NCC-WCH

Version 1.0

Bronchiolitis: diagnosis and management of bronchiolitis in children

Bronchiolitis in children

Clinical Guideline <…>

Methods, evidence and recommendations

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Contents

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1 Introduction

Epidemiology of bronchiolitis

Acute viral bronchiolitis occurs predominantly in children under one year of age. Approximately 1 in 5 infants will develop clinical bronchiolitis in the first year of life and 2-3% of all infants require hospitalization.

The condition starts with an upper respiratory tract infection with nasal obstruction that over 3-4 days progresses to involvement of the bronchioles with associated progressive dyspnea and poor feeding. Most children present to medical services with respiratory distress or poor feeding, or in the very young, apnoea. When auscultated children have a variable mixture of wheeze and crackles. In primary care, the condition may often be confused with a common cold, though the presence of lower respiratory tract signs in an infant in mid winter would be consistent with this clinical diagnosis.

Bronchiolitis is caused by viral infection and as such is seasonal, peaking in the winter months, most significantly over a 6-8 week period. The most common viral infection is Respiratory Syncytial Virus (RSV) which occurs in up to 80% of cases, but the condition can be caused by many other respiratory viruses. It is increasingly recognized that co-infection of one or more respiratory viruses is common. Hospital admissions associated with RSV can be prevented by the use of a monthly-injected monoclonal antibody (Palivizumab), with some efficacy in high-risk populations. The GDG also noted that no vaccination is available and that children with comorbidities are susceptible to more severe disease.

Why this guideline is needed

The number of admissions to hospital with bronchiolitis has been increasing over the last 20 years, though there is a suggestion that rates are plateauing. Children are admitted to hospital for supportive care until clinical recovery has taken place. In hospital, infants are provided with nasal suction to facilitate oral feeding, support for hydration by nasogastric or intravenous fluids, and supplemental oxygen for hypoxaemia. A range of treatments has been trialled, including bronchodilators and steroids, but has not been recommended for use in previous evidence based guidelines[ab]. Treatment of bronchiolitis is variable.

The diagnosis is clinical and investigations are not considered helpful. Viral diagnostic testing may help with cohort screening in hospital (to enable RSV positive infants to be placed in same open cohort), but it does not provide supportive evidence for prognosis.

Recovery from the acute disease takes place over a 5-7 day period, though a persistent cough occurs in 50% of children for more than two weeks. In some children a chronic, relapsing episodic wheeze with subsequent viral infections may occur over the ensuing 6 months or so; the so called ‘post bronchiolitis syndrome’. This appears the result of temporary loss of cilial function during bronchiolitis and poor recovery during subsequent viral infections. Infants with RSV bronchiolitis have an increased frequency of subsequent wheeze in the following year and there are also data suggestive that infants with bronchiolitis have a higher incidence of asthma diagnosed in later childhood.

1.1 Aim of the guideline

Clinical guidelines have been defined as ‘systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific

a Network SIG. Bronchiolitis in Children (SIGN 91). NHS Quality Improvement Scotland, 2006.
b Pediatrics AAo. Diagnosis and management of bronchiolitis. Pediatrics 2006;118(4):1774-93 doi: 118/4/1774 [pii] 10.1542/peds.2006-2223[published Online First: Epub Date]|.

conditions'. This guideline has been developed with the aim of providing guidance on the care of children with bronchiolitis.

1.2 Areas within the remit of the guideline

- Children with bronchiolitis.
- Patient subgroups will be identified based on the available evidence – for example, premature birth, congenital heart disease, cystic fibrosis, immunodeficiency and chronic lung disease.

1.3 Areas outside the remit of the guideline

- Children with other respiratory conditions, such as recurrent viral induced wheeze or asthma.

1.4 For whom is the guideline developed

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England and Wales, in particular:

- all healthcare professionals who are involved in the care of children with bronchiolitis (including GPs, emergency medicine practitioners, paediatricians, nurses and pharmacists). The healthcare professionals providing care for children with bronchiolitis may vary depending on geographical service provision.
- those responsible for planning and commissioning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners, and public health managers
- families and carers of children with bronchiolitis

1.5 Who has developed the guideline

This guideline was developed by a multi-professional and lay working group (the Guideline Development Group or GDG) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). Membership included four paediatricians, two paediatric nurses, a paediatric specialist pharmacist, a GP, and two patient/carer members.

Staff from the NCC-WCH provided methodological support for the guideline development process, undertook systematic searches, retrieval and appraisal of the evidence, health economics modelling and, together with the Guideline Lead, wrote successive drafts of the guideline.

All GDG members' interests were recorded on declaration forms provided by NICE. The form covered consultancies, fee-paid work, shareholdings, fellowships, and support from the healthcare industry.

1.6 Guideline Development Methodology

1.6.1 Introduction

This guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups (available at www.nice.org.uk).

In accordance with NICE's Equality Scheme, ethnic and cultural considerations and factors relating to disabilities have been considered by the guideline development group (GDG) throughout the development process and specifically addressed in individual recommendations where relevant. Further information is available from: www.nice.org.uk/aboutnice/howwework/NICEEquality

1.6.2 Developing review questions and protocols and identifying evidence

The scope for this guideline (see Appendix B) outlines the main areas where guidance is needed. The GDG formulated review questions based on the scope and prepared a protocol for each review question (see Appendix E). Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for interventions reviews. These formed the starting point for systematic reviews of relevant evidence. A total of 19 review questions (see table 2) were identified. Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Published evidence was identified by applying systematic search strategies (see Appendix F) to the following databases: Medline (1948 onwards), Embase (1980 onwards), and four Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects and the Health Technology Assessment [HTA] database). Searches to identify economic studies were undertaken using the above databases and the NHS Economic Evaluation Database (NHS EED). Searches in Medline and Embase were limited to English language and studies in humans. None of the other searches were limited by language of publication (although publications in languages other than English were not reviewed). Search filters were used to identify particular study designs, such as randomised controlled trials (RCTs). There was no searching of grey literature, nor was hand searching of journals undertaken.

There was no systematic attempt to search grey literature [conference abstracts (except those describing RCTs), theses or unpublished trials], nor was hand searching of journals not indexed on the databases undertaken. Towards the end of the guideline development process, all the searches were updated and re-executed within 6 to 8 weeks of the start of the stakeholder consultation to ensure the reviews were up-to-date. This process was completed by August 2014.

1.6.3 Reviewing and synthesising evidence

Evidence relating to clinical effectiveness was reviewed and synthesised according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. A modified GRADE approach was applied when assessing the quality of case-control studies: the methodology checklist for case-control studies reported in appendix E of NICE manual (2012) was used. For diagnostic studies, the QUADAS-2 tool was applied as reported in appendix F of the NICE manual (2012) when assessing the quality of such evidence. In the GRADE approach, the quality of the evidence identified for each outcome listed in the review protocol is assessed according to the factors listed below, and an overall quality rating (high, moderate, low or very low) is assigned by combining the ratings for the individual factors.

- Study design (as an indicator of intrinsic bias; this determines the initial quality rating).
- Limitations in the design or execution of the study (including concealment of allocation, blinding, loss to follow up; these can reduce the quality rating).
- Inconsistency of effects across studies (this can reduce the quality rating).
- Indirectness (the extent to which the available evidence fails to address the specific review question; this can reduce the quality rating).
- Imprecision (reflects the confidence in the estimate of effect and this can reduce the quality rating). Within GRADE it is necessary to predetermine values for minimum

important differences in outcomes to assess imprecision. The GDG was asked to predefine minimally important differences (the smallest difference between treatments that health professionals or patients think is clinically beneficial). However, the GDG was unable to agree these so imprecision was graded based on the GRADE default thresholds of -0.75/1.25 for risk ratios and odds ratios; and +/- 0.5 * (SD) for continuous outcomes. When the 95% CI crossed one default MID, this was graded as serious imprecision. When the 95% CI crossed two default MID, this was graded as very serious imprecision.

- Other considerations (including large magnitude of effect, evidence of a dose–response relationship, or confounding variables likely to have reduced the magnitude of an effect; these can increase the quality rating in observational studies, provided no downgrading for other features has occurred).

The type of review question determines the highest level of evidence that may be sought. For interventions, the highest possible evidence level is a well-conducted systematic review or meta-analysis of RCTs, or an individual RCT. In GRADE, a body of evidence based entirely on such studies has an initial quality rating of high, and this may be downgraded to moderate, low, or very low if factors listed above are not addressed adequately. For questions on prognosis, the highest possible level of evidence is a controlled observational study (a cohort study or case–control study), and a body of evidence based on such studies would have an initial quality rating of high, which might be downgraded to moderate, low or very low, depending on the factors listed above. For diagnostic tests, studies examining the performance of the test were used if information on accuracy was required, but where an evaluation of the effectiveness of the test in the clinical management of the condition was required, evidence from RCTs or cohort studies was considered optimal.

Where appropriate, the body of evidence corresponding to each outcome specified in the review protocol was subject to quantitative meta-analysis. In such cases, pooled effect sizes were presented as pooled risk ratios (RRs), pooled ORs or weighted mean differences. By default, meta-analyses were conducted by fitting fixed effects models, but where statistically significant heterogeneity was identified, random effects models were used to investigate the impact of the heterogeneity. Where quantitative meta-analysis could not be undertaken (for example because of heterogeneity in the included studies) the range of effect sizes reported in the included studies was presented.

For studies evaluating the accuracy of a diagnostic test (for example in the chest x-ray evidence review), summary statistics (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV] and likelihood ratios for positive and negative test results [LR+ and LR–, respectively]) were calculated or quoted where possible (see Table 4). The following definitions were used when summarising the likelihood ratios for the GDG:

- Convincing: positive likelihood ratio (LR+) 10 or higher, negative likelihood ratio (LR-) 0.1 or lower
- Strong: LR+ 5 or higher (but less than 10), LR- 0.2 or lower (but higher than 0.1)
- Not strong: LR+ 4.9 or lower, LR- higher than 0.2

The following definitions were used when summarising the levels of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the GDG:

- High: 90% and above
- Moderate: 75% to 89%
- Low: 74% or below

Particular emphasis was placed on the positive likelihood ratio, with a ratio of 5 or higher being considered a good indicator that a symptom or sign should be used.

Some studies were excluded from the guideline reviews after obtaining copies of the publications because they did not meet inclusion criteria (see Appendix H). The characteristics of each included study were summarised in evidence tables for each review

question (see Appendix I). Where possible, dichotomous outcomes were presented as relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs), and continuous outcomes were presented as mean differences with 95% CIs or standard deviations (SDs).

Table 1: '2 x 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	Reference standard negative	Total
Index test result positive	a (true positive)	b (false positive)	a+b
Index test result negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d = N (total number of tests in study)

1.6.4 Outcome measures

For this guideline, the GDG assessed the evidence by outcome in order to determine if there was a benefit or harm, or no difference between interventions. The justification for using these outcomes was based on their relevance to the groups covered by the guideline and consensus among members of the GDG's values and preferences. Outcomes include those that were considered to be clinically important and unwanted effects of treatment that it would be important to reduce to a minimum. When assessing the accuracy of a test or the effectiveness of a particular treatment, appropriate information about the effect on one or more primary outcomes was sought.

The following table lists the critical outcomes (prioritised for decision-making) used in each evidence review.

Table 2: List of critical outcomes in the guideline

Type of review	Review question	Critical outcomes
Descriptive	What symptoms, signs and clinical course are typical of bronchiolitis, and allow differentiation from other respiratory conditions?	Description of: At what ages does bronchiolitis typically occur? What are the typical symptoms of bronchiolitis? What is the typical duration of symptoms?
Prognostic	What are the risk factors for severe bronchiolitis?	Relative risks and odds ratios for severe bronchiolitis
Prognostic	At the time of assessment, what clinical features predict deterioration?	Relative risks and odds ratios for progressing to severe bronchiolitis
Prognostic	What are the criteria for a) referral to secondary care, b) hospital admission, c) discharge from hospital?	For interventions/comparators a and b: Referral rate to secondary care Admission to hospital For intervention/comparator c: Change in respiratory rate Change in oxygen saturation Reported feeding difficulty
Intervention	What is the indication for	Duration of oxygen

Type of review	Review question	Critical outcomes
	capillary blood gas testing?	supplementation Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation.
Intervention	What are the indications for fluids and nutritional support?	Change in O2 saturation Length of hospital stay Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation.
Intervention	When is pulse oximetry oxygen saturation monitoring (SpO_2) indicated in bronchiolitis?	Admission rates Length of hospital stay
Diagnostic	What are the indications for chest radiography in bronchiolitis?	Admission rates Duration of admission Antibiotics administration
Intervention	What is the efficacy of chest physiotherapy in the management of bronchiolitis?	Change in disease severity score Change in respiratory rate Change in O2 saturation
Intervention	What is the efficacy of antibiotic treatment?	Admission rates Length of stay Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
Intervention	What is the efficacy of inhaled bronchodilator therapy?	Admission rates Length of stay Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
Intervention	What is the efficacy of systemic corticosteroid therapy?	Admission rates Length of stay Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
Intervention	What is the efficacy of combined bronchodilator and corticosteroid therapy?	Admission rates Length of stay Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
Intervention	What is the efficacy of nebulised hypertonic saline?	Admission rates Length of stay Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
Intervention	What is the efficacy of heliox?	Length of stay

Type of review	Review question	Critical outcomes
		Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
Intervention	What is the efficacy of Montelukast?	Admission rates Length of stay Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
Intervention	What is the efficacy of oxygen supplementation (non humidified, humidified and high flow) and of CPAP?	Length of stay Need for continuous positive airway pressure (CPAP) or mechanical ventilation
Intervention	What is the efficacy of suction to remove secretions from the upper respiratory tract?	Oral feed toleration Length of hospital stay

1.6.5 Incorporating health economics

The aim of the economic input into the guideline was to inform the GDG of potential economic issues relating to bronchiolitis in children, and to consider whether the recommendations represent a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on benefits (ideally in terms of quality adjusted life years [QALYs]), harms and costs of different care options.

The health economist helped the GDG by identifying topics within the guideline that might benefit from economic analysis, reviewing the available economic evidence and, where necessary, conducting economic analysis.

Systematic searches for published economic evidence were undertaken for all clinical questions in the guideline. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation. Reviews of the relevant published health economic literature identified in the literature search are presented alongside the clinical effectiveness reviews.

The GDG prioritised a number of clinical questions where it was thought that economic considerations would be particularly important in formulating recommendations. For this guideline the areas prioritised for economic analysis were:

- What is the efficacy of chest physiotherapy
- What is the efficacy of nebulised hypertonic saline?
- What is the efficacy of heliox?
- What is the efficacy of; bronchodilator therapy, corticosteroid therapy or combined bronchodilator and corticosteroid therapy?
- What is the efficacy of oxygen supplementation, including humidified oxygen, CPAP or humidified high flow oxygen?
- What is the efficacy of suction to remove secretions from the upper respiratory tract?

However, after reviewing the clinical evidence the prioritised areas were reviewed:

- The clinical evidence demonstrated that chest physiotherapy was not-effective and therefore no cost-effectiveness analysis was needed.
- As heliox is not commonly used in the UK it was not possible to identify related costs. The clinical evidence was limited and therefore an economic evaluation was not considered useful for decision making.
- No clinical evidence was identified in the systematic review for nasal suctioning and therefore a cost analysis was developed for this area rather than a full economic evaluation.

The economic evidence resulting from the analyses were considered by the GDG members in drafting the recommendations. Summaries of the economic evidence resulting from these analyses are presented before the recommendations.

1.6.6 Evidence to recommendations

Recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. Informal consensus methods were used by the GDG to agree short clinical and, where appropriate, cost effectiveness evidence statements which were presented alongside the evidence profiles. Statements summarising the GDG's interpretation of the evidence and any extrapolation from the evidence used when making recommendations were also written to ensure transparency in the decision-making process. The criteria used in moving from evidence to recommendations were:

- relative value placed on the outcomes considered
- consideration of clinical benefits and harms
- consideration of net health benefits and resource use
- quality of the evidence
- other considerations (including equalities issues).

The GDG also identified areas where evidence to answer its review questions was lacking and used this information to formulate recommendations for future research.

The GDG identified 10 'key priorities for implementation' (key recommendations) and five high-priority research recommendations. The key priorities for implementation were those recommendations thought likely to have the greatest impact on clinical care and outcomes in the NHS as a whole; they were selected using a variant of the nominal group technique (see the NICE guidelines manual). The priority research recommendations were selected in a similar way.

1.6.7 Research recommendations

For areas where good quality evidence was limited, the GDG considered the development of research recommendations. The GDG based their decisions on areas for further research on:

- The importance to patients
- National priorities
- Potential impact on the NHS and future NICE guidance
- Ethical and technical feasibility

1.6.8 Stakeholder involvement

Registered stakeholder organisations were invited to comment on the draft scope and the draft guideline. The GDG carefully considered and responded to all comments received from stakeholder organisations. The comments and responses were reviewed by NICE in accordance with the NICE guideline development process.

2 Summary of recommendations and care pathway

2.1 Key priorities for implementation

Diagnose bronchiolitis if the child has a coryzal prodrome lasting 1 to 3 days, followed by:

- persistent cough **and**
- either tachypnoea or chest recession (or both) **and**
- either wheeze or crackles on chest auscultation (or both) [Rec 3].

When diagnosing bronchiolitis, take into account that young infants (in particular those under 6 weeks of age) may present with apnoea without other clinical signs [Rec 4].

Immediately refer children with bronchiolitis for emergency hospital care (usually by 999 ambulance) if they have any of the following:

- apnoea (observed or reported)
- child looks seriously unwell to a healthcare professional
- severe respiratory distress, for example grunting, marked chest recession, or a respiratory rate of over 70 breaths/minute
- central cyanosis
- persistent oxygen saturation of 92% or less when breathing air[Rec 9].

Consider referring children with bronchiolitis to secondary care if they have any of the following:

- a respiratory rate of over 60 breaths/minute
- difficulty with breastfeeding or inadequate oral fluid intake (less than 75% of usual volume)
- clinical dehydration [Rec 10].

Provide key safety information for children who will be looked after at home. This should include information:

- for parents and carers on how to recognise developing 'red flag' symptoms:
  - worsening work of breathing (for example grunting, nasal flaring, marked chest recession)
  - fluid intake is less than 75% of normal or no wet nappy for 12 hours
  - apnoea or cyanosis
  - exhaustion (for example, not responding normally to social cues, wakes only with prolonged stimulation)
- on how to get immediate help from an appropriate professional if any red flag symptoms develop
- on arrangements for follow-up if necessary [Rec 15].

When assessing a child in a secondary care setting, admit them to hospital if they have any of the following:

- apnoea (observed or reported)
- persistent oxygen saturation of 92% or less when breathing air
- inadequate oral fluid intake (less than 75% of usual volume)
- persisting severe respiratory distress, for example grunting, marked chest recession, or a respiratory rate of over 70 breaths/minute [Rec 16].

Do not perform a chest x-ray in children with bronchiolitis, because changes on x-ray may mimic pneumonia and should not be used to determine the need for antibiotics [Rec 28].

Do not use any of the following to treat bronchiolitis in children:

- antibiotics
- hypertonic saline
- adrenaline (nebulised)
- salbutamol
- Montelukast
- ipratropium bromide
- systemic or inhaled corticosteroids
- a combination of systemic corticosteroids and nebulised adrenaline [Rec 34].

Give oxygen supplementation to children with bronchiolitis if their oxygen saturation is persistently 92% or less [Rec 35].

Give fluids by nasogastric or orogastric tube in children with bronchiolitis if they cannot take in enough fluid by mouth [Rec 24].

2.2 Summary of recommendations

1. When diagnosing bronchiolitis, take into account that it occurs in children under 2 years of age and most commonly in the first year of life, peaking between 3 and 6 months.
2. When diagnosing bronchiolitis, take into account that symptoms usually peak between 3 and 5 days, and that cough resolves in 90% of infants within 3 weeks.
3. Diagnose bronchiolitis if the child has a coryzal prodrome lasting 1 to 3 days, followed by:
    - persistent cough **and**
    - either tachypnoea or chest recession (or both) **and**
    - either wheeze or crackles on chest auscultation (or both)
4. When diagnosing bronchiolitis, take into account that young infants (in particular those under 6 weeks of age) may present with apnoea without other clinical signs.
5. When diagnosing bronchiolitis, take into account that the following symptoms are common:
    - fever (in around 30% of cases, usually of less than 39°C)
    - poor feeding (typically after 3 to 5 days of illness)
6. Consider a diagnosis of pneumonia if the child has:
    - high fever (over 39°C), and/or
    - persistently focal crackles
7. Think about a diagnosis of viral-induced wheeze or early-onset asthma rather than bronchiolitis in older infants and young children if they have:
    - persistent wheeze without crackles or
    - recurrent episodic wheeze or

- a personal or family history of atopy

Take into account that these conditions are unusual in children under 1 year of age

8. Check for the following potential risk factors for developing more severe bronchiolitis:
    - chronic lung disease (including bronchopulmonary dysplasia)
    - congenital heart disease, particularly if this is hemodynamically significant
    - age in young infants (under 3 months)
    - premature birth, particularly under 32 weeks
    - neuromuscular disorders
    - immunodeficiency
    - male sex
    - if the child has not been breast fed
    - if the child comes from a household with people who smoke
9. Immediately refer children with bronchiolitis for emergency hospital care (usually by 999 ambulance) if they have any of the following:
    - apnoea (observed or reported)
    - child looks seriously unwell to a health care professional
    - severe respiratory distress, for example grunting, marked chest recession, or respiratory rate over 70 breaths/minute
    - central cyanosis
    - persistent oxygen saturation of 92% or less when breathing air.
10. Consider referring children with bronchiolitis to secondary care if they have any of the following:
    - a respiratory rate of over 60 breaths/minute
    - difficulty with breastfeeding or inadequate oral fluid intake (less than 75% of usual volume)
    - clinical dehydration.
11. When deciding whether to refer a child with bronchiolitis to secondary care, take account of the following risk factors for more severe bronchiolitis:
    - chronic lung disease (including bronchopulmonary dysplasia)
    - haemodynamically significant congenital heart disease
    - age in young infants (under 3 months)
    - premature birth, particularly under 32 weeks
    - neuromuscular disorders
    - immunodeficiency.
12. When deciding whether to refer to secondary care a child, take into account factors which might affect a carer's ability to look after a child with bronchiolitis, for example:
    - social circumstances

- the skill and confidence of the carer in looking after a child with bronchiolitis at home
- confidence in being able to spot red flag symptoms (see recommendation 15)
- distance to healthcare in case of deterioration.

13. Clinically assess the hydration status of children with bronchiolitis.
14. Do not routinely perform blood tests in the assessment of a child with bronchiolitis.
15. Provide key safety information for children who will be looked after at home. This should include information:
    - for parents and carers on how to recognise developing 'red flag' symptoms:
        - worsening work of breathing (for example grunting, nasal flaring, marked chest recession)
        - fluid intake is less than 75% of normal or no wet nappy for 12 hours
        - apnoea or cyanosis
        - exhaustion (for example, not responding normally to social cues, wakes only with prolonged stimulation)
    - on how to get immediate help from an appropriate professional if any red flag symptoms develop
    - on arrangements for follow-up if necessary.
16. When assessing a child in a secondary care setting, admit them to hospital if they have any of the following:
    - apnoea (observed or reported)
    - persistent oxygen saturation of 92% or less when breathing air
    - inadequate oral fluid intake (less than 75% of usual volume)
    - persisting severe respiratory distress, for example grunting, marked chest recession, or a respiratory rate of over 70 breaths/minute.
17. When deciding whether to admit a child with bronchiolitis, take account of the following risk factors for more severe bronchiolitis:
    - chronic lung disease (including bronchopulmonary dysplasia)
    - haemodynamically significant congenital heart disease
    - age in young infants (under 3 months)
    - premature birth, particularly under 32 weeks
    - neuromuscular disorders
    - immunodeficiency.
18. When deciding whether to admit a child, take into account factors which might affect a carer’s ability to look after a child with bronchiolitis, for example:
    - social circumstances
    - the skill and confidence of the carer in looking after a child with bronchiolitis at home

- confidence in being able to spot red flag symptoms (see recommendation 15)
- distance to healthcare in case of deterioration.

19. Provide parents or carers with key safety information (see Recommendation 15) if the child is not admitted.
20. When deciding on the timing of discharge for children admitted to hospital, make sure that the child:
    - is clinically stable
    - is taking adequate oral fluids
    - has maintained oxygen saturation over 92% in air for 4 hours, including a period of sleep.
21. When deciding whether to discharge a child, take into account factors which might affect a carer's ability to look after a child with bronchiolitis, for example:
    - social circumstances
    - the skill and confidence of the carer in looking after a child with bronchiolitis at home
    - confidence in being able to spot red flag symptoms (see recommendation 15)
    - distance to healthcare in case of deterioration.
22. Provide parents or carers with key safety information (see Recommendation 14) when the child is discharged.
23. Give fluids by nasogastric or orogastric tube in children with bronchiolitis if they cannot take enough fluid by mouth.
24. Give intravenous isotonic fluids (see NPSA guidance) to children who:
    - do not tolerate nasogastric or orogastric fluids or
    - have impending respiratory failure.
25. Measure oxygen saturation in every child presenting with suspected bronchiolitis, including those presenting to primary care if pulse oximetry is available.
26. Measure pulse oxygen saturation using pulse oximetry in every child presenting to secondary care with clinical evidence of bronchiolitis.
27. Ensure healthcare professionals performing pulse oximetry are appropriately trained in its use specifically in infants and young children.
28. Do not perform a chest x-ray in children with bronchiolitis, because changes on x-ray may mimic pneumonia and should not be used to determine the need for antibiotics.
29. Do not routinely carry out blood gas testing in children with bronchiolitis.
30. Consider carrying out capillary blood gas testing in children with severe worsening respiratory distress (when supplemental oxygen concentration is greater than 50%) or suspected impending respiratory failure (see recommendation 31).
31. Suspect impending respiratory failure if the child has any of the following:
    - signs of exhaustion, for example listlessness or decreased respiratory effort

- recurrent apnoea
- failure to maintain adequate oxygen saturation despite oxygen supplementation

32. Do not perform chest physiotherapy on children with bronchiolitis who do not have relevant comorbidities (for example spinal muscular atrophy, severe tracheomalacia).
33. Consider requesting a chest physiotherapy assessment in children who have relevant comorbidities (for example spinal muscular atrophy, severe tracheomalacia) when there may be additional difficulty clearing secretions.
34. Do not use any of the following to treat bronchiolitis in children:
    - antibiotics
    - hypertonic saline
    - adrenaline (nebulised)
    - salbutamol
    - Montelukast
    - ipratropium bromide
    - systemic or inhaled corticosteroids
    - a combination of systemic corticosteroids and nebulised adrenaline.
35. Give oxygen supplementation to children with bronchiolitis if their oxygen saturation is persistently 92% or less.
36. Consider continuous positive airway pressure (CPAP) in children with bronchiolitis who have impending respiratory failure (see recommendation 31)
37. Do not routinely perform upper airway suctioning in children with bronchiolitis.
38. Consider upper airway suctioning in children who have respiratory distress or feeding difficulties because of upper airway secretions.
39. Perform upper airway suctioning in children with bronchiolitis presenting with apnoea even if there are no obvious upper airway secretions.

2.3 Research recommendations

1. In children with bronchiolitis can paediatric early warning score (PEWS) predict deterioration?
    1.1. In children with bronchiolitis there is clinical uncertainty about the prediction of deterioration. There are a number of clinical scores for bronchiolitis that include objective and subjective measures. No bronchiolitis score is currently in widespread use in clinical practice. Increasingly, PEWS are being employed generically in paediatric practice in the UK. The effectiveness of PEWS scores in predicting deterioration for infants with bronchiolitis needs to be assessed.
2. In children with bronchiolitis what features predict progressive recovery?

2.1. In bronchiolitis there is usually a period of increasing severity of symptoms followed by a period of gradual recovery. The ability to predict progressive recovery would be helpful when making management decisions – for example with regard to the gradual withdrawal of treatments. Such information could also potentially avoid unnecessary admissions to hospital and might shorten hospital stay in those who are admitted.

3. What is the clinical and cost effectiveness of SpO_2 measurement in a primary care setting in children with bronchiolitis?

    3.1. There are no studies to inform the use of SpO_2 measurement in primary care. SpO_2 is used routinely in secondary care to help decide on the need for admission to hospital. The clinical and cost effectiveness of SpO_2 measurement in primary care is also important. SpO_2 measurement is not routinely measured in infants and young children with bronchiolitis in primary care. The value of SpO_2 measurement to help identify those who need admission to hospital should be assessed. Possible outcomes might be fewer or more infants being referred to hospital, or admitted.

4. What is the effectiveness of chest physiotherapy in children with bronchiolitis and impending respiratory failure?

    4.1. Whilst chest physiotherapy appears ineffective in the early and routine management of bronchiolitis,it is possible that it may be effective in those children with impending respiratory failure. In that setting it is possible that clearing of airway secretions might effect an important improvement in the infant or child's condition avoiding the need for other more intensive interventions such as mechanical ventilation. A multi-centre RCT should be conducted to assess its efficacy in this important sub-group of infants and children. Important outcomes would include admission to intensive care, the need for mechanical ventilation and improvement in oxygen saturation.

5. What is the efficacy of combined bronchodilator and corticosteroid therapy?

    5.1. There are no effective therapies for the treatment of bronchiolitis. One study reported that those infants provided with both nebulised adrenaline and systemic steroids had improved clinical outcomes. This was a subgroup analysis was not anticipated in the trial design and consequently not adequately powered to answer this question. A multi-centre RCT that assesses the clinical and cost effectiveness of combined adrenaline and corticosteroids as a useful therapy for bronchiolitis is required.

6. What is the efficacy of Montelukast in the treatment of acute bronchiolitis in infants and children?

    6.1. Montelukast is a leukotriene receptor antagonist that has proven effectiveness in the treatment of asthma in infants and children. The inflammatory mediators known as leukotrienes are known to be increased in infants and children with bronchiolitis. Exising trials have been inconsistent in their findings with regard to the efficacy of Montelukast in bronchiolitis. A multi-centre RCT is required comparing the clinical and cost effectiveness of Montelukast with placebo for the treatment of bronchiolitis.

Important outcomes would include hospital admission rate, duration of symptoms and hospital length of stay.

7. What is the efficacy of heliox?

    7.1. There is some evidence that heliox therapy may reduce the need for CPAP in infants and children with severe bronchiolitis. The evidence is however inconclusive. Moreover, heliox is administered using a tight-fitting face mask and there may be difficulties with patient tolerance. A multi-centre RCT of the clinical and cost effectiveness of this treatment is required. Provision of heliox through a hospital piped supply is not widely available and has cost implication.

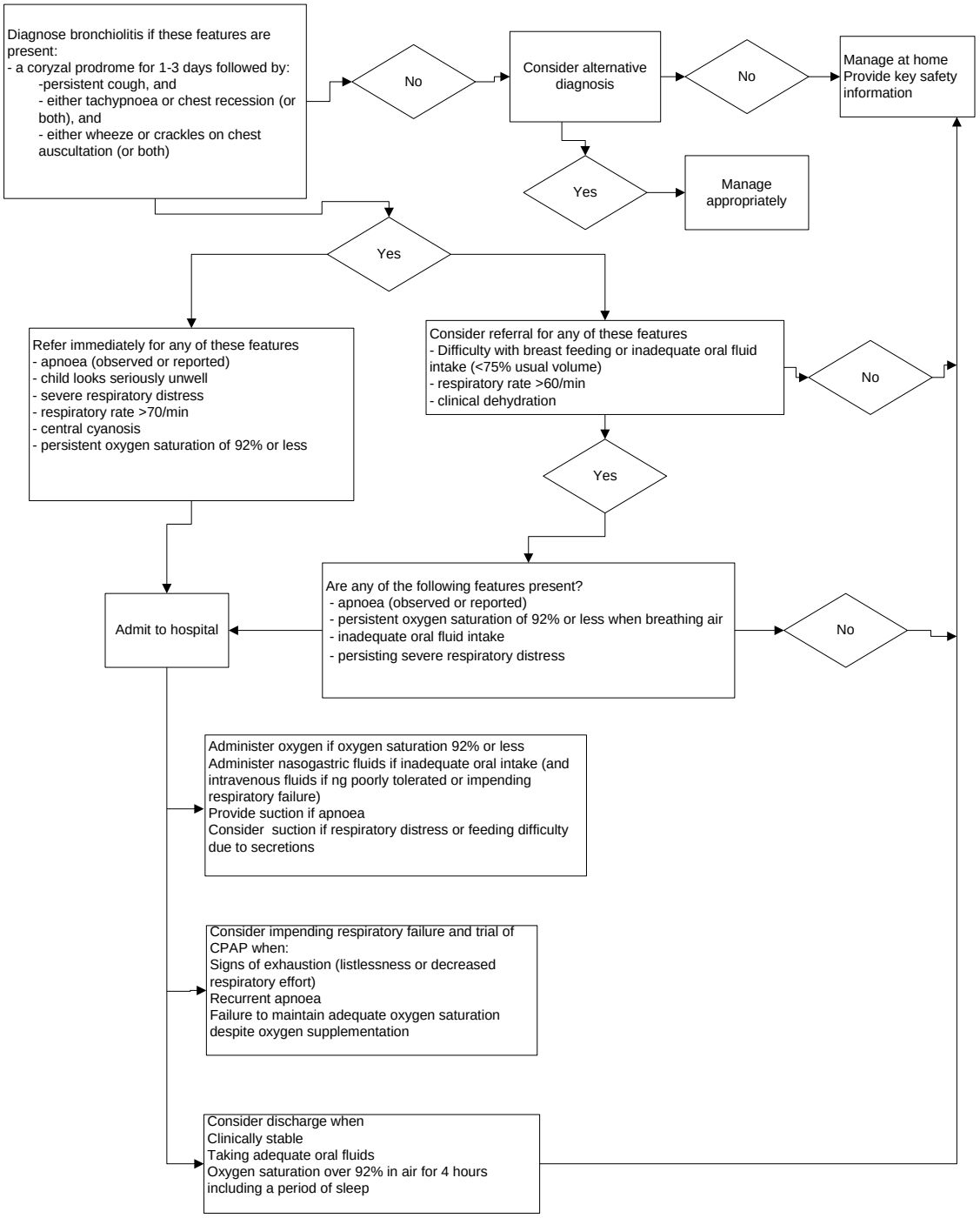
8. What is the clinical and cost effectiveness of high-flow humidified oxygen versus standard supplemental oxygen?

    8.1. Providing oxygen (typically by nasal cannula) is standard care for bronchiolitis. Newly-developed medical devices can now deliver high-flow humidified oxygen that is thought to provide more comfortable and effective delivery of gases while retaining airway humidity. The use of this medical device is becoming widespread without demonstration of additional efficacy. A multicentre RCT comparing high-flow humidified oxygen and standard supplemental oxygen would be of benefit, as would including weaning strategies for high-flow humidified oxygen.

9. What is the clinical and cost effectiveness of suction to remove secretions from the upper respiratory tract compared with minimal handling?

    9.1. Suction is a commonly used therapy in bronchiolitis. Infants are obligate nasal breathers, so removal of secretions is thought to relieve respiratory distress. However, suction is distressing to infants and parents. Methods vary and there is no evidence on which approach, if any, is most effective. In some trials it appears that minimal handling is more effective than therapies. A multicentre RCT comparing the clinical and cost effectiveness of suction (also covering different suction strategies, for example superficial versus deep) with minimal handling is needed.

2.4 Care pathway



3 Diagnosis and assessment of bronchiolitis

3.1 Symptoms and signs

3.1.1 Review question

What symptoms, signs and clinical course are typical of bronchiolitis, and allow differentiation from other respiratory conditions:

- What are the typical symptoms of bronchiolitis?
- At what ages does bronchiolitis typically occur?
- What is the typical duration of symptoms?
- How do symptoms change during the course of a bronchiolitis episode?
- When do symptoms peak?

Further details on the protocol for this review question are provided in Appendix E

3.1.2 Introduction

Bronchiolitis is a clinical diagnosis and, as such, it is important to recognise indicative clinical characteristics. Typical features have significant potential overlap with other diagnoses including viral induced wheeze and pneumonia, highlighting the importance of a thorough, detailed history and clinical examination.

3.1.3 Description of included studies

Seven studies were included in this review (El-Radhi et al, 1999; Swingler et al, 2000; Petruzella et al, 2010, USA; Thompson et al, 2013; Tsolia et al, 2003; Gajdos et al, 2009; Mansbach et al, 2008).

One study was a systematic review and meta-analysis (Thompson et al, 2013,), one study was a diagnostic validation study (Gajdos et al, 2009) and five were cohort studies (El-Radhi et al, 1999; Swingler et al, 2000; Petruzella et al, 2010; Tsolia et al, 2003; Mansbach et al, 2008). Studies were undertaken in the USA, UK, South Africa, France, and Greece. Sample size ranged from 90 to 636.

Four studies presented information on symptoms associated with bronchiolitis (El-Radhi et al, 1999; Tsolia et al, 2003; Gajdos et al, 2009; Mansbach et al, 2008), one study examined the age that bronchiolitis typically occurs (Tsolia et al, 2003), and four studies examined the duration of symptoms (Swingler et al, 2000; Petruzella et al, 2010; Thompson et al, 201?; Mansbach et al, 2008).

No studies were identified on the age at which bronchiolitis typically occurs, how symptoms change during the course of illness or when symptoms peak during the illness.

Further details on each study are provided in the evidence table in Appendix I.

3.1.4 Evidence profile

Study quality was assessed using the GRADE methodology. Comparative observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 3: GRADE profile for typical symptoms of bronchiolitis

Table 3: GRADE profile for typical symptoms of bronchiolitis

Number of studies		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
What are the typical symptoms of bronchiolitis?								
1 (El-Radhi et al, 1999)	28 of 90 were febrile (38+C); Febrile infants had more severe symptoms than afebrile p < 0.005	Very Low	Cohort	Seriousa	None	None	Serious[b]	None
1 (Tsolia et al, 2003)	Symptom: RSC+ (n = 291), RSV- (n = 182) 30% of infants RSV+ bronchiolitis were febrile compared to 25.5% of RSV- negative bronchiolitis (NS) 75.5% of infants RSV+ bronchiolitis were tachypnea (=> 50 per minute) compared to 69.5% of RSV- negative bronchiolitis (NS) 71% of infants RSV+ bronchiolitis were retractions compared to 65% of RSV- negative bronchiolitis (NS) 75% of infants RSV+ bronchiolitis were crackles compared to 63% of RSV- negative bronchiolitis (NS)	Very Low	Cohort	Seriousa	None	Serious[c]	Serious[b]	None
1(Gajdos et al,	Review of literature Review of clinical scores for bronchiolitis identified 13 scores (including one developed by authors. All scores included measures of: 13 of 13 used respiratory rate 13 of 13 used retraction signs 13 of 13 Wheezing 4 of 13 used general appearance 3 of 13 used cyanosis 7 of 13 used other measures, usually oxygen saturation	Very low	Systematic review of diagnostic validation	Very serious[d]	None	None	Serious[b]	None
Mansbach et al,	Outcome: RSV only, RV only, RSV and RV, Other Relapse within 2-weeks (%):12, 8, 15, 13 Duration of symptoms (days)(from onset to 2 week follow-up): 8 (4 to 10), 3 (2 to 8), 6 (2 to 9), 8 (2 to 9)	Very low	Cohort	Serious[e]	None	Serious[c]	Very Serious[b, f]	None
At what ages does bronchiolitis typical occur?								
1 (Tsolia et al, 2003)	Symptom: RSC+ (n = 291), RSV- (n = 182) Age (months) median: 2.8, 4.5	Very Low	Cohort	Very serious[g]	None	None	Serious[b]	None
What is the typical duration of symptoms?								
1 (Swingler et al,	Median duration of illness = 12 days (95% CI 11 to 14 days). 39% of children were still symptomatic after 14 days, 18% after 21 days and 9% after 28 days.	Very low	Prospective cohort	Serious[h]	None	Serious[i]	Serious[b]	None

Number of studies		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Petruzella et al,	Median time to resolution of symptoms 15 days 25% of infants continued to be symptomatic at day 20 At end of follow-up period 11% of infants continued to be symptomatic	Low	Prospective cohort	Serious[j]	None	None	Serious[b]	None
1 (Thompson et al,	4 bronchiolitis studies identified – Cough Patel, 2003 - RCT of 61 infants followed up until symptoms resolution. Median duration 8.4 days Plint, 2009 - RCT of 201 infants followed-up for 22 days. Median duration 13.3 days (IQR 8.2 to 19.5) Petruzella, 2010 - observational study of 95 infants followed-up unitl symptoms resolution. Median duration 15 days (IQR 11-20) Plint, 2004 - observational study of 163 infants followed-up for 3 weeks. Median duration 12 days (IQR 8 to 20) Pooled results Time for symptoms to resolve in 50% of infants was 13 days Time for symptoms to resolve in 90% of infants was 21 days (estimate)	Low	Systematic Review and meta-analysis	None	None	Serious[k]	Serious[b]	None
1 (Mansbach et al,	Outcome: RSV only, RV only, RSV and RV, Other Relapse within 2-weeks (%):12, 8, 15, 13 Duration of symptoms (days)(from onset to 2 week follow-up): 8 (4 to 10), 3 (2 to 8), 6 (2 to 9), 8 (2 to 9)	Very low	Cohort	Serious[e]	None	Serious[c]	Very Serious[b, f]	None
How do symptoms change during the course of a bronchiolitis episode? – No data								
When do symptoms peak? – No data								

RCT Randomised Controlled Trial, p-value
a Analysis does not account for confounders
b Imprecision could not be calculated
c comparing RSV+/-
d no evidence of search strategy or systematic data extraction
e Descriptive only. Study population includes infants with previous wheeze. Duration of symptoms censored at 2 weeks
f Study population includes infants with previous wheeze
g Admission based on symptoms of Bronchiolitis. High proportion of eligible infants did not have RSV test. Reliability assessing outcomes not reported
h High loss to follow-up not explained (26.5%) or analysed
I Limited to mild Bronchiolitis only
j truncated follow-up
k Study focused on cough as a general symptom for respiratory conditions.

3.1.5 Evidence statements

What are the typical symptoms of bronchiolitis?

Evidence from four studies with 1020 children reported that the following symptoms were associated with bronchiolitis: tachypnea, chest recession, crackles, fever, increased respiratory rate, cough, wheezing, cyanosis, and general appearance. However, no comparative data was available on the diagnostic usefulness of these. The quality of the evidence was very low.

At what ages does bronchiolitis typical occur?

Evidence from one study with 473 children showed the median range of when bronchiolitis occurred was between 2.8 and 4.5 months. The quality of the evidence was very low.

What is the typical duration of symptoms?

Evidence from four studies with 1150 children showed median duration of symptoms ranged from 8 to 15 days. Furthermore, a meta-analysis of studies found the time for symptoms to resolve in 90% of infants was 21 days. The quality of the evidence was very low.

How do symptoms change during the course of a bronchiolitis episode?

No studies reported data on this outcome.

When do symptoms peak?

No studies reported data on this outcome.

3.1.6 Health economics profile

No health economic studies were identified and no health economic analysis was planned for this question.

3.1.7 Evidence to recommendations

3.1.7.1 Relative value placed on the outcomes considered

The aim of this review was to retrieve evidence to describe the manifestations and clinical course of bronchiolitis in children. The following were considered to be critical outcomes for this review: at what ages does bronchiolitis typically occur, what are the typical symptoms of bronchiolitis, and what is the typical duration of symptoms. Other important outcomes were: how do symptoms change during the course of a bronchiolitis episode, and when do symptoms peak. The GDG stated that it would be preferable to review evidence on the diagnostic usefulness of various symptoms and signs but this was not possible because an objective diagnostic gold standard does not exist, as bronchiolitis is a clinical syndrome.

3.1.7.2 Consideration of clinical benefits and harms

Evidence for signs and symptoms of bronchiolitis was often poor or not present. As a consequence the GDG used their range of clinical knowledge of the condition to inform recommendations.

Four studies reported that tachypnea, chest recession, crackles, fever, increased respiratory rate, cough, wheezing, cyanosis, and general appearance were associated with bronchiolitis.

Based on this and their consensus opinion, the GDG developed a recommendation defining the range of symptoms and signs which would constitute a clinical diagnosis of bronchiolitis. The GDG similarly derived clinical indicators suggestive of alternative diagnoses (such as pneumonia, viral-induced wheeze or early-onset asthma). The GDG considered that bronchiolitis is preceded by a coryzal prodrome, even though this is not presented as evidence in the literature. It was similarly considered that young infants (particularly those under 6 weeks of age) may present with apnoea without other clinical signs.

The GDG developed a recommendation based on one very low quality study, together with their consensus knowledge that the median age for the development of bronchiolitis was between 2.8 and 4.5 months. The GDG agreed that bronchiolitis occurs in children under two years of age, most commonly in the first year of life, peaking between 3 and 6 months.

Evidence from four studies that showed that the median duration of symptoms ranged from 8 to 15 days and a meta-analysis that found that the time for symptoms to resolve in 90% of infants was 21 days which informed the GDG in terms of recommendations regarding the clinical course.

As there was lack of evidence, the GDG provided consensus opinion about the temperature as a clinical feature in bronchiolitis. Children with bronchiolitis commonly have pyrexia, but this is not typically above 39oC. A temperature above 39oC was considered possibly consistent with additional bacterial infection, which in the case of persistent focal crepitations could be pneumonia.

It was recognised by the GDG that children, in particular those above one year of age, who wheeze with a virus infection may have a diagnosis of viral induced wheeze or early onset asthma. The GDG used consensus clinical opinion to identify those children with a higher probability of these conditions rather than bronchiolitis, recognising that differentiating the conditions can be difficult in some children.

3.1.7.3 Consideration of health benefits and resource uses

The diagnosis of bronchiolitis based on the identification of evidence based symptoms and signs at initial assessment, will allow health professionals to give appropriate information and advice to parents and carers. This should reduce variation in practice, and avoid unnecessary additional appointments to primary care and secondary care. It should also enable health professionals to differentiate serious from non-serious cases, to ensure that resources are focused on those who need further investigations and treatment, and avoid misdiagnosis and potentially unnecessary tests and treatment.

3.1.7.4 Quality of evidence

Evidence was limited to non-comparative observational studies. The main source of bias was the lack of any comparative groups or gold standard for identifying bronchiolitis. The quality of the evidence ranged from low to very low.

3.1.7.5 Other considerations

No equality issues were identified for this question.

3.1.8 Recommendations

1. **When diagnosing bronchiolitis, take into account that it occurs in children under 2 years of age and most commonly in the first year of life, peaking between 3 and 6 months.**

2. **When diagnosing bronchiolitis, take into account that symptoms usually peak between 3 and 5 days, and that cough resolves in 90% of infants within 3 weeks.**

3. **Diagnose bronchiolitis if the child has a coryzal prodrome lasting 1 to 3 days, followed by:**
    - persistent cough **and**
    - either tachypnoea or chest recession (or both) **and**
    - either wheeze or crackles on chest auscultation (or both)

4. **When diagnosing bronchiolitis, take into account that young infants (in particular those under 6 weeks of age) may present with apnoea without other clinical signs.**

5. **When diagnosing bronchiolitis, take into account that the following symptoms are common:**
    - fever (in around 30% of cases, usually of less than 39°C)
    - poor feeding (typically after 3 to 5 days of illness)

6. **Consider a diagnosis of pneumonia if the child has:**
    - high fever (over 39°C), and/or
    - persistently focal crackles

7. **Think about a diagnosis of viral-induced wheeze or early-onset asthma rather than bronchiolitis in older infants and young children if they have:**
    - persistent wheeze without crackles or
    - recurrent episodic wheeze or
    - a personal or family history of atopy

    Take into account that these conditions are unusual in children under 1 year of age

3.2 Risk factors

3.2.1 Introduction

A number of factors have been identified as potential risk factors for developing severe bronchiolitis. The early identification of risk factors is important as this may help to inform an appropriate management strategy. It was not practical or useful to assess all possible risk factors; therefore the GDG selected those that were most commonly considered in clinical practice:

- History of prematurity (degree of prematurity may be relevant and should be reported)
- Bronchopulmonary dysplasia / chronic lung disease
- Congenital heart disease
- Cystic fibrosis
- Immunodeficiency
- Neuromuscular disorders
- Non-breast fed
- Young infants (for example, less than 3 months old)
- Sex (Male)
- Previous hospitalisation
- Ethnicity
- Down's syndrome
- Family Smoking
- Multiple birth

Individual systematic reviews were undertaken for each of these and the results are reported below.

The overarching review question was "What are the risk factors for severe bronchiolitis?" Risk-factors can be assessed using either case-control studies or cohort studies. The information obtained will depend on the study design type. For example, retrospective case-control studies provide information on the prevalence of an outcome, such as intensive care admission, amongst those who have been exposed to a risk factor for instance prematurity, compared with those who have not been exposed. Whilst a cohort study will provide information on whether the incidence of severe bronchiolitis differs between the exposed and unexposed groups.

Study quality was assessed using the GRADE approach. Cohort or case-control studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias. Outcomes are reported as described in the original papers, so reflect the variation in reporting. Only studies reporting adjusted odds ratios have been included.

3.2.2 Review question

What are the risk factors for severe bronchiolitis?

Further details on the protocol for this review question are provided in Appendix E.

3.2.3 Risk factor reviews

3.2.3.1 Prematurity

3.2.3.1.1 Description of included studies

Twenty six observational studies were identified for this review (Al-Shehri et al., 2005; Boyce et al., 2000; Bockova et al., 2002; Carbonell-estrany et al., 2000; Carbonell-estrany et al., 2001; Chan et al.,1999; Chan et al., 2002; Cilla et al., 2006; Dotan et al., 2013; Garcia et al., 2010; Grimwood et al., 2008; Hervas et al., 2012; Joffe et al., 1999; Kristensen et al., 2009; Lanari et al., 2013; Murray et al., 2014; Nielsen et al., 2003; Papenburg et al., 2012; Paranjothy et al., 2013; Pezzotti et al., 2009; Rietveld et al., 2006; Ricart et al., 2013; Semple et al., 2011; Simon et al., 2007; Wilkesmann et al., 2007; Zhang et al., 2014).

Eleven were retrospective cohort studies (Boyce et al., 2000; Chan et al.,1999; Chan et al., 2002; Cilla et al., 2006; Dotan et al., 2013; Garcia et al., 2010; Grimwood et al., 2008; Joffe et al., 1999; Paranjothy et al., 2013; Pezzotti et al., 2009; Rietveld et al., 2006), ten were prospective cohort studies (Bockova et al., 2002; Carbonell-estrany et al., 2000; Carbonell-estrany et al., 2001; Lanari et al., 2013; Murray et al., 2014; Papenburg et al., 2012; Ricart et al., 2013; Semple et al., 2011; Simon et al., 2007; Wilkesmann et al., 2007), two were retrospective matched case-control studies (Kristensen et al., 2009; Nielsen et al., 2003), one was a prospective matched case-control study (Al-Shehri et al., 2005) and two were retrospective chart reviews (Hervas et al., 2012; Zhang et al., 2014).

Five studies were undertaken in Spain (Carbonell-estrany et al., 2000; Carbonell-estrany et al., 2001; Cilla et al., 2006; Hervas et al., 2012; Ricart et al., 2013), four in the USA (Boyce et al., 2000; Bockova et al., 2002; Garcia et al., 2010; Joffe et al., 1999); two in Malaysia (Chan et al.,1999; Chan et al., 2002), one in Saudi Arabia (Al-Shehri et al., 2005) one in New Zealand (Grimwood et al., 2008), two in Denmark (Kristensen et al., 2009; Nielsen et al., 2003), one in Canada (Papenberg et al., 2012), two in Italy (Lanari et al., 2013; Pezzotti et al., 2009), one in the Netherlands (Rietveld et al., 2006), two in Germany (Simon et al., 2007; Wilkesmann et al., 2007), one in China (Zhang et al., 2014), one in Israel (Dotan et al., 2013) and three in the UK (Murray et al., 2014; Paranjothy et al., 2013; Semple et al., 2011). Sample sizes ranged from 166 to 14343.

The age of the subjects varied including infants less than 24 months in nine studies (Bockova et al., 2002; Chan et al., 1999; Chan et al., 2002; Cilla et al., 2006; Garcia et al., 2010; Grimwood et al., 2008; Hervas et al., 2012; Nielsen et al., 2003; Semple et al., 2011), less than 12 months in three studies (Murray et al., 2014; Rietveld et al., 2006; Ricart et al., 2013), less than 6 months of age in one study (Carbonell-Estrany et al., 2001), premature infants in two studies (Carbonell-Estrany et al., 2000; Joffe et al., 1999) and children less than 3 years of age in three studies (Boyce et al., 2000; Papenburg et al., 2012; Pezzotti et al., 2009). One study which included children less than 3 years of age however restricted the risk factor analysis to the first year of life (Boyce et al., 2000). Another study which included children less than three years of age, also restricted the risk factor analysis but to infants in the first 18 months of life (Pezzotti et al., 2009). The third study which included children less than 3 years of age reported a mean age of 8 and 12.5 months for the cases and controls respectively (Papenburg et al., 2012). Two studies enrolled children up to 5 years of age (Al-Shehri et al., 2005; Paranjothy et al., 2013). One study (Kristensen et al., 2009) initially enrolled children up to the age of 14 years but included children with a mean age at RSV diagnosis of 362 days (range: 15 to 2379 days). Two studies included children irrespective of age (Simon et al., 2007; Wilkesmann et al., 2007) - the median age (range) of infants in one of these studies (Simon et al., 2007) was 159 (64 to 340) days and 142 (75 to 288) days for terms and preterm respectively and in the other study (Wilkesmann et al., 2007), 430 days and 145 days for the neuromuscular impairment group and controls respectively. Of the remaining studies, one study included children up to 3720 days old (Dotan et al., 2013), one

study included newborns of various gestational ages (Lanari et al., 2013) and one study included children of which the majority was aged <2 years (Zhang et al., 2014).

The definition of prematurity was reported in twenty five studies (Boyce et al., 2000; Bockova et al., 2002; Carbonell-estrany et al., 2000; Carbonell-estrany et al., 2001; Chan et al.,1999; Chan et al., 2002; Cilla et al., 2006; Dotan et al., 2013; Garcia et al., 2010; Grimwood et al., 2008; Hervas et al., 2012; Joffe et al., 1999; Lanari et al., 2013; Murray et al., 2014; Kristensen et al., 2009; Nielsen et al., 2003; Papenburg et al., 2012; Paranjothy et al., 2013; Pezzotti et al., 2009; Rietveld et al., 2006; Ricart et al., 2013; Simon et al., 2007; Semple et al., 2011; Wilkesmann et al., 2007; Zhang et al., 2014) and varied including definitions such as 23 to 32 weeks gestational age, ≤28 weeks, <37 weeks and increasing gestational age (not defined in study). The reference categories to which premature infants were compared to also varied across the studies.

The studies reported various outcomes including bronchiolitis/RSV hospitalisation in twelve studies (Boyce et al., 2000; Rietveld et al., 2006; Nielsen et al., 2003; Grimwood et al., 2008; Cilla et al., 2006; Kristensen et al., 2009; Papenburg et al., 2012; Pezzotti et al., 2009; Al-Shehri et al., 2005; Murray et al., 2014; Paranjothy et al., 2013; Lanari et al., 2013), RSV rehospitalisation in three studies (Joffe et al., 1999; Carbonell-estrany et al., 2001; Carbonell-estrany et al., 2000), severe bronchiolitis/ respiratory syncytial virus disease defined by severity scores in four studies (Bockova et al., 2002; Chan et al., 1999; Ricart et al., 2013; Papenburg et al., 2012), ICU admission in six studies (Hervas et al., 2012; Simon et al., 2007; Garcia et al., 2010; Dotan et al., 2013; Wilkesmann et al., 2007; Zhang et al., 2014), oxygen requirement in three studies (Garcia et al., 2010; Semple et al., 2011; Kristensen et al., 2009), mechanical ventilation in four studies (Garcia et al., 2010; Chan et al., 2002; Semple et al., 2011; Grimwood et al., 2008), respiratory failure in one study (Wilkesmann et al., 2007) and hypoxemia in one study (Chan et al., 2002) – some studies examined more than one of these outcomes.

The diagnosis of infants varied from nasopharyngeal aspirate tests, antigen tests and immunofluorescence and/or viral cultures (Al-Shehri et al., 2005; Bockova et al., 2002; Carbonell-estrany et al., 2000; Carbonell-estrany et al., 2001; Chan et al.,1999; Chan et al., 2002; Cilla et al., 2006; Grimwood et al., 2008; Hervas et al., 2012; Nielsen et al., 2003; Papenburg et al., 2012; Rietveld et al., 2006; Simon et al., 2007; Zhang et al., 2014; Dotan et al., 2013;) to International Classification of Disease codes (Boyce et al., 2000; Garcia et al., 2010; Joffe et al., 1999; Kristensen et al., 2009; Pezzotti et al., 2009; Murray et al., 2014; Paranjothy et al., 2013; Lanari et al., 2013) and/or severity scores (Al-Shehri et al., 2005; Bockova et al., 2002; Papenburg et al., 2012; Ricart et al., 2013). In the final study, all RSVinfections were microbiologically confirmed but the study did not stipulate the precise method of detection (Wilkesmann et al., 2007).

The settings of the studies varied including hospitals in twenty studies (Boyce et al., 2000; Bockova et al., 2002; Chan et al., 1999; Chan et al., 2002; Cilla et al., 2006; Dotan et al., 2013; Garcia et al., 2010; Grimwood et al., 2008; Hervas et al., 2012; Kristensen et al.., 2009; Murray et al., 2014; Nielsen et al., 2003; Papenburg et al., 2012; Paranjothy et al., 2013; Pezzotti et al., 2009; Rietveld et al., 2006; Simon et al., 2007; Semple et al., 2011; Wilkesmann et al., 2007; Zhang et al., 2014) and neonatal units in four studies (Carbonell-estrany et al., 2000; Carbonell-estrany et al., 2001; Lanari et al., 2013; Joffe et al., 1999). One study specified the paediatric emergency room and paediatric ward (Al-Shehri et al., 2005) and another study specified the paediatric ward or paediatric intensive care unit of a tertiary hospital (Ricart et al., 2013).

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on each individual study can be found in the evidence tables in Appendix I.

