Protocol for REVIEW A: Incidence and health consequences of neonatal GBS infection: a rapid review

Authors

Alex Todhunter-Brown, Wei Xu, Candida Fenton, Bridget Davis, Katie Thomson, Ceri Sellers, on behalf of NESSIE

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Table of Contents

Background

Group B Streptococcus (GBS) is recognised clinically as a contributor to neonatal morbidity and mortality [1] causing newborn sepsis, pneumonia and meningitis. A global incidence of 0.49 per 1000 live births has been estimated previously [2]. GBS is a common commensal bacterium found in gastrointestinal or genitourinary tracts [3]. While there are regional variations [4], globally around one fifth of pregnant women[a] carry GBS, with a transmission rate from mother to baby of around 36% during labour and delivery, and an incidence of GBS disease of around 3% in babies colonised with GBS [6].

Neonatal infections are typically categorised as early or late onset although definitions vary, with National Institute for Health and Care Excellence (NICE) defining early onset as within 72 hours of birth [7], World Health Organisation (WHO) within the first 6 days [8] and Royal College of Obstetricians and Gynaecologists (RCOG) within 7 days of birth [6]. Late onset is defined as post 72 hours – 28 days [7] or 7-89 days including infants by WHO [8]. Neonatal infection risk factors include pre-labour rupture of membranes, pre-term birth, maternal infection [9], infection of a previous baby or other neonates within a multiple pregnancy [10].

Short-term health outcomes of maternal GBS may include premature birth and stillbirth [4] and/or infant invasive GBS disease (iGBS) [11]. Severe neonatal sepsis with respiratory failure, cardiovascular dysfunction and impairment in at least two other organs has also been reported [12]. Recent studies suggest that long term health outcomes of iGBS meningitis include

[a] In line with the UK Network of Professors of Midwifery and Maternal and Newborn Health, we use the words women and woman throughout this protocol, recognising that this reflects the biology and identity of the great majority of those who are childbearing; for the purpose of this protocol, these terms include girls, and people whose identity does not correspond with their birth sex or who may have a non-binary identity 5. UK Network of Professors of Midwifery and Maternal and Newborn Health. *Position Statement: Use of sexed language in relation to women's reproductive health*. UK: Council of Deans of Health; 2023. URL: https://www.councilofdeans.org.uk/2024/02/midwifery-network-position-paper-use-of-sexed-language/ (accessed 27 January, 2025).

neurodevelopmental impairments [11] such as cerebral palsy, epilepsy and hearing impairments [13].

Previous reviews [4, 11] and the WHO [8] have highlighted knowledge gaps in relation to the impact of GBS infection on health outcomes and wider society. In addition, high income countries such as the United Kingdom and the Netherlands have in the past reported increased incidence of iGBS [14, 15]. In 2015 in the UK and Ireland this resulted in a substantial increase in cases from 0.48 to 0.57 per 1000 births since 2000 [16] with GBS indicated as the main cause of bacterial meningitis in infants in England and Wales [17]. Recent reporting by the UK Health Security Agency (2023) [18] highlighted a decline in early onset GBS infection in England but this remains at a higher rate than late onset infection indicating an ongoing need to monitor the incidence and consequences of neonatal GBS infection.

In the UK, screening for maternal GBS was last considered by the UK National Screening Committee (UK NSC) in 2017, having previously been considered in 2012 [3]. The conclusion was not to recommend screening [3]. Previous evidence syntheses on this topic undertaken by, or on behalf of, the UK NSC have been primarily concerned with culture positive GBS. However, the ongoing GBS3 trial [19] aims to evaluate the effectiveness of screening for GBS, taking into account both culture positive and negative neonatal infection. The UK NSC has requested an update to some of the evidence syntheses undertaken for their 2017 report [3], to investigate any developments in the field that may inform discussion on continuing or changing the current recommendation on universal GBS screening. The findings should also help provide a context within which the results of the GBS3 trial can be considered and discussed by the UK NSC.

Three rapid reviews will be undertaken to support decisions of the UK NSC:

- Review A: Incidence in the UK and health consequences of neonatal GBS infection.
- Review B: Incidence in the UK and health consequences of all-cause neonatal infection.
- Review C: Benefits and harms of antenatal or intrapartum screening for maternal GBS carriage and subsequent use of intrapartum antibiotic prophylaxis versus risk-based protocols or no intervention.

This document outlines the protocol for Review A: Incidence in the UK and health consequences of neonatal GBS infection. Once completed, the findings of all three reviews will be used to help populate the UK NSC evidence summary template, which will be presented to the UK NSC prior to their consideration of universal GBS screening later in 2025.

Patient and Public Involvement (PPI) / Wider interest-holder involvement

A NESSIE PPI co-investigator is part of our rapid review team (contributing to Reviews A, B and C). We will follow national standards and principles, and will develop and implement an involvement plan, which will be detailed in our protocols and reported in final reports using GRIPP2 guidance [20] and ACTIVE framework [21]. We have established a small 'Reference Group' for these rapid reviews. This is considered particularly important as the NESSIE team do not have content expertise relating to these rapid reviews. The key role of the Reference Group will be to provide content expertise, ensuring appropriate use of terminology, relevant content, supporting study inclusion decisions, and advising on reporting and dissemination. Members comprise people with clinical and policy expertise, and people representing those with lived experience. Details of the planned Reference Group involvement are reported according to the ACTIVE framework [21] in Appendix A.

Key definitions

We use the following definitions:

- GBS: Group B streptococcus, also known as Streptococcus agalactiae, a facultative gram-positive organism.
- GBS colonisation: microbiological confirmation of GBS on swabs from nose, umbilicus, axilla, rectum or ear.
- Invasive GBS infection: microbiological culture of blood or cerebrospinal fluid (CSF) confirming GBS, together with any symptoms or signs of sepsis, pneumonia or meningitis.
- Early-onset GBS (EOGBS) infection: invasive GBS disease in infants aged 0–6 days after birth.

- Late-onset GBS (LOGBS) infection: invasive GBS disease in infants 7–89 days after birth.
- Culture positive GBS infection: a positive culture of a GBS from blood or cerebrospinal fluid, together with signs of clinical disease.
- Culture negative GBS infection: symptoms or signs of sepsis, pneumonia or meningitis with culture negative GBS (blood or cerebrospinal fluid culture) but mother is GBS positive [3].

However, we note that definitions used within the literature may vary. For example, some studies may distinguish between culture positive GBS infection and culture negative GBS infection, as defined above, while others may use terms such as "probable" or "suspected" GBS or define GBS according to different levels of certainty [22, 23]. Further, a clinical diagnosis of culture negative GBS infection may sometimes be given when the mother is GBS negative, or the mother's GBS status is unknown, but clinical expert judgement supports this diagnosis (for example where the risks for GBS are known to be high). Within our rapid review, we will adopt a pragmatic approach, documenting definitions used by study authors where these vary from those given above.

In the context of this review, we define short-, medium- and long-term health conditions as:

- Short-term: relates to the neonatal period, which has been defined by the World Health Organization (WHO) as "beginning at birth and ending at 28 completed days of life" [24].
- Medium-term: relates to infancy, a time extending from the first month after birth to approximately 12 months of age [2].
- Long-term: relates to childhood, a time extending from 1-18 years of age

However, as above, we will adopt a pragmatic approach, documenting definitions used by study authors where these vary from those given above.

Research questions

1: UK data on incidence and natural history

Q1.1 What are the reported incidences of early and late-onset GBS infection in the UK and how does incidence vary according to key characteristics of the population?

Q1.2 What are the reported rates of death, and short-, medium-, or long-term health conditions attributed to EOGBS or LOGBS infection in the UK?

2: UK and other high-income country data on the health consequences of EOGBS or LOGBS infection

Q2 What short-, medium- or long-term health conditions have been specifically shown to occur at higher rates in neonates/infants/children who had EOGBS or LOGBS infection compared with those who did not?

Objectives

1) To describe UK data relating to (i) incidence of EOGBS and LOGBS infection and (ii) rates (either proportion, prevalence or incidence) of death, short-, medium- or long-term health conditions:

1.1 To describe, where data are available, incidences of:

- culture positive EOGBS
- culture negative EOGBS
- culture positive LOGBS
- culture negative LOGBS

Also, where data are available, to describe incidences according to key characteristics of the study populations, including maternal risk factors, gestational age, participation in screening and/or use of intrapartum antibiotics.

1.2 For these populations, to describe the rates (either proportion, prevalence or incidence) of death and the following health conditions:

- Neonatal septicaemia and meningitis (requiring intensive care or ventilation)
- Neonatal pneumonia (requiring intensive care or ventilation)
- Neonatal encephalopathy (requiring intensive care or ventilation)
- Neurodevelopmental impairment

If studies report data relating to other health conditions, these will be noted and the rates described.

2) To summarise findings from studies in the UK and other high-income countries that have been explicitly designed to determine whether EOGBS infection and/or LOGBS infection are risk factors for other health conditions in later life, i.e., studies directly comparing data from neonates/infants/children who had neonatal GBS infection with those who did not.

Only studies which include a comparator group (a group who did not have GBS infection) will be included. Short-, medium- or long-term health conditions which have been shown to occur at higher rates in neonates/infants/children who had neonatal GBS infection will be identified. Where data are available, the relative risk of these conditions will be reported.

Design

This review follows methods recommended for Cochrane Rapid Reviews [25], combined with JBI guidance for systematic reviews relating to incidence and epidemiology [26, 27]. In line with accepted methods for rapid reviews, we will first search for up-to-date systematic reviews which address our objectives and will use these to identify primary studies, only conducting database searches for primary studies after the search date of the identified systematic review.

We will report our findings according to guidance for preferred reporting items for systematic reviews and meta-analyses (PRISMA) [28] and to guidance for Meta-Analyses Of Observational Studies in Epidemiology (MOOSE) [29].

Protocol registration: We will register this rapid review protocol on PROSPERO.

Methods

Inclusion and exclusion criteria for this review

Eligibility criteria

Selection criteria are defined separately for **objective 1.1, 1.2 and 2**:

Table 1 Eligibility criteria for objective 1.1

Objective 1.1	Inclusion	Exclusion

Population	Neonates and infants (including pre-term) (up to 90 days old) [Including babies born to women screened for GBS (and confirmed as either GBS+ or GBS-) or born to women with unknown GBS status; and Including babies born to women who did / did not take intrapartum antibiotics.]	>90 days old [If studies include a mixed population of infants up to and greater than 90 days old, we will exclude if separate data are not available for those ≤90 days, or if >10% of participants are >90 days old]
Condition	EOGBS or LOGBS, as defined by the study authors. All-cause neonatal infection, where the proportion with confirmed GBS are clearly reported. GBS may be confirmed (i.e., culture positive GBS) or suspected (i.e., culture negative GBS). We will report data relating to culture positive / negative, using definitions provided by study authors.	GBS colonisation, without infection / invasive disease. Infections other than GBS; Maternal GBS (without neonatal/infant GBS). All cause neonatal infection, unless the proportion with confirmed GBS are clearly reported.
Context	UK	Non-UK countries
Study design	Observational studies including a population of neonates and reporting the number of neonates with iGBS. These could include cohort studies cross-sectional studies or studies exploring routinely collected data (e.g. surveillance data).	Mathematical modelling studies.

Table 2 Eligibility criteria for objective 1.2

Objective 1.2	**Inclusion**	**Exclusion**
Population	Neonates and infants (including pre-term) (up to 90 days old) with EOGBS or LOGBS, as defined by the study authors. GBS may be confirmed (i.e., culture positive GBS) or suspected (i.e., culture negative GBS). We will report data relating to culture positive / negative, using definitions provided by study authors. [Including babies born to women screened for GBS (and confirmed as either GBS+ or GBS-) or born to women with unknown GBS status; and Including babies born to women who did / did not take intrapartum antibiotics.]	>90 days old GBS colonisation, without infection / invasive disease. Infections other than GBS; Maternal GBS (without neonatal/infant GBS). All cause neonatal infection, unless the proportion with confirmed GBS are clearly reported. [If studies include a mixed population of infants up to and greater than 90 days old, we

		will exclude if separate data are not available for those ≤90 days, or if >10% of participants are >90 days old]
Condition	Health conditions of: - Mortality - Neonatal septicaemia and meningitis - Neonatal pneumonia - Neonatal encephalopathy - Neurodevelopmental impairment If studies report data relating to other health conditions, we will also note data relating to these conditions.	Studies that do not report data relating to the number with at least one health condition.
Context	UK	Non-UK countries
Study designs	Non-comparative observational studies reporting health conditions for the population who had neonatal iGBS.	Mathematical modelling studies.

Table 3 Eligibility criteria for objective 2

Objective 2	**Inclusion**	**Exclusion**
Population	Exposed group: neonates or infants (up to 90 days old) with iGBS (i.e. population with EOGBS or LOGBS). Unexposed group: a comparator group who did not have iGBS. We will report culture positive/ negative, using definitions specified by the study.	Those with GBS who are >90 days old. Exposed group with GBS colonisation, but without invasive disease. Infections other than GBS; Maternal GBS (without neonatal/infant GBS). All cause neonatal infection, unless the proportion with confirmed GBS are clearly reported.
Condition	Health condition during neonatal period, infancy or childhood.	
Context	High-income countries (as defined by World Bank [30]).	Low- and Middle-income countries (as defined by World Bank [30])
Study designs	Observational studies with data for a group with EOGBS or LOGBS and an appropriate comparator group. This could either be a cohort study or case-control study which compare the	Studies without a comparator group. Experimental studies.

	proportions of neonates with/without EOGBS or LOGBS who later develop a health condition.	Mathematical modelling studies.

