in neonates for sepsis prediction.
- Subgroup analysis will allow investigating the particular role of setting, birth characteristics, sampling strategy and co-interventions for test performance and predictive values.
- Limitations of the systematic review will arise from the limitations of the included studies, particularly regarding consideration and reporting of confounders in the publications.

INTRODUCTION

Epidemiological and clinical background

At neonatal intensive care units (NICUs), sepsis due to gram-negative pathogens is an important cause of neonatal morbidity and mortality.[1] The majority of sepsis episodes (> 80%) occurs in preterm neonates. [2] Depending on individual factors, setting and species of bacteria, between 11 and 46% of very low birthweight infants (VLBW; < 1,500g) are affected.[3] Susceptibility to infection is strongly associated with low gestational age and low birth weight.[4 5]

Already in the 1970s, data were published indicating that infants at NICUs colonized with gram-negative bacteria are at increased risk of developing infections subsequently.[6] Consecutively, a number of studies investigated the value of routine surface cultures for the prediction of sepsis.[7-10] Today, hospitals conduct extensive and costly screening procedures to assess the colonization of non-sterile locations of the body surface of neonates by gram-negative bacteria to avoid complications like sepsis. However, the benefits of these screening procedures are controversially discussed. Moreover, since microbiological screening is often introduced as part of a bundle of measures (e.g., isolation, enhanced barrier nursing), it is often challenging to measure the particular effect of screening. So far, no systematic review has been published which investigated the prognostic value of routine screening for colonization by gram-negative bacteria in this at-risk group for the prediction of sepsis. Here, we present and explain the protocol for a respective systematic review that will be conducted as part of the piloting phase of the Project on a Framework for Rating Evidence in Public Health (PRECEPT).[11]

Prognostic/diagnostic test accuracy and risk factors

According to the *Cochrane handbook for systematic reviews of diagnostic test accuracy studies*, prognostic accuracy studies use test information to identify patients that will develop the outcome later on(see http://methods.cochrane.org/sdt/handbook-dta-reviews). In this sense, studies that use

screening for gramnegative bacteria to predict sepsis are prognostic accuracy studies. In such studies, the result of a test is compared to the (clinical) outcome. This differs from the approach of diagnostic test accuracy studies where the test result is compared to the result of a reference or "gold standard" test (**Fig. 1, Tab. 1**). Therefore, prognostic accuracy is not a surrogate for patient-important outcomes, as in diagnostic test accuracy studies.[12] This approach has consequences for the design of the studies to be considered. In contrast to diagnostic test accuracy studies where cross-sectional study designs are common practice, cohort studies (prospective or retrospective) are needed to obtain measures of prognostic accuracy.

A complementary approach to the analysis of the same data is to conceptualize a positive screening test as the presence of a risk (or prognostic) factor and to calculate a measure of relative risk of developing the outcome. However, it is important to consider that the presence of a high risk ratio (or odds ratio) which is often used to identify prognostic factors for a certain outcome does not indicate that the respective risk factor performs well in predicting this outcome.[13-15] As an example, Ware showed that a risk factor strongly associated with a hypothetical outcome (odds ratio 3.58) might have a sensitivity as low as 13% for predicting this outcome. Using the same data, he demonstrated that an odds ratio of 228 would be needed to reach a sensitivity of 80%.[15] Therefore, it may not be concluded that a risk factor which is strongly associated with the outcome provides a basis for an effective preventive measure.

Concepts for systematic reviews of prognostic studies

Various approaches exist regarding the systematic assessment and data synthesis of prognostic studies.[16] During recent years, it has become more and more accepted that systematic reviews in this field should not only focus on measures of association between the predictive/prognostic factor and the outcome, such as risk ratio, odds ratio or hazard ratio, but should comprise measures of prognostic accuracy like sensitivity and specificity (for example, see [17]). Liu et al. (2013)[18] proposed to

distinguish between systematic reviews of screening tests and those of diagnostic and prognostic studies. For screening and diagnosis, they suggested to assess sensitivity and specificity, whereas for questions related to prognosis the use of hazard ratios was proposed. The Agency for Health Care Research and Quality (AHRQ) suggests to use a particular framework for systematic reviews of prognostic test.[19] In that paper, Rector et al. conclude that it may be informative to assess the accuracy of a prognostic test by calculating sensitivity, specificity and predictive values. However, these authors emphasize that it is critical to consider the time interval between the test and the occurrence of the outcome.[19] In our own systematic review, we will compute both measures of prognostic accuracy and measures of relative risk and compare the results of these calculations to each other.

Risk of bias

Given the particularities of systematic reviews of prognostic accuracy studies, the question arises whether an established risk-of-bias tool exists that captures common sources of bias in this study design. A number of authors applied tools that were originally designed to address risk of bias in diagnostic test accuracy studies.[17 20 21] Currently, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool is the most advanced and widely used tool for the assessment of risk of bias in diagnostic accuracy studies.[22] QUADAS-2 comprises four domains: patient selection, index test, references standard and flow and timing. In each domain, questions related to risk of bias and concerns regarding applicability have to be answered.

However, as explained above, there are apparent differences in study design between diagnostic and prognostic accuracy studies. At least two sources of bias can be identified which are important in prognostic accuracy studies but are not relevant in diagnostic accuracy studies:

- *Attrition bias:* Due to the prospective character of the study design, loss-to-follow-up of study participants in the time interval between the conduct of the screening test and the detection of the outcome might create attrition bias. Depending on whether rates of loss-to-

follow-up differ between participants with positive and negative screening test results or not (differential vs non-differential loss-to-follow-up), sensitivity and specificity will change in effect size or confidence interval.