3.2.3.1.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 4: GRADE profile for the association between prematurity and risk of developing severe bronchiolitis

Table 4: GRADE profile for the association between prematurity and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
History of prematurity											
Risk of bronchiolitis/respiratory syncytial virus (rsv) hospitalisation											
Association between ≤28 weeks of gestational age (reference not reported) and RSV hospitalisation[a]											
1 (Boyce et al., 2000)	NR	NR	Adjusted IRR: 2.4 (1.8 to 3.3)[b]	-	Very low	Retrospective cohort	Very serious[c]	None	Serious[d]	None	None
Association between ≤28 weeks gestational age (vs ≥37 weeks) and RSV hospitalisation											
1 (Rietveld et al., 2006)	NR	NR	Adjusted OR: 3.2 (2.1 to 4.8)e	-	Very low	Retrospective cohort	Very serious[f]	None	Serious[g]	None	None
Association between 29 to 32 weeks gestational age (vs ≥37 weeks) and RSV hospitalisation											
1 (Rietveld et al., 2006)	NR	NR	Adjusted OR: 2.8 (2.1 to 3.8)[e]	-	Very low	Retrospective cohort	Very serious[f]	None	Serious[g]	None	None
Association between 29 to 33 weeks of gestational age (reference not reported) and RSV hospitalisation[a]											
1 (Boyce et al., 2000)	NR	NR	Adjusted IRR: 2.2 (1.8 to 2.7)b	-	Very low	Retrospective cohort	Very seriousc	None	Seriousd	None	None
Association between ≤32 weeks of gestational age (vs ≥40 weeks) and RSV hospitalisation											
1 (Nielsen et al., 2003)	49/1250 (3.9%)	54/5959 (0.9%)	Adjusted OR: 3.88 (2.74 to 7.75)[h]	-	Low	Retrospective, matched case-control	Very serious[i]	None	None	None	None
Association between <33 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis											
1 (Paranjothy	NR	NR	Adjusted	-	Low	Retrospective	Very	None	None	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
et al, 2013)			HR: 3.89 (3.55 to 4.25)[j]			cohort	serious[k]				
Association between 33 to 34 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis											
1 (Paranjothy et al, 2013)	NR	NR	Adjusted HR: 2.45 (2.21 to 2.71)[j]	-	Low	Retrospective cohort	Very serious[k]	None	None	None	None
Association between 33 to 34 weeks of gestational age (vs ≥38 weeks) and bronchiolitis hospitalisation											
1 (Lanari et al., 2013)	54/737 (7.3%)	25/706 (3.5%)	Adjusted HR: 2.1 (1.3 to 3.4)[l]	-	Moderate	Longitudinal multicentre cohort study	Serious[m]	None	None	None	None
Association between 33 to 34 weeks gestational age (vs ≥37 weeks) and RSV hospitalisation											
1 (Rietveld et al., 2006)	NR	NR	Adjusted OR: 2.3 (1.8 to 3.0)e	-	Very low	Retrospective cohort	Very serious[f]	None	Serious[g]	None	None
Association between 33 to 35 weeks of gestational age (vs ≥40 weeks) and RSV hospitalisation											
1 (Nielsen et al., 2003)	61/1250 (4.9%)	139/5959 (2.3%)	Adjusted OR: 1.73 (1.20 to 2.82)[h]	-	Very low	Retrospective, matched case-control	Very serious[i]	None	None	Serious[n]	None
Association between 33 to <36 weeks of gestational age (reference not reported) and RSV hospitalisation[a]											
1 (Boyce et al., 2000)	NR	NR	Adjusted IRR: 1.8 (1.6 to 2.1)[b]	-	Very low	Retrospective cohort	Very serious[c]	None	Serious[d]	None	None
Association between 35 to 36 weeks gestational age (vs ≥37 weeks) and RSV hospitalisation											
1 (Rietveld et al., 2006)	NR	NR	Adjusted OR: 1.6	-	Very low	Retrospective cohort	Very serious[f]	None	Serious[g]	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			(1.3 to 1.9)[e]								
Association between 35 to 36 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis											
1 (Paranjothy et al, 2013)	NR	NR	Adjusted HR: 1.89 (1.75 to 2.03)[j]	-	Low	Retrospective cohort	Very serious[k]	None	None	None	None
Association between 35 to 37 weeks of gestational age (vs ≥38) and bronchiolitis hospitalisation											
1 (Lanari et al, 2013)	41/767 (5.3%)	25/706 (3.5%)	Adjusted HR: 1.5 (0.9 to 2.5)[l]	-	Low	Longitudinal multicentre cohort study	Serious[m]	None	None	Serious[n]	None
Association between 35 to 37 weeks of gestational age (vs ≥40 weeks) and RSV hospitalisation											
1 (Nielsen et al., 2003)	119/1250 (9.5%)	393/5959 (6.6%)	Adjusted OR: 1.43 (1.10 to 1.97)[h]	-	Very low	Retrospective, matched case-control	Very serious[i]	None	None	Serious[n]	None
Association between <37 weeks gestational age (vs ≥37 weeks) and bronchiolitis hospitalisation											
1 (Grimwood et al., 2008)	32/141 (22.7%)	1178/11270 (10.5%)	Adjusted OR: 2.29 (1.48 to 3.56)[o]	p≤0.0005	Low	Retrospective cohort	Very serious[p]	None	None	None	None
Association between <37 weeks gestational age (vs ≥37 weeks) and RSV hospitalisation											
1 (Cilla et al., 2006)	NR	NR	Adjusted OR: 1.61 (1.07 to 2.42)[q]	p=0.022	Very low	Retrospective cohort	Very serious[r]	None	None	Serious [n]	None
1 (Kristensen et al., 2009)	49/313 (15.7%)	49/313 (15.7%)	Adjusted OR: 1.03 (0.65 to 1.64)[s]	-	Very low	Retrospective matched case-control	Very serious[t]	None	Very serious[q]	Very serious[n]	None
1 (Papenburg et al., 2012)	57/460 (12.4%)	16/141 (11.4%)	Adjusted OR: 1.29	-	Very low	Prospective cohort	None	None	Very serious[v]	Very serious[n]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			(0.68 to 2.43)[u]								
Association between <37 weeks (vs born at term) and bronchiolitis hospital admission											
1 (Murray et al., 2014)	NR	NR	Adjusted relative risk: 1.89 (1.77 to 2.02)[w]	-	Moderate	Prospective cohort	Serious[x]	None	None	None	None
Association between 37 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis											
1 (Paranjothy et al, 2013)	NR	NR	Adjusted HR: 1.59 (1.49 to 1.71)[j]	-	Low	Retrospective cohort	Very serious[k]	None	None	None	None
Association between 38 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis											
1 (Paranjothy et al, 2013)	NR	NR	Adjusted HR: 1.33 (1.26 to 1.40)[j]	-	Low	Retrospective cohort	Very serious[k]	None	None	None	None
Association between 39 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis											
1 (Paranjothy et al, 2013)	NR	NR	Adjusted HR: 1.16 (1.10 to 1.21)[j]	-	Very low	Retrospective cohort	Very serious[k]	None	None	Serious[n]	None
Association between 37 to 39 weeks of gestational age (vs ≥40 weeks) and RSV hospitalisation											
1 (Nielsen et al., 2003)	419/1250 (33.5%)	1890/5959 (31.7%)	Adjusted OR: 1.18 (1.00 to 1.40)[h]	-	Very low	Retrospective, matched case-control	Very serious[i]	None	None	Serious[n]	None
Association between gestational age per 1 week less and bronchiolitis hospitalisation											
1 (Pezzotti et al., 2009)	NR	NR	Adjusted IRR: 0.97 (0.88 to 1.07)[y]	p=0.58	Very low	Retrospective cohort	Very serious[z]	None	Seriousa[a]	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Association between prematurity (not defined) and bronchiolitis hospitalisation											
1 (Al-Shehri et al., 2005)	NR	NR	Adjusted OR: 3.44 (2.27 to 4.33)[ab]	-	Low	Prospective, matched case-control	Seriousa[c]	None	Serious[ad]	None	None
RISK OF RSV REHOSPITALISATION											
Association between 23 to 32 weeks of gestational age (vs 33 to 36 weeks) and RSV rehospitalisation											
1 (Joffe et al., 1999)	NR Number hospitalised for RSV/total 23 to 32 weeks gestation: 32/438 (7.3%)	NR Number hospitalised for RSV/total 33 to 36 weeks gestation: 23/1283 (1.8%)	Adjusted OR: 2.6 (1.4 to 5.1)[ae]	p= 0.003	Very low	Retrospective cohort	Very serious[af]		Very serious[ag]	None	None
Association between increasing gestational age and RSV rehospitalisation											
1 (Carbonell-estrany et al., 2000)	NR	NR	Adjusted OR: 0.85 (0.72 to 0.99)[ah]	p<0.047	Very low	Prospective cohort	Serious[ai]	None	Serious[aj]	Serious[n]	None
1 (Carbonell-estrany et al., 2001)	NR	NR	Adjusted OR: 0.87 (0.77 to 0.97)[ak]	p=0.019	Low	Prospective cohort	Serious[al]	None	Seriousa[m]	None	None
RISK OF SEVERE RSV DISEASE/BRONCHIOLITIS – BASED ON DISEASE SEVERITY SCORES											
Association between <36 weeks of gestational age (reference not reported) and severe RSV disease - severity score ≥3[an]											
1 (Bockova et al., 2002)	5/45 (11.1%)	58/831 (7.0%)	Adjusted OR: 1.8 (0.7 to 5.1)[ao]	-	Very low	Prospective cohort	Serious[ap]	None	Serious[aq]	Very serious[n]	None
Association between <36 weeks of gestational age (reference not reported) and respiratory distress - moderate or severe RDAI scoream											
1 (Chan et al.,1999)	NR	NR	Adjusted OR: 5.1	p=0.02	Very low	Retrospective cohort	Very serious[as]	None	None	Serious[n]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			(1.0 to 25.0)[ar]								
Association between <37 weeks gestational age (reference category not reported) and severe bronchiolitis (bronchiolitis clinical score ≥11)											
1 (Ricart et al., 2013)	21/82 (25.6%)	41/328 (12.5%)	Adjusted OR: 2.6 (1.3 to 5.1)[at]	p=0.005	Moderate	Prospective cohort	Serious[ap]	None	None	None	None
Association between <37 weeks gestational age (≥37 weeks) and severe RSV disease - disease severity score ≥2[au]											
1 (Papenburg et al., 2012)	NR	NR	Adjusted OR: 3.08 (1.63 to 5.83)av	-	Low	Prospective cohort	None	None	Very serious[aw]	None	None
RISK OF ICU ADMISSION											
Association between <32 weeks of gestational age (reference not reported) and ICU admission in non RSV bronchiolitis											
1 (Hervas et al., 2012)	NR	NR	Adjusted OR: 5.6 (1.89 to 16.59)[ax]	p<0.01	Low	Retrospective review	Very serious[ay]	None	None	None	None
Association between <32 weeks of gestational age (reference not reported) and ICU admission in RSV bronchiolitis											
1 (Hervas et al., 2012)	NR	NR	Adjusted OR: 4.92 (1.95 to 12.40)[ax]	p<0.001	Low	Retrospective review	Very serious[ay]	None	None	None	None
Association between birth before gestational age of 32 weeks (vs reference not reported) and intensive care requirement in RSV infection											
1 (Simon et al., 2007)	NR	NR	Adjusted OR: 2.80 (1.58 to 5.00)[az]	p=0.0001	Moderate	Prospective cohort	Serious[as]	None	None	None	None
Association between <32 weeks gestational age (vs reference not reported and ICU admission in RSV infection											
1 (Dotan et	NR	NR	Adjusted OR: 10.58	-	Low	Retrospective	Very	None	None	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
al., 2013)			(3.25 to 34.54)[aaa]			cohort	serious[aab]				
Association between born before gestational age of 32 weeks and intensive care requirement in RSV infection											
1 (Wilkesmann et al., 2007)	NR	NR	Adjusted OR: 2.80 (1.58 to 5.00)[aac]	p<0.001	Moderate	Prospective cohort	Serious[aad]	None	None	None	None
Association between <37 weeks gestational age (reference not reported) and PICU admission in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 1.63 (1.29 to 2.05)[aae]	p<0.0001	Low	Retrospective cohort	Very serious[aaf]	None	None	None	None
Association between prematurity <37 weeks gestation (vs term) and intensive care requirement in RSV infection											
1 (Simon et al., 2007)	NR	NR	Adjusted OR: 1.73 (1.08 to 2.72)[az]	p=0.0218	Low	Prospective cohort	Serious[aag]	None	None	Serious[n]	None
Association between prematurity (not defined) and intensive care requirement in RSV infection											
1 (Wilkesmann et al., 2007)	NR	NR	Adjusted OR: 1.73 (1.08 to 2.72)[aac]	p=0.022	Low	Prospective cohort	Serious[aad]	None	None	Serious[n]	None
1 (Zhang et al., 2014)	NR	NR	Adjusted OR: 2.46 (0.81 to 7.47)[aah]	p=0.113	Very low	Retrospective chart review	Very serious[aai]	None	None	Serious[n]	None
RISK OF OXYGEN REQUIREMENT											
Association between <37 weeks gestational age (reference not reported) and oxygen requirement in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 1.36 (1.17 to 1.59)[aae]	p<0.0001	Very low	Retrospective cohort	Very serious[aaf]	None	None	Serious[n]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Association between <37 weeks gestational age (vs ≥37 weeks) and oxygen supplementation in infants admitted for bronchiolitis											
1 (Semple et al., 2011)	54/241 (23%)	18/86 (21%)	Adjusted OR: 1.01 (0.94 to 1.08)[aaj]	p=0.843	Moderate	Prospective cohort	Serious[aak]	None	None	None	None
Association between gestational age <37 weeks (vs term) and need for supplemental oxygen											
1 (Kristensen et al., 2009)	NR	NR	Adjusted relative risk: 1.88 (1.16 to 3.04)[aal]	-	Very low	Retrospective matched case-control	Very serious[t]	None	Very serious[q]	Serious[n]	None
RISK OF MECHANICAL VENTILATION											
Association between <37 weeks gestational age (reference not reported) and intubation requirement in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 1.54 (1.02 to 2.33)[aae]	p=0.04	Very low	Retrospective cohort	Very serious[aaf]	None	None	Serious[n]	None
Association between <37 weeks gestational age (reference not reported) and respiratory failure - requiring intubation and positive pressure ventilation in RSV bronchiolitis											
1 (Chan et al., 2002)	4/7 (57.1%)	21/ 209 (10.0%)	Adjusted OR: 1.14 (1.02 to 2.07)[aam]	p=0.02	Very low	Retrospective cohort	Very serious[aan]	None	None	Serious[n]	None
Association between <37 weeks gestational age (vs ≥37 weeks) and mechanical ventilation in infants admitted for bronchiolitis											
1 (Semple et al., 2011)	27/51 (53%)	18/86 (21%)	Adjusted OR: 0.99 (0.89 to 1.11)[aaj]	p=0.868	Moderate	Prospective cohort	Serious[aak]	None	None	None	None
Association between <37 weeks gestational age (vs ≥37 weeks) and severe bronchiolitis - assisted ventilation or continuous positive airway pressure											
1 (Grimwood et al., 2008)	5/34 (14.7%)	27/107 (25.2%)	Adjusted OR: 0.58	-	Very low	Retrospective cohort	Very serious[aap]	None	None	Very serious[n]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			(0.19 to 1.78)[aao]								
RISK FOR HYPOXEMIA											
Association between <37 weeks gestational age (reference not reported) and hypoxemia (SpO_2 <90% in room air) in RSV bronchiolitis											
1 (Chan et al., 2002)	11/31 (35.5%)	14/185 (7.6%)	Adjusted OR: 1.17 (1.06 to 1.55)[aam]	p<0.01	Very low	Retrospective cohort	Very serious[aan]	None	None	Serious[n]	None
RISK OF RESPIRATORY FAILURE (not defined)											
Association between prematurity (not defined) and respiratory failure											
1 (Wilkesmann et al., 2007)	NR	NR	Adjusted OR: 4.73 (1.96 to 11.94)[aac]	p=0.001	Moderate	Prospective cohort	Serious[aad]	None	None	None	None

NR not reported, OR odds ratio, IRR incidence rate ratio, HR hazard ratio, P probability
a RSV hospitalisation defined as hospitalisation caused by RSV infection or bronchiolitis. Both of these outcomes based on ICD-9 codes - overall 6.3% of RSV associated hospitalisations were coded specifically for RSV and 93.7% were coded as bronchiolitis.
b Adjusted for BPD, CHD, number of siblings, presence of other conditions, male sex, white race, rural residence, maternal smoking and maternal education <12 years.
c Retrospective study design, outcome (RSV/bronchiolitis hospitalisation) based on reliability of coding systems. Gestational age missing for ~15% of children - if gestational age was missing from the birth certificate, this was estimated from birth weight with the use of the race and calendar-year specific distributions of gestational age in the population. Exclusion criteria not reported, reference not reported.
d Database used for this study contains information only on children enrolled in Medicaid therefore may not be generalizable.
e Adjusted for gender, birth weight, age, BPD, age.
f Retrospective study design, number of controls not reported and unclear whether controls were tested for RSV.
g Bronchiolitis or pneumonia were diagnosed in 93% whereas most of the remaining hospitalised children were diagnosed with upper respiratory tract infection.
h Adjusted for birthweight, number of older siblings, smoking in pregnancy, anti RSV titre.
I Retrospective study design, overlapping group intervals (eg: 33-35 weeks, 35-37 weeks), no indication that controls have been tested for RSV.
j Adjusted for maternal age, parity, Townsend score quintile for social deprivation, gender, major or minor congenital anomaly, multiple birth, breastfeeding, Apgar score at 5 min, neonatal admission to hospital and season of birth
k Retrospective study design, inclusion and exclusion criteria not reported
l Adjusted for gender and gestational age
m Bronchiolitis hospitalisation based on reliability of coding systems
n Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
o Adjusted for gender, ethnicity, multiple birth, mother smoking during pregnancy, month of birth and deprivation score.
p Retrospective study design, no indication that controls have been tested for RSV, exclusion criteria not reported, 66.5% of eligible participants (admitted during weekdays) were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregivers.

q Adjusted for haemodynamically unstable heart disease, maternal age, period of birth, birth weight and rural/urban residence.
r Retrospective study design, no indication that controls have been tested for RSV.
s Adjusted for underlying condition, type of heart disease and haemodynamic significance.
t Retrospective study design, inclusion based on reliability of coding systems.
u Adjusted for age <6 months, history or breast feeding, ≥3 children in the household, presence of comorbidity and viral coinfection.
v 34.5% of infants hospitalised for RSV were diagnosed with pneumonia, included children less than 3 years of age however mean age of cases and controls was 8 and 12.5 months.
w Adjusted for cystic fibrosis, congenital heart disease, chronic lung disease, immunodeficiency, nervous system congenital anomalies, down's syndrome, cerebral palsy
x Risk factor and bronchiolitis diagnoses based on reliability of coding systems
y Adjusted for age of mother, parity, years of education, birth country of mother, gender, calendar year, age, epidemic period, birth weight, apgar score, bronchopulmonary dysplasia and congenital heart disease.
z Retrospective study design, bronchiolitis hospitalisation (including bronchiolitis due to RSV and other or unknown etiologies) based on reliability of ICD-9 coding system, exclusion criteria not reported.
aa All infants premature (<36 weeks gestation).
ab Adjusted for congenital heart defects, chronic lung disease, atopic child, atopic father, atopic mother, atopic parents, breastfeeding, history of exposure to smoking, age.
ac Exclusion criteria not reported, prematurity not defined -unclear how this was determined.
ad Included children ≤5 years however mean age of cases and controls 7.6 and 8.8 months respectively.
ae Unclear what confounders were adjusted for.
af Retrospective study design, inclusion based on reliability of coding system.
ag All premature infants and also inclusion was based on the presence of ICD codes which included a broad range of conditions such as acute bronchitis and bronchiolitis, pneumonia, other diseases of lung.
ah Adjusted for gestational age, birth weight, family history of asthma, clinical risk index for babies, month of discharge, chronic lung disease and siblings at school age.
ai Identification of a causative pathogen was attempted in 89 (75.4%) of all hospital admissions; therefore not all subjects tested, increasing gestational age not defined
aj All premature infants <33 weeks.
ak Adjusted for gestational age, weight at birth, family history of asthma, CRIB index, age at entry RSV season, month of discharge, CLD, multiple births, heart disease, breast-feeding, smoke exposure, attendance at daycare and siblings at school age in the model.
al 10% of admissions not tested for RSV - because 10% of admissions were not tested for RSV, the overall hospitalisation rate for RSV illness was calculated by applying the RSV positive rate in tested patients (63%) to all respiratory hospitalisations (207) and dividing it by the total number of study patients (999), 54/207 lost to follow up (26%), increasing gestational age not defined
am All premature infants.
an Severity based on a previously published severity index (McConnochie et al., 1990), 1 point each was assigned for apnea, pH <7.35, PC02 >45, oxygen saturation <87% and length of stay >5 days, 2 points were assigned for mechanical ventilation. Severity index for each subject was the sum of the points, the maximum score is 7.
ao Adjusted for age, gender, underlying conditions (CHD, CLD of prematurity, reactive airway disease, 2 or more previous hospitalisations for respiratory infection, history of mechanical ventilation, or immunodeficiency).
ap Reference not reported.
aq Included children with mild respiratory symptoms or apnea.
ar Adjusted for <3 months of age, family history of asthma and underlying illness.
as Retrospective study design, exclusion criteria not reported, reference category not reported.
at Adjusted for BPD, hemodynamically significant CHD, temperature >38 degrees, age at admission, human rhinovirus (HRV), human respiratory syncytial virus (HRSV).
au Patients given 1 point for each of the following: admission to PICU, hospitalised for >5 days, require supplemental oxygen therapy (fraction of inhaled oxygen ≥0.3)
av Adjusted for age <6 months and viral coinfection
aw 34.5% of infants hospitalised for RSV were diagnosed with pneumonia, included children less than 3 years however mean age of cases and controls was 8 and 12.5 months.
ax Adjusted for nebulized epinephrine, nebulized salbutamol, year, congenital heart disease, atelectasis/condensation, age, gender.
ay Retrospective study design, diagnosis of bronchiolitis based on reliability of coding systems, reference not reported.

az Adjusted for CLD, CHD
aaa Adjusted for young age, male gender and twin birth
aab Retrospective study design, data sources not reported
aac Adjusted for CLDplus, congenital heart disease and neuromuscular impairment
aad Exclusion criteria not reported, prematurity not defined
aae Adjusted for RSV, weight, age at hospitalisation, gender, race, congenital heart defects, chronic lung disease, trisomy 21, congenital syndromes.
aaf Retrospective study design, inclusion of subjects based on reliability of ICD coding system , reference not reported.
aag Exclusion criteria not reported
aah Adjusted for sex, age and CHD
aai Retrospective, exclusion criteria not reported
aaj Adjusted for birth weight, sex, family history of atopy, index of deprivations, corrected age on admission, weight on admission and household tobacco smoker.
aak Infants both admitted and discharged on Saturdays and Sundays were not recruited and some infants admitted on weekdays for less than 24 hours were missed.
aal Adjusted for age, cardiac decompensation.
aam Unclear what factors were adjusted for.
aan Retrospective study design, very small number of cases, exclusion criteria not reported, unclear what confounders were adjusted for, reference not reported.
aao Adjusted for year, gender, month of birth, age at admission, mother smoking during pregnancy, ethnicity, number of other children living in the house.
aap Retrospective study design, exclusion criteria not reported, 66.5% of eligible participants (admitted during weekdays) were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregiver

3.2.3.1.3 Evidence statements

Twenty six studies evaluated the odds of developing various outcomes including bronchiolitis/ respiratory syncytial virus hospitalisation, RSVrehospitalisation, severe bronchiolitis/respiratory syncytial virus disease defined by a disease severity score, ICU admission, need for mechanical ventilation/oxygen and hypoxemia in premature children.

Risk of bronchiolitis/ respiratory syncytial virus hospitalisation

Twelve studies evaluated the odds of developing bronchiolitis/ respiratory syncytial virus hospitalisation in premature infants.

≤28 weeks gestational age (vs reference not reported)

One study (sample size not reported) found a significant association between ≤28 weeks of gestational age (reference not reported) and respiratory syncytial virus hospitalisation. The quality of the evidence was very low.

≤28 weeks gestational age (vs ≥37 weeks)

One study including 2649 cases reported a significant association between ≤28 weeks of gestational age (vs ≥37 weeks) and respiratory syncytial virus hospitalisation. The same study also found a significant association between 29 to 32 weeks gestational age (vs ≥37 weeks) and respiratory syncytial virus hospitalisation. The quality of the evidence was very low.

***29 to 33 weeks gestational age (vs reference not reported*)**

One study (sample size not reported) found a significant association between 29 to 33 weeks gestational age (vs reference not reported) and respiratory syncytial virus hospitalisation. The quality of the evidence was very low.

≤32 weeks gestational age (vs ≥40 weeks)

One study including 1252 cases reported a significant association between ≤32 weeks of gestational age (vs ≥40 weeks) and respiratory syncytial virus hospitalisation. The quality of the evidence was low.

<33 weeks of gestational age (vs 40 to 42 weeks)

One study (sample size not reported) found a significant association between <33 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis. The quality of the evidence was low.

33 to 34 weeks of gestational age (vs 40 to 42 weeks)

One study (sample size not reported) found a significant association between 33 to 34 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis. The quality of the evidence was low.

33 to 34 weeks of gestational age (vs ≥38 weeks)

One study including 2210 children reported a significant association between 33 to 34 weeks of gestational age (vs ≥38 weeks) and bronchiolitis hospitalisation. The quality of the evidence was moderate.

33 to 34 weeks gestational age (vs ≥37 weeks)

One study including 2649 cases reported a significant association between 33 to 34 weeks gestational age (vs ≥37 weeks) and respiratory syncytial virus hospitalisation. The quality of the evidence was very low.

33 to 35 weeks gestational age (vs ≥40 weeks)

One study including 1252 cases reported a significant association between 33 to 35 weeks gestational age (vs ≥40 weeks) and respiratory syncytial virus hospitalisation. The quality of the evidence was very low.

33 to <36 weeks gestational age (reference not reported)

One study (sample size not reported) found a significant association between 33 to <36 weeks gestational age (vs reference not reported) and respiratory syncytial virus hospitalisation. The quality of the evidence was very low.

35 to 36 weeks gestational age (vs ≥37 weeks)

One study including 2649 cases reported a significant association between 35 to 36 weeks gestational age (vs ≥37 weeks) and respiratory syncytial virus hospitalisation. The quality of the evidence was very low.

35 to 36 weeks gestational age (vs 40 to 42 weeks)

One study (sample size not reported) found a significant association between 35 to 36 weeks gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis. The quality of the evidence was low.

35 to 37 weeks gestational age (vs ≥38 weeks)

One study including 2210 children did not find a significant association between 35 to 37 weeks of gestational age (vs ≥38 weeks) and bronchiolitis hospitalisation. The quality of the evidence was low.

35 to 37 weeks gestational age (vs ≥40 weeks)

One study including 1252 cases reported a significant association between 35 to 37 weeks gestational age (vs ≥40 weeks) and respiratory syncytial virus hospitalisation. The quality of the evidence was very low.

≤37 weeks (vs ≥37 weeks)

One study including 11304 children reported a significant association between ≤37 weeks gestational age (vs ≥37 weeks) and bronchiolitis hospitalisation. The evidence was of low quality. Three studies including 15570 children evaluated the association between <37 weeks gestational age (vs ≥37 weeks) and respiratory syncytial virus hospitalisation. One study reported a statistically significant association between <37 weeks gestational age (vs ≥37 weeks) and respiratory syncytial virus hospitalisation. The evidence was of very low quality. The other two studies did not find a statistically significant association between <37 weeks gestational age (vs ≥37 weeks) and respiratory syncytial virus hospitalisation. The quality of the evidence was very low.

<37 weeks (vs born at term)

One study including 7189 cases reported a significant association between <37 weeks (vs born at term) and hospital admission. The quality of the evidence was moderate.

37 weeks gestational age (vs 40 to 42 weeks)

One study (sample size not reported) reported a significant association between 37 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis. The quality of the evidence was low.

38 weeks of gestational age (vs 40 to 42 weeks)

One study (sample size not reported) reported a significant association between 38 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis. The quality of the evidence was low.

39 weeks gestational age (vs 40 to 42 weeks)

One study (sample size not reported) reported a significant association between 39 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis. The quality of the evidence was very low.

37 to 39 weeks of gestational age (vs ≥40 weeks)

One study including 1252 cases did not find a significant association between 37 to 39 weeks of gestational age (vs ≥40 weeks) and respiratory syncytial virus hospitalisation. The quality of the evidence was very low.

Gestational age per 1 week less

One study including 2407 children did not find a significant association between gestational age per 1 week less and bronchiolitis hospitalisation. The quality of the evidence was very low.

Prematurity (not defined)

One study including 166 children reported a significant association between prematurity (not defined) and bronchiolitis hospitalisation. The quality of the evidence was low.

Risk of respiratory syncytial virus rehospitalisation

23 to 32 weeks gestational age (vs 33 to 36 weeks)

One study including 1721 children reported a significant association between 23 to 32 weeks of gestational age (vs 33 to 36 weeks) and respiratory syncytial virus rehospitalisation. The quality of the evidence was very low.

Increasing gestational age

Two studies including 1593 children reported a significant association between increasing gestational age and respiratory syncytial virus rehospitalisation. The quality of the evidence was very low.

Risk of severe respiratory syncytial virus disease/bronchiolitis – based on disease severity scores

Four studies evaluated the odds of developing severe respiratory syncytial virus disease/bronchiolitis in premature infants.

<36 weeks of gestational age (reference not reported)

One study including 876 children did not find a significant association between <36 weeks of gestational age (reference not reported) and severe respiratory syncytial virus disease, defined by a disease severity score ≥3. The quality of the evidence was very low.

<36 weeks of gestational age (reference not reported)

One study including 185 children did not find a significant association between <36 weeks of gestational age (reference not reported) and respiratory distress defined by a moderate or severe respiratory distress assessment instrument (RDAI) score. The quality of the evidence was very low.

<37 weeks gestational age (reference category not reported)

One study including 410 children found a significant association between <37 weeks gestational age (reference category not reported) and severe bronchiolitis defined by a bronchiolitis clinical score ≥11. The quality of the evidence was moderate.

<37 weeks gestational age (vs ≥37 weeks)

One study including 460 children found a significant association between <37 weeks gestational age (vs ≥37 weeks) and severe respiratory syncytial virus disease defined by a disease severity score ≥2. The quality of the evidence was low.

Risk of ICU admission

Six studies evaluated the odds of developing ICU admission in premature children.

<32 weeks of gestational age (reference not reported)

One study including 2384 children reported a significant association between <32 weeks of gestational age (reference not reported) and ICU admission in both respiratory syncytial virus and non- respiratory syncytial virus bronchiolitis. The evidence was of low quality. Another three studies only one of which reported a sample size of 1541 children found a statistically significant association between birth before 32 weeks gestational age (vs reference not reported) and risk of ICU admission in respiratory syncytial virus infection. The quality of the evidence was moderate to low.

<37 weeks gestational age (reference not reported)

One study including 4285 children reported a significant association between <37 weeks gestational age (reference not reported) and PICU admission. The quality of the evidence was low.

Prematurity <37 weeks (vs term)

One study (sample size not reported) found a significant association between prematurity <37 weeks (vs term) and ICU admission in respiratory syncytial virus infection. The quality of the evidence was low.

Prematurity (not defined)

One study including 1541 children reported a statistically significant association between prematurity (not defined) and intensive care requirement in respiratory syncytial virus infection. The evidence was of low quality. One other study including 959 children did not find

a statistically significant association between prematurity (not defined) and intensive care requirement in respiratory syncytial virus infection. The quality of the evidence was very low.

Risk of oxygen requirement/supplementation

Three studies evaluated the odds of requiring oxygen supplementation in premature infants.

<37 weeks gestational age (reference not reported)

One study including 4285 children reported a significant association between <37 weeks gestational age (reference not reported) and oxygen requirement in respiratory syncytial virus /non respiratory syncytial virus bronchiolitis. The quality of the evidence was very low.

<37 weeks gestational age (vs ≥37 weeks)

One study including 626 children reported a significant association between <37 weeks gestational age (vs ≥37 weeks) and oxygen supplementation but one other study including 292 children did not. The quality of the evidence was very low and moderate respectively.

Risk of mechanical ventilation

<37 weeks gestational age (reference not reported)

One study including 4285 children reported a significant association between <37 weeks gestational age (reference not reported) and intubation requirement. The evidence was of very low quality. One other study including 216 children reported a statistically significant association between <37 weeks gestational age (reference not reported) and respiratory failure defined as requiring intubation and positive pressure ventilation. The quality of the evidence was very low.

<37 weeks gestational age (vs ≥37 weeks gestational age)

One study including 137 children did not find a significant association between <37 weeks gestational age (vs ≥37 weeks gestational age) and mechanical ventilation in infants admitted for bronchiolitis. The evidence was of moderate quality. One other study including 11304 children did not find a statistically significant association between <37 weeks gestational age (vs ≥37 weeks gestational age) and severe bronchiolitis defined as assisted ventilation or continuous positive airway pressure. The quality of the evidence was very low.

Risk of hypoxemia

<37 weeks gestational age (reference not reported)

One study including 216 children reported a significant association between <37 weeks gestational age (reference not reported) and hypoxemia (SpO_2 less than 90% in room air) in respiratory syncytial virus bronchiolitis. The quality of the evidence was very low.

Risk of respiratory failure (not defined)

Prematurity (not defined) vs reference not reported

One study including 1541 children reported a significant association between prematurity (not defined) and respiratory failure. The quality of the evidence was moderate.

3.2.3.1.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5.

3.2.3.1.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7

3.2.3.2 Bronchopulmonary dysplasia /Chronic lung disease of prematurity

3.2.3.2.1 Description of included studies

Four observational studies were identified for this bronchopulmonary dysplasia. (Boyce et al., 2000; Kristensen et al., 2012; Pezzotti et al., 2009; Ricart et al., 2013). Three were retrospective cohort studies (Boyce et al., 2000; Kristensen et al., 2012; Pezzotti et al., 2009) and one was a prospective cohort study (Ricart et al., 2013). One study was undertaken in Spain (Ricart et al., 2013), one in Denmark (Kristensen et al., 2012), one in Italy (Pezzotti et al., 2009) and one in the USA (Boyce et al., 2000). Sample sizes was reported in three studies (Kristensen et al., 2012; Pezzotti et al., 2009; Ricart et al., 2013) and ranged from 410 to 391983. The age of the subjects varied from less than 12 months in one study (Ricart et al., 2013), less than 24 months in another study (Kristensen et al., 2012) and less than 3 years in another study (Boyce et al., 2000). The study which included children less than 3 years (Boyce et al., 2000) however restricted the risk factor analysis to the first year of life. The fourth study also included children less than 3 years of age however the risk factor analysis was restricted to children in the first 18 months of life (Pezzotti et al., 2009).

All four studies reported on bronchopulmonary dysplasia identified in various ways such as the presence of International Classification of Disease codes or the definition adopted by Jobe and Bancalari – criteria not reported in the study itself. The studies reported different outcomes including RESPIRATORY SYNCYTIAL VIRUS/bronchiolitis hospitalisation in three studies (Boyce et al., 2000; Kristensen et al., 2012; Pezzotti et al., 2009) and severe bronchiolitis defined by a bronchiolitis clinical score in one study (Ricart et al., 2013).

Diagnosis of bronchiolitis/respiratory syncytial virus included a clinical severity score in one study (Ricart et al., 2013) and International Classification of Disease codes in the remaining three studies (Boyce et al., 2000; Kristensen et al., 2012; Pezzotti et al., 2009).

The settings of the studies varied including hospitals in two studies (Boyce et al., 2000; Pezzotti et al., 2009) and a paediatric ward or PICU in one study (Ricart et al., 2013). The remaining study was a national population based study from Denmark (Kristensen et al., 2012).

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on each individual study can be found in the evidence tables.

Six observational studies were identified for this chronic lung disease (Al-Shehri et al., 2005; Carbonell-Estrany et al., 2000; Garcia et al., 2010; Liese et al., 2003; Murray et al., 2014; Wilkesmann et al., 2007). Two were retrospective cohort studies (Garcia et al., 2010; Liese et al., 2003), three were prospective cohort studies (Carbonell-Estrany et al., 2000; Murray et al., 2014; Wilkesmann et al., 2007) and one was a prospective matched case-control study (Al-Shehri et al., 2005). One study was undertaken in Saudi Arabia (Al-Shehri et al., 2005), one in USA (Garcia et al., 2010), two in Germany (Liese et al., 2003; Wilkesmann et al., 2007) one in Spain (Carbonell-Estrany et al., 2000) and one in the UK (Murray et al., 2014). Sample sizes ranged from 166 to 4589. The age of the subjects varied including premature infants in two studies (Liese et al., 2003; Carbonell-Estrany et al., 2000), infants less than 24 months of age in one study (Garcia et al., 2010) and infants less than 1 year of age in one study (Murray et al., 2014). The fourth study (Al-Shehri et al., 2005) enrolled children up to 5 years of age, however the mean age of the cases and controls was 7.6 and 8.8 months

respectively. The remaining study (Wilkesmann et al., 2007) included children irrespective of age, however the median age at diagnosis was 430 days for the neuromuscular impairment group and 145 days for the controls.

All six studies reported on chronic lung disease identified in various ways such as the review of medical records or definitions such as infants who still required oxygen therapy at 36 weeks postconceptional age. The studies reported different outcomes such oxygen and PICU requirement in one study (Garcia et al., 2010), respiratory syncytial virus rehospitalisation in two studies, (Carbonell-Estrany et al., 2000; Liese et al., 2003) respiratory failure in one study (Wilkesmann et al., 2007) and bronchiolitis hospitalisation in two studies (Al-Shehri et al., 2005; Murray et al., 2014).

Diagnosis of bronchiolitis/ respiratory syncytial virus varied from antigen tests in two studies (Carbonell-Estrany et al., 2000; Liese et al., 2003; Wilkesmann et al., 2007), a clinical severity score and nasopharyngeal aspirate test in one study (Al-Shehri et al., 2005) and International Classification of Disease codes in two studies (Garcia et al., 2010; Murray et al., 2014).

The settings of the studies varied including neonatal units in two studies (Carbonell-Estrany et al., 2000; Liese et al., 2003), hospitals in two studies (Murray et al., 2014; Wilkesmann et al., 2007) a children's medical centre in one study (Garcia et al., 2010) and a paediatric emergency room and paediatric ward in another study (Al-Shehri et al., 2005).

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on each individual study can be found in the evidence tables.

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

Two GRADE profiles have been produced for this review:

- Table 5: GRADE profile for the association between BPD and risk of developing severe bronchiolitis
- Table 6: GRADE profile for the association between chronic lung disease and risk of developing severe bronchiolitis

Table 5: GRADE profile for the association between BPD and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Bronchopulmonary dysplasia											
RISK OF RSV/BRONCHIOLITIS HOSPITALISATION											
Association between bronchopulmonary dysplasia (not defined) and RSV hospitalisationa											
1 (Boyce et al., 2000)	NR	NR	Adjusted IRR: 10.7 (8.4 to 13.6)[b]	-	Very low	Retrospective cohort	Very serious[c]	None	Serious[d]	None	None
1 (Kristensen et al., 2012)	NR Number with RSV hospitalisation/Total number with Bronchopulmonary dysplasia: 89/504 (17.7%)	NR	Adjusted IRR: 2.58 (2.06 to 3.24)e	p<0.001	Low	Retrospective cohort	Very serious[f]	None	None	None	None
Association between bronchopulmonary dysplasia (not defined) and hospitalisation for bronchiolitis											
1 (Pezzotti et al., 2009)	NR Number hospitalised/Total with Bronchopulmonary dysplasia: 6/61 (9.8%)	NR Number hospitalised/Total without Bronchopulmonary dysplasia: 131/2346 (5.6%)	Adjusted IRR: 1.70 (0.68 to 4.28)[g]	p=0.26	Very low	Retrospective cohort	Very serious[h]	None	Serious[i]	Very serious[j]	None
RISK OF SEVERE BRONCHIOLITIS DEFINED BY A BRONCHIOLITIS CLINICAL SCORE											
Association between bronchopulmonary dysplasia (defined by Jobe and Bancalari – criteria not reported) and severe bronchiolitis - bronchiolitis clinical score ≥11											
1 (Ricart et al., 2013)	6/82 (7.3%)	4/328 (1.2%)	Adjusted OR: 7.2 (1.2 to 43.3)[k]	p=0.031	Moderate	Prospective cohort	None	None	None	Serious[j]	None

NR not reported, p-value, IRR incidence rate ratio, OR odds ratio
a Boyce: RSV hospitalisation defined as hospitalisation caused by RSV infection or bronchiolitis. Both of these outcomes based on ICD-9 codes - overall 6.3% of RSV associated hospitalisations were coded specifically for RSV and 93.7% were coded as bronchiolitis.
b Adjusted for congenital heart disease, gestational age, other conditions, number of siblings, sex, race, rural residence, maternal smoking and maternal education <12 years.*
** (other conditions identified included asthma, previous respiratory hospitalisation, cystic fibrosis, cancer, human immunodeficiency virus infection, immunodeficiency, use of chronic oral steroids, chronic renal disease, diabetes, congenital anomalies of the respiratory system, tracheoesophageal fistula, esophageal atresia and stenosis, neonatal respiratory distress syndrome and other respiratory conditions of the fetus and newborn).*

c Retrospective study design, both risk factor (BPD) and outcome (RSV/bronchiolitis hospitalisation) based on reliability of coding systems, gestational age missing for ~15% of children (hence estimated from birth weight with the use of the race and calendar-year specific distributions of gestational age in the population), exclusion criteria not reported.
d Database used for this study contains information only on children enrolled in Medicaid therefore may not be generalizable.
e Unclear what confounders were adjusted for.
f Retrospective study design, both presence of risk factor (BPD) and outcome (RSV hospitalisation) based on reliability of coding systems, number of cases and controls not explicitly reported, all variables were entered into 1 final multivariable model with no variable selection procedures.
g Adjusted for age of mother, parity, years of education, birth country of mother, gender, calendar year, age, epidemic period, birth weight, gestational age, apgar score and CHD.
h Retrospective study design, both bronchopulmonary-dysplasia and bronchiolitis hospitalisation (including bronchiolitis due to RSV and other or unknown etiologies) based on reliability of ICD-9 coding system, exclusion criteria not reported.
I All infants premature (<36 weeks gestation).
j Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
k Adjusted for hemodynamically significant congenital heart disease, gestational age <37 weeks, temperature >38 degrees, age at admission, human rhinovirus (HRV) and human respiratory syncytial virus (HRSV).

Table 6: GRADE profile for the association between chronic lung disease and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Chronic lung disease											
RISK OF BRONCHIOLITIS HOSPITALISATION											
Association between chronic lung diseases (not defined) and bronchiolitis hospitalisation											
1 (Al-Shehri et al., 2005)	NR	NR	Adjusted OR: 3.12 (2.19 to 3.78)[a]	-	Low	Prospective, matched case-control	Serious[b]	None	Serious[c]	None	None
1 (Murray et al., 2014)	NR	NR	Adjusted relative risk: 1.61 (1.42 to 1.82)[d]	-	Moderate	Prospective cohort	Serious[e]	None	None	None	None
RISK OF RSV REHOSPITALISATION											
Association between chronic lung disease (oxygen requirement at 36 weeks postconceptional age) and RSV rehospitalisation in premature infants ≤32 weeks gestation											
1 (Carbonell-Estrany et al., 2000)	8/53 (15%)	27/509 (5.3%)	Adjusted OR: 3.1 (1.22 to 7.91)[f]	p<0.016	Very low	Prospective cohort study	Serious[g]	None	Serious[h]	Serious[i]	None
Association between chronic lung disease (oxygen requirement beyond 36 weeks post-conceptional age) and RSV rehospitalisation in premature infants ≤35 weeks gestation											
1 (Liese et al., 2003)	8/37 (21.6%)	45/680 (6.6%)	Adjusted OR: 3.99 (1.4 to 11.2)[j]	p=0.009	Very low	Retrospective cohort	Very serious[k]	None	Very serious[l]	None	None
RISK OF OXYGEN REQUIREMENT											
Association between chronic lung disease (not defined) and oxygen requirement in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 3.27 (2.14 to	p<0.0001	Low	Retrospective cohort	Very serious[n]	None	None	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			5.00)[m]								
RISK OF PICU REQUIREMENT											
Association between chronic lung disease (not defined) and PICU requirement in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 1.80 (1.12 to 2.89)[m]	p=0.01	Very low	Retrospective cohort	Very serious[n]	None	None	Serious[i]	None
RISK OF RESPIRATORY FAILURE											
Association between CLDplus (chronic lung disease of prematurity and treatment within the last 6 months before diagnosis of the RSV infection) and respiratory failure											
1 (Wilkesmann et al., 2007)	NR	NR	Adjusted OR: 5.42 (2.00 to 14.17)[o]	p=0.0008	Moderate	Prospective cohort	Serious[p]	None	None	None	None

NR not reported, p-value, OR odds ratio
a Adjusted for prematurity, congenital heart defects, atopic child, atopic father, atopic mother, atopic parents, breastfeeding, history of exposure to smoking, age
b Exclusion criteria not reported, unclear how chronic lung disease was determined (definition not reported)
c Included children less than or equal to 5 years of age
d Adjusted for premature birth, cystic fibrosis, congenital heart disease, immunodeficiency, nervous system congenital anomalies, down's syndrome, cerebral palsy
e Risk factor and bronchiolitis diagnoses based on reliability of coding systems
f Adjusted for gestational age, birth weight, family history of asthma, clinical risk index for babies, month of discharge, and siblings at school age
g Identification of a causative pathogen was attempted in 89 (75.4%) of all hospital admissions; therefore not all subjects tested
h All premature infants <33 weeks
I Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
j Adjusted for gender, birth weight, gestational age, mechanical ventilation, cardiac abnormalities, neurological abnormalities, multiple birth, month of discharge, breast feeding, number of siblings, siblings in day care group, family history of allergies
k Retrospective study design, data collection largely based on questionnaires sent to parents therefore subject to recall bias, unclear whether controls were tested for RSV, among the 24 infants with probable RSV-RH, 15 were not tested for RSV infection.
l All preterm infants, also children were classified as having a probable rehospitalisation due to RSV infection, if they had been hospitalised between October and May with such clinical diagnoses typical for RSV infection as acute bronchitis, bronchiolitis, obstructive bronchitis, pneumonia or apnea.
m Adjusted for RSV, weight, age at hospitalisation, gender, race, prematurity, congenital heart defects, trisomy 21, congenital syndromes
n Retrospective study design, inclusion of subjects based on reliability of ICD coding system
o Adjusted for prematurity, congenital heart disease, neuromuscular impairment and nosocomial infection
p Exclusion criteria not reported

3.2.3.2.2 Evidence statements

Four studies evaluated the odds of developing various outcomes including RSV/bronchiolitis hospitalisation, and severe bronchiolitis defined by a bronchiolitis clinical score in infants with bronchopulmonary dysplasia.

Risk of bronchiolitis/RSV hospitalisation

Two studies, one of which reported the study's sample size of several thousand children found a significant association between bronchopulmonary dysplasia and RSV hospitalisation. The quality of the evidence was low to very low. Another study including 2407 children did not find a significant association between bronchopulmonary dysplasia and bronchiolitis hospitalisation. The quality of the evidence was very low.

Risk of bronchiolitis clinical score ≥11

One study including 410 children found a significant association between bronchopulmonary dysplasia and severe bronchiolitis defined by a bronchiolitis clinical score ≥11. The quality of the evidence was moderate.

Six studies evaluated the odds of developing various outcomes including bronchiolitis hospitalisation, RSV rehospitalisation, oxygen requirement and PICU requirement in infants with chronic lung disease.

Risk of bronchiolitis hospitalisation

Two studies including 7355 children reported a significant association between chronic lung disease (not defined) and bronchiolitis hospitalisation. The quality of the evidence was moderate to low.

Risk of RSV rehospitalisation

Two studies including 1311 children reported a significant association between chronic lung disease (defined as oxygen requirement at or beyond 36 weeks postconceptional age) and RSV rehospitalisation in premature infants. The quality of the evidence was very low.

Risk of oxygen/PICU requirement

One study including 4285 children found a significant association between chronic lung disease (not defined) and oxygen requirement as well as chronic lung disease and PICU requirement. The quality of the evidence was low and very low respectively.

Risk of respiratory failure

The remaining study including 1541 children found a significant association between CLDplus (chronic lung disease of prematurity and treatment within the last 6 months before diagnosis of RSV infection) and respiratory failure. The quality of the evidence was moderate.

3.2.3.2.3 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5.

3.2.3.2.4 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7.

3.2.3.3 Congenital heart disease

3.2.3.3.1 Description of included studies

Thirteen observational studies were identified for this review (Al-Shehri et al., 2005; Boyce et al., 2000; Cilla et al., 2006; Garcia et al., 2010; Hervas et al., 2012; Kaneko et al., 2001; Kristensen et al., 2012; Murray et al., 2014; Pezzotti et al., 2009; Ricart et al., 2013; Simon et al., 2007; Wilkesmann et al., 2007; Zhang et al., 2014).

Five were retrospective cohort studies (Cilla et al., 2006; Boyce et al., 2000; Garcia et al., 2010; Kristensen et al., 2012; Pezzotti et al., 2009), four were prospective cohort studies (Murray et al., 2014; Ricart et al., 2013; Simon et al., 2007; Wilkesmann et al., 2007) one was a prospective matched case-control study (Al-Shehri et al., 2005) and three were retrospective chart reviews (Hervas et al., 2012; Kaneko et al., 2001; Zhang et al., 2014). Three studies were undertaken in Spain (Cilla et al., 2006; Hervas et al., 2012; Ricart et al., 2013), two in USA (Boyce et al., 2000; Garcia et al., 2010), one in Denmark (Kristensen et al., 2012), one in Italy (Pezzotti et al., 2009), one in Japan (Kaneko et al., 2001), two in Germany (Simon et al., 2007; Wilkesmann et al., 2007) one in Saudi Arabia (Al-Shehri et al., 2005) one in China (Zhang et al., 2014) and one in the UK (Murray et al., 2014). Sample sizes ranged from 157 to 391983.

The age of the subjects varied including infants less than twelve months of age in two studies (Murray et al., 2014; Ricart et al., 2013) and infants less than 24 months of age in four studies (Cilla et al., 2006; Kristensen et al., 2012; Garcia et al., 2010; Hervas et al., 2012). One study included children less than 3 years of age however the risk factor analysis was restricted to children in the first 18 months of life (Pezzotti et al., 2009). Another study (Boyce et al., 2000) also included children less than 3 years of age, however the risk factor analysis was restricted to the first year of life. One study (Al-Shehri et al., 2005) enrolled children up to 5 years of age, however the mean age of the cases and controls was 7.6 and 8.8 months respectively. One study included children younger than 4 years, with the mean age of each of the study groups ranging from 1.3 to 21.3 months (Kaneko et al., 2001). One study included children of which the majority was aged <2 years (Zhang et al., 2014). One study (Simon et al., 2007) included children irrespective of age, however the median age (range) of infants in the study was 159 (64 to 340) days and 142 (75 to 288) days for terms and preterms respectively. The remaining study (Wilkesmann et al., 2007) included children irrespective of age, however the median age at diagnosis was 430 days for the neuromuscular impairment group and 145 days for the controls.

Eleven studies (Al-Shehri et al., 2005; Pezzotti et al., 2009; Murray et al., 2014; Kristensen et al., 2012; Boyce et al., 2000; Garcia et al., 2010; Hervas et al., 2012; Kaneko et al., 2001; Simon et al., 2007; Wilkesmann et al., 2007; Zhang et al., 2014) reported on congenital heart disease most commonly identified from medical records. One study reported on hemodynamically unstable heart disease (Cilla et al., 2006) and one other reported on hemodynamically significant congenital heart disease (Ricart et al., 2013). The studies reported different outcomes including RSV /bronchiolitis hospitalisation in six studies (Murray et al., 2014; Kristensen et al., 2012; Boyce et al., 2000; Cilla et al., 2006; Al-Shehri et al., 2005; Pezzotti et al., 2009) and ICU admission in five studies (Garcia et al., 2010; Hervas 2012; Simon et al., 2007; Wilkesmann et al., 2007; Zhang et al., 2014). One of the studies which looked at ICU admission also examined oxygen requirement (Garcia et al., 2010). One study looked at severe RSV-LRTI defined as requiring oxygen supplementation or mechanical ventilation (Kaneko et al., 2001) and one study looked at severe bronchiolitis defined by a bronchiolitis clinical score (Ricart et al., 2013).

Diagnosis of bronchiolitis/RSV varied from a clinical severity score in two studies (Al-Shehri et al., 2005; Ricart et al., 2013), International Classification of Disease codes in five studies (Boyce et al., 2000; Kristensen et al., 2012; Garcia et al., 2010; Murray et al., 2014; Pezzotti et al., 2009) and/or nasopharyngeal aspirates or immunoassay tests in six studies (Al-Shehri

et al., 2005; Cilla et al., 2006; Hervas et al., 2012; Kaneko et al., 2001; Wilkesmann et al., 2007; Zhang et al., 2014).

Nine studies were based in a hospital setting (Boyce et al., 2000; Cilla et al., 2006; Kaneko et al., 2001; Hervas et al., 2012; Murray et al., 2014; Pezzotti et al., 2009; Simon et al., 2007; Wilkesmann et al., 2007; Zhang et al., 2014), one study specified a paediatric ward or PICU (Ricart et al., 2013), one study a children's medical centre (Garcia et al., 2010) and one study a pediatric emergency room or pediatric ward (Al-Shehri et al., 2005). The remaining study was a national population based study (Kristensen et al., 2012).

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on each individual study can be found in the evidence tables.

3.2.3.3.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 7: GRADE profile for the association between congenital heart disease and risk of developing severe bronchiolitis

Table 7: GRADE profile for the association between congenital heart disease and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Congenital heart disease											
RISK OF BRONCHIOLITIS/RSV HOSPITALISATION											
Association between congenital heart defects and bronchiolitis hospitalisation											
1 (Al-Shehri et al., 2005)	NR	NR	Adjusted OR: 1.11 (0.85 to 1.95)[a]	-	Very low	Prospective, matched case-control	Seriousb	None	Seriousc	Serious [d]	None
Association between congenital heart disease and bronchiolitis hospitalisation											
1 (Pezzotti et al., 2009)	NR Number hospitalised/Total with congenital heart disease 3/34 (8.8%)	NR Number hospitalised/Total without congenital heart disease 134/2373 (5.6%)	Adjusted IRR: 1.64 (0.52 to 5.19)e	P=0.40	Very low	Retrospective cohort	Very serious[f]	None	Serious[g]	Very serious[d]	None
Association between congenital heart disease and RSV hospitalisationh											
1 (Kristensen et al., 2012)	NR Number with RSV hospitalisation/total number with risk factor: 292/2720 (10.7%)	NR	Adjusted IRR: 1.70 (1.45 to 1.99)[i]	p<0.001	Low	Retrospective cohort	Very serious[i]	None	None	None	None
1 (Boyce et al., 2000)	NR	NR	Adjusted IRR: 2.8 (2.3 to 3.3)k	-	Very low	Retrospective cohort	Very serious[l]	None	Seriousm	None	None
Association between haemodynamically unstable heart disease and RSV hospitalisation											
1 (Cilla et al., 2006)	Number of infants with haemodynamically unstable heart disease out of all infants hospitalised for RSV 4/357 (1.1%)	Number of infants with haemodynamically unstable heart disease out of all infants not hospitalised for RSV 22/13986 (0.2%)	Adjusted OR: 12.77 (3.89 to 41.89)n	p<0.001	Low	Retrospective cohort	Very seriouso	None	None	None	None
Association between congenital heart disease and bronchiolitis hospital admission											
1 (Murray et al., 2014)	NR	NR	Adjusted OR: 3.35 (2.92 (3.84)p	-	Moderate	Prospective cohort	Seriousq	None	None	None	None
RISK OF OXYGEN REQUIREMENT											
Association between congenital heart disease and oxygen requirement in RSV/non-RSV bronchiolitis											
1 (Garcia et	NR	NR	Adjusted	p=0.0005	Low	Retrospective	Very	None	None	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
al., 2010)			OR: 1.88 (1.32 to 2.67)r			cohort	seriouss				
RISK OF ICU ADMISSION											
Association between congenital heart disease and PICU admission in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 2.77 (1.89 to 4.05)r	p<0.0001	Low	Retrospective cohort	Very seriouss	None	None	None	None
Association between congenital heart disease and ICU admission in RSV bronchiolitis											
1 (Hervas et al., 2012)	NR	NR	Adjusted OR: 3.08 (1.14 to 8.3)t	P<0.0001	Very low	Retrospective review	Very seriousu	None	Seriousv	Serious [d]	None
Association between congenital heart disease and intensive care requirement in RSV infection											
1 (Simon et al., 2007)	NR	NR	Adjusted OR: 2.97 (1.81 to 4.82)w	p<0.001	Moderate	Prospective cohort	Seriousx	None	None	None	None
1 (Wilkesmann et al., 2007)	NR	NR	Adjusted OR: 2.97 (1.81 to 4.82)y	p<0.001	Moderate	Prospective cohort	Seriousz	None	None	None	None
1 (Zhang et al., 2014)	NR	NR	Adjusted OR: 8.20 (3.10 to 21.70)aa	p<0.001	Low	Retrospective chart review	Very seriousab	None	None	None	None
RISK OF SEVERE RSV-LRI - OXYGEN SUPPLEMENTATION OR MECHANICAL VENTILATION											
Association between congenital heart disease and severe RSV-LRI (oxygen supplementation or mechanical ventilation)											
1 (Kaneko et al., 2001)	6/20 (30%)	1/137 (0.7%)	Adjusted OR: 99.2 (8.5 to 1160.1)ac	p<0.0005	Very low	Retrospective chart review	Very seriousad	None	Seriousae	None	None
RISK OF SEVERE BRONCHIOLITIS - DEFINED BY A BRONCHIOLITIS CLINICAL SCORE											
Association between hemodynamically significant congenital heart disease (defined either by the use of medication to control congestive heart failure, infants with moderate to severe pulmonary hypertension or with cyanotic heart disease) and severe bronchiolitis- bronchiolitis clinical score ≥11											
1 (Ricart et al., 2013)	5/82 (6.1%)	7/328 (2.1%)	Adjusted OR: 4.7 (1.1 to 19.9)af	p=0.038	Moderate	Prospective cohort	None	None	None	Serious [d]	None

NR not reported, OR odds ratio, IRR incidence rate ratio, P p-value
a Adjusted for prematurity, chronic lung disease, atopic child, atopic father, atopic mother, atopic parents, breastfeeding, history of exposure to smoking, age.
b Exclusion criteria not reported, unclear how congenital heart defects was identified (definition not reported).
c Included children ≤5 yrs but mean age of cases and controls 7.6 and 8.8 months respectively.

d Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.e Adjusted for age of mother, parity, years of education, birth country of mother, gender, calendar year, age, epidemic period, birth weight, gestational age, apgar score, bronchopulmonary-dysplasia.
f Retrospective study design, bronchiolitis hospitalisation (including bronchiolitis due to RSV and other or unknown aetiologies) based on reliability of ICD-9 coding system, exclusion criteria not reported, CHD identified from hospital discharge database (no other details reported).
g All infants premature (<36 weeks gestation).
h Boyce: RSV hospitalisation defined as hospitalisation caused by RSV infection or bronchiolitis. Both of these outcomes based on ICD-9 codes - overall 6.3% of RSV associated hospitalisations were coded specifically for RSV and 93.7% were coded as bronchiolitis.
I Unclear what confounders were adjusted for.
j Retrospective study design, both presence of risk factor (CHD) and outcome (RSV hospitalisation) based on reliability of coding systems, number of cases and controls not explicitly reported, all variables were entered into 1 final multivariable model with no variable selection procedures.
k Adjusted for BPD, gestational age, number of siblings, presence of other conditions, male sex, white race, rural residence, maternal smoking and maternal education <12 years.
l Retrospective study design, both risk factor (CHD) and outcome (RSV/bronchiolitis hospitalisation) based on reliability of coding systems, gestational age missing for ~15% of children (if gestational age was missing from the birth certificate, this was estimated from birth weight with the use of the race and calendar-year specific distributions of gestational age in the population), exclusion criteria not reported.
m Database used for this study contains information only on children enrolled in Medicaid therefore may not be generalizable.
n Adjusted for gestational age, maternal age, period of birth, birth weight and rural/urban residence.
o Retrospective study design, no indication that controls have been tested for RSV, CHD identified from medical records, no other details reported.
p Adjusted for premature birth, cystic fibrosis, chronic lung disease, immunodeficiency, nervous system congenital anomalies, down's syndrome, cerebral palsy
q Risk factor and bronchiolitis diagnoses based on reliability of coding systems
r Adjusted for RSV, weight, age at hospitalisation, gender, race, prematurity, chronic lung disease, trisomy 21, congenital syndromes.
s Retrospective study design, inclusion of subjects based on reliability of ICD coding system
t Adjusted for nebulized epinephrine, nebulized salbutamol, year, atelectasis/condensation, age, male sex, gestational age.
u Retrospective study design, diagnosis of bronchiolitis based on reliability of coding systems, CHD identified from medical records (no other details reported).
v Includes children with ICD codes of acute bronchiolitis, RSV bronchiolitis, RSV pneumonia and RSV not otherwise specified.
w Adjusted for prematurity, CLD.
x Exclusion criteria not reported, unclear how data on CHD was obtained – details not reported
y Adjusted for prematurity, CLDplus, neuromuscular impairment and nosocomial infection
z Exclusion criteria not reported
aa Adjusted for sex, young age, prematurity
ab Exclusion criteria not reported, retrospective
ac Adjusted for age <3 months.
ad Retrospective study design, CHD identified from review of patient records (no other details reported).
ae Included children younger than 4 years although the mean age of each of the study groups ranged from 1.3 to 21.3 months.
af Adjusted for BPD, gestational age <37 weeks, temperature >38 degrees, age at admission, human rhinovirus (HRV), human respiratory syncytial virus (HRSV).

3.2.3.3.3 Evidence statements

Thirteen studies evaluated the odds of developing various outcomes including bronchiolitis/ respiratory syncytial virus hospitalisation, ICU admission, oxygen requirement, severe RSV-LRI defined as requiring oxygen supplementation or mechanical ventilation and severe bronchiolitis defined by a bronchiolitis clinical score in infants with congenital heart disease.

Risk of bronchiolitis/ RSV hospitalisation

Two studies including 2573 children did not find a significant association between congenital heart defects/disease and bronchiolitis hospitalisation. The quality of the evidence was very low. Three studies, two of which reported a sample size including several thousand children found a significant association between congenital heart disease and RSV /bronchiolitis hospitalisation. The quality of the evidence was moderate to very low. One other study also including several thousand children reported a significant association between hemodynamically unstable heart disease and respiratory syncytial virus hospitalisation. The quality of the evidence was low.