Additional eligibility criteria

Language: we will include papers published in English language only.

Dates: We will not apply any date cut-off for inclusion of studies. However, our search methods mean that primary studies published prior to the search date of the most recent, high quality, systematic review will only be included if they were included within the relevant systematic review. We will only consider systematic reviews published after 2016. Justification: we will adopt a pragmatic approach to searching, building on previously published systematic reviews. This is appropriate for a rapid review. A 2016 search date for systematic reviews is appropriate as this is the year of known systematic reviews / evidence summaries conducted for the UK NSC.

Outcomes of interest

For objective 1.1, we are interested in incidence (studies must report number with invasive GBS from a denominated UK population).

For objective 1.2, we are interested in rates (either proportion, prevalence or incidence) of health conditions from a UK population with EOGBS or LOGBS of:

- Mortality
- Neonatal septicaemia and meningitis (requiring intensive care or ventilation)
- Neonatal pneumonia (requiring intensive care or ventilation)
- Neonatal encephalopathy (requiring intensive care or ventilation)
- Neurodevelopmental impairment
- Other health conditions, as reported by studies

(studies must report number with invasive GBS infection, and proportion with subsequent health condition).

For objective 2, we are interested in any health condition for which the study authors find that EOGBS or LOGBS is associated with a higher risk of that condition, compared with the risk in

a matched comparator group, as well as any health conditions which are included in these studies and are not found to be associated with prior neonatal GBS infection.

For objectives 1.2 and 2 short-, medium- and long-term conditions reported will be eligible. However, we will document the time since birth (i.e. age) as reported by study authors.

Search methods and study selection

Searching

We will use a two-stage process to identify relevant primary studies which meet our criteria.

Stage 1: An information specialist will conduct an initial, targeted (or 'focussed') search for systematic reviews included in bibliographic databases (including Medline and Embase) since 2016. This search will involve knowledgeable identification (using both MESH terms and free text) and selection of the most relevant and up-to-date systematic reviews addressing one or more of the three research objectives. This focussed approach will serve to efficiently / rapidly (i) identify primary research for assessment and possible incorporation into the review (i.e. eligible primary studies included in one or more of the identified systematic reviews), (ii) help refine the systematic search strategy for use in stage 2 and (iii) identify the date from when to run the stage 2 systematic search. We will use the EPPI-Centre definition of a systematic review as a review that uses explicit and transparent methods, follows a standard set of stages and can be considered accountable, replicable and updateable [31]. We will exclude scoping reviews, narrative reviews (i.e. reviews which do not follow PRISMA guidance) and intervention reviews (i.e. systematic reviews focussing on effectiveness of an intervention). This stage 1 searching process will be iterative, involving feedback between the information specialist and other members of the research team. A description of the final process will be reported in the methods of the completed review and all systematic reviews considered for inclusion will be listed along with reasons for their ultimate inclusion or exclusion following screening (see below).

Stage 2: Systematic search for primary studies published after the most recent systematic review for each research question. We will search Medline and Embase databases via the OVID platform, using the pre-defined, peer-reviewed search strategy for primary studies. Studies

published after the search date(s) of the selected systematic reviews will be identified. The use of only two databases aligns with recommendations for rapid reviews [22]. Searches will be restricted to English language. Database search results will be de-duplicated and entered into Covidence. Our MEDLINE search strategy is provided in Appendix B.

Screening

Selection of relevant systematic reviews: One reviewer will consider the identified systematic reviews and note the search date and number of included studies for each systematic review. Two reviewers will discuss the identified systematic reviews and reach agreement on comprehensive, up-to-date systematic reviews which address each review objective. These decisions will be made through discussion, with consideration of key criteria, including: date of search, comprehensiveness/quality of search strategy, inclusion/exclusion criteria, number of studies with high-quality design (i.e., cohort studies), relevance to our review objectives, and overlap with other reviews. Decisions will be transparently reported. If considered appropriate, we will include several systematic reviews, to ensure comprehensive identification of primary studies.

Identification of primary studies to include: All primary studies included in the identified systematic reviews will be extracted and entered into Covidence, alongside all additional primary studies identified in the stage 2 systematic search published since the search date(s) of the included systematic reviews. One reviewer will screen titles and abstracts, excluding obviously irrelevant studies. Two reviewers will then independently apply eligibility criteria to full texts of remaining studies; any disagreements will be resolved by a third reviewer or through discussion between reviewers. Overall, we will apply our inclusion criteria to:

- all studies included within the systematic reviews identified in stage 1.
- results of the systematic search for recent primary studies (stage 2).
- the primary studies included within Review C of these three linked rapid reviews (which is focussed on benefits and harms of maternal screening), as this will identify studies which provide observational data which address the objectives for this review.

Justification for approaches to searching and screening

First considering the primary studies included within relevant systematic reviews is pragmatic and aligns with rapid review methods for identification of studies [32]. Use of the focussed search approach will accelerate the identification of key systematic reviews, requiring significantly less time and resource than conducting a comprehensive search. Conducting comprehensive searches to identify primary studies published after the search dates of selected high-quality systematic reviews will ensure that recent studies are included. Only including primary studies (i.e. using previous systematic reviews to aid identification of primary studies but not considering these as included studies) is pragmatic and efficient. This avoids having to deal with complex (and time-consuming) issues relating to quality of systematic reviews (i.e. assessment of methodological quality or risk of bias), overlapping systematic reviews (systematic reviews which include the same, or similar, primary studies), and varied data extraction and quality assessment within systematic reviews (i.e. systematic review data which are not comparable due to application of different criteria, tools and judgements). Finally, considering the primary studies from Review C provides an efficient way to ensure that any relevant data from studies investigating screening strategies are included within our review, without the need to expand our search strategies to consider intervention/experimental studies.

Although Cochrane rapid review guidance proposes that it may be appropriate to have one reviewer only, we will use two reviewers to complete full text screening. This is in order to minimise errors, as the reviewers are not previously familiar with the topic area. Involving a third reviewer where there are disagreements will enable a member of the Reference Group, with topic expertise, to contribute to decision-making.

Critical appraisal

Systematic reviews (used to identify primary studies): We will not conduct formal critical appraisal of systematic reviews, as we are using systematic reviews as a tool to identify primary studies, rather than as "included" studies. However, when determining which systematic reviews are eligible for consideration, we will consider study quality, with particular reference to the search strategy. Therefore, we will consider the AMSTAR2 'critical' domains [33] of:

- Protocol registered before commencement of the review (item 2)
- Adequacy of the literature search (item 4)
- Justification for excluding individual studies (item 7)

We will reject any systematic reviews that are judged to be high risk of bias for these domains. We will document our decision-making transparently.

Included primary studies: We will use CASP tools [34] (selected according to study design; i.e. CASP tool for cohort studies, case-control studies or cross-sectional studies). Justification for use of CASP tools are that these are commonly used, evidence-based tools, considered easy to use (and therefore suitable for rapid reviews). CASP tools [34] provide a structured approach to consider important factors, supporting decision-making and transparent recording. The recent addition of an appraisal summary is considered beneficial for supporting interpretation of the findings of this rapid review.

Critical appraisal will be conducted by two reviewers, with consensus reached through discussion. Where disagreements cannot be resolved, a third reviewer will be involved.

Data extraction

For *all* included studies, we will extract the following information (where reported by study authors):

- Study name and year
- Aim
- Study design, categorised as either:
    - Cohort (prospectively collected data)
    - Cohort (retrospectively collected data)
    - Cross-sectional (data from one time point only)
    - Case-control study (where case is individuals with a given health condition and control is those without that health condition)
- Population
    - Gestational age
    - Maternal participation in screening

    - Use of intrapartum antibiotics (IAP)
    - Maternal risk factors
    - Other characteristics reported by the study that potentially affect incidence
- Condition
    - EOGBS (detailing where this is culture positive or culture negative)
    - LOGBS (detailing where this is culture positive or culture negative)
- Health conditions
    - Health conditions assessed
    - Timepoints of assessed health conditions (e.g., short-, medium- or long-term)
- Context
    - Country (UK only for Objectives 1.1 and 1.2; high income countries for objective 2)
    - Maternal screening and IAP strategies
    - Study data source (e.g., registry, hospital)
- Results data (where studies have a comparator group, we will extract data for both the GBS group and the comparator group):
    - Number of recruited participants
    - Number of participants at each outcome assessment
    - For studies addressing objective 1.1:
        - Incidence of GBS
    - For studies addressing objective 1.2:
        - Results data (in the form of n/N) for:
            - Mortality
            - Pneumonia
            - Septicaemia
            - Meningitis
            - Encephalopathy

        - Neurodevelopmental impairment
        - Any other health conditions reported by the included studies

    - For studies addressing objective 2:
        - Results data as presented in the studies, including, for both GBS group and comparator group
            - Number of participants
            - Population details (as detailed above)
            - Health condition (e.g., neurodevelopmental impairment, visual impairment)
            - Cases (number with condition)
            - Statistical measures of association/risk, as reported by the study authors

Data will be extracted by one reviewer and checked by a second reviewer. Any disagreements will be resolved through discussion.

Data synthesis and analysis

For all objectives we will produce a narrative summary of relevant systematic reviews and of primary studies. We will tabulate extracted data and produce summary tables of results reported in the included studies relevant to each objective (see Tables 4-6, below).

We will discuss the summarised/tabulated results data with reference to:

- Our confidence in the findings (based on study quality)
- Previously published data, including data from UK NSC reviews [3, 35], and other relevant data (e.g. data from previous systematic reviews or relevant modelling studies [10, 36].

Results will be summarised in the format required for the UK NSC Evidence Summary.

For objective 1.1, we will produce a table of UK incidence data:

Table 4 UK incidence data

Study	Study design	Geographic location	Study setting	Time period of data collection	Population characteristics						Condition		Incidence (n/N)	Study quality (appraisal summary)
					Size of population (N)	Gestational age	Maternal participation in screening (including type / timing of screening, e.g. antenatal, intrapartum)	Use of IAP	Maternal risk factors	Other relevant population characteristics	EOGBS, LOGBS; Culture positive or culture negative	Number with condition (n)		
Study 1														
Study 2														
Study 3 etc														

For objective 1.2 we will produce a summary table for each health condition reported by at least one UK study which meets our inclusion criteria:

Table 5 UK data on frequency of health conditions

Study	Study design	Geographic location	Study setting	Time period of data collection	Characteristics of GBS population							Health condition		Frequency of health condition (n/N)	Study quality (appraisal summary)
					GBS 'type' (EOGBS, LOGBS; Culture positive or culture negative)	Size of population (N)	Gestational age	Maternal participation in screening (including type / timing of screening, e.g. antenatal, intrapartum)	Use of IAP	Maternal risk factors	Other relevant population characteristics	Mortality, Pneumonia, Septicaemia, Meningitis, Encephalopathy, or Neurodevelopmental impairment	Number with health condition (n)		
Study 1															
Study 2															
Study 3 etc															

For objective 2 we will produce a summary table for each health condition for which at least one included study has results data indicating that EOGBS or LOGBS may be a risk factor, tabulating information about the GBS group and the comparator group, and results data as presented by the study authors.

Table 6 UK and high-income country data on short-, medium- and long-term health conditions associated with EOGBS or LOGBS

Study	Country / Geographic location	Study setting	Time period of data collection	Study Group	Characteristics of population (specify details)							Health condition				Statistical measures of association	Study quality (appraisal summary)
				(GBS or comparator)	GBS 'type' (EOGBS, LOGBS; Culture positive or culture negative)	Size of population (N)	Gestational age	Maternal participation in screening (eg.type/timing)	Use of IAP	Maternal risk factors	Other relevant population characteristics	Condition e.g. neurodevelopmental impairment, visual impairment	Assessment time point (short-, medium- or long-term)	Number with health condition (n)	Rate of health condition (n/N)		
Study 1				GBS group													
				Comparator group													
Study 2				GBS group													
				Comparator group													

Governance

Protocol

This protocol has been developed by NESSIE (NIHR Evidence Synthesis Scotland InitiativE) in order to address questions proposed by the UK NSC Evidence team. This has involved an iterative process of development and feedback to ensure that the protocol will provide the evidence required by the UK NSC Evidence team.

Review

The review will be conducted by the NESSIE team, according to the agreed protocol (as registered with PROSPERO). Any deviations from the protocol will be discussed with the UK NSC evidence team before finalisation of the reviews and will be stated (with reasons) in the final review as deviations from the original protocol.

Evidence summary

Findings from this review will be integrated into a UK NSC Evidence Summary produced by NESSIE in collaboration with the UK NSC Evidence Team who will provide feedback and co-ordinate feedback from the fetal, maternal and child health (FMCH) reference group and from public consultation (if applicable). NESSIE will integrate findings from the completed review, and responding to relevant feedback relating to review findings. The final Evidence Summary, co-produced by NESSIE and the UK NSC evidence team, will be used by the UK National Screening Committee to support discussions on GBS screening. The UK National Screening Committee will make the final decision on any recommendation related to a GBS screening programme.