- *Confounding:* Confounding will occur if, , interventions are delivered to study participants depending on the result of the screening test. This may influence the probability of developing the outcome. Again estimates for sensitivity and specificity might be affected.

Theoretically, it is possible that domain four of the QUADAS-2 tool ("flow and timing") sufficiently captures attrition bias as well as confounding in the time interval between screening test and outcome assessment. If this appears not to be the case, we may test whether the additional application of a risk of bias tool for risk factor/prognostic studies such as the Quality in Prognosis Studies (QUIPS) tool[23] is of additional value.

General objective

To assess the usefulness and value of routine screening for colonization by gram-negative bacteria performed in NICUs as predictive measures for sepsis.

Research question

This systematic review will focus on the following primary research questions:

1) What is the prognostic value (in terms of sensitivity and specificity) of routine screening for colonization by gram-negative bacteria in neonates at intensive care units for the prediction of sepsis?
2) Is colonization by gram-negative bacteria in neonates at intensive care units a risk factor for later development of sepsis?

METHODS

This systematic review protocol follows the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline. [24] A copy of the completed PRISMA-P checklist is attached to this protocol (**Appendix 1**). This systematic review is registered in the Prospective Register of Systematic Reviews (Reg. No. 42016036664).

Eligibility criteria

Study designs

Studies of any design will be considered. No restrictions will be made regarding publication language or publication status.

Participants

Studies that include infants up to an age of 12 months will be considered, irrespective of gestational age, birth weight and geographical region where the study has been conducted.

Study setting

Studies that were performed in neonatal intensive care units will be considered.

Search strategy

Data base search

We will search MEDLINE and EMBASE from inception to 2016, using the DIMDI (Deutsches Institut für Medizinische Dokumentation und Information) platform. The planned search strategy is shown in **Table 2**.

Reference lists

These searches will be supplemented by "snowballing", i.e. searching for additional studies in the reference lists of identified original studies and reviews.

Grey literature

We will search for grey literature using the Grey Matters Light checklist of the Canadian Agency for Drugs and Technologies in Health (CADTH) (http://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-base-medicine).

Study selection

The study selection process will involve the following steps:

- Screening of titles and abstracts
- Screening of full texts

At both steps, screening will be conducted by two independent reviewers. Potential disagreement will be resolved by discussion or by involving a third reviewer. We will construct a flow chart to document the selection process. A list of excluded studies will be prepared, along with reasons for exclusion.

Data extraction

From the included studies, we will extract data on study characteristics and study results. We will construct a data extraction form and pilot test it prior to the start of the review process. One researcher will perform data extraction while a second researcher will independently check for accuracy and details. The following data will be extracted from the original studies:

- *General study characteristics:*
  - complete reference of the study (author, year of publication, title, journal, citation details)
  - date of study
  - place
  - setting (hospital, department, unit, ward)
  - study design
  - funding source
- *Patient/population characteristics:*
  - inclusion criteria
  - exclusion criteria
  - gestational age at birth
  - birth weight
  - age at screening
  - sex
  - ethnicity
  - length of follow-up (time interval between index test and outcome assessment)
- *Index test characteristics:*
  - description of sampling device
  - sampling time point(s)
  - sampling location(s) (e.g., umbilicus, tracheal, rectal etc)

- sampling intervals (if repetitive)
- processing of specimen
- detected bacteria (species, characterization)

- *Outcome:*
  - definition of sepsis
  - detected bacteria (species, characterisation)
- *(Co)-interventions*
  - antibiotic use
  - isolation
  - hand hygiene
- *Prognostic accuracy measures:*
  - true positives
  - true negatives
  - false positives
  - false negatives
- *Measures of association (risk factor approach):*
  - Unadjusted relative risk (or odds ratio)
  - Adjusted relative risk (or odds ratio)
  - Confounders considered in adjusted analysis

Risk of bias assessment

Following the guidance of the PRECEPT framework, [11 25] we will use the QUADAS-2 tool to assess risk of bias in the included individual studies which report measures of prognostic accuracy. [22] **Table 3** shows the main components of the tool. The results of the risk of bias assessment will be documented in a separate table for each study along the items of QUADAS-2. For studies reporting on prognostic measures in terms of a risk factor (or prognostic study), we will use the QUIPS tool.[23]

We will construct bar charts as suggested by Van't Hooft et al.[21] for reporting summary results of the risk of bias assessments.

Subgroup analyses

We will extract detailed information on study participants, definitions and settings to enable stratified analysis. In particular, we aim at stratifying the results of the systematic review and meta-analysis, respectively, according to the following variables:

- *General study characteristics:*
  - geographic region (Europe vs North America etc.)
  - developed country vs developing country
  - study period (<1970, 1971-1980, 1981-1990, 1991-2000, 2001-2010, >2010)
- *Patient/population characteristics:*
  - gestational age (<37 weeks vs ≥ 37 weeks)
  - birth weight (<2500g vs <1500g vs ≥ 2500g)
  - length of follow-up (time interval between index test and outcome assessment)
- *Index test characteristics:*
  - sampling time point(s)
  - sampling location(s) (umbilicus vs tracheal etc.)
- *Outcome characteristics:*
  - different definitions of sepsis
- *Study setting*
  - clinical routine
  - study
  - outbreak investigation

Statistical analysis

Prognostic accuracy approach: For quantitative data synthesis on prognostic accuracy, we will construct 2x2 tables to calculate sensitivity and specificity for each included study. If sufficient comparable data from more than one study are available, we will perform meta-analysis. To account for the correlation between sensitivity and specificity, we will calculate summary estimates using hierarchical summary receiver operating characteristics models[26] as well as bivariate models.[27] Results will be displayed graphically using SROC plots. We will investigate sources of heterogeneity, using subgroup analysis.

