National Institute for Health and Care Excellence

Final

Postnatal care

[L1] Signs and symptoms of serious illness in babies

NICE guideline NG194

Evidence review underpinning recommendations 1.4.1 and 1.4.3 to 1.4.10

April 2021

Final

This evidence review was developed by the National Guideline Alliance, part of the Royal College of Obstetricians and Gynaecologists

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Signs and symptoms of serious illness in babies

Review question

What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

Introduction

Following the neonatal period, the highest incidence of illness and death occurs in the first six months of life compared to the rest of childhood. Although many children showing signs and symptoms will have a self-limiting illness, a minority will have a serious or even life-threatening illness. Early recognition of signs and symptoms in young babies, and early treatment, is therefore important to help reduce the severity of illness and prevent deaths. The aim of this review is to find out what signs and symptoms in babies are associated with serious illness or mortality.

Summary of the protocol

Please see Table 1 for a summary of the population, index tests/prognostic factors, confounding factors and outcome characteristics of this review.

Table 1: Summary of the protocol

Population	Babies born at term, between 37 and 42 weeks of pregnancy
Index tests/prognostic factors	One or more of the following symptoms or signs within the first 8 weeks after birth: • abnormal skin or mucosal colour (such as pallor or cyanosis) • appearing ill to a healthcare professional or parent/carer • altered responsiveness or altered cry (such as reduced responsiveness, drowsiness, irritability, reduced or increased crying) • altered breathing (such as nasal flaring, grunting, chest in-drawing) • abnormal respiratory rate, pulmonary (lung) crackles and other sounds • bradycardia or tachycardia • oxygen desaturation • dehydration • prolonged capillary refill time, cold hands and feet • deterioration in usual feeding • fever • height of fever • limb or joint swelling • not using a limb • bulging fontanelle • rash (blanching or non-blanching) • focal neurological signs

	• seizures • new lumps • recent onset vomiting • recent onset diarrhoea • abdominal distension • abdominal tenderness or rigidity • reported reduction in urine output • change in muscle tone, including hypotonia (such as floppy, limp) and hypertonia (such as stiffness, rigidity, back arching) • hyperglycaemia or hypoglycaemia • jaundice (hyperbilirubinaemia).
Confounding factors for prognostic estimates	• Sex • Age
Outcomes	• Serious illness within the first 8 weeks after birth (justifying admission to hospital) • Death of the baby within the first 8 weeks after birth

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until March 2018. From April 2018 until June 2019, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. From July 2019 onwards, the declarations of interest were recorded according to NICE's 2019 conflicts of interest policy. Those interests declared before July 2019 were reclassified according to NICE's 2019 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

One prospective cohort study was included in this review (Morley 1991a). It describes the frequency of clinical signs and symptoms reported in well babies and those seriously ill.

The included study is summarised in Table 2.

See the literature search strategy in appendix B and also the study selection flow chart in Appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of studies included in the evidence review

A summary of the study included in this review is presented in Table 2.

Table 2: Summary of included study.

Study	Population	Prognostic factors	Outcomes
Morley 1991a Prospective cohort study UK, Australia	N=1007 infants younger than 6 months of age	Signs: • respiratory rate >50/min • intermittent cry during examination • persistent cry during examination • cry - weak or whimpering • cry - high pitched or moaning • rash (moderate or severe • mild hypotonia • peripheral cyanosis • hyperinflation of the chest • distended and tense abdomen • expiratory grunt - audible • stridor • tender abdomen • transient loss of awareness of surroundings • rectal temperature >38.2 degrees Celsius • crepitations • reduced hydration • central cyanosis • no awareness of surroundings • partially extended posture • completely extended posture. Symptoms: • increased irritability • not himself/herself • abnormal cry • not feeding normally • noisy breathing • feels hot • vomiting (not posseting) • bile-stained vomiting • diarrhoea • cold hands and feet • pallor • fluids intake, approx. half normal • fluids less than /3 normal intake • convulsions.	• Serious illness

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Quality assessment of studies included in the evidence review

See the evidence profile in appendix F.

Economic evidence

Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No economic modelling was conducted for this review question because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Signs

- Very low quality evidence from 1 prospective cohort study (N=1007) showed a clinically important increase in the following signs in babies who were seriously ill compared to well babies:
  - intermittent or persistent cry during examination
  - weak or whimpering cry
  - high pitches or moaning cry
  - moderate or severe rash
  - mild hypotonia
  - peripheral cyanosis
  - hyperinflation of the chest
  - audible expiratory grunt
  - distended and tense abdomen
  - tender abdomen
  - transient loss of awareness or no awareness of surroundings
  - rectal temperature >38 degrees Celsius
  - crepitations (no auscultation)
  - reduced hydration
  - central cyanosis
  - partially or completely extended posture

However, no clinically important difference between those babies who were seriously ill and well babies with the following signs:

- inrespiratory rate >50/min
- stridor.

Symptoms

- Very low quality evidence from 1 prospective cohort study (N=1007) showed a clinically important increase in the following symptoms in babies who were seriously ill compared to well babies:
  - increased irritability
  - not himself/herself
  - abnormal cry
  - not feeding normally
  - noisy breathing
  - feels hot
  - not posseting vomiting
  - bile-stained vomiting
  - diarrhoea
  - cold hand and feet
  - pallor
  - approximately half normal intake of fluids
  - less than 1/3 normal intake of fluids
  - convulsions.

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Mortality and serious illness (justifying admission to hospital) within the first 8 weeks after birth were considered to be critical outcomes for decision making.

The committee agreed that the signs and symptoms listed in the protocol are most likely to be predictors of serious illness within the first 8 weeks after birth. The committee arrived at the listed signs and symptoms by using the signs and symptoms from the NICE guideline on fever in under 5s (CG160) as a basis and then the list was reviewed against the signs and symptoms from the NICE guideline on sepsis (NG51) and neonatal infection (early onset) (CG149) to check for omissions.

The committee discussed that it was difficult to prioritise predictors that are most likely to cause serious illness as infants usually present with a combination of signs and symptoms as opposed to a single sign or symptom, however fever, hypothermia, and unresponsiveness are considered red flags and should prompt further action.

The quality of the evidence

The quality of the evidence ranged from very low to low mainly due to risk of bias in the individual study (no adjustment for confounders). The quality of the evidence was downgraded for indirectness as the population included were infants under 6 months old, whereas the population of interest for this review were infants under 8 weeks of age. For 2 signs or symptoms, evidence was further downgraded due to imprecision of the effect estimates, i.e. the confidence interval crossed the null effect.

The committee agreed that there were gaps in the evidence about signs and symptoms for serious illness, with only one study meeting the inclusion criteria for the review. This may have been partially due to the restriction in outcomes set out in the review protocol to ensure that this guideline doesn't overlap with other disease specific NICE guidelines.

Benefits and harms

Due to the low quality and paucity of evidence that fit the protocol, the recommendations were drafted by the committee through consensus using their experience and expertise and existing NICE guidelines.

Foremost, the committee discussed the importance of parental concern when it comes to serious illness. The committee agreed that parents knew their babies best and feelings of "something not being quite right" with their baby should be taken seriously and treated as an important indicator of possible serious illness in itself.

The committee emphasised the importance of recognising early onset infection during the first 72 hours after birth when assessing for serious illness. The committee acknowledged that the NICE guideline on neonatal infection (early onset) applied to signs and symptoms of serious illness in babies, therefore the committee agreed to cross refer to this guideline when assessing babies for serious illness in the first 72 hours after birth. The committee were aware that this guideline was currently being updated and the update would also include consideration for late onset neonatal infection.

The committee agreed that fever with a temperature ≥38^{0}C in an infant less than 8 weeks' old is a red flag that requires further assessment to rule out serious illness. Nonetheless, the committee emphasised that not all young babies with a serious infection will present with fever, therefore the committee agreed to make a recommendation to highlight this and ensuring serious infection isn't overlooked in very young babies. The committee acknowledged that the NICE guideline on fever under 5s applied to signs and symptoms of serious illness in babies, therefore the committee agreed to cross refer to this guideline when assessing babies for serious illness who present with fever.

Concerns about the baby's growth may also be a serious concern or indicate a serious illness in the early days and weeks of life. The committee therefore added a reference to the NICE guideline on faltering growth.

The committee discussed the significance of a change in the baby's behaviour or symptoms compared to usual behaviour when assessing for serious illness, for example refusing feeds or a change in the level of responsiveness. This could be an important observation and an indication of illness.

Identification of signs and symptoms for serious illness enables parents and healthcare professionals to effectively identify infants who are more likely to develop a serious illness and act promptly to prevent or treat life-threatening conditions. The

committee agreed that it was important to assess independent predictors associated with serious illness, but they emphasised that in clinical practice signs and symptoms don't usually present independently, and that decisions would be based on combinations of signs and symptoms.

The committee highlighted that the evidence included in this review was not helpful for parents or healthcare professionals in identifying babies at risk of serious illness, as single signs and symptoms rarely present independently. However, certain symptoms and signs are indeed 'red flags' on their own and should prompt immediate assessment. The committee agreed that the list of 'red flags' would help identify seriously unwell babies and facilitate assessment by the appropriate healthcare professionals. The 'red flags' were identified through various NICE guidelines: fever in under 5s: clinical assessment of children with fever, neonatal infection (early onset): risk factors for infection and clinical indicators for possible infection, sepsis: identifying people with suspected sepsis, meningitis (bacterial) and meningococcal septicaemia in under 16s: symptoms, signs and initial assessment, gastroesophageal reflux disease in children and young people: diagnosing and investigating GORD, diarrhoea and vomiting caused by gastroenteritis in under 5s: assessing dehydration and shock, and urinary tract infection in under 16s: diagnosis.