Acknowledgements

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Appendices

Appendix A: Plans for Reference Group, described according to ACTIVE Framework

ACTIVE Framework construct	**Plans for NESSIE GBS Reference Group**
Who will be involved?	People who have expertise / knowledge relating to screening for neonatal GBS, including those with expertise relating to: • Midwifery • Microbiology • Neonatal care (neonatologist / neonatal nurse) • Paediatrics And those with personal lived experience relevant to the topic, for example, parents who chose to pay for GBS screening during the antenatal period or people involved in organisation of mother and baby groups. As of 27/01/2025, the following people have agreed to be members of this Reference Group: 1. Rosie Hill, NESSIE Co-applicant with Policy and Public Health experience 2. Prof Helen Cheyne, Royal College of Midwives (Scotland) Professor of Midwifery 3. Dr Ryan Kean, Lecturer in Clinical Microbiology, Glasgow Caledonian University 4. Prof Narendra Aladangady, Consultant Neonatologist, Homerton University Hospital, Homerton Healthcare NHS Foundation Trust; Hon Clinical Professor in Child Health, Barts and the London School of Medicine and Dentistry 5. Dr Charlotte-Eve Short, Clinical Senior Lecturer in HIV and GU Medicine, Department of Infectious Disease, Imperial College London. 6. Mrs Amanda Rees, has lived experience of Strep B screening, being a mother of 2 young children who chose private screening for Strep B (she is not affiliated to any 3rd sector organisation). We are seeking additional members who have lived experience of Strep B screening, and choices associated with this.

	We will have a pragmatic approach to membership, and if – during the review process – we come across issues requiring specific expertise not held by current members (e.g. decisions relating to inclusion of specific research papers), then we will seek additional members with suitable expertise. This approach is appropriate given the rapid nature of these reviews.
How will people be recruited to the reference group?	We will use a closed approach, inviting named people with specific expertise/experience to join the reference group. As NESSIE only has limited existing contacts, we will use a 'snowball' approach, where we invite initially identified individuals to propose names of additional people. The use of a closed, invitation-based approach, is appropriate given the rapid nature of these reviews, and the need to involve people able to provide topic expertise.
What will the mode of involvement be?	The Reference group will be involved using a continuous approach. The method of interaction will primarily be indirect, through emails. However, we anticipate having a small number of online meetings, one at the start of the review, and a second during the data synthesis / write up. If necessary, we will have direct interaction with individual members (e.g. to seek clarification around specific terminology)
At what stage in the review process will involvement occur? **What will the level of involvement be (at each stage)?**	
1. Develop question	No involvement (questions will be developed through discussion with UK NSC)
2. Plan methods	No involvement (methods will be developed through discussion with UK NSC)
3. Write & publish protocol	Contributing/Influencing – draft protocols will be shared with Reference Group members, and members invited to comment on language, terminology, accessibility and presentation of the information.
4. Develop search	Contributing – members will be asked to view a draft search strategy and provide suggestions for any additional or alternative search terms. (The search strategy will then be developed by an information specialist and peer review provided by UK NSC).
5. Run search	No involvement (search will be run by NESSIE information specialist)

6. Select studies	Contributing/Influencing – where there are conflicts in agreements between review team, these may be discussed with individual Reference Group members (according to expertise required).
7. Collect data	Contributing/Influencing – where there are conflicts in data extracted by review team, or uncertainty in relation to data presented in an included study, these may be discussed with individual Reference Group members (according to expertise required).
8. Assess risk of bias	Contributing/Influencing – where there are uncertainties in relation to risk of bias within an included study, these may be discussed with individual Reference Group members (according to expertise required).
9. Analyse data	Contributing/Influencing – where there are uncertainties in relation to data presented within an included study (e.g. details of the population to which the data relates), these may be discussed with individual Reference Group members (according to expertise required).
10. Interpret findings	Contributing/Influencing – Reference Group members will be invited to comment on draft presentation of review results. They will not be able to influence the review results (i.e. objective data presented from individual studies), but will be invited to comment on the presentation of the findings, including structure of tables and figures, and language used to express findings.
11. Write & publish	As above. Where Reference Group members have contributed sufficient to meet criteria for authorship, they will be listed as authors on the published reviews.
12. Knowledge translation & impact	Contributing/Influencing – Reference Group members will be invited to offer views on where (i.e. which journals) the rapid reviews should be published. Receiving/contributing – Reference Group members would be informed of how the rapid review results were being used within the UK NSC Evidence Summary. Those who were authors on the publications may have opportunities to comment on how the rapid review results were used within the evidence summary. There would be no direct role / responsibility of the Reference Group members in the development of screening recommendations.

Appendix B: Search strategy

Ovid MEDLINE(R)

1	exp Streptococcus agalactiae/
2	"group b streptococc*".ti,ab.
3	"streptococcus agalactiae".ti,ab.
4	"Streptococcus Group B".ti,ab.
5	EOGBS.ti,ab.
6	GBS.ti,ab.
7	iGBS.ti,ab.
8	LOGBS.ti,ab.
9	or/1-8
10	exp Infant, Newborn/
11	Infant.ti,ab.
12	newborn*.ti,ab.
13	neonat*.ti,ab.
14	exp Pregnancy/ep [Epidemiology]
15	exp Infant Death/
16	Preterm.ti,ab.
17	prematurity.ti,ab.
18	or/10-17
19	9 and 18
20	Pregnancy Complications, Infectious/ep
21	19 or 20
22	limit 21 to english language

Protocol for REVIEW B: Incidence and health consequences of all-cause neonatal infection: a rapid review

Authors

Alex Todhunter-Brown, Wei Xu, Candida Fenton, Bridget Davis, on behalf of NESSIE

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Table of Contents

Background

In 2017 more than 50% of global sepsis cases occurred in children including a high percentage of neonates [1]. Globally, sepsis is a significant contributor to neonatal morbidity and mortality with an approximate incidence of 2824 cases per 100,000 live births and a mortality rate of 17.6% [2]. Whilst there is currently no agreed global definition for neonatal sepsis it is generally considered to involve an infective organism identified within the blood or cerebrospinal fluid [3] or with negative or unknown culture status identified through clinical signs such as apnoea, shock or seizures [4].

Neonatal infections are typically categorised as early or late onset although definitions vary, with National Institute for Health and Care Excellence (NICE) NICE defining early onset as within 72 hours of birth [4], World Health Organisation (WHO) within the first 6 days [5] and RCOG within 7 days of birth [6]. Late onset is defined as post 72 hours – 28 days [7] or 7-89 days including infants by WHO [5]. Neonatal infection risk factors include pre-labour rupture of membranes, pre-term birth, maternal infection [8], infection of a previous baby or other neonates within a multiple pregnancy [4].

Short-term health outcomes of severe neonatal sepsis can involve respiratory failure, cardiovascular dysfunction and impairment in at least two other organs [9]. Long term health implications can include neonatal brain injury [10] with subsequent impaired neurodevelopment such as poor motor outcomes [11]. As the recommended treatment for neonatal sepsis includes the use of antibiotics [4] the development of antibiotic resistance in the treatment of neonates is particularly concerning [12] together with uncertainty regarding the long-term effects on children [13].

Within England neonatal infection occurs in approximately 5120 births per annum [14] of which sepsis is attributable to 10% of neonatal deaths [7]. In 2015, NHS England created a National Maternity Safety Ambition to reduce neonatal deaths by 50% [15] aligning with the key United Nations target of ending preventable newborn deaths by 2030 [16]. Strategies to reduce neonatal infection are central to these targets.

Previous UK National Screening Committee (UK NSC) reviews [17] of screening to prevent invasive neonatal GBS infection have been primarily concerned with culture positive GBS [17]. More recently the GBS3 trial has focused attention on the wider landscape of both culture positive and negative neonatal infection. The GBS3 trial [18] aims to evaluate the effectiveness of screening for GBS within this context.

This project will develop the first review of the evidence relating to the incidence and health consequences of all-cause neonatal infection to be considered by the UK NSC as part of its decision-making process. More particularly, it will provide a context within which the results of the GBS3 trial can be considered and discussed.

This rapid review is part of a series commissioned by the UK NSC to identify and summarise new research and data related to GBS incidence in the UK, GBS health outcomes, benefits and harms of screening followed by intrapartum antibiotic prophylaxis (IAP).

Three rapid reviews will be undertaken to support decisions of the UK NSC:

- Review A: Incidence in the UK and health consequences of neonatal GBS infection.
- Review B: Incidence in the UK and health consequences of all-cause neonatal infection.
- Review C: Benefits and harms of antenatal or intrapartum screening for maternal GBS carriage and subsequent use of intrapartum antibiotic prophylaxis versus risk-based protocols or no intervention.

This document outlines the protocol for Review B: Incidence in the UK and health consequences of all-cause neonatal infection. Once completed, the findings of all three reviews will be used to help populate the UK NSC evidence summary template, which will be presented to the UK NSC prior to their consideration of universal GBS screening later in 2025.

Patient and Public Involvement (PPI) / Wider interest-holder involvement

A NESSIE PPI co-investigator is part of our rapid review team (contributing to Reviews A, B and C). We will follow national standards and principles, and will develop and implement an involvement plan, which will be detailed in our protocols and reported in final reports using

GRIPP2 guidance [19] and ACTIVE framework [20]. We have established a small 'Reference Group' for these rapid reviews. This is considered particularly important as the NESSIE team do not have content expertise relating to these rapid reviews. The key role of the Reference Group will be to provide content expertise, ensuring appropriate use of terminology, relevant content, supporting study inclusion decisions, and advising on reporting and dissemination. Members comprise people with clinical and policy expertise, and people representing those with lived experience. Details of the planned Reference Group involvement are reported according to the ACTIVE framework [20] in Appendix A.

Key definitions

We use the following definitions:

Early-onset all-cause neonatal infection [definition based on Daniels et al (2024)[18]]:

- A positive culture of a pathogenic bacteria from microbiological tests (e.g., from blood; cerebrospinal fluid; pleural fluid; peritoneal fluid urine sample) taken at <7 days after birth
- Negative/ unknown culture status with ≥3 agreed clinical signs or symptoms, for which intravenous antibiotics are given for ≥5 days, starting within 7 days of birth
- Death which is <7 days after birth, if infection or sepsis was recorded on the death certificate

Late-onset all-cause neonatal infection:

- A positive culture of a pathogenic bacteria taken at ≥7 days and <28 days after birth
- Negative/ unknown culture status with ≥3 agreed clinical signs or symptoms, for which intravenous antibiotics are given for ≥5 days, starting within 28 days of birth
- Death which is <28 days after birth, if infection or sepsis was recorded on the death certificate

The following acute onset clinical or laboratory features will be used as part of the definition of clinically suspected neonatal infection, if the blood and CSF cultures are negative/ unknown and intravenous antibiotics are given for ≥5 days (7 days for early-onset, 28 days for late-onset)[18] :

- increase in oxygen requirement or increase in ventilatory support or *new or an increase in frequency of episodes of apnoea
- increase in frequency of episodes of bradycardia or hypotension (needing inotrope support or other intervention)
- temperature ≥37.5C or <36.5C
- enteral feeds intolerance or abdominal distension
- *reduced urine output to <1 ml/kg/hr
- *impaired peripheral perfusion (capillary refill time >3 seconds or skin mottling or core peripheral temperature gap >2°C)
- irritability or lethargy or hypotonia (clinician-defined)
- *serum C-reactive protein levels >15 mg/L or procalcitonin ≥2 mg/mL
- *white blood cells count 20×10^9 cells/L or platelet count $<100\text{x}10^9$/L
- glucose intolerance (blood glucose <2.2mmol/l or >10mmol/l) or metabolic acidosis (base excess <-10 mmol/L or lactate >2 mmol/L)

* It is acknowledged that these signs or symptoms may not be able to be identified from some routine data sources.

However, we note that definitions used within the literature may vary. Therefore, we will include any studies which focus on "all-cause neonatal infection" or "all-cause neonatal sepsis" (or other terms with definitions that align with the focus of our review), as defined by the study authors, as long as this occurs <28 days after birth. We use this cut-off (i.e., <28 days) as this aligns with definitions of "neonate" [21]. Where we find studies that state they focus on all-cause neonatal sepsis, but have a cut-off of ≥28 days, including participants who are both <28 days and ≥28 days old, we will adopt a pragmatic approach (in line with our rapid review methodology) and include these if judged to be relevant to our research questions.

In the context of this review, we define short-, medium- and long-term health conditions as:

- Short-term: relates to the neonatal period, which has been defined by the World Health Organization (WHO) as "beginning at birth and ending at 28 completed days of life" [22].

- Medium-term: relates to infancy, a time extending from the first month after birth to approximately 12 months of age [23].
- Long-term: relates to childhood, a time extending from 1-18 years of age.

However, we note that different studies may use different thresholds to define their study outcomes as short-, medium- and long-term. Therefore, we will adopt a pragmatic approach, documenting definitions used by study authors where these vary from those given above.

Research questions

1: UK data on incidence and natural history

Q1.1 What are the reported incidences of early-onset and/or late-onset all-cause neonatal infection in the UK and how does incidence vary according to key characteristics of the population?

Q1.2 What are the reported rates of death, and short-, medium-, or long-term health conditions attributed to early-onset and/or late-onset all-cause neonatal infection in the UK?

2: UK and other high-income country data on the health consequences of all-cause neonatal infection

Q2 What short-, medium- or long-term health conditions have been specifically shown to occur at higher rates in neonates/infants/children who had early-onset or late-onset all-cause neonatal infection compared with those who did not?