Risk of oxygen requirement

One study including 4285 children reported a significant association between congenital heart disease and oxygen requirement. The quality of the evidence was low.

Risk of ICU admission

Five studies, four of which reported their sample size, including in total 9169 children found a significant association between congenital heart disease and ICU admission. The quality of the evidence was moderate to very low.

Risk of severe RSV-LRI requiring oxygen supplementation or mechanical ventilation

One study including 157 children reported a significant association between congenital heart disease and severe RSV-LRI defined as requiring oxygen supplementation or mechanical ventilation. The quality of the evidence was very low.

Risk of severe bronchiolitis (bronchiolitis clinical score ≥11)

One study including 410 children reported a significant association between hemodynamically significant congenital heart disease (defined either by the use of medication to control congestive heart failure, infants with moderate to severe pulmonary hypertension or with cyanotic heart disease) and severe bronchiolitis defined as a bronchiolitis clinical score ≥11. The quality of the evidence was moderate.

3.2.3.3.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5.

3.2.3.3.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7.

3.2.3.4 Cystic fibrosis

3.2.3.4.1 Description of included studies

Two studies were identified for this review (Kristensen et al., 2012; Murray et al., 2014). One was a retrospective cohort study (Kristensen et al., 2012) and the other was a prospective

cohort study (Murray et al., 2014). One study was undertaken in Denmark with a sample size of 391983. Infants up to the age of 24 months were included. The second study was undertaken in the UK with a sample size of 7189. This study included children less than 1 year of age.

Both studies examined the association between cystic fibrosis and respiratory syncytial virus /bronchiolitis hospitalisation defined using International Classification of Disease codes.

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on this study can be found in the evidence tables.

3.2.3.4.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 8: GRADE profile for the association between cystic fibrosis and risk of developing severe bronchiolitis

Table 8: GRADE profile for the association between cystic fibrosis and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Cystic fibrosis											
RISK OF HOSPITALISATION											
Association between cystic fibrosis and RSV hospitalisation											
1 (Kristensen et al., 2012)	NR	NR	Adjusted IRR: 4.32 (2.42 to 7.71)[a]	p<0.001	Low	Retrospective cohort	Very serious[b]	None	None	None	None
	Number with RSV hospitalisation/Total number with cystic fibrosis: 13/72 (18.1%)										
Association between cystic fibrosis and bronchiolitis hospital admission											
1 (Murray et al., 2014)	NR	NR	Adjusted relative risk: 2.45 (1.36 to 4.43)[c]	-	Moderate	Prospective cohort	Serious[d]	None	None	None	None

NR not reported, p-value, IRR incidence rate ratio
a Unclear what confounders were adjusted for
b Retrospective study design, both presence of risk factor (cystic fibrosis) and outcome (RSV hospitalisation) based on reliability of coding systems, number of cases and controls not explicitly reported, all variables were entered into 1 final multivariable model with no variable selection procedures
c Adjusted for premature birth, congenital heart disease, chronic lung disease, immunodeficiency, nervous system congenital anomalies, down's syndrome, cerebral palsy
d Risk factor and bronchiolitis diagnoses based on reliability of coding system

3.2.3.4.3 Evidence statements

Risk of bronchiolitis/RSV hospitalisation

Two studies both including several thousand children evaluated the odds of developing RSV/bronchiolitis hospitalisation in infants with cystic fibrosis. Both studies reported a statistically significant association. The quality of the evidence was moderate to low.

3.2.3.4.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5.

3.2.3.4.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7.

3.2.3.5 Immunodeficiency

3.2.3.5.1 Description of included studies

Three studies were identified for this review (Kristensen et al., 2012; Murray et al., 2014; Moyes et al.,2013). One was a retrospective cohort study (Kristensen et al., 2012) and two were prospective cohort studies (Murray et al., 2014; Moyes et al., 2013). One study was from Denmark (Kristensen et al., 2012), one from the UK (Murray et al., 2014) and one from South Africa (Moyes et al., 2013). Sample sizes ranged from 802 to 391983. The age of the subjects ranged from infants up to 1 year of age in one study (Murray et al., 2014), infants up to the age of 24 months in one study (Kristensen et al., 2012) and infants aged 2 weeks to 3 months in the third study (Moyes et al., 2013).

One study examined congenital immunodeficiencies defined using International Classification of Disease codes (Kristensen et al., 2012), one study defined immunodeficiency as immunity disorders including hypogammaglobulinemia and severe combined immunodeficiency (Murray et al., 2014) and the remaining study examined HIV. The studies looked at various outcomes including RSV/bronchiolitis hospitalisation in two studies (Kristensen et al., 2012; Murray et al., 2014) and prolonged hospitalisation or death in one study (Moyes et al., 2013).

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on this study can be found in the evidence tables.

3.2.3.5.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 9: GRADE profile for the association between immunodeficiency and risk of developing severe bronchiolitis

Table 9: GRADE findings for the association between immunodeficiency and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Immunodeficiency											
RISK OF HOSPITALISATION											
Association between congenital immunodeficiencies and RSV hospitalisation											
1 (Kristensen et al., 2012)	NR Number with RSV hospitalisation/Total number with congenital immunodeficiencies: 26/122 (21.3%)	NR	Adjusted IRR: 3.80 (2.49 to 5.80)[a]	p<0.001	Low	Retrospective cohort	Very serious[b]	None	None	None	None
Association between immunodeficiency and bronchiolitis hospitalisation											
1 (Murray et al., 2014)	NR	NR	Adjusted relative risk: 1.69 (0.80 to 3.58)[c]	-	Low	Prospective cohort	Serious[d]	None	None	Serious[e]	None
RISK OF PROLONGED HOSPITALISATION > 5 DAYS											
Association between HIV and prolonged hospitalisation >5 days in children hospitalised with RSV-associated ALRTI											
1 (Moyes et al., 2013)	HIV infected: 23/49 (47%)	HIV uninfected: 132/753 (18%)	Adjusted OR: 4.0 (1.5 to 10.6)	p<0.001	Moderate	Prospective cohort	Serious[f]	None	None	None	None
RISK OF DEATH											
Association between HIV and death in children hospitalised with RSV-associated ALRTI											
1 (Moyes et al., 2013)	HIV infected: 9/1153 (1%)	HIV uninfected: 3/751 (<1%)	Adjusted OR: 31.1 (5.4 to 179.8)	p<0.001	Moderate	Prospective cohort	Serious[f]	None	None	None	None

NR not reported, p-value, IRR incidence rate ratio
a Unclear what confounders were adjusted for
b Retrospective study design, both presence of risk factor (congenital immunodeficiencies) and outcome (RSV hospitalisation) based on reliability of coding systems, number of cases and controls not explicitly reported, all variables were entered into 1 final multivariable model with no variable selection procedures
c Adjusted for prematurity, cystic fibrosis, congenital heart disease, chronic lung disease, nervous system congenital anomalies, down's syndrome, cerebral palsy
d Risk factor and bronchiolitis diagnoses based on reliability of coding systems
e Serious imprecision when 95% CI crosses one default MID.f Unclear what factors were adjusted for

3.2.3.5.3 Evidence statements

Risk of RSV /bronchiolitis hospitalisation

One study including several thousand children reported a significant association between congenital immunodeficiencies and RSV hospitalisation. The quality of the evidence was low. One other study also including several thousand children did not find a significant association between immunodeficiency and bronchiolitis hospitalisation. The quality of the evidence was low.

Risk of prolonged hospitalisation >5 days or death

One study with 802 children reported a significant association between HIV and prolonged hospitalisation >5 days and also between HIV and death. The quality of the evidence was moderate.

3.2.3.5.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5.

3.2.3.5.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7

3.2.3.6 Non-breast fed

3.2.3.6.1 Description of included studies

Six observational studies were identified for this review (Al-Shehri et al., 2005; Bulkow et al., 2002; Figueras-Aloy et al., 2004; Koehoorn et al., 2008; Lanari et al., 2013; Papenberg et al., 2012). Two were prospective matched case-control studies (Al-Shehri et al., 2005; Figueras-Aloy et al., 2004), two were prospective cohort studies (Lanari et al., 2013; Papenberg et al., 2012), one was a retrospective matched case-control study (Bulkow et al., 2002) and one was a retrospective cohort study (Koehoorn et al., 2008). Two studies were undertaken in Canada (Koehoorn et al., 2008; Papenberg et al., 2012), one in Spain (Figueras-Aloy et al., 2004), one in USA (Bulkow et al., 2002) one in Italy (Lanari et al., 2013) and one in Saudi Arabia (Al-Shehri et al., 2005). Sample sizes ranged from 166 to 93026. The age of the subjects varied from preterm infants born between 33 and 35 weeks gestational age (current age of subjects not reported) in one study (Figueras-Aloy et al., 2004), newborns in one study (Lanari et al., 2013), subjects less than 12 months of age in one study (Koehoorn et al., 2008) and subjects less than 3 years of age in two studies (Bulkow et al., 2002; Papenberg et al., 2012). One of the studies which included children less than 3 years of age reported a median age of 5.9 months for the case-patients (Bulkow et al., 2002), the other reported a mean age of 8 and 12.5 months for the cases and controls respectively (Papenburg et al., 2012). In the fifth study, subjects up to the age of 5 years were enrolled, however the mean age of the cases and controls was 7.6 and 8.8 months respectively. (Al-Shehri et al., 2005).

The definition of breast-feeding varied with only one study (Al-Shehri et al.,2005) examining this risk factor as specified in the protocol (non-breast fed). The same study also reported on mixed breast and formula milk and exclusive breastfeeding. All other studies reported on varying degrees of breastfeeding including ever breastfed, ever breastfed more than half of feedings and breastfed within 8 weeks of age of admission in one study (Bulkow et al., 2002), breast-feeding for less than two months in one study (Figueras-Aloy et al., 2004), absence of breast-feeding initiation at hospital in one study (Koehoorn et al., 2008) lack of breastfeeding in one study (Lanari et al., 2013) and history of breastfeeding in one study (Papenberg et al., 2012). All studies reported on RSV/bronchiolitis hospitalisation.

Diagnosis of RSV/bronchiolitis varied from clinical severity scores and/or nasopharyngeal aspirate tests or immunofluorescence and/or viral culture tests (Al-Shehri et al., 2005; Bulkow et al., 2002; Figueras-Aloy et al., 2004; Papenberg et al., 2012) to International Classification of Disease codes (Koehoorn et al., 2008; Lanari et al, 2013).

The settings of the studies included hospitals in three studies (Bulkow et al., 2002; Figueras-Aloy et al., 2004; Koehoorn et al., 2008), neonatology units in one study (Lanari et al., 2013) a pediatric clinic and hospital in one study (Papenburg et al., 2012) and a pediatric emergency room and paediatric ward of a hospital in one study (Al-Shehri et al., 2005)

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on each individual study can be found in the evidence tables.

3.2.3.6.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 10: GRADE profile for the association between non- breast fed and risk of developing severe bronchiolitis

Table 10: GRADE profile for the association between non- breast fed and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Non-breast fed											
RISK OF BRONCHIOLITIS/RSV HOSPITALISATION											
Association between exclusive breast milk (reference not reported) and bronchiolitis hospitalisation											
1 (Al-Shehri et al., 2005)	4/51 (7%)	43/115 (37%)	Adjusted OR: 0.43 (0.22 to 1.13)[a]	-	Very low	Prospective, matched case-control	Serious[b]	None	Serious[c]	Serious[d]	None
Association between mixed breast and formula milk (reference not reported) and bronchiolitis hospitalisation											
1 (Al-Shehri et al., 2005)	NR	NR	Adjusted OR: 4.15 (3.68 to 5.24)[a]	-	Low	Prospective, matched case-control	Serious[b]	None	Serious[c]	None	None
Association between infants never receiving breast milk (reference not reported) and bronchiolitis hospitalisation											
1 (Al-Shehri et al., 2005)	NR	NR	Adjusted OR: 2.51 (2.11 to 3.73)[a]	-	Low	Prospective, matched case-control	Serious[b]	None	Serious[c]	None	None
Association between no breastfeeding initiation (vs breastfeeding initiation) at hospital and bronchiolitis hospitalisation											
1 (Kooehorn et al., 2008)	205/1588 (12.9%)	6766/91438 (7.4%)	Adjusted HRR: 1.33 (1.14 to 1.54)[e]	-	Very low	Retrospective cohort	Very serious[f]	None	None	Serious[d]	None
Association between infants ever breastfed more than half of feedings (vs no breastfeeding) and RSV hospitalisation (complete data set)											
1 (Bulkow et al., 2002)	103/195 (53%)	245/327 (75%)	Adjusted OR: 0.38[g]	p=0.001	Very low	Retrospective, matched case-control	Very serious[h]	None	Serious[i]	NC[j]	None
Association between infants ever breastfed more than half of feedings (vs no breastfeeding) and RSV hospitalisation (infants <6 months)											
1 (Bulkow et al., 2002)	NR	NR	Adjusted OR: 0.33[g]	p=0.001	Low	Retrospective, matched case-control	Very serious[h]	None	None	NC[j]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Association between breastfed within 8 weeks of age of admission (vs no breastfeeding) and RSV hospitalisation (complete data set)											
1 (Bulkow et al., 2002)	65/204 (32%)	171/338 (51%)	Adjusted OR: 0.44[g]	p=0.004	Very low	Retrospective, matched case-control	Very serious[h]	None	Serious[i]	NC[j]	None
Association between breastfed within 8 weeks of age of admission (vs no breastfeeding) and RSV hospitalisation (infants ≥6 months)											
1 (Bulkow et al., 2002)	NR	NR	Adjusted OR: 0.27[k]	p=0.004	Very low	Retrospective, matched case-control	Very serious[h]	None	Serious[i]	NC[j]	None
Association between infants ever breastfed (vs no breastfeeding) and RSV hospitalisation (infants ≥6 months)											
1 (Bulkow et al., 2002)	128/204 (63%)	272/337 (81%)	Adjusted OR: 0.25[k]	p=0.001	Very low	Retrospective, matched case-control	Very serious[h]	None	Serious[i]	NC[j]	None
Association between breast-feeding ≤2 months (vs >2 months) and RSV hospitalisation											
1 (Figueras-Aloy et al., 2004)	159/186 (85.5%)	251/371 (67.6%)	Adjusted OR: 3.26 (1.96 to 5.42)[l]	-	Low	Prospective case-control	Serious[m]	None	Serious[n]	None	None
Association between a history of breast-feeding (yes vs no) and RSV hospitalisation											
1 (Papenburg et al., 2012)	341/460 (74.1%)	25/141 (17.7%)	Adjusted OR: 0.55 (0.33 to 0.92)[o]	-	Low	Prospective cohort	None	None	Very serious[p]	None	None
Association between lack of breastfeeding and bronchiolitis hospitalisation											
1 (Lanari et al., 2013)	42/482 (8.7%)	78/1728 (4.5%)	Adjusted HR: 1.8 (1.2 to 2.6)[q]	-	Low	Longitudinal multicentre cohort study	Serious[r]	None	None	Serious[d]	None

NR not reported, HRR hazard rate ratio, OR odds ratio, P p-value
a Adjusted for prematurity, congenital heart defects, chronic lung diseases, atopic child, father, mother, parents, history of exposure to smoking, age (one year or less).
b Exclusion criteria not reported, reference category not reported.
c Included children ≤5 years but mean age of cases and controls 7.6 and 8.8 months respectively.
d Serious imprecision when 95% CI crosses one default MID. .
e Adjusted for gender, maternal age, maternal education, maternal smoking during pregnancy, First Nations status, older siblings, birth weight, congenital anomalies.
f Retrospective study design, bronchiolitis diagnosis based on reliability of coding systems.
g Adjusted for high risk infant, ≥4 others aged <12 years in household and ≥2 persons/room in household.
h Retrospective study design, confidence intervals not presented therefore imprecision could not be assessed.

l Complete data set includes children <3 years- case patients age ranged from <1 month to 34 months (median: 5.9 months).
j Could not be assessed due to the way results were presented (no confidence intervals reported).
k Adjusted for high risk infant, shares bed ≥1 other.
l Adjusted for medical centre, absolute chronologic age, school age siblings, residents and/or visitors at home ≥4, history of wheezing in the family.
m Current age of subjects not reported, data sources not reported.
n All subjects premature and previously hospitalised for prematurity.
o Adjusted for age <6 months, prematurity (<37 weeks), ≥3 children in the household, presence of comorbidity and viral coinfection.
p 34.5% of infants hospitalised for RSV were diagnosed with pneumonia, also included children less than 3 years of age however mean age of cases and controls was 8 and 12.5 months.
q Adjusted for gender, gestational age, treatment with corticosteroids, cigarette smoke exposure, singleton delivery, respiratory diseases, surfactant therapy, siblings, crowding, humidity, exposed to epidemic RSV season
r Bronchiolitis hospitalisation based on reliability of coding systems

3.2.3.6.3 Evidence statements

Six studies evaluated the odds of developing bronchiolitis or RSV hospitalisation in infants with various levels of breastfeeding.

Never receiving breast milk, mixed breast and formula milk, exclusive breast milk

One study including 166 children reported a significant association between never receiving breast milk (reference not reported) and bronchiolitis hospitalisation as well as between mixed breast and formula milk (reference not reported) and bronchiolitis hospitalisation. The quality of the evidence was low. The same study however did not find a significant association between exclusive breast milk (reference not reported) and bronchiolitis hospitalisation. The quality of the evidence was very low.

No breast-feeding initiation at hospital

One study including several thousand children reported a significant association between the absence of breastfeeding initiation at hospital (vs breastfeeding initiation at hospital) and risk of bronchiolitis hospitalisation. The quality of the evidence was very low.

Ever breastfed, ever breastfed more than half of feedings and breastfed within 8 weeks of age of admission

One study including 542 children reported a significant association between ever breast fed (vs no breastfeeding) and RSV hospitalisation in infants ≥6 months. The same study reported a significant association between ever breastfed more than half of feedings (vs no breastfeeding) for both the complete data set and for a subgroup analysis of infants <6 months. This study additionally reported a significant association between breastfed within 8 weeks of age of admission (vs no breastfeeding) for both the complete data set and for infants ≥6 months. The quality of the evidence was very low.

Breast-feeding for less than two months

One study including 567 children reported a significant association between breast-feeding for less than 2 months (vs >2 months) and risk of RSV hospitalisation. The quality of the evidence was low.

History of breastfeeding

One study including 601 children reported a significant association between history of breastfeeding (yes vs no) and RSV hospitalisation. The quality of the evidence was low.

Lack of breastfeeding

One study including 2210 children reported a significant association between lack of breastfeeding and bronchiolitis hospitalisation. The quality of the evidence was low.

3.2.3.6.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5.

3.2.3.6.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7.

3.2.3.7 Young infants

3.2.3.7.1 Description of included studies

Sixteen observational studies were identified for this review (Al-Shehri et al., 2005; Ambrose et al., 2014; Bockova et al., 2002; Carbonell-Estrany et al., 2001; Chan et al., 1999; Damore et al., 2008; Dotan et al., 2013; Figueras-Aloy et al., 2004; Figueras-Aloy et al., 2008; Grimwood et al., 2008; Kaneko et al., 2001; Rossi et al., 2007; Papoff et al., 2011; Papenburg et al., 2012; Pezzotti et al., 2009; Zhang et al., 2014). Seven were prospective cohort studies (Ambrose et al., 2014; Bockova et al., 2002; Carbonell-Estrany et al., 2001; Damore et al., 2008; Figueras-Aloy et al., 2008; Papoff et al., 2011; Papenburg et al., 2012), four were retrospective cohort studies (Chan et al., 1999; Dotan et al., 2013; Grimwood et al., 2008; Pezzotti et al., 2009), two were retrospective chart reviews (Kaneko et al., 2001; Zhang et al., 2014) and three were prospective case-control studies (Al-Shehri et al., 2005; Figueras-Aloy et al., 2004; Rossi et al., 2007).

Three studies were undertaken in Spain (Carbonell-Estrany et al., 2001; Figueras-Aloy et al., 2004; Figueras-Aloy et al., 2008), three in Italy (Rossi et al., 2007; Papoff et al., 2011; Pezzotti et al., 2009), three in the USA (Ambrose et al., 2014; Bockova et al., 2002; Damore et al., 2008), one in Saudi Arabia (Al-Shehri et al., 2005), one in Malaysia (Chan et al., 1999), one in New Zealand (Grimwood et al., 2008), one in Japan (Kaneko et al., 2001) one in Israel (Dotan et al., 2013), one in China (Zhang et al., 2014) and one in Canada (Papenburg et al., 2012). Sample sizes ranged from 157 to 11500.

The age of the subjects varied from less than 6 months in two studies (Ambrose et al., 2014; Carbonell-Estrany et al., 2001), less than 12 months in one study (Papoff et al., 2011), less than 24 months in four studies (Bockova et al., 2002; Chan et al., 1999; Damore et al., 2008; Grimwood et al., 2008) and less than three years of age in two studies (Papenburg et al., 2012; Pezzotti et al., 2009). One of the studies which included children less than three years (Pezzotti et al., 2009) restricted the risk factor analysis to children in the first 18 months of life. The mean age of subjects in the other study which included children less than three years of age (Papenburg et al., 2012) was 8 and 12.5 months respectively for the cases and controls. Two studies included children up to 4 years of age (Rossi et al., 2007; Kaneko et al., 2001). The median age of cases and controls in the first study was 3.5 and 5 months respectively and the mean age subjects in the second study (Kaneko et al., 2001) was 11.3 and 1.3 months for the 2 study groups and 21.3 months for the controls. One study included children up to 5 years of age (Al-Shehri et al., 2005), however the mean age of the cases and controls was 7.6 and 8.8 months respectively. One study included children of which the majority was aged <2 years (Zhang et al., 2014). Two other studies (Figueras-Aloy et al., 2004, Figueras-Aloy et al., 2008) included preterm infants (current age of subjects not reported). The final study included children up to 3720 days old (Dotan et al., 2013).

All studies looked at young infants defined in various ways including age less than 30 days in one study (Papoff et al., 2011), less than two months in three studies (Damore et al., 2008; Dotan et al., 2013; Grimwood et al., 2008), less than three months in three studies (Chan et al., 1999; Kaneko et al., 2001; Rossi et al., 2007), less than six months in four studies (Bockova et al., 2002; Papenburg et al., 2012; Pezzotti et al., 2009; Zhang et al., 2014) and less than or equal to 1 year of age in one study (Al-Shehri et al., 2005). Two further studies evaluated absolute chronologic age at start of the RSV season ≤10 weeks (Figueras-Aloy et al., 2004; Figueras-Aloy et al., 2008). One of the studies which looked at age less than three months also examined 3 to 5 months and 6 to 11 months of age (Rossi et al., 2007). One other study examined age less than 3 months however, this was used as the reference category to which age >3 months was compared to (Carbonell-Estrany et al., 2001). A further study examined both less than 3 months and 3 to <6 months (Ambrose et al., 2014).

The studies reported on various outcomes including bronchiolitis/RSV hospitalisation in seven studies (Al-Shehri et al., 2005; Ambrose et al., 2014; Pezzotti et al., 2009; Figueras-Aloy et al., 2004; Figueras-Aloy et al., 2008; Rossi et al., 2007; Papenburg et al., 2012), RSV

rehospitalisation in one study (Carbonell-Estrany et al., 2001), severe RSV disease defined by a severity score in three studies (Bockova et al., 2002; Chan et al., 1999; Papenburg et al., 2012), severe RSV-LRI requiring oxygen or mechanical ventilation in one study (Kaneko et al., 2001), severe RSV bronchiolitis defined as assisted ventilation or CPAP in one study (Grimwood et al., 2008) and ICU admission in four studies (Papoff et al., 2009; Damore et al., 2008; Dotan et al., 2013; Zhang et al., 2014). One of the studies which looked at severe RSV bronchiolitis defined as assisted ventilation or CPAP (Grimwood et al., 2008) also reported on length of stay greater than or equal to 5 days.

Diagnosis of bronchiolitis/RSV infection was reported in fifteen studies (Al-Shehri et al., 2005; Bockova et al., 2002; Carbonell-Estrany et al., 2001; Chan et al., 1999; Damore et al., 2008; Dotan et al., 2013; Figueras-Aloy et al., 2004; Figueras-Aloy et al., 2008; Grimwood et al., 2008; Kaneko et al., 2001; Rossi et al., 2007; Papoff et al., 2011; Papenburg et al., 2012; Pezzotti et al., 2009; Zhang et al., 2014) and was based on clinical severity score and/or nasopharyngeal aspirate or immunofluorescence and/or viral culture tests in thirteen studies (Al-Shehri et al., 2005; Bockova et al., 2002; Carbonell-Estrany et al., 2001; Chan et al., 1999; Dotan et al., 2013; Figueras-Aloy et al., 2004; Figueras-Aloy et al., 2008; Grimwood et al., 2008; Kaneko et al., 2001; Rossi et al., 2007; Papoff et al., 2011; Papenburg et al., 2012; Zhang et al., 2014), International Classification Diagnostic codes in one study (Pezzotti et al., 2009) and the physician's clinical diagnosis in the remaining study (Damore et al., 2008).

The setting of the studies included hospitals in eleven studies (Bockova et al., 2002; Chan et al., 1999; Dotan et al., 2013; Figueras-Aloy et al., 2004; Figueras-Aloy et al., 2008; Grimwood et al., 2008; Kaneko et al., 2001; Rossi et al., 2007; Papenburg et al., 2012; Pezzotti et al., 2009; Zhang et al., 2014), an emergency department in one study (Damore et al., 2008), neonatal units in two studies (Papoff et al., 2011; Carbonell-Estrany et al., 2001), outpatients clinic in one study (Ambrose et al., 2014) and pediatric emergency room and pediatric ward in one study (Al-Shehri et al., 2005).

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on each individual study can be found in the evidence tables.

3.2.3.7.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 11: GRADE profile for the association between young infants and risk of developing severe bronchiolitis

Table 11: GRADE profile for the association between young infants and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalised	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Young infants e.g. <2 months											
RISK OF BRONCHIOLITIS/RSV HOSPITALISATION											
Association between absolute chronologic age at start of RSV season ≤10 weeks of age (reference not reported) and RSV hospitalisation											
1 (Figuras-Aloy et al., 2004)	125/186 (67.2%)	131/371 (35.3%)	Adjusted OR: 3.95 (2.65 to 5.90)[a]	-	Low	Prospective case-control	Serious[b]	None	Serious[c]	None	None
1 (Figuras-Aloy et al., 2008)	126/202 (62.4%)	1944/5239 (37.1%)	Adjusted OR: 2.99 (2.23 to 4.01)[d]	-	Low	Prospective cohort	Serious[e]	None	Serious[c]	None	None
Association between age <3 months (vs ≥6 months) and RSV hospitalisation											
1 (Ambrose et al., 2014)	NR	NR	Adjusted HR: 2.82[f]	p=0.004	Moderate	Prospective cohort	Seriousg	None	None	NC	None
Association between chronological age at the beginning of RSV season <3 months of age (vs ≥12 months) and RSV hospitalisation											
1 (Rossi et al., 2011)	60/145 (41.4%)	61/292 (20.9%)	Adjusted OR: 8.462 (3.088 to 23.185)[h]	-	Moderate	Prospective, case-control	None	None	Serious[i]	None	None
Association between chronological age at the beginning of RSV season 3 to 5 months of age (vs ≥12 months) and RSV hospitalisation											
1 (Rossi et al., 2011)	48/145 (33.1%)	85/292 (29.1%)	Adjusted OR: 4.153 (1.506 to 11.451)[h]	-	Moderate	Prospective, case-control	None	None	Serious[i]	None	None
Association between 3 to <6 months vs ≥6 months and RSV hospitalisation											
1 (Ambrose et al., 2014)	NR	NR	Adjusted HR: 1.77[f]	p=0.108	Moderate	Prospective cohort	Serious[g]	None	None	NC	None
Association between infants <6 months of age (vs ≥12 months) and bronchiolitis hospitalisation											
1 (Pezzotti et al., 2009)	NR	NR	Adjusted IRR: 14.54 (6.75 to 31.35)[j]	p<0.01	Very low	Retrospective cohort	Very serious[k]	None	Serious[l]	None	None
Association between infants <6 months of age (vs 18 to 36 months) and RSV hospitalisation											
1	270/460	30/141	Adjusted	-	Low	Prospective	None	None	Very serious[n]	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalised	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
(Papenburg et al., 2012)	(58.6%)	(21.3%)	OR: 4.63 (2.94 to 7.28)[m]			cohort					
Association between infants 6 to 11 months of age (vs ≥12 months) and bronchiolitis hospitalisation											
1 (Pezzotti et al., 2009)	NR	NR	Adjusted IRR: 5.98 (2.68 to 13.35)[j]	p<0.01	Very low	Retrospective cohort	Very serious[k]	None	Serious[l]	None	None
Association between chronological age at the beginning of RSV season 6 to 11 months of age (vs ≥12 months) and RSV hospitalisation											
1 (Rossi et al., 2011)	31/145 (21.4%)	98/292 (33.6%)	Adjusted OR: 2.467 (0.879 to 6.925)[h]		Low	Prospective, case-control	None	None	Serious[i]	Serious[o]	None
Association between infants ≤1 year of age (reference not reported) and bronchiolitis hospitalisation											
1 (Al-Shehri et al., 2005)	33/51 (65%)	57/115 (49.5%)	Adjusted OR: 3.44 (2.27 to 4.33)[p]	-	Low	Prospective, matched case-control	Serious[q]	None	Serious[r]	None	None
RISK OF RSV REHOSPITALISATION											
Association between age at entry RSV season >3 months of age (vs <3 months) and RSV rehospitalisation											
1 (Carbonell-Estany et al., 2001)	24/309 (7.7%)	285/309 (92.2%)	Adjusted OR: 0.44 (0.25 to 0.77)[s]	p=0.004	Low	Prospective cohort	Serious[t]	None	Serious[u]	None	None
RISK OF SEVERE RSV DISEASE – BASED ON DISEASE SEVERITY SCORES											
Association between infants <3 months of age (reference not reported) and respiratory distress - moderate or severe RDAI score											
1 (Chan et al., 1999)	21/68 (31%)	12/117 (10%)	Adjusted OR: 4.5 (1.2 to 17.6)[v]	p=0.001	Very low	Retrospective cohort	Very serious[w]	None	None	Serious[x]	None
Association between infants <6 months of age (reference not reported) and severe RSV disease - severity score ≥3y											
1 (Bockova et al., 2002)	37/45 (82.2%)	377/831 (45.4%)	Adjusted OR: 6.6 (3.0 to 14.4)[z]	-	Moderate	Prospective cohort	None	None	Seriousa[a]	None	None
Association between infants <6 months of age (vs 18 to 36 months) and severe RSV disease - severity score ≥2ab											
1	NR	NR	Adjusted	-	Low	Prospective	None	None	Very serious[n]	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalised	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
(Papenburg et al., 2012)			OR: 2.26 (1.31 to 3.89)[m]			cohort					
RISK OF SEVERE RSV-LRI - REQUIRING OXYGEN OR MECHANICAL VENTILATION											
Association between infants <3 months of age (reference not reported) and severe RSV-LRI - requiring oxygen supplementation or mechanical ventilation											
1 (Kaneko et al., 2001)	13/20 (65%)	6/137 (4.4%)	Adjusted OR: 59.9 (14.7 to 244.0)[ac]	p<0.0001	Very low	Retrospective chart review	Very serious[ad]	None	Serious[ae]	None	None
RISK OF SEVERE RSV BRONCHIOLITIS - ASSISTED VENTILATION OR CPAP											
Association between age at admission <2 months of age (vs ≥2 months) and severe RSV bronchiolitis - assisted ventilation or CPAP											
1 (Grimwood et al., 2008)	13/34 (38.2%)	22/107 (20.6%)	Adjusted OR: 2.50 (0.98 to 6.39)[af]	-	Very low	Retrospective cohort	Very serious[ag]	None	None	Serious[x]	None
RISK OF LENGTH OF STAY ≥5 DAYS											
Association between age at admission <2 months of age (vs ≥2 months) and length of stay ≥5 days in RSV positive children hospitalised with bronchiolitis											
1 (Grimwood et al., 2008)	22/64 (34.4%)	38/77 (49.4%)	Adjusted OR: 1.92 (0.63 to 5.83)[ah]	-	Very low	Retrospective cohort	Very serious[ag]	None	None	Very serious[x]	None
RISK OF ICU ADMISSION											
Association between postnatal age <30 days of age (reference not reported) and PICU admission for infants with bronchiolitis											
1 (Papoff et al., 2009)	NR	NR	Adjusted OR: 8.382 (2.352 to 29.864)[ai]	p=0.001	Moderate	Prospective cohort	Serious[aj]	None	None	None	None
Association between young age <42 days and ICU admission in RSV infection											
1 (Dotan et al., 2013)	NR	NR	Adjusted OR: 3.39 (1.46 to 7.9)[ak]	-	Low	Retrospective cohort	Very serious[al]	None	none	None	None
Association between infants <2 months of age (≥12 months) and ICU admission in children with bronchiolitis											
1 (Damore et al., 2008)	27/50 (53%)	138/533 (26%)	Adjusted OR: 4.14 (2.05 to 8.34)[am]	p<0.001	Moderate	Prospective cohort	Serious[an]	None	None	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalised	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Association between ≤6 months and ICU admission in RSV disease											
1 (Zhang et al., 2014)	NR	NR	Adjusted OR: 2.81 (1.36 to 5.80)[ao]	p=0.005	Low	Retrospective chart review	Very serious[ap]	None	None	None	None

NR not reported, OR odds ratio, IRR incidence rate ratio, p-value
a Adjusted for medical centre, breast feeding, school age siblings, residents and/or visitors at home ≥4 (without school age siblings and the subject him/herself), history of wheezing in the family
b Current age of subjects not reported, data sources not reported, reference category not reported
c All subjects premature and previously hospitalised for prematurity
d Adjusted for school age siblings or day care attendance and tobacco smoking during pregnancy
e Current age of subjects not reported
f Adjusted for preschool-aged non-multiple birth siblings, exposure to smoking and multiple birth
g Imprecision could not be assessed as confidence intervals not reported, control group not defined
h Adjusted for birth weight category and birth order
I Included infants ≤4 years of age, median age=5 months
j Adjusted for age of mother, parity, years of education, birth country of mother, gender, calendar year, epidemic period, birth weight, gestational age, apgar score, bronchopulmonary-dysplasia and congenital heart disease
k Retrospective study design, bronchiolitis hospitalisation (including bronchiolitis due to RSV and other or unknown etiologies) based on reliability of ICD-9 coding system, exclusion criteria not reported
l All infants premature (<36 weeks gestation)
m Adjusted for prematurity (<37 weeks) and viral coinfection
n 34.5% of infants hospitalised for RSV were diagnosed with pneumonia, included children less than 3 years of age however mean age of cases and controls was 8 and 12.5 months respectively
o Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
p Adjusted for prematurity, congenital heart defects, chronic lung disease, atopic child, atopic father, atopic mother, atopic parents, breastfeeding, history of exposure to smoking
q Exclusion criteria not reported, reference category not reported
r Included children ≤5 years of age however mean age of cases and controls 7.6 and 8.8 months respectively
s Adjusted for: gestational age, weight at birth, CRIB index, month of discharge, smoke exposure and siblings at school age in the model
t 10% of admissions not tested for RSV - because 10% of admissions were not tested for RSV, the overall hospitalisation rate for RSV illness was calculated by applying the RSV positive rate in tested patients (63%) to all respiratory hospitalisations (207) and dividing it by the total number of study patients (999), 54/207 lost to follow up (26%)
u All premature infants
v Adjusted for prematurity (<36 weeks), family history of asthma and underlying illness
w Retrospective study design, exclusion criteria not reported, reference category not reported
x Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
y Severity based on a previously published severity index (McConnochie et al., 1990), 1 point each was assigned for apnea, pH <7.35, PC02 >45, oxygen saturation <87% and length of stay >5 days, 2 points were assigned for mechanical ventilation. Severity index for each subject was the sum of the points, the maximum score is 7.

z Adjusted for prematurity, gender, underlying conditions (congenital heart disease, chronic lung disease of prematurity, reactive airway disease, 2 or more previous hospitalisations for respiratory infection, history of mechanical ventilation, or immunodeficiency)
aa Included children with mild respiratory symptoms or apnea
ab Patients given 1 point for each of the following: admission to PICU, hospitalised for >5 days, require supplemental oxygen therapy (fraction of inhaled oxygen ≥0.3)
ac Adjusted for CHD
ad Retrospective study design, reference category not stated
ae Included children younger than 4 years although the mean age of each of the study groups ranged from 1.3 to 21.3 months
af Adjusted for year, gender, month of birth, mother smoking during pregnancy, ethnicity, number of other children living in the house and gestational age
ag Retrospective study design, no indication that controls have been tested for RSV, exclusion criteria not reported, 66.5% of eligible participants were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregivers
ah Adjusted for year, gender, multiple birth, ethnicity, number of other children, birth weight
ai Adjusted for birth weight, RSV infection, lymphocytes, pulmonary consolidation and CRP
aj Reference not reported
ak Adjusted for gestational age, male gender and being a twin
al Retrospective study design, data sources not reported
am Adjusted for emergency department visit during past week, moderate/severe retractions and oral intake (adequate, inadequate, unknown)
an Some infants have a history of wheezing (26% of cases and 27% of controls) - unclear whether this might be family history of wheezing
ao Adjusted for sex, congenital heart disease and prematurity
ap Exclusion criteria not reported, retrospective

3.2.3.7.3 Evidence statements

Sixteen studies evaluated the odds of developing various outcomes including bronchiolitis/RSV hospitalisation, severe RSV disease defined by a severity score, RSV rehospitalisation, need for oxygen/mechanical ventilation, length of stay and ICU admission in young infants (various cut-offs).

Risk of bronchiolitis/RSV hospitalisation

Seven studies evaluated the odds of developing bronchiolitis/ RSV hospitalisation in young infants.

Absolute chronologic age at start of RSV season ≤10 weeks (reference not reported)

Two studies including over 5000 children reported a significant association between absolute chronologic age at start of RSV season ≤10 weeks (reference not reported) and risk of RSV hospitalisation. The quality of the evidence was low.

Age <3 months (vs ≥6 months)

One study (sample size not reported) found a significant association between age <3 months (vs ≥6 months) and RSV hospitalisation. The quality of the evidence was moderate.

Chronological age at beginning of RSV season <3 months (vs ≥12 months), 3 to 5 months (vs ≥12 months)

One study including 440 children reported a significant association between chronological age at beginning of RSV season <3 months (vs ≥12 months) and RSV hospitalisation. The same study reported a statistically significant association between chronological age at beginning of RSV season 3 to 5 months (vs ≥12 months) and risk of RSV hospitalisation. The quality of the evidence was both moderate.

Age 3 to <6 months (vs ≥6 months)

One study (sample size not reported) did not find a significant association between 3 to <6 months of age (vs ≥6 months) and RSV hospitalisation. The quality of the evidence was moderate.

Age <6 months (vs ≥12 months)

One study including 2407 children reported a significant association between age less than 6 months (vs ≥12 months) and bronchiolitis hospitalisation. The quality of the evidence was very low.

Age <6 months of age (vs 18 to 36 months)

One study including 601 children reported a significant association between <6 months of age (vs 18 to 36 months) and RSV hospitalisation. The quality of the evidence was low.

Age 6 to 11 months (vs ≥12 months)

One study including 2407 children reported a significant association between age 6 to 11 months (vs ≥12 months) and bronchiolitis hospitalisation. The evidence was of very low quality. One other study including 440 children did not find a significant association between age 6 to 11 months (vs ≥12 months) and RSV hospitalisation. The quality of the evidence was very low and low respectively.

Age <=1 year (reference not reported)

One study including 166 children reported a significant association between age <=1 year (reference not reported) and bronchiolitis hospitalisation. The quality of the evidence was low.

Risk of RSV rehospitalisation

Age at entry RSV season >3 months (vs <3 months)

One study including 999 children reported a significant association between age at entry RSV season >3 months (vs <3 months) and RSV rehospitalisation. The quality of the evidence was low.

Risk of severe RSV disease (defined by a severity score)

Three studies evaluated the odds of developing severe RSV disease in young infants.

Age <3 months (vs reference not reported)

One study including 185 children reported a significant association between infants less than 3 months of age (reference not reported) and risk of respiratory distress defined by a moderate/severe RDAI score. The quality of the evidence was very low.

Age <6 months (vs reference not reported)

One study including 876 children reported a significant association between infants less than 6 months of age (reference not reported) and risk of severe RSV disease defined by a disease severity score ≥3. The quality of the evidence was moderate.

Age <6 months (vs 18 to 36 months)

One study including 420 children reported a significant association between infants <6 months of age (vs 18 to 36 months) and risk of severe RSV disease defined by a severity score ≥2. The quality of the evidence was low.

Risk of severe RSV-LRI requiring oxygen or mechanical ventilation

Age less than 3 months (reference not reported)

One study including 157 children reported a significant association between age less than 3 months (reference not reported) and severe RSV-LRI (requiring oxygen or mechanical ventilation). The quality of the evidence was very low.

Risk of severe RSV bronchiolitis requiring assisted ventilation or CPAP/length of stay ≥5 days

Age at admission less than 2 months (vs ≥2 months)

One study including several thousand children did not find a significant association between age at admission less than 2 months (vs ≥2 months) and severe RSV bronchiolitis (assisted ventilation or CPAP). The same study did not find a significant association between age less than 2 months (vs ≥2 months) and length of stay greater than or equal to 5 days. The quality of the evidence was very low.

Risk of ICU admission

Four studies evaluated the odds of developing ICU admission in young infants.

Postnatal age less than 30 days (reference not reported)

One study including 310 children reported a significant association between postnatal age less than 30 days (reference not reported) and risk of PICU admission for infants with bronchiolitis. The quality of the evidence was moderate.

Young age <42 days (reference not reported)

One study (sample size not reported) reported a significant association between young age <42 days and ICU admission in RSV infection. The quality of the evidence was low.

Age less than 2 months (vs ≥12 months)

One study including 583 children reported a significant association between age less than 2 months (vs ≥12 months) and ICU admission in children with bronchiolitis. The quality of the evidence was moderate.

Age ≤6 months (reference not reported)

One study including 959 children reported a significant association between age ≤6 months and ICU admission in RSV disease. The quality of the evidence was low.

3.2.3.7.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5.

3.2.3.7.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7.

3.2.3.8 Sex (Male)

3.2.3.8.1 Description of included studies

Seventeen observational studies were identified for this review (Bockova et al., 2002; Boyce et al., 2000; Doering et al., 2006; Dotan et al., 2013; Garcia et al., 2010; Gavin et al., 2007; Grimwood et al., 2008; Hervas et al., 2012; Koehoorn et al., 2008; Kristensen et al., 2009; Lanari et al., 2013; Law et al., 2004; Liese et al., 2003; Mansbach et al., 2005; Pezzotti et al., 2009; Rietveld et al., 2006; Semple et al., 2011). Ten of these were retrospective cohort studies (Boyce et al., 2000; Doering et al., 2006; Dotan et al., 2013; Garcia et al., 2010; Gavin et al., 2007; Grimwood et al., 2008; Koehoorn et al., 2008; Liese et al., 2003; Mansbach et al., 2005; Pezzotti et al., 2009; Rietveld et al., 2006), four of those were prospective cohort studies (Bockova et al., 2002; Lanari et al., 2013; Law et al., 2004; Semple et al., 2011),one a retrospective case-control study (Kristensen et al., 2009) and one was a retrospective chart review (Hervas et al., 2012).

Five studies were conducted in the USA (Bockova et al., 2002; Boyce et al., 2000; Garcia et al., 2010; Gavin et al., 2007; Mansbach et al., 2005), one in New Zealand (Grimwood et al., 2008), one in Spain (Hervas et al., 2012), two in Canada (Koehoorn et al., 2008; Law et al., 2004), one in Germany (Liese et al., 2003), two in Italy (Lanari et al., 2013; Pezzotti et al., 2009), one in the Netherlands (Rietveld et al., 2006), one in the UK (Semple et al., 2011), one in Austria and Germany (Doering et al., 2006), one in Israel (Dotan et al., 2013) and one in Denmark (Kristensen et al., 2009). The sample size ranged from 157 to 93026.

The age of the subjects varied from less than 12 months in two studies (Koehoorn et al., 2008; Rietveld et al., 2006) and less than 24 months in six studies (Bockova et al., 2002; Garcia et al., 2010; Grimwood et al., 2008; Hervas et al., 2012; Mansbach et al., 2005; Semple et al., 2011). Two studies (Boyce et al., 2000; Pezzotti et al., 2009) included children up to three years of age. One of these (Pezzotti et al., 2009) restricted the risk factor analysis to children in the first 18 months of life, the other (Boyce et al., 2000) restricted analysis to the first year of life. Four studies included premature infants (Doering et al., 2006; Gavin et al., 2007; Law et al., 2004; Liese et al., 2003) and one study included newborns of various gestational ages (Lanari et al., 2013). One study included children up to the age of 3720 days (Dotan et al., 2013). The remaining study (Kristensen et al., 2009) initially enrolled children up to the age of 14 years but included children with a mean age at RSV diagnosis of 362 days (range: 15 to 2379 days).

All studies reported on male gender identified in various ways such as the use medical records or birth certificates. The studies reported different outcomes including bronchiolitis/RSV hospitalisation in ten studies (Lanari et al., 2013; Mansbach et al., 2005; Pezzotti et al., 2009; Koehoorn et al., 2008; Boyce et al., 2000; Doering et al., 2006; Gavin et al., 2007; Kristensen et al., 2009; Law et al., 2004; Rietveld et al., 2006), ICU admission in one study (Dotan et al., 2013), RSV rehospitalisation in one study (Liese et al., 2003), severe RSV disease defined by a severity score in one study (Bockova et al., 2002) and oxygen requirement in three studies (Garcia et al., 2010; Hervas et al., 2012; Semple et al., 2011). One of the studies which examined need for oxygen also looked at need for mechanical ventilation (Semple et al., 2011). One other study examined three outcomes including bronchiolitis hospitalisation, need for ventilation/CPAP and length of stay ≥5 days (Grimwood et al., 2008).

Diagnosis of bronchiolitis/ RSV varied from International Classification of Disease codes in seven studies (Boyce et al., 2000; Garcia et al., 2010; Koehoorn et al., 2008; Kristensen et al., 2009; Lanari et al., 2013; Mansbach et al., 2005; Pezzotti et al., 2009) nasopharyngeal aspirates in six studies (Bockova et al., 2002; Dotan et al., 2013; Grimwood et al., 2008; Hervas et al., 2012; Rietveld et al., 2006; Semple et al., 2011), viral culture and/or rapid tests in one study (Law et al., 2004) and antigen tests in two studies (Doering et al., 2006; Liese et al., 2003). One of these studies also used the physicians clinical diagnosis when an antigen test was not performed (Doering et al., 2006).

The settings of the studies included hospitals in thirteen studies (Bockova et al., 2002; Boyce et al., 2000; Dotan et al., 2013; Garcia et al., 2010; Gavin et al., 2007; Grimwood et al., 2008; Hervas et al., 2012; Koehoorn et al., 2008; Kristensen et al., 2009; Law et al., 2004; Pezzotti et al., 2009; Rietveld et al., 2006; Semple et al., 2011), neonatal units in three studies (Doering et al., 2006; Lanari et al., 2013; Liese et al., 2003) and an emergency department in one study (Mansbach et al., 2005).

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on each individual study can be found in the evidence tables.

3.2.3.8.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 12: GRADE profile for the association between sex (male) and risk of developing severe bronchiolitis

Table 12: GRADE profile for the association between sex (male) and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Sex (male)											
RISK OF BRONCHIOLITIS/RSV HOSPITALISATION											
Association between male gender and admission to hospital from the emergency department in children with bronchiolitis											
1 (Mansbach et al., 2005)	NR	NR	Adjusted OR: 1.2 (0.7 to 2.3)[a]	p=0.511	Very low	Retrospective cohort	Very serious[b]	None	Serious[c]	Very serious[d]	None
Association between male gender and hospitalisation for bronchiolitis											
1 (Pezzotti et al., 2009)	NR Number hospitalised/Total males: 85/1282 (6.6%)	NR Number hospitalised/Total females: 52/1125 (4.6%)	Adjusted IRR: 1.48 (1.04 to 2.10)[e]	p=0.03	Very low	Retrospective cohort	Very serious[f]	None	Serious[g]	Serious[d]	None
1 (Koehoorn et al., 2008)	960/1588 (60.5%)	46888/91438 (51.3%)	Adjusted hazard rate ratio: 1.49 (1.34 to 1.64)[h]	-	Low	Retrospective cohort	Very serious[i]	None	None	None	None
Association between male gender and hospital admission for RSV positive bronchiolitis											
1 (Grimwood et al., 2008)	82/141 (58.2%)	5816/11270 (51.6%)	Adjusted RR: 1.25 (0.89 to 1.75)j	-	Very low	Retrospective cohort	Very serious[k]	None	None	Serious[d]	None
Association between male gender and RSV hospitalisation											
1 (Rietveld et al., 2006)	NR	NR	Adjusted OR: 1.4 (1.3 to 1.5)l	-	Very low	Retrospective cohort	Very serious[m]	None	Serious[n]	None	None
1 (Doering et al., 2006)	NR	NR	Adjusted OR: 2.8 (1.6 to 5.5)o	p<0.01	Very low	Retrospective cohort	Very serious[p]	None	Very serious[q]	None	None
1 (Boyce et al., 2000)	NR	NR	Adjusted IRR: 1.3 (1.2 to 1.4)r	-	Very low	Retrospective cohort	Very serious[s]	None	Serious[t]	Serious[d]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Gavin et al., 2007)	NR	NR	Adjusted OR: 1.07 (0.70 to 1.64)u	-	Very low	Retrospective cohort	Very serious[v]	None	Very serious[w]	Very serious[d]	None
1 (Kristensen et al., 2009)	165/313 (52.7%)	158/313 (50.5%)	Adjusted OR: 1.14 (0.81 to 1.59)x	-	Very low	Retrospective matched case-control	Very serious[y]	None	Very serious[z]	Serious[d]	None
1 (Law et al., 2004)	NR Number hospitalised/total ale: 46/961 (4.8%)	NR Number hospitalised/Total female: 20/796 (2.5%)	Adjusted OR: 1.91 (1.10 to 3.31)[aa]	p=0.02	Very low	Prospective cohort	Serious[ab]	None	Serious[ac]	Serious[d]	None
1 (Lanari et al., 2013)	76/1150 (6.6%)	44/1060 (4.2%)	Adjusted HR: 1.6 (1.1 to 2.4)[ad]	-	Low	Longitudinal multicentre cohort study	Serious[ae]	None	None	Serious[d]	None
RISK OF RSV REHOSPITALISATION											
Association between male gender and RSV rehospitalisation											
1 (Liese et al., 2003)	33/37 (89.2%)	342/680 (50.3%)	Adjusted OR: 8.7 (2.6 to 29.1)[af]	p<0.001	Very low	Retrospective cohort	Very serious[ag]	None	Very serious[ah]	None	None
RISK OF SEVERE RSV DISEASE – BASED ON DISEASE SEVERITY SCORE											
Association between male gender and severe RSV disease - severity score ≥3ai											
1 (Bockova et al., 2002)	25/45 (55.6%)	418/831 (50.3%)	Adjusted OR: 1.2 (0.6 to 2.2)[aj]	-	Very low	Prospective cohort	None	None	Serious[ak]	Very serious[d]	None
RISK OF OXYGEN REQUIREMENT											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 0.80 (0.71 to 0.91)[al]	p<0.0005	Very low	Retrospective cohort	Very serious[am]	None	None	Serious[d]	None
Association between male gender and oxygen requirement in children with non-RSV bronchiolitis											
1 (Hervas et al., 2012)	NR	NR	Adjusted OR: 0.68	p<0.001	Very low	Retrospective review	Very serious[ao]	None	None	Serious[d]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			(0.51 to 0.91)[an]								
Association between male gender and oxygen supplementation in children admitted with bronchiolitis											
1 (Semple et al., 2001)	140/241 (58%)	44/86 (51%)	Adjusted OR: 0.77 (0.43 to 1.38)[ap]	p=0.374	Very low	Prospective cohort	Serious[aq]	None	None	Very serious[d]	None
RISK OF MECHANICAL VENTILATION											
Association between male gender and mechanical ventilation in children admitted with bronchiolitis											
1 (Semple et al., 2001)	31/51 (61%)	44/86 (51%)	Adjusted OR: 1.28 (0.52 to 3.13)[ar]	p=0.592	Very low	Prospective cohort	Serious[as]	None	None	Very serious[d]	None
Association between male gender and severe RSV bronchiolitis – severe defined as the need for assisted ventilation or CPAP in hospitalised children											
1 (Grimwood et al., 2008)	18/34 (52.9%)	64/107 (59.8%)	Adjusted OR: 0.79 (0.34 to 1.85)at	-	Very low	Retrospective cohort	Very seriousau	None	None	Very serious[d]	None
RISK OF LENGTH OF STAY ≥5 DAYS											
Association between male gender and length of stay ≥5 days in RSV positive children hospitalised with bronchiolitis											
1 (Grimwood et al., 2008)	40/64 (62.5%)	42/77 (54.5%)	Adjusted OR: 2.25 (0.85 to 6.00)[av]	-	Very low	Retrospective cohort	Very serious[au]	None	None	Serious[d]	None
ICU ADMISSION											
Association between male gender and ICU admission in RSV infection											
1 (Dotan et al., 2013)	NR	NR	Adjusted OR: 1.97 (1.05 to 3.69)[aw]	-	Very low	Retrospective cohort	Very serious[ax]	None	None	Serious[d]	None

NR not reported, p-value, RR rate ratio, CPAP continuous positive airway pressure, IRR incidence rate ratio, OR odds ratio
a Adjusted for race, ethnicity, insurance status, metropolitan statistical areas, region, season, urgent/emergent visit.
b Retrospective study design, bronchiolitis diagnosis based on reliability of coding system, exclusion criteria not reported, sample size unclear.
c Study is ED based therefore generalizability questionable, bronchiolitis cases were identified using an ICD code which captures both bronchiolitis and bronchitis - 70% of the final sample had code for acute bronchiolitis.
d Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
e Adjusted for age of mother, parity, years of education, birth country of mother, calendar year, age, epidemic period, birth weight, gestational age, apgar score and CHD and BPD.

f Retrospective study design, bronchiolitis hospitalisation (including bronchiolitis due to RSV and other or unknown etiologies) based on reliability of ICD-9 coding system, exclusion criteria not reported.
g All infants premature (<36 weeks gestation).
h Adjusted for maternal age, maternal education, maternal smoking during pregnancy, breastfeeding initiation at hospital, first nations status, parity(older siblings), birth weight, congenital anomalies.
I Retrospective study design, bronchiolitis diagnosis based on reliability of coding systems.
j Adjusted for month of birth, multiple birth, mother smoking during pregnancy, ethnicity, deprivation score, gestational age.
k Retrospective study design, no indication that controls have been tested for RSV, exclusion criteria not reported, 66.5% of eligible participants (admitted during weekdays) were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregivers.
l Adjusted for gestational age, birth weight, BPD, age.
m Retrospective study design, number of controls not reported and unclear whether controls were tested for RSV.
n Bronchiolitis or pneumonia were diagnosed in 93% whereas most of the remaining hospitalised children were diagnosed with upper respiratory tract infection.
o Adjusted for neurologic problems, older sibling, discharge between October to December.
p Retrospective study design, only 31 of 57 children had laboratory proven RSV hospitalisation. Among 26 of 57 children classified as probable RSV-H, 21 were not tested for RSV infection.
q All infants were preterm (29 to 35 weeks gestational age) and also an additional clinical case definition for RSV hospitalisation was used: children hospitalised between October and May with a clinical diagnosis of obstructive bronchitis, bronchiolitis, apnea or a diagnosis of pneumonia in the presence of wheezing were classified as suffering from a probable RSV infection.
r Adjusted for bronchopulmonary dysplasia, congenital heart disease, gestational age, other conditions, number of siblings, race, rural residence, maternal smoking and maternal education <12 years (*other conditions identified included asthma, previous respiratory hospitalisation, cystic fibrosis, cancer, human immunodeficiency virus infection, immunodeficiency, use of chronic oral steroids, chronic renal disease, diabetes, congenital anomalies of the respiratory system, tracheoesophageal fistula, esophageal atresia and stenosis, neonatal respiratory distress syndrome and other respiratory conditions of the fetus and newborn)*
s Retrospective study design, outcome (RSV/bronchiolitis hospitalisation) based on reliability of coding systems. Gestational age missing for ~15% of children - if gestational age was missing from the birth certificate, this was estimated from birth weight with the use of the race and calendar-year specific distributions of gestational age in the population. Exclusion criteria not reported.
t Database used for this study contains information only on children enrolled in Medicaid therefore may not be generalizable.
u Adjusted for race/ethnicity (non-Hispanic white, non-Hispanic black, mixed race, and other/unknown), twin or multiple birth, Medicaid eligibility category, urban/rural residence, whether mother had adequate prenatal care, number of hospital beds per square mile in county, presence of NICU beds in county, % of foreign-born medical graduates in county, presence of a teaching hospital in the county, month of birth, birth weight, presence of siblings, unmarried mother, birth stay ≥7 days, teenaged mother, NICU stay, maternal smoking during pregnancy, ventilator assistance at birth.
v Retrospective study design, outcome based on reliability of coding systems.
w All premature infants (32 to 35 weeks gestation) and infants in low-income families who had continuous Medicaid coverage, also included subjects with one of the following ICD-9-CM codes: 466.11 (acute bronchiolitis due to RSV), 079.6 (RSV infection), or 480.1 (pneumonia due to RSV).
x Adjusted for underlying condition, type of heart disease and haemodynamic significance.
y Retrospective study design, inclusion based on reliability of coding systems.
z Children with heart disease, also children 0-14 years were enrolled, mean age at RSV diagnosis was 362 days (range: 15 to 2379 days).
aa Adjusted for month of birth, small for gestational age, subject attending day care, any preschool age siblings, smokers in the household, >5 individuals in the home, eczema in first degree relative.
ab Controls not tested for RSV.
ac All infants born prematurely.
ad Adjusted for gestational age, treatment with corticosteroids, cigarette smoke exposure, singleton delivery, respiratory diseases, surfactant therapy, lack of breastfeeding, siblings, crowding, humidity, exposed to epidemic RSV season
ae Bronchiolitis hospitalisation based on reliability of coding systems
af Adjusted for birth weight, gestational age, mechanical ventilation, chronic lung disease, cardiac abnormalities, neurological abnormalities, multiple birth, month of discharge, breast feeding, number of siblings, siblings in day care group, family history of allergies.

ag Retrospective study design, data collection largely based on questionnaires sent to parents therefore subject to recall bias, unclear whether controls were tested for RSV, among the 24 infants with probable RSV-RH, 15 were not tested for RSV infection.
ah All preterm infants, also as RSV tests were not regularly performed in all hospitals where infants had been readmitted for ARI-RH, children were classified as having a probable rehospitalisation due to RSV infection, if they had been hospitalised between October and May with such clinical diagnoses typical for RSV infection as acute bronchitis, bronchiolitis, obstructive bronchitis, pneumonia or apnea.
ai Severity based on a previously published severity index (McConnochie et al., 1990), 1 point each was assigned for apnea, pH <7.35, PC02 >45, oxygen saturation <87% and length of stay >5 days, 2 points were assigned for mechanical ventilation. Severity index for each subject was the sum of the points, the maximum score is 7.
aj Adjusted for age, prematurity, underlying condition (CHD, CLD of prematurity, reactive airway disease, 2 or more previous hospitalisations for respiratory infection, history of mechanical ventilation, or immunodeficiency.
ak Included children with mild respiratory symptoms or apnea.
al Adjusted for RSV, weight, age at hospitalisation, race, prematurity, CHD, CLD, trisomy 21, congenital syndromes.
am Retrospective study design, inclusion of subjects based on reliability of ICD coding system.
an Adjusted for nebulised epinephrine, nebulised salbutamol, year, congenital heart disease, atelectasis/condensation, age, gestational age.
ao Retrospective study design, diagnosis of bronchiolitis based on reliability of coding systems.
ap Adjusted for gestation, birth weight, family history of atopy, index of multiple deprivations, corrected age on admission, weight on admission, household tobacco smoker.
aq Infants both admitted and discharged on Saturdays and Sundays were not recruited and some infants admitted on weekdays for less than 24 hours were missed.
ar Adjusted for gestation, birth weight, family history of atopy, index of multiple deprivations, corrected age on admission, weight on admission, household tobacco smoker.
as Infants both admitted and discharged on Saturdays and Sundays were not recruited and some infants admitted on weekdays for less than 24 hours were missed.
at Adjusted for year, month of birth, age at admission, mother smoking during pregnancy, ethnicity, number of other children, gestational age.
au Retrospective study design, exclusion criteria not reported, 66.5% of eligible participants (admitted during weekdays) were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregivers.
av Adjusted for year, multiple birth, age at admission, ethnicity, number of other children living in the house, birth weight.
aw Adjusted for young age, gestational age <32 weeks and being a twin
ax Retrospective study design, data sources not reported

3.2.3.8.3 Evidence statements

Seventeen studies evaluated the odds of developing various outcomes including bronchiolitis/ respiratory syncytial virus hospitalisation, respiratory syncytial virus rehospitalisation, need for oxygen or mechanical ventilation, length of stay ≥5 days and severe respiratory syncytial virus disease defined by a severity score in male infants.