Cost effectiveness and resource use

No economic evidence is available for this review question. The committee agreed that identifying signs and symptoms that are associated with serious illness or mortality in babies may have modest resource implications comprising health professional's time spent on observing the baby, listening to parental concerns and applying appropriate scoring systems to assess multiple symptoms and signs. Arranging an urgent assessment with an appropriate emergency service if a baby is thought to be seriously unwell has more important resource implications. However, identification of signs and symptoms that are associated with serious illness or mortality is likely to lead to great benefits for the babies and their parents and cost-savings to the health service, if serious illness is identified and treated earlier, as late identification of serious illness will likely lead to higher mortality and morbidity for the baby, more intensive intervention required and increased rates and length of hospitalisation, including resource-intensive stays in neonatal intensive care units (NICU). Therefore, the committee agreed that the recommendations ensure efficient use of healthcare resources.

References

Cole 1991

Cole TJ, Morley CJ, Thornton AJ, et al. A scoring system to quantify illness in babies under 6 months of age. Royal Statistical Society 1991; 2: 287-304

Morley 1991a

Morley CJ, Thornton AJ, Cole TJ, Fowler MA, Hewson PH. Symptoms and signs in infants younger than 6 months of age correlated with the severity of their illness. Pediatrics, 88(6):1119-24, 1991

Morley 1991b

Morley CJ, Thornton AJ, Cole TJ, et al. Baby check: a scoring system to grade the severity of acute systemic illness in babies under 6 months old. Arch of Dis in Child 1991; 66: 100-106

Thornton 1991

Thornton AJ, Morley CJ, Cole TJ, et al. Field trials of the Baby Check score card in hospital. Arch of Dis in Child1991; 66: 115-120

Appendices

Appendix A – Review protocol

Review protocol for review question: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

Table 3: Review protocol

Field (based on PRISMA-P)	Content
Review question	What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?
Type of review question	Diagnostic accuracy and prognostic review
Objective of the review	To determine the signs and symptoms (alone or in combination) in babies that are associated with serious illness or mortality.
Eligibility criteria – population	Exclude studies with a specific population of babies who were born pre-term. This means babies born before 37 weeks since 'term' is considered to be between 37 and 42 weeks of pregnancy. For studies with a mixed population, they will be included if at least 66% of babies are born at term. Exclude studies specifically focused on babies in which fever was an entry criterion. Exclude babies in neonatal units when signs and symptoms occur. Exclude studies focused on babies with a major underlying morbidity (e.g. congenital heart disease).
Eligibility criteria – index tests /prognostic factors	One or more of the following symptoms or signs within the first 8 weeks after birth: • abnormal skin or mucosal colour (for example, pallor or cyanosis) • appearing ill to a healthcare professional or parent/carer

	• altered responsiveness or altered cry (for example, reduced responsiveness, drowsiness, irritability, reduced or increased crying) • altered breathing (for example, nasal flaring, grunting, chest in-drawing) • abnormal respiratory rate, pulmonary (lung) crackles and other sounds • bradycardia or tachycardia • oxygen desaturation • dehydration • prolonged capillary refill time, cold hands and feet • deterioration in usual feeding • fever • height of fever • limb or joint swelling • not using a limb • bulging fontanelle • rash (blanching or non-blanching) • focal neurological signs • seizures • new lumps • recent onset vomiting • recent onset diarrhoea • abdominal distension • abdominal tenderness or rigidity • reported reduction in urine output • change in muscle tone, including hypotonia (for example, floppy, limp) and hypertonia (for example, stiffness, rigidity, back arching) • hyperglycaemia or hypoglycaemia • jaundice (hyperbilirubinaemia).
Confounding factors for prognostic estimates	• Sex • Age
Outcomes and prioritisation	• Serious illness within the first 8 weeks after birth (justifying admission to hospital) • Death of the baby within the first 8 weeks after birth

	For the prognostic component of the review, odds ratios and risk ratios will be reported. For the diagnostic component, sensitivity, specificity and likelihood ratios will be reported. Exclude studies specifically focused on infection in babies with onset in the first 72 hours after birth. Exclude studies focused on a specific disorder already covered by separate NICE guidelines (sepsis, bacterial meningitis and meningococcal septicaemia, early onset neonatal infection, urinary tract infection, gastro-oesophageal reflux disease).
Eligibility criteria – study design	Include published full text papers: For the prognostic component of the review: • systematic reviews • prospective or retrospective comparative cohort studies if at least 100 infants in each arm • only if cohort studies unavailable to inform decision making: case-control studies if at least 100 infants in each arm • prospective study design will be prioritised over retrospective study designs • multivariate analysis will be prioritised over univariate analysis • population-based studies and multicentre studies will be prioritised. For the diagnostic component of the review: • systematic reviews • cross-sectional studies • cohort studies • prospective cohort studies will be prioritised. If insufficient data are available from prospective cohort studies, then retrospective cohort studies will be considered. For both components of the review exclude: • conference abstracts • follow-up of RCTs • studies with a sample size <200.

Other inclusion exclusion criteria	**Inclusion** • English-language Studies from low- and middle-income countries, as defined by the World Bank, will be excluded, as the configuration of antenatal and postnatal services in these countries might not be representative of that in the UK. • Studies published from 1990 Studies published from 1990 will be considered for this review question.
Proposed sensitivity/sub-group analysis, or meta-regression	No groups will be reviewed or analysed separately.
Selection process – duplicate screening/selection/analysis	Sifting, data extraction and appraisal of methodological quality will be performed by the systematic reviewer. Any disputes will be resolved in discussion with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. This review question was not prioritised for health economic analysis and so no formal dual weeding, study selection (inclusion/exclusion) or data extraction into evidence tables will be undertaken. (However, internal (NGA) quality assurance processes will include consideration of the outcomes of weeding, study selection and data extraction and the committee will review the results of study selection and data extraction).
Data management (software)	NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations. For the diagnostic component of the review, a modified 'GRADE' method will be used to assess the quality of evidence for each index test. This will be described in the separate methods chapter for the guideline.
Information sources – databases and dates	The following databases will be searched: • DARE • Embase

	• EMCare • HTA Database • MEDLINE and MEDLINE IN-PROCESS Searches will be restricted by: • date limitations: 1990 to 4th February 2019 • English language • human studies • observational studies • systematic reviews. Other searches: • inclusion lists of systematic reviews.
Identify if an update	This is an update. However, the review and drafting of recommendations are being completed afresh. The 2006 version of the postnatal care guideline included these recommendations: 1.4.1 Healthy babies should have normal colour for their ethnicity, maintain a stable body temperature, and pass urine and stools at regular intervals. They initiate feeds, suck well on the breast (or bottle) and settle between feeds. They are not excessively irritable, tense, sleepy or floppy. The vital signs of a healthy baby should fall within the following ranges: • respiratory rate normally 30−60 breaths per minute • heart rate normally between 100 and 160 beats per minute in a newborn • temperature in a normal room environment of around 37°C (if measured). [2006] 1.4.2 At each postnatal contact, parents should be offered information and advice to enable them to: • assess their baby's general condition • identify signs and symptoms of common health problems seen in babies • contact a healthcare professional or emergency service if required. [2006]
Author contacts	National Guideline Alliance https://www.nice.org.uk/guidance/indevelopment/gid-ng10070
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
Search strategy – for one database	For details please see appendix B of the full guideline

Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables) of the full guideline.
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables) of the full guideline.
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014 **Appraisal of methodological quality:** The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Quality in prognostic studies (QUIPS) tool • QUADAS 2 for diagnostic studies.
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual 2014
Methods for analysis – combining studies and exploring (in)consistency	For a full description of methods see Supplement 1.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
Rationale/context – Current management	For details please see the introduction to the evidence review
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Dr David Jewell in line with section 3 of Developing NICE guidelines: the manual 2014

	Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For a full description of methods see Supplement 1.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	This protocol has not been registered in PROSPERO

GORD: gastro-oesophageal reflux disease; GRADE: Grading of Recommendations Assessment, Development and Evaluation; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; PRISMA-P: Preferred Reporting Items for Systematic and Meta-analysis Protocols; QUADAS: quality assessment of diagnostic accuracy studies; QUIPS: quality in prognosis studies; RCT: randomised controlled trial; ROBIS: risk of bias in non-randomised studies of interventions

Appendix B – Literature search strategies

Literature search strategies for review question: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

Clinical search

The search for this topic was last run on 4th February 2019.