Objectives

1) To describe UK data relating to (i) incidence of early-onset and/or late-onset all-cause neonatal infection and (ii) rates (either proportion, prevalence or incidence) of death, short-, medium-, or long-term health conditions:

1.1 To describe, where data are available, incidences of:

- culture positive early all-cause neonatal infection
- culture negative early all-cause neonatal infection

- culture positive late all-cause neonatal infection
- culture negative late all-cause neonatal infection

Also, where data are available, to describe incidences according to key characteristics of the study populations, including maternal risk factors, gestational age, participation in screening and/or use of intrapartum antibiotics.

1.2 For these populations, to describe the rates (either proportion, prevalence or incidence) of death and the following health conditions:

- Neonatal septicaemia and meningitis (requiring intensive care or ventilation)
- Neonatal pneumonia (requiring intensive care or ventilation)
- Neonatal encephalopathy (requiring intensive care or ventilation)
- Neurodevelopmental impairment

If studies report data relating to other health conditions, these will be noted and the rates described.

2) To summarise findings from studies in the UK and other high-income countries that have been explicitly designed to determine whether early-onset and/or late-onset all-cause neonatal infection are risk factors for other health conditions in later life, i.e., studies directly comparing data from neonates/infants/children who had all-cause neonatal infection with those who did not.

Only studies which include a comparator group (a group who did not have all-cause neonatal infection) will be included. Short-, medium- or long-term health conditions which have been observed with higher rates in neonates/infants/children who had all-cause neonatal infection will be identified. Where data are available, the relative risk of these conditions will be reported.

Design

This review follows methods recommended for Cochrane Rapid Reviews [24], combined with JBI guidance for systematic reviews relating to incidence and epidemiology [25, 26]. In line with accepted methods for rapid reviews, we will first search for up-to-date systematic reviews

which address our objectives and will use these to identify primary studies, only conducting database searches for primary studies after the search date of the identified systematic review.

We will report our findings according to guidance for preferred reporting items for systematic reviews and meta-analyses (PRISMA) [27] and to guidance for Meta-Analyses Of Observational Studies in Epidemiology (MOOSE) [28].

Protocol registration: We will register this rapid review protocol on PROSPERO.

Methods

Inclusion and exclusion criteria for this review

Eligibility criteria

Selection criteria are defined separately for **objective 1.1, 1.2 and 2**:

Table 1 Eligibility criteria for objective 1.1

Objective 1.1	**Inclusion**	**Exclusion**
Population	Neonates (including pre-term) (up to 28 days old).	>28 days old. [If studies include a mixed population of neonates ≤28 and >28 days old, we will exclude if separate data are not available for those ≤28 days, or if >10% of participants are >28 days old]
Condition	Early-onset and/or late-onset "all-cause neonatal infection" or "all-cause neonatal sepsis", as defined by the study authors. We will report culture positive/ negative, using definitions specified by the study.	Conditions other than infection / sepsis. Infection / sepsis occurring >28 days since birth.
Context	UK	Non-UK countries
Study design	Observational studies including a population of neonates and reporting the number of neonates with all-cause infection. These could include cohort studies, cross-sectional studies or case-control studies.	Mathematical modelling studies.

Table 2 Eligibility criteria for objective 1.2

Objective 1.2	Inclusion	Exclusion
Population	Neonates (including pre-term) (up to 28 days old) with early-onset and/or late-onset "all-cause neonatal infection" or "all-cause neonatal sepsis", as defined by the study authors. We will report culture positive/ negative, using definitions specified by the study.	Neonates without all-cause neonatal infection / sepsis. [If studies include a mixed population of neonates ≤28 and >28 days old, we will exclude if separate data are not available for those ≤28 days, or if >10% of participants are >28 days old] All-cause Infection / sepsis occurring >28 days since birth.
Condition	Health conditions of: - Mortality - Neonatal septicaemia and meningitis - Neonatal pneumonia - Neonatal encephalopathy - Neurodevelopmental impairment If studies report data relating to other health conditions, we will also note data relating to these conditions.	Studies that do not report data relating to the number with at least one health condition.
Context	UK	Non-UK countries
Study designs	Non-comparative observational studies reporting health conditions for the population who had all-cause neonatal infection.	Mathematical modelling studies.

Table 3 Eligibility criteria for objective 2

Objective 2	Inclusion	Exclusion
Population	Exposed group: Neonates (including pre-term) (up to 28 days old) with early-onset and/or late-onset "all-cause neonatal infection", or infants/children who had a history of "all-cause neonatal infection", defined by the study authors. Unexposed group: a comparator group who did not have all-cause neonatal infection.	Population either exposed to only one group: with/without all-cause neonatal infection. All-cause Infection / sepsis occurring >28 days since birth.

	We will report culture positive/ negative, using definitions specified by the study.	
Condition	Health condition during neonatal period, infancy or childhood.	Studies that do not report data relating to the number with at least one of these conditions.
Context	High-income countries (as defined by World Bank [29]).	Low- and Middle-income countries (as defined by World Bank [29]).
Study designs	Observational studies with data for a group with all-cause neonatal infection and an appropriate comparator group. This could either be a cohort study or case-control study which compares the proportions of neonates with/without infection who later develop a health condition.	Studies without a comparator group. Experimental/intervention studies. Mathematical modelling studies.

Additional eligibility criteria

Language: we will include papers published in English language only.

Dates: We will not apply any date cut-off for inclusion of studies. However, our search methods mean that primary studies published prior to the search date of the most recent, high quality, systematic review will only be included if they were included within the relevant systematic review. We will initially consider systematic reviews published after 2016, as this aligns with the year of known systematic reviews / evidence summaries conducted for the UK NSC [17]. However, if we do not identify high-quality reviews addressing our research question in this time-period, we will expand our search to earlier dates. Justification: we will adopt a pragmatic approach to searching, building on previously published systematic reviews. Using an initial 2016 search date for systematic reviews but expanding this if no suitable reviews are identified aligns with this pragmatic approach. This is appropriate for a rapid review.

Outcomes of interest

For objective 1.1, we are interested in incidence (studies must report number with all-cause neonatal infection from a denominated UK population).

For objective 1.2, we are interested in rates (either proportion, prevalence or incidence) of health conditions from a UK population with all-cause neonatal infection of:

- Mortality
- Neonatal septicaemia and meningitis (requiring intensive care or ventilation)
- Neonatal pneumonia (requiring intensive care or ventilation)
- Neonatal encephalopathy (requiring intensive care or ventilation)
- Neurodevelopmental impairment
- Other health conditions, as reported by studies

(studies must report number with all-cause neonatal infection, and proportion with subsequent health condition).

For objective 2, we are interested in any health condition for which the study authors find that all-cause neonatal infection is associated with a higher risk of that condition, compared with the risk in a matched comparator group, as well as any health conditions which are included in these studies and are not found to be associated with prior all-cause neonatal infection.

For objectives 1.2 and 2, short-, medium- and long-term conditions reported will be eligible. However, we will document the time since birth (i.e., age) as reported by study authors.

Search methods and study selection

Searching

We will use a two-stage process to identify relevant primary studies which meet our criteria.

Stage 1: An information specialist will conduct an initial, targeted (or 'focussed') search for systematic reviews included in bibliographic databases (including Medline and Embase) since 2016. This search will involve knowledgeable identification (using both MESH terms and free text) and selection of the most relevant and up-to-date systematic reviews addressing one or more of the three research objectives. This focussed approach will serve to efficiently / rapidly (i) identify primary research for assessment and possible incorporation into the review (i.e. eligible primary studies included in one or more of the identified systematic reviews), (ii) help refine the systematic search strategy for use in stage 2 and (iii) identify the date from when to run the stage 2 systematic search. We will use the EPPI-Centre definition of a systematic

review as a review that uses explicit and transparent methods, follows a standard set of stages and can be considered accountable, replicable and updateable [30]. We will exclude scoping reviews, narrative reviews (i.e. reviews which do not follow PRISMA guidance) and intervention reviews (i.e. systematic reviews focussing on effectiveness of an intervention). This stage 1 searching process will be iterative, involving feedback between the information specialist and other members of the research team. A description of the final process will be reported in the methods of the completed review and all systematic reviews considered for inclusion will be listed along with reasons for their ultimate inclusion or exclusion following screening (see below).

Stage 2: Systematic search for primary studies published after the most recent systematic review for each research question. We will search Medline and Embase databases via the OVID platform, using the pre-defined, peer-reviewed search strategy for primary studies. Studies published after the search date(s) of the selected systematic reviews will be identified. The use of only two databases aligns with recommendations for rapid reviews [24]. Searches will be restricted to English language. Database search results will be de-duplicated and entered into Covidence. Our MEDLINE search strategy is provided in Appendix B.

Screening

Selection of relevant systematic reviews: One reviewer will consider the identified systematic reviews and note the search date and number of included studies for each systematic review. Two reviewers will discuss the identified systematic reviews and reach agreement on comprehensive, up-to-date systematic reviews which address each review objective. These decisions will be made through discussion, with consideration of key criteria, including: date of search, comprehensiveness/quality of search strategy, inclusion/exclusion criteria, number of studies with high-quality design (e.g., cohort studies), relevance to our review objectives, and overlap with other reviews. Decisions will be transparently reported. If considered appropriate, we will include several systematic reviews, to ensure comprehensive identification of primary studies.

Identification of primary studies to include: All primary studies included in the identified systematic reviews will be extracted and entered into Covidence, alongside all additional

primary studies identified in the stage 2 systematic search published since the search date(s) of the included systematic reviews. One reviewer will screen titles and abstracts, excluding obviously irrelevant studies. Two reviewers will then independently apply eligibility criteria to full texts of remaining studies; any disagreements will be resolved by a third reviewer or through discussion between reviewers. Overall, we will apply our inclusion criteria to:

- all studies included within these systematic reviews identified in stage 1.
- results of the systematic search for recent primary studies (stage 2).
- the primary studies included within Review C of these three linked rapid reviews (which is focussed on benefits and harms of maternal screening), as this will identify studies which provide observational data which address the objectives for this review.

Justification for approaches to searching and screening

First considering the primary studies included within relevant systematic reviews is pragmatic and aligns with rapid review methods for identification of studies [31]. Use of the focussed search approach will accelerate the identification of key systematic reviews, requiring significantly less time and resource than conducting a comprehensive search. Conducting comprehensive searches to identify primary studies published after the search dates of selected high-quality systematic reviews will ensure that recent studies are included. Only including primary studies (e.g., using previous systematic reviews to aid identification of primary studies, but not considering these as included studies) is pragmatic and efficient. This avoids having to deal with complex (and time-consuming) issues relating to quality of systematic reviews (i.e., assessment of methodological quality or risk of bias), overlapping systematic reviews (systematic reviews which include the same, or similar, primary studies), and varied data extraction and quality assessment within systematic reviews (i.e., systematic review data which are not comparable due to application of different criteria, tools and judgements). Finally, considering the primary studies from Review C provides an efficient way to ensure that any relevant data from studies investigating screening strategies are included within our review, without the need to expand our search strategies to consider intervention/experimental studies.

Although Cochrane rapid review guidance proposes that it may be appropriate to have one reviewer only, we will use two reviewers to complete full text screening. This is in order to minimise errors, as the reviewers are not previously familiar with the topic area. Involving a third reviewer where there are disagreements will enable a member of the Reference Group, with topic expertise, to contribute to decision-making.

Critical appraisal

Systematic reviews (used to identify primary studies): We will not conduct formal critical appraisal of systematic reviews, as we are using systematic reviews as a tool to identify primary studies, rather than as "included" studies. However, when determining which systematic reviews are eligible for consideration, we will consider study quality, with particular reference to the search strategy. Therefore, we will consider the AMSTAR2 'critical' domains [32] of:

- Protocol registered before commencement of the review (item 2)
- Adequacy of the literature search (item 4)
- Justification for excluding individual studies (item 7)

We will reject any systematic reviews that are judged to be high risk of bias for these domains. We will document our decision-making transparently.

Included primary studies: We will use CASP tools [33] (selected according to study design; i.e., CASP tool for cohort studies, case-control studies or cross-sectional studies). Justification for use of CASP tools are that these are commonly used, evidence-based tools, considered easy to use (and therefore suitable for rapid reviews). CASP tools [33] provide a structured approach to consider important factors, supporting decision-making and transparent recording. The recent addition of an appraisal summary is considered beneficial for supporting interpretation of the findings of this rapid review.

Critical appraisal will be conducted by two reviewers, with consensus reached through discussion. Where disagreements cannot be resolved, a third reviewer will be involved.