Risk of bronchiolitis/respiratory syncytial virus hospitalisation

Eleven studies evaluated the odds of developing bronchiolitis/ respiratory syncytial virus hospitalisation in male infants. Two studies including several thousand children reported a statistically significant association between male gender and bronchiolitis hospitalisation. The evidence was of low to very low quality. One study (sample size not reported) did not find a statistically significant association between male gender and admission to the hospital from the emergency department in children with bronchiolitis. The evidence was of very low quality. One other study including several thousand children did not report a statistically significant association between male gender and hospital admission for respiratory syncytial virus positive bronchiolitis. The evidence was of very low quality. Five other studies, four of which reported their sample size including several thousand children found reported a statistically significant association between male gender and respiratory syncytial virus hospitalisation, two studies did not. The evidence was of low to very low quality.

Risk of respiratory syncytial virus rehospitalisation

One study including 717 children reported a statistically significant association between male gender and respiratory syncytial virus rehospitalisation. The evidence was of very low quality.

Risk of severe respiratory syncytial virus disease defined by a severity score

One study including 876 children did not find a statistically significant association between male gender and severe respiratory syncytial virus disease defined by a disease severity score ≥3. The evidence was of very low quality.

Risk of oxygen requirement/supplementation

Three studies including over 6000 children evaluated the odds of requiring oxygen supplementation in male infants. Two studies reported a statistically significant association between male gender and oxygen requirement. The evidence was of very low quality. The third study did not find a statistically significant association between male gender and oxygen supplementation. The evidence was of very low quality.

Risk of mechanical ventilation

One study including 137 children did not find a statistically significant association between male gender and mechanical ventilation. The evidence was of very low quality. One other study including several thousand children did not find a statistically significant association between male gender and severe respiratory syncytial virus bronchiolitis defined as the need for assisted ventilation or CPAP. The evidence was of very low quality.

Risk of length of stay ≥5 days

One study including several thousand children did not find a statistically significant association between male gender and length of stay ≥5 days. The evidence was of very low quality.

Risk of ICU admission

One study (sample size not reported) reported a statistically significant association between male gender and ICU admission. The evidence was of very low quality.

3.2.3.8.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5.

3.2.3.8.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7.

3.2.3.9 Previous hospitalisation

3.2.3.9.1 Description of included studies

No evidence was identified for this review.

3.2.3.9.2 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5

3.2.3.9.3 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7.

3.2.3.10 Ethnicity

3.2.3.10.1 Description of included studies

Four observational studies were identified for this review (Boyce et al., 2000; Garcia et al., 2010; Grimwood et al., 2008; Mansbach et al., 2005), all of which were retrospective cohorts. Three studies were conducted in the USA (Boyce et al., 2000; Garcia et al., 2010; Mansbach et al., 2005) and one in New Zealand (Grimwood et al., 2008). Sample size was reported in two studies (Garcia et al., 2010; Grimwood et al., 2008) and were 4589 and 11500 respectively. The age of subjects varied from less than 24 months in three studies (Garcia et al., 2010; Grimwood et al., 2008; Mansbach et al., 2005) to up to 3 years in the remaining study (Boyce et al., 2000). The study which included children less than 3 years of age (Boyce et al., 2000) however restricted the risk factor analysis to the first year of life.

The studies reported on various ethnicities/race including White race (reference not reported) in one study (Boyce et al., 2000), Maori and Pacific race (vs European, Pakeha) in one study (Grimwood et al., 2008), Hispanic (vs non-Hispanic) and Black (vs White) race in one study (Mansbach et al., 2005) and Black (vs White) and Hispanic (vs White) race in one study (Garcia et al., 2010).

The studies reported on various outcomes including RSV/bronchiolitis hospitalisation in three studies (Boyce et al., 2000; Grimwood et al, 2008; Mansbach et al., 2005), and oxygen requirement in one study (Garcia et al., 2010). One of the studies which reported on bronchiolitis hospitalisation (Grimwood et al., 2008) also reported on severe RSV disease defined as assisted ventilation or continuous positive airway pressure as well as length of stay ≥5 days. The study which reported on oxygen requirement (Garcia et al., 2010) also reported on PICU and intubation requirement.

Diagnosis of bronchiolitis/ RSV was based on International Classification of Disease codes in three studies (Boyce et al., 2000; Garcia et al., 2010; Mansbach et al., 2005) and clinical symptoms and signs plus nasopharyngeal aspirates in the remaining study (Grimwood et al., 2008).

The setting of the studies included hospitals in three studies (Boyce et al., 2000; Garcia et al., 2010; Grimwood et al., 2008) and an emergency department in one study (Mansbach et al., 2005).

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on each individual study can be found in the evidence tables.

3.2.3.10.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 13: GRADE profile for the association between ethnicity and risk of developing severe bronchiolitis

Table 13: GRADE profile for the association between ethnicity and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Ethnicity											
RISK OF RSV/BRONCHIOLITIS HOSPITALISATION											
Association between white race (reference not reported) and RSV hospitalisationa											
1 (Boyce et al., 2000)	NR	NR	Adjusted IRR: 1.3 (1.2 to 1.4)[b]	-	Very low	Retrospective cohort	Very serious[c]	None	Serious[d]	Serious[e]	None
Association between Māori ethnicity (vs European, Pakeha) and RSV positive bronchiolitis hospitalisation											
1 (Grimwood et al., 2008)	49/141 (34.8%)	1533/11270 (13.6%)	Adjusted rate ratio: 3.64 (2.27 to 5.85)[f]	p≤0.0001	Low	Retrospective cohort	Very serious[g]	None	None	None	None
Association between Pacific ethnicity (vs European, Pakeha) and RSV positive bronchiolitis hospitalisation											
1 (Grimwood et al., 2008)	37/141 (26.2%)	1207/11270 (10.7%)	Adjusted rate ratio: 3.60 (2.14 to 6.06)[f]	p≤0.0001	Low	Retrospective cohort	Very serious[g]	None	None	None	None
Association between Hispanic ethnicity (vs non-Hispanic) and bronchiolitis hospitalisation from the emergency department											
1 (Mansbach et al., 2005)	NR	NR	Adjusted OR: 2.3 (1.1 to 5.0)h	p=0.029	Very low	Retrospective cohort	Very seriousi	None	Serious[j]	Serious[e]	None
Association between black race (vs white race) and bronchiolitis hospitalisation from the emergency department											
1 (Mansbach et al., 2005)	NR	NR	Adjusted OR: 1.6 (0.9 to 3.2)[k]	p=0.132	Very low	Retrospective cohort	Very serious[i]	None	Serious[j]	Serious[e]	None
RISK OF MECHANICAL VENTILATION											
Association between Māori ethnicity (vs European, Pakeha) and severe RSV bronchiolitis - assisted ventilation or continuous positive airway pressure											
1 (Grimwood et al., 2008)	12/34 (35.3%)	37/107 (34.6%)	Adjusted OR: 1.34 (0.42 to 4.28)[l]	-	Very low	Retrospective cohort	Very serious[m]	None	None	Very serious[e]	None
Association between Pacific ethnicity (vs European, Pakeha) and severe RSV bronchiolitis - assisted ventilation or continuous positive airway pressure											

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Grimwood et al., 2008)	9/34 (26.5%)	28/107 (26.2%)	Adjusted OR: 1.42 (0.36 to 5.52)[l]	-	Very low	Retrospective cohort	Very serious[m]	None	None	Very serious[e]	None
Association between black race (vs white race) and intubation requirement in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 1.73 (0.93 to 3.19)[n]	p=0.999	Very low	Retrospective cohort	Very serious[o]	None	None	Serious[e]	None
Association between Hispanic race (vs white race) and intubation requirement in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 2.17 (1.32 to 3.58)n	p=0.136	Low	Retrospective cohort	Very serious[o]	None	None	None	None
RISK OF LENGTH OF STAY ≥5 DAYS											
Association between Māori ethnicity (vs European, Pakeha) and length of stay ≥5 days in RSV positive children hospitalised with bronchiolitis											
1 (Grimwood et al., 2008)	22/64 (34.4%)	27/77 (35.1%)	Adjusted OR: 1.44 (0.38 to 5.51)[p]	-	Very low	Retrospective cohort	Very serious[m]	None	None	Very serious[e]	None
Association between Pacific ethnicity (vs European, Pakeha) and length of stay ≥5 days in RSV positive children hospitalised with bronchiolitis											
1 (Grimwood et al., 2008)	19/64 (29.7%)	18/77 (23.4%)	Adjusted OR: 2.21 (0.49 to 10.02)[p]	-	Very low	Retrospective cohort	Very serious[m]	None	None	Very serious[e]	None
RISK OF OXYGEN REQUIREMENT											
Association between black race (vs white race) and oxygen requirement in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 0.49 (0.41 to 0.60)[n]	p<0.001	Low	Retrospective cohort	Very serious[o]	None	None	None	None
Association between Hispanic race (vs white race) and oxygen requirement in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 1.12 (0.96 to 1.31)[n]	p=0.149	Very low	Retrospective cohort	Very serious[o]	None	None	Serious[e]	None
RISK OF PICU REQUIREMENT											

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Association between black race (vs white race) and PICU requirement in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 0.89 (0.65 to 1.23)[n]	p=0.486	Very low	Retrospective cohort	Very serious[o]	None	None	Serious[e]	None
Association between Hispanic race (vs white race) and PICU requirement in RSV/non-RSV bronchiolitis											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 1.01 (0.79 to 1.31)[n]	p=0.917	Very low	Retrospective cohort	Very serious[o]	None	None	Serious[e]	None

NR not reported, p-value, OR odds ratio, IRR incidence rate ratio
a Boyce: RSV hospitalisation defined as hospitalisation caused by RSV infection or bronchiolitis. Both of these outcomes based on ICD-9 codes - overall 6.3% of RSV associated hospitalisations were coded specifically for RSV and 93.7% were coded as bronchiolitis.
b Adjusted for BPD, CHD, prematurity, other conditions, number of siblings, gender, rural residence, maternal smoking, maternal education <12 years.
c Retrospective study design, outcome (RSV/bronchiolitis hospitalisation) based on reliability of coding systems, gestational age missing for ~15% of children (if gestational age was missing from the birth certificate, this was estimated from birth weight with the use of the race and calendar-year specific distributions of gestational age in the population), exclusion criteria not reported, reference category not reported.
d Database used for this study contains information only on children enrolled in Medicaid therefore may not be generalizable.
e Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
f Adjusted for gender, month of birth, multiple birth, mother smoking during pregnancy, deprivation score, gestational age.
g Retrospective study design, no indication that controls have been tested for RSV, exclusion criteria not reported, 66.5% of eligible participants (admitted during weekdays) were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregivers.
h Adjusted for sex, race, insurance status, metropolitan statistical areas, region, season and urgent/emergent visit.
I Retrospective study design, bronchiolitis diagnosis based on reliability of coding system, exclusion criteria not reported, sample size unclear.
j Study is ED based therefore generalizability questionable, bronchiolitis cases were identified using an ICD code which captures both bronchiolitis and bronchitis (70% of the final sample had code for acute bronchiolitis).
k Adjusted for sex, ethnicity, insurance status, metropolitan statistical areas, region, season and urgent/emergent visit.
l Adjusted for year, gender, month of birth, age at admission, mother smoking during pregnancy, number of other children, gestational age.
m Retrospective study design, exclusion criteria not reported, 66.5% of eligible participants (admitted during weekdays) were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregivers.
n Adjusted for RSV, weight, age at hospitalisation, gender, prematurity, congenital heart defects, chronic lung disease, trisomy 21, congenital syndromes.
o Retrospective study design, inclusion of subjects based on reliability of ICD coding system.
p Adjusted for year, gender, multiple birth, age at admission, number of other children <16 years living in the house, birth weight.

3.2.3.10.3 Evidence statements

Four studies evaluated the odds of developing various outcomes including RSV /bronchiolitis hospitalisation, need for mechanical ventilation or oxygen, length of stay ≥5 days, and PICU requirement in infants of various ethnicities.

Risk of RSV/bronchiolitis hospitalisation

White race (vs reference not reported)

One study (sample size not reported) found a statistically significant association between white race (reference not reported) and RSV hospitalisation. The quality of the evidence was very low.

Māori ethnicity (vs European, Pakeha), Pacific ethnicity (vs European, Pakeha)

One study including several thousand children reported a significant association between Māori ethnicity (vs European, Pakeha) and RSV positive bronchiolitis hospitalisation. The same study reported a significant association between Pacific ethnicity (vs European, Pakeha) and RSV positive bronchiolitis hospitalisation. The quality of the evidence was low in both cases.

Hispanic ethnicity (vs non-Hispanic), black (vs white race)

One other study (sample size not reported) found a significant association between Hispanic ethnicity (vs non-Hispanic) and bronchiolitis hospitalisation from the emergency department but not for black race (vs white race) and risk of bronchiolitis hospitalisation from the emergency department. The quality of the evidence was very low.

Risk of mechanical ventilation

Māori ethnicity (vs European, Pakeha), Pacific ethnicity (vs European, Pakeha)

One study including several thousand children did not find a significant association between Māori ethnicity (vs European, Pakeha) and severe RSV bronchiolitis defined as assisted ventilation or continuous positive airway pressure. The same study did not find a significant association between Pacific ethnicity (vs European, Pakeha) and severe respiratory syncytial bronchiolitis. The quality of the evidence was very low.

Hispanic race (vs white), black race (vs white)

One study including 448 children reported a significant association between Hispanic race (vs white race) and intubation requirement but not between black race (vs white race) and intubation requirement. The quality of the evidence was low and very low..

Risk of length of stay ≥5 days

Māori ethnicity (vs European, Pakeha), Pacific ethnicity (vs European, Pakeha)

One study including several thousand children did not find a significant association between Māori ethnicity (vs European, Pakeha) and length of stay ≥5 days in RSV positive children hospitalised with bronchiolitis. The same study did not find a significant association between Pacific ethnicity (vs European, Pakeha) and length of stay ≥5 days. The quality of the evidence was very low in both cases.

Risk of oxygen requirement in RSV /non- RSV bronchiolitis

Black race (vs white), Hispanic race (vs white)

One study including 4285 children reported a significant association between black race (vs white race) and oxygen requirement but not between Hispanic race (vs white race) and oxygen requirement. The quality of the evidence was low and very low respectively.

Risk of PICU requirement in RSV/non-respiratory syncytial virus bronchiolitis

Black race (vs white), Hispanic race (vs white)

One study including 4285 children did not find a significant association between black race (vs white race) and PICU requirement nor between Hispanic race (vs white race) and PICU requirement. The quality of the evidence was very low.

3.2.3.10.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5

3.2.3.10.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7

3.2.3.11 Down's syndrome

3.2.3.11.1 Description of included studies

Three studies were identified for this review (Kristensen et al., 2012; Kristensen et al., 2009; Murray et al., 2014). One was a retrospective cohort study (Kristensen et al., 2012), one a retrospective matched case-control study (Kristensen et al., 2009) and one a prospective cohort study (Murray et al., 2014). Two studies were from Denmark and one from England (Murray et al., 2014). Sample sizes ranged from 626 to 391983. The first study (Kristensen et al., 2012) included children up to the age of 24 months. The second study (Kristensen et al., 2009) initially enrolled older children up to the age of 14 years but included children with a mean age at RSV diagnosis of 362 days (range: 15 to 2379 days). The third study included children under 1 year of age (Murray et al., 2014). In terms of setting, the first study (Kristensen et al., 2012) was a National population based study and the remaining two studies (Kristensen et al., 2009; Murray et al., 2014) were hospital based.

All studies examined the association between Down's syndrome and RSV /bronchiolitis hospitalisation – RSV /bronchiolitis hospitalisation was identified using the International Classification of Disease codes.

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on this study can be found in the evidence tables.

3.2.3.11.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 14: GRADE profile for the association between Down's syndrome and risk of developing severe bronchiolitis

Table 14: GRADE profile for the association between Down's syndrome and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Down's syndrome											
Association between Down's syndrome and RSV/bronchiolitis hospitalisation											
1 (Kristensen et al., 2012)	NR Number with RSV hospitalisation/Total number with Down's syndrome: 78/399 (19.5%)	NR	Adjusted IRR: 3.43 (2.66 to 4.42)[a]	P<0.001	Low	Retrospective cohort	Very serious[b]	None	None	None	None
1 (Kristensen et al., 2009)	50/313 (16.0%)	18/313 (5.8%)	Adjusted OR: 3.24 (1.80 to 5.80)[c]	-	Very low	Retrospective matched case-control	Very serious[d]	None	Very serious[e]	None	None
1 (Murray et al., 2014)	NR	NR	Adjusted relative risk: 2.53 (1.72 to 3.72)[f]	-	Moderate	Prospective cohort	Serious[g]	None	None	None	None

NR not reported, p-value, IRR incidence rate ratio, OR odds ratio
a Unclear what confounders were adjusted for
b Retrospective study design, both presence of risk factor (down's syndrome) and outcome (RSV hospitalisation) based on reliability of coding systems, number of cases and controls not explicitly reported, all variables were entered into 1 final multivariable model with no variable selection procedures
c Adjusted for underlying condition, type of heart disease and haemodynamic significance
d Retrospective study design, inclusion based on reliability of coding systems, unclear how presence of down's syndrome was determined (definition not reported)
e Children with heart disease, children aged 0-14 years were enrolled however mean age at RSV diagnosis was 362 days (range: 15 to 2379 days)
f Adjusted for premature birth, cystic fibrosis, congenital heart disease, chronic lung disease, immunodeficiency, nervous system congenital anomalies and cerebral palsy
g Risk factor and bronchiolitis diagnoses based on reliability of coding systems

3.2.3.11.3 Evidence statements

Risk of bronchiolitis/RSV hospitalisation

Three studies including several thousand children evaluated the odds of developing respiratory syncytial virus/bronchiolitis hospitalisation in infants with Down's syndrome. All three studies reported a statistically significant association. The quality of the evidence was moderate to very low.

3.2.3.11.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5.

3.2.3.11.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7.

3.2.3.12 Family smoking

3.2.3.12.1 Description of included studies

Five observational studies were identified for this review (Al-Shehri et al., 2005; Carbonell-Estrany et al., 2001; Lanari et al., 2013; Law et al., 2004; Semple et al., 2001). Four were prospective cohort studies (Carbonell-Estrany et al., 2001; Lanari et al., 2013; Law et al., 2004; Semple et al., 2011) and one was a prospective matched case-control study (Al-Shehri et al., 2005).

One study was undertaken in Saudi Arabia (Al-Shehri et al., 2005), one in Spain (Carbonell-Estrany et al., 2001), one in Italy (Lanari et al., 2013), one in Canada (Law et al., 2004) and one in the UK (Semple et al., 2001). Sample sizes ranged from 166 to 2210.

The age of subjects varied including premature infants in one study (Law et al., 2004), infants less than 6 months of age in one study (Carbonell-Estrany et al., 2001) and infants less than 24 months of age in one study (Semple et al., 2001). One study (Al-Shehri et al., 2005) enrolled children up to 5 years of age, however the mean age of the cases and controls was 7.6 and 8.8 months respectively. The remaining study included consecutive newborns of varying gestational ages (Lanari et al., 2013).

The definition of family smoking varied including a history of smoke exposure (Al-Shehri et al., 2005; Carbonell-Estrany et al., 2001), a smoker in the household (Semple et al., 2001) to greater than two smokers in household (Law et al., 2004) and passive cigarette smoke exposure (Lanari et al., 2013). The studies reported different outcomes such as bronchiolitis/ RSV hospitalisation in three studies (Al-Shehri et al., 2005; Lanari et al., 2013; Law et al., 2004) RSV rehospitalisation in one study (Carbonell-Estrany et al., 2001) and need for oxygen/mechanical ventilation (as separate outcomes) in one study (Semple et al., 2001).

Diagnosis of bronchiolitis/ RSV was based on a bronchiolitis clinical score and nasopharyngeal aspirates in one study (Al-Shehri et al., 2005) clinical symptoms and signs and nasopharyngeal aspirates in one study; Semple et al., 2001) use of coding systems in one study (Lanari et al., 2013) and a viral culture and/or rapid test in one study (Law et al., 2004); the remaining study did not describe the method of diagnosis but some form of RSV testing was performed (Carbonell-Estrany et al., 2001).

The settings of the studies included hospitals in two studies (Law et al., 2004; Semple et al., 2001) a paediatric emergency room and paediatric ward in one study (Al-Shehri et al., 2005) and neonatal units in two studies (Carbonell-Estrany et al., 2001; Lanari et al., 2013).

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on each individual study can be found in the evidence tables.

3.2.3.12.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 15: GRADE profile for the association between family smoking and risk of developing severe bronchiolitis

Table 15: GRADE profile for the association between family smoking and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalised	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Family smoking											
RISK OF BRONCHIOLITIS/RSV HOSPTALISATION											
Association between history of exposure to smoking and bronchiolitis hospitalisation											
1 (Al-Shehri et al., 2005)	Passive smoking: 19/51 (37%)	Passive smoking: 15/115 (13%)	Adjusted OR: 2.51 (2.11 to 3.73)[a]	-	Low	Prospective matched case-control	Serious[b]	None	Serious[c]	None	None
Association between passive cigarette smoke exposure and bronchiolitis hospitalisation											
1 (Lanari et al., 2013)	8/108 (7.4%)	112/2102 (5.3%)	Adjusted HR: 1.5 (0.7 to 3.1)[d]	-	Very low	Longitudinal multicentre cohort study	Serious[e]	None	None	Very serious[f]	None
Association between ≥2 smokers in the household (vs factor not present) and RSV hospitalisation											
1 (Law et al., 2004)	NR Number hospitalised/Total with ≥2 smokers in the household: 20/321 (6.2%)	NR Number hospitalised/Total without ≥2 smokers in the household: 46/1437 (3.2%)	Adjusted OR: 1.71 (0.97 to 3.00)[g]	p=0.064	Very low	Prospective cohort	Serious[h]	None	Seriousi	Serious[j]	None
RISK OF RSV REHOSPITALISATION											
Association between tobacco smoke exposure and RSV rehospitalisation											
1 (Carbonell-Estrany et al., 2001)	45/87 (51.7%)	269/812 (33.1%)	Adjusted OR: 1.63 (1.05 to 2.56)[k]	p=0.031	Very low	Prospective cohort study	Seriousl	None	Serious[m]	Serious[j]	None
RISK OF OXYGEN SUPPLEMENTATION											
Association between household tobacco smoker (yes vs no) and oxygen supplementation in infants admitted with bronchiolitis											
1 (Semple et al., 2001)	154/241 (64%)	41/86 (48%)	Adjusted OR: 2.23 (1.21 to 4.10)[n]	p=0.01	Low	Prospective cohort	Serious[o]	None	None	Serious[j]	None
RISK OF MECHANICAL VENTILATION											
Association between household tobacco smoker (yes vs no) and mechanical ventilation in infants admitted with bronchiolitis											
1 (Semple et al., 2001)	32/51 (63%)	41/86 (48%)	Adjusted OR: 7.19	p=0.001	Moderate	Prospective cohort	Serious[o]	None	None	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalised	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			(2.28 to 22.60)[n]								

NR not reported, p-value, OR odds ratio
a Adjusted for prematurity, congenital heart defects, chronic lung disease, atopic child, father, mother, parents, breastfeeding, age.
b Exclusion criteria not reported, unclear how exposure to smoking was determined.
c Included children ≤5 years but mean age of cases and controls 7.6 and 8.8 months respectively.
d Adjusted for gender and gestational age
e Bronchiolitis hospitalisation based on reliability of coding systems
f Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
g Adjusted for born in November, December or January, gender, small for gestational age, subject attending day care, any preschool age siblings, >5 individuals in the home, eczema in 1st degree relative.
h Controls not tested for RSV.
I All premature infants.
j Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.k Adjusted for gestational age, birth weight, clinical risk index for babies, age at entry to RSV season, month of discharge, siblings at school age
l 10% of admissions not tested for RSV - because 10% of admissions were not tested for RSV, the overall hospitalisation rate for RSV illness was calculated by applying the RSV positive rate in tested patients (63%) to all respiratory hospitalisations (207) and dividing it by the total number of study patients (999), 54/207 lost to follow up (26%).
m All infants born prematurely.
n Adjusted for gestation, birth weight, sex, family history of atopy, index of multiple deprivations 2004, corrected age on admission, weight on admission.
o Infants both admitted and discharged on Saturdays and Sundays were not recruited and some infants admitted on weekdays for less than 24 hours were missed.

3.2.3.12.3 Evidence statements

Five studies evaluated the odds of developing various outcomes including bronchiolitis/ RSV hospitalisation, RSV rehospitalisation, oxygen supplementation and mechanical ventilation in infants with family smoking.

Risk of bronchiolitis/RSV hospitalisation

History of exposure to smoking (vs reference not reported), ≥2 smokers in the household (vs factor not present)

One study including 166 children reported a significant association between history of exposure to smoking and bronchiolitis hospitalisation. The quality of the evidence was low. One study including 440 children did not find a significant association between passive cigarette smoke exposure and bronchiolitis hospitalisation. The quality of the evidence was very low. One other study including 1832 children did not find a significant association between ≥2 smokers in the household (vs factor not present) and RSV hospitalisation. The quality of the evidence was very low.

Risk of RSV rehospitalisation

Tobacco smoke exposure (vs reference not reported)

One study including 999 children reported a significant association between tobacco smoke exposure and RSV rehospitalisation. The quality of the evidence was very low.

Risk of oxygen supplementation/mechanical ventilation

Household tobacco smoker (yes vs no)

One study including 378 children reported a significant association between household tobacco smoker and oxygen supplementation as well as between household tobacco smoker and mechanical ventilation in infants admitted with bronchiolitis. The quality of the evidence was low and moderate respectively.

3.2.3.12.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5

3.2.3.12.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7.

3.2.3.13 Multiple birth

3.2.3.13.1 Description of included studies

Three observational studies were identified for this review (Ambrose et al., 2014; Grimwood et al., 2008; Lanari et al., 2013). Two studies were prospective cohort studies (Ambrose et al., 2014; Lanari et al., 2013) and one was a retrospective cohort study (Grimwood et al., 2008). One study was undertaken in USA (Ambrose et al., 2014), one in Italy (Lanari et al., 2013) and one in New Zealand (Grimwood et al., 2008). Sample size ranged from 57 to 11500 subjects. The age of subjects was infants aged less than or equal to 6 months in one study (Ambrose et al., 2014), infants up to the age of 24 months in one study (Grimwood et al., 2008), and newborns of varying gestational ages in one study (Lanari et al., 2013).

Two studies (Ambrose et al., 2014; Grimwood et al., 2008) examined the association between multiple birth and RSV/bronchiolitis hospitalisation. One of these studies (Grimwood et al., 2008) also examined the association between multiple birth and length of stay greater than or equal to 5 days. The remaining study (Lanari et al., 2013) looked at the association between singleton delivery and bronchiolitis hospitalisation. Bronchiolitis/RSV was diagnosed based on the presence of clinical symptoms and signs in one study (Grimwood et al., 2008) and international classification of diseases codes in one study (Lanari et al., 2013). The remaining study (Ambrose et al., 2014) did not report how RSV diagnosis was made.

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on this study can be found in the evidence tables.

3.2.3.13.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 16: GRADE profile for the association between multiple birth and risk of developing severe bronchiolitis

Table 16: GRADE profile for the association between multiple birth and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Multiple birth											
RISK OF BRONCHIOLITIS/RSV HOSPITALISATION											
Association between multiple birth (yes vs no) and RSV positive bronchiolitis hospitalisation											
1 (Grimwood et al., 2008)	10/141 (7.1%)	524/11270 (4.6%)	Adjusted RR: 1.25 (0.62 to 2.54)[a]	-	Very low	Retrospective cohort	Very serious[b]	None	None	Very serious[c]	None
Association between multiple birth (yes vs no) and RSV hospitalisation											
1 (Ambrose et al., 2014)	NR	NR	Adjusted HR: 0.48d	p=0.043	Moderate	Prospective cohort	Serious[e]	None	None	NC	None
Association between singleton delivery and bronchiolitis hospitalisation											
1 (Lanari et al., 2013)	97/1673 (5.8%)	23/537 (4.3%)	Adjusted HR: 1.8 (1.1 to 2.9)[f]	-	Low	Longitudinal multicentre cohort study	Serious[g]	None	None	Serious[c]	None
RISK OF LENGTH OF STAY ≥5 DAYS											
Association between multiple birth (yes vs no) and length of stay ≥5 days in RSV positive children hospitalised with bronchiolitis											
1 (Grimwood et al., 2008)	8/64 (12.5%)	2/77 (2.6%)	Adjusted OR: 6.52 (0.89 to 47.96)[h]	-	Very low	Retrospective cohort	Very serious[b]	None	None	Serious [c]	None

RR rate ratio, OR odds ratio, p-value
a Adjusted for gender, month of birth, mother smoking during pregnancy, ethnicity, deprivation score and gestational age
b Retrospective study design, no indication that controls have been tested for RSV, exclusion criteria not reported, 66.5% of eligible participants (admitted during weekdays) were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregivers
c Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
d Adjusted for preschool-aged non-multiple birth siblings, age, exposure to smoking
e Imprecision could not be assessed as confidence intervals not reported, control group not defined
f Adjusted for gender, gestational age, treatment with corticosteroids, cigarette smoke exposure, singleton delivery, respiratory diseases, surfactant therapy, lack of breastfeeding, siblings, crowding, humidity, exposed to epidemic RSV season
g Bronchiolitis hospitalisation based on reliability of coding systems
h Adjusted for year, gender, age at admission, ethnicity, number of other children and birth weight

3.2.3.13.3 Evidence statements

Risk of bronchiolitis/RSV hospitalisation

Two studies evaluated the odds of developing RSV /bronchiolitis hospitalisation in infants with multiple birth. One study with several thousand children did not report a statistically significant association, the other did, however this was a statistically significant lower risk of hospitalisation. The quality of the evidence was very low and moderate respectively. One other study with 2210 children reported a statistically significant association between singleton delivery and bronchiolitis hospitalisation. The quality of the evidence was low.

Risk of length of stay ≥5 days

One study including several thousand children did not find a significant association between multiple birth and length of stay ≥5 days. The quality of the evidence was very low.

3.2.3.13.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5.

3.2.3.13.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7.

3.2.3.14 Neuromuscular disorders

3.2.3.14.1 Description of included studies

Six observational studies were identified for this review (Wilkesmann et al., 2007; Garcia et al., 2010; Doering et al., 2006; Kristensen et al., 2012; Murray et al., 2014; Onoyama et al., 2013). Three were retrospective cohort studies (Garcia et al., 2010; Doering et al., 2006; Kristensen et al., 2012), two were prospective cohort studies, (Murray et al., 2014; Wilkesmann et al., 2007) and one was a retrospective case control study (Onoyama et al., 2013). One study was undertaken in Germany (Wilkesmann et al., 2007), one in the USA (Garcia et al., 2010), one in Austria and Germany (Doering et al., 2006), one in Denmark (Kristensen et al., 2012), one in England (Murray et al., 2014) and one in Japan (Onoyama et al., 2013). Sample sizes was reported in five studies (Wilkesmann et al., 2007; Garcia et al., 2010; Kristensen et al., 2012; Murray et al., 2014; Onoyama et al., 2013) and ranged from 61 to 7189. The age of the subjects varied from infants born prematurely in one study (Doering et al., 2006), infants less than 1 year in one study (Murray et al., 2014), and infants less than 24 months in two studies (Garcia et al., 2007; Kristensen et al., 2012). The fourth study (Wilkesmann et al., 2007) included children irrespective of age, however the median age at diagnosis was 430 days for the neuromuscular impairment group and 145 days for the controls. The remaining study (Onoyama et al., 2013) included children less than 16 years of age however the median age of subjects with neurodisability was 21 months and 8 months for the controls.

The definition of neurodisability was reported in five studies (Wilkesmann et al., 2007; Doering et al., 2006; Kristensen et al., 2012; Murray et al., 2014; Onoyama et al., 2013) and varied from identification based on the presence of specific International Classification of Disease codes or a wide range of conditions including, neuromuscular disorders and other neuromuscular impairment.

The studies reported different outcomes including intensive care requirement in two studies (Wilkesmann et al., 2007; Garcia et al., 2010) and RSV /bronchiolitis hospitalisation in three studies (Kristensen et al., 2012 and Doering et al., 2006; Murray et al., 2014). Of the two studies which reported on intensive care requirement, one study additionally reported on respiratory failure (Wilkesmann et al., 2007) and the other reported on oxygen requirement

(Garcia et al., 2010). The remaining study (Onoyama et al., 2013) examined both duration of hospitalisation > 9 days and need for mechanical ventilation.

Diagnosis of bronchiolitis/ RSV included International Classification of Disease codes in three studies (Garcia et al., 2010; Kristensen et al., 2012; Murray et al., 2014) and an antigen test/physician diagnosis in two studies (Doering et al., 2006; Onoyama et al., 2013). In the remaining study, all RSV infections were microbiologically confirmed but the study protocol did not stipulate the precise method of detection (Wilkesmann et al., 2007).

The settings of the studies varied including hospitals in four studies (Wilkesmann et al., 2007; Garcia et al., 2010; Murray et al., 2014; Onoyama et al., 2013) and neonatal units in one study (Doering et al., 2006). The remaining study was a national population based study from Denmark (Kristensen et al., 2012).

In order to address the issue of confounding and ensure that the association observed between the potential risk factor and outcome is largely due to the effect of the risk factor studied rather than any other influencing factors, only studies with adjusted odds ratios/relative risks have been included in this review.

More details on each individual study can be found in the evidence tables.

3.2.3.14.2 Evidence profile

Study quality was assessed using the GRADE methodology. Observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 17: GRADE profile for the association between neurodisability and risk of developing severe bronchiolitis

Table 17: GRADE profile for the association between neurodisability and risk of developing severe bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Neuromuscular disorders											
RISK OF INTENSIVE CARE REQUIREMENT											
Association between neuromuscular impairmenta and intensive care											
1 (Wilkesmann et al., 2007)	NR	NR	Adjusted OR: 4.94 (2.69 to 8.94)[b]	p<0.001	Moderate	Prospective cohort	Serious[c]	None	None	None	None
Association between neuromuscular disorders (not defined) and PICU requirement											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 2.79 (1.43 to 5.46)[d]	p=0.003	Low	Retrospective cohort	Very serious[e]	None	None	None	None
RISK OF RESPIRATORY FAILURE											
Association between neuromuscular impairmenta and respiratory failure											
1 (Wilkesmann et al., 2007)	NR	NR	Adjusted OR: 3.85 (1.28 to 10.22)[b]	p=0.017	Moderate	Prospective cohort	Serious[c]	None	None	None	None
RISK OF RSV/BRONCHIOLITIS HOSPITALISATION											
Association between neurologic problemsf and RSV hospitalisation											
1 (Doering et al., 2006)	NR	NR	Adjusted OR: 3.6 (1.3 to 9.9)g	p=0.01	Very low	Retrospective cohort	Very serious[h]	None	Very serious[i]	None	None
Association between encephalocele (based on ICD code) and RSV hospitalisation											
1 (Kristensen et al., 2012)	NR	NR	Adjusted IRR: 1.54 (1.14 to 2.08)[j]	p=0.005	Very low	Retrospective cohort	Very serious[k]	None	None	Serious[l]	None
	Number with RSV hospitalisation/Total number with encephalocele: 58/542 (10.7%)										
Association between spina bifida and malformations of the spinal cord (based on ICD code) and RSV hospitalisation											
1 (Kristensen et al., 2012)	NR	NR	Adjusted IRR: 2.16 (1.31 to 3.55)j	p=0.002	Low	Retrospective cohort	Very serious[k]	None	None	None	None
	Number with RSV hospitalisation/Total number with										

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
	spina bifida and malformations of the spinal cord: 17/172 (9.9%)										
Association between spinal muscular atrophy (based on ICD code) and RSV hospitalisation											
1 (Kristensen et al., 2012)	NR	NR	Adjusted IRR: 1.02 (0.24 to 4.27)[j]	p=0.983	Very low	Retrospective cohort	Very serious[k]	None	None	Very serious[l]	None
	Number with RSV hospitalisation/Total number with spinal muscular atrophy: 2/39 (5.1%)										
Association between muscular dystrophy (based on ICD code) and RSV hospitalisation											
1 (Kristensen et al., 2012)	NR	NR	Adjusted IRR: 2.49 (1.36 to 4.56)j	p=0.003	Low	Retrospective cohort	Very serious[k]	None	None	None	None
	Number with RSV hospitalisation/Total number with muscular dystrophy: 13/82 (15.9%)										
Association between congenital disturbances of muscle tonus, peripheral nerve disease, congenital myasthenia (based on ICD code) and RSV hospitalisation											
1 (Kristensen et al., 2012)	NR	NR	Adjusted IRR: 1.21 (0.78 to 1.88)j	p=0.4	Very low	Retrospective cohort	Very serious[k]	None	None	Serious[l]	None
	Number with RSV hospitalisation/Total number with congenital disturbances of muscle tonus, peripheral nerve disease, congenital myasthenia: 23/344 (6.7%)										
Association between cerebral palsy (based on ICD code) and RSV hospitalisation											
1 (Kristensen et al., 2012)	NR	NR	Adjusted IRR: 1.59 (1.27 to 1.99)[j]	p<0.001	Low	Retrospective cohort	Very serious[k]	None	None	None	None
	Number with RSV hospitalisation/Total number with cerebral palsy: 93/905 (10.3%)										
Association between cerebral palsy and bronchiolitis hospitalisation											
1 (Murray et al., 2014)	NR	NR	Adjusted relative risk: 2.43 (1.48 to 3.99)[m]	-	Moderate	Prospective cohort	Serious[n]	None	None	None	None
Association between nervous system congenital anomalieso and bronchiolitis hospitalisation											
1 (Murray et al., 2014)	NR	NR	Adjusted relative risk: 1.73	-	Moderate	Prospective cohort	Serious[n]	None	None	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With severe bronchiolitis eg: hospitalisation	Without severe bronchiolitis eg: sent home	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			(1.26 to 2.36)[p]								
RISK OF HOSPITALISATION >9 DAYS											
Association between severe motor intellectual disabilities (SMID)q and hospitalisation > 9 days in RSV infection											
1 (Onoyama et al., 2013)	NR	NR	Adjusted OR: 2.544 (0.677 to 10.294)[r]	p=0.172	Very low	Retrospective case-control	Very serious[s]	None	None	Very serious[l]	None
RISK OF OXYGEN REQUIREMENT											
Association between neuromuscular disorders (not defined) and oxygen requirement											
1 (Garcia et al., 2010)	NR	NR	Adjusted OR: 1.52 (0.87 to 2.64)[d]	p=0.139	Very low	Retrospective cohort	Very serious[e]	None	None	Serious[l]	None
RISK OF MECHANICAL VENTILATION											
Association between severe motor intellectual disabilities (SMID)q and mechanical ventilation in RSV infection											
1 (Onoyama et al., 2013)	NR	NR	Adjusted OR: 5.100 (0.769 to 46.473)[t]	p=0.104	Very low	Retrospective case-control	Very serious[s]	None	None	Serious[l]	None

NR not reported, p-value probability, OR odds ratio, IRR incidence rate ratio
a NMI was an item to be checked in the primary database by the local nurse and the attending physician. Information obtained from free text fields (admission note, discharge summary) was also used to identify all RSV-infected children with NMI. The NMI group included children with: hydrocephalus n=3, cerebral palsy and central hypoventilation syndromes n=41, genetic defects/chromosomal abnormalities n=8, neuromuscular disorders n=8, severe developmental delay n=5, peripheral nerve defects n=2, other NMI as CNS neoplasia or epilepsy n=3.
b Adjusted for prematurity (not defined), born before gest. wk 32, CLDplus, congenital heart disease and nosocomial infection.
c Exclusion criteria not reported
d Adjusted for RSV, weight, age at hospitalisation, male gender, race, prematurity, CHD, CLD, trisomy 21, congenital syndromes, respiratory tract abnormalities
e Retrospective study design, inclusion of subjects based on reliability of ICD coding system.
f The presence of 1 or more of the following diagnoses: intracranial hemorrhage (ICH), grade III or IV (periventricular hemorrhage), cystic periventricular leukomalacia (cPVL), cerebral infarction, hydrocephalus or other symptomatic neurologic conditions.
g Adjusted for male gender, presence of older sibling and discharge from October to December
h Retrospective study design, only 31 of 57 children had laboratory proven RSV hospitalisation. Among 26 of 57 children classified as probable RSV-H, 21 were not tested for RSV infection.

I All infants were preterm (29 to 35 weeks gestational age) and also an additional clinical case definition for RSV hospitalisation was used: children hospitalised between October and May with a clinical diagnosis of obstructive bronchitis, bronchiolitis, apnea or a diagnosis of pneumonia in the presence of wheezing were classified as suffering from a probable RSV infection.
j Unclear what factors were adjusted for, all variables were entered into 1 final multivariable model with no variable selection procedures
k Retrospective study design, both presence of risk factor and outcome based on reliability of coding systems, number of cases and controls not explicitly reported, all variables were entered into 1 final multivariable model with no variable selection procedures.
l Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
m Adjusted for premature birth, cystic fibrosis, congenital heart disease, chronic lung disease, immunodeficiency, downs syndrome and congenital anomalies
n Risk factor and bronchiolitis diagnoses based on reliability of coding systems
o incorporates conditions such as spina bifida, anencephaly, and other congenital malformations of the nervous system
p Adjusted for premature birth, cystic fibrosis, congenital heart disease, chronic lung disease, immunodeficiency, downs syndrome and cerebral palsy
q SMID was diagnosed according to the classical criteria (Oshima's criteria)
r Adjusted for mechanical ventilation and duration of supplemental oxygen
s Retrospective study design, exclusion criteria not reported
t Adjusted for duration of hospitalisation and duration of supplemental oxygen >7 days

3.2.3.14.3 Evidence statements

Six studies evaluated the odds of developing various outcomes including intensive care requirement, respiratory failure, RSV hospitalisation and oxygen requirement in infants with neurodisability.

Risk of intensive care requirement

One study including 1541 children reported a significant association between neuromuscular impairment (which included children with: hydrocephalus, cerebral palsy and central hypoventilation syndromes, genetic defects/chromosomal abnormalities, neuromuscular disorders, severe developmental delay, peripheral nerve defects, other NMI as CNS neoplasia or epilepsy) and intensive care requirement. The quality of the evidence was moderate. One other study including 4285 children reported a significant association between neuromuscular disorders (not defined) and PICU requirement. The quality of the evidence was low.

Risk of respiratory failure

One study including 1541 children reported a significant association between neuromuscular impairment (which included children with: hydrocephalus, cerebral palsy and central hypoventilation syndromes, genetic defects/chromosomal abnormalities, neuromuscular disorders, severe developmental delay, peripheral nerve defects, other NMI as CNS neoplasia or epilepsy) and respiratory failure. The quality of the evidence was moderate.

Risk of RSV/bronchiolitis hospitalisation

One study including 1158 children reported a significant association between neurologic problems (the presence of 1 or more of the following diagnoses: intracranial hemorrhage (ICH), grade III or IV (periventricular hemorrhage), cystic periventricular leukomalacia (cPVL), cerebral infarction, hydrocephalus or other symptomatic neurologic conditions) and RSV hospitalisation. The quality of the evidence was very low.

One study including several thousand children reported a significant association between various neuromuscular diseases including encephalocele, spina bifida and malformations of the spinal cord, muscular dystrophy, and cerebral palsy and RSV hospitalisation (as separate analyses) but not between spinal muscular atrophy, congenital disturbances of muscle tonus, peripheral nerve disease, congenital myasthenia and RSV hospitalisation. The quality of the evidence was low to very low.

One other study including several thousand children reported a significant association between cerebral palsy and bronchiolitis hospitalisation and also between nervous system congenital anomalies and bronchiolitis hospitalisation. The quality of the evidence was moderate.

Risk of hospitalisation >9 days

One study including 61 children did not find a significant association between severe motor intellectual disabilities and hospitalisation greater than 9 days in RSV infection. The quality of the evidence was very low.

Risk of oxygen requirement

One study including 4285 children did not find a significant association between neuromuscular disorders (not defined) and oxygen requirement. The quality of the evidence was very low.

Risk of mechanical ventilation

One study including 61 children did not find a significant association between severe motor intellectual disabilities and mechanical ventilation in RSV infection. The quality of the evidence was very low.

3.2.3.14.4 Evidence to recommendations

The evidence to recommendations covering risk-factors can be found in section 3.2.5.

3.2.3.14.5 Recommendations

The recommendations covering risk-factors can be found in section 3.2.7.

3.2.4 Health economics profile

No health economic data was identified on risk-factors and no health economic evaluation was undertaken.

3.2.5 Evidence to recommendations

3.2.5.1 Relative value placed on the risk-factors considered

The GDG considered that as part of the evaluation of any infant or child presenting with bronchiolitis consideration of any known risk factor for progression to severe bronchiolitis should be given. The GDG prioritised the following risk factors to be reviewed: history of prematurity, congenital heart disease, chronic lung disease, cystic fibrosis, immunodeficiency, non-breast fed, young infants (under 3 months), sex (male), previous hospitalisation, ethnicity, Down's syndrome, family smoking, multiple birth, neuromuscular disorders. These were given priority because they are often assumed to be associated with more severe bronchiolitis and they are at least reasonably common in clinical practice.

The GDG considered that the size of the associated risk could help determine the need for further investigation and early identification of those at risk and help to inform the management strategy.

3.2.5.2 Consideration of clinical usefulness of risk-factor

History of premature birth

The GDG discussed the risk of severe bronchiolitis in prematurely born infants, acknowledging that those born prematurely may often be admitted to hospital as a matter of protocol. The GDG therefore was uncertain how reliable the available evidence regarding hospital admission may have been in demonstrating "history of prematurity" as a true risk factor for severe disease. The GDG recognised that the studies reviewed used a variety of definitions for severe bronchiolitis and they considered that admission to ICU was a more reliable marker than admission to hospital. They looked particularly at the evidence from five studies examining various degrees of prematurity that showed an increasing risk of severe bronchiolitis with increasing degrees of prematurity. However, the GDG noted that in recent years the general consensus was that only marked prematurity was a serious risk factor. Using the limited evidence that showed significant associations for risk of RSV hospitalisation; RSV re-hospitalisation; ICU admission; mechanical ventilation; hypoxemia; and respiratory failure with gestational age and their clinical knowledge, the GDG agreed that a history of premature birth should be recognised as a risk factor but particularly in those born before 32 weeks of gestation.

Congenital heart disease

As with prematurity, the GDG was aware that evidence linking congenital heart might reflect clinical practice rather that being a true marker for severity of bronchiolitis. While patients might have been admitted because their bronchiolitis was severe, it was also possible that some admission might have reflected medical caution based on the knowledge that the child also had a congenital heart disorder. The GDG noted that it is important to take account of the type of congenital heart disease both in terms of its nature and severity. They noted that only 2 of the 13 studies included considered this. Based on their clinical knowledge, the GDG believed that there is more likely an increased risk of severe bronchiolitis in children with congenital heart disease if it is hemodynamically significant such as associated with a degree of heart failure (even if controlled with medication). Infants with heart failure, for example due to a ventricular septal defect, may have faltering growth and often have difficulty with feeding due to the associated increase in work of breathing with their condition. The GDG recognised that such infants would clearly be further compromised were they to experience additional breathing difficulties with bronchiolitis.

Chronic lung disease (including bronchopulmonary dysplasia)

The GDG considered that the most common form of chronic lung disease was bronchopulmonary dysplasia, a disorder seen in prematurely born infants and children. Other forms of chronic lung disease, although less frequent, also existed and were likely to be important in this context for those affected, for example the lung disease associated with cystic fibrosis (see below) and also interstitial lung disease. The GDG noted the evidence of increased risk for severe bronchiolitis in babies with bronchopulmonary dysplasia. Because it is a condition associated with premature birth, it was not possible to separate the lung condition per se from other aspects of prematurity. However, it was considered that it was likely to be an important factor, a serious underlying chronic respiratory condition almost certainly contributing to the risk of severe symptoms in those developing bronchiolitis. Many infants with bronchiolitis require long-term O2 supplementation and hypoxia was of course a common manifestation of severe bronchiolitis. The GDG concluded that chronic lung disease should therefore be considered a potential risk factor for developing serious illness with bronchiolitis.

Cystic fibrosis

Evidence was limited to two studies for this risk factor. The GDG noted that evidence from one of these was unsatisfactory because the comparison did not identify the risk of hospitalisation for children with cystic fibrosis with bronchiolitis, but identified the children with cystic fibrosis that were in hospital for any reason. Cystic fibrosis was therefore not recommended as a risk factor for severe bronchiolitis. There are children with cystic fibrosis who do not have clinical manifestations of chronic lung disease. However, it was recognised that many infants and children with cystic fibrosis do have chronic lung disease and in some this is severe. The recommendation on chronic lung disease as a risk factor would include such individuals.

Immunodeficiency

Severe immunodeficiency states including congenital immunodeficiencies such as agammaglobulinaemia and severe combined immune deficiency are rare conditions and their management is a specialist area. The available evidence regarding congenital immunodeficiency as a risk factor for severe bronchiolitis was very limited, and again as with other presumed risk factors, the decision to admit to hospital was an outcome that might well reflect clinical caution rather than disease severity. The same was true for length-of-stay in the study of children with HIV infection. Nevertheless, based on their clinical knowledge and taking account of the well known vulnerability of children with these rare and serious

conditions to severe viral infections generally, the GDG agreed that such conditions should be considered a potential risk factor for severe bronchiolitis.

Non-breast fed

Evidence from six studies showed that some breastfeeding was better than not being breast fed at all in terms of the risk for severe bronchiolitis. Moreover, the risk of severe bronchiolitis was found to decrease the longer the duration of breast feeding. The GDG recognised that breast-feeding might be linked to other socioeconomic confounding factors, but nevertheless they were persuaded by the evidence that if a child with bronchiolitis was not breast fed this should be considered a risk factor for severe bronchiolitis.

Age

The GDG considered the evidence regarding the possibility that young infants might be at increased risk for severe bronchiolitis. The GDG recognised that again the evidence might be misleading, if for example parents were more inclined to take younger infants to hospital and doctors might be more likely to admit them to the hospital for observation. The GDG did note however that studies comparing the risk for different age categories found a progressive effect, the younger the child the greater the risk of severe bronchiolitis. Most persuasively, the GDG noted that the risk of admission to ICU was particularly increased in infants under 2 months of age and even more so in infants less than 30 days of age. Clinical experience supported the importance of young age as a contributor to the seriousness of respiratory difficulties – for example pertussis in young infants can be a life threatening condition. The GDG concluded that young age should be considered a risk factor and based on these considerations and based on consensus they agreed that being under 3 months of age was likely to be particularly greater risk for severe disease.

Sex (male)

The GDG considered the possibility that male gender might be a risk factor for severe bronchiolitis as it is generally considered that male infants are at increased risk from serious illness including respiratory conditions. The GDG noted although once admitted to hospital there was no evidence that male infants fared less well than female infants (no differences in reported outcomes), there was evidence that a significantly higher proportion were actually admitted to hospital and this clearly suggested more severe disease and so they considered that male sex should be considered as a risk factor.

Previous hospitalisation

Although the GDG considered the possibility that previous hospitalisation might also be a risk factor for severe bronchiolitis, no evidence was found to support this and so the recommendations do not include it as a risk factor.

Ethnicity

Although the GDG considered the possibility that ethnicity might also be a risk factor for severe bronchiolitis, the lack of evidence from the UK meant that the recommendation does not include it as a risk factor.

Down’s syndrome

Evidence was limited to three studies for this review. In one of these studies, RSV testing was only undertaken in patients admitted to hospital and the GDG was concerned that this his could have led to an over-estimate of effect. The GDG noted that a further study included children with heart disease (a known comorbidity in Down’s syndrome) and this itself was a potential risk for severe bronchiolitis. Given these limitations in the evidence, the GDG

therefore did not recommend Down's syndrome be considered a risk factor for severe bronchiolitis.

Family smoking

The available evidence on the importance of family smoking consisted of five studies in this review. The definitions of household smoking exposure varied among the studies and there was variation in the findings. Some an increased risk of hospital admission, or of need for oxygen supplementation or in one study need for mechanical ventilation in those exposed compared with controls. The studies were not consistent in their findings, no effect being found in some, but the GDG considered that the available evidence together with current knowledge of the adverse effects of passive smoke inhalation generally were sufficient for them to recommend that household smoke exposure should be considered a risk factor for severe disease.

Multiple birth

Evidence was limited to three studies for this review. The GDG noted that in one of these studies reported that multiple birth was associated with a reduced risk of RSV hospitalisation and another reported that singleton birth increases the risk of hospitalisation. The GDG's considered that multiple birth might perhaps be associated with a reduced clinical threshold for admission to hospital – based on the perceived or real difficulties of coping with such a situation at home. The GDG therefore did consider there was sufficient evidence or a rationale to recommend multiple birth be included as a risk factor for severe bronchiolitis.

Neuromuscular disorders

Evidence from six studies was found for this review, with the majority showing significant findings. The GDG recognised that the studies included a very varied mix of neuromuscular conditions and that it was not possible to determine the particular types of disorder or subgroups of those disorders who were at risk of severe bronchiolitis. Nevertheless, based on the GDG's knowledge and experience they were persuaded that such disorders generally are potential risk factors for severe bronchiolitis, and if present they should be taken into account when determining the risk of progression to severe disease.

3.2.5.3 Consideration of health benefits and resource uses

The lack of simple, sensitive tests available for this condition meant that initial diagnosis would have to be based on risk factors, signs and symptoms and examination in the first instance. Defining which risk factors should be considered and which should not will lead to more appropriate diagnosis of bronchiolitis. Infants with risk factors for severe disease will then be admitted and treated promptly, and unnecessary admissions can be avoided therefore reducing resource use without impacting on health benefits.

3.2.5.4 Quality of evidence

History of prematurity

The main sources of bias were: retrospective study design, inclusion based on reliability of coding system (researchers selected all subjects with the bronchiolitis ICD code from a database), and imprecision in the results which meant that the usefulness of a risk factor was uncertain. The evidence was of moderate to very low quality.

Congenital heart disease

The main sources of bias in these were: retrospective study design, diagnoses based on reliability of coding systems, and imprecision in the results which meant that the usefulness of a risk factor was uncertain. Some studies also enrolled older children, although the mean age of the included subjects was generally less than 2 years. The GDG was less convinced with data from retrospective chart reviews because they are dependent on the reliability of coding systems/people's memory but this was taken into account and downgraded as appropriate. The evidence was of moderate to very low quality.

Chronic lung disease

The main sources of bias in these were: retrospective study design, lack of testing of control subjects for RSV, diagnoses based on reliability of coding systems, and imprecision in the results which meant that the usefulness of a risk factor was uncertain. The evidence was of moderate to very low quality.

Cystic fibrosis

This review was limited to two observational studies. The main sources of bias were: both risk factor and outcome based on reliability of coding systems and inadequate adjustment of confounding factors (all variables were entered into one multivariate model with no variable selection procedures). The evidence was of moderate to low quality.

Immunodeficiency

This review was limited to three observational studies. The main sources of bias were: both risk factor and outcome based on reliability of coding systems and inadequate adjustment of confounding factors (all variables were entered into one multivariate model with no variable selection procedures). The evidence was of moderate to low quality.

Non-breast fed

The main sources of bias were: retrospective study design and imprecision in the results which meant that the usefulness of a risk factor was uncertain. One study did not report confidence intervals which meant that imprecision could not be assessed in the standard way. The evidence was of low to very low quality.

Young infants (for example, less than 3 months)

The main sources of bias were: retrospective study design, indirect population in a number of studies (e.g. all premature infants, inclusion of older children) and lack of clarity for the reference groups used in the risk factor analysis. The evidence was of moderate to very low quality.

Sex (male)

The main sources of bias were: retrospective study design, inclusion based on reliability of coding system, and imprecision in the results which meant that the usefulness of a risk factor was uncertain. The evidence was of low to very low quality.

Previous hospitalisation

No evidence was identified for this review.

Ethnicity

The main sources of bias were: retrospective study design, inclusion of subjects based on reliability of coding systems, and imprecision in the results which meant that the usefulness of a risk factor was uncertain. The evidence was of low to very low quality.

Down's syndrome

This review was limited to three observational studies, two of which had a retrospective design. The main sources of bias were: inclusion based on reliability of coding systems and inadequate adjustment of confounding factors (all variables were entered into one multivariate model with no variable selection procedures). One study also enrolled older children aged 0 to 14 years, however the mean age at RSV diagnosis was 362 days (range: 15 to 2379 days). The evidence was of moderate to very low quality.

Family smoking

The main sources of bias were: lack of RSV testing in controls, and imprecision in the results which meant that the usefulness of a risk factor was uncertain. The evidence was of moderate to very low quality.

Multiple birth

This review was limited to three observational studies. The main sources of bias were: no indication that controls have been tested for RSV, exclusion criteria not reported and only 66.5% of eligible participants (admitted during weekdays) enrolled, the main reason for non-participation was discharge from hospital before research staffs were able to approach their caregivers. The evidence was of moderate to very low quality.

Neuromuscular disorder

The main sources of bias in these were: retrospective study design and diagnoses based on reliability of coding systems. The evidence was of moderate to very low quality.

3.2.5.5 Other considerations

No equality issues were specified for this question.

3.2.6 Conclusion

The GDG concluded that nine of the 15 factors should be considered as risk factors for severe bronchiolitis. These were: chronic lung disease (including bronchopulmonary dysplasia), congenital heart disease, particularly if this is hemodynamically significant, young age, particularly less than 3 months, prematurity, particularly less than 32 weeks, neuromuscular disorders, immunodeficiency, male sex, if the child has not been breast fed and if the child comes from a household with people who smoke.

3.2.7 Recommendations

8. Check for the following potential risk factors for developing more severe bronchiolitis:

- chronic lung disease (including bronchopulmonary dysplasia)
- congenital heart disease, particularly if this is hemodynamically significant
- age in young infants (under 3 months)

- premature birth, particularly under 32 weeks
- neuromuscular disorders
- immunodeficiency
- male sex
- if the child has not been breast fed
- if the child comes from a household with people who smoke

3.3 Predictors of deterioration

3.3.1 Review question

At the time of assessment, what clinical features predict deterioration?

Further details on the protocol for this review question are provided in Appendix E.

3.3.2 Introduction

Bronchiolitis has a broad spectrum of disease severity. The majority of children have a mild self-limiting form of the disease that can be successfully managed at home. Some patients develop progressive respiratory distress, which requires medical intervention and support. A small proportion of children can rapidly deteriorate and develop a more severe or life threatening form of bronchiolitis which requires urgent medical intervention. It is therefore vital that health care professionals are aware of and can recognise those clinical features that can predict deterioration to ensure appropriate management of those at risk and to improve health outcomes. This evidence review is related to the evidence review on "risk factors for severe bronchiolitis", but considers clinical features of the illness itself.

3.3.3 Description of included studies

Eight studies assessing the association between clinical features and deterioration were included in this review.

Three studies used a retrospective design (Corneli et al., 2012; Walsh et al., 2004; Yusuf et al., 2012), four were conducted using a prospective multicentre cohort design (Corrard et al., 2013; Damore et al., 2008; Mansbach et al., 2012; Schroeder et al., 2013), while one was a prospective cohort (Parker et al., 2009).

One study was performed in an Emergency Department Observation Unit of a children's hospital (Yusuf et al., 2012); one study used data from 18 community paediatrician clinics (Corrard et al., 2013); two studies were performed in a paediatric hospital ED (Walsh et al., 2004 and Parker et al., 2009); three studies were part of the Multicenter Airway Collaboration, two of them used data from 16 different paediatric hospital EDs (Schroeder et al., 2013 and Mansbach et al., 2012), while the third one involved a total of 30 different sites (Damore et al., 2008); and finally, one study was performed in 20 different paediatric hospital EDs of the Paediatric Emergency Care Applied Network (Corneli et al., 2012).

