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ABSTRACT

Introduction Young febrile infants are at higher risk of invasive bacterial infections (IBIs) compared with older children. The clinical features of IBI are subtle in this cohort mandating that clinicians take a cautious approach to their initial assessment and management. This includes the measurement of blood biomarkers of infection such as C reactive protein (CRP) and procalcitonin (PCT). In the UK, PCT is not widely available and not recommended for routine use in hospital. This is in contrast to Europe and the USA where PCT is regularly used to assist clinical decision-making. The objective of this review and meta-analysis is to report the diagnostic test accuracy of PCT in detecting IBI in febrile infants less than 91 days old, compare its accuracy with CRP and define optimal PCT cut-off values in this cohort.

Methods and analysis A search strategy will include MEDLINE, EMBASE, Web of Science, The Cochrane Library and grey literature. There will be no language or date limitations. Diagnostic accuracy studies compliant with STARD criteria will be considered against eligibility criteria. Abstracts, then full texts, of potentially eligible studies will be independently screened for selection. Data extraction and quality assessment, using the QUADAS-2 tool, will be completed by two independent authors and a third author used for any inconsistencies. True positives, false positives, true negatives and false negatives will be pooled to collate specificity and sensitivity with 95% CIs. Results will be portrayed in forest plots, alongside their quality assessments.

Ethics and dissemination This review does not require ethical clearance. This review will be published in peer-reviewed journals and key messages will be disseminated through presentations at local and international conferences related to this field. The authors aim for this review to be completed and published in 2023.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Invasive bacterial infection is rare, even among young febrile infants, so a large number of patients from a range of studies will be required to reliably report the diagnostic test accuracy of procalcitonin (PCT). A significant volume of evidence has become available in the last decade ideal for meta-analysis.
⇒ Since the last review in this field, almost a decade ago, international practice has evolved significantly but still varies globally.
⇒ This review will scrutinise the diagnostic accuracy of PCT and may demonstrate its ability to identify target populations, which would streamline clinical pathways, particularly in the UK.
⇒ The limitations of this review will be in the heterogeneity among selected studies, in particular the lack of a unifying definition of serious bacterial infection.

INTRODUCTION

Context and target condition

Young febrile infants (defined as 90 days of age or younger with a history of fever) are at a relatively high risk of invasive bacterial infections (IBIs) compared with older children.[1–3] Invasive bacterial infections include bacterial meningitis and symptomatic bacteraemia and are reported in 1%–3% of young febrile infants.[1–5] In addition to IBI, a further 10%–15% of young febrile infants will be diagnosed with other serious bacterial infections (SBIs); typically urinary tract infections (UTIs) requiring antibiotic treatment.[1 3 6] Unfortunately, it is clinically difficult to differentiate those infants with an evolving IBI from those with a self-limiting viral infection, particularly in the prodrome of their illness and in the youngest of this cohort.[4 7 8]

The approach to this clinically challenging population has evolved considerably over the past few decades. Traditionally, all young febrile infants were treated as a high-risk group with all typically receiving parenteral antibiotics and undergoing extensive testing including blood, urine and lumbar puncture tests. More recently, a number of research

groups have produced validated clinical practice guidelines (CPGs) that consider the child's age, clinical status and biomarker results when determining treatment plans and specifically identify a lower risk cohort that can be managed in the community without parenteral antibiotics or extensive investigation. These newer, validated CPGs all require procalcitonin testing. Procalcitonin testing is widely available in Europe and the USA but is currently not recommended for use in the UK.[2 4 9 10]

Index test and alternatives

Procalcitonin (PCT) is a naturally found peptide prehormone which is cleaved to calcitonin; ordinarily, it inhibits parathyroid hormone and vitamin D to maintain calcium and phosphate homeostasis.[11] Procalcitonin is also an acute phase reactant, released from all tissues, rising by 4 hours after exposure to endotoxin, peaking by 8 hours and remaining elevated for 24 hours.[12] PCT is thought to be a more specific biomarker for bacterial infections due to its responsiveness to a cytokine profile including IL-I beta, TNF-alpha and IL-6. PCT is also inhibited by cytokines such as interferon-gamma which are more commonly released in viral infections.[13] These characteristics make PCT a promising biomarker in a cohort of febrile infants, who typically present early in their illness, with little differentiating clinical features between bacterial and viral illness, but where early diagnosis is important.