Data extraction

For *all* included studies, we will extract the following information (where reported by study authors):

- Study name and year
- Aim
- Study design, categorised as either:
    - Cohort (prospectively collected data)
    - Cohort (retrospectively collected data)
    - Cross-sectional (data from one time point only)
    - Case-control study (where case is individuals with a given health condition and control is those without that health condition)
- Population
    - Gestational age
    - Maternal participation in screening
    - Use of intrapartum antibiotics (IAP)
    - Maternal risk factors
    - Other characteristics reported by the study that potentially affect incidence
- Condition
    - Early-onset all-cause neonatal infection (detailing where this is culture positive or culture negative)
    - Late-onset all-cause neonatal infection (detailing where this is culture positive or culture negative)
- Health conditions
    - Health conditions assessed
    - Timepoints of assessed health conditions (i.e., short-, medium- or long-term)
- Context
    - Country (UK only for Objectives 1.1 and 1.2; high-income countries for objective 2)
    - Maternal screening and IAP strategies
    - Study data source (e.g., registry, hospital)

- Results data (where studies have a comparator group, we will extract data for both the all-cause neonatal infection group and the comparator group):
    - Number of recruited participants
    - Number of participants at each outcome assessment

    - For studies addressing objective 1.1:
        - Incidence of all-cause neonatal infection

    - For studies addressing objective 1.2:
        - Results data (in the form of n/N) for:
            - Mortality
            - Pneumonia
            - Septicaemia
            - Meningitis
            - Encephalopathy
            - Neurodevelopmental impairment
            - Any other health conditions reported by the included studies

    - For studies addressing objective 2:
        - Results data as presented in the studies, including, for both all-cause neonatal infection group and comparator group
            - Number of participants
            - Population details (as detailed above)
            - Health condition (e.g., neurodevelopmental impairment, visual impairment)
            - Cases (number with condition)
            - Statistical measures of association/risk, as reported by the study authors

Data will be extracted by one reviewer and checked by a second reviewer. Any disagreements will be resolved through discussion.

Data synthesis and analysis

For all objectives, we will produce a narrative summary of relevant systematic reviews and of primary studies. We will tabulate extracted data and produce summary tables of results reported in the included studies relevant to each objective (see Tables 4-6, below).

We will discuss the summarised/tabulated results data with reference to:

- Our confidence in the findings (based on study quality)
- Previously published data, including data from UK NSC reviews [17, 34], and other relevant data (e.g., data from previous systematic reviews or relevant modelling studies [14, 35])

Results will be summarised in the format required for the UK NSC Evidence Summary.

For objective 1.1, we will produce a table of UK incidence data:

Table 4 UK incidence data

Study	Study design	Geographic location	Study setting	Time period of data collection	Population characteristics						Condition		Incidence (n/N)	Study quality (appraisal summary)
					Size of study population (N)	Gestational age	Maternal participation in screening (including type / timing of screening, e.g. antenatal, intrapartum)	Use of IAP	Maternal risk factors	Other relevant population characteristics	Early-onset/late-onset all-cause neonatal infection; Culture positive or culture negative	Number with condition (n)		
Study 1														
Study 2														
Study 3 etc														

For objective 1.2 we will produce a summary table for each health condition reported by at least one UK study which meets our inclusion criteria:

Table 5 UK data on frequency of health conditions

Study	Study design	Geographic location	Study setting	Time period of data collection	Characteristics of all-cause neonatal infection population							Health condition		Rate of health condition (n/N)	Study quality (appraisal summary)
					Early-onset/late-onset all-cause neonatal infection; Culture positive or culture negative; organism (if reported)	Size of study population (N)	Gestational age	Maternal participation in screening (including type / timing of screening, e.g. antenatal, intrapartum)	Use of IAP	Maternal risk factors	Other relevant population characteristics	Mortality Neonatal septicaemia and meningitis Neonatal pneumonia Neonatal encephalopathy Neurodevelopmental impairment	Number with health condition (n)		
Study 1															
Study 2															
Study 3 etc															

For objective 2 we will produce a summary table for each health condition for which at least one included study has results data indicating that early-onset and/or late-onset all-cause neonatal infection may be a risk factor, tabulating information about the infection group and the comparator group, and results data as presented by the study authors.

Table 6 UK and high-income country data on short-, medium- and long-term health conditions associated with early-onset and/or late-onset all-cause neonatal infection

Study	Country / Geographic location	Study setting	Time period of data collection	Study Group	Characteristics of population (specify details)							Health condition				Statistical measures of association (e.g., OR with 95% CI)	Study quality (appraisal summary)
				(all-cause neonatal infection or comparator)	All-cause neonatal infection 'type' (EO, LO; Culture positive or culture negative)	Size of study population (N)	Gestational age	Maternal participation in screening (eg.type/tming)	Use of IAP	Maternal risk factors	Other relevant population characteristics	Condition (e.g., neurodevelopmental impairment, visual impairment)	Assessment time point (short-, medium- or long-term)	Number with health condition (n)	Rate of health condition (n/N)		
Study 1				Infection group													
				Comparator group													
Study 2				Infection group													
				Comparator group													

Governance

Protocol

This protocol has been developed by NESSIE (NIHR Evidence Synthesis Scotland InitiativE) in order to address questions proposed by the UK NSC Evidence team. This has involved an iterative process of development and feedback to ensure that the protocol will provide the evidence required by the UK NSC Evidence team.

Review

The review will be conducted by the NESSIE team, according to the agreed protocol (as registered with PROSPERO). Any deviations from the protocol will be discussed with the UK NSC evidence team before finalisation of the reviews and will be stated (with reasons) in the final review as deviations from the original protocol.

Evidence summary

Findings from this review will be integrated into a UK NSC Evidence Summary produced by NESSIE in collaboration with the UK NSC Evidence Team who will provide feedback and co-ordinate feedback from the fetal, maternal and child health (FMCH) reference group and from public consultation (if applicable). NESSIE will integrate findings from the completed review, and responding to relevant feedback relating to review findings. The final Evidence Summary, co-produced by NESSIE and the UK NSC evidence team, will be used by the UK National Screening Committee to support discussions on GBS screening. The UK National Screening Committee will make the final decision on any recommendation related to a GBS screening programme.

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Appendices

Appendix A: Plans for Reference Group, described according to ACTIVE Framework

ACTIVE Framework construct	**Plans for NESSIE GBS Reference Group**
Who will be involved?	People who have expertise / knowledge relating to screening for neonatal GBS, including those with expertise relating to: • Midwifery • Microbiology • Neonatal care (neonatologist / neonatal nurse) • Paediatrics And those with personal lived experience relevant to the topic, for example, parents who chose to pay for GBS screening during the antenatal period or people involved in organisation of mother and baby groups. As of 27/01/2025, the following people have agreed to be members of this Reference Group: 1. Rosie Hill, NESSIE Co-applicant with Policy and Public Health experience 2. Prof Helen Cheyne, Royal College of Midwives (Scotland) Professor of Midwifery 3. Dr Ryan Kean, Lecturer in Clinical Microbiology, Glasgow Caledonian University 4. Prof Narendra Aladangady, Consultant Neonatologist, Homerton University Hospital, Homerton Healthcare NHS Foundation Trust; Hon Clinical Professor in Child Health, Barts and the London School of Medicine and Dentistry 5. Dr Charlotte-Eve Short, Clinical Senior Lecturer in HIV and GU Medicine, Department of Infectious Disease, Imperial College London. 6. Mrs Amanda Rees, has lived experience of Strep B screening, being a mother of 2 young children who chose private screening for Strep B (she is not affiliated to any 3rd sector organisation). We are seeking additional members who have lived experience of Strep B screening, and choices associated with this.

	We will have a pragmatic approach to membership, and if – during the review process – we come across issues requiring specific expertise not held by current members (e.g., decisions relating to inclusion of specific research papers), then we will seek additional members with suitable expertise. This approach is appropriate given the rapid nature of these reviews.
How will people be recruited to the reference group?	We will use a closed approach, inviting named people with specific expertise/experience to join the reference group. As NESSIE only has limited existing contacts, we will use a 'snowball' approach, where we invite initially identified individuals to propose names of additional people. The use of a closed, invitation-based approach, is appropriate given the rapid nature of these reviews, and the need to involve people able to provide topic expertise.
What will the mode of involvement be?	The Reference group will be involved using a continuous approach. The method of interaction will primarily be indirect, through emails. However, we anticipate having a small number of online meetings, one at the start of the review, and a second during the data synthesis / write up. If necessary, we will have direct interaction with individual members (e.g., to seek clarification around specific terminology)
At what stage in the review process will involvement occur? **What will the level of involvement be (at each stage)?**	
1. Develop question	No involvement (questions will be developed through discussion with UK NSC)
2. Plan methods	No involvement (methods will be developed through discussion with UK NSC)
3. Write & publish protocol	Contributing/Influencing – draft protocols will be shared with Reference Group members, and members invited to comment on language, terminology, accessibility and presentation of the information.
4. Develop search	Contributing – members will be asked to view a draft search strategy and provide suggestions for any additional or alternative search terms. (The search strategy will then be developed by an information specialist and peer review provided by UK NSC).
5. Run search	No involvement (search will be run by NESSIE information specialist)

6. Select studies	Contributing/Influencing – where there are conflicts in agreements between review team, these may be discussed with individual Reference Group members (according to expertise required).
7. Collect data	Contributing/Influencing – where there are conflicts in data extracted by review team, or uncertainty in relation to data presented in an included study, these may be discussed with individual Reference Group members (according to expertise required).
8. Assess risk of bias	Contributing/Influencing – where there are uncertainties in relation to risk of bias within an included study, these may be discussed with individual Reference Group members (according to expertise required).
9. Analyse data	Contributing/Influencing – where there are uncertainties in relation to data presented within an included study (e.g., details of the population to which the data relates), these may be discussed with individual Reference Group members (according to expertise required).
10. Interpret findings	Contributing/Influencing – Reference Group members will be invited to comment on draft presentation of review results. They will not be able to influence the review results (i.e. objective data presented from individual studies), but will be invited to comment on the presentation of the findings, including structure of tables and figures, and language used to express findings.
11. Write & publish	As above. Where Reference Group members have contributed sufficient to meet criteria for authorship, they will be listed as authors on the published reviews.
12. Knowledge translation & impact	Contributing/Influencing – Reference Group members will be invited to offer views on where (e.g., which journals) the rapid reviews should be published. Receiving/contributing – Reference Group members would be informed of how the rapid review results were being used within the UK NSC Evidence Summary. Those who were authors on the publications may have opportunities to comment on how the rapid review results were used within the evidence summary. There would be no direct role / responsibility of the Reference Group members in the development of screening recommendations.

Appendix B: Search strategy

Ovid MEDLINE(R)

1	exp Neonatal Sepsis/
2	exp Streptococcus agalactiae/
3	"all cause neonatal infection*".ti,ab.
4	"all cause neonatal sepsis".ti,ab.
5	"neonatal sepsis".ti,ab.
6	"neonatal early onset sepsis".ti,ab.
7	"neonatal early onset infection*".ti,ab.
8	"neonatal EOS".ti,ab.
9	"group b streptococc*".ti,ab.
10	"streptococcus agalactiae".ti,ab.
11	"streptococcus group b".ti,ab.
12	"early onset sepsis".ti,ab.
13	EOGBS.ti,ab.
14	GBS.ti,ab.
15	iGBS.ti,ab.
16	LOGBS.ti,ab.
17	or/1-16
18	exp Infant, Newborn/
19	exp Infant Death/
20	exp Pregnancy/ep
21	Infant.ti,ab.
22	newborn*.ti,ab.
23	neonat*.ti,ab.
24	Preterm.ti,ab.
25	prematurity.ti,ab.
26	or/18-25
27	17 and 26
28	Pregnancy Complications, Infectious/ep
29	27 or 28
30	limit 29 to english language

Protocol for Review C: Benefits and harms of antenatal or intrapartum screening for maternal GBS carriage and subsequent use of intrapartum antibiotic prophylaxis versus risk-based protocols or no intervention: a rapid review

Authors

Pauline Campbell, Julie Cowie, Candida Fenton, Bridget Davis, Wei Xu, Alex Todhunter-Brown, on behalf of NESSIE

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Table of Contents

Background

Group B Streptococcus (GBS) is recognised clinically as a contributor to neonatal morbidity and mortality [1] causing newborn sepsis, pneumonia and meningitis. A global incidence risk of 0.49 per 1000 live births was estimated in 2017 [2]. GBS is a common commensal bacterium with around one fifth of pregnant women[a] carrying it in their gastrointestinal or genitourinary tracts [4] resulting in a 36% chance of infecting their newborn during labour [5]. Whilst vaccines aimed at protection against GBS bacteria are currently in development they are not yet routinely available [6].

Intrapartum antibiotic prophylaxis (IAP) are widely used to prevent vertical transmission from the pregnant woman to the neonate. However, recommendations on screening strategies differ on the timing of screening for GBS colonisation (antenatal or intrapartum), and the administration of IAP (i.e. type of antibiotic and/or dose delivered).

Globally, three approaches to the identification of women eligible for IAP are currently recommended to prevent vertical GBS transmission:

- Universal screening: involves collecting cultures from the vaginal and rectal swabs of all pregnant women at 35-37 weeks of gestation and administering IAP to those with a positive GBS culture. Individuals with an undetermined GBS status or negative GBS screening test are managed according to a risk-based approach.
- Risk-based strategy: entails the identification of pregnant women at risk of GBS colonisation during labour through the evaluation of risk factors. These strategies vary

[a] In line with the UK Network of Professors of Midwifery and Maternal and Newborn Health, we use the words women and woman throughout this protocol, recognising that this reflects the biology and identity of the great majority of those who are childbearing; for the purpose of this protocol, these terms include girls, and people whose identity does not correspond with their birth sex or who may have a non-binary identity 3. UK Network of Professors of Midwifery and Maternal and Newborn Health. *Position Statement: Use of sexed language in relation to women's reproductive health*. UK: Council of Deans of Health; 2023. URL: https://www.councilofdeans.org.uk/2024/02/midwifery-network-position-paper-use-of-sexed-language/ (accessed 27 January, 2025).

internationally but may include preterm labour (< 37 weeks' gestation), prolonged rupture of membranes, fever during labour (≥ 38 degrees Celsius), a previous history of early onset GBS (EOGBS), and GBS bacteriuria in the current pregnancy.