One study was performed in Ireland (Walsh et al., 2004), five in the Unites States (Schroeder et al., 2013; Corneli et al., 2012; Damore et al., 2008; Mansbach et al., 2012; Yusuf et al., 2012), one study in France (Corrard et al., 2013), and one in Canada (Parker et al., 2009).

The age of included infants varied between studies: five of them considered children aged up to 2 years (Walsh et al., 2004; Schroeder et al., 2013; Damore et al., 2008; Mansbach et al., 2012; Yusuf et al., 2012); one included children aged 2 to 23 months (Parker et al., 2009); one considered children aged 2 to 12 months (Corneli et al., 2012), and one included infants up to 6 months of age (Corrard et al., 2013).

Diagnosis of bronchiolitis was determined by a consultant paediatrician in one study (Walsh et al., 2004), by an attending physician in four studies (Schroeder et al., 2013; Damore et al., 2008; Mansbach et al., 2012; Yusuf et al., 2012), and by trained study clinicians in another study (Corneli et al., 2012). Two studies based the diagnosis of bronchiolitis on the presence of signs and symptoms: rhinorrhoea, cough, dyspnoea and expiratory breath sounds (Corrard et al., 2013) or coryza, cough, and the first episode of respiratory distress (Parker et al., 2009).

Definition of deterioration varied, including admission to hospital in four studies (Walsh et al., 2004; Corneli et al., 2012; Corrard et al., 2013; Yusuf et al., 2012), apnoea in one study (Schroeder et al., 2013), the need for CPAP and/or intubation in one study (Mansbach et al., 2012), the need for a major medical intervention in one study (Parker et al., 2009), and finally one study defined deterioration as the need for ICU admission (Damore et al., 2008).

The clinical features specified as predictors of deterioration by the GDG for this review were:

- Duration of illness (days from onset)
- Heart rate (taking account of age)
- Respiratory rate (taking account of age)
- Fever (height of fever)
- SpO_2 (e.g., <92%)
- Ability to feed (e.g., <50% or <75% normal)
- Subjective assessments, e.g., social responses

In order to ensure that the association observed between the clinical feature and outcome is independent of any other factors, only studies that undertook case-mix adjustment have been included in this review.

The evidence presented for this question overlaps with that used for the question on criteria for referral.

More details on each individual study can be found in the evidence tables in Appendix I.

3.3.4 Evidence profile

Study quality was assessed using the GRADE methodology. Prospective observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 18: GRADE profile for association between clinical features and risk for progressing to severe bronchiolitis

Table 18: GRADE profile for association between clinical features and risk for progressing to severe bronchiolitis

	Number of children		Effect				Quality assessment				
Number of studies	With Bronchiolitis deterioration: e.g. Hospitalization	Without deterioration: e.g. Discharge	Relative (95% CI)	Absolute (95% CI)	Quality	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Heart Rate											
ADMISSION TO HOSPITAL – vs. discharge											
Heart rate > 97th percentile (derivation set – 1st Hospital)											
1 study (Walsh et al. 2004)	N = 62	N = 37	Adjusted OR a: 3.78 (1.05 to 13.57)	P=0.041	Very low	Retrospective review	Very Serious [b]	None	Serious [c]	Serious [d]	Some [e]
Heart rate > 97th percentile (validation set – 2nd Hospital)											
1 study (Walsh et al. 2004)	N = 43	N = 139	Adjusted OR a: 5.58 (1.42-21.98)	P=0.014	Very Low	Retrospective review	Very Serious [b]	None	Serious [c]	None	None
Respiratory Rate											
ADMISSION TO HOSPITAL – vs. discharge											
Respiratory rate > 60 breaths/min											
1. Corneli et al. 2012	Admitted n=240 Mean RR= 55.8 breaths/min	Discharged n=358 Mean RR= 51.5 breaths/min	Adjusted OR f: 2.6 (1.7-4.1)	P<0.0001	Very Low	Secondary analysis of a multicentre randomized trial	Very Serious [g]	None	Serious [h]	None	Some [i]
APNOEA j – vs. no apnoea											
Respiratory rate < 30 breaths/min k											
1. Schroeder et al. 2013	N = 13/108	N = 102/2048	Adjusted OR l: 4.05 (2.00-8.20)	P<0.001	Moderate	Prospective multicentre cohort study	Serious [m]	None	Serious [n]	None	None
Respiratory rate 30-39 breaths/min k											
1. Schroeder et al. 2013	N = 26/108	N = 369/2048	Adjusted OR l: 2.35 (1.52-3.64)	P<0.001	Moderate	Prospective multicentre cohort study	Serious [m]	None	Serious [n]	None	None
Respiratory rate 50-59 breaths/min k											
1.	N = 16/108	N = 348/2048	Adjusted	P=0.46	Low	Prospective	Serious	None	Serious [n]	Very Serious	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With Bronchiolitis deterioration: e.g. Hospitalization	Without deterioration: e.g. Discharge	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Schroeder et al., 2013			OR l: 1.29 (0.66-2.51)			multicentre cohort study	[m]			[d]	
Respiratory rate 60-69 breaths/min k											
1. Schroeder et al., 2013	N = 15/108	N = 389/2048	Adjusted OR l: 1.06 (0.62-1.81)	P=0.84	Low	Prospective multicentre cohort study	Serious [m]	None	Serious [n]	Very Serious [d]	None
Respiratory rate >70 breaths/min k											
1. Schroeder et al., 2013	N = 14/108	N = 205/2048	Adjusted OR l: 2.26 (1.03-4.95)	P=0.04	Low	Prospective multicentre cohort study	Serious m	None	Serious n	Serious [d]	None
MAJOR MEDICAL INTERVENTION o – vs. no MMI											
Respiratory rate ≥ 60 breaths/min											
1. Parker et al., 2009	N = 25/52	N = 32/260	Adjusted OR p: 1.85 (0.97-3.54)	-	Low	Prospective cohort study	Serious [q]	None	Serious [r]	Serious [d]	None
Oxygen Saturation											
ADMISSION TO HOSPITAL – vs. discharge											
Initial oximetry value < 94%											
1. Corneli et al. 2012	SpO_2, % Admitted=95.7	SpO_2, % Discharged=97.2	Adjusted OR s: 5.5 (2.9-10.2)	P<0.0001	Low	Secondary analysis of a multicentre randomized trail	Very Serious [g]	None	Serious [h]	None	Some [i]
SpO_2 < 95%											
1. Corrard et al., 2013	N = 11/17	N = 4/154	Adjusted OR t: -	P<0.0001	Very Low	Prospective multicentre observational study	Very Serious [u]	None	Serious v	NC [w]	None
Pulse oximetry < 93%											
1. Yusuf et al., 2012	N = 8/85 *	N = 5/240 *	Adjusted OR x: 4.72	P=0.009	Low	Retrospective cohort study	Serious [y]	None	Serious [z]	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With Bronchiolitis deterioration: e.g. Hospitalization	Without deterioration: e.g. Discharge	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			(1.47-15.18)								
APNOEA j – vs. no apnoea											
Lowest documented oxygen saturation over entire preadmission visit <90%											
1. Schroeder et al., 2013	N = 44/108	N = 573/2048	Adjusted OR aa: 1.60 (1.03-2.46)	P=0.04	Low	Prospective multicentre cohort study	Serious [m]	None	Serious [n]	Serious [d]	None
CPAP/INTUBATION – vs. no cpap/intubation											
Oxygen saturation <85%											
1. Mansbach et al., 2012	N = 17/161	N = 3/1998	Adjusted OR bb: 3.28 (2.02-4.82)	-	Moderate	Prospective multicentre cohort study	Serious cc	None	Serious dd	None	None
Oxygen saturation 85-87,9%											
1. Mansbach et al., 2012	N = 6/161	N = 3/1998	Adjusted OR bb: 1.34 (0.57-3.43)	-	Low	Prospective multicentre cohort study	Serious cc	None	Serious dd	Very serious [d]	None
Oxygen saturation 88-89,9%											
1. Mansbach et al., 2012	N = 6/161	N = 4/1998	Adjusted OR bb: 1.91 (0.79-3.80)	-	Low	Prospective multicentre cohort study	Serious cc	None	Serious dd	Serious [d]	None
Oxygen saturation 90-93.9%											
1. Mansbach et al., 2012	N = 16/161	N = 17/1998	Adjusted OR bb: 1.15 (0.70-1.52)	-	Low	Prospective multicentre cohort study	Serious cc	None	Serious dd	Very serious [d]	None
MAJOR MEDICAL INTERVENTION o – vs. no MMI											
Oxygen saturation ≤92%											
1. Parker et	N = 9/52	N = 16/260	Adjusted	-	Low	Prospective	Serious	None	Serious [r]	Serious [d]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	With Bronchiolitis deterioration: e.g. Hospitalization	Without deterioration: e.g. Discharge	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
al., 2009			OR p: 2.41 (0.96-6.14)			cohort study	[q]				
Ability to feed											
ADMISSION TO HOSPITAL – vs. discharge											
24h Food Intake <50%											
1. Corrard et al., 2013	N = 9/17	N = 15/150	Adjusted OR ee: 10.6 (3.0-37.3)	-	Low	Prospective multicentre observational study	Very Serious [u]	None	Serious [v]	None	None
CPAP/INTUBATION – vs. no cpap/intubation											
Inadequate oral intake											
1. Mansbach et al., 2012	N = 63/161	N = 41/1998	Adjusted OR ff: 2.51 (1.34-4.26)	-	Moderate	Prospective multicentre cohort study	Serious [c]	None	Serious dd	None	Some [gg]
ICU ADMISSION – compared to regular floor admissions											
Inadequate oral intake											
1. Damore et al., 2008	N = 26/50 *	N = 165/533 *	Adjusted OR hh: 3.31 (1.55-7.07)	P=0.002	Moderate	Prospective multicentre cohort study	Serious [ii]	None	Serious [jj]	None	None

NC not calculable, NR not reported, p-value, OR odds ratio
** Calculated by the NCC-WCH technical team from data reported in the article*
a. Adjusted for age, increased work of breathing and dehydration status
b. Unclear which treatments were received by participants in the ED; demographic characteristics are based on the number of episodes of bronchiolitis (118) instead of the number of patients: also, 23 of 99 patients were excluded from the analysis because of missing values. Is then unclear how many analysed patients (n=76) in the derivation phase were admitted or discharged. No significance level reported for the inclusion in the statistical model; unclear definition of "severe disease" (refers both to admission and LOS); authors defined "need for admission" as a hospital stay of more than 24 h, retrospectively categorizing those who were discharged on initial consultant review as fit for discharge; retrospective study design.
c. Children aged up to 2 years (The GDG has specified that it is likely that older children will not have bronchiolitis); outcome definition based on length of stay.
d. Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
e. Disposition was reviewed by a consultant paediatrician within 24 h. A substantial number are discharged at this initial review. Therefore, authors defined "need for admission" as a hospital stay of more than 24 h, retrospectively categorizing those who were discharged on initial consultant review as fit for discharge.
f. Adjusted for initial oximetry value and RDAI score.

g. The study excluded children with risk factors, premature infants, infants with bronchiolitis complications (apnoea), and those younger than 2 months; unclear timing of baseline measurements. Also, no significance level for included variables in the multivariate model is specified; retrospective study design.
h. Very small children excluded from the study (younger than 2 months).
i. In the original trial, patients were randomized to receive either oral dexamethasone or placebo (no treatment effect demonstrated in the original trial); 22 patients were subsequently hospitalized during the 7 days after ED discharge and their data were not treated as admission in the analysis.
j. To examine inpatient apnoea among children admitted to the hospital with bronchiolitis, authors identified all children who experienced apnoea at any time during their hospitalization.
k. Respiratory rate recorded at preadmission visit (ED)
l. Adjusted for age, gender, race, birth weight and lowest documented oxygen saturation over entire preadmission visit <90%; reference = respiratory rate 40-49.
m. Patients enrolled in academic medical centres, and therefore results may not be generalizable to community medical centres; ED and daily hospital data were obtained by chart review.
n. Children aged up to 2 years (The GDG has specified that it is likely that older children will not have bronchiolitis).
o. MMI defined as oxygen administration for 30 min or more for saturation <90% in room air, IV fluid bolus of 20ml/kg or more, any treatment for apnoea, or admission to Critical Care Unit.
p. Adjusted for decreased dehydration, accessory muscle score ≥6/9, oxygen saturation/respiratory rate, age, prolonged stay>12 hr.
q. Premature infants and those younger than 2 months were excluded from the study; overall population baseline characteristics not reported; some data were obtained through retrospective chart review.
r. Children aged up to 23 months (The GDG has specified that it is likely that older children will not have bronchiolitis).
s. Adjusted for respiratory rate and RDAI score.
t. Adjusted for age<2months, food intake <50%, intercostal retractions.
u. The study excluded patients with risk factors (prematurity, chronic lung or heart disease) and breast-fed children; the statistical analysis is unclear about how they constructed the regression model (no significance level reported); incomplete results; ORs not adjusted for other relevant clinical signs reported in the study like respiratory rate and temperature.
v. Only infants aged 0-6 months were considered for the study.
w. it was not possible to assess imprecision because of the lack of information provided (No OR and CI reported).
x. Adjusted for IVF in ED.
y. Not reported how prognostic factors were measured; authors report that primary reason for admission from the EDOU was sometimes absent from the chart; univariate association table difficult to interpret because of the way results are reported (patients demographics only reported as the admitted frequency); patients received treatments (i.e. oxygen supplementation) while in the ED, before disposition; retrospective study design.
z. Children aged up to 2 years (The GDG has specified that it is likely that older children will not have bronchiolitis).
aa. Adjusted for respiratory rate, age, gender, race, birth weight.
bb.Adjusted for age, gender, race, birth weight, mother smoked during pregnancy, difficulty breathing, presence of apnoea, retractions, oral intake. Reference = oxygen saturation ≥94%.
cc. Patients enrolled in academic medical centres, and therefore results may not be generalizable to community medical centres; variations in the use of CPAP/intubation by institution not explained nor explored; ED and daily hospital data obtained by chart review.
dd. Children aged up to 2 years (The GDG has specified that it is likely that older children will not have bronchiolitis).
ee. Adjusted for age<2 months, intercostal retractions, and NOT for oxygen saturation. When SpO_2 is introduced in the model, 24 FI becomes no longer significant.
ff. Adjusted for age, gender, race, birth weight, mother smoked during pregnancy, difficulty breathing, presence of apnoea, retractions, oxygen saturation. Reference = adequate oral intake.
gg. Adjusted OR calculated for missing data for Oral Intake (see evidence table for details).
hh. Adjusted for age < 2 months, ED visit during the past week, moderate/severe retractions, duration of symptoms >4 d

3.3.5 Evidence statements

Heart Rate

Hospital admission

One study with 99 (derivation phase) and 201 (validation phase) children reported a significant association between heart rate > 97th percentile and hospital admission. The quality of the evidence was very low.

Respiratory Rate

Hospital admission

Evidence from one study with 598 children reported a significant association between respiratory rate > 60 breaths/min and hospital admission. The quality of the evidence was very low.

Apnoea

Evidence from one study with 2156 children reported on the association between respiratory rates and apnoea. It found an association when respiratory rates were either low (<40 breaths/minute) or high (>70 breaths/minute), but not between these figures. The quality of the evidence was low.

Major Medical Intervention

One study with 312 children did not find a statistically significant association between respiratory rates ≥60 breaths/min and the need for major medical interventions. The quality of the evidence was low.

Oxygen Saturation

Hospital admission

Three studies with 1094 children reported an association between oxygen saturation levels (<93% to <95%) and need for hospital admission. The quality of the evidence was low to very low.

Apnoea

One study with 2156 children reported a statistically significant association between oxygen saturation levels of <90% and apnoea. The quality of the evidence was low.

CPAP and/or Intubation

One study with 2159 children reported a statistically significant association between oxygen saturation levels of <85% and need for CPAP/intubation. The quality of the evidence was moderate. However, the same study found no association with other levels of oxygen saturation ((SpO_2 85.0-87.9%; SpO_2 88.0-89.9%; SpO_2 90.0-93.9%) and CPAP/intubation. The quality of the evidence was low.

3.3.5.1.1 Major Medical Intervention

One study with 312 children did not find a statistically significant association between oxygen saturation levels of ≤92% and need for major medical intervention. The quality of the evidence was low.

3.3.5.2 Ability to feed

3.3.5.2.1 Hospital admission

One study with 167 children reported a statistically significant association between 24-hour food intake <50% of normal and hospital admission. The quality of the evidence was low.

3.3.5.2.2 CPAP and/or Intubation

One study with 2159 children reported a statistically significant association between inadequate oral intake and need for CPAP/intubation. The quality of the evidence was moderate.

3.3.5.2.3 ICU Admission

One study with 583 children reported a statistically significant association between inadequate oral intake and ICU admission. The quality of the evidence was moderate.

3.3.5.2.4 Duration of Illness

No studies reported data on this outcome.

3.3.5.2.5 Fever

No studies reported data on this outcome.

3.3.5.2.6 Subjective Assessments

No studies reported data on this outcome.

3.3.6 Health economics profile

No published economic evaluations were identified for this question and this question was not prioritised for analysis.

3.3.7 Evidence to recommendations

3.3.7.1 Relative value placed on the outcomes considered

The aim of this review was to identify clinical features at the time of assessment that might predict likely worsening of the child's condition. This question is related to the question on "risk factors for severe bronchiolitis", but considers clinical features of the illness itself. The critical outcome for this review was identified by the GDG as the risk for progressing to a more severe state of the disease (deterioration), which was defined by the GDG as admission to hospital.

The GDG was interested in the prevalence of clinical features at initial assessment in children who go on to develop severe bronchiolitis compared with their prevalence in those who did not. The group indicated that the following clinical features might plausibly be important predictors of deterioration: duration of illness, heart rate, respiratory rate, fever, oxygen saturation level, ability to feed, and subjective assessments.

An additional definition of "problematic" bronchiolitis was also given by the GDG and indicated as the presence of symptoms like apnoea, chest recession, stridor, retractions, nasal flaring, prolonged expiration, cyanosis, irritability, drowsiness, age at presentation, grunting, shortness of breath, head movement with breathing difficulty, tracheal tug, and parental or health professional concerns in general.

3.3.7.2 Consideration of clinical benefits and harms

The GDG noted that this evidence review was closely linked to the evidence review on the criteria for referral, admission and discharge. However, neither review contained evidence that directly answered the questions, as no studies compared groups of patients who did and did not progress from less severe to more severe bronchiolitis. Rather they examined the association between various clinical parameters (heart rate, respiratory rate, O2 saturation, ability to feed) and various clinical decisions including decision to admit, decision to use CPAP or to perform endotracheal intubation or to admit to an intensive care unit. One study looked at the association between respiratory rate and apnoea and another at the association between oxygen saturation levels less than 90% and the occurrence of apnoea. Again these studies examined association rather than the predictive value of the parameters for deterioration.

From the GDG's perspective an important issue in relation to predicting the likelihood of deterioration was in the context of deciding whether or not to refer a child to secondary care, admit a child with bronchiolitis to hospital or discharge them from the hospital. The retrieved studies did not therefore assist them in making these recommendations.

The GDG went on to consider recommendations for referral, admission and discharge based on their own expertise and clinical experience and taking account of the risk factors for developing severe bronchiolitis previously reviewed.

When discussing oxygen saturation level as a clinical feature that might indicate deterioration or improvement of the condition, the GDG reached a consensus on using a SpO_2 level equal or above 92%, even though some evidence indicated 90% as a safe level.

Children considered from the available evidence and the consensus of the GDG to be at most risk of clinical deterioration were those with apnoea, persisting oxygen saturation ≤92%, inadequate oral fluid intake and persisting severe respiratory distress. It was considered that these infants should be observed in hospital until demonstrating stability or recovery.

The GDG also agreed by consensus to add a recommendation to take into account social circumstances (for example, a single parent with other children [especially if one has another illness]); the skill and confidence of the carer in looking after a child with bronchiolitis at home; confidence in being able to spot red flag symptoms; and the distance to healthcare in case of deterioration as someone living near a paediatric assessment unit is in a better position to get help quickly than someone very distant from a hospital, when deciding to refer, admit or discharge.

3.3.7.3 Consideration of health benefits and resource uses

Prediction of deterioration will determine whether a child is referred for secondary or emergency care. It is important not to over-diagnose, resulting in unnecessary referrals and the associated resource use. Bronchiolitis occurs primarily in the winter months at a time when demand on beds is already increased. However, it is equally important to ensure accurate prediction to prevent adverse events due to delaying appropriate referral and interventions, which will result in increased resource use.

3.3.7.4 Quality of evidence

This review was based on observational studies which have a number of potential biases associated with them. However, the included studies were restricted to those that undertook case-mix adjustment. This minimises selection bias between groups, which is a major source of bias in observational studies. Other sources of bias identified in these studies were exclusion of children with risk factors for severe disease and imprecision in the results due to the uncertainty of the effect. The evidence ranged from moderate to very low quality.

3.3.7.5 Other considerations

Any other relevant considerations such as those related to equalities

3.3.8 Key conclusions

The GDG concluded that apnoea, persisting oxygen saturation ≤92%, inadequate oral fluid intake and persisting severe respiratory distress indicate the need for admission to hospital. In addition, the GDG also concluded that the following risk factors need to be considered: chronic lung disease, haemodynamically significant congenital heart disease, young age, prematurity, neuromuscular disorders, immunodeficiency.

3.3.9 Recommendations

Recommendations for this section are in criteria for referral in section 3.4.8

3.3.10 Research recommendations

1. **In children with bronchiolitis can paediatric early warning score (PEWS) predict deterioration?**

Why this is important

1.1. **In children with bronchiolitis there is clinical uncertainty about the prediction of deterioration. There are a number of clinical scores for bronchiolitis that include objective and subjective measures. No bronchiolitis score is currently in widespread use in clinical practice. Increasingly PEWS are being employed generically in paediatric practice in the UK. The effectiveness of PEWS in predicting deterioration for infants with bronchiolitis needs to be assessed.**

2. **In children with bronchiolitis what features predict progressive recovery?**

Why this is important

2.1. **In bronchiolitis there is usually a period of increasing severity of symptoms followed by a period of gradual recovery. The ability to predict progressive recovery would be helpful when making management decisions – for example with regard to the gradual withdrawal of treatments. Such information could also potentially avoid unnecessary admissions to hospital and might shorten hospital stay in those who are admitted.**

3.4 Criteria for referral

3.4.1 Review question

What are the criteria for a) referral to secondary care, b) hospital admission for observation or treatment, c) discharge from hospital?

Further details on the protocol for this review question are provided in Appendix E.

3.4.2 Introduction

Bronchiolitis has a broad spectrum of disease severity. The majority of affected children can be successfully managed at home with appropriate support whilst a minority (2-3%) will require admission to hospital for treatment.

Bronchiolitis admission rates and length of stay differ significantly across the UK suggesting substantial variation in clinical management. It is therefore important to have clear criteria to ensure appropriate hospital referral, admission and discharge.

3.4.3 Description of included studies

No studies were identified that assessed the effect of using referral criteria on outcome, such as readmission rates. Therefore, the review examined individual factors that could be used to outline a set of referral criteria based on the review protocol outlined by the GDG. The results of this review overlaps with that used for the question on predictors of deterioration.

Five studies were identified for this review (Corneli et al., 2012; Mansback et al., 2008; Yusuf et al., 2012; Walsh et al., 2004; Schuh et al., 2014)). Two studies were retrospective cohorts (Yusuf et al., 2012; Walsh et al., 2004), one study was a prospective cohort (Mansback et al., 2008), one was a randomised clinical trial (Schuh et al., 2014) and one study was a secondary analysis of a RCT (Corneli et al., 2012). Three studies were undertaken in the USA (Corneli et al., 2012; Mansback et al., 2008; Yusuf et al., 2012), one in Canada (Schuh et al., 2014) and the remaining study was undertaken in Ireland (Walsh et al., 2004). Sample sizes ranged from 281 (Walsh et al., 2004) to 1459 (Mansback et al., 2008).

The age of subjects ranged from less than two years of age in three studies (Mansback et al., 2008; Walsh et al., 2004; Yusuf et al., 2012) to less than 12 months in the remaining two studies (Corneli et al., 2012 and Schuh et al., 2014). Diagnosis of bronchiolitis was based on the evaluation of the infant by the attending physician or clinician, none of the studies reported diagnostic criteria.

A list of important factors to be considered for this review question has been proposed by the GDG in the protocol:

1. Change in respiratory rate
2. Change in oxygen saturation
3. Dehydration
4. Reported feeding difficulty (need for intravenous fluids or nasogastric tubing)
5. Work of breathing
6. Adverse events (including mortality)

Four studies reported on oxygen saturation (Corneli et al,, 2012; Mansback et al., 2008; Yusuf et al., 2012; Schuh et al., 2014), and one of them compared true oxygen saturation levels with altered oximetry measurements (Schuh et al., 2014). Two studies reported on respiratory rate (Corneli et al., 2012; Mansback et al., 2008). Two studies reported on feeding difficulty; this was defined by one study (Yusuf et al., 2012) as requiring intravenous fluids and by the second study (Mansback et al., 2008) as adequate, inadequate or unknown. Two studies reported on breathing difficulty; one study (Mansback et al., 2008) based this on the severity of retractions whilst the second study (Walsh et al., 2004) determined breathing difficulty by implicit review with at least one mild recession to be noted on the chart. One study reported on dehydration (Walsh et al., 2004) and classified it on an ordinal scale as none, mild, moderate or severe.

All four studies were performed in the emergency department. Three studies assessed the predictors of admission from the emergency department (Corneli et al., 2012; Walsh et al., 2004; Yusuf et al 2012) and the remaining study assessed the predictors of discharge from the emergency department (Mansback et al., 2008). None of the studies compared referral/no referral and admission/no admission.

In order to ensure that the association observed between the clinical feature and outcome is independent of any other factors, only studies that undertook case-mix adjustment have been included in this review.

More details on each individual study can be found in the evidence tables in Appendix I.

3.4.4 Evidence profile

Study quality was assessed using the GRADE methodology. Prospective observational studies were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

Two GRADE profiles have been produced for this review:

- Table 19 GRADE: profile for criteria for admission and discharge.
- Table 20 GRADE: profile for comparison of true oximetry values with altered (elevated) oximetry values.

Table 19: GRADE profile for criteria for admission and discharge

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Admitted to hospital from the emergency department	Discharged from the emergency department	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Oxygen saturation											
Association between an initial oxygen saturation <94% and admission to hospital from the emergency department											
1 (Corneli et al, 2012)	N=240	N=358	Adjusted OR: 5.5 (2.9 to 10.2) [a]	P<0.001	Very low	Secondary analysis of a RCT	Very serious [b]	None	Serious [c]	None	None
Association between an initial oxygen saturation ≥94% and discharge from the emergency department											
1 (Mansback et al, 2008)	N=619	N=837	Adjusted OR: 2.28 (1.56 to 3.34) [d]	P<0.001	Low	Prospective cohort	Serious [e]	None	Serious [f]	None	None
Association between oxygen saturation <93% in the emergency department observation unit and admission to hospital											
1 (Yusuf et al, 2012)	N=85	N=240	Adjusted OR: 4.72 (1.47 to 15.18) [g]	P=0.009	Low	Retrospective cohort	Serious [h]	None	Serious [i]	None	None
Respiratory rate											
Association between respiratory rate >60/min in the emergency department and admission to hospital											
1 (Corneli et al, 2012)	N=240	N=358	Adjusted OR: 2.6 (1.7 to 4.1) [a]	P<0.0001	Very low	Secondary analysis of a RCT	Very serious [b]	None	Serious [c]	None	None
Association between a respiratory rate less than normal for age and discharge from the emergency department j											
1 (Mansback et al, 2008)	N=619	N=837	Adjusted OR: 2.02 (1.46 to 2.80) [d]	P<0.001	Low	Prospective cohort	Serious [e]	None	Serious [f]	None	None
Dehydration											
Association between dehydration in the emergency department and admission to hospital k											
1 (Walsh et al, 2004) (Derivation set)	N=62	N=37	Adjusted OR: 2.54 (1.34 to 4.82) [l]	P=0.004	Very low	Retrospective review	Very serious [m]	None	Serious [n]	None	None
1 (Walsh et al, 2004)	N=43	N=139	Adjusted OR: 10.97	P<0.001	Very low	Retrospective review	Very serious	None	Serious [n]	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Admitted to hospital from the emergency department	Discharged from the emergency department	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
(Validation set)			(4.00 to 30.08) [l]				[o]				
Difficulty feeding											
Association between adequate oral intake (reference: inadequate) and discharge from the emergency department											
1 (Mansback et al, 2008)	N=619	N=837	Adjusted OR: 6.02 (3.87 to 9.35) d	P<0.001	Low	Prospective cohort	Serious [e]	None	Serious [f]	None	None
Association between unknown oral intake (reference: inadequate) and discharge from the emergency department											
1 (Mansback et al, 2008)	N=619	N=837	Adjusted OR: 3.80 (1.89 to 7.63) d	P<0.001	Low	Prospective cohort	Serious [e]	None	Serious [f]	None	None
Association between receiving intravenous fluids in the emergency department observation unit and admission to hospital											
1 (Yusuf et al, 2012)	N=85	N=240	Adjusted OR: 2.51 (1.43 to 4.41) [g]	P=0.001	Low	Retrospective cohort	Serious [h]	None	Serious [i]	None	None
Difficulty breathing											
Association between mild retractions (reference: moderate/severe) and discharge from the emergency department											
1 (Mansback et al, 2008)	N=619	N=837	Adjusted OR: 2.78 (1.91 to 4.06) d	P<0.001	Low	Prospective cohort	Serious [e]	None	Serious [f]	None	None
Association between increased work of breathing in the emergency department and admission to hospital p											
1 (Walsh et al, 2004) (Derivation set)	N=62	N=37	Adjusted OR: 3.39 (1.29 to 8.92) [l]	P=0.013	Very low	Retrospective review	Very serious [m]	None	Serious [n]	None	None
1 (Walsh et al, 2004) (Validation set)	N=43	N=139	Adjusted OR: 6.94 (3.04 to 15.84) [l]	P<0.001	Very low	Retrospective review	Very serious [o]	None	Serious [n]	None	None

OR odds ratio, RCT randomised controlled trial, p-value
a Corneli et al., 2012 adjusted for: initial oxygen saturation <94%, respiratory rate >60/min and RDAI score >11.
b Corneli et al., 2012 risk of bias: Infants were diagnosed by a trained study clinicians, but their diagnosis appears to be based on the inclusion criteria. It is unclear from the methods how measurements were timed and included in the model. The population is taken from a RCT for dexamethasone, therefore the original study exclusion and inclusion criteria apply here.

c Corneli et al., 2012 indirectness: Do not predefine criteria for admission to hospital.
d Mansback et al., 2008 adjusted for: age ≥2 months, female, non-white race/ethnicity, ≥1 parent with asthma, no history of intubation, eczema, duration of symptoms >7 days, respiratory rate less than normal for age, number of β-receptor agonists and epinephrine treatments during the first hour Initial room air oxygen saturation ≥94%, respiratory rate less than normal for age, retractions, oral intake and no ED visit during the past week.
e Mansback et al., 2008 risk of bias: The final model includes 1012 infants with complete data (444 without complete data) but they do not report how many of those infants were admitted or discharged. Only 1459 out of 2129 (68%) of the eligible infants were enrolled, the remaining were missed by site personnel (89%) or other reasons such as refusal to participate. Infants were diagnosed by the attending physician, diagnostic criteria are not reported.
f Mansback et al., 2008 indirectness: Many infants covered by Medicaid insurance: admitted group 59%, discharged group 63%. Infants up to 24 months of age included. Do not predefine criteria for admission to hospital.
g Yusuf et al., 2012 adjusted for: oxygen saturation <93% and intravenous fluids in the ED.
h Yusuf et al., 2012 risk of bias: Infants diagnosed by the emergency room physician, diagnostic criteria is not reported. Patient demographics are only reported as the admitted frequency. The primary reason for admission from the emergency department observation unit was sometimes absent from the chart. Retrospective study design.
i Yusuf et al., 2012 indirectness: Infants received treatment in the ED before the disposition decision was reached. Infants up to 24 months of age included. Do not predefine criteria for admission to hospital.
j Normal respiratory values for age: 0 to 1.9 months 45 breaths/min; 2 to 5.9 months 43 breaths/min; 6 to 23.9 months 40 breaths/min.
k Dehydration determined either explicitly when documented or implicitly by the reviewer using the criteria described in Berhman & Orernstein 2000 and Baker & Ruddy 2000, classified on an ordinal scale as none, mild, moderate or severe.
l Walsh et al., 2004 adjusted for: increased work of breathing, tachycardia, age and dehydration.
m Walsh et al., 2004 risk of bias (derivation set): Demographics only reported for the three category model (fit for discharge, LOS 2 to 3 days, LOS ≥4 days) not the two-category model (discharged or admitted). 23 of the 99 patients were excluded because of missing data, it is then unclear how many analysed infants (n=76) in the derivation phase were admitted or discharged. Include infants who are readmitted in the 'need for admission' group. Return visits that did not lead to admission were also counted as discharges. Infants diagnosed by attending paediatrician, diagnostic criteria not reported. The calculation for age was unclear. Demographics are based on the number of episodes of bronchiolitis, not the number of patients. Unclear how the model was 'trimmed', no significance level is discussed. Unclear which treatments were received in the ED. Retrospective study design.
n Walsh et al., 2004 indirectness: Infants up to 24 months of age included (the GDG has specified that it is likely that older children will not have bronchiolitis). Do not predefine the criteria for admission to hospital.
o Walsh et al., 2004 risk of bias (validation set): Demographics only reported for the entire validation set, demographics are not reported separately for infants admitted or discharged. Include infants who are readmitted in the 'need for admission' group. Return visits that did not lead to admission were also counted as discharges. Infants diagnosed by attending paediatrician, diagnostic criteria not reported. The calculation for age was unclear. Demographics are based on the number of episodes of bronchiolitis, not the number of patients. Unclear how the model was 'trimmed', no significance level is discussed. Unclear which treatments were received in the ED.
p Increased work of breathing determined by implicit review, but required at least more than one mild recession to be noted on the chart.

Table 20: GRADE profile for comparison of true oximetry values with altered (elevated) oximetry values

Number of studies	Number of patients		Effect		Quality	Design	Quality assessment				
	True values	Altered values	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Admission to hospital											
Within 72 hours											
1. Schuh et al., 2014	44/108	26/105	OR = 2.1 (1.2 to 3.8)	-	Low	RCT	Serious [a]	NA	Some [b]	Serious [c]	None

NA not applicable NC not calculable, NR not reported, RCT randomised controlled trial, P probability-value, OR odds ratio
** Calculated by the NCC-WCH technical team from data reported in the article*
a The two groups were comparable at baseline although there was a limited number of patients presenting with low oxygen saturation levels which in the end did not allow to determine a specific threshold for admission; also, there was a high number of refusals (but 0 lost at follow-up or discontinued the intervention).
b The comparison used in the study is different from what indicated in the review protocol as no specific threshold is applied.
c Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.

3.4.5 Evidence statements

3.4.5.1 Criteria for admission

Oxygen saturation

One study with 598 children found a significant association between an initial oxygen saturation <94% and admission to hospital from the emergency department. The quality of the evidence was very low.

One study with 325 children found a significant association between oxygen saturation <93% in the emergency department observation unit and admission to hospital. The quality of the evidence was very low.

One study with 213 children found that patients with an artificially elevated pulse oximetry reading were significantly less likely to be admitted to hospital within 72 hours, compared to those with unaltered oximetry readings. The quality of the evidence was low.

Respiratory rate

One study with 598 children found a significant association between respiratory rate >60 per minute in the emergency department and admission to hospital. The quality of the evidence was very low. One study with 325 children found a significant association between receiving intravenous fluids in the emergency department observation unit and admission to hospital. The quality of the evidence was low.

Breathing difficulty

One study with 99 (derivation phase) and 201 (validation phase) children found a significant association between increased work of breathing in the emergency department and admission to hospital. The quality of the evidence was very low.

Dehydration

One study with 99 (derivation phase) and 201 (validation phase) children found a significant association between dehydration in the emergency department and admission to hospital. The quality of the evidence was very low.

Feeding difficulty

One study with 325 children found a significant association between receiving IV fluids in the emergency department observation units and admission to hospital. The quality of the evidence was low.

Referral rate to secondary care

No studies reported data on this outcome.

Adverse events

No studies reported data on this outcome.

3.4.5.2 Criteria for discharge

Oxygen saturation

One study with 1456 children found a significant association between an initial oxygen saturation ≥94% and discharge from the emergency department. The quality of the evidence was low.

Respiratory rate

One study with 1456 children found a significant association between a respiratory rate less than normal for age and discharge from the emergency department. The quality of the evidence was low.

Feeding difficulty

One study with 1456 children found a significant association between oral intake and discharge from the emergency department. The quality of the evidence was low.

Breathing difficulty

One study with 1456 children found a significant association between mild retractions and discharge from the emergency department. The quality of the evidence was low.

Readmission

No studies reported data on this outcome.

Dehydration

No studies reported data on this outcome.

Adverse events

No studies reported data on this outcome.

3.4.6 Health economics profile

No health economic studies were identified for this question and no health economic analysis was undertaken.

3.4.7 Evidence to recommendations

3.4.7.1 Relative value placed on the outcomes considered

The aim of this review was to identify:

a) the criteria for referral to secondary care
b) the criteria for hospital admission
c) the criteria for discharge from hospital

The critical outcomes for criteria for referral and hospital admission were: referral rate to secondary care; and admission to hospital. Other important outcomes considered by the GDG were: change in oxygen saturation; change in respiratory rate; dehydration; reported feeding difficulty; work of breathing; and adverse events (including mortality).

The critical outcomes for criteria for discharge from hospital were: change in respiratory rate; change in oxygen saturation; and reported feeding difficulty. Other important outcomes

considered by the GDG were: readmission rate; dehydration; work of breathing; and adverse events (including mortality).

3.4.7.2 Consideration of clinical benefits and harms

The GDG noted that this review was closely linked to the review on predictors of deterioration. However, neither review contained evidence that fully answered the review questions, as no studies compared groups of patients for whom different criteria were applied. For example, the reported associations between decision to admit and various parameters might have reflected clinical practice rather than suggesting that such parameters are useful in determining the need for admission. There were no studies that compared the use of particular criteria and then reported the relevant outcomes.

The GDG noted that the evidence available was very limited and of very low quality. They were not aware of any further relevant studies that had not been identified. For these reasons, the GDG based the recommendations on their own clinical experience and on existing guidance. For example, when addressing criteria for referral to secondary care, the GDG indicated clinical features referred to in the Feverish illness in children clinical guideline (CG 160).

They developed recommendations on the clinical criteria which demanded immediate referral to hospital for emergency care. The GDG considered by consensus that a child with apnoea is at high risk of future apnoeic events and so should be observed in a hospital until clinically stable (typically a number of hours).They advised that those with an oxygen saturation of 92% or lower should be referred immediately – taking account of the rapid reduction in blood oxygen carriage when the O2 saturation is below 90% they believed that using 92% allowed an additional margin of safety. Evidence from one study highlighted that infants observed to have an oxygen saturation of 92% were more likely to fall to 90% as the illness progressed. As oxygen saturation monitoring is not available for use on infants in primary care in many settings, the GDG considered that evidence of cyanosis (typically considered an oxygen saturation of 85% or less) should prompt immediate referral to hospital. Similarly a child who looks seriously unwell to a healthcare professional should prompt immediate referral to hospital. Infants with marked respiratory distress (i.e. a respiratory rate >70 breaths/min) are at high risk of a reduced oral fluid intake and of respiratory failure. The GDG considered from evidence available that 70 breaths/min represented a respiratory rate that should prompt referral to hospital. Those with a respiratory rate between 60 and 70 breaths/min could be considered for referral taking into account other factors, i.e. ability to feed, work of breathing and risk factors for severe disease.

Infants who are unable to feed adequately (due to lethargy, nasal airway obstruction or increased work of breathing) are at high risk of dehydration and hypoglycaemia and should be referred to hospital. The GDG considered by consensus that an intake of 50-75% usual volumes should be considered as borderline intake. The lower limit of 50% may apply to an older infant with previous good health who is anticipated to improve over the subsequent 24 hours (i.e. illness day 3 or 4), with the upper limit of 75% applicable to a younger infant with possible risk factors (i.e. preterm) who may have poorer ability to tolerate a reduced calorie and fluid intake. The GDG considered by consensus that in primary care an assessment of oral intake between 50 and 75% of typical volume should take into account other clinical (i.e. work of breathing) and risk factors (i.e. age, chronic lung disease, Haemodynamically significant congenital heart disease etc) when deciding whether to refer to hospital. By consensus the GDG considered that infants who were clinically dehydrated should be referred to secondary care if they could not be anticipated to take an adequate oral intake in the community.

Regarding criteria for admission to hospital, the GDG discussed that there is variation in the assessment and monitoring of children. The GDG noted that there was the need to be clear and specify if the admission is required for monitoring or treatment.

The GDG prioritised which risk factors should inform whether to refer or admit a child with bronchiolitis to secondary care. The risk factors listed were considered to be of more immediate clinical risk for more severe disease. The GDG considered that from the list of potential risk factors for developing more severe bronchiolitis, breast-feeding, male sex, and smoking in the household were not of the same significance.

They developed recommendations on the clinical criteria which required admission to hospital. For those who would not be admitted they developed recommendations on the information to be given to their parents or carers so that they would be able to recognise the need to seek further advice if there was a deterioration in the child's condition. They also made recommendations on the clinical criteria and oxygen saturation status that would need to be fulfilled for safe discharge following admission to hospital. The GDG reached a consensus on using a SpO_2 level above 92%.

When a child with bronchiolitis is sent home following assessment or admission, they may re-present or require readmission. While this could on occasion reflect inappropriate decision making, the GDG believed that this often reflects the natural course of the disease. Because bronchiolitis can worsen over a period of days, unpredictable marked deterioration might in some cases require reassessment and sometimes readmission. Compared with the overall numbers seen these were relatively few in number. The GDG believed that the use of the admission and discharge criteria they recommended should help minimise unnecessary admissions, and should optimise the period of inpatient care.

The GDG also agreed by consensus to add a recommendation to take into account social circumstances (for example, a single parent with other children [especially if one has another illness]); the skill and confidence of the carer in looking after a child with bronchiolitis at home; confidence in being able to spot red flag symptoms; and the distance to healthcare in case of deterioration as someone living near a paediatric assessment unit is in a better position to get help quickly than someone very distant from a hospital, when deciding to refer, admit or discharge.

The GDG agreed by consensus that in a child with a clinical diagnosis of bronchiolitis, blood tests do not help to confirm the diagnosis, and should therefore not be undertaken for this reason. The GDG noted that children with bronchiolitis and poor feeding may develop dehydration. As in other conditions causing dehydration, the assessment of hydration status is based on a clinical assessment and does not require blood test investigation..

3.4.7.3 Consideration of health benefits and resource uses

It is important not to over refer children, as bronchiolitis occurs primarily in winter months, the demand on beds is likely to be increased. However, it is important to identify children at risk of deterioration as delaying appropriate referral and treatment could result in a more rapid deterioration in health which requires a longer hospital stay and potentially admission to intensive care.

3.4.7.4 Quality of evidence

The quality of the evidence presented ranged from low to very low. The poor quality of the evidence was determined by the retrospective design used, imprecision in the estimates due to the uncertainty of the effect, and because often the timing of measurements and assessments of the patients was unclear or unreported. There were very limited data so recommendations are based on the collective experience of the GDG.

3.4.8 Recommendations

9. Immediately refer children with bronchiolitis for emergency hospital care (usually by 999 ambulance) if they have any of the following:

- apnoea (observed or reported)
- child looks seriously unwell to a health care professional
- severe respiratory distress, for example grunting, marked chest recession, or respiratory rate over 70 breaths/minute
- central cyanosis
- persistent oxygen saturation of 92% or less when breathing air.

10. Consider referring children with bronchiolitis to secondary care if they have any of the following:

- a respiratory rate of over 60 breaths/minute
- difficulty with breastfeeding or inadequate oral fluid intake (less than 75% of usual volume)
- clinical dehydration.

11. When deciding whether to refer a child with bronchiolitis to secondary care, take account of the following risk factors for more severe bronchiolitis:

- chronic lung disease (including bronchopulmonary dysplasia)
- haemodynamically significant congenital heart disease
- age in young infants (under 3 months)
- premature birth, particularly under 32 weeks
- neuromuscular disorders
- immunodeficiency.

12. When deciding whether to refer to secondary care a child, take into account factors which might affect a carer's ability to look after a child with bronchiolitis, for example:

- social circumstances
- the skill and confidence of the carer in looking after a child with bronchiolitis at home
- confidence in being able to spot red flag symptoms (see recommendation 15)
- distance to healthcare in case of deterioration.

13. Clinically assess the hydration status of children with bronchiolitis.

14. Do not routinely perform blood tests in the assessment of a child with bronchiolitis.

15. Provide key safety information for children who will be looked after at home. This should include information:

- for parents and carers on how to recognise developing 'red flag' symptoms:
  - worsening work of breathing (for example grunting, nasal flaring, marked chest recession)
  - fluid intake is less than 75% of normal or no wet nappy for 12 hours
  - apnoea or cyanosis
  - exhaustion (for example, not responding normally to social cues, wakes only with prolonged stimulation)

- on how to get immediate help from an appropriate professional if any red flag symptoms develop
- on arrangements for follow-up if necessary.

16. **When assessing a child in a secondary care setting, admit them to hospital if they have any of the following:**
    - apnoea (observed or reported)
    - persistent oxygen saturation of 92% or less when breathing air
    - inadequate oral fluid intake (less than 75% of usual volume)
    - persisting severe respiratory distress, for example grunting, marked chest recession, or a respiratory rate of over 70 breaths/minute.

17. **When deciding whether to admit a child with bronchiolitis, take account of the following risk factors for more severe bronchiolitis:**
    - chronic lung disease (including bronchopulmonary dysplasia)
    - haemodynamically significant congenital heart disease
    - age in young infants (under 3 months)
    - premature birth, particularly under 32 weeks
    - neuromuscular disorders
    - immunodeficiency.

18. **When deciding whether to admit a child, take into account factors which might affect a carer's ability to look after a child with bronchiolitis, for example:**
    - social circumstances
    - the skill and confidence of the carer in looking after a child with bronchiolitis at home
    - confidence in being able to spot red flag symptoms (see recommendation 15)
    - distance to healthcare in case of deterioration.

19. **Provide parents or carers with key safety information (see Recommendation 15) if the child is not admitted.**

20. **When deciding on the timing of discharge for children admitted to hospital, make sure that the child:**
    - is clinically stable
    - is taking adequate oral fluids
    - has maintained oxygen saturation over 92% in air for 4 hours, including a period of sleep.

21. **When deciding whether to discharge a child, take into account factors which might affect a carer's ability to look after a child with bronchiolitis, for example:**
    - social circumstances
    - the skill and confidence of the carer in looking after a child with bronchiolitis at home
    - confidence in being able to spot red flag symptoms (see recommendation 15)
    - distance to healthcare in case of deterioration.

22. **Provide parents or carers with key safety information (see Recommendation 15) when the child is discharged.**

3.5 Fluids and nutritional support

3.5.1 Review question

What are the indications for fluids and nutritional support?

Further details on the protocol for this review question are provided in Appendix E.

3.5.2 Introduction

Children with bronchiolitis frequently experience feeding difficulties. In many this is a relatively minor problem which can be managed by giving smaller more frequent feeds. As respiratory distress becomes more marked, children may be unable to take an adequate fluid volume by mouth. At these times fluid intake can be supported with an enteral tube (nasogastric or orogastric) or alternatively intravenous fluids. Occasionally, in those with marked respiratory distress, the inability to take an adequate volume of fluid leads to dehydration. In some instances, children with bronchiolitis may have associated SIADH (Syndrome of inappropriate anti-diuretic hormone secretion). In general, many children with bronchiolitis can tolerate a reduction in feeding by 25-50% of normal for 2-3 days until symptoms resolve. Feeding problems typically resolve as breathing improves.

3.5.3 Description of included studies

Two studies were identified for this review (Kugelman et al., 2013; Oakley et al., 2013). One was an open randomised controlled clinical pilot study (Kugelman et al., 2013) and the other was a multicentre open randomised trial (Oakley et al., 2013). The first study compared intravenous fluids with gastric tube feeding (Kugelman et al., 2013) and the second compared nasogastric hydration with intravenous hydration (Oakley et al., 2013). One study was undertaken in Israel (Kugelman et al., 2013) and the other was undertaken in Australia and New Zealand (Oakley et al., 2013). Sample size was 51 infants (Kugelman et al., 2013) and 759 infants (Oakley et al., 2013). The definition of bronchiolitis in both studies was based on clinical symptoms and signs. All children were less than 12 months old, with the mean age being between 2 and 3 months old in one study (Kugelman et al., 2013) and between 5 and 6 months old in the other study (Oakley et al., 2013).

The important outcomes chosen by the GDG were:

- Change in hydration (clinical hydration status/change in body weight/serum sodium concentration)
- Change in oxygen saturation
- Change in disease severity score
- Length of hospital stay
- Change in respiratory rate
- Need for high flow humidified oxygen, CPAP, or mechanical ventilation
- Adverse effects (including mortality)

More details on each individual study can be found in the evidence tables in Appendix I.

3.5.4 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

Two GRADE profiles have been produced for this review.

- Table 21: GRADE profile for comparison of intravenous fluids with comparator gastric tube feeding.
- Table 22: GRADE profile for comparison of nasogastric hydration with comparator intravenous hydration.

Table 21: GRADE profile for comparison of intravenous fluids with comparator gastric tube feeding

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	IV fluids	GT feeding	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Change in hydration (clinical hydration status/change in body weight/serum sodium concentration) – Not reported											
Change in oxygen saturation – Not reported											
Change in disease severity score – Not reported											
Length of hospital stay (hours)											
1 (Kugelman et al., 2013)	n=20 Mean (SD): 98 (48)	n=31 Mean (SD): 119 (55)	-	p=0.12a MD: -21.00 (-49.59 to 7.59)[b]	Very low	Open randomised controlled clinical pilot study	Very serious[c]	None	None	Serious[d]	None
Change in respiratory rate – Not reported											
Need for high flow humidified oxygen, CPAP or mechanical ventilation – Not reported											
Adverse effects (including mortality)											
Clinical aspiration											
1 (Kugelman et al., 2013)	0/20	0/31	NC	-	Low	Open randomised controlled clinical pilot study	Very serious[c,e]	None	None	NC	None

NC not calculable, p-value, MD mean difference, SD standard deviation
a As reported in the study
b Calculated by the NCC-WCH technical team from data reported in the article
c Method of randomisation and allocation concealment not described, small sample size (based on sample size calculation reported in study, sufficient numbers not reached)
d Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
e it was not possible to assess imprecision because of the lack of information reported in the paper.

Table 22: GRADE profile for comparison of nasogastric hydration with comparator intravenous hydration

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Nasogastric hydration	Intravenous hydration	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Change in hydration (clinical hydration status/change in body weight/serum sodium concentration) – Not reported											
Change in oxygen saturation											
Reported as number with oxygen saturation <90%											
1 (Oakley et al., 2013)	19/381 (5%)	14/378 (4%)	OR: 1.36 (0.67 to 2.76)[a]	p=0.39b	Very low	Multicentre open randomised trial	None	None	Very serious[c]	Very serious[d]	None
Change in disease severity score – Not reported											
Length of hospital stay (hours)											
Measured to time ready for discharge in hours											
1 (Oakley et al., 2013)	n=381 Mean (SD): 84.1 (57.9)	n=378 Mean (SD): 80.2 (58.3)	-	Difference: 3.9 (-4.3 to 12.2)[b] p=0.35[b]	Low	Multicentre open randomised trial	None	None	Very serious[c]	None	None
Change in respiratory rate – Not reported											
Need for high flow humidified oxygen, CPAP or mechanical ventilation											
CPAP											
1 (Oakley et al., 2013)	12/381 (3%)	13/378 (3%)	OR: 0.91 (0.41 to 2.03)[a]	p=0.83[b]	Very low	Multicentre open randomised trial	None	None	Very serious[c]	Very serious[d]	None
Intubated and ventilated											
1 (Oakley et al., 2013)	5/381 (1%)	5/378 (1%)	OR: 0.99 (0.28 to 3.46)[a]	p=0.99b	Very low	Multicentre open randomised trial	None	None	Very serious[c]	Very serious[d]	None
Adverse effects (including mortality)											
Intensive care unit admission											
1 (Oakley et al., 2013)	21/381 (6%)	25/378 (7%)	OR: 0.82 (0.45 to 1.50)[a]	p=0.53b	Very low	Multicentre open randomised trial	None	None	Very serious[c]	Very serious[d]	None
Intravenous line-site bruising											
1 (Oakley et al., 2013)	3/336 (1.0%)	33/342 (10%)	OR: 0.08 (0.03 to 0.28)a	-	Low	Multicentre open randomised trial	None	None	Very serious[c]	None	None
Sore nose											
1 (Oakley et al., 2013)	9/336 (3%)	1/342 (0.3%)	OR: 9.39 (1.18 to 74.49)[a]	-	Very low	Multicentre open randomised	None	None	Very serious[c]	Serious[d]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Nasogastric hydration	Intravenous hydration	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
						trial					
Intravenous line-site soreness											
1 (Oakley et al., 2013)	0/336 (0%)	9/342 (3%)	OR: 0.05 (0.00 to 0.90)[a]	-	Very low	Multicentre open randomised trial	None	None	Very serious[c]	Serious[d]	None
Epistaxis											
1 (Oakley et al., 2013)	4/336 (1%)	1/342 (0.3%)	OR: 4.11 (0.46 to 36.95)[a]	-	Very low	Multicentre open randomised trial	None	None	Very serious[c]	Very serious[d]	None
Any sign nasal trauma											
1 (Oakley et al., 2013)	3/336 (1%)	0/342 (0%)	OR: 7.19 (0.37 to 139.71)[a]	-	Very low	Multicentre open randomised trial	None	None	Very serious[c]	Very serious[d]	None
Intravenous line-site infection											
1 (Oakley et al., 2013)	0/336 (0%)	0/342 (0%)	NC	-	Low	Multicentre open randomised trial	None	None	Very serious[c]	NC	None
Other[e]											
1 (Oakley et al., 2013)	11/336 (3%)	11/342 (3%)	OR: 1.02 (0.44 to 2.38)[a]	-	Very low	Multicentre open randomised trial	None	None	Very serious[c]	Very serious[d]	None

NC not calculable, p-value, OR odds ratio
a Calculated by the NCC-WCH technical team from data reported in the article
b As reported in the study
c Includes subjects with history of previous wheeze (14% in nasogastric hydration group vs 13% in intravenous hydration group) history of previous bronchiolitis (28% vs 27%) and history of asthma (1% in nasogastric hydration vs 1% in intravenous hydration). Please note that it was not possible to assess imprecision because of the lack of information reported in the paper.
d Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
e Includes unspecified events 8 vs 7, vomiting 1 vs 2, worsened cough 1 vs 1, rash 1 vs 0 and crying 0 vs 1

3.5.5 Evidence statements

3.5.5.1 Intravenous fluids versus gastric tube feeding

Change in hydration (clinical hydration status/change in body weight/serum sodium concentration)

No studies reported data on this outcome.

Change in oxygen saturation

No studies reported data on this outcome.

Change in disease severity score

No studies reported data on this outcome.

Length of hospital stay

One RCT with 51 children found no significant difference in length of hospital stay in children receiving intravenous fluids compared to children receiving gastric tube feeding. The quality of the evidence was very low.

Change in respiratory rate

No studies reported data on this outcome.

Need for high flow humidified oxygen, CPAP or mechanical ventilation

No studies reported data on this outcome.

Adverse effects (including mortality)

Clinical aspiration

One RCT with 51 children found no significant difference in clinical aspiration in children receiving intravenous fluids compared to children receiving gastric tube feeding. The quality of the evidence was low.

3.5.5.2 Nasogastric hydration versus intravenous hydration

Change in hydration (clinical hydration status/change in body weight/serum sodium concentration)

No studies reported data on this outcome.

Change in oxygen saturation

Reported as number with oxygen saturation <90%

One RCT with 759 children found no significant difference in the number with oxygen saturation <90% in children receiving nasogastric hydration compared to children receiving intravenous hydration. The quality of the evidence was very low.

Change in disease severity score

No studies reported data on this outcome.

Length of hospital stay

Measured to time ready for discharge

One RCT with 759 children found no significant difference in length of hospital stay in children receiving nasogastric hydration compared to children receiving intravenous hydration. The quality of the evidence was low.

Change in respiratory rate

No studies reported data on this outcome.

Need for high flow humidified oxygen, CPAP or mechanical ventilation

CPAP

One RCT with 759 children found no significant difference in need for CPAP in children receiving nasogastric hydration compared to children receiving intravenous hydration. The quality of the evidence was very low.

Intubated and ventilated

One RCT with 759 children found no significant difference in need for intubation and ventilation in children receiving nasogastric hydration compared to children receiving intravenous hydration. The quality of the evidence was very low.

Adverse effects (including mortality)

Intensive care unit admission

One RCT with 759 children found no significant difference in intensive care unit admission in children receiving nasogastric hydration compared to children receiving intravenous hydration. The quality of the evidence was very low.

Intravenous line-site bruising

One RCT with 759 children found that intravenous line-site bruising was lower (better) in children receiving nasogastric hydration compared to children receiving intravenous hydration. The quality of the evidence was low.

Sore nose

One RCT with 759 children found that sore nose was higher (worse) in children receiving nasogastric hydration compared to children receiving intravenous hydration. The quality of the evidence was very low.

Intravenous line-site soreness

One RCT with 759 children found that intravenous line-site soreness was lower (better) in children receiving nasogastric hydration compared to children receiving intravenous hydration. The quality of the evidence was very low.

Epistaxis

One RCT with 759 children found no significant difference in epistaxis in children receiving nasogastric hydration compared to children receiving intravenous hydration. The quality of the evidence was very low.

Any sign nasal trauma

One RCT with 759 children found no significant difference in any sign of nasal trauma in children receiving nasogastric hydration compared to children receiving intravenous hydration. The quality of the evidence was very low.

Intravenous line-site infection

One RCT with 759 children found no significant difference in intravenous line-site infection in children receiving nasogastric hydration compared to children receiving intravenous hydration. The quality of the evidence was low.

Other (includes unspecified events 8 vs 7, vomiting 1 vs 2, worsened cough 1 vs 1, rash 1 vs 0 and crying 0 vs 1)

One RCT with 759 children found no significant difference in the incidence of other adverse events in children receiving nasogastric hydration compared to children receiving intravenous hydration. The evidence was of very low quality.

3.5.6 Health economics profile

No health economic studies were identified for this question. There was limited clinical evidence available to compare intravenous fluids with gastric tube feeding, or nasogastric hydration. The GDG requested a costing analysis for this area. A costing analysis was developed for the NICE guideline on diarrhoea and vomiting in children under 5 years (CG84) and this has been updated for this guideline. The total costs for nasogastric feeding or IV fluids for a 24 hour period are presented in Table 23. Full details of the costs included in the analysis are reported in Appendix A.

Table 23: Total costs for nasogastric feeding or IV fluids for 24 hours

	Staff costs	Consumable costs	Capital costs	TOTAL
Nasogastric feeding	£133.64	£12.63	£0	£146.20
IV fluids	£137.06	£8.80	£0.34	£146.27

3.5.7 Evidence to recommendations

3.5.7.1 Relative value placed on the outcomes considered

The aim of this review was to determine what factors indicate the need for fluids and nutritional support. The review question therefore focussed on the most appropriate means of providing fluid and nutritional support when a clinical judgement has deemed that support is necessary. The interventions on which evidence was sought were enteral tube feeding and intravenous fluid administration and the comparators were continued oral feeding, enteral tube feeding and intravenous fluid administration. The GDG agreed that change in oxygen saturation; length of stay; and need for high flow humidified oxygen, CPAP or mechanical ventilation were the critical outcomes for this review. Other important outcomes agreed by the GDG were: change in hydration (clinical hydration status /change in body weight/serum sodium concentration); change in disease severity score; change in respiratory rate; and adverse effects (including mortality).

No data was retrieved for the following outcomes: change in hydration, change in disease severity score and change in respiratory rate. In some situations where the chosen outcome was not available the GDG accepted similar outcomes such as number with oxygen saturation <90% instead of change in oxygen saturation.

3.5.7.2 Consideration of clinical benefits and harms

The GDG were not aware of any relevant studies other than the two identified for the evidence review.