The most commonly used alternative to PCT is C reactive protein (CRP). CRP is also an acute phase reactant, synthesised and released from the liver within 6 hours of inflammatory signalling, doubles every 8 hours, before peaking around 36 hours.[11 14 15] The performance of these two biomarkers have been extensively compared in different contexts, inclusive of febrile children and neonates, where PCT often performs superiorly to CRP. In particular, PCT is thought to act better with a shorter duration of fever and often demonstrates higher specificity to bacterial infections.[13 15–18]

Novel immunological biomarkers may include individual cytokines, cytokine profiles and mid-regional pro-adrenomedullin (MR-Pro-ADM).[11 19 20] Promising research looking at RNA biosignatures may help diagnosis of bacterial infection in the future.[21] However, this research is in relative infancy and less available for clinical practice compared with PCT.

PCT is typically more expensive than CRP, a commonly stated reason for not yet being widely available in the UK and for which NICE have called for further research.[22 23] However, young febrile infants incur a significantly greater burden of healthcare resources than other febrile children presenting to hospital and are more likely to be prescribed antibiotics. The estimated cost of admission and parental antibiotic therapy for a febrile infant in the UK is £1352 per infant, far in excess of the cost of a PCT test, demonstrating substantial opportunity for improvement in diagnostic efficiency based on cost-effective practice alone.[24]

Clinical pathway

In the UK, guidance regarding the management of febrile infants is provided by the National Institute for Health and Care Excellence (NICE). The NICE Sepsis Guidance NG51 advises that all young febrile infants are treated with parenteral antibiotics and admitted to hospital without delay. NICE recommend that all febrile infants complete their initial assessment and treatment within 1 hour of presentation to hospital with parenteral antibiotics given to all irrespective of age, clinical features or laboratory results.[25 26] In contrast, international guidelines, such as those from the American Academy of Pediatrics and the European 'step-by-step' approach, recommend a sequential assessment. On arrival to hospital, well-appearing infants aged over 28 days of age can undergo clinical assessment and limited testing before making treatment decisions whereas younger infants or those that appeared unwell would be treated immediately with parenteral antibiotics. For those well-appearing older infants, they would then undergo re-assessment in conjunction with the results of biomarker testing. Typically, those that remain well and have PCT levels <0.5 ng/mL would be considered suitable for management in the community.[2 10]

If PCT was found to be highly accurate for the assessment of potential IBI and SBI in young febrile infants, it could be adopted in the UK as part of a tailored, sequential assessment similar to international practice. Figure 1 demonstrates the current UK pathway described earlier and the possible clinical pathway using PCT, similar to the described international practice.

Objectives

The primary objective of this systematic review is to report the diagnostic test accuracy of PCT for detecting IBI in febrile infants 90 days of age or younger.

The secondary objectives include reporting the test accuracy of PCT in detecting SBI and comparing the test accuracy of PCT compared with CRP in this population for both IBI and SBI.

This review will also compare the diagnostic test accuracy in infants over a range of age groups within the population, and between different subgroups. Specifically, there will be a comparison of test accuracy of PCT for detecting SBI and IBI in those presenting without an apparent source- of infection and for those appearing well on initial assessment.

Finally, this review will aim to report the optimum cut-off value for PCT and CRP for the detection of IBI and SBI in febrile infants.