Database: Emcare, Embase, Medline, Medline Ahead of Print and In-Process & Other Non-Indexed Citations – OVID [Multifile]

#	Search
1	perinatal period/ or exp postnatal care/
2	1 use emczd, emcr
3	postpartum period/ or peripartum period/ or postnatal care/
4	3 use ppez
5	(((first time or new) adj mother*) or nullipara* or peri natal* or perinatal* or postbirth or post birth or postdelivery or post delivery or postnatal* or post natal* or postpartum* or post partum* or primipara* or puerpera* or puerperium* or ((after or follow*) adj2 birth*)).ti,ab.
6	or/2,4-5
7	exp infant/ use emczd, emcr
8	exp infant/ or exp infant, newborn/
9	8 use ppez
10	(baby or babies or infant or infants or neonat* or newborn* or child* or toddler*).ti,ab.
11	or/7,9-10
12	cyanosis/ use emczd, emcr or (((ill or sick) adj3 (look* or appear*)) or (cyano* or unwell)).ti,ab.
13	exp skin/ use emczd, emcr or (skin* or pallor).ti,ab.
14	exp rash/ use emczd, emcr or exp purpura/ use ppez or (purpura* or petechia* or rash or mottled or blanching).ti,ab.
15	vomiting/ use emczd, emcr or (vomit* or emes*).ti,ab.
16	nose/ use emczd, emcr or ((nose or nasal or nostril? or alar) adj3 flar*).ti,ab.
17	abnormal respiratory sound/ use emczd, emcr or respiratory sounds/ use ppez or (((respirat* or breath*) adj3 sound?) or (crackl* or grunt*) or altered breath* or ((nasal or nose) adj2 flar*) or (in*1 draw adj2 chest)).ti,ab.
18	exp fontanel/ use emczd, emcr or cranial fontanelles/ use ppez or (fontanel* adj3 (bulg* or tens*)).ti,ab.
19	dehydration/ use emczd, emcr or dehydrat*.ti,ab.
20	oliguria/ use emczd, emcr or (oliguri* or ((reduc* or low*) adj2 urin* adj2 (output* or level* or volume*))).ti,ab.
21	exp edema/ use emczd, emcr or exp edema/ use ppez or (bump* or edem* or lump* or oedem* or sw#ll* or ((inability or unwill* or unable) adj3 (bear weight or weight bear* or weightbear* or weight bear* or "use limb*")) or (limb* adj3 tender*) or (focal adj2 (neurologic* or cns) adj2 (deficit* or dysfunction* or manifestation* or sign* or symptom*))).ti,ab.

#	Search
22	epileptic state/ use emczd, emcr or status epilepticus/ use ppez or ((stat* adj3 (absence or epileptic* or grand mal or petit mal)) or (fit? or convuls* or seiz*)).ti,ab.
23	respiratory rate/ use emczd, emcr
24	respiratory rate/ or tachypnea/
25	24 use ppez
26	(((breath* or respirat*) adj3 rate*) or tachypn*).ti,ab.
27	or/23,25-26
28	behavior change/ or irritability/
29	28 use emczd, emcr
30	exp behavior/ or irritable mood/
31	30 use ppez
32	(behav* or cries or cry* or drows* or irritab* or non respons* or nonresponse* or respon*).ti,ab.
33	or/29,31-32
34	breathing disorder/ or tachypnea/
35	34 use emczd, emcr
36	respiration disorders/
37	36 use ppez
38	(((respirat* or breath*) adj3 (alter* or disorder* or distress*)) or ((chest or intercostal or inter costal or sternal or sternum) adj3 (in*1 drawing or indrawing or recess* or retract*))).ti,ab.
39	or/35,37-38
40	feeding behavior/ or sucking/ or exp infant feeding/
41	40 use emczd, emcr
42	feeding behavior/ or sucking behavior/ or bottle feeding/ or breast feeding/
43	42 use ppez
44	((chang* or deterior* or reduced or poor* or refus*) adj3 (fed or feed* or suck*)).ti,ab.
45	or/41,43-44
46	oxygen saturation/ or exp oximetry/
47	46 use emczd, emcr
48	oxygen/bl or exp oximetry/
49	48 use ppez
50	(oxygen adj2 (desaturat* or saturat*)).ti,ab.
51	or/47,49-50
52	blood flow/ or capillary/ or capillary flow/ or microcirculation/
53	52 use emczd, emcr
54	capillaries/ or regional blood flow/ or microcirculation/
55	54 use ppez
56	(capilliar* refill tim* or crt).ti,ab.

#	Search
57	or/53,55-56
58	chill/ or shivering/ or rigor/
59	58 use emczd, emcr
60	chills/ or shivering/
61	60 use ppez
62	(((chill* or cold) adj3 (feet or foot or hand*)) or (chill* or rigor* or shiver*)).ti,ab.
63	or/59,61-62
64	seizure/ use emczd, emcr
65	exp neurological manifestations/ or seizures/
66	65 use ppez
67	((focal or local* or partial) adj3 seiz*).ti,ab.
68	or/64,66-67
69	muscle rigidity/ or neck pain/
70	69 use emczd, emcr
71	muscle rigidity/ or neck pain/
72	71 use ppez
73	((cervical or neck) adj3 (ache or pain* or stiff*)).ti,ab.
74	or/70,72-73
75	fever/ or hyperthermia/ or hyperpyrexia/ or pyrexia idiopathica/
76	75 use emczd, emcr
77	exp fever/ use ppez
78	(fever* or febri* or hyperpyrex* or hyper pyrex* or hypertherm* or hyper therm* or pyrex* or temperature).ti,ab.
79	or/76-78
80	(or/12-22,27,33,39,45,51,57,63,68,74,79) or (((high or low or reduced or increase*) adj2 blood sugar) or ((abdom* or stomach or tummy) adj2 (disten* or pain* or swell*)) or ((floppy or limp) adj baby) or ((high* or increase* or low* or reduc*) adj2 heart rate) or ((limb* or joint*) adj2 (swell* or swollen)) or ((abdom* or stomach) adj2 (rigid* or tender*)) or ((yellow or green*) adj2 (pallor* or palor* or skin*)) or (arch adj2 back) or (muscle adj2 tone) or bradycardi* or diarrhea or diarrhoea or hyperbilirubinaemi* or hyperbilirubinemi* or hypergluc* or hyperglyc* or hypertoni* or hypoglyc* or hypotoni* or icterus or jaundice or rigididy or stiffness or tachyarrhythmi* or tachycardi*).ti,ab,hw.
81	exp symptomatology/ use emczd, emcr or exp "signs and symptoms"/ use ppez or (sign? adj2 symptom*).tw.
82	(complain* or sign* or symptom* or complain* or (clinical adj3 (aspect* or feature* or finding* or manifestation* or marker*)) or (presenting adj3 (factor* or feature* or finding*)) or presentation* or (physical adj3 (characteristic* or feature* or finding* or manifestation*))).ti,ab.
83	or/81-82
84	acute disease/ or case management/ or critical illness/ or emergency medicine/ or emergency nursing/ or exp emergency treatment/ or injury severity/ or exp intensive care/ or morbidity/ or infant mortality/ or exp mortality rate/ or exp perinatal mortality/

#	Search
85	84 use emczd, emcr
86	acute disease/ or case management/ or exp critical care/ or critical illness/ or exp emergency medical services/ or emergency medicine/ or emergency nursing/ or exp emergency treatment/ or life support care/ or morbidity/ or *mortality/ or exp infant mortality/ or infant/mo or exp infant, newborn/mo
87	86 use ppez
88	(case management or ((acute* or critical* or emergency or intensive or serious* or sever*) adj2 (care or ill or illness* or therap* or treatment)) or ((admission or admit*) adj2 emergenc* adj2 (depart* or hospital* or ward*)) or death* or first aid or emergency triage or life support or morbidit* or mortalit* or ((referral or urgent) adj2 care) or resuscitation).ti,ab.
89	or/85,87-88
90	exp bacterial infection/ or critical illness/ or acute disease/
91	90 use emczd, emcr
92	exp bacterial infections/ or critical illness/ or acute disease/
93	92 use ppez
94	((acute* or bacteri* or critical* or serious* or sever* or streptococc* or staphylococc*) adj (disease* or ill* or infect*)).ti,ab.
95	or/91,93-94
96	bacterial meningitis/ or meningoencephalitis/
97	96 use emczd, emcr
98	exp meningitis, bacterial/ or meningoencephalitis/
99	98 use ppez
100	mening*.ti,ab.
101	or/97,99-100
102	septicemia/ or exp bacteremia/
103	102 use emczd, emcr
104	sepsis/ or exp bacteremia/
105	104 use ppez
106	(bacteraemi* or bacteremi* or sepsis or septicaemi* or septicemi*).ti,ab.
107	or/103,105-106
108	exp pneumonia/ use emczd, emcr or pneumon*.ti,ab.
109	herpes simplex encephalitis/ use emczd, emcr or encephalitis, herpes simplex/ use ppez or (encephalit* adj5 (herpe* or hsv)).ti,ab.
110	exp infectious arthritis/ use emczd, emcr or exp arthritis, infectious/ use ppez or ((arthrit* adj3 (bacteri* or infect* or pyogen* or purulent* or septic* or suppurat*)) or py?arth*).ti,ab.
111	exp osteomyelitis/ use emczd, emcr or exp osteomyelitis/ use ppez or osteomyelit*.ti,ab.
112	exp urinary tract infection/ use emczd, emcr or exp urinary tract infections/ use ppez or (((bladder* or genito urin* or genito urin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen* or uro gen*) adj5 infect*) or ((lower or upper) adj5 urin*) or uti).ti,ab.
113	exp cystitis/ use emczd, emcr or exp cystitis/ use ppez or (cystit* or pyocystit* or pyelocystit* or cystopyelit*).ti,ab.