They noted that the evidence from these two randomised controlled trials which both compared enteral tube (intragastric) fluids with intravenous fluids administration did not report any significant differences with these interventions on chosen outcomes. They noted that there was no reported difference in the length of hospital stay, the incidence of hypoxia (O2 saturation < 90%), the need for CPAP, mechanical ventilation or intensive care, or the incidence of pulmonary aspiration (a potential adverse effect of enteral tube feeding), between the study groups. One of the studies did report a difference in relation to two adverse effects, namely line-site bruising (higher in those given intravenous fluids) and of nasal soreness (higher in those receiving enteral fluids via a nasogastric tube). While these adverse effects were not surprising, the GDG recognised that they could be important when choosing between these treatment modalities. The GDG noted that there was no evidence from these studies regarding their other chosen outcomes – change in hydration, bronchiolitis severity score, change in respiratory rate or use of high flow humidified oxygen.

The GDG noted that the evidence did not establish any specific advantage in relation to the use of enteral tube versus intravenous administration. Although the evidence was of low or very low quality, they did note that there was no evidence to suggest that enteral feeding was associated with an increased risk of pulmonary complications such as aspiration or deterioration in pulmonary function as is sometimes suggested. They noted that there is currently considerable variation in practice regarding the use of enteral versus intravenous fluid administration in children with bronchiolitis, although nasogastric administration was probably more generally preferred. Placement of a nasogastric tube may be slightly unpleasant and can cause distress in infants and young children and it is possible for them to be accidentally displaced requiring re-insertion. However, venepuncture for intravenous access is also distressing and is sometimes difficult.

The GDG pointed out that the decision to give fluids and nutritional support is multifactorial. In some cases less than 75% usual intake may be appropriate for a healthy 10 month old but may be less appropriate in smaller infants or those with comorbidities.

There is a generally accepted principle in clinical practice that if fluids and nutrition can be safely and effectively provided via the gastrointestinal tract this is to be preferred to intravenous fluids.

The GDG therefore recommended that in children with bronchiolitis who were unable to take adequate fluids by mouth, fluid should be given via an nasogastric or orogastric tube. Provision of enteral feeds would mean that the child could receive significant nutrition during the course of the illness whereas intravenous fluids would not have this possible advantage. On the other hand, the GDG recognised that for most children with bronchiolitis oral feeding would only be markedly impaired for a relatively short period. They recommended that if children failed to tolerate enteral tube administered fluids or if there was evidence of impending respiratory failure consideration should be given to administering intravenous fluids instead. In keeping with the NPSA guidance[c] they advised that an isotonic fluid (such as 0.9% sodium chloride) should be used.

[c] http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60073&type=full&servicetype=Attachment

3.5.7.3 Consideration of health benefits and resource uses

The clinical evidence did not demonstrate any difference in terms of health benefits or adverse events between the fluid and nutritional support strategies in terms of length of stay or need for additional interventions. Resource use does not appear to be different for nasogastric feeding or IV fluids, and so these aspects cannot guide the decision on how to give fluids.

3.5.7.4 Quality of evidence

This review was limited to two randomised controlled trials. The evidence was of low to very low quality because of indirect populations (children with previous history of wheeze, bronchiolitis and asthma) and serious imprecision because of small sample sizes and therefore wide confidence intervals in the results.

3.5.7.5 Other considerations

No further considerations were noted.

3.5.8 Key conclusions

The GDG concluded that fluids should be given via the nasogastric or orogastric tube in children with bronchiolitis in whom oral hydration is inadequate. The GDG also decided to recommend giving isotonic intravenous fluids (based on the NPSA guidance) to children who fail to tolerate nasogastric or orogastric fluids and in those with impending respiratory failure.

3.5.9 Recommendations

23. **Give fluids by nasogastric or orogastric tube in children with bronchiolitis if they cannot take enough fluid by mouth.**

24. **Give intravenous isotonic fluids (see NPSA guidance[d]) to children who:**
    - do not tolerate nasogastric or orogastric fluids or
    - have impending respiratory failure.

3.6 Pulse oximetry monitoring

3.6.1 Review question

When is pulse oximetry oxygen saturation monitoring (SpO_2) indicated in bronchiolitis?

Further details on the protocol for this review question are provided in Appendix E.

3.6.2 Introduction

The function of the lungs, heart and vasculature is to ensure a continuous and adequate supply of oxygen to the tissues to maintain cellular integrity and function. Oxygen is primarily carried in arterial blood bound to haemoglobin. The oxygen content of blood can be assessed by analysing the oxygen saturation level in arterial blood (SaO2), which is the ratio of oxygenated haemoglobin concentration to total haemoglobin concentration. SaO2 can also be evaluated noninvasively by pulse oximetry, which exploits the different light absorption spectra for oxygenated and deoxygenated haemoglobin and the analysis of photoplethysmographic signals acquired at two wavelengths. Pulse oximetry provides an accurate assessment of SaO2 (referred to as SpO_2) in most clinical scenarios.

d http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60073&type=full&servicetype=Attachment

Bronchiolitis is characterised by variable hypoxaemia, resulting from both impaired gas exchange and ventilation-perfusion mismatch due to heterogeneous obstruction of the airways. Pulse oximetry provides a safe, convenient, painless means of assessing oxygenation in this group of patients.

3.6.3 Description of included studies

One study (Choi et al., 2006) was identified that assessed the efficacy of using pulse oximetry oxygen saturation monitoring in children with bronchiolitis. The study used a retrospective design, and it compared pre- and post-intervention patient groups.

The study was undertaken in the United States, and it included infants with a mean age of 11.4 months (pre-intervention group) and 8.2 months (post-intervention group). The sample sizes were 159 and 89 patients in the pre- and post-intervention group respectively.

The ICD-9 code for bronchiolitis was used to identify appropriate charts.

The study compared the two groups by quantifying the difference that the addition of pulse oximetry to the triage assessment (post-intervention group) made in overall throughput time for patients in whom assessment of oxygenation was indicated. The study reported on admission rates and total time spent in the Emergency Department.

More details on the included paper can be found in the evidence table in Appendix I.

3.6.4 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) or comparative observational studies were the most appropriate study designs for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 24: GRADE profile for comparison of pre-intervention (no pulse oximetry monitoring) with post-intervention (pulse oximetry monitoring added to ED triage).

Table 24: GRADE profile for comparison of pre-intervention (no pulse oximetry monitoring) with post-intervention (pulse oximetry monitoring added to ED)

Number of studies	Number of patients		Effect		Quality	Design	Quality assessment				
	Pre-intervention	Post-intervention	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Admission rates											
1. (Choi et al., 2006)	N= 32/159 (20%)	N= 16/89 (18%)	RR = 0.89 95%CI (0.52-1.53) *	P=0.61	Very Low	Retrospective cohort	Very Serious [a]	None	Serious [b]	Very serious [c]	None
Duration of admission											
Reported as triage to disposition time (either to home or to an inpatient bed)											
1. (Choi et al., 2006)	N=159 259 min	N=89 249 min	-	P=0.033	Very Low	Retrospective cohort	Very Serious [d]	None	Serious [e]	NC [f]	None

NA not applicable, NC not calculable, NR not reported, RCT randomised controlled trial, p-value, RR relative risk
** Calculated by the NCC-WCH technical team from data reported in the article*
a Cases and controls are taken from comparable populations: poorly addressed (population characteristics poorly reported); participants and non-participants are compared to establish their similarities and differences: not reported; main potential confounders are identified and taken into account: not addressed; the paper used a retrospective design.
b Outcome: triage to disposition time, rather than actual duration of admission.
c Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
d Cases and controls are taken from comparable populations: poorly addressed (population characteristics poorly reported); participants and non-participants are compared to establish their similarities and differences: not reported; Main potential confounders are identified and taken into account: not addressed. Also, confidence intervals and means were not reported, therefore it was not possible to grade imprecision (study has been downgraded because of this).
e Outcome: triage to disposition time rather than actual duration of admission.
f it was not possible to assess imprecision because of the lack of information reported in the paper (CI and means not reported).

3.6.5 Evidence statements

Admission rates

One study with 248 children found that the admission rate was lower in a group of patients who underwent pulse oximetry monitoring as part of the triage assessment in the Emergency Department, compared to a patient group who did not. However, this difference was not significant. The quality of the evidence was very low.

Duration of admission

Reported as triage to disposition time (either to home or to an inpatient bed)

One study with 248 children found that a group of patients who underwent pulse oximetry monitoring as part of the triage assessment spent a shorter time in ED, compared to patients who did not. This finding was significant. The quality of the evidence was very low.

Readmission rates

No studies reported data on this outcome.

Duration of oxygen supplementation

No studies reported data on this outcome.

Change in disease severity score

No studies reported data on this outcome.

Need for oxygen supplementation

No studies reported data on this outcome.

Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation

No studies reported data on this outcome.

Adverse effects (including mortality)

No studies reported data on this outcome.

3.6.6 Health economics profile

No published economic evaluations were identified for this question. This area was not prioritised for economic evaluation.

Costs were identified for pulse oximetry monitors to consider the impact of introducing this monitoring to primary care, full details can be found in the appendix. Digital oximeters suitable for primary care can cost from £349 for a basic hand held device to over £1,000 for a device with memories, alarms and ability to monitor temperature or blood pressure as well as O2 saturation. A reusable paediatric finger probe costs £65. The number of meters and finger probes required will depend on the size of the primary care practice.

The majority of attendances for acute bronchiolitis, complications score 0, is for a non-elective inpatient short stay (less than or equal to 1 day) (NHS reference costs data 2012/13, DH). For paediatrics the national average unit cost of an attendance is £526 (interquartile range £380 to £606).

3.6.7 Evidence to recommendations

3.6.7.1 Relative value placed on the outcomes considered

The aim of this review was to determine whether oxygen saturation monitoring is effective in the management of bronchiolitis. The GDG considered hospital admission rate and length of stay to be critical outcomes for this review. The GDG also identified the following as important outcomes: readmission rates; need for oxygen supplementation; duration of oxygen supplementation; change in disease severity score; the need for high flow humidified oxygen or continuous positive airway pressure (CPAP) or mechanical ventilation; and the occurrence of adverse effects (including mortality).

3.6.7.2 Consideration of clinical benefits and harms

The GDG noted that the evidence available was very limited and was of very low quality. They were not aware of any other relevant studies that had not been identified by the evidence search. They considered that the triage time considered in the paper by Choi et al. was too short.

The GDG noted that evidence was not available in relation to most of the prioritised outcomes, and so they based their recommendations on the limited data available and on their own clinical knowledge and expertise.

The GDG considered that in secondary care measurement of SPO_2 saturation was available and was already part of routine practice. It had the potential to identify children with borderline and marked hypoxia who might otherwise be missed and it therefore provided an additional element of safety and information for clinicians in deciding on the need for admission. Pulse oximetry is a non-invasive technique that does not cause distress or discomfort. It is easily carried out, although the GDG commented that those using it needed to be appropriately trained. There were aspects to its use in infants and children that required specific training. The GDG therefore concluded that it was inappropriate to send a child home from hospital without measuring their oxygen saturation. They therefore developed a recommendation for its use in this setting. The GDG recognised that it could also be helpful in a primary care setting, however, they recognised that the equipment and staff training might not always be available in primary care. Moreover, the severity of symptoms would on average be less severe in the children seen in primary care than those seen in the Emergency Department. They therefore recommended that the oxygen saturation be measured in children presenting with bronchiolitis in primary care if the technique was available. Given the resource implications and the lack of research evidence, the GDG developed a recommendation that research be carried out on the value of universal saturation monitoring for children presenting to primary care with bronchiolitis.

3.6.7.3 Consideration of health benefits and resource uses

The cost of a simple device is low and therefore the cost per use in primary care will be minimal. If using pulse oximetry in primary care avoids unnecessary referrals to hospital then it is likely to be cost saving.

3.6.7.4 Quality of evidence

The quality of the evidence was very low. Main sources of bias identified in the study were the retrospective design, lack of data on baseline demographic or clinical characteristics

(only mean age was reported), lack of adjustment for potential confounders, and very serious imprecision in the estimates due to the uncertainty of the effect.

3.6.7.5 Other considerations

Any other relevant considerations such as those related to equalities

3.6.8 Key conclusions

The GDG concluded that oxygen saturation should be measured and monitored in children presenting to secondary care with bronchiolitis; if available, SpO_2 monitoring should be used in primary care settings too. The GDG agreed that health care professionals would need appropriate training and highlighted the need for further research in primary care.

3.6.9 Recommendations

25. **Measure oxygen saturation in every child presenting with suspected bronchiolitis, including those presenting to primary care if pulse oximetry is available.**

26. **Measure pulse oxygen saturation using pulse oximetry in every child presenting to secondary care with clinical evidence of bronchiolitis.**

27. **Ensure healthcare professionals performing pulse oximetry are appropriately trained in its use specifically in infants and young children.**

3.6.10 Research recommendations

3. **What is the clinical and cost effectiveness of SpO_2 measurement in a primary care setting in children with bronchiolitis?**

Why this is important

3.1. **There are no studies to inform the use of SpO_2 measurement in primary care. SpO_2 is used routinely in secondary care to help decide on the need for admission to hospital. The clinical and cost effectiveness of SpO_2 measurement in primary care is also important. SpO_2 measurement is not routinely measured in infants and young children with bronchiolitis in primary care. The value of SpO_2 measurement to help identify those who need admission to hospital should be assessed. Possible outcomes might be fewer or more infants being referred to hospital, or admitted.**

3.7 Chest radiography

3.7.1 Review question

What are the indications for chest radiography in bronchiolitis?

Further details on the protocol for this review question are provided in Appendix E.

3.7.2 Introduction

There remains wide variation in the management of bronchiolitis including investigation with chest radiography. Bacterial infection in children with bronchiolitis is rare but, despite this, radiographs are often performed to rule out pneumonia and rare respiratory conditions other

than bronchiolitis. Chest radiography results in radiation exposure, has significant cost implications and can lead to unnecessary interventions if not interpreted correctly.

3.7.3 Description of included studies

Three observational studies and one cost-effectiveness analysis were identified for this review. One of these studies was performed at the Emergency Department of a children's hospital (Shaw et al., 1991), one was performed in a paediatric department (Dawson et al., 1990), one was performed in a tertiary care ED (Yong et al., 2009) and one used data from a paediatric information system database involving 30 different Children's hospitals (Christakis et al., 2005).

Two studies (Shaw et al., 1991; Dawson et al., 1990) used a cross-sectional design, a third study (Christakis et al., 2005) was a retrospective cohort, and the last study (Yong et al., 2009) was a cost-effectiveness analysis. Two studies were performed in the United States (Shaw et al., 1991; Christakis et al., 2005), one in Canada (Yong et al., 2009) and one in New Zealand (Dawson et al., 1990).

One study (Shaw et al., 1991) considered chest x-ray in order to see if radiological findings (atelectasis and hyperaeration) can be used to predict more severe disease; one study (Dawson et al., 1990) examined the association between radiological change (hyperinflation, infiltrates and the combination of hyperinflation, infiltrates and atelectasis together) and parallel clinical assessment using a score; one study (Yong et al., 2009) reported diagnostic accuracy results for the detection of pneumonia cases and alternate diagnoses using chest x-ray; one study (Christakis et al., 2005) aimed to determine which potentially modifiable process of care measures (including chest radiography) are associated with longer length of stay and antibiotic usage.

Two studies included infants aged 12 months or younger (Shaw et al., 1991; Christakis et al., 2005), one study considered infants aged up to 24 months (Dawson et al., 1990) and another study included children aged from 2 to 23 months (Yong et al., 2009).

The definition of bronchiolitis and its diagnosis varied between studies; one study (Shaw et al., 1991) defined children with bronchiolitis as those presenting with signs of lower airway disease such as tachypnoea, rales or wheezing and then compared infants with mild disease (infant remained alert and active and was well hydrated while he/she was taking fluids orally throughout the illness) with those with severe disease (all others without mild disease). One study (Dawson et al., 1990) reported information on diagnosis of bronchiolitis elsewhere (from Dawson et al. "Acute Bronchiolitis: a Three Year Study", 1989: children with clinical diagnosis of acute bronchiolitis, with no previous history of a similar illness, as evidenced by a brief prodrome of upper respiratory symptoms followed by rapid onset of cough wheeze, tachypnoea and poor feeding associated with hyperinflation, recession and fine crackles were studied). One study (Yong et al., 2009) defined typical bronchiolitis as the presence of non-toxic appearance with coryza, cough, and respiratory distress with wheezing for the first time. Only one study (Christakis et al., 2005) defined bronchiolitis based on International Classification of Diseases, Ninth Revision (codes 466.11 or 466.19) and based on All-Patient Refined Diagnosis Related Groups of bronchiolitis/asthma (code 141).

All four studies considered chest radiograph as the index test administered as part of patient assessment (Dawson et al., 1990; Shaw et al., 1991; Christakis et al., 2005; Yong et al., 2009); one study considered infants who received chest radiograph and attempted to define the reasons individual chest radiographs were taken (Dawson et al., 1990). One study included children who underwent chest radiography as part of the diagnostic process (Christakis et al., 2005).

The outcomes specified by the GDG for this review were:

- Identification of an additional or alternate diagnosis, including association between results of chest radiography and severity of bronchiolitis
- Antibiotic administration
- Admission rates
- Duration of admission
- Change in disease severity
- Need for high flow humidified oxygen, continuous positive airway pressure (CPAP), or mechanical ventilation
- Adverse effects

The studies did not report data on all the outcomes identified by the GDG. Three studies reported data on the identification of additional or alternate diagnoses (Shaw et al., 1991; Dawson et al., 1990; Yong et al., 2009); one study presented data on antibiotic administration (Christakis et al., 2005) and one study reported data on duration of admission (Christakis et al., 2005).

More details on each individual study can be found in the evidence tables in Appendix I.

3.7.4 Evidence profile

Study quality was assessed using the GRADE methodology. The data are presented in two separate GRADE profiles, one for diagnostic test accuracy and one for intervention studies.

Two GRADE profiles have been produces for this review:

- Table 25: GRADE profile for the diagnostic value of chest radiography vs no chest radiography in identifying alternative diagnosis to bronchiolitis.
- Table 26: GRADE profile for the effect that chest radiography has on the management of bronchiolitis.

Table 25: GRADE profile for the diagnostic value of chest radiography vs. no chest radiography in identifying alternative diagnoses to bronchiolitis.

Number. of studies	Number of patients	Measure of diagnostic accuracy						Quality	Quality assessment					
		Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	Positive likelihood ratio (95% confidence interval)	Negative likelihood ratio (95% confidence interval)	Positive Predictive Value (95% confidence interval)	Negative Predictive Value (95% confidence interval)		Design	Limita-tions	Inconsist-ency	Indirect-ness	Impreci-sion	Other considera-tions
Identification of additional or alternate diagnosis														
Detection of alternate diagnoses (lobar consolidation, cardiomegaly, congenital lung anomaly, pleural effusion, and mediastinal or parenchymal mass) pre-radiography														
1 (Yong et al,2009)	265	0% (0-0.84)[a]	97% (94-98) [a]	0 (0-0.18) [a]	1.03 (1.02-1.04) [a]	0% (0-0.33) [a]	99% (97-100) [a]	Very low	Economic Evaluation	Serious [b, c, g]	None	Serious [m]	Serious [h]	None
Detection of alternate diagnoses (lobar consolidation, cardiomegaly, congenital lung anomaly, pleural effusion, and mediastinal or parenchymal mass) post-radiography														
1 (Yong et al, 2009)	265	0% (0-0.84) [a]	89% (84-92) [a]	0 (0-0.06) [a]	1.13 (1.08-1.17) [a]	0% (0-0.11) [a]	99% (96-100) [a]	Very low	Economic Evaluation	Serious [b, c, g]	None	Serious m	Serious [j]	None
Detection of cases of pneumonia, pre-radiography														
1 (Yong et al, 2009)	265	12% (3-27) [a]	89% (85-93) [a]	1.12 (0.29-4.34) [a]	0.98 (0.82-1.18) [a]	7% (2-16) [a]	94% (91-97) [a]	Very low	Economic Evaluation	Very serious b, c, g	None	Serious [m]	Serious [j]	None
Detection of cases of pneumonia, post-radiography														
1 (Yong et al, 2009)	265	41% (17-64) a	84% (79 - 88) [a]	2.55 (1.35-4.82) [a]	0.70 (0.47-1.05) [a]	15% (4 - 25) [a]	95% (93 - 98) [a]	Very low	Economic Evaluation	Serious [b, c, g]	None	Serious [m]	Serious [l]	None
Detection of severe cases of bronchiolitis (atelectasis on chest x-ray)														
1 (Shaw et al, 1991)	213	21% (12-30) [a]	98% (95-100) a	10.47 (3.01-36.37) [a]	0.81 (0.71-0.91) [a]	82% (68-100) [a]	70% (63-76) [a]	Very Low	Cross-sectional	Very serious [b, d, f]	None	None	Very Serious [k]	Some [e]

a- Calculated by the NCC-WCH technical team from data reported in the article
b- Lack of a gold standard
c- The researchers excluded premature infants (selection bias)
d- No clear method of diagnosis stated and severity of illness may have been lower than in other studies
e- Unclear applicability ("history of previous upper tract respiratory infection" inclusion criterion)
f- Infants in the mild disease group and those in the severe disease group are significantly different in terms of baseline characteristics historical information (gestational age, perinatal complications, URI symptoms, exposure to a smoker in the family, whether the baby had been breastfed, family history of wheezing) and no control for confounding
g- The study radiologist knew the patients were suspected of having bronchiolitis
h- Thresholds used: <74% low, 75-89% moderate, >90% high (for sensitivity, specificity and predictive values); <5 not useful, 5-10 moderately useful, >10 very useful (for positive likelihood ratio); >0.5 not useful, 0.1-0.5 moderately useful, 0-0.1 very useful (for negative likelihood ratio). In this case: low sensitivity, high specificity, low PPV, high NPV, not useful to inf +LR, not useful –LR (one of them spans over two or more thresholds).
i- In this case: low sensitivity, moderate to high specificity, low PPV, high NPV, not useful to inf +LR and not useful –LR (two measures cross the thresholds).

j- In this case: low sensitivity, moderate to high specificity, low PPV, high NPV, not useful +LR, and not useful to moderately useful –LR (two measures cross the thresholds).
k- In this case: low sensitivity, high specificity, low to high PPV, low to moderate NPV, not useful to very useful +LR, not useful –LR (three measures cross thresholds).
l- In this case: low sensitivity, moderate specificity, low PPV, high NPV, not useful +LR, and moderately useful to very useful –LR (one measure crosses thresholds).
m- Included infants up to 23 months of age. The GDG has specified that it is likely that older children will not have bronchiolitis.

Table 26: GRADE profile for the effect that chest radiography has on the management of bronchiolitis.

Number of studies	Number of patients		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Identification of additional or alternate diagnosis – association between radiograph findings and severe bronchiolitis											
Atelectasis and disease severity											
1 (Shaw et al, 1991)	Mild disease: 3 of 139 with Atelectasis	Severe 16 of 74 had atelectasis	RR 2.70 (1.97-3.70)	P<0.001	Very low	Cross-sectional	Very serious [a, b, e]	None	None	None	Some [d]
Hyperaeration and disease severity											
1 (Shaw et al, 1991)	Mild disease: 52 of 139 showed hyperaeration	Severe disease: 69 of 74 had hyperaeration	RR 1.58 (1.03-2.42)	P<0.05	Very low	Cross-sectional	Very serious [a, b, e]	None	None	Serious [k]	Some [d]
Radiological change and disease severity											
1 (Dawson et al, 1990)	-	-	Chi-square 9.92	P<0.10	Very Low	Cross-sectional	Serious [a, g, f]	None	Serious [n]	NC [l]	None
1 (Dawson et al, 1990)	-	-	Chi-square 4.56	P<0.10	Very Low	Cross-sectional	Serious [a, g, f]	None	Serious [n]	NC [l]	None
1 (Dawson et al, 1990)	-	-	Chi-square 6.55	P<0.10	Very Low	Cross-sectional	Serious [a, g , f]	None	Serious [n]	NC [l]	None
Antibiotic administration – with radiograph compared to no radiograph											
Children aged less than 3 months											
1 (Christakis et al, 2005)	-	-	Adjusted OR 1.11 (0.96-1.28)	P>0.05	Very low	Retrospective cohort study	Very serious [a, c, h]	None	None	Serious [k]	Some [i, j]

Number of studies	Number of patients		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Children aged 3 months or more											
1 (Christakis et al, 2005)	-	-	Adjusted OR 1.22 (1.10-1.36)	P<0.001	Very low	Retrospective cohort study	Very serious [a, c, h]	None	None	Serious [k]	Some [i, j]
Duration of admission (days) – with radiograph compared to no radiograph											
Children aged less than 3 months											
1 (Christakis et al, 2005)	-	-	-	Adjusted MD 0.34 (0.22-0.46) P<0.001	Very low	Retrospective cohort study	Very serious [a, c, h]	None	None	None [m]	Some [i, j]
Children aged 3 months or more											
1 (Christakis et al, 2005)	-	-	-	Adjusted MD 0.30 (0.19-0.40) P<0.001	Very low	Retrospective cohort study	Very serious [a, c, h]	None	None	None [m]	Some [i, j]

NA not applicable, NC not calculable, P = p-value, MD Mean Difference, RR Relative Risk.

** Calculated by the NCC-WCH technical team from data reported in the article*
[a] Lack of a gold standard
[b] No clear method of diagnosis stated and severity of illness may have been lower than in other studies
[c] Data collected retrospectively
[d] Unclear applicability ("history of previous upper tract respiratory infection" inclusion criterion)
[e] Two groups significantly different in terms of historical information and no control for confounding
[f] The study radiologist knew the patients were suspected of having bronchiolitis
[g] Method of diagnosis and inclusion/exclusion criteria reported elsewhere in Dawson et al., "Acute Bronchiolitis: A Three Year Study", 1989: Children with a clinical diagnosis of bronchiolitis, with no previous history of a similar illness, as evidenced by a brief prodrome of upper respiratory symptoms following by rapid onset of cough, wheeze, tachypnea and poor feeding associated with hyperinflation, recession, and fine crepitations/crackles.
[h] Baseline information about the two groups are not reported
[i] Information on how the index test was performed are not reported
[j] Statistical analyses controlled for confounders
[k] Wide confidence interval crossing +0.25 around line of no effect
[l] Imprecision could not be investigated due to way the results have been reported (no confidence intervals)
[m] SMD cannot be calculated due to way the results have been reported (no mean differences for both control and intervention group), therefore imprecision could not be evaluated
[n] Included infants up to 22 months of age. The GDG has specified that it is likely that older children will not have bronchiolitis.

3.7.5 Evidence statements

In the following statements the following definitions have been used when summarising the levels of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV):

- High – 90% and above
- Moderate – 75% to 89%
- Low – 74% or below

The following terms have been used when summarising the positive and negative likelihood ratios

Positive likelihood ratio:

- Very useful – > 10
- Moderately useful – > 5 to 10
- Not useful – < 5

Negative likelihood ratio:

- Very useful – 0 to 0.1
- Moderately useful – > 0.1 to 0.5
- Not useful – > 0.5

Identification of additional or alternate diagnosis

Detection of alternate diagnoses (lobar consolidation, cardiomegaly, congenital lung anomaly, pleural effusion, and mediastinal or parenchymal mass) post-radiography

One study with 265 children evaluated the diagnostic accuracy of chest radiography in children with bronchiolitis. The study reported not useful positive likelihood ratio, and not useful negative likelihood ratio. Chest radiography was found not to be a useful test in order to identify alternate diagnoses. The quality of the evidence was very low.

Detection of cases of pneumonia post-radiography

One study with 265 children evaluated the diagnostic accuracy of chest radiography in children with bronchiolitis. The study reported not useful positive or negative LR. Chest radiography was found not to be a useful test in order to identify cases of pneumonia. The quality of the evidence was very low.

Identification of severe cases of bronchiolitis

One study with 213 children reported very useful positive likelihood ratio, and not useful negative likelihood ratio for the identification of severe cases of bronchiolitis. Chest radiography was found to be a very useful test to identify severe cases and a not useful test to detect negative cases (positive and negative likelihood ratio respectively). The quality of the evidence was very low.

Association between atelectasis and disease severity

One study with 213 children found that children who had atelectasis on chest radiograph were significantly more likely to have severe bronchiolitis than mild bronchiolitis, compared to those who don’t have atelectasis. The quality of the evidence was very low.

Association between hyperinflation and disease severity

One study with 213 children found that children who had hyperinflation on chest radiograph were significantly more likely to have severe bronchiolitis than mild bronchiolitis, compared to those who don't have hyperinflation. This finding was significant. The quality of the evidence was very low.

Association between radiological change and disease severity score

One study with 153 children found that there is no significant association between various radiological changes (hyperinflation, infiltrates and the combination of hyperinflation, infiltrates and atelectasis together) and clinical severity of bronchiolitis. The quality of the evidence was very low.

Antibiotic administration

Children aged less than 3 months

One study with 17397 children found that children with bronchiolitis who had chest radiography were significantly more likely to receive antibiotics than those who did not have chest radiograph. The quality of the evidence was very low.

Children aged 3 months or more

One study with 17397 children found that children with bronchiolitis who had chest radiography were significantly more likely to receive antibiotics than those who did not have chest radiograph. The quality of the evidence was very low.

Duration of admission

Children aged less than 3 months

One study with 17397 children found that children who had a chest radiograph had a significantly longer duration of admission compared to those who did not receive chest radiograph. The quality of the evidence was low.

Children aged 3 months or more

One study with 17397 children found that children who had a chest radiograph had a significantly longer duration of admission compared to those who did not receive chest radiograph. The quality of the evidence was low.

Admission rates

No studies reported data on this outcome

Change in disease severity

No studies reported data on this outcome

Need for high flow, humidified oxygen, CPAP, or mechanical ventilation

No studies reported data on this outcome

Adverse effects

No studies reported data on this outcome

3.7.6 Health economics profile

One published economic evaluation was identified for this question (Yong et al., 2009). The study compared diagnosis after initial patient assessment with diagnosis after a chest radiograph was obtained; all infants in the study had a chest x-ray.

The costs of emergency department visits, observation unit stays, and hospitalization, medication, and chest radiographs were included. This was a Canadian study and based on a provincial health care system. The outcomes of the study were identification of alternative diseases and detection of pneumonia. The time horizon of the analysis was restricted to the episode of acute care, re-admissions were not reported.

The conclusion of the analysis was that performing chest x-rays did not add diagnostic value when identifying alternative diseases. The costs of observation unit stay and hospitalisation was higher when using a chest x-ray as part of the diagnostic work-up and this seems to be due to incorrect diagnosis of pneumonia. Therefore, it was concluded that chest x-rays were not cost-effective. However, because only the episode of acute care was considered it is not possible to understand the impact of missed cases of pneumonia. It is important when considering the cost-effectiveness of the two diagnosis strategies to understand the trade-off between missed cases of pneumonia and over-diagnosis of pneumonia and therefore unnecessary antibiotic treatment in infants and young children. It was not a full economic evaluation and therefore it was excluded as cost-effectiveness evidence.

3.7.7 Evidence to recommendations

3.7.7.1 Relative value placed on the outcomes considered

The aim of this review was to determine the clinical criteria for performing a chest radiograph in children with bronchiolitis. In particular, the GDG wanted information on the possible association between radiological findings on chest x-ray results and the severity of illness in bronchiolitis. They wished to determine whether the use of chest radiography influenced critical outcomes in bronchiolitis, including antibiotic administration, admission rates, and duration of admission. Other important outcomes were: change in disease severity; the use of high flow humidified oxygen; continuous positive airway pressure (CPAP); or mechanical ventilation and the occurrence of adverse effects. The GDG considered identification of additional diagnoses or of an alternative diagnosis to bronchiolitis and antibiotic administration to be especially important outcomes for this review.

3.7.7.2 Consideration of clinical benefits and harms

The GDG noted that the evidence available was of very low quality. The exact criteria employed for the diagnosis of bronchiolitis varied in the included studies. They did not know of any other relevant studies that had not been identified for the review.

The GDG agreed that the evidence did not support the routine use of chest x-ray in children presenting to secondary care with bronchiolitis. It was not useful in identifying either unsuspected alternative diagnoses in children with a clinical diagnosis of bronchiolitis or in identifying unsuspected complications in those with bronchiolitis. While clinicians must bear in mind the possibility of alternative diagnoses and complications when assessing children with suspected bronchiolitis performing a chest x-ray in a child with a clinical presentation typical of bronchiolitis is not advisable.

The GDG considered the potential reasons why chest x-ray is frequently included in the diagnostic workup. They believed that it was perceived as an additional safety check in terms of diagnosis and identification of complications, but there was little to support this. Moreover, in bronchiolitis the commonly observed radiological changes are often incorrectly interpreted as indicative of possible bacterial pneumonia. Consequently antibiotic treatment is often

given, which is both unnecessary and potentially associated with adverse effects. The suspicion of pneumonia would also likely result in a decision to admit the child from the Emergency Department to the hospital and intravenous antibiotic treatment is likely to prolong the child's stay in hospital. The GDG observed that in most hospitals the radiology department is in close proximity to the Emergency Department and that children presenting with bronchiolitis most often had a chest x-ray performed while in the Emergency Department rather than after admission to the hospital in-patient wards.

The GDG also noted that parents and carers have some anxiety about the radiation exposure associated with any x-ray procedure.

3.7.7.3 Consideration of health benefits and resource uses

The staff time and equipment costs for providing x-rays do not appear to be associated with any health benefits in terms of diagnosis for children with bronchiolitis. Therefore resources can be saved by not routinely using chest x-rays in a diagnostic work-up for this group.

3.7.7.4 Quality of evidence

The quality of the evidence was very low. Main sources of bias identified in the included studies were: the lack of a gold standard (comparisons were made pre- and post-radiography), retrospective design, lack of data on baseline demographic or clinical characteristics, and imprecision due to wide 95% confidence intervals.

3.7.7.5 Other considerations

No other considerations were identified.

3.7.8 Key conclusions

The GDG concluded that chest x-ray should not be performed in children with bronchiolitis.

3.7.9 Recommendations

28. Do not perform a chest x-ray in children with bronchiolitis, because changes on X-ray may mimic pneumonia and should not be used to determine the need for antibiotics.

3.8 Capillary blood gas testing

3.8.1 Review question

What is the indication for capillary blood gas testing?

Further details on the protocol for this review question are provided in Appendix E.

3.8.2 Introduction

Arterial blood gas sampling remains the gold standard for determining a child's acid-base and ventilatory status. However, it has many drawbacks and is technically difficult in small children. Capillary blood gas analysis requires a less invasive method of collection and has been shown to accurately reflect arterial pH and PC_{O2}. Impending respiratory failure in children with bronchiolitis is associated with a rising PaC_{O2}, and the need for additional respiratory support or movement to a clinical area that can provide a higher dependency of care.

3.8.3 Description of included studies

No evidence was identified for this review.

3.8.4 Evidence profile

No evidence was identified for this review.

3.8.5 Health economics profile

No published economic evaluations were identified for this question.

3.8.6 Evidence to recommendations

3.8.6.1 Relative value placed on the outcomes considered

The aim of this review was to determine which factors indicate the need for capillary blood gas testing and the role of arterialised carbon dioxide values in guiding the use of high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation.

The GDG indicated duration of oxygen supplementation; and need for high flow humidified oxygen, CPAP or mechanical ventilation as the critical outcomes for this review. Other important outcomes were: length of stay; readmission rates; change in disease severity score; and need for oxygen supplementation.

The GDG however acknowledged that some of these outcomes may be confounded by the severity of bronchiolitis (i.e. children with more severe disease may be more likely to undergo capillary blood gas testing and so the outcomes from testing may be worse, as the children were more ill to start with).

3.8.6.2 Consideration of clinical benefits and harms

No relevant evidence was found for this review and the GDG were not aware of any other relevant studies that had not been identified. The GDG developed consensus recommendations based on their own knowledge and expertise.

The GDG agreed that it was neither necessary nor advisable to carry out blood gas testing routinely on children with bronchiolitis. In the vast majority of infants and children with bronchiolitis this would not reveal any relevant findings. Oxygen saturation could be assessed non-invasively using pulse oximetry. They did advise that consideration be given to performing a capillary blood gas test if there was severe worsening respiratory distress, because in such cases it might reveal evidence of carbon dioxide retention indicating respiratory failure. There was no evidence to guide a definition of severe worsening respiratory distress, but a consensus was reached that children with an oxygen requirement over 50% FiO2 could be considered to be in severe worsening respiratory distress and therefore capillary blood gas testing may help guide further management.

The GDG also discussed other key features that should be considered suggestive of impending respiratory failure. They agreed that important indicators were: signs of exhaustion such as increased listlessness and decreased respiratory effort; recurrent apnoea; and failure to maintain adequate oxygen saturation levels even with supplementation. Recognition of impending respiratory failure was essential to help guide timely interventions such as referral to intensive care and mechanical ventilation.

3.8.6.3 Consideration of health benefits and resource uses

There is unlikely to be any health benefits from routine blood gas testing on children with bronchiolitis. Resources in terms of staff time, test consumables etc. can be saved by not carrying out this test.

3.8.6.4 Quality of evidence

No relevant studies were identified for this review. The recommendations developed were consensus based.

3.8.6.5 Other considerations

No other considerations were identified.

3.8.7 Key conclusions

The GDG concluded that it was neither necessary nor advisable to carry out blood gas testing routinely on children with bronchiolitis, however they did advise that consideration be given to performing a capillary blood gas test if there was severe worsening respiratory distress.

3.8.8 Recommendations

29. **Do not routinely carry out blood gas testing in children with bronchiolitis.**

30. **Consider carrying out capillary blood gas testing in children with severe worsening respiratory distress (when supplemental oxygen concentration is greater than 50%) or suspected impending respiratory failure (see recommendation 31).**

31. **Suspect impending respiratory failure if the child has any of the following:**
    - signs of exhaustion, for example listlessness or decreased respiratory effort
    - recurrent apnoea
    - failure to maintain adequate oxygen saturation despite oxygen supplementation

4 Management of bronchiolitis

4.1 Chest physiotherapy

4.1.1 Review question

What is the efficacy of chest physiotherapy in the management of bronchiolitis?

Further details on the protocol for this review question are provided in Appendix E.

4.1.2 Introduction

Chest physiotherapy is widely used in the management of children with acute and chronic respiratory conditions. The aim of the therapy is to assist the child in clearing secretions from the airways. The administration of chest physiotherapy can be uncomfortable for the child and distressing for the carers. There is also the potential that it can worsen the condition or precipitate a deterioration.

4.1.3 Description of included studies

Seven RCTs (Castro-Rodriguez et al., 2014; Gajdos et al., 2010; Gomes et al., 2012; Nicholas et al., 1999; Postiaux et al., 2011; Rochat et al., 2012; Webb et al., 1985) were identified that assessed the efficacy of chest physiotherapy (CPT) in the management of bronchiolitis.

Two studies were undertaken in the United Kingdom (Nicholas et al., 1999; Webb et al., 1985), one in Chile (Castro-Rodriguez et al., 2014), one in France (Gajdos et al., 2010), one in Brazil (Gomes et al., 2012), one in Belgium (Postiaux et al., 2011), and one in Switzerland (Rochat et al., 2012). Sample sizes ranged from 20 infants (Postiaux et al., 2011) to 496 (Gajdos et al., 2010).

With regards to the population considered, the age of the infants ranged from less than one year in four studies (Castro-Rodriguez et al., 2014; Nicholas et al., 1999; Postiaux et al., 2011; Rochat et al., 2012) to less than two years in the remaining three studies (Gajdos et al., 2010; Gomes et al., 2012; Webb et al., 1985). Diagnosis of bronchiolitis was based on clinical findings consistent with the disease in two studies (Castro-Rodriguez et al., 2014; Gajdos et al., 2010), on positive outcome of RSV infection in nasopharyngeal secretions in other two studies (Gomes et al., 2012; Postiaux et al., 2011), and on the clinical assessment at admission in the remaining three studies (Nicholas et al., 1999; Rochat et al., 2012; Webb et al., 1985).

Two studies compared a combined technique using slow and long expiration techniques, assisted cough and bronchodilator against bronchodilator only (Castro-Rodriguez et al., 2014; Postiaux et al., 2011); two studies reported on the comparison of combined technique using increased exhalation techniques, assisted cough and upper airways suction against upper airways suction only (Gajdos et al., 2010; Gomes et al., 2012); two studies reported findings for a comparison of combined percussion/vibration techniques and suction with the use of suction alone (Gomes et al., 2012; Nicholas et al., 1999); one study compared the use of prolonged expiration techniques with percussion/vibration techniques (Gomes et al., 2012); one study reported on the comparison of combined slow expiration techniques, slow accelerated expiratory flow and induced cough against no treatment (Rochat et al., 2012); finally, one study compared a combined technique using of chest percussion, assisted cough and oropharyngeal suction against no intervention (Webb et al., 1985).

Six studies reported on clinical score (Castro-Rodriguez et al., 2014; Gomes et al., 2012; Nicholas et al., 1999; Postiaux et al., 2011; Rochat et al., 2012; Webb et al., 1985), and four

studies reported on oxygen saturation (Castro-Rodriguez et al., 2014; Gomes et al., 2012; Postiaux et al., 2011; Rochat et al., 2012). One study reported on respiratory rate (Castro-Rodriguez et al., 2014); one study reported on time to recovery and side effects (Gajdos et al., 2010); one study reported on length of stay and provision of inspired O2 and requirement of nasogastric feeding (Nicholas et al., 1999), while one study reported on time to clinical stability and total length of illness (Rochat et al., 2012).

Four studies were performed in paediatric departments (Gajdos et al., 2010; Gomes et al., 2012; Postiaux et al., 2011; Webb et al., 1985), two were carried out in paediatric hospitals (Nicholas et al., 1999 and Rochat et al., 2012), while one study was performed in an outpatient clinic (Castro-Rodriguez et al., 2014).

More details on each individual study can be found in the evidence tables in Appendix I.

4.1.4 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

Six GRADE profiles have been produced for this review:

- Table 27: GRADE profile for comparison of slow and long expiration techniques + assisted cough + bronchodilator with bronchodilator only
- Table 28: GRADE profile for comparison of increased exhalation/expiration techniques + assisted cough + upper airways suction with suction only
- Table 29: GRADE profile for comparison of percussion and vibration techniques + suction with suction only
- Table 30: GRADE profile for comparison of prolonged slow expiration techniques with percussion and vibration techniques
- Table 31: GRADE profile for comparison of prolonged slow expiration techniques + slow accelerated expiratory flow + induced cough with no intervention
- Table 32: GRADE profile for comparison of chest percussion in 5 drainage positions + assisted cough + oropharyngeal suction with no intervention

Table 27: GRADE profile for comparison of slow and long expiration techniques + assisted cough + bronchodilator with bronchodilator only

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Clinical score											
Proportion of patients discharged a (comparator: salbutamol)											
1. Castro-Rodriguez et al. 2014	N = 23/25 (92%)	N = 20/23 (87%)	RR 1.06 (0.87-1.29) *	P=0.66	Low	RCT	Serious [b]	None	Serious [c]	Serious [d]	None
Tal's clinical score e (comparator: salbutamol)											
1. Castro-Rodriguez et al. 2014	Mean (95% CI): 2.8 (2.2-3.3) N = 25	Mean (95% CI): 3.4 (2.8-4.1) N = 23	NC	MD -0.60 (-1.40 to 0.20) * ns	Low	RCT	Serious [b]	None	Serious [c]	None [f]	None
Wang's total clinical score (comparator: albuterol) at 30 min											
1. Postiaux et al., 2011	Mean ±SD: 3.6 ±2.3 N =12, 31 sessions	Mean ±SD: 5.1 ±2.6 N =8, 27 sessions	NC	MD -1.50 (-3.72 to 0.72) * P=0.02	Moderate	RCT	Serious [g]	None	None	Serious [h]	None
Wang's total clinical score (comparator: albuterol) at 150 min											
1. Postiaux et al., 2011	Mean ±SD: 3.7 ±2.7 N =12, 31 sessions	Mean ±SD: 4.6 ±2.9 N =8, 27 sessions	NC	MD -0.90 (-2.35 to 0.55) * P=0.21	Low	RCT	Serious [g]	None	None	Very Serious [i]	None
Respiratory rate section of Wang's clinical score at 30 min (comparator: albuterol)											
1. Postiaux et al., 2011	Mean ±SD: 1.3 ±0.9 N =12, 31 sessions	Mean ±SD: 2.0 ±0.7 N =8, 27 sessions	NC	MD - 0.70 (-1.11 to -0.29) * P=0.001	Moderate	RCT	Serious [g]	None	None	Serious [n]	None
Respiratory rate section of Wang's clinical score at 150 min (comparator: albuterol)											
1. Postiaux et al., 2011	Mean ±SD: 1.3 ±0.8 N =12	Mean ±SD: 1.7 ±0.7 N =8	NC	MD - 0.40 (-0.78 to -0.01) * P=0.06	Moderate	RCT	Serious [g]	None	None	Serious [o]	None
O2 Saturation , %											
Comparator: salbutamol											
1. Castro-Rodriguez et	Mean (95% CI): 96.4 (95.7-	Mean (95% CI): 96.0 (94.9-96.5)	NC	MD 0.40 (-0.83 to	Very Low	RCT	Serious [b]	None	Serious [c]	Very Serious [j]	None

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
al., 2014	97.1) N = 25	N = 23		1.63) * ns							
Measurement at 30 min, comparator: albuterol											
1. Postiaux et al., 2011	Mean±SD: 95 ±3 N =12, 31 sessions	Mean±SD: 95 ±3 N =8, 27 sessions	NC	MD 0.00 (-2.68 to 2.68) * P=0.61	Low	RCT	Serious [g]	None	None	Very Serious [k]	None
Measurement at 150 min, comparator: albuterol											
1. Postiaux et al., 2011	Mean±SD: 96 ±2 N =12, 31 sessions	Mean±SD: 96 ±2 N =8, 27 sessions	NC	MD 0.00 (-1.03 to 1.03) * p=0.83	Low	RCT	Serious [g]	None	None	Very Serious [i]	None
Respiratory rate											
Comparator: salbutamol											
1. Castro-Rodriguez et al., 2014	Mean ±SD: 43.0 ±11 N = 25	Mean±SD: 48.9 ±9 N = 23	NC	MD - 5.90 (-11.57 to -0.23) * ns	Low	RCT	Serious [b]	None	Serious [c]	Serious [m]	None

MD Mean Difference, SD standard deviation, NC not calculable, NR not reported, Ns non-significant, RCT randomised controlled trial, p-value, RR relative risk
** Calculated by the NCC-WCH technical team from data reported in the article*
a. primary outcome was defined as the proportion of patients discharged after the first hour of treatment if clinical score ≤5/12 and SpO_2≥93%
b. performance bias: not reported if physiotherapists administering the intervention were aware of treatment allocation; detection bias: investigators not blind to confounding and prognostic factors
c. "most infants were under one year of age" and some of the participants had previous wheezy episodes
d. Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
e. Tal's clinical score e (min 0 – max 12) assessing respiratory rate, wheeze, cyanosis and accessory respiratory muscle utilization
f. SMD calculation by NCC-WCH: SMD (95%CI) = -0.60 (-1.88 to -0.68). No imprecision (Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID)..
g. Selection bias: concealment of allocation not described, as well as the random sequence generation is not reported
h. SMD calculation by NCC-WCH: SMD (95%CI) = -1.50 (-2.77 to -0.22). Serious imprecision when 95% CI crosses one default MID.
i. SMD calculation by NCC-WCH: SMD (95%CI) = -0.90 (-2.35 to 0.55). Very serious imprecision when 95% CI crosses two default MID..
j. SMD calculation by NCC-WCH: SMD (95%CI) = 0.40 (-0.83 to 1.63). Very serious imprecision when 95% CI crosses two default MID..
k. SMD calculation by NCC-WCH: SMD (95%CI) = 0.00 (-0.55 to 1.55). Very serious imprecision when 95% CI crosses two default MID..
l. SMD calculation by NCC-WCH: SMD (95%CI) = 0.00 (-0.03 to 1.03). Very serious imprecision when 95% CI crosses two default MID..
m. SMD calculation by NCC-WCH: SMD (95%CI) = -5.90 (-11.56 to -0.23). Serious imprecision when 95% CI crosses one default MID.
n. SMD calculation by NCC-WCH: SMD (95%CI) = -0.70 (-1.11 to -0.28). Serious imprecision when 95% CI crosses one default MID.
o. SMD calculation by NCC-WCH: SMD (95%CI) = -0.40 (-0.78 to -0.01). Serious imprecision when 95% CI crosses one default MID.

Table 28: GRADE profile for comparison of increased exhalation/expiration techniques + assisted cough + upper airways suction with suction only

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Clinical score											
Wang's total clinical score											
1. Gomes et al., 2012	Median (range) = 4.0 (2-7) N =10	Median (range) = 7.0 (4-10) N =10	NC	ns	Very Low	RCT	Very Serious [a]	None	Serious [b]	NC [c]	None
Wheezing section of Wang's score											
1. Gomes et al., 2012	Median (range) = 0.0 (0-1) N =10	Median (range) = 0.0 (0-2) N =10	NC	ns	Very Low	RCT	Very Serious [a]	None	Serious [b]	NC [c]	None
Respiratory rate section of Wang's score											
1. Gomes et al., 2012	Median (range) = 2.0 (0-3) N =10	Median (range) = 2.0 (1-3) N =10	NC	ns	Very Low	RCT	Very Serious [a]	None	Serious [b]	NC [c]	None
Retractions section of Wang's score											
1. Gomes et al., 2012	Median (range) = 1.0 (0-2) N =10	Median (range) = 1.0 (0-3) N =10	NC	ns	Very Low	RCT	Very Serious [a]	None	Serious [b]	NC [c]	None
General condition section of Wang's score											
1. Gomes et al., 2012	Median (range) = 3.0 (0-3) N =10	Median (range) = 3.0 (0-3) N =10	NC	ns	Very Low	RCT	Very Serious [a]	None	Serious [b]	NC [c]	None
O2 saturation											
1. Gomes et al., 2012	Mean±s.d. = 89 ±4.47 N =10	Mean±s.d. = 90.3 ±2.62 N =10	NC	MD = -1.30 (-4.51 to 1.91) * ns	Very Low	RCT	Very Serious [a]	None	Serious [b]	Very Serious [d]	None
Time to recovery [e]											
Overall population											
1. Gajdos et al., 2010	Median, days (95%CI): 2.02 (1.96-2.34) N = 246	Median, days (95%CI): 2.31 (1.97-2.73) N = 250	HR = 1.09 (0.91-1.31)	P=0.33	Moderate	RCT	Low risk [f]	None	Serious [g]	Serious [h]	None
< 2 months (n=238)											
1. Gajdos et al., 2010	Median, days (95%CI): 2.47 (1.98-3.31)	Median, days (95%CI): 2.64 (2.25-3.08)	HR = 1.09 (0.84-1.41)	P=0.51	Moderate	RCT	Low risk [f]	None	Serious [g]	Serious [h]	None

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
≥ 2 months (n=258)											
1. Gajdos et al., 2010	Median, days (95%CI): 2.00 (1.51-2.25)	Median, days (95%CI): 2.01 (1.65-2.44)	HR = 1.09 (0.85-1.40)	P=0.48	Moderate	RCT	Low risk [f]	None	Serious [g]	Serious [h]	None
Reported side effects											
Bradycardia with desaturation											
1. Gajdos et al., 2010	N = 3/246 (1.2%)	N = 3/250 (1.2%)	RR = 1.0 (0.2-5.00)	P=1.00	Low	RCT	Low risk [f]	None	Serious [g]	Very Serious [h]	None
Bradycardia without desaturation											
1. Gajdos et al., 2010	N = 7/246 (2.8%)	N = 2/250 (0.8%)	RR = 3.6 (0.7-16.9)	P=0.10	Low	RCT	Low risk [f]	None	Serious [g]	Very Serious [h]	None
Vomiting											
1. Gajdos et al., 2010	N = 10/246 (4.1%)	N = 1/250 (0.4%)	RR = 10.2 (1.3-78.8)	P=0.005	Moderate	RCT	Low risk [f]	None	Serious [g]	None	None
Respiratory destabilization											
1. Gajdos et al., 2010	N = 16/246 (6.5%)	N = 3/250 (1.2%)	RR = 5.4 (1.6-18.4)	P=0.002	Moderate	RCT	Low risk [f]	None	Serious [g]	None	None
Hypotonia											
1. Gajdos et al., 2010	N = 2/246 (0.8%)	N = 0/250 (0.0%)	RR = 5.08 (0.24-105.29)	P=0.24	Low	RCT	Low risk [f]	None	Serious [g]	Very Serious [h]	None
Need for ventilation											
1. Gajdos et al., 2010	N = 5/246 (2.0%)	N = 2/250 (0.8%)	RR = 2.5 (0.5-13.0)	P=0.29	Low	RCT	Low risk [f]	None	Serious g	Very Serious [h]	None

MD Mean Difference, SD standard deviation, NA not applicable, NC not calculable, NR not reported, Ns non-significant, RCT randomised controlled trial, p-value, RR relative risk

** Calculated by the technical team from data reported in the article*

a. Selection bias: method of randomization and concealment of allocation were not reported; performance bias: the third group (suction) didn't receive the same techniques as G1 and G2 during hospitalization; blinding of those who administered the treatment was not described; attrition bias: the third group did not receive assessment at follow up (low risk); detection bias: low risk of bias. Also, the study was downgraded because imprecision was not assessable (see footnote c).

b. Children aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis), authors excluded infants without RSV.

c. It was not possible to grade for imprecision due to lack of information (95%CI were not reported).

d. SMD calculation by NCC-WCH: SMD (95%CI) = -1.30 (-4.51 to 1.91). Very serious imprecision when 95% CI crosses two default MID.
e. Time to recovery: an infant was considered to be cured if no oxygen supplementation had been given for 8 h, and the child had minimal or no chest recession and was ingesting more than two-thirds of daily needs.
f. Selection bias: low risk; performance bias: low risk; attrition bias: low risk; detection bias: low risk.
g. Infants aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis)
h. Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.

Table 29: GRADE profile for comparison of percussion and vibration techniques + suction with suction only

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Clinical score											
Webb's total clinical score a											
1. Nicholas et al., 1999	NR N = 26	NR N = 24	NC	ns	Very Low	RCT	Very Serious [b]	None	None	NC [c]	None
Wang's total clinical score											
1. Gomes et al., 2012	Median (range) = 5.5 (1-7) N =10	Median (range) = 7.0 (4-10) N =10	NC	ns	Very Low	RCT	Very Serious [d]	None	Serious [e]	NC [f]	None
Wheezing section of Wang's score											
1. Gomes et al., 2012	Median (range) = 0.0 (0-1) N =10	Median (range) = 0.0 (0-2) N =10	NC	ns	Very Low	RCT	Very Serious [d]	None	Serious [e]	NC [f]	None
Respiratory rate section of Wang's score											
1. Gomes et al., 2012	Median (range) = 2.0 (1-2) N =10	Median (range) = 2.0 (1-3) N =10	NC	ns	Very Low	RCT	Very Serious [d]	None	Serious [e]	NC [f]	None
Retractions section of Wang's score											
1. Gomes et al., 2012	Median (range) = 1.0 (0-2) N =10	Median (range) = 1.0 (0-3) N =10	NC	P<0.05	Very Low	RCT	Very Serious [d]	None	Serious [e]	NC [f]	None
General condition section of Wang's score											
1. Gomes et al., 2012	Median (range) = 3.0 (0-3) N =10	Median (range) = 3.0 (0-3) N =10	NC	ns	Very Low	RCT	Very Serious [d]	None	Serious [e]	NC [f]	None
O2 saturation											
1. Gomes et al., 2012	Mean±s.d. = 93 ±4.05 N =10	Mean±s.d. = 90.3 ±2.62 N =10	NC	MD = 2.70 (-0.29 to 5.69) * Ns	Very Low	RCT	Very Serious [d]	None	Serious [e]	Serious [g]	None

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Length of stay											
1. Nicholas et al., 1999	Mean, days (range) = 6.7 (3-9.5)	Mean, days (range) = 6.6 (2.3-11.5)	NC	ns	Very Low	RCT	Very Serious [b]	None	None	NC [c]	None
Provision of inspired O2 and requirement of nasogastric feeding											
1. Nicholas et al., 1999	Mean, h = 86 N = 26	Mean, h = 92 N = 24	NC	ns	Very Low	RCT	Very Serious [b]	None	None	NC [c]	None

MD Mean Difference, SD standard deviation, NA not applicable, NC not calculable, NR not reported, NS non-significant, RCT randomised controlled trial, p-value, RR relative risk
** Calculated by the NCC-WCH technical team from data reported in the article*
a. Clinical score: a score of 0 to 3 was allocated for each of ten clinical signs (heart rate, respiratory rate, hyperinflation, use of respiratory muscles, recession, rhinitis, wheeze, cough, crackles, and ronchi)
b. Selection bias: allocation concealment not described, performance bias: blinding not reported, attrition bias: not clear how data were treated, detection bias: description of the outcomes not appropriately reported, blinding not described. Also, the study was downgraded because imprecision was not assessable (see footnote c).
c. It was not possible to grade for imprecision due to lack of information (95%CI were not reported).
d. Selection bias: method of randomization and concealment of allocation were not reported; performance bias: the third group (suction) didn't receive the same techniques as G1 and G2 during hospitalization; blinding of those who administered the treatment was not described; attrition bias: the third group did not receive assessment at follow up (low risk); detection bias: low risk of bias.
e. Children aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis), authors excluded infants without RSV.
f. It was not possible to grade for imprecision due to lack of information (95%CI were not reported).
g. SMD calculation by NCC-WCH: SMD (95%CI) = 2.70 (-0.29 to 5.69). Serious imprecision when 95% CI crosses one default MID.

Table 30: GRADE profile for comparison of prolonged slow expiration techniques with percussion and vibration techniques

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Clinical score											
Wang's total clinical score											
1. Gomes et al., 2012	Median (range) = 4.0 (2-7) N =10	Median (range) = 5.5 (1-7) N =10	NC	ns	Very Low	RCT	Very Serious [a]	None	Serious [b]	NC [c]	None
Wheezing section of Wang's score											
1. Gomes et al., 2012	Median (range) = 0.0 (0-1) N =10	Median (range) = 0.0 (0-1) N =10	NC	ns	Very Low	RCT	Very Serious [a]	None	Serious [b]	NC [c]	None
Respiratory rate section of Wang's score											
1. Gomes et al.,	Median (range) = 2.0 (0-3)	Median (range) = 2.0 (1-2)	NC	ns	Very Low	RCT	Very Serious [a]	None	Serious [b]	NC [c]	None

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
2012	N =10	N =10									
Retractions section of Wang's score											
1. Gomes et al., 2012	Median (range) = 1.0 (0-2) N =10	Median (range) = 1.0 (0-2) N =10	NC	P<0.05	Very Low	RCT	Very Serious [a]	None	Serious [b]	NC [c]	None
General condition section of Wang's score											
1. Gomes et al., 2012	Median (range) = 3.0 (0-3) N =10	Median (range) = 3.0 (0-3) N =10	NC	ns	Very Low	RCT	Very Serious [a]	None	Serious [b]	NC [c]	None
O2 saturation											
1. Gomes et al., 2012	Mean±s.d. = 89 ±4.47 N =10	Mean±s.d. = 93 ±4.05 N =10	NC	MD = -4.00 (-7.74 to -0.26) * ns	Very Low	RCT	Very Serious [a]	None	Serious [b]	Serious [d]	None

MD Mean Difference, SD standard deviation, NA not applicable, NC not calculable, NR not reported, Ns non-significant, RCT randomised controlled trial, p-value, RR relative risk

** Calculated by the NCC-WCH technical team from data reported in the article*

a. Selection bias: method of randomization and concealment of allocation were not reported; performance bias: the third group (suction) didn't receive the same techniques as G1 and G2 during hospitalization; blinding of those who administered the treatment was not described; attrition bias: the third group did not receive assessment at follow up (low risk); detection bias: low risk of bias. Also, the study was downgraded because imprecision was not assessable (see footnote c).

b. Children aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis), authors excluded infants without RSV.

c. It was not possible to grade for imprecision due to lack of information (95%CI were not reported).

d. SMD calculation by NCC-WCH: SMD (95%CI) = -4.00 (-7.74 to 0.26). Serious imprecision when 95% CI crosses one default MID..