METHODS

This systematic review and metanalysis will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Diagnostic Test Accuracy (PRISMA-DTA) standards[27 28] (online supplemental appendix 1: PRISMA Checklist for protocols). A systematic search will be performed using the search strategy below and then

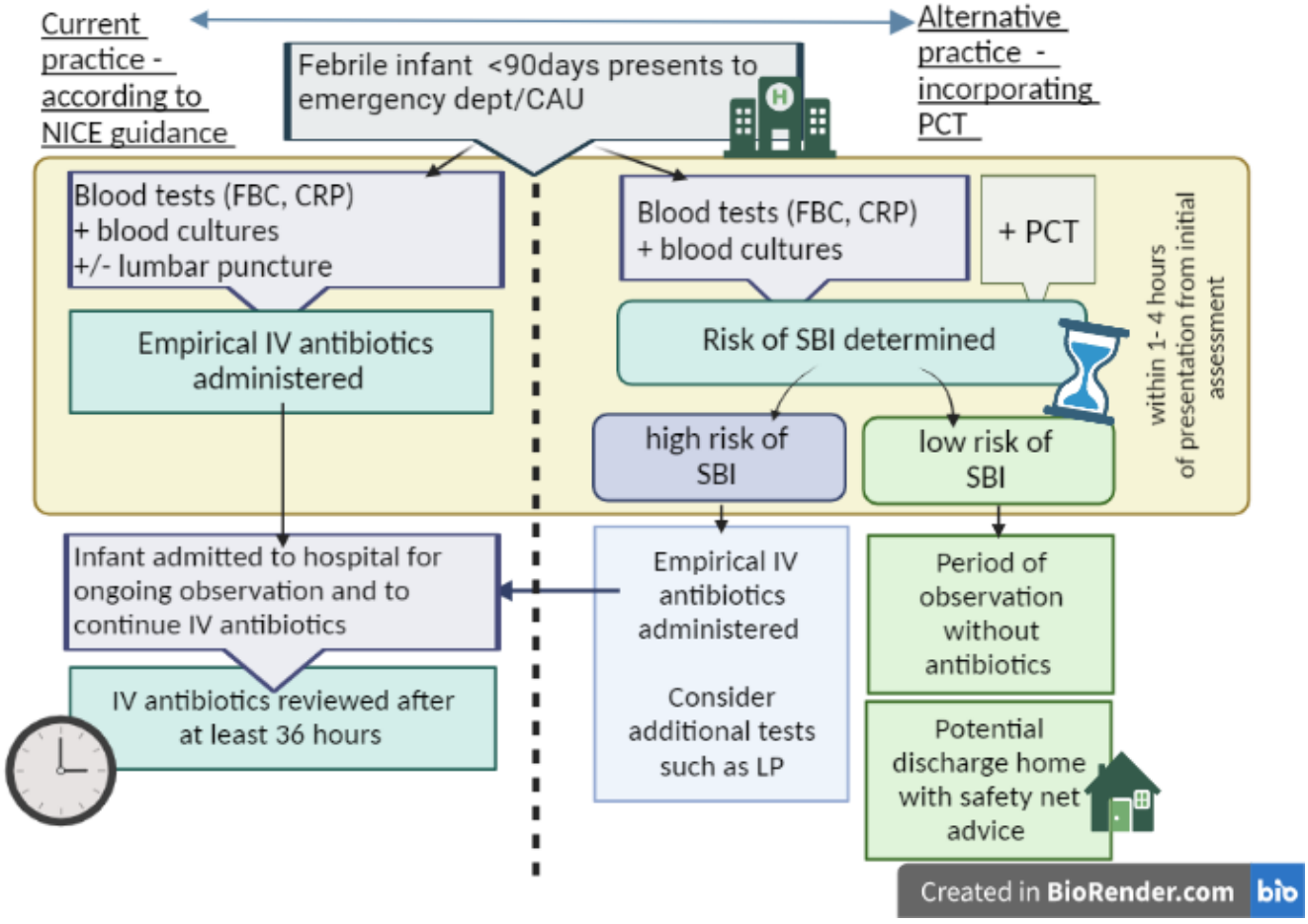

Figure 1 Summary of current clinical pathway in the UK and practice if PCT was incorporated and able to differentiate infants according to their risk of SBI. CAU, clinical assessment unit; CRP, C reactive protein; FBC, full blood count; IV, intravenous; LP, lumbar puncture; NICE, National Institute for Health and Care Excellence; PCT, procalcitonin; SBI, serious bacterial infection.

all studies will be reviewed by two independent authors in reference to the eligibility criteria for inclusion into meta-analyses.