#	Search
114	exp pyelonephritis/ use emczd, emcr or (pyelonephr* or pyonephr*).ti,ab.
115	mucocutaneous lymph node syndrome/ use emczd, emcr, ppez or ((mucocutaneous adj3 lymph*) or mcls or (kawasaki* adj (disease* or syndrome*))).ti,ab.
116	exp pyrogen/ use emczd, emcr or exp pyrogens/ use ppez or pyrogen*.ti,ab.
117	(or/89,95,101,107-116) or ((gastro* adj2 reflux disease) or gord).ti,ab,sh.
118	exp case control study/ or cohort analysis/ or cross-sectional study/ or follow up/ or longitudinal study/ or observational study/ or prospective study/ or retrospective study/
119	118 use emczd, emcr
120	exp case control studies/ or exp cohort studies/ or cross-sectional studies/ or epidemiologic studies/ or observational study/
121	120 use ppez
122	(cohort*1 or cross section* or crosssection* or followup* or follow up* or followed or longitudinal* or prospective* or retrospective*).ti,ab.
123	(case adj2 (control or series)).ti,ab.
124	or/119,121-123
125	meta-analysis/
126	meta-analysis as topic/
127	systematic review/
128	meta-analysis/
129	(meta analy* or metanaly* or metaanaly*).ti,ab.
130	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
131	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
132	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
133	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
134	(search* adj4 literature).ab.
135	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
136	cochrane.jw.
137	((pool* or combined) adj2 (data or trials or studies or results)).ab.
138	(or/125-126,129,131-136) use ppez
139	(or/127-130,132-137) use emczd, emcr
140	or/138-139
141	or/124,140
142	letter.pt. or conference paper.sh.
143	(editorial or note).pt. or case report/ or case study/
144	(or/142-143) use emczd, emcr
145	letter/ or editorial/ or news/ or historical article/ or anecdotes as topic/ or comment/ or case report/
146	145 use ppez

#	Search
147	(letter or comment* or abstracts).ti.
148	or/144,146-147
149	148 not 141
150	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/
151	150 use ppez
152	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/
153	152 use emczd, emcr
154	(rat or rats or mouse or mice).ti.
155	or/149,151,153-154
156	(6 and 11 and 80 and 83 and 117) not 155
157	(6 and 11 and 117 and 83 and 124) not 155
158	(6 and 11 and 80 and 117 and (test* or score*).tw.) not 155
159	or/156-158
160	limit 159 to yr="1990 -current"
161	limit 160 to english language

Database: CDSR (global) [Wiley]

#	Search
#1	mesh descriptor: [postpartum period] explode all trees
#2	mesh descriptor: [peripartum period] this term only
#3	mesh descriptor: [postnatal care] this term only
#4	((((“first time” or new) near/1 mother*) or nullipara* or "peri natal*" or perinatal* or postbirth or "post birth" or postdelivery or "post delivery" or postnatal* or "post natal*" or postpartum* or "post partum*" or primipara* or puerpera* or puerperium* or ((after or follow*) near/2 birth*))):ti,ab,kw
#5	#1 or #2 or #3 or #4

Database: DARE, HTA (global) [CRD Web]

#	Search
1	mesh descriptor postpartum period in dare,hta
2	mesh descriptor peripartum period in dare,hta
3	mesh descriptor postnatal care in dare,hta
4	(nullipara* or peri natal* or perinatal* or postbirth or post birth or postdelivery or post delivery or postnatal* or post natal* or postpartum* or post partum* or primipara* or puerpera* or puerperium* or ((after or follow*) near2 birth*)) in dare, hta
5	#1 or #2 or #3 or #4
6	mesh descriptor breast feeding explode all trees in dare,hta
7	mesh descriptor lactation in dare,hta
8	(breastfeed* or breast feed* or breastfed* or breastfeed* or breast fed or breastmilk or breast milk or expressed milk* or lactat* or (nursing next (baby or infant* or mother* or neonate* or newborn*))) in dare, hta

#	Search
9	#6 or #7 or #8
10	mesh descriptor bottle feeding in dare,hta
11	mesh descriptor infant formula in dare,hta
12	(((bottle or formula or synthetic) near2 (artificial or fed or feed* or infant* or milk*)) or (artificial next (formula or milk)) or bottlefed or bottlefeed or cup feeding or (milk near2 (substitut* or supplement*)) or ((infant or milk or water or glucose or dextrose or formula) next supplement) or formula supplement* or supplement feed or milk feed or ((baby or babies or infant* or neonate* or newborn*) next (formula* or milk)) or formulafeed or formulated or (milk near2 powder*) or hydrolyzed formula* or (((feeding or baby or infant) next bottle*) or infant feeding or bottle nipple* or milk pump*)) in dare, hta
13	#10 or #11 or #12
14	#5 or #9 or #13

Health economic search

The search for this topic was last run on 5th December 2019.

Database: Emcare, Embase, Medline, Medline Ahead of Print and In-Process & Other Non-Indexed Citations (global) – OVID [Multifile]

#	Search
1	puerperium/ or perinatal period/ or postnatal care/
2	1 use emczd, emcr
3	postpartum period/ or peripartum period/ or postnatal care/
4	3 use ppez
5	(nullipara* or peri natal* or perinatal* or postbirth or post birth or postdelivery or post delivery or postnatal* or post natal* or postpartum* or post partum* or primipara* or puerpera* or puerperium* or ((after or follow*) adj2 birth*)).ti,ab.
6	or/2,4-5
7	breast feeding/ or breast feeding education/ or lactation/
8	7 use emczd, emcr
9	exp breast feeding/ or lactation/
10	9 use ppez
11	(breastfeed* or breast feed* or breastfed* or breastfeed* or breast fed or breastmilk or breast milk or expressed milk* or lactat* or (nursing adj (baby or infant* or mother* or neonate* or newborn*))).ti,ab.
12	or/8,10-11
13	artificial food/ or bottle feeding/ or infant feeding/
14	13 use emczd, emcr
15	bottle feeding/ or infant formula/
16	15 use ppez
17	(((bottle or formula or synthetic) adj2 (artificial or fed or feed* or infant* or milk*)) or (artificial adj (formula or milk)) or bottlefed or bottlefeed or cup feeding or (milk adj2 (substitut* or supplement*)) or ((infant or milk or water or glucose or dextrose or formula) adj supplement) or formula supplement* or supplement feed or milk feed or ((baby or babies or infant* or neonate* or newborn*) adj (formula* or milk)) or formulafeed or formulated or (milk adj2 powder*) or hydrolyzed formula* or (((feeding or baby or infant) adj bottle*) or infant feeding or bottle nipple* or milk pump*)).ti,ab.
18	or/14,16-17

#	Search
19	or/6,12,18
20	budget/ or exp economic evaluation/ or exp fee/ or funding/ or exp health care cost/ or health economics/
21	20 use emczd, emcr
22	exp budgets/ or exp "costs and cost analysis"/ or economics/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or exp "fees and charges"/ or value of life/
23	22 use ppez
24	budget*.ti,ab. or cost*.ti. or (economic* or pharmaco?economic*).ti. or (price* or pricing*).ti,ab. or (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. or (financ* or fee or fees).ti,ab. or (value adj2 (money or monetary)).ti,ab.
25	or/21,23-24
26	economic model/ or quality adjusted life year/ or "quality of life index"/
27	(cost-benefit analysis.sh. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.)
28	((quality of life or qol).tw. and cost benefit analysis.sh.)
29	or/26-28 use emczd, emcr
30	models, economic/ or quality-adjusted life years/
31	(cost-benefit analysis.sh. and (cost-effectiveness ratio* and (perspective* or life expectanc*)).tw.)
32	((quality of life or qol).tw. and cost-benefit analysis.sh.)
33	or/30-32 use ppez
34	(eq-5d* or eq5d* or eq-5* or eq5* or euroqual* or euro qual* or euroqual 5d* or euro qual 5d* or euro qol* or euroqol*or euro quol* or euroquol* or euro quol5d* or euroquol5d* or eur qol* or eurqol* or eur qol5d* or eurqol5d* or eur?qul* or eur?qul5d* or euro* quality of life or european qol).tw.
35	(euro* adj3 (5 d* or 5d* or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).tw.
36	(hui or hui2 or hui3).tw.
37	(illness state* or health state*).tw.
38	(multiattibute* or multi attribute*).tw.
39	(qaly* or qal or qald* or qale* or qtime* or qwb* or daly).tw.
40	(quality adjusted or quality adjusted life year*).tw.
41	(sf36 or sf 36 or sf thirty six or sf thirtysix).tw.
42	sickness impact profile.sh.
43	(time trade off*1 or time tradeoff*1 or tto or timetradeoff*1).tw.
44	(utilit* adj3 (score*1 or valu* or health* or cost* or measur* or disease* or mean or gain or gains or index*)).tw.
45	utilities.tw.
46	((qol or hrqol or quality of life).tw. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (change*1 or declin* or decreas* or deteriorat* or effect or effects or high* or impact*1 or impacted or improve* or increas* or low* or reduc* or score or scores or worse)).ab.
47	quality of life.sh. and ((health-related quality of life or (health adj3 status) or ((quality of life or qol) adj3 (chang* or improv*)) or ((quality of life or qol) adj (measure*1 or score*1))).tw. or (quality of life or qol).ti. or ec.fs.)
48	or/29,33-47
49	or/25,48

