Review protocol for what investigations should be performed before starting treatment in babies with symptoms of late-onset neonatal infection?

ID	Field	Content
0.	PROSPERO registration number	CRD42020157804
1.	Review title	Investigations before starting treatment for late-onset neonatal infection in babies
2.	Review question	What investigations should be performed before starting treatment in babies with symptoms of late-onset neonatal infection?
3.	Objective	To determine the diagnostic test accuracy and cost effectiveness of tests used for detection of late-onset neonatal infection in neonates with symptoms and signs or risk factors that indicate the need to start antibiotic treatment This question also includes consideration of the intervals between presentation and testing, testing and treatment, and the timing of decisions to continue or stop treatment
4.	Searches	The following databases will be searched:

		• Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE (including 'in process' and 'E-pub ahead of print') • Database of Abstracts of Reviews of Effect (DARE) Searches will be restricted by: • English language • Human studies • Conference abstracts • No date limit will be included Other searches: None The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Neonatal infection is a significant cause of mortality and morbidity in neonates. It may be early-onset (within 72 hours of birth) or late-onset

		(more than 72 hours after birth). Neonatal infection can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. Late-onset neonatal infection is present in 7 of every 1000 newborn babies and responsible for 61 of every 1000 neonatal admissions. Coagulase-negative staphylococci, Enterobacteriaceae and *Staphylococcus aureus* are the most common organisms identified.
6.	Population	Inclusion: • Term babies up to 28 days of age and preterm babies up to 28 days corrected gestational age with symptoms or signs of, or risk factors for, late-onset neonatal infection presenting after 72 hours of birth or from study-defined period for development of late-onset neonatal infection Exclusion: • Babies with suspected or confirmed non-bacterial infections. • Babies with suspected or confirmed syphilis. • Babies with suspected or confirmed localised infections. • Babies with suspected or confirmed bacterial infection resulting from therapeutic interventions such as surgery. Babies with a

		history of surgery which was not the cause of the infection will not be excluded. • Babies with suspected or confirmed meningitis who are not receiving care in neonatal units (covered by the NICE guideline on bacterial meningitis and meningococcal septicaemia)
7.	Test	• C-reactive protein (CRP) and other acute phase reactants • procalcitonin (PCT) • interleukins • cytokines • white blood cell count (including neutrophil count, which can be high or low, and the ratio of immature to total neutrophils, left shift, band granulocyte) • platelet count • cerebrospinal fluid (CSF) examination • urine microscopy or culture, including mode of collection (for example, catheter, suprapubic aspiration) • rapid tests (for example, polymerase chain reaction (PCR) (excluding CSF PCR) • surface swabs (skin, nose, ear, umbilical, rectal, axilla and groin, eye, throat)

		• Samples from tip of IV long line • chest X-ray
8.	Reference standard	• For tests based on CSF parameters (CSF examination): CSF culture or CSF-PCR test on sample taken from 72 hours after birth to 28 days (corrected age) • For all other tests (excluding CSF examination): blood culture on sample taken from 72 hours after birth to 28 days (corrected age)
9.	Types of study to be included	Cross sectional diagnostic test accuracy studies Systematic reviews of the diagnostic test accuracy studies
10.	Other exclusion criteria	Non-English language studies Case-control studies will be excluded
11.	Context	NICE guideline CG149 Neonatal infection will be updated by this question.
12.	Primary outcomes (critical outcomes)	Diagnostic/predictive accuracy measures including: • sensitivity (detection rate) • specificity

		• positive and negative predictive values • positive and negative likelihood ratios
13.	Secondary outcomes (important outcomes)	Not applicable.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Data will be extracted from the included studies into a standardised form for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias. Study investigators may be contacted for missing data where time and resources allow. This review will make use of the priority screening functionality within the EPPI-reviewer software.

		A stopping rule will be used to terminate screening if the following criteria are met: - At least 50% of the database has been screened - 500 records have been screened with no further included studies Reference lists of systematic reviews will also be checked for potential includes
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the QUADAS-2 checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analyses of diagnostic test accuracy data will be conducted for all diagnostic tests that are reported by more than one study, with reference to the Cochrane Handbook for systematic reviews of diagnostic test accuracy. Random-effects models will be fitted for all analyses. A bivariate model will be fitted when 5 or more studies are available to be meta-analysed. A univariate model will be fitted when there are fewer than 5 studies available. • Bivariate meta-analyses will be performed in R using the 'mada' package • Univariate meta-analysis will be performed in excel.

		Modified GRADE will be used to assess certainty in the evidence base. In cases where heterogeneity make meta-analysis inappropriate, data for each study will be presented as separate lines in the GRADE profile.
17.	Analysis of sub-groups	**Stratifications:** • term vs preterm babies • babies who have been admitted to hospital from home
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	01/01/2018

22.	Anticipated completion date	12/08/2020		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Piloting of the study selection process	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Formal screening of search results against eligibility criteria	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Data extraction	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐

		Risk of bias (quality) assessment	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
		Data analysis	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** NIupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline Updates Team: • Dr Kathryn Hopkins • Dr Clare Dadswell • Mr Fadi Chehadah • Mr Wesley Hubbard		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from NICE.		

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication

		• publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Late onset neonatal infection, diagnostic test accuracy
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	The guideline with supporting evidence reviews will be published on the NICE website.