Review protocol for Timing of prelabour rupture of membranes to birth and risk of early onset neonatal infection in singleton pregnancies at term

ID	Field	Content
1.	Review title	Timing of prelabour rupture of membranes to birth and risk of early onset neonatal infection in singleton pregnancies at term.
2.	Review question	What is the risk of early onset neonatal infection at different time intervals between prelabour rupture of membranes (PROM) and birth for singleton pregnancies at term?
3.	Objective	To review the evidence on the timing of prelabour rupture of membranes (PROM) to birth in singleton pregnancies at term and its association with early onset neonatal infection with a view to updating the bullet point: 'Confirmed rupture of membranes for more than 24 hours before a term birth' in recommendation 1.3 (Box 1) on risk factors for early-onset neonatal infection, as outlined in NG195: Neonatal infection – antibiotics for prevention and treatment. The aim is to provide guidance on which term babies should be assessed for the risk of early onset neonatal infection if the mother has had pre-labour rupture of membranes.
4.	Searches	The following databases will be searched: • Medline All (Ovid platform) • Embase (Ovid platform) • Cochrane Database of systematic reviews (Wiley platform) • Cochrane Central Register of Controlled Trials (CENTRAL, Wiley platform) • Epistemonikos (for systematic reviews only)

		The principal search strategy will be developed in MEDLINE and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage. In addition, we will seek to find relevant studies via: Forward citation searching (using CitationChaser/Lens.org), based on identified key references. The guideline committee or other stakeholders will be asked for details of any additional, relevant studies they may be aware of. Database functionality will be used, where available, to exclude: • Animal studies • Editorials, letters, news items and commentaries • Conference abstracts and posters • Registry entries for ongoing clinical trials or those that contain no results • Theses and dissertations • Papers not published in the English language. • Preprints The information services team at NICE will quality assure the principal search strategy. Any revisions or additional steps will be agreed by the review team before being implemented. The full search strategies for all databases will be published as an appendix to the final evidence review.

5.	Condition or domain being studied	Prelabour rupture of membranes (PROM)
6.	Population	Inclusion: • Women and people with confirmed prelabour rupture of membranes (PROM) at term (37 to 42 weeks gestation) with singleton pregnancies • Babies born at term following PROM Exclusion: • Women and people with PROM with multiple pregnancies • Women and people with PROM at pre-term (<37 weeks gestation) • Babies born pre-term following PROM (also known as preterm, prelabour rupture of membranes PPROM) • Babies with confirmed or suspected non-bacterial infections • Babies with localised infections

7.	Intervention/Exposure/Test	• Time between PROM and birth at the following intervals
		  • <12 hours
		  • ≥12 to <18 hours
		  • ≥18 hours to <24 hours

		• ≥24 to <36 hours • ≥36 to <48 hours • ≥48 hours to <72 hours Include all time intervals as reported in the studies. If there is not enough data reported for the timing intervals between PROM and birth, then studies reporting this duration as a continuous variable will be considered for inclusion. Note: If there are no sufficient studies reporting prelabour rupture of membranes to birth, then all cases of ROM (before, during and after the onset of labour) to birth will be included.
8.	Reference group and Covariates	Reference groups: • comparing PROM to birth at different time intervals (listed above) to those without PROM. • comparing PROM to birth interval to a PROM to birth interval of < 12 hours • comparing one PROM to birth interval to another (e.g., >36 hours vs. 24 hours) <u>Covariates:</u> Cohort studies will only be included if they adjust for any covariate(s) in their analysis. The committee chose not to specify the covariates to avoid excluding relevant studies. However, the committee identified some covariates that are important and will be considered when interpreting the findings:

		• Group B streptococcus (GBS) status of mother • chorioamnionitis status • ethnicity of mother • mode of birth. Due to expected variation in the covariates considered across studies, the list of covariates is not intended to be exhaustive.
9.	Types of study to be included	• Prospective cohort studies • Retrospective cohort studies • Systematic reviews of cohort studies Only studies with multivariable analysis will be included. For a systematic review (SR) to be included it must be conducted in line with the methodological processes described in the NICE manual. If sufficient details are provided, the SR will be fully included, or it will be used as the basis for further analyses where possible. If sufficient details are not provided to include a relevant SR, the review will only be used for citation searching.
10.	Other exclusion criteria	• Language limitation: non-English-language papers will be excluded • Conference abstracts, dissertation and unpublished data will not be included • Studies where multivariable regression analysis is not conducted • Studies where any covariate is not adjusted for in the analysis will be excluded.