Eligibility criteria

All studies that examine the diagnostic accuracy of PCT for potential IBI or SBI will be considered against the eligibility criteria (as summarised in table 1) for inclusion in the review.

Participants of eligible studies will be infants aged 90 days or less presenting to a hospital with a fever ≥37.5°C, or history of a fever within 48 hours of presentation. Infants must be previously well, consistent with previously published definition by *Gomez et al*: "*Born at term, not treated for unexplained hyperbilirubinemia, not hospitalized longer than the mother, not receiving current or previous antimicrobial therapy, no previous hospitalization, and no chronic or underlying illness.*"[2]

The index test will be serum or plasma measurement of PCT, using commercially available tests, in both laboratory and point-of-care settings. The author must clarify if this is a quantitative or semi-quantitative test, although its quantitive nature will not be an exclusion criterion. The secondary index test, if used in the study, will be plasma or serum CRP measurement using commercially available laboratory tests. All index and reference tests must be sampled on presentation to hospital for assessment. The primary cut-off value is 0.5 ng/mL for PCT and 20 mg/L for CRP. These reflect the key international guidance and will therefore provide the most applicable results to international practice.[1 2] Where these cut-offs are unavailable, or diagnostic accuracy for additional cut-off values are given, the data will be extracted at the authors' given cut-offs and further incorporated into analysis model.

The reference standard, IBI, is defined as isolation of a bacterial pathogen in blood or cerebrospinal fluid (CSF) culture or using a quantitive PCR assay. The secondary reference standard, SBI, lacks a unifying definition. Where it is usually defined as isolation of a bacterial pathogen in urine, blood or CSF culture or using a quantitive PCR assay, this can vary considerably and may include other localised bacterial infections, such as gastroenteritis or pneumonia. The review will take the author's definition of SBI, reflecting the heterogeneity of the studies. Authors must describe the urine collection

Table 1 Inclusion criteria for meta-analysis

Study characteristics	Inclusion criteria
Population	Febrile (≥37.5°C) infants ≤90 days of age (fever measured within 48 hours of attendance)
Primary index test	Procalcitonin (serum or plasma measurement)
Reference test	IBI: ► Bacterial meningitis defined as pathogenic bacteria identified by qPCR or bacterial culture from CSF ► Symptomatic bacteraemia defined as pathogenic bacteria identified by qPCR or bacterial culture from blood SBI: Author definition of SBI to include, but not be limited by, all IBI and urinary tract infections (UTIs), where UTI is defined as pathogenic bacteria identified by qPCR or pathogenic bacterial culture from urine
Primary outcome	True positives, true negatives, false positives, false negatives Sensitivity, specificity
Study design	Diagnostic test accuracy studies

CSF, cerebrospinal fluid; IBI, invasive bacterial infection; qPCR, quantitative PCR; SBI, serious bacterial infection.

method in their protocol and the threshold of bacterial growth to define a 'UTI' in their study.

Studies examining PCT alongside other biomarkers may be included assuming that data on the diagnostic performance of PCT alone can be extracted. Similarly, studies looking at PCT for infants beyond the age range specified may be included and the study authors will be contacted to assist with data extraction.

Exclusion criteria

Studies that were exclusively conducted in neonatal units and only included newborns with suspected neonatal sepsis will be excluded. Studies investigating the diagnostic test accuracy of PCT for conditions other than IBI or SBI, will be excluded.

Standards of reporting Diagnostic Accuracy Studies (STARD) criteria and quality assessments using the Quality assessment of Diagnostic Accuracy Studies (QUADAS-2) tool will be used to guide inclusion into the final meta-analyses.[29 30]

Search strategy

An electronic search strategy will be performed using MEDLINE, EMBASE, Web of Science and The Cochrane Library. The search strategy will be broad; using *Procalcitonin,* and *bacterial infection* or *fever,* as key MeSH terms, exploded where available. In addition, "Invasive bacterial infection*" and "Serious bacterial infection*" will be searched as a keywords to find studies not labelled with the listed MeSH terms. The age group of the population will be defined using database limits where possible or using key words if not available. There will be no time or language restrictions; papers not in English will be reviewed using the translation services available through Queen's University Belfast. If further literature, such as clinical trial protocols and conference abstracts, are identified, they will also be considered against eligibility criteria. Unpublished data will be sought through clinical trial registries and during title and abstract screening further literature may be identified, and assessed for eligibility (online supplemental appendix 2—Example search strategy).