Risk factor approach: For quantitative data synthesis using the risk factor approach, pooled summary estimates will be calculated as relative risk or odds ratio with 95% confidence intervals, using fixed-effects and random-effects models. I-squared will be used to assess heterogeneity. If >=10 studies per outcome are available, publication bias will be assessed by inspection of funnel plots and applying Begg's and Egger's test.

All calculations will be performed in STATA. The results of the meta-analysis will be used to calculate positive predictive value, negative predictive value and number needed to screen to prevent one case of sepsis.

Certainty in the evidence (GRADE)

We will use two complementary approaches to assess the certainty in the evidence (formerly: quality of the evidence) according to the methodology suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.

Prognostic accuracy approach: We will adopt the GRADE approach to diagnostic accuracy test reviews for the purpose of our systematic review on prognostic test accuracy. The certainty in the evidence will be assessed for true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN), as suggested by GRADE.[12] In brief, the application of GRADE will be conducted as follows:

- For each body of evidence on diagnostic studies, all studies start as "high". "True positives", "true negatives", "false positives" and "false negatives" are defined as outcomes.
- Risk of bias is assessed by the QUADAS-2 tool, and evidence quality can be downgraded, if necessary.
- Thereafter, the other GRADE criteria for downgrading quality of evidence (inconsistency, indirectness, imprecision, publication bias) are applied, according to the approach published by the GRADE working group.[12]

Risk factor approach: We will use the GRADE approach to risk factor/prognostic factor studies. The certainty in the evidence will be assessed for the outcome sepsis according to the GRADE methodology [28] as follows:

- For each body of evidence, certainty in the evidence is initially rated as "high", irrespective of study design.
- Risk of bias is assessed by the appropriate risk of bias tool, and evidence certainty can be downgraded, if necessary.
- Thereafter, the other GRADE criteria for downgrading quality of evidence (inconsistency, indirectness, imprecision, publication bias) are applied.
- Upgrading of the quality of evidence is possible, according to the criteria introduced by GRADE.

Reporting of this review

The systematic review will be reported according to the PRISMA guidelines. The PRISMA checklist will be published with the report.

Ethical considerations and dissemination of findings

This study will not require ethical approval since it is not carried out in humans. The resulting systematic review will be published in a peer-reviewed journal as an open-access paper.

Acknowledgements

This systematic review will be performed as part of the piloting phase of the PRECEPT project. PRECEPT is funded by the European Centre for Disease Prevention and Control (ECDC; tenders no. 2012/040; 2014/008). The funder had no role in developing and writing of this protocol.

Contributors

TH, JS and SH developed the concept of this protocol. TH wrote the first draft. JS, BW, TE and SH provided important intellectual input to revise the draft protocol. All authors approved the final manuscript as submitted. TH is the guarantor of this protocol.

Competing interests

None declared.

Tab. 1: Calculation of test results for diagnostic test accuracy vs. prognostic accuracy

	Diagnostic test		Prognostic test	
	Reference test +	**Reference test -**	**Future outcome +**	**Future outcome -**
Test +	TP	FP	TP	FP
Test -	FN	TN	FN	TN

TP, true positives; FP, false positives; FN, false negatives; TN, true negatives

Table 2: Search strategy of the systematic review

#1 neonat*
#2 newborn*
#3 infant*
#4 colonization
#5 “mucosal site*”
#6 “mucosal sample*”
#7 “mucosal culture*”
#8 “superficial culture*”
#9 “surveillance culture*”
#10 aspirate
#11 “predictive value”
#12 sensitivity
#13 specificity
#14 sepsis
#15 “body fluid*”
#16 “systemic inflammatory response syndrome”
#17 “routine culture”
#18 “skin culture”
#19 “surface culture”
#20 “bacterial colonization”
#21 “microbiological screening”
#22 swab*
#23 #1 OR #2 OR #3
#24 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#25#14 OR #15 OR #16
#26 #23 AND #24 AND #25

Table 3: Structure of the QUADAS-2 tool [22]

Domain	Risk of bias		Concerns regarding applicability	
1. Patient selection	Was a consecutive or random sample of patients enrolled?	Yes/no/unclear	**Is there concern that the included patients do not match the review question?**	**CONCERN: LOW/HIGH/UNCLEAR**
	Was a case-control design avoided?	Yes/no/unclear		
	Did the study avoid inappropriate exclusions?	Yes/no/unclear		
	Could the selection of patients have introduced bias?	**Risk: LOW/HIGH/UNCLEAR**		
2. Index test(s)	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes/no/unclear	**Is there concern that the index test, its conduct, or interpretation differ from the review question?**	**CONCERN: LOW/HIGH/UNCLEAR**
	If a threshold was used, was it pre-specified?	Yes/no/unclear		
	Could the conduct or interpretation of the index test results have introduced bias?	**Risk: LOW/HIGH/UNCLEAR**		
3. Reference standard	Is the reference standard likely to correctly classify the target condition?	Yes/no/unclear	**Is there concern that the target condition as defined by the reference standard does not match the review question?**	**CONCERN: LOW/HIGH/UNCLEAR**
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/no/unclear		
	Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk: LOW/HIGH/UNCLEAR**		
4. Flow and timing	Was there an appropriate interval between index test and reference standard?	Yes/no/unclear		
	Did all patients receive a reference standard?	Yes/no/unclear		
	Did patients receive the same reference standard?	Yes/no/unclear		
	Were all patients included in the analysis?	Yes/no/unclear		
	Could the patient flow have introduced bias?	**Risk: LOW/HIGH/UNCLEAR**		