Table 31: GRADE profile for comparison of prolonged slow expiration techniques + slow accelerated expiratory flow + induced cough with no intervention

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Time to clinical stability [a]											
1. Rochat et al., 2012	Mean ±sd, days = 2.9 ±2.1 N = 50	Mean ±sd, days = 3.2 ±2.8 N = 49	NC	MD -0.30 (-1.27 to 0.67) * P=0.45	Low	RCT	Serious [b]	None	None	Very Serious [c]	None
Clinical score											
Clinical state [d]											
1. Rochat	points/day	points/day	NC	MD -0.03	Moderate	RCT	Serious [b]	None	None	None [e]	None

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
et al., 2012	measured as daily changes = -0.12 (-0.08 to -0.15)	measured as daily changes = -0.09 (-0.06 to -0.13)		(-0.08 to 0.02) * P=0.37							
Respiratory score [f]											
1. Rochat et al., 2012	points/day measured as daily changes = -1.6 (-1.4 to -1.8)	points/day measured as daily changes = -1.3 (-1.1 to -1.5)	NC	MD -0.30 (-0.57 to -0.02) * P=0.04	Low	RCT	Serious [b]	None	None	Serious [g]	None
O2 Saturation											
1. Rochat et al., 2012	%/day measured as daily changes = 1.0 (0.7-1.2)	%/day measured as daily changes = 1.0 (0.8-1.2)	NC	MD 0.00 (-0.35 to 0.35) * P=0.85	Moderate	RCT	Serious [b]	None	None	None [h]	None
Respiratory rate											
1. Rochat et al., 2012	rate/day measured as daily changes = -1.1 (-0.6 to -1.7)	rate/day measured as daily changes = -0.7 (-0.2 to -1.2)	NC	MD -0.40 (-1.6 to 0.36) * P=0.24	Low	RCT	Serious [b]	None	None	Serious [i]	None

MD Mean Difference, SD standard deviation, NC not calculable, NR not reported, RCT randomised controlled trial, p-value, RR relative risk
** Calculated by the NCC-WCH technical team from data reported in the article*
a. Time to clinical stability: based on feeding more than 50% of the required amount, the absence of vomiting, undisrupted sleep and SpO_2≥92% for more than 10 h
b. This was an open trial: all children underwent daily clinical evaluations performed by a physiotherapist who was different from the one administering the treatment (performance and detection bias)
c. SMD calculation by NCC-WCH: SMD (95%CI) = -0.30 (-1.27 to 0.67). Very serious imprecision when 95% CI crosses two default MID.
d. Clinical state measured by a general score made of three well-being items (feeding, vomiting and quality of sleep).
e. SMD calculation by NCC-WCH: SMD (95%CI) = -0.03 (-0.08 to -0.02). No imprecision (Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID).
f. Change in respiratory state measured by a respiratory score made of seven items: respiratory rate, SpO_2, presence and severity of retractions, adventitious respiratory sounds, presence of vesicular murmur, thoracic distension.
g. SMD calculation by NCC-WCH: SMD (95%CI) = -0.30 (-0.57 to -0.02). Serious imprecision when 95% CI crosses one default MID.
h. SMD calculation by NCC-WCH: SMD (95%CI) = 0.00 (-0.35 to 0.35). No imprecision (Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID).
i. SMD calculation by NCC-WCH: SMD (95%CI) = -0.40 (-1.16 to 0.36). Serious imprecision when 95% CI crosses one default MID. .

Table 32: GRADE profile for comparison of chest percussion in 5 drainage positions + assisted cough + oropharyngeal suction with no intervention

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Clinical score [a]											
After 1 day											
1. Webb et al., 1985	Median (range) = 7 (2-24) N = 42	Median (range) = 10 (2-27) N = 45	NC	Ns	Very low	RCT	Very Serious [b]	None	Serious [c]	NC [d]	None
After 2 days											
1. Webb et al., 1985	Median (range) = 7 (2-21) N = 38	Median (range) = 8 (2-17) N = 39	NC	Ns	Very low	RCT	Very Serious [b]	None	Serious [c]	NC [d]	None
After 3 days											
1. Webb et al., 1985	Median (range) = 7 (3-28) N = 28	Median (range) = 6 (2-21) N = 31	NC	Ns	Very low	RCT	Very Serious [b]	None	Serious [c]	NC [d]	None
After 4 days											
1. Webb et al., 1985	Median (range) = 4 (2-18) N = 16	Median (range) = 6 (2-17) N = 21	NC	Ns	Very low	RCT	Very Serious [b]	None	Serious [c]	NC [d]	None
After 5 days											
1. Webb et al., 1985	Median (range) = 6 (3-10) N = 11	Median (range) = 5 (1-11) N = 18	NC	Ns	Very low	RCT	Very Serious [b]	None	Serious [c]	NC [d]	None
Length of stay, days											
1. Webb et al., 1985	Median, (range) = 4 (2-11) N = 44	Median, (range) = 14 (4-27) N = 46	NC	Ns	Very low	RCT	Very Serious [b]	None	Serious [c]	NC [d]	None
Total length of illness, days											
1. Webb et al., 1985	Median, (range) = 13 (7-26) N = 44	Median, (range) = 14 (4-27) N = 46	NC	Ns	Very low	RCT	Very Serious [b]	None	Serious [c]	NC [d]	None

NA not applicable, NC not calculable, NR not reported, Ns non-significant, RCT randomised controlled trial, p-value, RR relative risk
** Calculated by the NCC-WCH technical team from data reported in the article*
a. Clinical score: a score of 0 to 3 was allocated for each of ten clinical signs (heart rate, respiratory rate, hyperinflation, use of respiratory muscles, recession, rhinitis, wheeze, cough, crackles, and ronchi)

b. Selection bias: randomization method was not described, concealment of allocation was not reported; performance bias: blinding was reported not to be possible; attrition bias: a follow-up of two weeks has been described in the article, but data of such assessment are not reported. Also, 90 patients were analysed, but not clear how many were randomized and if there was attrition of patients; detection bias: unclear. Also, the study was downgraded because imprecision was not assessable (see footnote d).
c. children aged up to 15 months (the GDG has specified that it is likely that older children will not have bronchiolitis)
d. It was not possible to grade for imprecision due to lack of information (95%CI were not reported).

4.1.5 Evidence statements

4.1.5.1 Slow and long expiration techniques + assisted cough + bronchodilator vs. bronchodilator alone

Clinical score

Proportion of patients discharged

One study with 48 children found no difference in the proportion of patients discharged between the infants who received CPT + assisted cough + bronchodilator and those who received bronchodilator only. The quality of the evidence was low.

Tal's clinical score

One study with 48 children found no difference in Tal's clinical score between the infants who received CPT + assisted cough + bronchodilator and those who received bronchodilator only. The quality of the evidence was low.

Wang's clinical score at T30

One study with 20 children found that infants who received CPT + assisted cough + bronchodilator had a significantly better Wang's total clinical score immediately after the 30-min treatment session than those who received bronchodilator only. The quality of the evidence was moderate.

Wang's clinical score at T150

One study with 20 children found no difference in Wang's total clinical score 2 hours after the treatment session between the infants who received CPT + assisted cough + bronchodilator and those who received bronchodilator only. The quality of the evidence was low.

Respiratory rate section of Wang's clinical score at T30

One study with 20 children found that infants who received CPT + assisted cough + bronchodilator had a significantly better RR section of Wang's clinical score immediately after the 30-min treatment session than those who received bronchodilator only. The quality of the evidence was moderate.

Respiratory rate section of Wang's clinical score at T150

One study with 20 children found no difference in RR section of Wang's clinical score 2 hours after the treatment session between the infants who received CPT + assisted cough + bronchodilator and those who received bronchodilator only. The quality of the evidence was moderate.

Oxygen saturation

One study with 48 children found no difference in O2 saturation between the infants who received CPT + assisted cough + bronchodilator and those who received bronchodilator only. The quality of the evidence was very low.

Measurement at T30

One study with 20 children found no difference in O2 saturation immediately after the 30-min treatment session between the infants who received CPT + assisted cough + bronchodilator and those who received bronchodilator only. The quality of the evidence was low.

Measurement at T150

One study with 20 children found no difference O2 saturation 2 hours after the treatment session between the infants who received CPT + assisted cough + bronchodilator and those who received bronchodilator only. The quality of the evidence was low.

Respiratory rate

One study with 48 children found no difference in respiratory rate between the infants who received CPT + assisted cough + bronchodilator and those who received bronchodilator only. The quality of the evidence was low.

4.1.5.2 Increased exhalation techniques + assisted cough + upper airways suction vs. suction alone

Clinical score

Wang's clinical score

One study with 20 children found no difference in the Wang's total clinical score between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was very low.

Wheezing section of Wang's clinical score

One study with 20 children found no difference in the wheezing section of Wang's clinical score between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was very low.

Respiratory rate section of Wang's clinical score

One study with 20 children found no difference in the RR section of Wang's clinical score between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was very low.

Retractions section of Wang's clinical score

One study with 20 children found no difference in the retractions section of Wang's clinical score between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was very low.

General condition section of Wang's clinical score

One study with 20 children found no difference in the general condition section of Wang's clinical score between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was very low.

Oxygen saturation

One study with 20 children found no difference in O2 saturation between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was very low.

Time to recovery

Overall population

One study with 496 children found no difference in time to recovery between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was moderate.

Aged < 2 months

One study with 496 children found no difference in time to recovery between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was moderate.

Aged ≥ 2 months

One study with 496 children found no difference in time to recovery between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was moderate.

Reported side effects

Bradycardia with desaturation

One study with 496 children found no difference in the occurrence of bradycardia with desaturation between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was low.

Bradycardia without desaturation

One study with 496 children found no difference in the occurrence of bradycardia without desaturation between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was low.

Vomiting

One study with 496 children found infants who received CPT + assisted cough + suction were more likely to experience vomiting compared to those who received suction only. The quality of the evidence was moderate.

Respiratory destabilization

One study with 496 children found that infants who received CPT + assisted cough + suction were significantly more likely to experience respiratory destabilization than those who received suction only. The quality of the evidence was moderate.

Hypotonia

One study with 496 children found no difference in the occurrence of hypotonia between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was low.

Need for ventilation

One study with 496 children found no difference in the occurrence of need for ventilation between the infants who received CPT + assisted cough + suction and those who received suction only. The quality of the evidence was low.

4.1.5.3 Percussion and vibration techniques + suction vs. suction alone

Clinical score

Webb's clinical score

One study with 30 children found no difference in the Webb's total clinical score between the infants who received CPT+ suction and those who received suction only. The quality of the evidence was very low. .

Wang's clinical score

One study with 20 children found no difference in the Wang's total clinical score between the infants who received CPT+ suction and those who received suction only. The quality of the evidence was very low.

Wheezing section of Wang's clinical score

One study with 20 children found no difference in the wheezing section of Wang's clinical score between the infants who received CPT+ suction and those who received suction only. The quality of the evidence was very low.

Respiratory rate section of Wang's clinical score

One study with 20 children found no difference in the respiratory rate section of Wang's clinical score between the infants who received CPT+ suction and those who received suction only. The quality of the evidence was very low.

Retractions section of Wang's clinical score

One study with 20 children found a that infants who received CPT+ suction had a significantly better retractions section of Wang's clinical score than those who received suction only. The quality of the evidence was very low.

General condition section of Wang's clinical score

One study with 20 children found no difference in the general condition section of Wang's clinical score between the infants who received CPT+ suction and those who received suction only. The quality of the evidence was very low.

Oxygen saturation

One study with 20 children found no difference in O2 saturation between the infants who received CPT + suction and those who received suction only. The quality of the evidence was very low.

Length of stay

One study with 30 children found no difference in length of stay between the infants who received CPT + suction and those who received suction only. The quality of the evidence was very low.

Provision of inspired O2 and requirement of nasogastric feeding

One study with 30 children found no difference in the provision of O2 and requirement of nasogastric feeding between the infants who received CPT + suction and those who received suction only. The quality of the evidence was very low.

4.1.5.4 Prolonged slow expiration techniques vs. percussion and vibration (PV) techniques

Clinical score

Wang's clinical score

One study with 20 children found no difference in the Wang's total clinical score between the infants who received prolonged slow expiration techniques and those who received PV techniques. The quality of the evidence was very low.

Wheezing section of Wang's clinical score

One study with 20 children found no difference in the wheezing section of Wang's clinical score between the infants who received prolonged slow expiration techniques and those who received PV techniques. The quality of the evidence was very low.

Respiratory rate section of Wang's clinical score

One study with 20 children found no difference in the respiratory rate section of Wang's clinical score between the infants who received prolonged slow expiration techniques and those who received PV techniques. The quality of the evidence was very low.

Retractions section of Wang's clinical score

One study with 20 children found that infants who received prolonged slow expiration techniques had a significantly better retractions section of Wang's clinical score than those who received PV techniques. The quality of the evidence was very low.

General condition section of Wang's clinical score

One study with 20 children found no difference in the general condition section of Wang's clinical score between the infants who received prolonged slow expiration techniques and those who received PV techniques. The quality of the evidence was very low.

Oxygen saturation

One study with 20 children found no difference in O2 saturation between the infants who received prolonged slow expiration techniques and those who received PV techniques. The quality of the evidence was very low.

4.1.5.5 Prolonged slow expiration techniques + slow accelerated expiratory flow + induced cough vs. no intervention

Clinical score

***Clinical state (daily change*)**

One study with 99 children found no difference in daily changes in the clinical state between the infants who received CPT + induced cough and those who received no intervention. The quality of the evidence was moderate.

Respiratory score (daily change)

One study with 99 children found that infants who received CPT + induced cough showed a significantly better change in respiratory score than those who received no intervention. The quality of the evidence was low.

Oxygen saturation

One study with 99 children found no difference in daily changes in O2 saturation between the infants who received CPT + induced cough and those who received no intervention. The quality of the evidence was moderate.

Respiratory rate

One study with 99 children found no difference in daily changes in RR between the infants who received CPT + induced cough and those who received no intervention. The quality of the evidence was low.

Time to clinical stability

One study with 99 children found no difference in time to clinical stability between the infants who received CPT + induced cough and those who received no intervention. The quality of the evidence was low.

4.1.5.6 Chest percussion in 5 drainage positions + assisted cough + oropharyngeal suction vs. no intervention

Clinical score (Webb's)

After one day

One study with 87 children found no difference in Webb's clinical score after one day between the infants who received CPT + assisted cough + oropharyngeal suction and those who received no intervention. The quality of the evidence was very low.

After two days

One study with 87 children found no difference in Webb's clinical score after two days between the infants who received CPT + assisted cough + oropharyngeal suction and those who received no intervention. The quality of the evidence was very low.

After three days

One study with 90 children found no difference in Webb's clinical score after three days between the infants who received CPT + assisted cough + oropharyngeal suction and those who received no intervention. The quality of the evidence was very low.

After four days

One study with 90 children found no difference in Webb's clinical score after four days between the infants who received CPT + assisted cough + oropharyngeal suction and those who received no intervention. The quality of the evidence was very low.

After five days

One study with 90 children found no difference in Webb's clinical score after five days between the infants who received CPT + assisted cough + oropharyngeal suction and those who received no intervention. The quality of the evidence was very low.

Length of stay

One study with 90 children found no difference in length of stay between the infants who received CPT + assisted cough + oropharyngeal suction and those who received no intervention. The quality of the evidence was very low.

Total length of illness

One study with 90 children found no difference in the total length of illness between the infants who received CPT + assisted cough + oropharyngeal suction and those who received no intervention. The quality of the evidence was very low.

4.1.5.6.1 Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation

No studies reported data on this outcome.

4.1.6 Health economics profile

No health economic studies were identified for this question, and this question was not prioritised for detailed economic modelling.

4.1.7 Evidence to recommendations

4.1.7.1 Relative value placed on the outcomes considered

The aim of this evidence review was to determine whether chest physiotherapy is an effective treatment in the management of bronchiolitis. Change in disease severity score and effects on respiratory rate and oxygen saturation were considered to be the critical outcomes for this evidence review. Other important outcomes identified by the GDG were: need for high flow humidified oxygen, continuous airway pressure (CPAP) or mechanical ventilation, length of hospital stay, and adverse events (including mortality).

4.1.7.2 Consideration of clinical benefits and harms

The GDG noted that the evidence available ranged from moderate to very low quality, and the group was aware of the complex comparisons that were reviewed to address the question. They did not know of any further relevant studies that had not been identified.

The GDG agreed that the evidence provided did not support the use of chest physiotherapy in children with bronchiolitis, especially for those who show wheeze as a predominant symptom. However, the group wanted to take into account specific subgroups of patients who may benefit from chest physiotherapy. The GDG considered children with other disorders (for example children with spinal muscular atrophy or those with severe tracheomalacia) that make it difficult for them to clear secretions may potentially benefit from physiotherapy.

Since the evidence presented did not report results stratified by clinical severity of bronchiolitis, the GDG developed a research recommendation to evaluate the possible value of using chest physiotherapy in children with bronchiolitis and "impending respiratory failure",

defined as: signs of exhaustion, recurrent apnoea, and failure to maintain adequate oxygen saturation despite oxygen supplementation.

4.1.7.3 Consideration of health benefits and resource uses

Children with other respiratory comorbidities are the patients targeted to physiotherapy in current UK practice. This mainly involves children in PICU. Physiotherapy is not currently used in patients with bronchiolitis who are well in the UK and this has not been associated with evidence of increased length of stay. Given the lack of evidence of health benefits there is potential to save resources in terms of a physiotherapists time.

4.1.7.4 Quality of evidence

The quality of the evidence ranged from moderate to very low. Main sources of bias identified in the studies were the lack of description of randomisation method or concealment of allocation, and imprecision in the results mainly due to 95% confidence intervals being either wide or unreported.

The variation in interventions used meant they were not suitable for meta-analysis.

4.1.7.5 Other considerations

No other considerations were noted.

4.1.8 Key conclusions

The GDG concluded that chest physiotherapy should not be performed in children presenting with bronchiolitis. However, the GDG agreed that consideration should be given to requesting a chest physiotherapy assessment for patients who have comorbidities which may lead to particular difficulties with clearing secretions.

4.1.9 Recommendations

32. Do not perform chest physiotherapy on children with bronchiolitis who do not have relevant comorbidities (for example spinal muscular atrophy, severe tracheomalacia).

33. Consider requesting a chest physiotherapy assessment in children who have relevant comorbidities (for example spinal muscular atrophy, severe tracheomalacia) when there may be additional difficulty clearing secretions.

4.1.10 Research recommendations

4. What is the effectiveness of chest physiotherapy in children with bronchiolitis and impending respiratory failure?

Why this is important

4.1. Whilst chest physiotherapy appears ineffective in the early and routine management of bronchiolitis, it is possible that it may be effective in those children with impending respiratory failure. In that setting it is possible that clearing of airway secretions might effect an important improvement in the infant or child's condition avoiding the need for other more intensive interventions such as mechanical ventilation. A multi-centre RCT should be conducted to assess its efficacy in this important sub-group of infants and

children. Important outcomes would include admission to intensive care, the need for mechanical ventilation and improvement in oxygen saturation.

4.2 Pharmacological interventions

4.2.1 Antibiotics

4.2.1.1 Review question

What is the efficacy of antibiotic treatment?

Further details on the protocol for this review question are provided in Appendix E.

4.2.1.2 Introduction

Systemic antibiotics are the mainstay of therapy for bacterial lower respiratory tract infection in young children. Macrolide antibiotics have concomitant anti-inflammatory properties that could potentially have additional beneficial effects in inflammatory disorders such as bronchiolitis. Bronchiolitis has a viral aetiology and the rate of secondary bacterial infection is extremely low. Antibiotic use has significant potential disadvantages including common adverse reactions, cost implications and the development of bacterial resistance.

4.2.1.3 Description of included studies

Seven RCTs were included in this review (Field et al., 1966; Kneyber et al., 2008; Tahan et al., 2007; Kabir et al., 2009; Mazumder et al., 2009; Rasul et al., 2008; Pinto et al, 2013) from a variety of locations (UK [1 trial], The Netherlands [1 trial], Bangladesh [3 trials], Turkey [1 trial, and Brazil [1 study]]).

Of the seven RCTs, four compared an oral antibiotic (either ampicillin, clarithromycin or azithromycin) with placebo (Field et al., 1966; Kneyber et al., 2008; Tahan et al., 2007; Pinto et al, 2013). The remaining three studies were all three-arm trials comparing supportive care with supportive care plus oral antibiotic (erythromycin) or supportive care plus parenteral antibiotic (either ampicillin or amoxicillin) (Kabir et al., 2009; Mazumder et al., 2009; Rasul et al., 2008). The included systematic review pooled the data for the two antibiotic arms and compared this with data for the supportive care arm.

All of the children included in the studies were under 2 years of age and were hospitalised with clinically diagnosed bronchiolitis. Two studies classified severity of symptoms at baseline as mild, moderate and severe, with the majority of children experiencing moderate symptoms (Field et al., 1996; Tahan et al., 2007). In one study 5% of children were referred to paediatric intensive care and were excluded from that study's analysis (Kabir et al., 2009). Duration of antibiotic treatment was 3 days, 7 days or 3 weeks in three studies. In the remaining three studies duration of treatment was not reported.

A Cochrane review (Spurling et al., 2011) was available for this review question. However, the results were not directly used for the following reasons: the Cochrane review included data based on graphical figures without standard deviations, data was combined for placebo and standard care arms of trial which was felt to be inappropriate, and additional studies needed to be added.

The GDG outlined the following outcomes:

- Hospital admission rate
- Length of hospital stay

- Duration of cough
- Change in respiratory rate
- Change in O2 saturation
- Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
- Adverse effects (including mortality)

The studies did not report data on all these outcomes and in some situations other outcomes are presented (e.g. total duration of symptoms, oxygen use rates, duration on oxygen use).

More details on each individual study can be found in the evidence tables in Appendix I.

4.2.1.4 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

Two GRADE profiles have been produced for this review:

- Table 33: GRADE profile for oral antibiotics compared with placebo for bronchiolitis in children
- Table 34: GRADE profile for oral or parenteral antibiotics compared with supportive treatment in children with bronchiolitis

Table 33: GRADE profile for oral antibiotics compared with placebo for bronchiolitis in children

Number of studies	Number of children		Effect		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
	Antibiotics	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Duration of cough											
Total duration of symptoms (days)											
1 study (Kneyber et al., 2008)	4.94 ± 3.78 (n=32)	4.62 ± 2.05 (n=39)	NC	MD 0.32 higher (1.14 lower to 1.78 higher)	Moderate	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[c]	Yes[a]
Length of hospital stay (days)											
3 studies (Kabir et al., 2009; Kneyber et al., 2008; Pinto et al., et al, 2013))	-	-	NC	MD 0.01 [-0.97, 1.00]	Very low	Meta-analysis of RCT	no serious risk of bias	very serious [b]	no serious indirectness	serious[c]	Yes [d]
Change in O2 saturation											
Oxygen use											
1 study (Kneyber et al., 2008)	20/32 (62.5%)	31/39 (79.5%)	OR 0.43 (0.15 to 1.24)	170 fewer per 1000 (from 427 fewer to 33 more)	Low	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[e]	none
Duration of oxygen use (days)											
2 studies (Kneyber et al., 2008; Pinto et al., et al, 2013)	-	-	NC	MD -0.05 [-0.64, 0.55]	Moderate	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	None	Yes[g]
Hospital admission rate											
PICU admission											
1 study (Kneyber et al., 2008)	0/32 (0%)	1/39 (2.6%)	OR 0.39 (0.02 to 10.03)	15 fewer per 1000 (from 25 fewer to 183 more)	Low	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[e]	none
Re-admission for wheezing within 6 months of discharge											
1 study (Tahan et al., 2007)	1/12 (8.3%)	4/9 (44.4%)	OR 0.11 (0.01 to 1.29)	364 fewer per 1000 (from 437 fewer to 63 more)	Very low	RCT	very serious [f]	no serious inconsistency	no serious indirectness	very serious [e]	none
Change in respiratory rate – not reported											
Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation – not reported											

Number of studies	Number of children		Effect		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
	Antibiotics	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Adverse events											
Mortality											
4 study (Field et al., 1966; Kneyber et al., 2008; Pinto et al., et al, 2013; Tahan et al., 2007)	-	-	-	No reported deaths	Low	RCT	very serious [f]	no serious inconsistency	no serious indirectness	NC	none

NC not calculable, SD standard deviation, RCT randomised controlled trial, MD mean difference, OR odds ratio
a Cochrane review by Spurling included data from a second study (Tahan et al., 2007) was presented in forest plot but SD not reported so data not meta-analysed (mean for antibiotic group 9.54 (n=28), mean for placebo group 9.4 (n=24)). Unclear what "symptoms" were included in the outcome. Cochrane author confirmed that this is outcome data and not baseline data (as we suspected from study report); they had access to additional data from this trial.
b I2 = 78%
c Calculated on SMD (Serious imprecision when 95% CI crosses one default MID)
d Cochrane review by Spurling included two studies excluded from this meta-analysis. One of the studies was underpowered to detect a difference in length of hospital stay. Data from a second study (Tahan et al., 2007 was presented in forest plot but SD not reported so the data does not contribute to pooled effect estimate (mean for antibiotic group was 2.13 (n=12), mean for placebo group = 3.67 (n=9))
e Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID and allocation concealment unclear. 9/30 ((30%) children randomised were excluded as they received corticosteroid therapy
f Information on death was not explicitly reported.

Table 34: Oral or parenteral antibiotics compared with supportive treatment for bronchiolitis in children

Number of studies	Number of children		Effect		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
	Antibiotics	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Length of hospital stay (days)											
1 study (Rasul et al., 2008)	6.49 ± 1.32 (n=45)	6.2 ± 1.4 (n=15)	NC	MD 0.29 higher (0.52 lower to 1.10 higher)	Low	RCT	serious[a]	no serious inconsistency	no serious indirectness	Serious [b]	none
Change in O2 saturation											
Oxygen saturation (<96%) on day 3											
1 study (Mazumder et al.,	15/61 (24.6%)	5/43 (11.6%)	OR 2.48 (0.83 to 7.44)	130 more per 1000 (from 18 fewer to 378	Very low	RCT	very serious[c]	no serious inconsistency	no serious indirectness	Serious [f]	none

Number of studies	Number of children		Effect		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
	Antibiotics	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)							
2009)				more)							
Oxygen saturation (<96%) on day 5											
1 study (Mazumder et al., 2009)	5/61 (8.2%)	2/43 (4.7%)	OR 1.83 (0.34 to 9.91)	35 more per 1000 (from 30 fewer to 279 more)	Very low	RCT	very serious[c]	no serious inconsistency	no serious indirectness	very serious[d]	none
Duration of cough											
Cough on day 3											
1 study (Rasul et al., 2008)	10/45 (22.2%)	4/15 (26.7%)	OR 0.79 (0.21 to 3.01)	44 fewer per 1000 (from 196 fewer to 256 more)	Very low	RCT	serious[a]	no serious inconsistency	no serious indirectness	very serious[d]	none
Cough on day 7											
1 study (Kabir et al., 2009)	19/198 (9.6%)	3/97 (3.1%)	OR 3.33 (0.96 to 11.53)	65 more per 1000 (from 1 fewer to 238 more)	Low	RCT	serious[e]	no serious inconsistency	no serious indirectness	serious[f]	none
Hospital admission rate - not reported											
Change in respiratory rate – not reported											
Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation - not reported											
Adverse events											
Mortality											
1 study (Rasul et al., 2008; Kabir et al., 2009)	-	-	-	No reported deaths	Very low	RCT	very seriousg	no serious inconsistency	no serious indirectness	NC	none

NC not calculable, RCT randomised controlled trial, MD mean difference, OR odds ratio
a Unclear whether participants, clinicians or outcome assessors were blinded to intervention and unclear whether any children were withdrawn from the trial due to deterioration in condition
b Calculated on SMD (Serious imprecision when 95% CI crosses one default MID)
c Inadequate method of randomisation, unclear method of allocation concealment, blinding and losses to follow up not reported
d Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
e Unclear allocation concealment, blinding not reported, Cochrane review authors assessed study as being at high risk of reporting bias (selective reporting)
f Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
g Information on death was not explicitly reported.

4.2.1.5 Evidence statements

Oral antibiotics

Duration of symptoms

One study with 71 children showed that there was no difference in the total duration of symptoms between children who received antibiotic treatment and children who received a placebo. The quality of the evidence was moderate.

Length of hospital stay

Three studies with 583 children showed that there was no difference in the length of hospital stay between children who received antibiotic treatment and children who received a placebo. The quality of the evidence was very low.

Oxygen therapy

One study with 71 children showed that there was no difference in the need for oxygen therapy. In children where oxygen therapy was required (O2 was initiated when SpO_2 fell below 90% and ended when it rose to above 90%), there was no difference in the duration of treatment between children who received antibiotic treatment and children who received a placebo. The quality of the evidence was moderate to very low.

Hospital admissions

One study with 71 children showed that there was no difference in the need for admission to the paediatric intensive care unit between children who received antibiotic treatment and children who received a placebo. The quality of the evidence was low. Similarly, one study with 30 children showed no difference in the number of children who were re-admitted to hospital within 6 months of discharge between children who received antibiotic treatment and children who received a placebo. The quality of the evidence was very low.

Adverse events

Four studies with 338 children reported no deaths. The quality of the evidence was low.

Oral or parenteral antibiotics

Length of hospital stay

One study with 60 children showed that there was no difference in the length of hospital stay between children who received antibiotic treatment (either orally or intravenously) and children who received supportive care. The quality of the evidence was low.

Change in O2 saturation

One study with 126 children showed there was no difference in the number of children with oxygen saturation <96% on days 3 and 5 of treatment. The quality of the evidence was very low.

Duration of cough

One study with 60 children showed there was no difference in the number of children with cough on days 3 and 7 of treatment. The quality of the evidence was very low.

Adverse events

Three studies reported no deaths. The quality of the evidence was very low.

Hospital admission rate

No studies reported data on this outcome.

Change in respiratory rate

No studies reported data on this outcome.

Need for ventilation

No studies reported data on this outcome.

4.2.2 Health economics profile

No published economic evaluations were identified for this question. This question was not prioritised for health economic analysis.

4.2.3 Evidence to recommendations

4.2.3.1.1 Relative value placed on the outcomes considered

The aim for this question was to determine whether antibiotics are effective in the immediate management of bronchiolitis in relation to the predefined outcomes of interest. The GDG identified the following critical outcomes for the evidence review: hospital admission rate; length of stay; and need for high flow humidified oxygen, CPAP or mechanical ventilation. Other important outcomes prioritised by the GDG were: duration of cough; change in respiratory rate; change in oxygen saturation; and adverse effects (including mortality). It was not the aim of the evidence review to determine whether antibiotics were effective in those with particular complications of bronchiolitis.

4.2.3.1.2 Consideration of clinical benefits and harms

The GDG was satisfied that the evidence presented in the review was complete and they were not aware of any relevant studies that had not been identified. The GDG noted that evidence was not available in relation to various outcomes.

The GDG considered that it is important to avoid unnecessary antibiotic treatments because it can have severe repercussions on the child's health. Furthermore, the widespread use of antibiotics is associated with a risk of developing bacterial resistance.

The GDG was conscious of the fact that children can sometimes present with bronchiolitis and associated pneumonia. In such cases antibiotic therapy might be effective and indeed essential, and such cases should not be overlooked. The GDG agreed that there might be a need to give antibiotic treatment to some children with a significant clinical deterioration due to such complications. Antibiotic treatment might occasionally be justified in a sick child where the diagnosis of bronchiolitis was in doubt. There might be a suspicion of an alternative infection in a child with an unexpectedly high temperature, for example above 39°C.

There were no trials evaluating the use of antibiotic therapy in a primary care setting. Based on the available evidence, the GDG considered it unlikely that most children in this setting would benefit from antibiotics.

The GDG noted that the three RCTs undertaken in Bangladesh included study subjects with a relatively high risk of secondary bacterial infection and yet there was no evidence of benefit

from antibiotic therapy in this population. The GDG concluded that there was insufficient evidence to recommend prophylactic use of antibiotic therapy in children presenting with acute bronchiolitis.

The GDG concluded that there are particular situations in which the use of antibiotic treatment might be justified, for example in children who are at special risk. However, the GDG concluded that there is not sufficient evidence on particular subgroups of children who might benefit from antibiotic treatment and therefore the GDG has used the evidence identified in chapters 3.1 and 3.2 to identify these subgroups.

4.2.3.1.3 Consideration of health benefits and resource uses

No health benefits were identified from the use of antibiotics in children with bronchiolitis. Resources will be made available for other uses by limiting antibiotic use in this population.

4.2.3.1.4 Quality of evidence

Data was not available for most of the outcomes specified by the GDG. Therefore, admission to PICU, re-admission rates, oxygen use and duration of oxygen therapy use were reported when available. The quality of the available evidence ranged from moderate to very low. The main reason for this was imprecision in the findings.

A Cochrane review (Spurling et al., 2011) was available for this review question. However, the results were not directly used for the following reasons: the Cochrane review included data taken from graphical figures which did not provide standard deviations, and data was combined for placebo and standard care arms of the trial which was felt to be inappropriate.

4.2.3.1.5 Other considerations

No other considerations were identified.

4.2.3.2 Key conclusions

The GDG concluded that the evidence presented was unable to demonstrate any clear benefit in the routine use of antibiotics in children presenting to primary or secondary care with worsening bronchiolitis. Therefore, they recommended that antibiotics should not routinely be used in this population.

4.2.3.3 Recommendations

The recommendations covering the clinical and cost effectiveness of antibiotics are presented in section 4.2.12.

4.2.4 Hypertonic saline

4.2.4.1 Review question

What is the efficacy of nebulised hypertonic saline?

4.2.4.2 Introduction

Hypertonic Saline (HS) is defined as a saline solution possessing an osmotic pressure greater than that of physiologic isotonic salt solution (0.9% NaCl). Nebulised HS has been demonstrated to improve mucous rheology (elasticity and viscosity) and mucociliary clearance and studies in patients with Cystic Fibrosis have demonstrated beneficial effects on lung function and rate of pulmonary exacerbations. There are a number of pathophysiological features of bronchiolitis, including increased mucous production, airway oedema and mucous plugging, which could potentially be amenable to treatment with HS .

4.2.4.3 Description of included studies

Seventeen randomised controlled trials were identified for this review that investigated nebulised hypertonic saline (HS) compared to nebulised normal saline (NS). In addition, one randomised controlled trial was identified that compared hypertonic saline (HS) to usual care in children with bronchiolitis. Eight studies were performed at emergency departments (Anil et al., 2010; Al-Ansari et al., 2010; Grewal et al., 2009; Ipek et al., 2011; Kuzik et al., 2010; Jacobs et al., 2014; Wu et al., 2014; Florin et al., 2014), nine were performed in inpatient settings (Del Guidice et al., 2012; Kuzik et al., 2007; Luo et al., 2010; Luo et al., 2011; Mandelberg et al., 2003; Tal et al., 2006; Sharma et al., 2013; Teunissen et al., 2014; Everard et al., 2014) and one was performed in an outpatient setting (Sarrell et al., 2002).

Two studies were multi-centre trials involving one hospital in the United Arab Emirates and two hospitals in Canada (Kuzik et al., 2007) and eleven general hospitals and one tertiary medical centre in The Netherlands (Teunissen et al., 2014). Another multi-centre trial (Kuzik et al., 2010) included four hospitals in Canada. One was a multi-centre trial involving ten participating centres in England and Wales (Everard et al., 2014). Three trials were conducted in Israel (Mandelberg et al., 2003; Sarrell et al., 2002; Tal et al., 2006), three in the United States (Jacobs et al., 2014; Wu et al., 2014; Florin et al., 2014), two in China (Luo et al., 2010; Luo et al., 2011), two in Turkey (Anil et al., 2010; Ipek et al., 2011), one in India (Sharma et al., 2013), Canada (Grewal et al., 2009), Qatar (Al-Ansari et al., 2010) and Italy (Del Giudice et al., 2012). The sample size ranged from 44 to 408 children.

Eleven studies included infants less than 24 months of age (Anil et al., 2010; Ipel et al., 2011; Kuzik et al., 2010; Luo et al., 2010; Luo et al., 2011; Del Guidice et al., 2012; Sarrell et al., 2002; Wu et al., 2014; Florin et al., 2014; Sharma et al., 2013; Teunissen et al., 2014), three studies included infants less than 18 months of age (Al-Ansari et al., 2010; Kuzik et al., 2007; Jacobs et al., 2014) and the remaining four studies included infants less than 12 months of age (Grewal et al., 2009; Mandelberg et al., 2003; Tal et al., 2006; Everard et al., 2014).

The definition of bronchiolitis varied, with studies using presence of RSV or clinical symptoms and signs. One study included infants with recurrent wheeze, but presented sub-group data on infants without recurrent wheeze (Kuzik et al, 2010). Oxygen or compressed air-driven jet nebulisers were used for administration in eleven out of twelve studies; the remaining study (Tal et al., 2006) used an ultrasonic nebuliser.

Treatments varied between studies:

- Fifteen studies compared nebulised 3% HS to nebulised 0.9% NS. One study (Al-Ansari et al., 2010) included a third treatment group which received 5% HS, while another study (Teunissen et al., 2014) included a third group of patients who received 6% HS. One study compared 7% HS to nebulised 0.9% NS (Jacobs et al., 2014). None of the studies included 7% NS as a study solution. One study compared 3% HS with usual care which was defined as standard supportive care involving oxygen as required, minimal handling and fluid administration as appropriate to the severity of the disease.
- Only two studies administered 3% HS solution and 0.9% NS solution without any additional bronchodilators (Kuzik et al., 2007; Luo et al., 2011). The remaining ten studies also included bronchodilators (epinephrine, salbutamol or terbutaline) which were nebulised with HS and NS.
- Seven studies included epinephrine (Anil et al., 2010; Al-Ansari et al., 2010; Del Guidice et al., 2012; Grewal et al., 2009; Mandelberg et al., 2003; Tal et al., 2006; Jacobs et al., 2014), eight studies included salbutamol or albuterol (Anil et al., 2010; Ipek et al., 2011; Kuzik et al., 2010; Luo et al., 2010; Sharma et al., 2013; Teunissen et al., 2014; Wu et al., 2014; Florin et al., 2014) and one study included terbutaline (Sarrell et al., 2002).

- One study included four treatment groups (Ipek et al., 2011): group one received 3% HS and salbutamol, group two received 0.9% NS and salbutamol, group three received 3% HS and group four received 0.9% NS.
- One study included five treatment groups (Anil et al., 2010): group one received 3% HS and salbutamol, group two received 0.9% NS and salbutamol, group three received 3% HS and epinephrine, group four received 0.9% NS and epinephrine and group five received 0.9% NS.

Additional treatments: thirteen studies (Al-Ansari et al., 2010; Anil et al., 2010; Grewal et al., 2009; Ipek et al., 2011; Kuzik et al., 2010; Kuzik et al., 2007; Luo et al., 2010; Luo et al 2011; Mandelberg et al., 2003; Tal et al., 2006; Jacobs et al., 2014; Sharma et al., 2013; Florin et al., 2014) allowed additional treatment such as supplemental oxygen and epinephrine in 0.9% saline solution at the discretion of the physician, but only six of these reported the results of this (Grewal et al., 2009; Ipek et al., 2011; Kuzik et al., 2007; Mandelberg et al., 2003; Teunissen et al., 2014; Wu et al., 2014). Of these six studies, one allowed a second dose of the study treatment (Grewal et al., 2009), another (Ipek et al., 2011) allowed corticosteroids, a third (Kuzik et al., 2007) allowed albuterol, racemic epinephrine and steroids at the discretion of the attending physicians, another one (Teunissen at al., 2014) allowed nasal-decongestants, paracetamol, antibiotics, salbutamol, ibuprofen, nystadine and raniditine, and finally one study (Wu et al., 2014) allowed additional oxygen supplementation, albuterol, inhaled epinephrine, systemic corticosteroid and diuretics.

The outcomes identified by the GDG for this evidence review were:

- Hospital admission rate
- Length of hospital stay
- Change in respiratory rate
- Change in disease severity score at 2 to 4 hours after treatment
- Change in O2 saturation
- Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
- Need for/use of feeding support (tube feeding, IV fluids)
- Adverse effects (including mortality)

One Cochrane review was identified that addressed this question. However, this could not be directly used for all outcomes because it combined trials which recruited multiple groups and different treatment regimen (Al-Ansari et al., 2010; Anil et al., 2010; Ipek et al., 2011) into the HS group and the NS group, or it did not report the outcome of interest. The Cochrane reviewers contacted Mandelberg et al., 2003 for additional data on the clinical score which this review has used. The Cochrane excluded Kuzik et al., 2010 because this study included infants with a previous history of wheeze, however this study reported subgroups for infants with and without a previous history of wheeze. This data was included in the current review.

The studies did not report data on all these outcomes and in some situations other outcomes are presented (for example change in disease severity score was reported at different times). More details on each individual study can be found in the evidence tables.

4.2.4.4 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

Two GRADE profiles have been produced for this review:

- Table 35: GRADE profile for comparison of hypertonic saline (HS) (and bronchodilators) with 0.9% saline (and bronchodilators) in all settings.
- Table 36: GRADE profile for comparison of hypertonic saline (HS) with usual care.

Table 35: GRADE profile for comparison of hypertonic saline (HS) (and bronchodilators) with 0.9% saline (and bronchodilators) in all settings

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Intervention Hypertonic saline (HS)	Comparator 0.9% Normal saline (NS)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Hospital admission rate											
All concentrations HS vs. 0.9% NS											
8 (Anil et al., 2010; Grewal et al., 2009; Ipek et al., 2011; Kuzik et al., 2010; Sarrell et al., 2002; Jacobs et al., 2014; Florin et al., 2014; Wu et al., 2014)	123/486	156/460	RR 0.79 (0.66, 0.95) *	-	Very low	RCT	Very serious [a, b, c, d, e, r, s, t]	Serious [u]	Serious [g, h, i, j, k, v, w, x]	Serious [y]	Yes [l, m, n, o, p, q, z, aa, ab]
Hospital readmission rate											
HS vs. 0.9% saline											
3 (Anil et al., 2010; Al-Ansari et al., 2010; Grewal et al., 2009)	32/213	22/153	RR = 1.04 (0.62, 1.76) *	-	Very low	RCT	Serious [a, e, ac]	None [aj]	Serious [g, k, af]	Very Serious [ag]	Yes [m, o, ah, ai, aj]
Length of stay											
All concentrations HS vs. 0.9% NS											
10 (Al-Ansari et al., 2010; Del Giudice et al., 2012; Kuzik et al., 2007; Luo et al., 2010; Luo et al., 2011; Mandelberg et al., 2003; Tal et al., 2006; Wu et al., 2014;	607	558	-	SMD -0.45 (-0.71, -0.19) *	Very low	RCT	Very serious [ac, al, am, an, ao, ap, t, av, r]	Very serious [aw]	Very serious [af, aq, ar, as, at, v, x, ax]	Serious [ad]	Yes [o, p ,ai, av, au, ak, z, ae]

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Intervention Hypertonic saline (HS)	Comparator 0.9% Normal saline (NS)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Sharma et al., 2013; Jacobs et al., 2014)											
Disease severity score at 60 minutes (increased severity indicated by higher values)											
All concentrations HS vs. 0.9% NS											
4 (Anil et al., 2010; Ipek et al., 2011; Kuzik et al., 2010; Florin et al., 2014)	191	186	-	SMD 0.11 (-0.21 to 0.43) *	Very low	RCT	Very serious [b, e, c, s]	Serious [ay]	Serious [h, i, k, w]	None	Yes [m, n, p, ah, aa]
Disease severity score at 120 minutes (increased severity indicated by higher values)											
3% HS vs. 0.9% saline											
2 (Anil et al., 2010; Gewal et al., 2009)	98	97	-	SMD 0.31 (-0.21, 0.83) *	Very low	RCT	Serious [a, e]	Serious [ba]	Serious [g, k]	Serious [bb]	Yes [m, o, aj]
Disease severity score at 24 hours/1 day (increased severity indicated by higher values)											
All concentrations HS vs. 0.9% NS											
7 (Al-Ansari et al., 2010; Del Giudice et al., 2012; Luo et al., 2010; Luo et al., 2011; Mandelberg et al., 2003; Tal et al., 2006; Jacobs et al., 2014)	374	302	-	SMD -0.51 (-0.83, -0.19) *	Very low	RCT	Very serious [ac, al, am, an, ao, ap, r]	Very serious [bc]	Serious or more [af, aq, ar, as, v]	None	Yes [o, p, ai, au, az, z, ak]
Respiratory rate											
All concentrations HS vs. 0.9% NS											
2 (Ipek et al., 2011; Florin et al., 2014)	91	91	-	SMD 0.10 (-0.47 to 0.67) *	Very low	RCT	Serious [b, s]	Very serious [be]	Serious [h, w]	Serious [bf]	Yes [n, bd, aa]
02 saturation (improvement indicated by higher values)											

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Intervention Hypertonic saline (HS)	Comparator 0.9% Normal saline (NS)	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
60 minutes, 3% HS vs. 0.9% saline											
2 (Anil et al., 2010; Ipek et al., 2011)	135	134	-	SMD 0.00 (-0.24, 0.24)*	Low	RCT	Serious b, e	None f	Serious h, k	None	Yes m, n, ah
120 minutes, 3% HSvs. 0.9% saline											
2 (Anil et al., 2010; Grewal et al., 2009)	98	97	-	SMD -0.22 (-0.50, 0.06)*	Low	RCT	None a, e	None f	Serious g, k	Serious bb	Yes m, o, ah
Need for mechanical ventilation											
1 (Mandelberg et al., 2003)	0/27	2/26	RR 0.19 (0.01, 3.84)	-	Very low	RCT	Serious al	NA	Serious ar	Very serious ag	Yes o, bg
Need for tube feeding											
3% HS vs. 0.9% Normal Saline											
1. Teunissen et al., 2014	29/84	22/80	-	RR = 1.26 (0.79, 1.99) *	Low	RCT	Serious bh	NA	Serious bi	Serious bj	Yes bk
6% HS vs. 0.9% Normal Saline											
1. Teunissen et al., 2014	31/86	22/80	-	RR = 1.31 (0.83, 2.06) *	Low	RCT	Serious bh	NA	Serious bi	Serious bj	Yes bn
Adverse effects											
1 (Grewal et al., 2012)	4/23 (3 vomiting, 1 diarrhoea)	0/23	RR 9.00 (0.51, 158.17) *	-	Very low	RCT	None a	None	Serious g	Very serious ag	Yes o, ah

RCT randomised controlled trial, RR relative risk, SMD standard mean difference, NA not applicable.
** Calculated by the NCC-WCH technical team from data reported in the article*
a. Grewal et al., 2009 - Restricted recruitment times, usually 4pm to 2am when research assistant available (included infants with mild to moderate bronchiolitis presented to the emergency department)
b. Ipek et al., 2011 - Randomisation unclear (assigned to one of four groups according to consecutive order of admission). Blinding unclear (only study physician described as blinded)
c. Kuzik et al., 2010 - Longer duration of illness before presentation in NS group p=0.06
d. Sarrell et al., 2002 - Randomisation not described (Cochrane reports randomisation in blocks of 4 using an online randomiser). Inclusion criteria unclear. Five patients hospitalised and excluded

e. Anil et al., 2010 - Enrollment between 8am and 5pm in the emergency department (severe cases may present outside of these hours). Randomisation unclear (random number table generated by a computer). Four infants from HS group did not complete RDAI scoring
f. I2=0 (0-40% represents no heterogeneity)
g. Grewal et al., 2009 - Additional interventions and second dose of study drug at physician's discretion (second dose received by 13 HS group patients and 11 NS group patients)
h. Ipek et al., 2011 - Additional corticosteroid administration (group 1: 8[26.7%], group 2: 7[23.3%], group 3: 7[23.3%], group 4: 11[37.7%]) when clinical score deteriorated and/or arterial oxygen saturation detected <85% on room air after treatment
i. Kuzik et al., 2010 - Included infants presented to the emergency department with moderately severe viral bronchiolitis, 38 out of 88 infants had a previous history of wheezing. Data from the subgroup containing infants without a previous history of wheeze is presented here. Patients received supplemental oxygen if necessary
j. Sarrell 2002 - Excluding infants with oxygen saturation <96% in room air appears restrictive
k. Anil et al., 2010 - Additional treatments included oxygen to maintain 90-92%, nasal suction if nose blocked and antipyretics to stabilise if necessary
l. All of the studies were performed in the emergency department, except Sarrell et al., 2002 which was performed in an outpatient setting
m. Anil et al., 2010 – 5 groups: hypertonic 3% saline & salbutamol vs. normal 0.9% saline & salbutamol vs. hypertonic 3% saline & epinephrine vs. normal 0.9% saline & epinephrine vs normal 0.9% saline
n. Ipek et al., 2011 – 4 groups: hypertonic 3% saline & salbutamol vs. normal 0.9% saline & salbutamol vs. hypertonic 3% saline vs. normal 0.9% saline
o. Hypertonic 3% saline & epinephrine vs. normal 0.9% saline & epinephrine: Grewal et al., 2009; Mandelberg et al., 2003; Del Giudice et al., 2012; Tal et al., 2006
p. Hypertonic 3% saline & salbutamol vs. normal 0.9% saline & salbutamol: Kuzik et al., 2010; Luo et al., 2010
q. Sarrell et al., 2002 - hypertonic 3% saline & terbutaline vs. normal 0.9% saline & terbutaline
r. Jacobs et al., 2014 – groups statically different at baseline with regards to family history of atopy; the study reported that any co-interventions were at the discretion of the clinician, but no data are reported that specify the different treatments received by the groups.
s. Florin et al., 2014 – additional therapies were requested at the discretion of the study physician, but not recorded nor specified in the study; patients with risk factors for more severe bronchiolitis were excluded from the study.
t. Wu et al., 2014 – an additional 39 patients were enrolled after admission and not included in the analysis, however they have been included in the descriptive analysis and no reason nor explanation has been provided in the article; not reported whether investigators were kept blind to important confounding and prognostic factors; "medical readiness" was used as a criterion for discharge; admission and discharge were at discretion of the attending physician; the study failed to achieve the planned sample size; children with risk factors for severe bronchiolitis were excluded from the study.
u. I2 = 43% (41-69% may represent substantial heterogeneity)
v. Jacobs et al., 2014 – children aged up to 18 months; those with risk factors for severe bronchiolitis were excluded.
w. Florin et al., 2014 – children aged 2-24 months (the GDG has specified that it is likely that older children will not have bronchiolitis).
x. Wu et al., 2014 – children aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis).
y. Serious imprecision when 95% CI crosses one default MID.
z. Jacobs et al., 2014 – 7% HS and racemic epinephrine vs. 0.9% NS and racemic epinephrine.
aa.Florin et al., 2014 – 3% HS and albuterol vs. 0.9% NS and albuterol.
ab. Wu et al., 2014 – 3% HS and albuterol vs. 0.9% NS and albuterol.
ac. Al-Ansari et al., 2010 - Discharge frequently determined by social factors, such as availability and consensus of family members. Three infants were lost to follow-up after discharge, two in the HS group and one in the NS group
ad. Wide 95% CI crossing +/-0.50 around the line of no effect.
ae. Al-Ansari et al., 2010 readmission within 2 days, Anil et al., 2010 short-stay readmission, Grewal et al., 2009 returns to the emergency department
af. Al-Ansari et al., 2010 - Additional treatments at discretion of physician included nebulised epinephrine 5ml and supplementary oxygen
ag. Very serious imprecision when 95% CI crosses two default MID.
ah. Emergency department setting
ai. Al-Ansari et al., 2010 – hypertonic 3% saline & epinephrine vs. normal 0.9% saline & epinephrine
aj. I 2 = 0% (0-40% represents no heterogeneity)
ak. Al-Ansari et al., 2010 B - hypertonic 5% saline & epinephrine vs. 0.9% normal saline and epinephrine.

al. Mandelberg et al., 2003 - Randomisation unclear (Cochrane report randomisation in block of 4 using online randomiser). Results presented in figures (values taken from Cochrane)
am. Del Giudice et al., 2012 - Randomisation unclear (computer based randomisation programme)
an. Luo et al., 2010 - Randomisation unclear (infants recruited were assigned to a treatment group or a control group)
ao. Luo et al., 2011 - Seven patients from each group discharged within 12 hours after enrolment
ap. Tal et al., 2006 - Randomisation not described (Cochrane report randomisation in block of 4 using online randomiser)
aq. Luo et al., 2010 and Luo et al., 2011 - Patients received supportive and comprehensive treatments including sputum aspiration, water electrolyte balance maintenance and oxygen therapy
ar. Mandelberg et al., 2003 - Mean doses of add-on inhalation epinephrine in 0.9% saline solution needed per day: NS group 1.2 SD 0.9, HS group 0.9 SD 0.7
as. Tal et al., 2006 - Add-on inhalation treatments of epinephrine in 0.9% saline solution. Discharge criteria suggests supplementary oxygen and intravenous fluids may be provided
at. Kuzik et al., 2007 - Many additional treatments (albuterol, racemic epinephrine and steroids) at discretion of physician, treatment at SKMC was more likely to include antibiotics (p=0.002) as well as the addition of racemic epinephrine to the inhaled study solution (p=0.003)
au . All studies performed in an inpatient setting, except Al-Ansari which was performed in the emergency department
av . Sharma et al., 2013 – missing data for 2 patients and no explanation provided; no mention of important confounding factors nor blinding to those prognostic factors is reported; no information provided for additional treatments; patients with risk factors for severe bronchiolitis have been excluded; figures and p-values for secondary outcomes not reported.
Aw . I2=78% (70-100% may represent considerable heterogeneity).
Ax . Sharma et al., 2013 – children aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis).
Ay .I2=60% (41-69% may represent substantial heterogeneity).
Az . Grewal et al., 2009 and Kuzik et al., 2010 use RACS which have the same relative effect but in the opposite direction, the remaining studies use Wang.
Ba . I2=69% (41-69% may represent substantial heterogeneity).
Bb . Serious imprecision when 95% CI crosses one default MID; Very serious imprecision when 95% CI crosses two default MID..
Bc . I2=74% (70-100% may represent considerable heterogeneity).
Bd . Ipek et al., 2011 – performed in an emergency department setting.
Be . I2=73% (70-100% may represent considerable heterogeneity).
Bf . Serious imprecision when 95% CI crosses one default MID; Very serious imprecision when 95% CI crosses two default MID.Bg . Mandelberg et al., 2003 – performed in an inpatient setting.
Bh . Teunissen et al., 2014 – the study didn't report how the randomisation sequence was prepared and concealment of allocation was unclear.
Bi . Teunissen et al., 2014 – patients aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis).
Bj . Serious imprecision when 95% CI crosses one default MID.
Bk . Teunissen et al., 2014 – 3% HS and salbutamol vs. 0.9% NS and salbutamol.

Table 36: GRADE profile for comparison of hypertonic saline (HS) with usual care.

	Number of children		Effect				Quality assessment				
Number of studies	Intervention 3%Hypertonic saline	Comparator Usual care	Relative (95% CI)	Absolute (95% CI)	Quality	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Length of stay											
Time to fit for discharge (hours) a											
1 Everard M.L. et al., 2014	[redacted]	[redacted]	[redacted]	-	Moderate	RCT	Serious [b]	n/a	None	Very Serious [c]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Intervention 3%Hypertonic saline	Comparator Usual care	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Time to actual discharge (hours)											
1 Everard M.L. et al., 2014	[redacted]	[redacted]	[redacted]	-	Moderate	RCT	Serious [b]	n/a	None	Very serious [c]	None

RCT randomised controlled trial, RR relative risk, MD mean difference, SD standard deviation, NA not applicable.
** Calculated by the technical team from data reported in the article*
a. The time until the infant was assessed as being to "fit for discharge" which was defined as point at which the infant was feeding adequately (taking >755 of usual intake), and had been in air with a saturation of at least 92% for 6 hours.
b. Detection bias: blinding was not possible for investigators; Performance bias: the study is not blinded.
c. Very serious imprecision when 95% CI crosses two default MID.

4.2.4.5 Evidence statements

Hospital admission rates

All concentrations HS vs. 0.9% NS

Eight studies with 946 children found the hospital admission rates were reduced when infants were treated with hypertonic saline compared to infants who were treated with normal saline. The quality of evidence was very low.

Hospital readmission rates

All concentrations HS vs. 0.9% NS

Four studies with 366 children found the hospital readmission rates were higher among children who received HS compared to those who received NS. However, the finding was not significant. The quality of evidence was very low.

Length of hospital stay

All concentrations HS vs. 0.9% NS

Eleven studies with 1165 children found the length of hospital stay reduced when children are treated with HS compared to children who are treated with NS. This finding was significant. The quality of evidence was very low.

HS vs. usual care

[redacted]

Change in respiratory rate

All concentrations HS vs. 0.9% NS

Two studies of 182 children found no significant difference in the respiratory rate when infants are treated with HS compared to infants who are treated with NS. The quality of evidence was very low.

Change in disease severity score at 2 to 4 hours after treatment

60 minutes

All concentrations HS vs. 0.9% NS

Four studies of 377 children found no significant difference in the disease severity score between the infants who received HS compared to infants who received NS. The quality of evidence was very low.

120 minutes

3% HS vs. 0.9% NS

Two studies of 195 children found no difference in the disease severity score between the infants who received HS compared to infants who received NS in emergency room setting. The quality of evidence was very low.

24 hours/1 day

All concentrations HS vs. 0.9% NS

Seven studies of 676 children found the disease severity score decreased (improved) when infants received HS compared to infants who received NS. The finding was significant. The quality of evidence was very low.

Change in O2 saturation

60 minutes

3% HS vs. 0.9% NS

Two studies of 269 children found no difference in oxygen saturation between the infants who received HS compared to infants who received NS in emergency room setting. The quality of evidence was low.

120 minutes

3% HS vs. 0.9% NS

Two studies of 195 children found no difference in oxygen saturation between the infants who received HS compared to infants who received NS in emergency room setting. The quality of evidence was low.

Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation

One study of 52 children found no difference in infants treated with NS than HS requiring mechanical ventilation in an inpatient setting. The quality of evidence was very low. No studies reported the need for high flow humidified oxygen or CPAP.

Need for/Use of feeding support (tube feeding, IV fluids)

One study of 250 children found that the need for tube feeding improved for children who received HS (either 3% or 6%) compared to those who received NS. However, the findings were not significant. The quality of the evidence was low.

Adverse effects (including mortality)

One study of 46 children found more infants treated with HS than NS to encounter adverse effects in an emergency room setting, but this finding was not significant. The quality of evidence was very low.

4.2.4.6 Health economics profile

No published economic evaluations were identified for this question. However, this was identified as a priority area for economic evaluation.

A decision tree model was developed in Excel based on the outcomes of the clinical review. Full details of the health economic analysis can be found in Appendix A.

HS was compared to the following in the model:

- Saline 0.9%
- Standard care (oxygen as required, minimal handling and fluid administration as appropriate)

In the studies identified, patients were given other treatments such as bronchodilators, salbutamol, and epinephrine. These treatments were given to both arms in the studies and so have not been taken into account in the model.

The model was developed from the perspective of the UK NHS, using 2012/13 costs. The time horizon for the model was less than a year and so no discount rate was applied.

The population of children being treated for bronchiolitis in the NHS was estimated using the NHS reference cost data. This data reports the number of finished consultant episodes due to bronchiolitis for paediatric care, N=33,154. As this figure includes re-admissions it was assumed that approximately 80% of these episodes will be initial admissions, N=26,523.

The number of admissions includes non-elective short and long stays. A short stay is defined as ≤1 day. There are other reference costs for attendances to accident and emergency, however these are not defined by condition and so it is not possible to identify attendances due to bronchiolitis.

A network meta-analysis of bronchodilators and corticosteroids (Harling et al. 2011) reported a baseline risk of admission from all studies of 20%. Therefore, if N=26,523 infants are admitted for bronchiolitis, then N=132,616 will have been diagnosed with bronchiolitis. The model was also run with a population of N=26,523, assuming that this figure reflects the number of infants referred to hospital from primary care or go straight to hospital.

All infants diagnosed with bronchiolitis at hospital are assumed to be treated with either saline 0.9% or HS for the base case analysis, or with standard treatment without saline for analysis based on the SABRE trial. Treatment will continue if an infant is admitted.

The main outcomes in the model were hospital admissions, length of stay, re-admissions, need for mechanical ventilation or tube feeding, and admission to ICU/HDU. Quality of life scores were not identified for bronchiolitis.

Using the mean inputs from the clinical review for HS compared to 0.9% normal saline, the base case results show that using HS could lead to reduced admissions and reduced need for mechanical ventilation. However, normal saline is associated with fewer re-admissions and reduced need for tube feeding (Table 37 - Table 38). Although HS does not consistently demonstrate health benefits compared to NS, the results show HS is less expensive than using NS. This is mainly driven by the number of admissions and re-admissions, in total 41,778 for NS and 37,729 for HS with a population of 132,616. Even though patients treated initially with HS were more likely to be re-admitted, this did not outweigh the increased likelihood of initial admission with normal saline.