- No screening protocol: pregnant women in labour are administered IAP on an individual basis.

The adoption of universal culture-based screening compared with a risk-based protocol is specific to each country and region. The Centers for Disease Control and Prevention (CDC) in the US now advocates for routine culture-based screening, often combined with the risk-based strategy. In the UK, guidelines do not endorse culture-based screening due to the current uncertainty regarding its overall benefits vs harms and instead recommend a risk-based strategy in which IAP are administered to pregnant women considered high-risk [4].

Potential harms of universal GBS screening include the unnecessary medicalisation of the birthing process [5] and increased burden on healthcare services [5]. The National Institute for Health and Care Excellence (NICE) [7] and Royal College of Obstetricians & Gynaecologists (RCOG) [8] recommend use of IAP for those pregnant, with the relevant risk factors and/or colonised with GBS. A universal screening approach brings concerns of unnecessary antibiotic use [7], uncertainty regarding the effects of maternal IAP on neonates [9], antibiotic resistance in the treatment of neonates [9] or long-term effects on children [10].

Two recent meta-analyses [11, 12] of international data concluded that universal screening reduced the risk of EOGBS infection compared to a risk-based approach without leading to antimicrobial resistance; however, they highlighted the lack of high quality randomised controlled trials (RCTs) in this area. A large multi-centre RCT investigating the clinical and cost effectiveness of universal GBS testing within England and Wales (GBS3) [5] is currently underway. The GBS3 trial also has two different testing groups: (1) an antenatal lab-based test at 3-5 weeks before anticipated delivery date (Enriched Culture Medium Testing), (2) Bedside Test at start of labour (Intrapartum Rapid Testing), and results are anticipated in late 2025.

In the UK, screening for GBS was last reviewed by the UK National Screening Committee (UK NSC) in 2017 [4]. The conclusion was not to recommend universal screening. [4]. An update to

this review is now required to investigate any developments in the field that may may inform discussion on continuing or changing the current recommendation on universal GBS screening and to take account of the issues raised by the GBS3 trial. The objective is to identify and summarise new research and data related to GBS incidence in the UK, GBS health outcomes, benefits and harms of antenatal or intrapartum screening followed by IAP. Previous UK NSC reviews of screening to prevent invasive neonatal GBS infection have been primarily concerned with culture positive GBS. More recently the GBS3 trial has focused attention on the wider landscape of both culture positive and negative neonatal infection. The trial aims to evaluate the effectiveness of screening for GBS within this context. The review will be considered by the UK NSC as part of its decision-making process. More particularly, it will provide a context within which the results of the GBS3 trial can be considered and discussed.

Three rapid reviews will be undertaken to support decisions of the UK NSC:

- Review A: Incidence in the UK and health consequences of neonatal GBS infection
- Review B: Incidence in the UK and health consequences of all-cause neonatal infection
- Review C: Benefits and harms of antenatal or intrapartum screening for maternal GBS carriage and subsequent use of intrapartum antibiotic prophylaxis versus risk-based protocols or no intervention

This document outlines the protocol for Review C: Benefits and harms of antenatal or intrapartum screening for maternal GBS carriage and subsequent use of intrapartum antibiotic prophylaxis versus risk-based protocols or no intervention. Once completed, the findings of all three reviews will be used to help populate the UK NSC evidence summary template, which will be presented to the UK NSC prior to their consideration of universal GBS screening later in 2025.

Patient and Public Involvement (PPI) / Wider interest-holder involvement

A NESSIE PPI co-investigator is part of our rapid review team (contributing to Reviews A, B and C). We will follow national standards and principles, and will develop and implement an involvement plan, which will be detailed in our protocols and reported in final reports using GRIPP2 guidance [13] and ACTIVE framework [14]. We have established a small ‘Reference Group’

for these rapid reviews. This is considered particularly important as the NESSIE team do not have content expertise relating to these rapid reviews. The key role of the Reference Group will be to provide content expertise, ensuring appropriate use of terminology, relevant content, supporting study inclusion decisions, and advising on reporting and dissemination. Members comprise people with clinical and policy expertise, and people representing those with lived experience. Details of the planned Reference Group involvement are reported according to the ACTIVE framework [14] in Appendix A.

Key definitions

We use the following definitions summarised below in Table 1.

Table 1. Key definitions used throughout this protocol

Term	Definition
Antenatal screening	Refers to culture-based screening to identify pregnant women with GBS maternal colonisation
Antibiotic prophylaxis:	Refers to the use of antibiotics in a pregnant woman with GBS colonisation or considered high risk for GBS colonisation or carriage to a newborn
Clinically suspected neonatal infection	The following acute onset clinical or laboratory features will be used as part of the definition for clinically suspected neonatal infection, if the blood and CSF cultures are negative/unknown and intravenous antibiotics are given for ≥5 days, starting within 7 days of birth for early-onset, and 28 days for late-onset) [15]: • Increase in oxygen requirement or increase in ventilatory support or *new or an increase in frequency of episodes of apnoea • Increase in frequency of episodes of bradycardia or hypotension (needing inotrope support or other intervention) • Temperature ≥37.5C or <36.5C • Enteral feeds intolerance or abdominal distension • *Reduced urine output to <1 ml/kg/hr • *Impaired peripheral perfusion (capillary refill time >3 seconds or skin mottling or core peripheral temperature gap >2°C) • Irritability or lethargy or hypotonia (clinician-defined) • *Serum C-reactive protein levels >15 mg/L or procalcitonin ≥2 mg/mL • *White blood cells count 20×10^9 cells/L or platelet count $<100x10^9$/L • Glucose intolerance (blood glucose <2.2mmol/l or >10mmol/l) or metabolic acidosis (base excess <-10 mmol/L or lactate >2 mmol/L)

	*It is acknowledged that these signs or symptoms may not be able to be identified from some routine data sources.
Culture positive neonatal infection	A positive culture of infection from blood or cerebrospinal fluid, together with signs of clinical disease in a neonate.
Culture negative neonatal infection	Symptoms or signs of sepsis, pneumonia or meningitis with a negative culture from blood or cerebrospinal fluid, in a neonate.
Early all-cause neonatal infection	Using the definition provided by Daniels et al (2024) [15] • A positive culture of a pathogenic bacteria from microbiological tests (e.g., from blood; cerebrospinal fluid; pleural fluid; peritoneal fluid urine sample) at <7 days after birth • Negative/ unknown culture status with ≥3 agreed clinical signs or symptoms, for which intravenous antibiotics are given for ≥5 days, starting within 7 days of birth • Death which is <7 days after birth, if infection or sepsis was recorded on the death certificate [15] We note that definitions used within the literature may vary. Therefore, we will adopt a pragmatic approach (in line with our rapid review methodology) and we will include any studies which focus on "all-cause neonatal infection" or "all-cause neonatal sepsis" (or other terms with definitions that align with the focus of our review), as defined by the study authors, as long as this occurs <28 days after birth. We use this cut-off (i.e., <28 days) as this aligns with definitions of "neonate" [16].
Early-onset GBS (EOGBS) infection	Invasive GBS disease in infants aged 0–6 days after birth.
GBS colonisation	Microbiological confirmation of GBS on swabs from nose, umbilicus, axilla, rectum or ear.
GBS	Group B streptococcus, also known as Streptococcus agalactiae, a facultative gram-positive organism.
GBS maternal colonisation	A pregnant woman with positive confirmation of GBS (from rectovaginal or peri-anal region) [17]
Intrapartum screening	Refers to screening at the start of labour
Invasive GBS infection	Microbiological confirmation of GBS together with any symptoms or signs of sepsis, pneumonia or meningitis.
Late-onset all-cause neonatal infection	• A positive culture of a pathogenic bacteria taken at ≥7 days and <28 days after birth • Negative/ unknown culture status with ≥3 agreed clinical signs or symptoms, for which intravenous antibiotics are given for ≥5 days, starting within 28 days of birth • Death which is <28 days after birth, if infection or sepsis was recorded on the death certificate

Late-onset GBS (LOGBS) infection	Invasive GBS disease in infants 7–89 days after birth.
Long-term health conditions	Relates to childhood, a time extending from 1-18 years of age. We note that different studies may use different thresholds to define their study outcomes. Therefore, we will adopt a pragmatic approach, documenting definitions used by study authors where these vary.
Maternal GBS disease	Laboratory isolation of GBS from a sterile site (blood or cerebrospinal fluid [CSF] only) in a pregnant or postpartum woman (up to 42 days postpartum), with a minimum of fever and physician suspicion of sepsis [18]
Medium-term health conditions	Relates to infancy, a time extending from the first month after birth to approximately 12 months of age [2]. We note that different studies may use different thresholds to define their study outcomes. Therefore, we will adopt a pragmatic approach, documenting definitions used by study authors where these vary.
Risk-based management strategies	Refers to approaches where an assessment of risks is used to identify newborn babies more likely to develop invasive GBS disease, with antibiotic prophylaxis offered to reduce the risk of the newborn developing GBS disease.
Short-term health conditions	Relates to the neonatal period, which has been defined by the World Health Organization (WHO) as "beginning at birth and ending at 28 completed days of life" [19]. We note that different studies may use different thresholds to define their study outcomes. Therefore, we will adopt a pragmatic approach, documenting definitions used by study authors where these vary.
Systematic review	EPPI-Centre definition of a systematic review as a review that uses explicit and transparent methods, follows a standard set of stages and can be considered accountable, replicable and updateable [20]

We note that several definitions employed in the literature may differ from those included in Table 1. For example, some studies may differentiate between culture positive GBS and culture negative GBS (where there are clinical signs and symptoms of invasive GBS disease, without the microbiological confirmation from a positive culture). Additionally, terms such as "probable" or "suspected" GBS may be employed, or GBS may be defined according to varying levels of certainty [21, 22]. Further, a clinical diagnosis of culture negative GBS infection may sometimes be given when the mother is GBS negative, or the mother's GBS status is unknown, but clinical expert judgement supports this diagnosis (for example where the risks for GBS are known to be high). In this rapid review, we will employ a pragmatic approach, recording the definitions utilised by study authors when they differ from those previously stated in Table 1.

Objectives and research questions

To compare the effectiveness (benefits versus harms) of antenatal or intrapartum maternal GBS screening followed by subsequent use of intrapartum antibiotic prophylaxis versus risk-based management strategies or no intervention in preventing EOGBS and late-onset GBS disease (LOGBS).

Specifically, this review aims to address the following two questions:

RQ1. Do maternal GBS screening-based protocols (antenatal or intrapartum) and subsequent use of intrapartum antibiotic prophylaxis reduce the risk of EOGBS, LOGBS and other cause neonatal infections compared with risk-based protocols or no intervention?

RQ2. What benefits and harms of undergoing (antenatal or intrapartum) screening for GBS and subsequent use of intrapartum antibiotic prophylaxis have been reported by high-quality research (i.e., studies with appropriate comparator groups) conducted in high-income countries?

Design

A series of preliminary scoping searches were conducted to inform this protocol, identifying several potentially relevant systematic reviews and meta-analyses (e.g. [9, 12, 23-27] published since the UK NSC review [4]). To address RQ1, we propose conducting a rapid overview of high-quality systematic reviews. RQ2 will be addressed through a rapid systematic review, identifying relevant primary studies that include a control group, and were conducted in high-income countries. For efficiency, primary studies addressing RQ2 will be identified based on the systematic review and meta-analyses publications included in RQ1.

We will report our findings according to guidance for preferred reporting items for systematic reviews and meta-analyses (PRISMA)[28].

Protocol registration: We will register this rapid review protocol on PROSPERO.

Methods

Criteria for considering studies for this review.

The eligibility criteria for systematic reviews/meta-analyses for RQ1 are reported in Table 2.

The eligibility criteria for primary studies for inclusion for RQ2 are specified in Table 3.

Table 2. Eligibility criteria for systematic reviews/meta-analyses that address RQ1

Abbreviations: AMSTAR2: Tool for Assessing the Methodological quality of Systematic Reviews [29] GBS: group B streptococcal bacteria; IAP: intrapartum antibiotic prophylaxis; NA: not applicable; ROB: Risk of bias; RQ: research question.