Figures

Figure 1: Diagnostic vs prognostic test accuracy

Appendix

Appendix 1: PRISMA-P checklist (see separate file)

References

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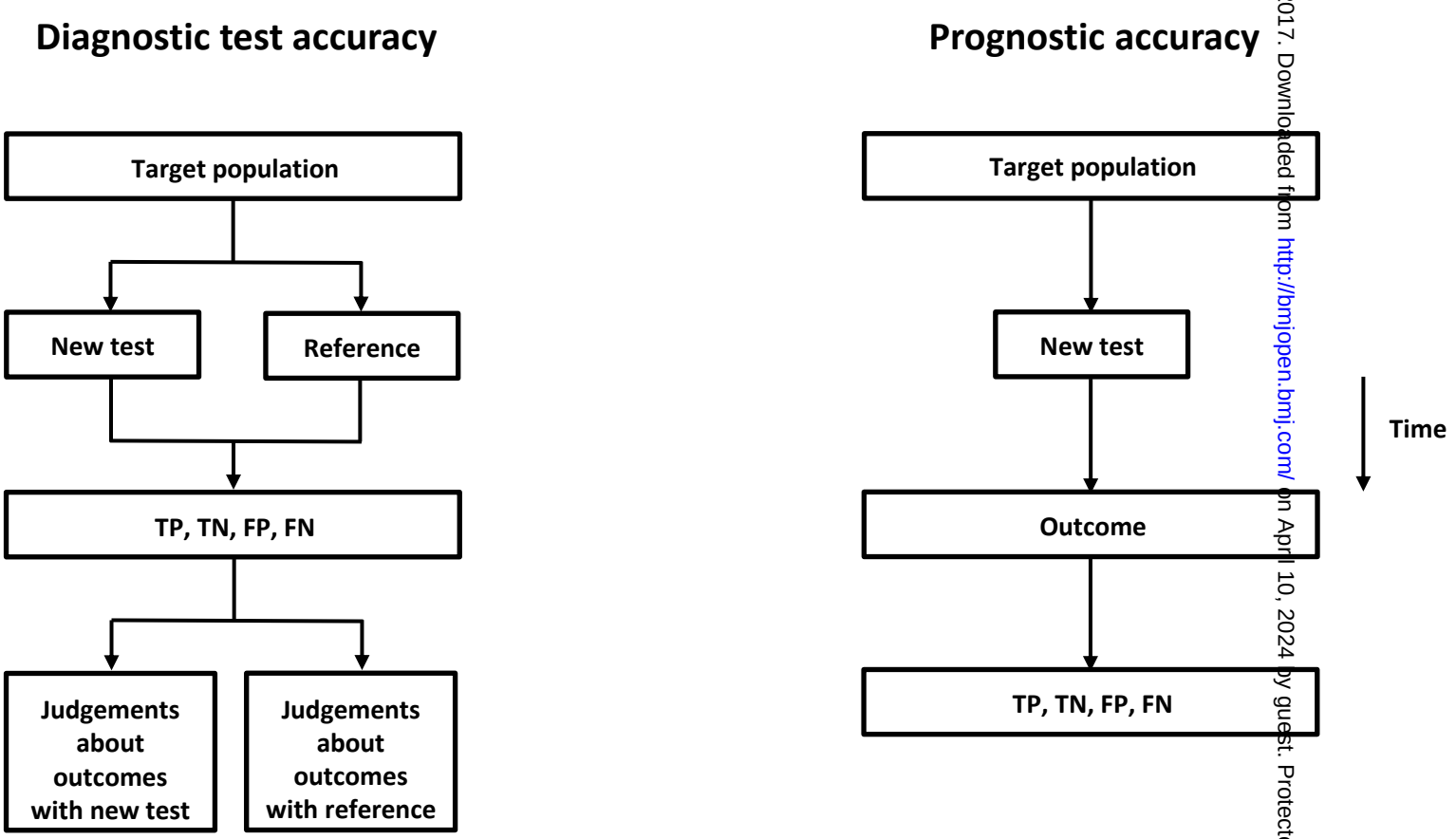

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Page 8, lines 1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 8, line 4
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	Page 15, lines 15-17
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	Not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 15, lines 11-12
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 15, lines 11-12
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 15, lines 12-13
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page 4, line 1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
					– page 7, line 12
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 7, lines 14-16
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 8, line 6 – line 16
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 9, line 1 – line 12
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Table 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 9, line 18 - 21
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 9, line 18 - 21
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 10, line 1-5
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 10, line 6 – page 11, line 19
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	Page 11, line 5-6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	page 11, line 21 – page 12, line 2
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 13, line

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
					4-5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	Page 13, line 1-16
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 12, line 4-24
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☐	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 13, line 11-13
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	Page 13, line 18-page 14 (end)

BMJ Open

Predicting late-onset sepsis by routine neonatal screening for colonization by gram-negative bacteria in neonates at intensive care units: protocol for a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014986.R1
Article Type:	Protocol
Date Submitted by the Author:	31-Jan-2017
Complete List of Authors:	Harder, Thomas; Robert Koch Institut, Infectious Disease Epidemiology Seidel, Juliane; Robert Koch Institut, Infectious Disease Epidemiology Eckmanns, Tim; Robert Koch Institute, Department for Infectious Disease Epidemiology Berlin, Germany Weiss, Bettina; Robert Koch Institut, Infectious Disease Epidemiology Haller, Sebastian; Robert Koch Institute, Infectious Diseases Epidemiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	Systematic review, Protocol, Prognostic accuracy, neonatal sepsis, screening

Protocol

Predicting late-onset sepsis by routine neonatal screening for colonization by gram-negative bacteria in neonates at intensive care units: protocol for a systematic review

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ABSTRACT

Introduction: Hospitals conduct extensive screening procedures to assess colonization of the body surface of neonates by gram-negative bacteria to avoid complications like late-onset sepsis. However, the benefits of these procedures are controversially discussed. So far, no systematic review investigated the value of routine screening for colonization by gram-negative bacteria in neonates for late-onset sepsis prediction.