Study selection

Two authors will independently screen the results of the search strategy, first by title and abstract and then by examination of the full articles according to the aforementioned inclusion and eligibility criteria. Any unresolved discrepancy between these two authors will be resolved by the third author. Duplicates and co-publication studies will be removed and incorporated into a table demonstrating excluded studies after each stage of selection.

After data extraction, all studies will be independently assessed by two authors using the QUADAS-2 tool to guide inclusion into the final metanalyses; any discrepancies will be resolved by the third author.

Data extraction

Two authors will independently extract data from each selected studies using a standardised data extraction tool summarised in table 2. Where there are insufficient data available for inclusion in the meta-analysis, the corresponding author will be contacted (maximum of three attempts over a 6-week period) and invited to submit the necessary data.

After independently screening two of the selected studies, each author will review the data extraction tool and modifications will be agreed. After this piloting process, the final data extraction tool will be used to assess all included studies. Data extraction will be managed using RevMan software (V.5.4). Although the primary objective is to analyse the diagnostic accuracy of PCT, the secondary objective is to compare its accuracy to CRP in

Table 2 Summary of data extraction for each study

Summary of components for the data extraction tool	
Study characteristics	Year of publication, authors, country of origin, study design, Sample size (number included in analysis), attrition rates, funding sources, setting of study
Population characteristics	Age of infants, gender, previous diagnoses, gestational age at birth Fever without apparent source on presentation (FWAS) Fever duration prior to presentation Symptoms on presentation ('unwell appearing' or not) Prior testing for viral illness
Index test	Serum PCT* (ng/mL) Serum CRP* (mg/L)—*if reported in study* *with cut-off values and time of sampling
Reference test	► Invasive bacterial infection (IBI) ► Author definition of serious bacterial infection (SBI)
Outcome measure	True positives, true negatives, false positives, false negatives Sensitivity and specificity if reported

CRP, C reactive protein; PCT, procalcitonin.

this context, and hence data for this second index test will be extracted from selected studies, where available.

A summary of included studies and their quality assessment (according to QUADAS-2 criteria) will be presented in a table. The data extracted from the selected studies will be reported in a narrative summary and presented in a further table detailing the key findings. Each study will have a 'two by two' diagnostic table to summarise the reference standard (I/SBI) and the index test (PCT), using the cut-off level of PCT used in each study. The primary diagnostic accuracy outcome of this review will be the sensitivity and specificity of the index tests, within the different analyses performed. However, to provide further clinical value positive and negative likelihood ratios will be extracted from the data.

Paired forest plots will be used to demonstrate all the results graphically and a visual inspection will be performed to evaluate initial heterogeneity. The meta-analysis will be conducted using a hierarchical summary receiver operating characteristic (HSROC) model, on R software (V.4.2.0), using pooled sensitivities and specificities along with 95% CIs. This will account for the anticipated variation in PCT cut-off thresholds used between studies. A degree of heterogeneity is expected across the studies and the I^2 statistic will provide numerical value for the heterogeneity.

For secondary outcome analysis, the extractable CRP data will be incorporated into the HSROC model to compare the two index tests. Where there is sufficient extractable data in the studies, subgroup analysis will be used to compare different age groups within the population. Subgroup analysis will also be performed on the key baseline co-variables within these populations. Two key subgroup analysis on the data is planned, reflecting the available data in the literature and clinical utility. This will be infants with fever without apparent source or not, and infants who appear well or not. All these analyses will still use HSROC model as described for total meta-analysis and presented in both tabular and graphical form.

Heterogeneity will be further assessed using sensitivity analysis for the key inter-study variables. This will include how the index test was conducted, for example, semi-quantitive or quantitive tests, or point-of-care or laboratory tests, and also the context in which the study was performed. In light of the selected studies spanning over a decade, sensitivity analysis will be used to compare the results of older and newer papers to exclude bias due to age of the study and improvements in manufacturing over time.