Research Question 1	**Inclusion criteria**	**Exclusion criteria**
Participants	Women in any stage of their pregnancy (any gestation, parity, age)	Non-pregnant women.
Intervention	Maternal antenatal or intrapartum screening for GBS with intrapartum antibiotic prophylaxis	Other types of interventions aimed at prevention of GBS (e.g. vaccines) [30] or studies evaluating diagnostic accuracy of commercially available tests for diagnosing GBS colonisation in women [31]
Comparator	Risk based management strategies for GBS No intervention (i.e. no strategy)	Other types of intervention/treatment strategies (e.g. GBS vaccines)
Outcomes	Relative risk of GBS neonatal infection (early-onset and late-onset) and other cause neonatal infections for antenatal or intrapartum screening versus risk-based screening approaches or no intervention	
Study designs	Systematic reviews* / Meta-analyses which are judged as low Risk of Bias (ROB) for any of the AMSTAR2 'critical' domains [29]	• Overviews (i.e. review of reviews) • All other type of review studies (e.g. scoping reviews, narrative reviews) • Systematic reviews* / Meta-analyses which are judged as high ROB for any of the AMSTAR2 'critical' domains [29] will be excluded, and placed in a table of excluded systematic reviews, with no further data extraction • Case-control studies • Time series • Interrupted time series • Case series • Mathematical modelling studies • Economic evaluations • Commentary / opinion/ editorials • Conference abstracts

Setting	Studies will not be limited by geographical setting	NA
Languages	English	Other languages
Dates	We will include all relevant systematic reviews published since 2016-present.	Systematic reviews published prior to 2016

Table 3. Eligibility criteria for primary studies that address RQ2

Abbreviations: GBS: group B streptococcal bacteria; IAP: intrapartum antibiotic prophylaxis; RCT: randomised controlled trial; RQ: research question

Research Question 2	**Inclusion criteria**	**Exclusion criteria**
Participants	Women in any stage of their pregnancy (any gestation, parity, age)	None
Intervention	Maternal antenatal or intrapartum screening for GBS with intrapartum antibiotic prophylaxis	Other types of interventions aimed at prevention of GBS (e.g. vaccines) [30] or studies evaluating diagnostic accuracy of commercially available tests for diagnosing GBS colonisation in women [31]
Comparator	Risk based management strategies for GBS No intervention (i.e. no strategy)	Other types of intervention/treatment strategies (e.g. GBS vaccines)
Outcomes	GBS neonatal, infant and child (short-, medium-, long-term) health outcomes including but not limited to: • Incidence of all-cause neonatal infection • Death • Pneumonia • Septicaemia and meningitis • Encephalopathy Maternal health outcomes including but not limited to: • Death • Infection including urinary tract infection and chorioamnionitis • Anaphylaxis Other reported short-, medium-, long-term health outcomes Any other additional harms and benefits reported by the included studies. Examples are reported below.	

	Potential harms of screening and use of intrapartum antibiotic prophylaxis [32] may include reports of: • short-, medium-, long-term health outcomes of exposure to antibiotics during labour • Overtreatment • Treatment risks • Difficult decisions • Anxiety or false reassurance • Incorrect results • Medium- and Longer-term outcomes in the infant/child (e.g. child obesity, asthma) Potential benefits of screening [32]: • Better future health outcomes e.g. a reduction in long-term adverse neurodevelopmental outcomes • More effective treatments • Reassurance • Informed decisions • Worthwhile use of resources	
Study designs	We will consider all primary studies (RCTs, non-randomised controlled trials) that are included in systematic reviews that met the selection criteria for RQ1. Only studies with an appropriate comparator group, against which to accurately assess the harms and benefits of screening will be included. Within this group of studies, we will not exclude further according to quality.	Studies without a comparator group which claim to be reporting harms and benefits of screening will be listed (with reasons for exclusion) in a table within the body of the review.
Setting	Only primary studies conducted in high-income countries	Primary studies conducted in low, low-middle income, upper-middle income countries will be excluded and listed in the Table of excluded studies
Languages	English	Other languages
Dates	We will not apply any date cut-off for inclusion of primary studies. However, primary studies will be identified from relevant systematic reviews published since 2016-present.	Systematic reviews published prior to 2016

Search methods for identification of studies

A comprehensive search strategy using MeSH headings and free text terms will be developed by an information specialist (CF). We will search Medline and Embase databases via the OVID platform, using pre-defined peer-reviewed search strategies for systematic reviews/meta-analyses focussed on the effectiveness of GBS screening interventions published after 2016. Searches will also include an appropriate study design filter for systematic reviews.

The use of only two databases aligns with recommendations for rapid reviews [33]. Searches will be restricted to English language. Database search results will be de-duplicated and entered into Covidence. Our MEDLINE search strategy is provided in Appendix B.

We will also employ other abbreviated systematic review methods in line with Cochrane rapid review methodology [33] which will include the following:

- No specific searches of grey literature
- Excluding studies that do not have an abstract
- Excluding studies in a language other than English

Should our searches fail to identify any relevant and up-to-date systematic review or meta-analyses (i.e. with a search date within the last 12 months of commencing this rapid review), (anticipated start February 2025), we will run additional searches of Medline and Embase restricted to English language for relevant primary studies (RCTs or cohort studies) published during this time period. These updated searches will be devised and run by an information specialist (CF). Our MEDLINE search strategy is provided in Appendix B.

Study selection, data management and critical appraisal

RQ1. Study selection.

In addressing RQ1, we will exclusively search for systematic reviews and/or meta-analyses that concentrate on the effectiveness of GBS screening interventions. This approach aims to minimise research waste and enables the quantification of key screening outcomes by documenting effectiveness data (i.e. allowing us to note whether there is statistically significant evidence of benefit or harm for each outcome reported in the meta-analyses, or if no evidence of benefit or harm was found).

We will use the EPPI-Centre definition of a systematic review as a review that uses explicit and transparent methods, follows a standard set of stages and can be considered accountable, replicable and updateable [20]. Consequently, included systematic reviews and meta-analyses may include data from cross-sectional studies, cohort studies (retrospective or prospective), case-control studies, and from national/regional registries. Where there is a more recent update of a systematic review or high overlap between reviews, older reviews are superseded and will be excluded and added to the Table of excluded studies with a reason for exclusion. All other types of reviews, such as scoping reviews and narrative reviews that do not adhere to PRISMA guidelines [28], will be excluded.

RQ1. Data management

Records will undergo de-duplication in Endnote, after which the remaining records will be imported into Covidence. Two members of the review team will independently screen titles and abstracts based on the eligibility criteria specified in Table 2. Full text publications will be retrieved and independently screened by two reviewers. Disagreements will be addressed through consensus meetings or by consulting a third content expert. The literature flow during the screening process will be recorded in a PRISMA flowchart [28].

The overlap between primary studies in reviews (judged as the proportion of primary studies in one systematic review found in another) will be assessed prior to data extraction using the Graphical Representation of Overlap for OVErviews (GROOVE) tool [34]. A visual presentation of overlap of primary studies within the systematic reviews will be presented to support interpretation of evidence [34].

RQ1. Critical appraisal

Two review authors will independently assess the methodological quality of the included reviews, using seven 'critical' domains from the AMSTAR-2 appraisal tool [29]. The criteria include:

- Item 2: Protocol registered before commencement of the review
- Item 4: Adequacy of the literature search
- Item 7: Justification for excluding individual studies
- Item 9: ROB from individual studies being included in the review
- Item 11: Appropriateness of meta-analytical methods

- Item 13: Consideration of ROB when interpreting the results of the review
- Item 15: Assessment of presence and likely impact of publication bias

Systematic reviews or meta-analyses assessed as having high risk of bias in any of the AMSTAR2 'critical' domains [29] will be excluded and listed in a table of excluded systematic reviews, without additional data extraction.

RQ2. Study selection and data management

To identify relevant studies for RQ2, we will systematically identify any relevant primary studies that meet the eligibility criteria reported in Table 3 based on the systematic review and meta-analyses publications included in RQ1.

This includes primary studies that:

- use a RCT or non-randomised controlled trials that include a control group (historical or concurrent)
- are conducted in high-income countries as defined by the World-Bank database [35].

We will systematically identify and retrieve the full text papers for all studies listed and import all the relevant studies into Covidence. One reviewer will screen titles and abstracts of the primary studies, excluding obviously irrelevant studies. Two reviewers will independently apply eligibility criteria to full texts of remaining studies; any disagreements will be resolved by a third reviewer or through discussion between reviewers. Cochrane rapid review guidance[33] suggests that a single reviewer may suffice; however, we will employ two reviewers for full text screening to reduce errors, given a lack of prior familiarity with the topic area.

RQ2: Critical appraisal

We will use the CASP checklists, selected based on study design (e.g. the CASP tool for randomised controlled trials or cohort studies), to conduct a critical appraisal of the primary studies [36]. The CASP checklists are widely utilised, evidence-based instruments recognised for their ease of use, making them appropriate for rapid reviews [36]. They provide a systematic method for evaluating significant factors, facilitating informed decision-making and ensuring transparent documentation. The recent inclusion of an appraisal summary is advantageous for facilitating the interpretation of the findings from this rapid review.

Two independent reviewers will conduct a critical appraisal, with any disagreements resolved through discussion with a third member of the review team.

Data extraction

Data will be extracted by one reviewer into standardised tables using a pre-developed data extraction form within Covidence; a second reviewer will check the data. Sample data extraction forms for RQ1 and RQ2 are presented in Appendix C.

Data extracted for RQ1 will include the following items extracted at the level of the systematic review/ meta-analysis:

- Details of study characteristics
    - Author
    - Publication year
    - Study design
        - Systematic review or meta-analysis
    - Countries
    - Settings
    - Inclusion / exclusion criteria
- EOGBS definition (as defined by the SR authors)
- LOGBS definition (as defined by the SR authors)
- Any / all cause neonatal infections reported
- IAP criteria (as defined by SR authors) including timing of screening
    - Universal strategies
    - Risk-based strategies
    - No treatment strategy
    - Any other strategy (if reported)
- Sample size
    - Number of included studies
    - Total number of participants reported across studies
- Characteristics of participants (as reported by the systematic review/meta-analyses)
    - Total number of eligible participants in each IAP screening group:
        - Universal screening
        - Risk-based screening

        - No treatment strategy
        - Any other screening protocols/treatments (if reported)
        - Demographic characteristics of mother, including age, gestation, prevalence of GBS colonisation and other risk factors for each IAP screening group (universal / risk-based/ no treatment / other)
- Description of the intervention (as reported by the systematic review/meta-analyses)
    - Number of studies reporting the following items:
        - Screening based criteria for IAP
        - Risk-based criteria for IAP
        - Types of IAP agent
        - Timing of IAP agent
- Description of any co-interventions
- From any systematic review that included meta-analyses we will extract the following:
    - Number of trials and participants in the meta-analysis
    - EOGBS incidence / 1000 live births reported as the relative risk (RR) (95% confidence intervals) (I^2) (or alternative measure of difference in risk) for the following comparisons:
        - Universal screening strategy vs no intervention
        - Risk-based screening strategies vs no intervention
        - Universal screening strategies vs risk-based screening strategies
    - LOGBS incidence / 1000 live births reported as the relative risk (RR) (95% confidence intervals) (I^2) (or alternative measure of difference in risk) for the following comparisons:
        - Universal screening strategy vs no intervention
        - Risk-based screening strategies vs no intervention
        - Universal screening strategies vs risk-based screening strategies
    - Incidence for other cause neonatal infections / 1000 live births reported as the relative risk (RR) (or alternative measure of difference in risk) (95% confidence intervals), heterogeneity (I^2) and statistical significance for the following comparisons:
        - Universal screening strategy vs no intervention
        - Risk-based screening strategies vs no intervention

        - Universal screening strategies vs risk-based screening strategies
- Other short-, medium- or long-term benefits or harms assessed by SRs
- Any relevant Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [37] judgements reported by the review authors.

Data extracted for RQ2 will include the following items extracted at the level of the primary study:

- Details of study characteristics
    - Author
    - Year
    - Study design
    - Control group
        - Historical control
        - Concurrent control
    - Country
    - Income using World Bank Definition (ref)
    - Study setting
- EOGBS definition (if reported)
- LOGBS definition (if reported)
- Any other cause neonatal infections reported
- Characteristics of intervention participants
    - Total number of eligible participants
    - Demographic characteristics of mother: age; gestation; ethnicity; prevalence of GBS colonisation; number of women with risk factors for vertical transmission
- Characteristics of control participants
    - Total number of eligible participants
    - Demographic characteristics of mother: age; gestation; ethnicity; prevalence of GBS colonisation; number of women with high risk of vertical GBS transmission
- IAP criteria (for intervention and control groups)
    - Universal screening
    - Risk factors

    - No strategy
    - Other
- Type, timing and dose of IAP agent
- Outcomes
    - GBS neonatal, infant and child health outcomes
        - Incidence of all-cause neonatal infection
        - Death
        - Pneumonia
        - Septicaemia and meningitis
        - Encephalopathy
    - Maternal health outcomes including but not limited to:
        - Death
        - Infection including urinary tract infection and chorioamnionitis
        - Anaphylaxis

- Any other short-, medium-, long-term health outcomes assessed by study authors.
- Any other additional harms and benefits of screening [32] as reported by the study authors (see Table 3 for examples).

Data synthesis and analysis

For RQ1 we will produce a narrative synthesis including a:

- PRISMA flowchart [28] summarising the searching and number of systematic reviews identified
- Table of characteristics of all included reviews (see Appendix 2)
- Risk of bias table and graphical summary of ROB using the Robvis web app to create ROB assessment visualisations [38]
- We will tabulate the intervention, control, outcome, number of studies and participants' data relating to effectiveness and any GRADE judgements reported by the review authors. Using the data relating to effectiveness, we will note whether there was statistically significant evidence of benefit or harm for each outcome (EOGBS,

LOGBS, other cause neonatal infection) reported in the meta-analyses, or if there was no evidence of benefit or harm (no statistically significant effect).

For RQ2 we will produce a narrative synthesis reported in accordance with the Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guidelines [39].

- PRISMA flowchart [28] summarising the systematic identification of primary studies identified from each review, the number of duplicate studies, the number of primary studies that met our selection criteria (as detailed in Table 3) and the number of excluded primary studies (with reasons for exclusion)
- Table of excluded primary studies with reasons for exclusion
- Risk of bias table and graphical summary of ROB highlighting where we have reported the authors judgments or where we have conducted our own critical appraisal. We will use the Robvis web app to create a series of study design, appraisal specific ROB assessment visualisations [38].
- Narrative synthesis of the harms and benefits (neonatal and maternal) evidence, signposting to studies providing further details relating to harms and benefits.