Methods and analysis: We will conduct a systematic review, considering studies of any design that include infants up to an age of 12 months. We will search MEDLINE and EMBASE (inception to 2016), reference lists and grey literature. Screening of titles, abstracts and full-texts will be conducted by two independent reviewers. We will extract data on study characteristics and study results. Risk of bias will be assessed using QUADAS-2 and QUIPS. Subgroup analyses are planned according to characteristics of studies, participants, index tests and outcome. For quantitative data synthesis on prognostic accuracy, sensitivity and specificity of screening to detect late-onset sepsis will be calculated. If sufficient data are available, we will calculate summary estimates using hierarchical summary receiver operating characteristics and bivariate models. Applying a risk factor approach, pooled summary estimates will be calculated as relative risk or odds ratio, using fixed-effects and random-effects models. I-squared will be used to assess heterogeneity. All calculations will be performed in Stata 14.1 (College Station, Texas, USA). The results will be used to calculate positive and negative predictive value and number needed to screen to prevent one case of sepsis. GRADE will be used to assess certainty in the evidence. The protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline.

Ethics and dissemination: This study will not require ethical approval since it is not carried out in humans. The systematic review will be published in an open-access peer-reviewed journal.

Prospero registration number: CRD42016036664

Strengths and limitations of this study

- This systematic review will provide a comprehensive overview on the available evidence regarding the value of routine screening for colonization by gram-negative bacteria in neonates for late-onset sepsis prediction.
- Subgroup analysis will allow investigating the particular role of setting, birth characteristics, sampling strategy and co-interventions for test performance and predictive values.
- Limitations of the systematic review will arise from the limitations of the included studies, particularly regarding consideration and reporting of confounders in the publications.

INTRODUCTION

Epidemiological and clinical background

At neonatal intensive care units (NICUs), late-onset sepsis due to gram-negative pathogens is an important cause of neonatal morbidity and mortality.[1] The majority of sepsis episodes (> 80%) occurs in preterm neonates. [2] Depending on individual factors, setting and species of bacteria, between 11 and 46% of very low birthweight infants (VLBW; < 1,500g) are affected.[3] Susceptibility to infection is strongly associated with low gestational age and low birth weight.[4 5]

Already in the 1970s, data were published indicating that infants at NICUs colonised with gram-negative bacteria were at increased risk of developing infections subsequently.[6] Consecutively, a number of studies investigated the value of routine surface cultures for the prediction of sepsis.[7-10] Some hospitals conduct extensive and costly screening procedures to assess the colonization of non-sterile locations of the body surface of neonates by gram-negative bacteria to avoid complications like sepsis. In Germany, routine screening for a selection of pathogens is recommended by the German Committee on Hospital Infections and Hygiene (KRINKO). However, the benefits of these screening procedures are controversially discussed. Moreover, since microbiological screening is introduced as part of a bundle of measures (e.g., isolation, enhanced barrier nursing), it is often challenging to measure the particular effect of screening. So far, no systematic review has been published which investigated the prognostic value of routine screening for colonization by gram-negative bacteria in this at-risk group for the prediction of late-onset sepsis. Here, we present and explain the protocol for a respective systematic review that will be conducted as part of the piloting phase of the Project on a Framework for Rating Evidence in Public Health (PRECEPT).[11]

Prognostic/diagnostic test accuracy and risk factors

According to the *Cochrane handbook for systematic reviews of diagnostic test accuracy studies*, prognostic accuracy studies are using test information to identify patients that will develop an

outcome later on (see http://methods.cochrane.org/sdt/handbook-dta-reviews). In this sense, studies that are using screening for gram-negative bacteria to predict sepsis are prognostic accuracy studies. In such studies, the result of a test is compared to the (clinical) outcome. This differs from the approach of diagnostic test accuracy studies where the test result is compared to the result of a reference or "gold standard" test (**Fig. 1**). Therefore, prognostic accuracy is not a surrogate for patient-important outcomes, as in diagnostic test accuracy studies.[12] This approach has consequences for the design of the studies to be considered. In contrast to diagnostic test accuracy studies where cross-sectional study designs are common practice, cohort studies (prospective or retrospective) are needed to obtain measures of prognostic accuracy.

A complementary approach to the analysis of the same data is to conceptualize a positive screening test as the presence of a risk (or prognostic) factor and to calculate relative risk of developing the outcome. However, it is important to consider that the presence of a high risk ratio (or odds ratio) which is often used to identify prognostic factors for a certain outcome does not indicate that the respective risk factor performs well in predicting this outcome.[13-15] Ware showed that a risk factor strongly associated with a hypothetical outcome (odds ratio 3.58) might have a sensitivity as low as 13% for predicting this outcome. Using the same data, he demonstrated that an odds ratio of 228 would be needed to reach a sensitivity of 80%.[15] Therefore, it may not be concluded that a risk factor which is strongly associated with the outcome provides a basis for an effective preventive measure.