		• Case-control studies, cross-sectional studies and case series will be excluded. • Women with suspected PROM • Women with twins and triplet pregnancies • Studies conducted in low-income countries (as defined by the OECD) • PROM is not clearly defined in the paper • time from ROM to onset of labour
11.	Context	The current NG195 guideline lists confirmed prelabour rupture of membranes (PROM) at term for more than 24 hours before the onset of labour as a risk factor for early onset neonatal infection. It has been highlighted by a stakeholder enquiry that this does not take into account the length of labour in addition to the length of PROM, which when combined could extend beyond 24 hours, potentially resulting in an increased risk of early onset neonatal infection. This review protocol seeks to address this query by determining the difference in risk of early onset neonatal infection depending on the length of time between PROM at term and birth. The findings of this analysis may impact NG235: Intrapartum care and NG229: Inducing labour
12.	Primary outcomes	• Culture-proven infection (blood or cerebrospinal fluid (CSF)) from a sample taken within 72 hours following birth or within the timeframe defined by the study for early-onset neonatal infection (this outcome may be reported as neonatal sepsis)

		• Culture negative suspected neonatal infection within 72 hours of birth where available or within the or within the timeframe defined by the study for early onset neonatal infection (in such cases baby is unwell or having elevated CRP but is not culture positive). • Admission to NICU for suspected infection within 72 hours of birth or within the timeframe defined by the study for early onset neonatal infection • Neonatal mortality associated with early onset infection • Meningitis within 72 hours of birth or within the timeframe defined by the study for early onset neonatal infection • Early onset pneumonia within 72 hours of birth or within the timeframe defined by the study for early onset neonatal infection (note: pneumonia may not be captured by blood or CSF culture) All follow-up time points will be included, as definitions of early-onset infection may vary across studies. Outcome measures: association measures such as odds ratios, risk ratios or hazard ratios.
13.	Secondary outcomes	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on

		at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two analysts, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the prognostic factors , relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • QUIPS checklist for prognostic factor studies The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Meta-analyses: Where appropriate, adjusted hazard ratios, odds ratios and risk ratios will be pooled using the generic inverse-variance method. Adjusted odds ratios, hazard ratios and risk ratios from multivariate models will only be pooled if the same set of factors are used across multiple studies, the same thresholds are applied to measure those factors, the prognostic effect measures are similar, the models are adjusted for the same core set of covariates, and the reference group is consistent.

		Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, the following criteria will be used to assess heterogeneity: not serious I^2 = <40%; serious I^2 = 40-60%; very serious I^2 = >60%. Where I^2 is 80% or above, the data will not be pooled. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis, then a random effects model will be used for meta-analysis, or the data will not be pooled. GRADE: The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ A modified approach will be applied using the GRADE framework. All data from cohort studies will be initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point. Minimally important differences: Importance and imprecision of findings will be assessed against minimally important differences (MIDs). For neonatal mortality, all culture positive early onset neonatal infections including culture positive meningitis, statistical significance will be used for assessing clinical importance. Sample size will be used for assessing imprecision. The below sample size cut-offs will be used: - >400 people - no imprecision

		- 200-400 people – serious imprecision - <200 people – very serious imprecision The following MID will be used for all other outcomes: 0.8 and 1.25. MID of 0.8 and 1.25 means the exposed group may have up to 20% lower or higher risk compared to the reference group. Note: We will use statistical significance for mortality due to the high clinical importance of preventing any avoidable deaths. We will also use statistical significance for the outcomes all culture positive early onset infections including culture positive meningitis, given its high risk of mortality. As the risk of neonatal mortality is lower with culture negative suspected early onset infections, early-onset pneumonia, and NICU admission for suspected infection, we will use MID thresholds for these outcomes. Post hoc change: A MID range of 0.8 to 1.25 will be used to assess imprecisions for all outcomes.
17.	Analysis of sub-groups	Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes: • GBS status of the mother (GBS positive vs. GBS negative mothers) Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence that prognostic factors have varying implications across groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume that the prognostic factors would behave similarly in that group compared to others.

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	October 2025
22.	Anticipated completion date	November 2025
23.	Named contact	**5a. Named contact** NICE **5b Named contact e-mail** Neonatalinfectionupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
24.	Review team members	

		• Topic Lead: Maija Kallioinen • Senior technical analyst: Sharangini Rajesh • Technical analyst: Sarah Dwyer • Information specialist: Stephanie Arnold • Project manager: Vonda Murray • Health Economist: Paul Jacklin
25.	Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.
26.	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.
27.	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: NICE guideline webpage.
28.	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.
29.	Keywords	Early-onset neonatal infection, prelabour rupture of membranes, PROM
30.	Details of existing review of same topic by same authors	This will be a new review for NG 195 Neonatal infection: antibiotics for prevention and treatment
31.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
32.	Additional information	None
33.	Details of final publication	www.nice.org.uk