#	Search
50	19 and 50
51	limit 50 to english language
52	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/
53	52 use ppez
54	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/
55	54 use emczd, emcr
56	(rat or rats or mouse or mice).ti.
57	or/53,55-56
58	51 not 57

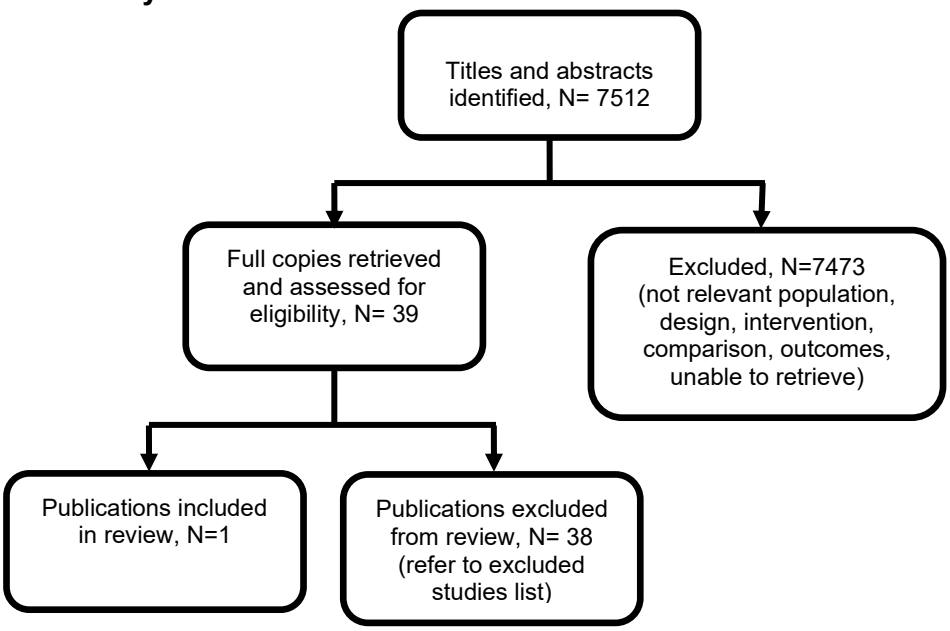
Database: HTA, NHS EED (global) [CRD Web]

#	Search
1	mesh descriptor postpartum period in hta, nhs eed
2	mesh descriptor peripartum period in hta, nhs eed
3	mesh descriptor postnatal care in hta, nhs eed
4	(nullipara* or peri natal* or perinatal* or postbirth or post birth or postdelivery or post delivery or postnatal* or post natal* or postpartum* or post partum* or primipara* or puerpera* or puerperium* or ((after or follow*) near2 birth*)) in hta, nhs eed
5	#1 or #2 or #3 or #4
6	mesh descriptor breast feeding explode all trees in hta, nhs eed
7	mesh descriptor lactation in hta, nhs eed
8	(breastfeed* or breast feed* or breastfed* or breastfeed* or breast fed or breastmilk or breast milk or expressed milk* or lactat* or (nursing next (baby or infant* or mother* or neonate* or newborn*))) in hta, nhs eed
9	#6 or #7 or #8
10	mesh descriptor bottle feeding in hta, nhs eed
11	mesh descriptor infant formula in hta, nhs eed
12	(((bottle or formula or synthetic) near2 (artificial or fed or feed* or infant* or milk*)) or (artificial next (formula or milk)) or bottlefed or bottlefeed or cup feeding or (milk near2 (substitut* or supplement*)) or ((infant or milk or water or glucose or dextrose or formula) next supplement) or formula supplement* or supplement feed or milk feed or ((baby or babies or infant* or neonate* or newborn*) next (formula* or milk)) or formula feed or formulated or (milk near2 powder*) or hydrolyzed formula* or (((feeding or baby or infant) next bottle*) or infant feeding or bottle nipple* or milk pump*)) in hta, nhs eed
13	#10 or #11 or #12
14	#5 or #9 or #13

Appendix C – Clinical evidence study selection

Clinical study selection for: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

Figure 1: Study selection



Appendix D – Clinical evidence tables

Evidence table for review question: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

Table 4: Evidence table

Study details	Participants	Factors	Methods	Outcomes and Results	Comments
Full citation Morley CJ, Thornton AJ, Cole TJ, Fowler MA, Hewson PH, Symptoms and signs in infants younger than 6 months of age correlated with the severity of their illness, Pediatrics, 88, 1119-1124, 1991 **Ref Id** 1078611 **Country/ies where the study was carried out** UK, Australia **Study type** Prospective cohort **Aim of the study** To describe the prevalence of individual symptoms and signs in infants who were well, mildly ill, moderately ill or seriously ill.	**Sample size** N=1007 infants younger than 6 months of age; n=298 home population (UK only); n=709 hospital population **Characteristics** No characteristics of the population reported **Inclusion criteria** Full-term infants whose mothers spoke English and lived within 5 miles of the hospital (for home UK population) and infants younger than 6 months of age when they were brought in for assessment of an illness of less than 15 days' duration (for UK and Australia). **Exclusion criteria** Not reported	**Interventions** **Signs:** Respiratory rate >50/min: no more detail given Intermittent cry during examination: no more detail given Rash (moderate or severe): no more detail given Mild hypotonia: no more detail given Persistent cry during examination: no more detail given Peripheral cyanosis: no more detail given Hyperinflation of the chest: no more detail given Stridor: no more detail given Partially extended posture: no more detail given Distended and tense abdomen: no more detail given	**Details** N=1007 infants younger than 6 months of age were assessed in 2 centres during 1 year: n=298 at home and n=709 when they presented at the hospital. Home population: n=298 participants were chosen at random from birth register and seen at home in Cambridge, UK. Hospital population: n=709 infants younger than 6 months of age were enrolled prospectively when they were brought in for assessment of an illness of less than 15 days' duration (n=682 in Melbourne, n=27 in Cambridge). Mothers were asked if the infant had exhibited any of 28 symptoms in the previous 24 hours. Categories of the severity of infant's illness: I. Well (290 (29%))	**Results** Note: the authors reported data as percentages and not as raw data, therefore percentages were calculated back to the underlying data (where possible, e.g. not possible if <1% reported) by the NGA technical team and they may not fully correspond the original data of the study. **Signs:** Respiratory rate >50/min: well infants = 220/290, seriously ill infants = 102/165 Intermittent cry during examination: well infants = 70/290, seriously ill infants = 102/165 Rash (moderate or severe): well infants = 9/290, seriously ill infants = 20/165 Mild hypotonia: well infants = 9/290, seriously ill infants = 59/165 Persistent cry during examination: well infants = 9/290, seriously ill infants = 17/165 Peripheral cyanosis: well infants = 6/290, seriously ill infants = 25/165	**Limitations** (assessed using QUIPS for prognostic studies) **Study participation** Low risk of bias **Study attrition** Low risk of bias **Prognostic factor measurement** Low risk of bias **Outcome measurement** Low risk of bias **Study confounding** High risk of bias as the analysis did not account for any confounders **Statistical analysis and reporting**

Study details	Participants	Factors	Methods	Outcomes and Results	Comments
Study dates Not reported **Source of funding** Supported by the baby Illness Research Project Appeal of the Foundation for the Study of Infant Deaths, Australian Institute of Health, Ross Trust, Felton Bequests, H.L. Hecht Trust, Percy Baxter Charitable Trust, and the A. Williams Private Fund.		Transient loss of awareness of surroundings Rectal temperature >38.2 degrees C Crepitations: no more detail given Cry - weak or whimpering: no more detail given Reduced hydration: no more detail given Tender abdomen: no more detail given Cry - high pitched or moaning Expiratory grunt - audible: no more detail given Central cyanosis: no more detail given No awareness of surroundings: no more detail given Completely extended posture: no more detail given **Symptoms:** Increased irritability: more fractious and difficult to settle than usual Not himself/herself: baby has not been his or her usual self Not feeding normally: taking less fluids or solids, or feeding more slowly than usual; the amount of fluid taken	II. Mildly ill (not needing medical treatment at the moment) (305 (30%)) III. Moderately ill (needs to be assessed, treated if necessary and reviewed) (247 (24.5%)) IV. Seriously ill (needs admitting to the hospital) (166 (16.5%))	Hyperinflation of the chest: well infants = 6/290, seriously ill infants = 32/165 Stridor: well infants = 6/290, seriously ill infants = 5/165 Partially extended posture: well infants = 0/290, seriously ill infants = 41/165 Distended and tense abdomen: well infants = 0/290, seriously ill infants = 2/165 Transient loss of awareness of surroundings: well infants = 0/290, seriously ill infants = 54/165 Rectal temperature >38.2 degrees C: well infants = 0/290, seriously ill infants = 48/165 Crepitations: well infants = 0/290, seriously ill infants = 22/165 Cry - weak or whimpering: well infants = 0/290, seriously ill infants = 38/165 Reduced hydration: well infants = 0/290, seriously ill infants = 20/165 Tender abdomen: well infants = 0/290, seriously ill infants = 28/165 Cry - high pitched or moaning: well infants = 0/290, seriously ill infants = 111/165 Expiratory grunt - audible: well infants = 0/290, seriously ill infants = 12/165 Central cyanosis: with well infants = 0/290, seriously ill infants = 8/165 No awareness of surroundings: well infants = 0/290, seriously ill infants = 5/165 Completely extended posture: well infants = 0/290, seriously ill infants = 3/165	Low risk of bias