Concepts for systematic reviews of prognostic studies

Various approaches exist regarding the systematic assessment and data synthesis of prognostic studies.[16] During recent years, it has become more and more accepted that systematic reviews in this field should not only focus on measures of association between the predictive/prognostic factor and the outcome, such as risk ratio, odds ratio or hazard ratio, but should comprise measures of prognostic accuracy like sensitivity and specificity (for example, see [17]). Liu et al. (2013)[18] proposed to

distinguish between systematic reviews of screening tests and those of diagnostic and prognostic studies. For screening and diagnosis, they suggested assessing sensitivity and specificity, whereas for questions related to prognosis the use of hazard ratios was proposed. The Agency for Health Care Research and Quality (AHRQ) suggests using a particular framework for systematic reviews of prognostic test.[19] In that paper, Rector et al. conclude that it may be informative to assess the accuracy of a prognostic test by calculating sensitivity, specificity and predictive values. However, these authors emphasize that it is critical to consider the time interval between the test and the occurrence of the outcome.[19] In our own systematic review, we will compute measures of prognostic accuracy and measures of relative risk and compare the results of these calculations to each other.

Risk of bias

Given the particularities of systematic reviews of prognostic accuracy studies, the question arises whether an established risk-of-bias tool exists that captures common sources of bias in this study design. A number of authors applied tools that were originally designed to address risk of bias in diagnostic test accuracy studies.[17 20 21] Currently, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool is the most advanced and widely used tool for the assessment of risk of bias in diagnostic accuracy studies.[22] QUADAS-2 comprises four domains: patient selection, index test, references standard and flow and timing. In each domain, questions related to risk of bias and concerns regarding applicability are included.

However, as explained above, there are apparent differences in study design between diagnostic and prognostic accuracy studies. At least two sources of bias can be identified which are important in prognostic accuracy studies but are not relevant in diagnostic accuracy studies:

- *Attrition bias:* Due to the prospective character of the study design, loss-to-follow-up of study participants in the time interval between the conduct of the screening test and the detection of the outcome might create attrition bias. Depending on whether or not rates of loss-to-follow-up differ between participants with positive and negative screening test

results (differential vs non-differential loss-to-follow-up), sensitivity and specificity will change in point estimate or confidence interval.

- *Confounding:* Confounding will occur if interventions are delivered to study participants depending on the result of the screening test. This may influence the probability of developing the outcome. Again, estimates of sensitivity and specificity might be affected.

Theoretically, it is possible that domain four of the QUADAS-2 tool ("flow and timing") sufficiently captures attrition bias as well as confounding in the time interval between screening test and outcome assessment. If this appears not to be the case, we may test whether the additional application of a risk of bias tool for risk factor/prognostic studies such as the Quality in Prognosis Studies (QUIPS) tool[23] is of additional value.

General objective

To assess the usefulness and value of routine screening for colonization by gram-negative bacteria performed in NICUs as predictive measures for late-onset sepsis.

Research question

This systematic review will focus on the following primary research questions:

1) What is the prognostic value (in terms of sensitivity and specificity) of routine screening for colonization by gram-negative bacteria in neonates at intensive care units for the prediction of late-onset sepsis?
2) Is colonization by gram-negative bacteria in neonates at intensive care units a risk factor for later development of late-onset sepsis?

METHODS

This systematic review protocol follows the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline. [24] A copy of the completed PRISMA-P checklist is attached to this protocol (**Appendix 1**). This systematic review is registered in the Prospective Register of Systematic Reviews (Reg. No. CRD42016036664).

Eligibility criteria

Study designs

Studies of any design will be considered. No restrictions will be made regarding publication language or publication status.

Participants

Studies that include infants up to an age of 12 months who are still in a NICU will be considered, irrespective of gestational age, birth weight and geographical region where the study has been conducted.

Study setting

Studies that were performed in neonatal intensive care units will be considered.

Search strategy

Data base search

We will search MEDLINE and EMBASE from inception to 2016, using the DIMDI (Deutsches Institut für Medizinische Dokumentation und Information) platform. The planned search strategy is shown in **Table 1**.

Reference lists

These searches will be supplemented by "snowballing", i.e. searching for additional studies in the reference lists of identified original studies and reviews.

Grey literature

We will search for grey literature using the Grey Matters Light checklist of the Canadian Agency for Drugs and Technologies in Health (CADTH) (http://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-base-medicine).

Study selection

The study selection process will involve the following steps:

- Screening of titles and abstracts
- Screening of full texts

At both steps, screening will be conducted by two independent reviewers. Potential disagreement will be resolved by discussion or by involving a third reviewer. We will construct a flow chart to document the selection process. A list of excluded studies will be prepared, along with reasons for exclusion.