The results will be then further reported considering QUADAS-2 assessment of each study and presented alongside the traffic light diagram. GRADE criteria will be used for the clinical interpretation of the results and what recommendations may be made.[31] All studies will be selected for review and data will be extracted within a timely fashion such that data analysis will be complete within 6 months of the search strategy being performed.

Patient and public involvement

Members of the public or patients have not been invited to review this protocol. However, the authors of this paper are involved in a study into the investigation of febrile infants for which a public involvement exercise has been undertaken. Parents and key stakeholders have corroborated the importance of improved diagnostic pathways for this cohort of infants which supports the value of this review.

DISCUSSION

This review and meta-analyses will provide an up-to-date assessment of the diagnostic test accuracy of PCT for detection of IBI and SBI in febrile infants aged 90 days or younger. The planned review and metanalysis will be

especially useful for healthcare planning in settings, such as in the UK, where PCT is not widely available. If PCT is found to be highly sensitive and specific for detecting IBI in this cohort, then policy-makers may choose to adopt the use of PCT in conjunction with a sequential risk assessment. This has the potential to reduce healthcare costs, reduce the need for invasive investigations such as lumbar puncture and improve antimicrobial stewardship.

The planned analysis will also provide a comparison between CRP at 20 mg/L and PCT at 0.5 ng/mL. If PCT and CRP are found to have similar performance characteristics at these cut-offs, then it may be possible to consider defining a sequential assessment with CRP instead of PCT that could be used in settings where PCT is currently unavailable.

The advantage of the planned review is that it will incorporate a variety of studies from different settings and including large numbers of patients. IBI is rare, even among young febrile infants, and a large number of patients from a range of studies will be required to reliably report the diagnostic test accuracy of PCT. The heterogeneity of the studies will likely increase the generalisability of the results.

The main limitation of the planned review and analysis is that there is no unifying definition of SBI. The lack of a unifying definition will mean that caution must be used when interpreting the test-accuracy results for recognising SBI alone. The results may not be applicable to all settings depending on local practices.

Contributors All six authors fulfil criteria of authorship according to the ICMJE Recommendations 2018. The protocol was designed and conceptualised by HN-B and TW. EU and CM have supported design of search and data extraction tools. HM and LM have contributed to the design of the statistical analysis. HN-B is lead author and guarantor, they provided first draft of manuscript and all authors have contributed to and approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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APPENDIX 1: **PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol** (24)

Administrative information		
Identification	1a Identify the report as a protocol of a systematic review	P1
Update	1b If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2 If registered, provide the name of the registry (such as PROSPERO) and registration number	P11
Authors:		
Contact	3a Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P11
Contributions	3b Describe contributions of protocol authors and identify the guarantor of the review	P11
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	n/a – protocol not yet published
Support:		
Sources	5a Indicate sources of financial or other support for the review	P11
Sponsor	5b Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION		
Rationale	6 Describe the rationale for the review in the context of what is already known	P2
Objectives	7 Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P4
METHODS		
Eligibility criteria	8 Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P5
Information sources	9 Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P7
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	Appendix 2
Study records:		
Data management	11a Describe the mechanism(s) that will be used to manage records and data throughout the review	P7
Selection process	11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility, and inclusion in meta-analysis)	P7

Data collection process	11c Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	P7
Data items	12 List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P5-7
Outcomes and prioritization	13 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P6
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	P7/8
Data synthesis		
	15a Describe criteria under which study data will be quantitatively synthesised	P8
	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 (such as I2, Kendall's τ)	P8
	15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P9
	15d If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17 Describe how the strength of the body of evidence will be assessed (such as GRADE)	P9

APPENDIX 2: **Example Search Strategy**

- Access 22.1.22
- Ovid MEDLINE(R) ALL <1946 to January 21, 2022>
- "bacterial infection" is MeSH heading
    - all exploded terms for bacterial infection* (inclusive of bacterial meningitis)