Study details	Participants	Factors	Methods	Outcomes and Results	Comments
		was scored in thirds of normal intake. Noisy breathing: persistent noises, including mucousy sounds, snuffles, stridor, grunt or wheeze Feels hot: feeling hotter than normal Abnormal cry: an unusual character to the cry Vomiting (not posseting): no more detail given Diarrhoea: excessively fluid motions; if present the number of stool in the last 24 hours was recorded Cold hands and feet: hands, feet or limbs felt cold Pallor: looking generally pale Fluids intake, approx. half normal: no more detail given Fluids less than /3 normal intake: no more detail given Convulsions: shaking movements with decreased awareness Bile-stained vomiting: episodes of green vomiting.		**Symptoms:** Increased irritability: well infants = 23/290, seriously ill infants = 129/165 Not himself/herself: well infants = 15/290, seriously ill infants = 130/165 Not feeding normally: well infants = 15/290, seriously ill infants = 117/165 Noisy breathing: well infants = 15/290, seriously ill infants = 71/165 Feels hot: well infants = 15/290, seriously ill infants = 87/165 An abnormal cry: well infants = 12/290, seriously ill infants = 114/165 Vomiting (not posseting): well infants = 9/290, seriously ill infants = 68/165 Diarrhoea: well infants = 9/290, seriously ill infants = 45/165 Cold hands and feet: well infants = 9/290, seriously ill infants = 64/165 Pallor: well infants = 9/290, seriously ill infants = 92/165 Fluids intake, approx. half normal: well infants = 3/290, seriously ill infants = 59/165 Fluids less than /3 normal intake: well infants = 0/290, seriously ill infants = 31/165 Convulsions: well infants = 0/290, seriously ill infants = 7/165 Bile-stained vomiting: well infants = 0/290, seriously ill infants = 5/165	

Appendix E – Forest plots

Forest plots for review question: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F – GRADE tables

GRADE tables for review question: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

Table 5: Clinical evidence profile for comparison of seriously ill babies to well babies: signs

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seriously ill babies	Well babies	Relative (95% CI)	Absolute		
Respiratory rate >50/min												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	102/165 (61.8%)	220/290 (75.9%)	RR 0.81 (0.71 to 0.93)	144 fewer per 1000 (from 53 fewer to 220 fewer)	VERY LOW	CRITICAL
Intermittent cry during examination												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	102/165 (61.8%)	70/290 (24.1%)	RR 2.56 (2.02 to 3.24)	377 more per 1000 (from 246 more to 541 more)	VERY LOW	CRITICAL
Persistent cry during examination												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	17/165 (10.3%)	9/290 (3.1%)	RR 3.32 (1.51 to 7.28)	72 more per 1000 (from 16 more to 195 more)	VERY LOW	CRITICAL
Cry - weak or whimpering												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	38/165 (23%)	0/290 (0%)	POR 20.13 (10.1 to 40.14)	230 more per 1000 (from 170 more to 290 more)	VERY LOW	CRITICAL
Cry - high pitches or moaning												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	111/165 (67.3%)	0/290 (0%)	POR 38.07 (24.41 to 59.38)	670 more per 1000 (from 600 more to 740 more)	VERY LOW	CRITICAL

Rash (moderate or severe)												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	20/165 (12.1%)	9/290 (3.1%)	RR 3.91 (1.82 to 8.38)	90 more per 1000 (from 25 more to 229 more)	VERY LOW	CRITICAL
Mild hypotonia												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	59/165 (35.8%)	9/290 (3.1%)	RR 11.52 (5.87 to 22.63)	326 more per 1000 (from 151 more to 671 more)	VERY LOW	CRITICAL
Peripheral cyanosis												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	25/165 (15.2%)	6/290 (2.1%)	RR 7.32 (3.07 to 17.48)	131 more per 1000 (from 43 more to 341 more)	VERY LOW	CRITICAL
Hyperinflation of the chest												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	32/165 (19.4%)	6/290 (2.1%)	RR 9.37 (4.0 to 21.95)	173 more per 1000 (from 62 more to 433 more)	VERY LOW	CRITICAL
Expiratory grunt – audible												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	12/165 (7.3%)	0/290 (0%)	POR 16.88 (5.13 to 55.56)	70 more per 1000 (from 30 more to 110 more)	VERY LOW	CRITICAL
Stridor												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	5/165 (3%)	6/290 (2.1%)	RR 1.46 (0.45 to 4.73)	10 more per 1000 (from 11 fewer to 77 more)	VERY LOW	CRITICAL
Distended and tense abdomen												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	10/165 (6.1%)	0/290 (0%)	POR 16.67 (4.53 to 61.28)	60 more per 1000 (from 20 more to 100 more)	VERY LOW	CRITICAL
Tender abdomen												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	28/165 (17%)	0/290 (0%)	POR 18.76 (8.48 to 41.53)	170 more per 1000 (from 110 more to 230 more)	VERY LOW	CRITICAL
Transient loss of awareness of surroundings												

1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	54/165 (32.7%)	0/290 (0%)	POR 22.69 (12.58 to 40.95)	330 more per 1000 (from 260 more to 400 more)	VERY LOW	CRITICAL
No awareness of surroundings												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	5/165 (3%)	0/290 (0%)	POR 16.15 (2.59 to 100.82)	30 more per 1000 (from 0 more to 60 more)	VERY LOW	CRITICAL
Rectal temperature >38.2 degrees C												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	48/165 (29.1%)	0/290 (0%)	POR 21.67 (11.64 to 40.35)	290 more per 1000 (from 220 more to 360 more)	VERY LOW	CRITICAL
Crepitations (no auscultation)												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	22/165 (13.3%)	0/290 (0%)	POR 18.02 (7.4 to 43.87)	130 more per 1000 (from 80 more to 190 more)	VERY LOW	CRITICAL
Reduced hydration												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	20/165 (12.1%)	0/290 (0%)	POR 17.78 (7.01 to 45.12)	120 more per 1000 (from 70 more to 170 more)	VERY LOW	CRITICAL
Central cyanosis												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	8/165 (4.8%)	0/290 (0%)	POR 16.46 (3.85 to 70.34)	50 more per 1000 (from 10 more to 80 more)	VERY LOW	CRITICAL
Partially extended posture												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	41/165 (24.8%)	0/290 (0%)	POR 20.57 (10.56 to 40.07)	250 more per 1000 (from 180 more to 310 more)	VERY LOW	CRITICAL
Completely extended posture												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	3/165 (1.8%)	0/290 (0%)	POR 15.96 (1.51 to 168.8)	20 more per 1000 (from 0 more to 40 more)	VERY LOW	CRITICAL

C: Celsius; CI: confidence interval; MID: minimally important difference; POR: Peto odds ratio; RR: relative risk; for the definitions of signs please see clinical evidence table in appendix D

[1] *No adjustment for any confounders.*

[2] Evidence downgraded by 1 levels for indirectness as population is infants under 6 months old and may include infants over 8 weeks of age.
[3] Evidence downgraded by 1 level due to risk of serious imprecision as 95% confidence interval crosses 1 default MID for dichotomous outcomes.
[4] Evidence downgraded by 2 levels due to risk of serious imprecision as 95% confidence interval crosses 2 default MIDs for dichotomous outcomes.

Table 6: Clinical evidence profile for comparison of seriously ill babies to well babies: symptoms

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seriously ill babies	Well babies	Relative (95% CI)	Absolute		
Increased irritability												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	129/165 (78.2%)	23/290 (7.9%)	RR 9.86 (6.61 to 14.71)	703 more per 1000 (from 445 more to 1000 more)	VERY LOW	CRITICAL
Not himself/herself												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	130/165 (78.8%)	15/290 (5.2%)	RR 15.23 (9.25 to 25.09)	736 more per 1000 (from 427 more to 1000 more)	VERY LOW	CRITICAL
Abnormal cry												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	114/165 (69.1%)	12/290 (4.1%)	RR 16.7 (9.51 to 29.33)	650 more per 1000 (from 352 more to 1000 more)	VERY LOW	CRITICAL
Not feeding normally												
1 (Morley 1991a)	observational studies	serious[1]	No serious inconsistency	serious[2]	no serious imprecision	none	117/165 (70.9%)	15/290 (5.2%)	RR 13.71 (8.3 to 22.66)	657 more per 1000 (from 378 more to 1000 more)	VERY LOW	CRITICAL
Noisy breathing												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	71/165 (43%)	15/290 (5.2%)	RR 8.32 (4.93 to 14.04)	379 more per 1000 (from 203 more to 674 more)	VERY LOW	CRITICAL
Feels hot												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	87/165 (52.7%)	15/290 (5.2%)	RR 10.19 (6.1 to 17.04)	475 more per 1000 (from 264 more to 830 more)	VERY LOW	CRITICAL
Vomiting (not posseting)												