Governance

Protocol

This protocol has been developed by NESSIE (NIHR Evidence Synthesis Scotland InitiativE) in order to address questions proposed by the UK NSC Evidence team. This has involved an iterative process of development and feedback to ensure that the protocol will provide the evidence required by the UK NSC Evidence team.

Review

The review will be conducted by the NESSIE team, according to the agreed protocol (as registered with PROSPERO). Any deviations from the protocol will be discussed with the UK NSC evidence team before finalisation of the reviews and will be stated (with reasons) in the final review as deviations from the original protocol.

Evidence summary

Findings from this review will be integrated into a UK NSC Evidence Summary produced by NESSIE in collaboration with the UK NSC Evidence Team who will provide feedback and co-ordinate feedback from the fetal, maternal and child health (FMCH) reference group and from public consultation (if applicable). NESSIE will integrate findings from the completed review, and responding to relevant feedback relating to review findings. The final Evidence Summary, co-produced by NESSIE and the UK NSC evidence team, will be used by the UK National Screening Committee to support discussions on GBS screening. The UK National Screening Committee will make the final decision on any recommendation related to a GBS screening programme.

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Appendices

Appendix A. Plans for Reference Group described according to ACTIVE Framework

ACTIVE Framework construct	**Plans for NESSIE GBS Reference Group**
Who will be involved?	People who have expertise / knowledge relating to screening for neonatal GBS, including those with expertise relating to: • Midwifery • Microbiology • Neonatal care (neonatologist / neonatal nurse) • Paediatrics And those with personal lived experience relevant to the topic, for example, parents who chose to pay for GBS screening during the antenatal period or people involved in organisation of mother and baby groups. As of 27/01/2025, the following people have agreed to be members of this Reference Group: 1. Rosie Hill, NESSIE Co-applicant with Policy and Public Health experience 2. Prof Helen Cheyne, Royal College of Midwives (Scotland) Professor of Midwifery 3. Dr Ryan Kean, Lecturer in Clinical Microbiology, Glasgow Caledonian University 4. Prof Narendra Aladangady, Consultant Neonatologist, Homerton University Hospital, Homerton Healthcare NHS Foundation Trust; Hon Clinical Professor in Child Health, Barts and the London School of Medicine and Dentistry 5. Dr Charlotte-Eve Short, Clinical Senior Lecturer in HIV and GU Medicine, Department of Infectious Disease, Imperial College London. 6. Mrs Amanda Rees, has lived experience of Strep B screening, being a mother of 2 young children who chose private screening for Strep B (she is not affiliated to any 3rd sector organisation). We are seeking additional members who have lived experience of Strep B screening, and choices associated with this.

	We will have a pragmatic approach to membership, and if – during the review process – we come across issues requiring specific expertise not held by current members (e.g. decisions relating to inclusion of specific research papers), then we will seek additional members with suitable expertise. This approach is appropriate given the rapid nature of these reviews.
How will people be recruited to the reference group?	We will use a closed approach, inviting named people with specific expertise/experience to join the reference group. As NESSIE only has limited existing contacts, we will use a 'snowball' approach, where we invite initially identified individuals to propose names of additional people. The use of a closed, invitation-based approach, is appropriate given the rapid nature of these reviews, and the need to involve people able to provide topic expertise.
What will the mode of involvement be?	The Reference group will be involved using a continuous approach. The method of interaction will primarily be indirect, through emails. However, we anticipate having a small number of online meetings, one at the start of the review, and a second during the data synthesis / write up. If necessary, we will have direct interaction with individual members (e.g. to seek clarification around specific terminology)
At what stage in the review process will involvement occur? What will the level of involvement be (at each stage)?	
1. Develop question	No involvement (questions will be developed through discussion with UK NSC)
2. Plan methods	No involvement (methods will be developed through discussion with UK NSC)
3. Write & publish protocol	Contributing/Influencing – draft protocols will be shared with Reference Group members, and members invited to comment on language, terminology, accessibility and presentation of the information.
4. Develop search	Contributing – members will be asked to view a draft search strategy and provide suggestions for any additional or alternative search terms. (The search strategy will then be developed by an information specialist and peer review provided by UK NSC).
5. Run search	No involvement (search will be run by NESSIE information specialist)
6. Select studies	Contributing/Influencing – where there are conflicts in agreements between review team, these may be

	discussed with individual Reference Group members (according to expertise required).
7. Collect data	Contributing/Influencing – where there are conflicts in data extracted by review team, or uncertainty in relation to data presented in an included study, these may be discussed with individual Reference Group members (according to expertise required).
8. Assess risk of bias	Contributing/Influencing – where there are uncertainties in relation to risk of bias within an included study, these may be discussed with individual Reference Group members (according to expertise required).
9. Analyse data	Contributing/Influencing – where there are uncertainties in relation to data presented within an included study (e.g. details of the population to which the data relates), these may be discussed with individual Reference Group members (according to expertise required).
10. Interpret findings	Contributing/Influencing – Reference Group members will be invited to comment on draft presentation of review results. They will not be able to influence the review results (i.e. objective data presented from individual studies) but will be invited to comment on the presentation of the findings, including structure of tables and figures, and language used to express findings.
11. Write & publish	As above. Where Reference Group members have contributed sufficient to meet criteria for authorship, they will be listed as authors on the published reviews.
12. Knowledge translation & impact	Contributing/Influencing – Reference Group members will be invited to offer views on where (i.e. which journals) the rapid reviews should be published. Receiving/contributing – Reference Group members would be informed of how the rapid review results were being used within the UK NSC Evidence Summary. Those who were authors on the publications may have opportunities to comment on how the rapid review results were used within the evidence summary. There would be no direct role / responsibility of the Reference Group members in the development of screening recommendations.

Appendix B. Search strategies

Search 1, for systematic reviews

Ovid MEDLINE(R)

1 exp Streptococcus agalactiae/
2 "group b streptococc*".ti,ab.
3 "streptococcus agalactiae".ti,ab.
4 "Streptococcus Group B".ti,ab.
5 EOGBS.ti,ab.
6 GBS.ti,ab.
7 iGBS.ti,ab.
8 LOGBS.ti,ab.
9 Pregnancy Complications, Infectious/di
10 or/1-9
11 exp Mass Screening/
12 Streptococcal Infections/di
13 Infectious Disease Transmission, Vertical/pc
14 test*.ti,ab.
15 screen*.ti,ab.
16 or/11-15
17 (systematic review or meta-analysis).pt.
18 meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
19 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.
20 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
21 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.
22 (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
23 (handsearch* or hand search*).ti,ab,kf.
24 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.

25 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.

26 (meta regression* or metaregression*).ti,ab,kf.

27 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.

28 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.

29 (cochrane or (health adj2 technology assessment) or evidence report).jw.

30 (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.

31 (outcomes research or relative effectiveness).ti,ab,kf.

32 ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.

33 (multi* adj3 treatment adj3 comparison*).ti,ab,kf.

34 (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.

35 (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.

36 (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.

37 (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.

38 or/17-37

39 10 and 16 and 38

40 limit 39 to english language

Search 2, for primary studies

Ovid MEDLINE(R)

1	exp Streptococcus agalactiae/
2	"group b streptococc*".ti,ab.
3	"streptococcus agalactiae".ti,ab.
4	"Streptococcus Group B".ti,ab.
5	EOGBS.ti,ab.
6	GBS.ti,ab.
7	iGBS.ti,ab.
8	LOGBS.ti,ab.
9	Pregnancy Complications, Infectious/di
10	or/1-9
11	exp Mass Screening/
12	Streptococcal Infections/di
13	Infectious Disease Transmission, Vertical/pc
14	test*.ti,ab.
15	screen*.ti,ab.
16	or/11-15
17	10 and 16
18	limit 17 to english language

Appendix C. Sample data extraction forms for RQ1 and RQ2

C1. Example data extraction form for Systematic review / meta-analysis characteristics (RQ1)

Review reference	Review Author and year of publication	Protocol and registration details	Review aim or objectives	Number of included studies	Country	Number of participants	Systematic review or meta-analysis?	Review eligibility criteria						Databases searched	Date of last search	Data extraction (reported at the level of the review)			Key findings	Effect measures reported (Y/N)?	Risk of bias conducted (Y/N)?	Certainty assessment reported (Y/N)?
						Women (n), Neonates (n)		Study designs (No. included by design)	Inclusion criteria	Exclusion criteria	Participant details	Strategies for IAP administration	Outcome measures			Study population	IAP strategies	Outcomes extracted				
Review 1																						
Review 2																						
Review 3																						

C2. Summary of comparisons reported in systematic reviews/ meta-analyses (RQ1)

Reference to review (Author, year)	Comparison	Country	Population	Outcome	Assessment times (if stated)	Number of studies (list authors / refs of primary studies included in MA)	n (total)	Effect size (95% confidence interval)	Heterogeneity (I^2)	GRADE LEVEL (as reported by SR authors)	GRADE evidence downgrades applied as reported by the SR authors 1. ROB 2. Imprecision, 3. Inconsistency, 4. Indirectness, 5. Publication bias
Review 1											
Review 2											
Review 3											
Review 4											
Review 5											

Key: Reasons for downgrading evidence: 1 = serious limitation in the Risk of bias; 2 = imprecision (e.g. wide confidence intervals or small sample size); 3 = Inconsistency (e.g. high I2); 4 = indirectness (e.g. variation in participants, intervention, comparisons or outcomes); 5 = publication bias; D1 = one downgrade; D2 = two downgrades

GRADE Working Group grades of evidence

- High quality: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: We are very uncertain about the estimate.

C3. Example data extraction form for key study characteristics for relevant primary studies identified from systematic reviews/meta-analysis studies (RQ2)

Reference for review from which the primary study was identified	Primary study (reference)	Country	Setting	Protocol and registration details	Study aim	Study design	Control group (historical / concurrent)	Inclusion criteria	Exclusion criteria	EOGBS definition	LOGBS definition	Any other cause neonatal infections reported
Review 1	Primary study 1											
	Primary study 2											
	Primary study 3											

C4. Example data extraction form for participant and intervention characteristics for relevant primary studies identified from systematic reviews/meta-analysis studies (RQ2)

Reference for review from which the primary study was identified	Primary study (reference)	IAP criteria including a description of whether screening was antenatal or intrapartum (as reported by the primary study authors)				IAP agent (as reported by the primary study authors)			Intervention participants (as reported by the primary study authors)								Control participants (as reported by the primary study authors)							
		Universal strategies	*Risk based strategies*	*No treatment strategy*	*Other strategies*	*Type*	*Timing*	Dose	*Women (n)*	*Neonates (n)*	*Women age n(SD)*	*Gestational age n(SD)*	*Ethnicity*	*Prevalence of GBS colonisation*	*Number of women with high risk GBS*	*Other clinical risk factors reported*	*Women (n)*	*Neonates (n)*	*Women age n(SD)*	*Gestational age n(SD)*	*Ethnicity*	*Prevalence of GBS colonisation*	*No. of women with high risk GBS*	*Other clinical risk factors reported*
Review 1	Primary study 1																							
	Primary study 2																							
	Primary study 3																							

C5. Example data extraction form summarising any short-term neonatal or maternal health outcomes, benefits or harms reported in relevant primary studies identified from systematic reviews/meta-analysis studies (RQ2)

Study reference	Neonatal outcomes								Maternal health outcomes					
	Incidence of all-cause neonatal infection	Death	Pneumonia	Septicaemia and meningitis	Encephalopathy	Any other short-term outcomes reported	Any other short-term harms of screening reported	Any other short-term benefits of screening reported	Death	Infection including UTI and chorioamnionitis	Anaphylaxis	Any other short-term outcomes reported	Any other short-term harms of screening reported	Any other short-term benefits of screening reported
Primary study 1														
Primary study 2														
Primary study 3														
Primary study 4														
Primary study 5														

Note: Neonatal / short term - beginning at birth and ending at 28 completed days of life

C6. Example data extraction form summarising any medium-term infant or maternal health outcomes, benefits or harms reported in relevant primary studies identified from systematic reviews/meta-analysis studies (RQ2)

Study reference	Infant outcomes							Maternal outcomes			
	Death	Pneumonia	Septicaemia and meningitis	Encephalopathy	Any other medium-term outcomes reported	Any other medium-term harms of screening reported	Any other medium-term benefits of screening reported	Death	Other medium-term health outcomes reported	Any other medium-term harms of screening reported	Any other medium-term benefits of screening reported
Primary study 1											
Primary study 2											
Primary study 3											
Primary study 4											
Primary study 5											
Primary study 6											

Note: Medium / infancy, a time extending from the first month after birth to approximately 12 months of age

C7. Example data extraction form summarising any long-term childhood or maternal health outcomes, benefits or harms reported in relevant primary studies identified from systematic reviews/meta-analysis studies (RQ2)

Study reference	Childhood outcomes				Maternal outcomes			
	Death	Any other longer-term health outcomes reported	Other longer-term harms of screening reported	Any other longer-term benefits of screening reported	Death	Other longer-term health outcomes reported	Any other longer-term harms of screening reported	Any other longer-term benefits of screening reported
Primary study 1								
Primary study 2								
Primary study 3								
Primary study 4								
Primary study 5								
Primary study 6								

Note: Long term / childhood, a time extending from 1-18 years of age