Data extraction and management

From the included studies, we will extract data on study characteristics and study results. We will construct a data extraction form and pilot test it prior to the start of the review process. Microsoft Office Excel will be used to construct specific extraction forms. One researcher will perform data extraction while a second researcher will independently check for accuracy and details. The following data will be extracted from the original studies:

- *General study characteristics:*
    - complete reference of the study (author, year of publication, title, journal, citation details)
    - date of study
    - place
    - setting (hospital, department, unit, ward)
    - study design
    - funding source
- *Patient/population characteristics:*
    - inclusion criteria
    - exclusion criteria
    - gestational age at birth
    - birth weight
    - age at screening
    - sex
    - ethnicity
    - length of follow-up (time interval between index test and outcome assessment)
    - comorbidities
    - central line use
    - need for surgery

- *Index test characteristics:*
  - description of sampling device
  - sampling time point(s)
  - sampling location(s) (e.g., umbilicus, tracheal, rectal etc)
  - sampling intervals (if repetitive)
  - processing of specimen
  - detected bacteria (species, characterization)
- *Outcome:*
  - definition of sepsis
  - detected bacteria (species, characterisation)
- *(Co)-interventions*
  - antibiotic use
  - isolation
  - hand hygiene
- *Prognostic accuracy measures:*
  - true positives
  - true negatives
  - false positives
  - false negatives
- *Measures of association (risk factor approach):*
  - Unadjusted relative risk (or odds ratio)
  - Adjusted relative risk (or odds ratio)
  - Confounders considered in adjusted analysis

Risk of bias assessment

Following the guidance of the PRECEPT framework, [11 25] we will use the QUADAS-2 tool to assess risk of bias in the included individual studies which report measures of prognostic accuracy. [22] **Table 2** shows the main components of the tool. The results of the risk of bias assessment will be documented in a separate table for each study along the items of QUADAS-2. For studies reporting on prognostic measures in terms of a risk factor (or prognostic study), we will use the QUIPS tool.[23] We will construct bar charts as suggested by Van't Hooft et al.[21] to report summary results of the risk of bias assessments.

Subgroup analyses

We will extract detailed information on study participants, definitions and settings to enable stratified analysis. In particular, we aim at stratifying the results of the systematic review and meta-analysis, respectively, according to the following variables:

- *General study characteristics:*
  - geographic region (Europe vs North America etc.)
  - developed country vs developing country
  - study period (<1970, 1971-1980, 1981-1990, 1991-2000, 2001-2010, >2010)
- *Patient/population characteristics:*
  - gestational age (<37 weeks vs ≥ 37 weeks; <32 weeks vs. ≥32 weeks; <26 weeks vs ≥26 weeks)
  - birth weight (<1000g vs ≥1000g; <1500g vs ≥1500g; <2500g vs ≥ 2500g)
  - length of follow-up (time interval between index test and outcome assessment)
- *Index test characteristics:*
  - sampling time point(s)
  - sampling location(s) (umbilicus vs tracheal etc.)
  - species: single species; groups (multidrug-resistant; difficult to treat)

- *Outcome characteristics:*
  - different definitions of sepsis
- *Study setting*
  - clinical routine
  - study
  - outbreak investigation
  - type of ward
- *Study design*

Statistical analysis

Prognostic accuracy approach: For quantitative data synthesis on prognostic accuracy, we will construct 2x2 tables to calculate sensitivity and specificity for each included study. If sufficient comparable data from more than one study are available, we will perform meta-analysis. To account for the correlation between sensitivity and specificity, we will calculate summary estimates using hierarchical summary receiver operating characteristics models[26] as well as bivariate models.[27] Results will be displayed graphically using SROC plots. We will investigate sources of heterogeneity, using subgroup analysis.

Risk factor approach: For quantitative data synthesis using the risk factor approach, pooled summary estimates will be calculated as relative risk or odds ratio with 95% confidence intervals, using fixed-effects and random-effects models. I-squared will be used to assess heterogeneity. If >=10 studies per outcome are available, publication bias will be assessed by inspection of funnel plots and applying Begg's and Egger's test.

All calculations will be performed in STATA. The results of the meta-analysis will be used to calculate positive predictive value, negative predictive value and number needed to screen to prevent one case of sepsis.

Certainty in the evidence (GRADE)

We will use two complementary approaches to assess the certainty in the evidence (formerly: quality of the evidence) according to the methodology suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.

Prognostic accuracy approach: We will adopt the GRADE approach to diagnostic accuracy test reviews for the purpose of our systematic review on prognostic test accuracy. The certainty in the evidence will be assessed for true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN), as suggested by GRADE.[12] In brief, the application of GRADE will be conducted as follows:

- For each body of evidence on diagnostic studies, all studies start as “high”. “True positives”, “true negatives”, “false positives” and “false negatives” are defined as outcomes.
- Risk of bias is assessed by the QUADAS-2 tool, and evidence quality can be downgraded, if necessary.
- Thereafter, the other GRADE criteria for downgrading quality of evidence (inconsistency, indirectness, imprecision, publication bias) are applied, according to the approach published by the GRADE working group.[12]

Risk factor approach: We will use the GRADE approach to risk factor/prognostic factor studies. The certainty in the evidence will be assessed for the outcome late-onset sepsis according to the GRADE methodology [28] as follows:

- For each body of evidence, certainty in the evidence is initially rated as “high”, irrespective of study design.
- Risk of bias is assessed by the appropriate risk of bias tool, and evidence certainty can be downgraded, if necessary.
- Thereafter, the other GRADE criteria for downgrading quality of evidence (inconsistency, indirectness, imprecision, publication bias) are applied.
- Upgrading of the quality of evidence is possible, according to the criteria introduced by GRADE.

Reporting of this review

The systematic review will be reported according to the PRISMA guidelines. The PRISMA checklist will be published with the report.

Ethical considerations and dissemination of findings

This study will not require ethical approval since it is not carried out in humans. The resulting systematic review will be published in a peer-reviewed journal as an open-access paper.

Acknowledgements

This systematic review will be performed as part of the piloting phase of the PRECEPT project. PRECEPT is funded by the European Centre for Disease Prevention and Control (ECDC; tenders no. 2012/040; 2014/008). The funder had no role in developing and writing of this protocol.