1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	68/165 (41.2%)	9/290 (3.1%)	RR 13.28 (6.81 to 25.91)	381 more per 1000 (from 180 more to 773 more)	VERY LOW	CRITICAL
Bile-stained vomiting												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	5/165 (3%)	0/290 (0%)	POR 16.15 (2.59 to 100.82)	30 more per 1000 (from 1 more to 60 more)	VERY LOW	CRITICAL
Diarrhoea												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	45/165 (27.3%)	9/290 (3.1%)	RR 8.79 (4.41 to 17.52)	242 more per 1000 (from 106 more to 513 more)	VERY LOW	CRITICAL
Cold hands and feet												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	64/165 (38.8%)	9/290 (3.1%)	RR 12.5 (6.39 to 24.45)	357 more per 1000 (from 167 more to 728 more)	VERY LOW	CRITICAL
Pallor												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	92/165 (55.8%)	9/290 (3.1%)	RR 17.97 (9.31 to 34.67)	527 more per 1000 (from 258 more to 1000 more)	VERY LOW	CRITICAL
Fluids intake, approx. half normal												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	59/165 (35.8%)	3/290 (1%)	RR 34.57 (11.01 to 108.53)	347 more per 1000 (from 104 more to 1000 more)	VERY LOW	CRITICAL
Fluids less than 1/3 normal intake												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	31/165 (18.8%)	0/290 (0%)	POR 19.16 (8.98 to 40.87)	190 more per 1000 (from 130 more to 250 more)	VERY LOW	CRITICAL
Convulsions												
1 (Morley 1991a)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	7/165 (4.2%)	0/290 (0%)	POR 16.35 (3.47 to 77.14)	40 more per 1000 (from 10 more to 70 more)	VERY LOW	CRITICAL

CI: confidence interval; MID: minimally important difference; POR: Peto odds ratio; RR: relative risk; for the definitions of symptoms please see clinical evidence table in appendix D.

[1] No adjustment for any confounders.

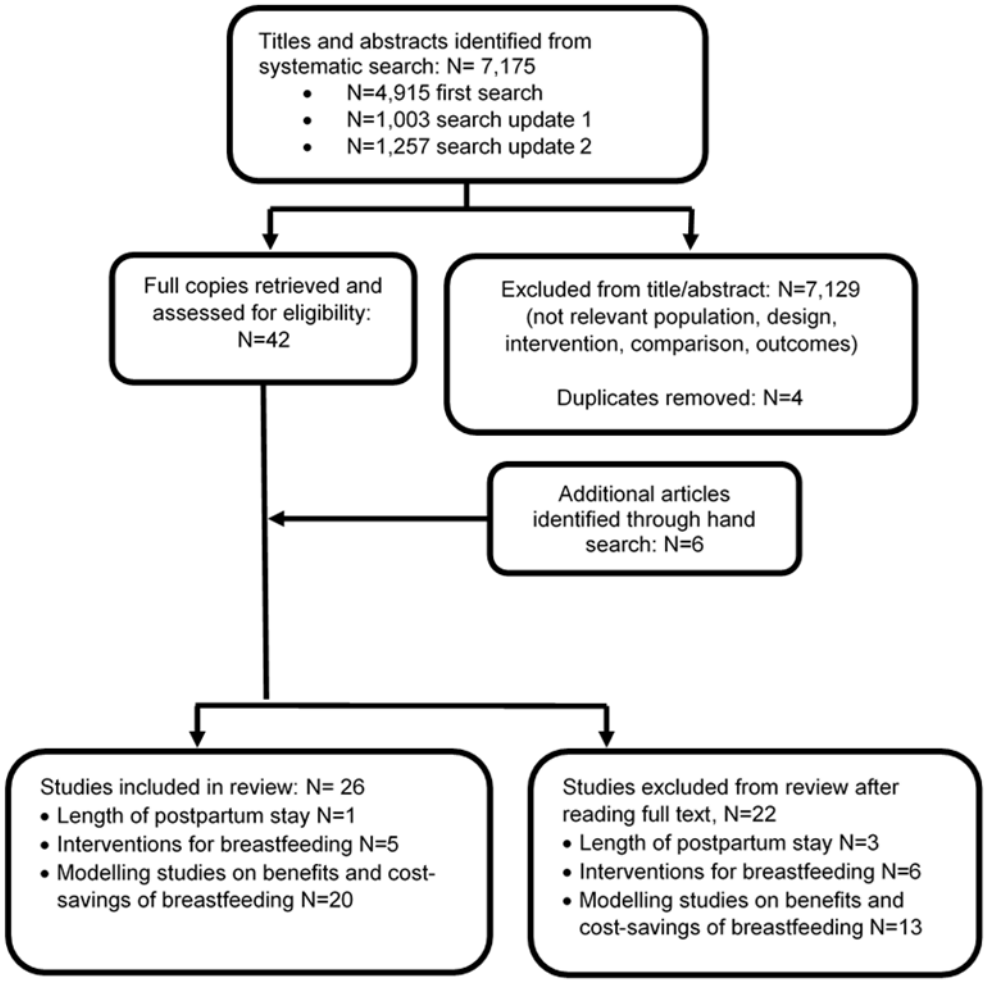
[2] Evidence downgraded by 1 levels for indirectness as population is infants under 6 months old and may include infants over 8 weeks of age.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

A global health economics search was undertaken for all areas covered in the guideline. Figure 2 shows the flow diagram of the selection process for economic evaluations of postnatal care interventions, including modelling studies on the benefits and cost-savings of breastfeeding.

Figure 2. Flow diagram of selection process for economic evaluations of postnatal care interventions and modelling studies on the benefits and cost-savings of breastfeeding



Appendix H – Economic evidence tables

Economic evidence tables for review question: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic analysis for review question: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

Clinical studies

Table 7: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Arpino,C., Domizio,S., Carrieri,M.P., Brescianini,D.S., Sabatino,M.G., Curatolo,P., Prenatal and perinatal determinants of neonatal seizures occurring in the first week of life, Journal of Child Neurology, 16, 651-656, 2001	Study does not meet protocol eligibility criteria - <100 eligible cases; not signs or symptoms of illness.
Bernson-Leung, M. E., Rivkin, M. J., Stroke in neonates and children, Pediatrics in Review, 37, 463-476, 2016	Study design does not meet protocol eligibility criteria - narrative review.
Bulbul, A., Cayonu, N., Sanli, M. E., Uslu, S., Evaluation of risk factors for development of severe hyperbilirubinemia in term and near term infants, Pakistan Journal of Medical Sciences, 30, 2014	Study setting does not meet protocol eligibility criteria - low/middle income country (Turkey).
Casey, B. M., Goldaber, K. G., McIntire, D. D., Leveno, K. J., Outcomes among term infants when two-hour postnatal pH is compared with pH at delivery, American Journal of Obstetrics & Gynecology, 184, 447-50, 2001	Study does not meet protocol eligibility criteria - comparisons between babies with and without acidaemia; respiratory symptoms presented as an outcome.
Douglas,P.S., Hiscock,H., The unsettled baby: Crying out for an integrated, multidisciplinary primary care approach, Medical Journal of Australia, 193, 533-536, 2010	Study design does not meet eligibility criteria - non-systematic review (references checked).
Dunbar, M., Kirton, A., Perinatal stroke: mechanisms, management, and outcomes of early cerebrovascular brain injury, The Lancet Child and Adolescent Health, 2, 666-676, 2018	Study design does not meet protocol eligibility criteria - non-systematic review (references checked).
Dunne, K. P., Fox, G. P., O'Regan, M., Matthews, T. G., Arousal responses in babies at risk of sudden infant death syndrome at different postnatal ages, Irish Medical Journal, 85, 19-22, 1992	Study does not meet protocol eligibility criteria - <200 eligible infants.
Escobar,G.J., Fischer,A., Li,D.K., Kremers,R., Armstrong,M.A., Score for neonatal acute physiology: validation in three Kaiser Permanente neonatal intensive care units, Pediatrics, 96, 918-922, 1995	Study does not meet protocol eligibility criteria - unclear what signs or symptoms of illness babies presented with; outcome data includes infants with congenital anomalies (including congenital heart disease).
Freedman SB, Al-Harthy N, Thull-Freedman J, The crying infant: diagnostic testing and frequency of serious underlying disease, Pediatrics, 123, 841-848, 2009	Study does not meet protocol eligibility criteria - unclear whether term babies; outcome data not presented separately in babies with signs or symptoms within first 8 weeks after birth; no relevant diagnostic outcome data for signs or symptoms.
Gane, B., Bhat, B. V., Adhisivam, B., Joy, R., Prasadkumar, P., Femitha, P., Shruti, B., Risk factors and outcome in neonatal necrotising	Study setting and population do not meet protocol eligibility criteria - low/middle income country (India); neonates <37 weeks gestational age.

Study	Reason for exclusion
enterocolitis, Indian Journal of Pediatrics, 81, 425-428, 2014	
Gupta,A.K., Shashi,S., Lamba,I.M., Anand,N.K., Do insults to the developing lung increase the incidence of wheezing in infants, Journal of Tropical Pediatrics, 40, 29-31, 1994	Study does not meet protocol eligibility criteria - low/middle income country (India); <200 infants assessed at >8 weeks after birth.
Heimler, R., Shekhawat, P., Huffman, R. G., Chetty, V. K., Sasidharan, P., Hospital readmission and morbidity following early newborn discharge, Clinical Pediatrics, 37, 609-616, 1998	Study design does not meet protocol eligibility criteria - no comparative data for prognostic component; no relevant diagnostic data presented.
Herlenius, E., Kuhn, P., Sudden Unexpected Postnatal Collapse of Newborn Infants: A Review of Cases, Definitions, Risks, and Preventive Measures, Translational Stroke Research, 4, 236-247, 2013	Study does not meet protocol eligibility criteria - case reports presented; no relevant prognostic or diagnostic outcome data presented.
Hoang, D., Charlagorla, P., Salafia, C., VanHorn, S., Dygulska, B., Narula, P., Gad, A., Histologic chorioamnionitis as a consideration in the management of newborns of febrile mothers, Journal of Maternal-Fetal & Neonatal Medicine, 26, 828-32, 2013	Study does not meet protocol eligibility criteria - does not include signs or symptoms of illness; assesses the development of clinical sepsis.
Holst,K., Hilden,J., Philip,J., Andersen,E., Goldstein,H., Henningsen,I., Which types of perinatal events are predictable? A look at a risk score model, Acta Obstetricia et Gynecologica Scandinavica, 69, 379-388, 1990	Study outcomes do not meet protocol eligibility criteria - prognostic and diagnostic data on signs or symptoms of illness not presented.
Jean-Baptiste,N., Benjamin,D.K.,Jr., Cohen-Wolkowiez,M., Fowler,V.G.,Jr., Laughon,M., Clark,R.H., Smith,P.B., Coagulase-negative staphylococcal infections in the neonatal intensive care unit, Infection Control and Hospital Epidemiology, 32, 679-686, 2011	Study does not meet protocol eligibility criteria for index tests/prognostic factors.
Kirton, A., Armstrong-Wells, J., Chang, T., DeVeber, G., Rivkin, M. J., Hernandez, M., Carpenter, J., Yager, J. Y., Lynch, J. K., Ferriero, D. M., Symptomatic neonatal arterial ischemic stroke: The international pediatric stroke study, Pediatrics, 128, e1402-e1410, 2011	Study design does not meet protocol eligibility criteria - non-comparative study for prognostic component; no relevant diagnostic data presented.
Lai,Y.H., Ho,C.S., Chiu,N.C., Tseng,C.F., Huang,Y.L., Prognostic factors of developmental outcome in neonatal seizures in term infants, Pediatrics and Neonatology, 54, 166-172, 2013	Study does not meet protocol eligibility criteria - data on relevant index tests/prognostic factors not presented.
Li, J., Wu, J., Du, L., Hu, Y., Yang, X., Mu, D., Xia, B., Different antibiotic strategies in transient tachypnea of the newborn: an ambispective cohort study, European Journal of Pediatrics, 174, 1217-1223, 2015	Study setting does not meet protocol eligibility criteria - low/middle income country (China).
Lori, S., Bertini, G., Molesti, E., Gualandi, D., Gabbanini, S., Bastianelli, M. E., Pinto, F., Dani, C., The prognostic role of evoked potentials in neonatal hypoxic-ischemic insult, Journal of Maternal-Fetal and Neonatal Medicine, 24, 69-71, 2011	Study does not meet protocol eligibility criteria - non-systematic review; not signs and symptoms of illness.

Study	Reason for exclusion
Luo, L., Chen, D., Qu, Y., Wu, J., Li, X., Mu, D., Association between hypoxia and perinatal arterial ischemic stroke: a meta-analysis, PLoS ONE [Electronic Resource], 9, e90106, 2014	Systematic review assessing risk factors in term and preterm babies - prognostic or diagnostic data on signs or symptoms of illness not presented (references checked).
Mignot, C., Clinical aspects of early-stage neurological forms of Gaucher disease, Revue de Medecine Interne, 27, S14-S17, 2006	Study does not meet protocol eligibility criteria - Non-English language article (French).
Milas,V., Puseljic,S., Stimac,M., Dobric,H., Lukic,G., Urinary tract infection (UTI) in newborns: risk factors, identification and prevention of consequences, Collegium Antropologicum, 37, 871-876, 2013	Study does not meet protocol eligibility criteria - <200 newborns included in the study.
Morley CJ, Thornton AJ, Cole TJ, et al. Baby check: a scoring system to grade the severity of acute systemic illness in babies under 6 months old. Arch of Dis in Child 1991; 66: 100-106	Study does not meet protocol eligibility criteria - study reports the accuracy of a range of score groups with well or mildly ill, moderately ill, and seriously ill babies derived from giving scores to different signs and symptoms. It does not report on the association or accuracy of a single or combination of signs and symptoms to detect serious illness.
Mukhopadhyay, S., Meyer, S. A., Permar, S. R., Puopolo, K. M., Symptomatic Postnatal Cytomegalovirus Testing among Very Low-Birth-Weight Infants: Indications and Outcomes, American Journal of Perinatology, 33, 894-902, 2016	Study population does not meet protocol eligibility criteria - babies born at <37 weeks gestational age.
Ostfeld BM, Esposito L, Perl H, Hegyi T, Concurrent risks in sudden infant death syndrome, Pediatrics, 125, 447-453, 2010	Study does not meet protocol eligibility criteria - unclear whether term babies; unclear whether babies presented with signs or symptoms within first 8 weeks after birth; focus on risk factors not relating to signs or symptoms.
Pan, D. H., Rivas, Y., Jaundice: Newborn to age 2 months, Pediatrics in Review, 38, 499-510, 2017	Study design does not meet protocol eligibility criteria - narrative review.
Pavone, P., Pettoello-Mantovano, M., Le Pira, A., Giardino, I., Pulvirenti, A., Giugno, R., Parano, E., Polizzi, A., Distefano, A., Ferro, A., Pavone, L., Ruggieri, M., Acute disseminated encephalomyelitis: A long-term prospective study and meta-analysis, Neuropediatrics, 41, 246-255, 2010	Study does not meet protocol eligibility criteria - not signs or symptoms within the first 8 weeks after birth; study population mean age 3.6 years (range 18 months to 8 years).
Ponsonby, A. L., Dwyer, T., Couper, D., Factors related to infant apnoea and cyanosis: a population-based study, Journal of Paediatrics & Child Health, 33, 317-23, 1997	Study does not meet protocol eligibility criteria - unclear gestational age; unclear whether signs or symptoms of illness within the first 8 weeks after birth.
Ponsonby, A. L., Dwyer, T., Couper, D., Sleeping position, infant apnea, and cyanosis: a population-based study, Pediatrics, 99, E3, 1997	Study does not meet protocol eligibility criteria - unclear gestational age; unclear whether signs or symptoms of illness within the first 8 weeks after birth.
Richardson, D. K., Corcoran, J. D., Escobar, G. J., Lee, S. K., SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores, Journal of Pediatrics, 138, 92-100, 2001	Study does not meet protocol eligibility criteria - unclear what signs or symptoms of illness babies presented with; unclear gestational ages for some populations.
Rubenwolf, P., Herrmann-Nuber, J., Schreckenberger, M., Stein, R., Beetz, R.,	Study does not meet protocol eligibility criteria - data on eligible population not reported

Study	Reason for exclusion
Primary non-refluxive megaureter in children: single-center experience and follow-up of 212 patients, International Urology and Nephrology, 48, 1743-1749, 2016	separately (children aged 0 to 15 years included in the study).
Sandberg-Bennich, S., Dahlquist, G., Kallen, B., Coeliac disease is associated with intrauterine growth and neonatal infections, Acta Paediatrica, 91, 30-3, 2002	Study does not meet protocol eligibility criteria - unclear when symptoms or illness occurred; outcomes for relevant gestational age population not reported separately.
Seabolt,J.P., Ribes,J.A., Perinatal complications in infants with Mycoplasma and Ureaplasma spp. infection, Laboratory Medicine, 34, 589-591, 2003	Study population does not meet protocol eligibility criteria - <200 babies; all premature babies.
Smitherman, H., Stark, A. R., Bhutan, V. K., Early recognition of neonatal hyperbilirubinemia and its emergent management, Seminars in Fetal and Neonatal Medicine, 11, 214-224, 2006	Study design does not meet protocol eligibility criteria - non-systematic review.
van Karnebeek, C. D., Tiebout, S. A., Niermeijer, J., Poll-The, B. T., Ghani, A., Coughlin, C. R., 2nd, Van Hove, J. L., Richter, J. W., Christen, H. J., Gallagher, R., Hartmann, H., Stockler-Ipsiroglu, S., Pyridoxine-Dependent Epilepsy: An Expanding Clinical Spectrum, Pediatric Neurology, 59, 6-12, 2016	Study design does not meet protocol eligibility criteria - description of 6 patients.
Vennemann MM, Findeisen M, Butterfass-Bahloul T, Jorch G, Brinkmann B, Kopcke W, et al, Infection, health problems, and health care utilisation, and the risk of sudden infant death syndrome, Arch Dis Child, 90, 520-2, 2005	Study does not meet protocol eligibility criteria - babies died between 8 days of age and completion of their first year of life; data not presented separately for babies who died within the first 8 weeks after birth; unclear what signs and symptoms babies were admitted to hospital within first 7 days of life.
Wailoo M, Thompson JR, Waite AJ, Coombs RC, Jackson JA, Signs and symptoms of illness in early infancy: associations with sudden infant death, Arch Dis Child, 88, 1001-1004, 2003	Study does not meet protocol eligibility criteria - <100 infants in each arm for prognostic component.

Economic studies

No economic evidence was identified for this review.

Appendix L – Research recommendations

Research recommendations for review question: What signs and symptoms (alone or in combination) in babies are associated with serious illness or mortality?

No research recommendations were made for this review question.