Contributors

TH, JS and SH developed the concept of this protocol. TH wrote the first draft. JS, BW, TE and SH provided important intellectual input to revise the draft protocol. All authors approved the final manuscript as submitted. TH is the guarantor of this protocol.

Competing interests

None declared.

Table 1: Search strategy of the systematic review

#1 neonat*
#2 newborn*
#3 infant*
#4 colonization
#5 “mucosal site*”
#6 “mucosal sample*”
#7 “mucosal culture*”
#8 “superficial culture*”
#9 “surveillance culture*”
#10 aspirate
#11 “predictive value”
#12 sensitivity
#13 specificity
#14 sepsis
#15 “body fluid*”
#16 “systemic inflammatory response syndrome”
#17 “routine culture”
#18 “skin culture”
#19 “surface culture”
#20 “bacterial colonization”
#21 “microbiological screening”
#22 swab*
#23 #1 OR #2 OR #3
#24 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#25#14 OR #15 OR #16
#26 #23 AND #24 AND #25

Table 2: Structure of the QUADAS-2 tool [22]

Domain	Risk of bias		Concerns regarding applicability	
1. Patient selection	Was a consecutive or random sample of patients enrolled?	Yes/no/unclear	**Is there concern that the included patients do not match the review question?**	**CONCERN: LOW/HIGH/UNCLEAR**
	Was a case-control design avoided?	Yes/no/unclear		
	Did the study avoid inappropriate exclusions?	Yes/no/unclear		
	Could the selection of patients have introduced bias?	**Risk: LOW/HIGH/UNCLEAR**		
2. Index test(s)	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes/no/unclear	**Is there concern that the index test, its conduct, or interpretation differ from the review question?**	**CONCERN: LOW/HIGH/UNCLEAR**
	If a threshold was used, was it pre-specified?	Yes/no/unclear		
	Could the conduct or interpretation of the index test results have introduced bias?	**Risk: LOW/HIGH/UNCLEAR**		
3. Reference standard*	Is the reference standard likely to correctly classify the target condition?	Yes/no/unclear	**Is there concern that the target condition as defined by the reference standard does not match the review question?**	**CONCERN: LOW/HIGH/UNCLEAR**
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/no/unclear		
	Could the reference standard, its conduct, or its interpretation have introduced bias?	**Risk: LOW/HIGH/UNCLEAR**		
4. Flow and timing	Was there an appropriate interval between index test and reference standard?	Yes/no/unclear		
	Did all patients receive a reference standard?	Yes/no/unclear		
	Did patients receive the same reference standard?	Yes/no/unclear		
	Were all patients included in the analysis?	Yes/no/unclear		
	Could the patient flow have introduced bias?	**Risk: LOW/HIGH/UNCLEAR**		

*Here: equivalent to outcome

Figures

Figure 1: Diagnostic vs prognostic test accuracy

Appendix

Appendix 1: PRISMA-P checklist (see separate file)

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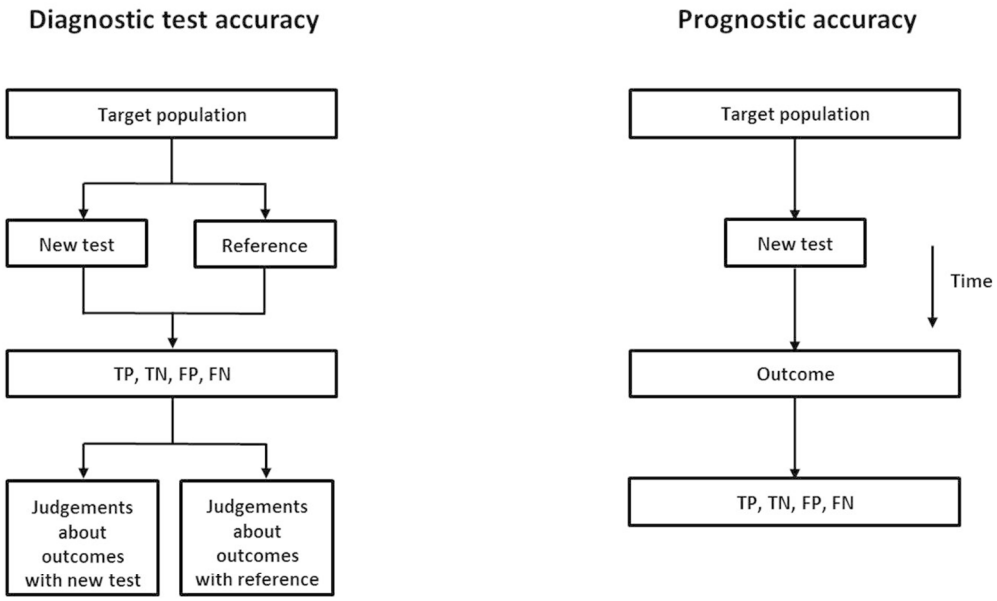

Figure 1: Diagnostic vs prognostic test accuracy

355x266mm (96 x 96 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Page 8, lines 1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 8, line 4
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	Page 15, lines 15-17
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	Not applicable
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 15, lines 11-12
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 15, lines 11-12
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 15, lines 12-13
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page 4, line 1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
					– page 7, line 12
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 7, lines 14-16
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 8, line 6 – line 16
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 9, line 1 – line 12
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	Table 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 10
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 9, line 18 - 21
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 10, line 1-5
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 10, line 6 – page 11, line 19
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	Page 11, line 5-6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	page 11, line 21 – page 12, line 2
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 13, line 4-5

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	Page 13, line 1-16
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 12, line 4-24
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☐	Not applicable
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 13, line 11-13
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	Page 13, line 18-page 14 (end)