Table 37: Results – 132,616 infants diagnosed with bronchiolitis and initially treated with nebulised saline 0.9% or hypertonic saline (all concentrations) – all studies

	N Admitted	N Re-admitted	N needing mechanical ventilation	N needing tube feeding	Mean cost per infant diagnosed and treated (probabilistic)
Saline 0.9%	26,523	15,255	1,250	4,469	£203
Hypertonic saline	20,953	16,776	272	5,180	£198

Table 38: Results – 26,523 infants diagnosed with bronchiolitis and initially treated with nebulised saline 0.9% or hypertonic saline (all concentrations) – all studies

	N Admitted	N Re-admitted	N needing mechanical ventilation	N needing tube feeding	Mean cost per infant diagnosed and treated (probabilistic)
Saline 0.9%	26,523	3,814	908	3,245	£760
Hypertonic saline	20,953	3,148	174	3,309	£659

Table 39: Results – infants diagnosed with bronchiolitis and initially treated with standard care or hypertonic saline 3%– SABRE, N=132,616

	N Admitted	N Re-admitted	N admitted to ICU	Mean cost per infant (probabilistic)
Saline 0.9%	26,523	5,305	3,204	£730
Hypertonic saline	26,523	3,315	2,690	£769

Table 40: Results – infants diagnosed with bronchiolitis and initially treated with standard care or hypertonic saline 3%– SABRE, N=26,523

	N Admitted	N Re-admitted	N admitted to ICU	Mean cost per infant (probabilistic)
Saline 0.9%	26,523	1,326	2,804	£1,361
Hypertonic saline	26,523	829	2,354	£1,388

To consider the variability in the inputs to the model a probabilistic sensitivity analysis (PSA) was developed. Distributions could be described for the clinical inputs, and the cost of a bed day. As parameters to describe the distributions were not available for the drug costs or mean length of stay, these remained deterministic (Appendix A).

When 1,000 simulations were run with the PSA, there was considerable uncertainty in the results comparing hypertonic saline with normal saline. With all studies included hypertonic saline would be cost saving in 59% of simulations (Table 41).

Using inputs from the SABRE trial showed HS would not be cost-effective compared to standard care, in only 7% of simulations HS was cost saving compared to standard care.

Table 41: Probabilistic sensitivity analysis results – cost differences

	Mean cost per infant diagnosed	Proportion of simulations where hypertonic saline is cost saving compared to 0.9% or standard care
All studies		
Hypertonic saline	£203	59%
0.9% saline	£198	
SABRE		
Hypertonic saline	£760	7%
Standard care	£721	

The direction of the results show hypertonic saline is cost saving compared to normal saline. However, there is considerable uncertainty in the results as seen in the probabilistic sensitivity analysis. When HS is compared to standard care, standard care is cost saving.

4.2.4.7 Evidence to recommendations

4.2.4.7.1 Relative value placed on the outcomes considered

The aim for this question was to determine whether nebulised HS is effective in the management of bronchiolitis. In order to do this the GDG considered hospital admission rate; length of stay; and need for high flow humidified oxygen, CPAP or mechanical ventilation to be the critical outcomes. Other important outcomes for the review were: change in respiratory rate; change in disease severity score at 2 to 4 hours after treatment; change in O2 saturation; need for/use of feeding support (tube feeding, IV fluids); and adverse effects (including mortality).

4.2.4.7.2 Consideration of clinical benefits and harms

Bronchiolitis involves airway inflammation with increased mucus production that can result in breathing difficulties and feeding problems. The GDG noted that it has been commonly believed that HS may have useful mucociliary clearance properties. Therefore, a 3% HS vaporized solution is sometimes used in the UK with the aim of assisting clearance of airway mucus.

Some of the evidence examined for this review indicated that HS compared with 0.9% saline was associated with reduced admission rates. However the quality of those studies was very low. The GDG found this effect even less plausible because they believed the absence of a beneficial effect on other parameters such as respiratory rate and O2 saturation made it less likely to be a true effect. Part of the same body of evidence indicated that compared with 0.9% saline, HS reduced the length of hospital stay in children with bronchiolitis. However, this evidence was also of very low quality.

The GDG pointed out that more recent trials were consistent in reporting no beneficial effect of HS when compared to 0.9% saline, and the quality of the evidence of these trials was

moderately better compared to the older trials. For this reason, a stratified analysis was undertaken to assess the difference in results and quality of evidence between new and older trials. In addition to that, a recent, large and UK based trial (SABRE) compared the use of HS with usual care for children with bronchiolitis and found that administering HS had no impact on length of stay. The GDG also noted that most of the evidence reported in relation of length of hospital admission rates was from non-UK studies, and in other settings the usual length of hospital stay may be different to that currently expected in the UK.

Only one study of very low quality examined by the GDG has reported side effects (episodes of vomiting and diarrhoea) in infants treated with HS.

No evidence reported improvements in other measurable outcomes (such as change in disease severity score or change in O2 saturation) in children with bronchiolitis treated with HS.

4.2.4.7.3 Consideration of health benefits and resource uses

HS is a relatively inexpensive treatment compared to normal saline. HS use was associated with fewer re-admissions and reduced need for mechanical ventilation which requires admission to a PICU. NS was associated with reduced need for tube feeding. However, there was considerable uncertainty in the results of the cost-effectiveness analysis and so the health benefits and resource use in the real world is unknown.

When compared to standard care without saline, the resource use associated with hypertonic saline needs to be considered, in terms of staff time and consumables. Although infants treated with HS were less likely to be re-admitted and less likely to be admitted to PICU, overall treatment with standard care was cost saving.

4.2.4.7.4 Quality of evidence

All the included studies were randomised controlled trials and all were published within the past ten years. However, a number of potential biases exist. Methods of randomisation and concealment of allocation were not always described in detail. The discretionary use of additional treatments is a potential source of bias. The differing settings (inpatient, outpatient and emergency department) and additional bronchodilators nebulised with the study solutions may also affect the interpretation of findings.

4.2.4.7.5 Other considerations

No other considerations were identified.

4.2.4.8 Key conclusions

The GDG concluded that the use of HS did not offer any reduction in hospital stay over no treatment and therefore recommended that it should not be used.

4.2.4.9 Recommendations

The recommendations covering the clinical and cost effectiveness of HS are presented in section 4.2.12.

4.2.5 Inhaled bronchodilator therapy

4.2.5.1 Introduction

Bronchodilators are medications that cause relaxation of the airway smooth muscle resulting in airway dilation. Bronchodilators are the mainstay of therapy in acute asthma and viral associated wheeze where bronchoconstriction is the most prominent feature. However,

whilst there can be similar clinical features, the disease process in bronchiolitis differs from asthma and is characterised by inflammation and airway debris. Bronchodilators may cause adverse effects (including tachycardia, desaturation and tremor) and have significant associated costs.

4.2.5.2 Review question

What is the efficacy of inhaled bronchodilator therapy?

4.2.5.3 Introduction

Inhaled bronchodilators such as salbutamol work by relaxing smooth muscle in the lungs. Some studies suggest that inhaled epinephrine might work by reducing swelling in the lining of the small airways. It is proposed that these therapies might help relieve the symptoms of bronchiolitis by opening up the airways.

4.2.5.4 Description of included studies

Twenty four RCTs were identified for this review (Anil et al., 2010; Can et al, 1998; Chevallier et al., 1995; Chowdhury et al., 1995; Dobson et al., 1998; Gadomski et al., 1994; Gadomski et al., 1994b; Goh et al., 1997; Henry et al., 1983; Ho et al., 1991; Ipek et al., 2011; Karadag et al., 2008; Khashabi et al., 2005; Klassen et al, 1991; Lines et al., 1990; Lines et al., 1992; Patel et al., 2002; Plint et al., 2009; Ralston et al., 2005; Schuh et al., 1990; Skjerven et al., 2013; Tinsa et al., 2009; Totapally et al, 2002; Wainwright et al., 2003). The type of bronchodilators examined included:

- Epinephrine in three studies (Plint et al., 2009; Wainwright et al., 2003; Skjerven et al., 2013)
- Albuterol/salbutamol in eleven studies (Dobson et al., 1998; Gadomski et al., 1994; Schuh et al., 1990; Totapally et al, 2002; Gadomski et al., 1994b; Can et al, 1998; Chevallier et al., 1995; Ho et al., 1991; Klassen et al., 1991; Lines et al., 1990; Ipek et al., 2011)
- Terbutaline in one study (Tinsa et al., 2009)
- Ipratropium bromide in two studies (Henry et al., 1983; Lines et al., 1992)

All studies compared the above bronchodilators against placebos such as 3% saline, 0.9% sodium chloride (normal saline).

Five studies (Plint et al., 2009; Gadomski et al., 1994b; Wainwright et al., 2003; Schuh et al., 1990; Ipek et al., 2011) allowed additional treatment at the discretion of the health professional, for example additional corticosteroid or bronchodilators, but only three of these reported the results of this (Wainwright et al., 2003; Schuh et al., 1990; Ipek et al., 2011).

Nine studies included children less than or equal to 12 months of age (Patel et al., 2002; Chevalier et al., 1995; Totapally et al., 2002; Wainwright et al., 2003; Karadag et al., 2008; Skjerven et al., 2013; Ho et al., 1991; Plint et al., 2009; Tinsa et al., 2009), five studies included children less than 18 months of age (Gadomski et al., 1994; Gadomski et al., 1994b; Henry et al., 1983; Lines et al., 1990; Lines et al., 1992) and ten studies included children less than or equal to 24 months of age (Klassen et al., 1991; Can et al., 1998; Dobson et al., 1998; Goh et al., 1997; Ipek et al., 2011; Chowdhury et al., 1995; Anil et al., 2010; Schuh et al., 1990; Ralston et al., 2005; Khashabi et al., 2005).

Ten trials were performed in outpatient settings (Khashabi et al., 2005; Plint et al., 2009; Anil et al., 2010; Gadomski et al., 1994; Gadomski et al., 1994b; Ralston et al., 2005; Schuh et al., 190; Can et al., 1998; Klassen et al., 1991; Ipek et al., 2011) most frequently paediatric emergency departments. The remaining trials were performed in inpatient settings (Patel et al., 2002; Wainwright et al., 2003; Dobson et al., 1998; Totapally et al., 2002; Chevalier et al.,

1995; Chowdhury et al., 1995; Goh et al., 1997; Ho et al., 1991; Karadag et al., 2008; Lines et al., 1990; Henry et al., 1983; Lines et al., 1992; Skjerven et al., 2013; Tinsa et al., 2009).

The definition of bronchiolitis was explicitly stated in 18 studies (Anil et al., 2010; Chevallier et al., 1995; Chowdhury et al., 1995; Dobson et al., 1998; Gadomski et al., 1994; Gadomski et al., 1994b; Goh et al., 1997; Henry et al., 1983; Ipek et al., 2011; Karadag et al., 2008; Khashabi et al., 2005; Patel et al., 2002; Plint et al., 2009; Ralston et al., 2005; Skjerven et al., 2013; Tinsa et al., 2009; Totapally et al, 2002; Wainwright et al., 2003), all of which used a definition based on the presence of clinical symptoms and signs and/or RSV testing. The remaining six studies did not explicitly define bronchiolitis (Klassen et al., 1991; Can et al., 1998; Schuh et al., 1990; Lines et al., 1990; Lines et al., 1992; Ho et al., 1991).

Four of the studies were undertaken in Turkey (Karadag et al., 2008; Anil et al., 2010; Can et al., 1998; Ipek et al., 2011); five in the USA (Schuh et al., 1990; Ralston et al., 2005; Dobson et al., 1998; Totapally et al., 2002; Gadomski et al., 1994b), three in Canada (Klassen et al., 1991; Plint et al., 2009; Patel et al., 2002), four in Australia (Lines et al., 1990; Lines et al., 1992; Wainwright et al., 2003; Ho et al., 1991), one in Saudi Arabia (Chowdhury et al., 1995), one in the UK (Henry et al., 1983), one in Singapore (Goh et al., 1997), one in Egypt (Gadomski et al., 1994), one in Norway (Skjerven et al., 2013), one in Iran (Khashabi et al., 2005), one in France (Chevallier et al., 1995) and one in Tunisia (Tinsa et al., 2009).

Two Cochrane reviews were identified that examined bronchodilators. However, they could not be used in this evidence review as they grouped together all bronchodilators (other than epinephrine) and did not assess all the outcomes specified by the GDG. Furthermore, the Cochrane reviews made an assumption that the effect of a treatment used across groups would cancel itself out, and therefore this allowed the inclusion of combined bronchodilator and corticosteroids compared with corticosteroids alone in a the meta-analysis of bronchodilators compared to placebo. No analysis was produced to support this assumption; therefore, the technical team excluded these studies from the analysis. However, in cases where data for separate arms of a study or outcomes including missing standard deviations were not presented in the individual studies but available in the Cochrane review (Gadomski et al., 2010) who contacted authors for additional data, this data has been used.

More details on each individual study can be found in the evidence tables.

4.2.5.5 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

Six GRADE profiles have been produced for this review:

- Table 42: GRADE profile for comparison of epinephrine with placebo
- Table 43: GRADE profile for comparison of albuterol/salbutamol with placebo
- Table 44: GRADE profile for comparison of ipratropium bromide with placebo
- Table 45: GRADE profile for comparison of salbutamol and ipratropium bromide (all subjects received both bronchodilators) with placebo
- Table 46: GRADE profile for comparison of salbutamol/ipratropium bromide/salbutamol and ipratropium bromide with placebo
- Table 47: GRADE profile for comparison of salbutamol/ipratropium bromide/salbutamol and ipratropium bromide with placebo

Table 42: GRADE profile for comparison of epinephrine with placebo

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Epinephrine	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Hospital admissions (outpatients)											
At enrolment or less than 24 hours											
3studies (Anil et al., 2010 3%* saline;; Khashabi et al 2005; Plint et al., 2009)	38/261 (14.6%)	54/262 (20.6%)	RR: 0.66 (0.37 to 1.16) [a]	-	Very low	RCT	Very serious[b]	None	None	Serious[c]	None
Readmission in 2 days											
1 (Anil et al., 2010) 0.9%** saline and 3%* saline	12/77 (15.6%)	12/74 (16.2%)	RR: 0.97 (0.46 to 2.02)a	-	Low	RCT	None	None	None	Very serious [d]	None
By day 7											
1 (Plint et al., 2009)	47/198 (23.7%)	53/201 (26.4%)	RR: 0.90 (0.64 to 1.26)[a]	-	Very low	RCT	None	None	Serious[f]	Very serious[d]	None
By day 22											
1 (Plint et al., 2009)	50/198 (25.3%)	54/201 (26.9%)	RR: 0.94 (0.68 to 1.31)[a]	-	Very low	RCT	None	None	Serious[f]	Very serious[d]	None
Hospital readmissions (inpatients)											
Within one month after discharge											
1 (Wainwright et al., 2003)	1/99 (1.0%)	2/95 (2.1%)	RR: 0.48 (0.04 to 5.20)[a]	-	Very low	RCT	None	None	Serious[g]	Very serious[d]	None
Length of stay in hours (outpatients)											
Reported as time to discharge – time between the triage time at enrolment visit and the time of discharge from the last emergency department visit or the last hospitalisation for each patient within the next 7 days											
1 (Plint et al., 2009)	N = 198 Median (Interquartile range): 4.9 (3.7 to 9.6)	n=200 Median (Interquartile range): 5.3 (3.8 to 21)	-	p=0.94[h]	Moderate	RCT	None	None	Seriousg	NC	None
Length of hospital stay in hours (inpatients)											
1 (Skjerven et al., 2013)	n=203 Mean (range): 78.7 (69.2 to 88.1)	n=201 Mean (range): 81.8 (72.6 to 91.0)	-	p=0.43 [h]	Moderate	RCT	Serious[i]	None	None	NC	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Epinephrine	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Patel et al., 2002)	n=50 Mean (SD): 59.8 (62)	n=48 Mean (SD): 63.3 (47)	-	MD (95%CI): -3.50 (-25.23 to 18.23)a	Moderate	RCT	Serious[j]	None	None	None	None
1 (Wainwright et al., 2003)	n=99 Mean (95%CI): 58.8 (49.4 to 70.0)	n=95 Mean (95%CI): 69.5 (59.3 to 81.4)	Ratio of means (95%CI): 0.85 (0.67 to 1.07)[i]	p=0.16i	Low	RCT	None	None	Serious[g]	Serious[c]	None
Change in respiratory rate (outpatients)											
At 30 minutes											
1 (Plint et al., 2009)	n=198 Mean (SD): -1.35 (8.53)	n=200 Mean (SD): -0.59 (8.34)	-	MD (95%CI): -0.76 (-2.42 to 0.90)a	High	RCT	None	None	None	None	None
At 60 minutes											
1 (Plint et al., 2009)	n=198 Mean (SD): -3.68 (8.89)	n=200 Mean (SD): -2.88 (10.2)	-	MD (95%CI): -0.80 (-2.68 to 1.08)a	High	RCT	None	None	None	None	None
After treatment (endpoint, time point not reported)											
1 (Khashabi et al., 2005)	n=24 Mean (SD): 37.7 (7.7)	n=24 Mean (SD): 45.8 (7.7)	-	MD (95%CI): -8.10 (-12.46 to -3.74)[a]	Moderate	RCT	Serious [b]	None	None	None	None
Change in disease severity score (outpatients)											
At 30 minutes											
2 studies (Plint et al., 2009; Anil et al., 2010 0.9%** saline, 3%* saline*)	n=275	n=274	-	SMD (95%CI): 0.09 (-0.29 to 0.48)[a]	Low	RCT	None	Very serious [l]	None	None	None
At 60 minutes											
2 studies (Plint et al., 2009;; Anil et al., 2010 0.9%** saline, 3%* saline)	n=275	n=274	-	SMD (95%CI): -0.05 (-0.43 to 0.33) [a]	Very low	RCT	Very serious	Serious [m]	None	None	None
At 120 minutes											
1 studies (Anil et al., 2010 0.9%** saline, 3%* saline)	n=92	n=89	-	MD (95%CI): 0.09 (-0.50 to 0.68)[a]	Very low	RCT	Very serious	Very serious [o]	None	Serious [p]	None
After treatment (endpoint, time point not reported)											
1 (Khashabi et al.,	n=24	n=24	-	MD (95%CI):	Moderate	RCT	Serious [b]	None	None	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Epinephrine	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
2005)	Mean (SD): 4.9 (4)	Mean (SD): 7.9 (5.2)		-3.00 (-5.62 to -0.38)[a]							
Change in disease severity score (inpatients)											
At 30 minutes											
1 (Wainwright et al., 2003)	NR	NR	-	p=0.04 (the epinephrine group had a lower respiratory-effort score than the placebo group)i	Low	RCT	Serious[k]	None	Serious[g]	NC	None
At 60 minutes (endpoint)											
1 (Wainwright et al., 2003)	n=99 Mean (95%CI): 2.44 (1.97 to 2.92)	n=95 Mean (95%CI): 3.35 (2.78 to 3.91)	-	p=0.02	Moderate	RCT	None	None	Serious[g]	NC	None
Change in oxygen saturation (outpatients)											
At 30 minutes											
2 studies (Plint et al., 2009; Anil et al., 2010 0.9%** saline, 3%* saline)	n=275	n=274	-	SMD (95%CI): 0.12 (-0.05 to 0.29)[a]	High	RCT	None	None	None	None	None
At 60 minutes											
2 studies (Plint et al., 2009; Anil et al., 2010 0.9%** saline, 3%* saline)	n=275	n=274	-	SMD (95%CI): 0.19 (0.01 to 0.38))[a]	Very low	RCT	Very serious	Serious[m]	None	None	None
At 120 minutes											
1 studies (Anil et al., 2010 0.9%** saline, 3%* saline)	n=77	n=74	-	SMD: -0.08 (-0.40 to 0.24) [a]	Very low	RCT	Very serious	Serious[n]	None	Serious [p]	None
After treatment (endpoint, time point not reported)											
1 (Khashabi et al., 2005)	n=24 Mean (SD): 91.9 (3.5)	n=24 Mean (SD): 88.8 (3.9)	-	MD (95%CI): 3.10 (1.00 to 5.20) [a]	Moderate	RCT	Serious [b]	None	None	None	None
Need for high flow humidified oxygen, CPAP or mechanical ventilation (inpatients)											
Reported as number requiring supplemental oxygen											

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Epinephrine	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
2 studies (Skjerven et al., 2013; Wainwright et al., 2003)	132/291 (45.4%)	121/284 (42.6%)	RR (95%CI): 1.07 (0.86 to 1.34)[a]	-	Very low	RCT	Serious[i]	None	Serious[g]	Serious[e]	None
Reported as number requiring ventilatory support											
1 (Skjerven et al., 2013)	15/203 (7.4%)	15/201 (7.5%)	RR (95%CI): 0.99 (0.50 to 1.97)[a]	-	Very low	RCT	Serious[i]	None	None	Very serious[d]	None
Need for/use of feeding support (inpatients)											
Reported as number requiring oxygen and intravenous feeding											
1 (Wainwright et al., 2003)	13/99 (13.1%)	24/95 (25.3%)	RR (95% CI): 0.52 (0.28 to 0.96)[a]	-	Moderate	RCT	None	None	Serious [g]	None	None
Reported as number requiring nasogastric tube feeding											
1 (Skjerven et al., 2013)	57/201 (28.4%)	59/199 (29.6%)	RR (95%CI): 0.96 (0.70 to 1.30)[a]	-	Very low	RCT	Serious[i]	None	None	Very serious[d]	None
Need for/use of feeding support (outpatients)											
Reported as time to return to normal feeding in days											
1 (Plint et al., 2009)	n=198 Median (interquartile range): 0.5 (0.2 to 1.2)	n=200 Median (interquartile range): 0.9 (0.3 to 2.1)	Mean ratio (95%CI): 0.60 (0.47 to 0.76)[h]	-	Moderate	RCT	None	None	Serious [f]	None	None
Adverse events (outpatients)											
Tremor											
1 (Plint et al., 2009)	4/198	2/201	RR (95%CI): 2.03 (0.38 to 10.96)[a]	-	Very low	RCT	None	None	Serious[f]	Very serious[d]	None
Pallor											
1 (Plint et al., 2009)	22/198	16/201	RR	-	Low	RCT	None	None	Serious[f]	Serious[e]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Epinephrine	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			(95%CI): 1.40 (0.76 to 2.58)[a]								
Vomiting											
1 (Plint et al., 2009)	4/198	3/201	RR (95%CI): 1.35 (0.31 to 5.97)[a]	-	Very low	RCT	None	None	Serious [f]	Very serious[d]	None
Varicella											
1 (Plint et al., 2009)	0/198	0/201	NC	-	Moderate	RCT	None	None	Serious[f]	NC	None
Dark stools											
1 (Plint et al., 2009)	14/198	16/201	RR (95%CI): 0.89 (0.45 to 1.77)[a]	-	Very low	RCT	None	None	Serious[f]	Very serious[d]	None
Hypertension											
1 (Plint et al., 2009)	1/198	0/201	RR (95%CI): 3.05 (0.12 to 74.31)[a]	-	Very low	RCT	None	None	Serious[f]	Very serious[d]	None
Hyperkalaemia											
1 (Plint et al., 2009)	0/198	0/201	NC	-	Moderate	RCT	None	None	Serious [f]	NC	None

NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, p-value, RR relative risk
** Inhalation of epinephrine, 1.5mg, diluted to 4ml with 3% saline solution*
*** Inhalation of epinephrine, 1.5mg, diluted to 4ml with 0.9% saline solution*
a Calculated by the NCC-WCH technical team from data reported in the article
b Khashabi: method of randomisation not described.
c Serious imprecision when 95% CI crosses one default MID.
d Very serious imprecision when 95% CI crosses two default MID.
e Serious imprecision when 95% CI crosses one default MID.
f Plint: Physician allowed to provide cointerventions after 90 minutes
g Wainwright: additional treatments at physician's discretion – 2 subjects in the placebo group were treated with bronchodilators other than epinephrine when their condition failed to improve
h As reported in the study
i Skjerven: 321/404 complete d the study (reasons for withdrawals reported)

j Patel: 10 withdrawn during the study (reasons not provided)
k Wainwright: numbers in each group not reported
l High heterogeneity: I2=70%
m Serious heterogeneity: I2=64%
n Serious heterogeneity: I2=61%
o Serious heterogeneity: I2=67%
p Serious imprecision when 95% CI crosses one default MID.

Table 43: GRADE profile for comparison of albuterol/salbutamol with placebo

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Albuterol/Salbutamol	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Hospital admissions (outpatients)											
At enrolment or <24 hours											
2 studies (; Anil et al., 2010 0.9%* saline; Khashabi et al., 2005)	13/60 (21.7%)	18/61 (29.5%)	RR (95% CI): 0.69 (0.44 to 1.09))[a]	-	Very low	RCT	Very serious[b]	None	None	Serious[c]	None
Readmission in 2 days											
1 (Anil et al., 2010) 0.9%* saline and 3%** saline	10/71 (14.1%)	12/74 (16.2%)	RR (95%CI): 0.87 (0.40 to 1.90)[a]	-	Low	RCT	None	None	None	Very serious[d]	None
After treatment (time point not reported)											
4 studies (Gadomski et al., 1994b; Schuh et al., 1990; Ipek et al., 2011; Klassen et al., 1991)	23/114 (20.2%)	20/108 (18.5%)	RR (95%CI): 1.11 (0.65 to 1.89)[a]	-	Very low	RCT	Very serious[e, f, g, h,]	None	Serious[i, j, k]	Very serious[d]	None
Length of hospital stay (inpatients)											
3 studies (Patel et al., 2002; Chowdhury et al., 1995; Karadag et al., 2008)	n=95	n=82	-	SMD (95%CI): -0.03 (-0.33 to 0.27)[a]	Moderate	RCT	Serious [g]	None	None	None	None
Reported as % of patients discharged at 24, 48 and 72 hours											
1 (Dobson et al., 1998)	24 hours: 0% 48 hours: 17.4% 72 hours: 52.2%	24 hours: 0% 48 hours: 24.1% 72 hours: 69%	-	p=0.24 [m]	Moderate	RCT	Serious [n]	None	None	NC	None
Change in respiratory rate (outpatients)											
After dose 1 (% decrease)											

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Albuterol/Salbutamol	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Schuh et al., 1990)	n=21 Mean (SD): -16.2 (15)	n=19 Mean (SD): -15.5 (15)	-	p=NSn MD (95%CI): -1.00(-10.31 to 8.31)[a]	Very low	RCT	Serious[e]	None	Serious[i]	Very serious[o]	None
After dose 2 (% decrease)											
1 (Schuh et al., 1990)	n=21 Mean (SD): -19.6 (16)	n=19 Mean (SD): -8 (13)	-	p=0.015n MD (95%CI): -12.00(-21 to -3)[a]	Low	RCT	Serious[e]	None	Serious[i]	None	None
At 30 minutes											
3 studies (Gadomski et al., 1994 and Gadomski et al., 1994b; Klassen et al., 1991)	n=95	n=91	-	SMD (95%CI): -0.13 (-0.49 to 0.22)[a]	Moderate	RCT	Seriousg,[h]	None	None	None	None
At 60 minutes											
3 studies (Gadomski et al., 1994 and Gadomski et al., 1994b; Klassen et al., 1991)	n=95	n=91	-	SMD (95%CI): -0.09 (-0.38 to 0.20)[a]	Moderate	RCT	Serious[f, g]	None	None	None	None
Post-treatment (time point not reported)											
2 studies (Ipek et al., 2011; Khashabi et al., 2005)	n=54	n=54	-	MD (95%CI): -1.66 (-4.94 to 1.61)[a]	Very low	RCT	Seriousc[g]	None	Serious[k]	Serious[p]	None
Change in respiratory rate (inpatients)											
30 minutes (% decrease)											
1 (Chevallier et al., 1995)	n=16 Mean (SD): -10.4 (1.6)	n=17 Mean (SD): -4.7 (1.5)	-	MD (95%CI): -5.70 (-6.76 to -	Moderate	RCT	Seriousr	None	None	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Albuterol/Salbutamol	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
				4.64)[a]							
150 minutes (% decrease)											
1 (Chevallier et al., 1995)	n=16 Mean (SD): -20.9 (1.5)	n=17 Mean (SD): -12.1 (1.4)	-	MD (95%CI): -8.80 (-9.79 to -7.81)[a]	Moderate	RCT	Serious[q]	None	None	None	None
After treatment (endpoint, time point not reported)											
1 (Totapally et al., 2002)	n=10 Mean (SD): 42 (10.7)	n=9 Mean (SD): 41 (10.8)	-	MD (95%CI): 1.00 (-8.68 to 10.68)[a]	Very low	RCT	Serious[r]	None	None	Very serious[o]	None
Change in disease severity score (outpatients)											
At 30 minutes											
4 studies (Gadomski et al., 1994 and Gadomski et al., 1994b; Can et al., 1998; Anil et al., 2010 0.9%* saline, 3%** saline)	n=177	n=176	-	SMD (95%CI): 0.06 (-0.45 to 0.58)[a]	Very low	RCT	Very serious[f,s]	Very serious[u]	None	Serious[u]	None
At 60 minutes											
4 studies (; Gadomski et al., 1994 and Gadomski et al., 1994b; Can et al., 1998; Anil et al., 2010 0.9%* saline, 3%** saline)	n=177	n=176	-	SMD (95% CI): -0.33 (-1.11 to 0.45) [a]	Very low	RCT	Very serious [f, s]	Very serious[y]	None	Serious[p]	None
At 120 minutes											
1 studies (; Anil et al., 2010; 0.9%* saline, 3%** saline)	n=72	n=74	-	MD: 0.12 (-0.66 to 0.90))[a]	Very low	RCT	Very serious	Very serious[w]	None	Serious[p]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Albuterol/Salbutamol	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Average clinical score after treatment (time point not reported)											
4 studies (Ralston et al., 2005; Ipek et al., 2011; Khashabi et al., 2005; Klassen et al., 1991)	n=119	n=120	-	SMD (95%CI): -0.32 (-0.57 to -0.06)[a]	Very low	RCT	Very serious[b, g, h]	None	Serious[k]	None	None
Change in disease severity score (inpatients)											
Day 1 (endpoint)											
1 (Goh et al., 1997)	n=30 Mean (SD): 7.5 (2.1)	n=29 Mean (SD): 8 (2.5)	-	MD (95%CI): -0.5 (-1.68 to 0.68)[a]	Low	RCT	Serious[x]	None	None	Serious[p]	None
Day 2 (endpoint)											
1 (Goh et al., 1997)	n=30 Mean (SD): 4.7 (2.2)	n=29 Mean (SD): 4.4 (2.4)	-	MD (95%CI): 0.30 (-0.88 to 1.48)[a]	Low	RCT	Serious[x]	None	None	Serious[u]	None
Day 3 (endpoint)											
1 (Goh et al., 1997)	n=30 Mean (SD): 3 (1.5)	n=29 Mean (SD): 3.1 (1.8)	-	MD (95%CI): -0.10 (-0.95 to 0.75)[a]	Low	RCT	Serious[x]	None	None	Serious[p]	None
Average clinical score after treatment											
3 studies (Totapally et al., 2002; Patel et al., 2002; Karadag et al., 2008)	n=85	n=69	-	SMD (95%CI): -0.27 (-0.86 to 0.32)[a]	Very low	RCT	Serious[l, r]	Serious	None	Serious[p]	None
No improvement in clinical score (dichotomous)											
1 (Lines et al., 1990)	4/26 (15.4%)	19/23 (8.3%)	RR (95%CI): 0.19 (0.07 to 0.47)[a]	-	Moderate	RCT	Serious[z]	None	None	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Albuterol/Salbutamol	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Change in oxygen saturation (outpatients)											
At 30 minutes											
4 studies (Gadomski et al., 1994 and Gadomski et al., 1994b; Klassen et al., 1991; Anil et al., 2010 0.9%* saline, 3%** saline)	n=167	n=165	-	SMD (95%CI): 0.17 (-0.05 to 0.39)[a]	Moderate	RCT	Serious[f, h]	None	None	None	None
At 60 minutes											
5 studies (; Gadomski et al., 1994 and Gadomski et al., 1994b; Can et al., 1998; Klassen et al., 1991; Anil et al., 2010 0.9%* saline, 3%** saline)	n=219	n=217	-	SMD: 0.02 (-0.17 to 0.21))[a]	Low	RCT	Very serious[f,k,s]	None	None	None	None
At 120 minutes											
1 studies (; Anil et al., 2010 0.9%* saline, 3%** saline)	n=72	n=74	-	MD (95%CI): 0.20 (-0.23 to 0.63) a	Low	RCT	Very serious	None	None	None	None
Average after treatment (time point not reported)											
3 studies (Ralston et al., 2005; Ipek et al., 2011; Khashabi et al., 2005)	n=77	n=79	-	MD (95%CI): 0.25 (-1.07 to 1.57)[a]	Low	RCT	Serious[b, g]	None	Serious[k]	None	None
After dose 1 (change from baseline)											
1 (Schuh et al., 1990)	n=21 Mean (SD): 0.71 (1.4)	n=19 Mean (SD): -0.47 (1.3)	-	p=0.01i MD (95%CI):	Low	RCT	Serious [e]	None	Serious [i]	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Albuterol/Salbutamol	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
				1.18 (0.34 to 2.02)a							
After dose 2 (change from baseline)											
1 (Schuh et al., 1990)	n=21 Mean (SD): 0.76 (0.18)	n=19 Mean (SD): -0.79 (3.49)	-	p=0.015i MD (95%CI): 1.55 (-0.02 to 3.12)a	Very low	RCT	Serious [e]	None	Serious [i]	Serious [u]	None
Change in oxygen saturation (inpatients)											
30 minutes (change from baseline)											
1 (Chevallier et al., 1995)	n=16 Mean (SD): 1.3 (0.2)	n=17 Mean (SD): -0.9 (0.1)	-	MD (95%CI): 2.20 (2.09 to 2.31)a	Moderate	RCT	Serious [q]	None	None	None	None
150 minutes (change from baseline)											
1 (Chevallier et al., 1995)	n=16 Mean (SD): 1.4 (0.3)	n=17 Mean (SD): -1.1 (0.2)	-	MD (95%CI): 2.50 (2.32 to 2.68)a	Moderate	RCT	Serious [q]	None	None	None	None
At 24 hours (endpoint)											
1 (Dobson et al., 1998)	n=23 Mean (SD): 93.2 (7.83)	n=29 Mean (SD): 93.5 (6.04)	-	MD (95%CI): -0.30 (-4.18 to 3.58)a	Low	RCT	Serious [n]	None	None	Serious [p]	None
After treatment (time point not reported)											
5 studies (Totapally et al., 2002; Patel et al., 2002; Lines et al., 1990; Karadag et al., 2008; Ho et al., 1991)	n=124	n=100	-	MD (95%CI): 0.43 (-1.55 to 2.41)a	Very low	RCT	Very serious [l, r, z, aa]	Very serious [ab]	None	Very serious [o]	None
Adverse events (outpatients)											
Flushing of the face at 60 minutes											
1 (Gadomski et al., 1994b)	3/19	0/18	RR (95%CI):	-	Very low	RCT	Serious [f]	None	None	Very serious [d]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Albuterol/Salbutamol	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			6.65 (0.37 to 120.36)a								
Hyperactivity											
1 (Gadomski et al., 1994b)	2/19	0/18	RR (95%CI): 4.75 (0.24 to 92.65)a	-	Very low	RCT	Serious [f]	None	Serious [j]	Very serious [d]	None
More coughing											
1 (Gadomski et al., 1994b)	0/19	1/18	RR (95%CI): 0.32 (0.01 to 7.30)a	-	Very low	RCT	Serious [f]	None	Serious [j]	Very serious [d]	None
Tremor											
1 (Gadomski et al., 1994b)	0/19	0/18	NC	-	Low	RCT	Serious [f]	None	Serious [j]	NC	None
Sustained heart rate >200 beats per minute for more than 30 minutes											
1 (Ralston et al., 2005)	2/23	0/25	RR (95%CI): 5.42 (0.27 to 107.20)a	-	Low	RCT	None	None	None	Very serious [d]	None

NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, p-value, RR relative risk
** Inhalation of salbutamol 2.5mg diluted to 4ml with 0.9% saline solution*
*** Inhalation of salbutamol 2.5mg diluted to 4ml with 3% saline solution*
a Calculated by the NCC-WCH technical team from data reported in the article b Khashabi: method of randomisation not described
c Serious imprecision when 95% CI crosses one default MID.d Very serious imprecision when 95% CI crosses two default MID.e Schuh: unclear definition of bronchiolitis
f Gadomski 1994b: 5 withdrawals (reasons explained)
g Ipek: randomisation according to consecutive order of admission
h Klassen: bronchiolitis not clearly defined
i Schuh: 4 subjects, 3/21 from albuterol group and 1/19 from placebo group received albuterol before arrival at the emergency department
j Gadomski: infants whose condition did not improve after 60 mins were given additional albuterol, time point of this measurement not reported
k Ipek: 26.7% and 37.7% (salbutamol, placebo respectively) received corticosteroid- the decision of corticosteroid use was made when clinical score deteriorated and/or arterial oxygen saturation detected <85%on room air after treatment
lPatel: 10 withdrawn during the study (reasons not provided)
m As reported in the study
n Dobson: Randomisation method not described, 6 subjects with incomplete outcome data (withdrawals explained)
o Very serious imprecision when 95% CI crosses two default MID.p Serious imprecision when 95% CI crosses one default MID.
q Chevallier: randomisation method and allocation concealment not described in detail

r Small sample size
s Can: randomisation and concealment not described, unclear definition of bronchiolitis
t Very serious heterogeneity: I2 =82%
u Serious imprecision when 95% CI crosses one default MID.
vVery serious heterogeneity: I=90%
w Very serious heterogeneity: I2=78%
x Goh: Randomisation and concealment of allocation not described in detail
y I2=59%
z Lines: randomisation method not described, unclear definition of bronchiolitis
aa Ho: randomisation not described, unclear definition of bronchiolitis
ab Very serious heterogeneity: I=91%

Table 44: GRADE profile for comparison of terbutaline with placebo

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Terbutaline	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Length of stay (inpatients)											
1 (Tinsa et al., 2009)	n=16 Mean (SD): 3.3 (1.99)	n=19 Mean (SD): 2.57 (1.99)	-	MD (95%CI): 0.73 (-0.58 to 2.04)[a]	Moderate	RCT	None	None	None	Serious[b]	None
Respiratory rate (inpatients)											
30 minutes (endpoint)											
1 (Tinsa et al., 2009)	n=16 Mean (SD): 54.2 (13.4)	n=19 Mean (SD): 59.8 (15.5)	-	MD (95%CI): -5.6 (-15.18 to 3.98)[a]	Moderate	RCT	None	None	None	Serious[c]	None
60 minutes (endpoint)											
1 (Tinsa et al., 2009)	n=16 Mean (SD): 54.3 (13.5)	n=19 Mean (SD): 56.1 (13.3)	-	MD (95%CI): -1.8 (-10.72 to 7.12)[a]	Low	RCT	None	None	None	Very serious[d]	None
120 minutes (endpoint)											
1 (Tinsa et al., 2009)	n=16 Mean (SD): 50.8 (12.8)	n=19 Mean (SD): 50 (9.6)	-	MD (95%CI): 0.80 (-6.81 to 8.41)[a]	Low	RCT	None	None	None	Very serious[d]	None
Clinical score (inpatients)											
30 minutes (endpoint)											
1 (Tinsa et al., 2009)	n=16 Mean (SD): 6.73 (2.5)	n=19 Mean (SD): 6.5 (0.7)	-	MD (95%CI): 0.23 (-1.03 to 1.49)[a]	Low	RCT	None	None	None	Very serious[d]	None
60 minutes (endpoint)											

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Terbutaline	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Tinsa et al., 2009)	n=16 Mean (SD): 6.05 (2.8)	n=19 Mean (SD): 5.5 (1)	-	MD (95%CI): 0.55 (-0.89 to 1.99)[a]	Moderate	RCT	None	None	None	Serious[b]	None
120 minutes (endpoint)											
1 (Tinsa et al., 2009)	n=16 Mean (SD): 4.7 (2.4)	n=19 Mean (SD): 4.6 (1.3)	-	MD (95%CI): 0.10 (-1.21 to 1.41[a]	Low	RCT	None	None	None	Very serious[d]	None
Oxygen saturation (inpatients)											
30 minutes (endpoint)											
1 (Tinsa et al., 2009)	n=16 Mean (SD): 96.1 (2.1)	n=19 Mean (SD): 95.5 (1.8)	-	MD (95%CI): 0.60 (-0.71 to 1.91)[a]	Moderate	RCT	None	None	None	Serious[b]	None
60 minutes (endpoint)											
1 (Tinsa et al., 2009)	n=16 Mean (SD): 96.8 (1.9)	n=19 Mean (SD): 96 (2.04)	-	MD (95%CI): 0.80 (-0.51 to 2.11)[a]	Moderate	RCT	None	None	None	Serious[b]	None
120 minutes (endpoint)											
1 (Tinsa et al., 2009)	n=16 Mean (SD): 97.2 (1.5)	n=19 Mean (SD): 97 (1.3)	-	MD (95%CI): 0.20 (-0.74 to 1.14)[a]	Low	RCT	None	None	None	Very serious[d]	None

NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, P p-value, RR relative risk
a Calculated by the technical team from data reported in the article
b Serious imprecision when 95% CI crosses one default MID.
c Serious imprecision when 95% CI crosses one default MID.
d Very serious imprecision when 95% CI crosses two default MID.

Table 45: GRADE profile for comparison of ipratropium bromide with placebo

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Ipratropium bromide	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Length of stay in days (inpatients)											
2 studies (Chowdhury et al., 1995; Karadag et al., 2008)	n=45	n=33	-	MD (95%CI): 0.22 (-0.37 to 0.81)[a]	Moderate	RCT	None	None	None	Serious[b]	None
Change in disease severity score (inpatients)											
Day 1 (endpoint)											
1 (Goh et al.,	n=30	n=29	-	MD	Low	RCT	Serious[c]	None	None	Serious[d]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Ipratropium bromide	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1997)	Mean (SD): 7.3 (1.9)	Mean (SD): 8 (2.5)		(95%CI): -0.70 (-1.84 to 0.44)[a]							
Day 2 (endpoint)											
1 (Goh et al., 1997)	n=30 Mean (SD): 4.6 (1.9)	n=29 Mean (SD): 4.4 (2.4)	-	MD (95%CI): 0.20 (-0.91 to 1.31)[a]	Low	RCT	Seriousc	None	None	Serious[b]	None
Day 3 (endpoint)											
1 (Goh et al., 1997)	n=30 Mean (SD): 3.4 (1.8)	n=29 Mean (SD): 3.1 (1.8)	-	MD (95%CI): 0.30 (-0.62 to 1.22)[a]	Low	RCT	Serious[c]	None	None	Serious[b]	None
No improvement in clinical score (dichotomous)											
1 (Lines et al., 1992)	5/17 (29.4%)	7/14 (50%)	RR (95%CI): 0.59 (0.24 to 1.45)[a]	-	Very low	RCT	Very serious[e]	None	None	Very serious[f]	None
Average clinical score after treatment (endpoint)											
1 (Karadag et al., 2008)	n=22 Mean (SD): 4.9 (1.8)	n=11 Mean (SD): 5.3 (1.4)	-	MD (95%CI): -0.40 (-1.52 to 0.72)a	Moderate	RCT	None	None	None	Serious [d]	None
Oxygen saturation (inpatients)											
Time point not reported											
2 studies (Lines et a., 1992; Karadag et al., 2008)	n=39	n=25	-	MD (95%CI): 1.01 (0.66 to 1.36)[a]	Very low	RCT	Very serious[e]	None	None	Serious[b]	None
Adverse events (inpatients)											
Tachycardia and persistent coughing											
1 (Henry et al., 1983)	2/34 (5.9%)	0/32 (0%)	RR (95%CI): 4.71 (0.23 to 94.58)[a]	-	Very low	RCT	Seriousg	None	None	Very serious[f]	None

NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, p-value, RR relative risk
a Calculated by the technical team from data reported in the article
b Serious imprecision when 95% CI crosses one default MID.
c Goh: randomisation and concealment of allocation not described in detail
d Serious imprecision when 95% CI crosses one default MID.e Lines: randomisation and allocation concealment not clearly described, unclear definition of bronchiolitis
f Very serious imprecision when 95% CI crosses two default MID.
g Henry: randomisation and concealment of allocation not described

Table 46: GRADE profile for comparison of salbutamol and ipratropium bromide (all subjects received both bronchodilators) with placebo

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Salbutamol and Ipratropium bromide	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Length of stay in days (inpatients)											
1 (Chowdhury et al., 1995)	n=24 Mean (SD): 4.6 (1.4)	n=22 Mean (SD): 4.3 (1.1)	-	MD (95%CI): 0.30 (-0.42 to 1.02)[a]	Low	RCT	None	None	Serious[b]	Serious[c]	None

NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, p-value, RR relative risk
a Calculated by the technical team from data reported in the article
b Combined bronchodilator treatment (salbutamol and ipratropium bromide)
c Serious imprecision when 95% CI crosses one default MID.

Table 47: GRADE profile for comparison of salbutamol/ipratropium bromide/salbutamol and ipratropium bromide with placebo

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Bronchodilator	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Change in disease severity score (inpatients)											
30 minutes (median change)											
1 (Chowdhury et al., 1995)	Salbutamol n= 20 Median (range): 3 (1.25 to 4.75) Ipratropium bromide n= 23 Median (range): 2 (1 to 3) Salbutamol and ipratropium bromide n= 24 Median (range): 2 (1 to 3)	n=22 Median (range): 2 (1 to 3)	-	p=0.23[a]	Moderate	RCT	None	None	Serious[b]	NC	None
60 minutes (median change)											
1 (Chowdhury et al., 1995)	Salbutamol n= 20 Median (range):	n=22 Median (range):	-	p=0.93[a]	Moderate	RCT	None	None	Serious[b]	NC	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Bronchodilator	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
	2.5 (1 to 4) Ipratropium bromide n= 23 Median (range): 3 (1 to 4) Salbutamol and ipratropium bromide n= 24 Median (range): 2.5 (1.25 to 3.75)	2.5 (1 to 4)									
6 hours (median change)											
1 (Chowdhury et al., 1995)	Salbutamol n= 20 Median (range): 2.5 (1 to 4.75) Ipratropium bromide n= 23 Median (range): 2 (2 to 5) Salbutamol and ipratropium bromide n= 24 Median (range): 3 (1 to 5)	n=22 Median (range): 2.5 (2 to 3.25)	-	p= 0.92[a]	Moderate	RCT	None	None	Serious[b]	NC	None
12 hours (median change)											
1 (Chowdhury et al., 1995)	Salbutamol n= 20 Median (range): 3.5 (2 to 6) Ipratropium bromide n= 23 Median (range): 2 (2 to 4) Salbutamol and ipratropium	n=22 Median (range): 2.5 (1.75 to 4.25)	-	p=0.54[a]	Moderate	RCT	None	None	Serious[b]	NC	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Bronchodilator	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
	bromide n= 24 Median (range): 4 (2 to 4.75)										
24 hours (median change)											
1 (Chowdhury et al., 1995)	Salbutamol n= 20 Median (range): 2.5 (1.25 to 4.5) Ipratropium bromide n= 23 Median (range): 4 (1 to 6) Salbutamol and ipratropium bromide n= 24 Median (range): 4 (2 to 4.75)	n=22 Median (range): 2.5 (1.75 to 4)	-	p=0.58[a]	Moderate	RCT	None	None	Serious[b]	NC	None
36 hours (median change)											
1 (Chowdhury et al., 1995)	Salbutamol n= 20 Median (range): 4.5 (3 to 6) Ipratropium bromide n= 23 Median (range): 5 (2 to 7) Salbutamol and ipratropium bromide n= 24 Median (range): 4 (2.25 to 5.75)	n= Median (range): 3 (1.75 to 5)	-	p= 0.49[a]	Moderate	RCT	None	None	Serious[b]	NC	None

NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, p-value, RR relative risk
a As reported in the study
b Combined bronchodilator treatment

4.2.5.6 Evidence statements

4.2.5.6.1 Epinephrine versus placebo

Hospital admissions

Four RCTs three of which were in outpatients with 523 children and one of which was in inpatients with 194 children, found that there is no difference in admission or readmission rates in infants treated with epinephrine compared to infants treated with placebo. The quality of evidence was low to very low.

Length of stay

Four RCTs, three of which were in inpatients with 696 children and one of which was in outpatients with 398 children, found that there is no difference in length of stay in infants treated with epinephrine compared to infants treated with placebo. The quality of evidence was moderate to low.

Change in respiratory rate

One RCT with 48 children performed in outpatients found that respiratory rate after treatment (time point not reported) was lower in infants treated with epinephrine compared to infants treated with placebo. The quality of evidence was moderate. However, one other RCT also performed in outpatients with 398 children found no difference in respiratory rate at any of the time points that were recorded. The quality of evidence was high.

Change in disease severity score

Two studies with 549 children showed no difference between the groups at any of the time points that were recorded. The quality of the evidence was low to very low. One other RCT with 48 children found that clinical score after treatment was better in infants treated with epinephrine compared to infants treated with placebo, however the time point was not reported. The quality of evidence was moderate.

One RCT performed in inpatients with 194 children found that clinical score at both 30 and 60 minutes were better in infants treated epinephrine compared to infants treated with placebo. The quality of evidence was moderate to low.

Change in oxygen saturation

One RCT with 549 children performed in outpatients found that oxygen saturation after treatment was better in infants treated with epinephrine compared to infants treated with placebo, however the time point was not reported. The quality of the evidence was moderate. One other study with 48 children found no difference in oxygen saturation at any of the time points recorded. The quality of evidence was high to very low.

Need for high flow humidified oxygen, CPAP or mechanical ventilation

Two RCTs with 575 children performed in inpatients found that there is no difference in the number requiring high flow humidified oxygen (reported as number requiring supplemental oxygen). One of these RCTs also found that there is no difference in the number requiring ventilatory support in infants treated with epinephrine compared to infants treated with placebo. The quality of evidence was very low.

Need for/Use of feeding support

One RCT with 194 children performed in inpatients found that the need for/use of feeding support (reported as number requiring oxygen and intravenous feeding) was lower in infants treated with epinephrine compared to infants treated with placebo. The quality of evidence was moderate. However, one other RCT with 404 children in inpatients found no difference in the number requiring nasogastric tube feeding. The quality of evidence was very low.

One RCT performed in outpatients with 398 children found that the need for/use of feeding support (reported as time to return to normal feeding in days) was quicker in infants treated with epinephrine compared to infants treated with placebo. The quality of evidence was moderate.

Adverse effects

One RCT with 398 children found no difference in adverse events (tremor, pallor, vomiting, varicella, dark stools, hypertension or hyperkalemia) in infants treated with epinephrine compared to infants treated with placebo. The quality of evidence was moderate to very low.

4.2.5.6.2 Albuterol/salbutamol versus placebo

Hospital admissions

Six RCTs, all of which were in outpatients with 343 children, found that there is no difference in admission rates in infants treated with albuterol/salbutamol compared to infants treated with placebo. The quality of evidence was very low to low.

Length of stay

Four RCTs, all of which were in inpatients with 229 children found that there is no difference in length of stay in infants treated with albuterol/salbutamol compared to infants treated with placebo. The quality of evidence was moderate.

Change in respiratory rate

One RCT performed in outpatients with 40 children found that respiratory rate after dose 2 of treatment showed a bigger percentage decrease in infants treated with albuterol/salbutamol compared to infants treated with placebo. The quality of evidence was low. However, the same study plus five other RCTs with 294 children found no difference in respiratory rate at any of the other time points recorded. The quality of evidence was moderate to very low.

One RCT performed in inpatients with 33 children found that respiratory rate showed a bigger percentage decrease in infants treated with albuterol/salbutamol at both 30 and 150 minutes. The quality of evidence was moderate. However, one other RCT with 19 children also in inpatients found no difference in respiratory rate between the groups (time point was not reported). The quality of evidence was very low.

Change in disease severity score

Four RCTs with 239 children found that average clinical score after treatment (time point not reported) was better in infants treated with albuterol/salbutamol compared to infants treated with placebo. The quality of the evidence was very low. Four other studies with 353 children showed no difference between the groups at any other time points that were recorded. The quality of evidence was very low.

One RCT performed in inpatients with 49 children found that the percentage of subjects with no improvement in clinical score was higher in infants treated with albuterol/salbutamol compared to infants treated with placebo. The quality of the evidence was moderate.

However, four other RCTs with 213 children also performed in inpatients found no difference in clinical score between the groups at any of the time points recorded. The quality of evidence was low to very low.

Change in oxygen saturation

One RCT performed in outpatients with 40 children found that oxygen saturation after both dose 1 and 2 of treatment showed a bigger increase in infants treated with albuterol/salbutamol compared to infants treated with placebo. The quality of evidence was low to very low. Eight other studies with 592 children found no difference in oxygen saturation at any of the time points recorded. The quality of evidence was moderate to very low.

One RCT performed in inpatients with 33 children found that oxygen saturation at both 30 and 150 minutes showed a bigger increase in infants treated with albuterol/salbutamol compared to infants treated with placebo. The quality of evidence was moderate. However, six other RCTs with 276 children found no difference between the groups at any of the time points recorded. The quality of evidence was low to very low.

Adverse effects

Two RCTs with 85 children found no difference in adverse events (flushing of the face at 60 minutes, hyperactivity, more coughing and tremor in the first study and sustained heart rate >200 beats per minutes for more than 30 minutes in the second study) in infants treated with albuterol/salbutamol compared to infants treated with placebo. The quality of evidence was low to very low.

4.2.5.6.3 Terbutaline versus placebo

One RCT performed in inpatients with 35 children found no difference in length of stay, respiratory rate, clinical score or oxygen saturation in infants treated with terbutaline compared to infants treated with placebo. The quality of evidence was moderate to low. No data was identified for the remaining outcomes including need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation, need for/use of feeding support (tube feeding, IV fluids) or adverse effects (including mortality).

4.2.5.6.4 Ipratropium bromide versus placebo

Length of stay

Two RCTs with 78 children, both of which were in inpatients, found that there is no difference in length of stay in infants treated with ipratropium bromide compared to infants treated with placebo. The quality of evidence was moderate.

Change in disease severity score

Three RCTs with 123 children performed in inpatients found no difference in clinical score in infants treated with ipratropium bromide compared to infants treated with placebo. The quality of evidence was moderate to very low.

Change in oxygen saturation

Two RCTs with 64 children performed in inpatients found oxygen saturation was better in infants treated with ipratropium bromide compared to infants treated with placebo (time point not reported). The quality of evidence was very low.

Adverse effects

One RCT with 66 children found no difference in adverse events (tachycardia and persistent coughing) in infants treated with ipratropium bromide compared to infants treated with placebo at any of the time points recorded. The quality of evidence was very low.

4.2.5.6.5 Salbutamol and ipratropium bromide (all subjects received both bronchodilators) versus placebo

Length of stay

One RCT performed in inpatients with 46 children found no difference in length of stay in infants treated with both salbutamol and ipratropium bromide compared to infants treated with placebo. The quality of evidence was low.

4.2.5.6.6 Salbutamol or ipratropium bromide or salbutamol and ipratropium bromide (separate analyses) versus placebo

One RCT performed in inpatients with 42 children found no difference in clinical score at 30 minutes, 60 minutes, 6 hours, 12 hours, 24 hours and 36 hours in infants treated with salbutamol or ipratropium bromide or salbutamol and ipratropium bromide compared to infants treated with placebo. The quality of evidence was moderate.

4.2.5.7 Evidence to recommendations

The evidence to recommendations covering the clinical and cost effectiveness of inhaled bronchodilators is presented in section 4.2.10.

4.2.5.8 Recommendations

The recommendations covering the clinical and cost effectiveness of inhaled bronchodilators is presented in section 4.2.12.

4.2.6 Inhaled corticosteroids

4.2.6.1 Review questions

What is the efficacy of inhaled corticosteroid therapy?

4.2.6.2 Introduction

Swelling of the lining of the airways in bronchiolitis is caused by inflammation resulting from the viral infection. Corticosteroids work by reducing inflammation so it has been suggested that these treatments may help reduce the swelling and relieve respiratory distress. Although the side effects for inhaled are considerably less than for systemic corticosteroids, they can cause problems in high dosage including growth and adrenal suppression. More common local side effects include hoarseness and throat irritation.

4.2.6.3 Description of included studies

Two RCTs were identified of inhaled corticosteroids (Budesonide) compared with placebo (Cade et al., 2000; Richter et al., 1998). Two trials allowed additional treatment (Cade et al., 2000; Richter et al., 1998). Two trials were of inpatients (Cade et al., 2000; Richter et al., 1998). Both the trials included only children aged under 1 year and both undertaken in the UK (Cade et al., 2000; Richter et al., 1998). Definition of Bronchiolitis varied between RSV to clinical symptoms and signs. Sample size ranged from 40 to 165.

Treatment regimens varied between the studies: twice daily dose (1 mg) of nebulised Budesonide for 14 to 21 days (Cade et al., 2000); to 1 mg/2mL of nebulised Budesonide twice daily for 5 days then 0.5 mg/2 mL 2 x daily for a further 6 weeks (Richter et al., 1998). The duration of studies varied from 28 days (Cade et al, 2000) or 6 weeks (Richter et al., 1998).

A Cochrane review was identified that covered this area. However, it could not be used in the review as it combined inhaled and systemic corticosteroids, and did not assess all the outcomes identified by the GDG.

The studies did not report data on all these outcomes and in some situations other outcomes are presented. More details on each individual study can be found in the evidence tables.

4.2.6.4 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 48: GRADE profile for inhaled corticosteroids compared with placebo for bronchiolitis in children.

Table 48: GRADE profile for inhaled corticosteroids compared with placebo for bronchiolitis in children

Number of studies	Number of children		Effect		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
	Inhaled corticosteroids	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Hospital admission rate											
Length of hospital stay (days)											
1 (Cade et al, 2000)	Median 2 (IQR 1 to 3)	Median 2 (IQR 1 to 4)	Hazard Ratio 1.10 (0.80 to 1.51)g	NC	Very low	RCT	Serious[b]	None	Serious[c]	Very serious[a]	None
1 (Richter et al, 1998)	Median 2 (range 1 to 11)	Median 3 (range 1 to 7)	p = 0.65 [f]	NC	Very low	RCT	Serious[d]	None	Serious[c]	None	None
Change in disease severity score at 1 to 7 days after starting treatment											
At 48 hours											
1 (Richter et al, 1998)	Median – 2.0 (-6 to +6)	Median – 1.0 (-9 to +2)	p = 0.92 [f]	NC	Low	RCT	Serious[c]	None	Serious[c]	None	None
Change in O2 saturation											
Duration of cough – Not reported											
Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation – Not reported											
Readmission											
Readmission for respiratory symptoms within 12 months											
2 (Cade et al, 2000; Richter et al, 1998)	23/102	16/98	RR: 1.85 [0.36, 9.53]	NC	Very low	RCT	Serious[b, d]	Serious	Serious[c]	Very serious[a]	None
Adverse effects (including mortality) – Not reported											

NC not calculable, RCT randomised controlled trial, RR relative risk, MD mean difference, SMD Standardised Mean Difference, p-value
a Very serious imprecision when 95% CI crosses two default MID.
b Cade – Method of randomisation and concealment not described in detail
c Cade and Richter allowed additional treatment with bronchodilators
d Richter - Method of randomisation and concealment not described in detail
e Groups not balanced at baseline
f As reported by authors

4.2.6.5 Evidence statements

Two RCTs showed no difference in admission rates, readmission rates, length of stay and clinical score for infants receiving inhaled corticosteroids compared to infants receiving placebo. The quality of the evidence was low to very low.

Oxygen saturation

No studies reported data on this outcome

Duration of cough

No studies reported data on this outcome

Supplemental oxygen

No studies reported data on this outcome

Adverse events

No studies reported data on this outcome

4.2.6.6 Evidence to recommendations

The evidence to recommendations covering the clinical and cost effectiveness of inhaled corticosteroids is presented in section 4.2.10.

4.2.6.7 Recommendations

The recommendations covering the clinical and cost effectiveness of inhaled corticosteroid therapy are presented in section 4.2.12.

4.2.7 Systemic corticosteroids

4.2.7.1 Review questions

What is the efficacy of systemic corticosteroid therapy?

4.2.7.2 Introduction

The swelling of the lining of the airways in bronchiolitis is caused by inflammation resulting from the viral infection. Corticosteroids work by reducing inflammation so it has been suggested that this treatment may help reduce the swelling and relieve respiratory distress. Side effects of systemic corticosteroids can be considerable and include impaired resistance to infection, growth retardation, adrenal suppression, altered bone metabolism, and others.

4.2.7.3 Description of included studies

Four RCTs were identified that investigated systemic corticosteroids (dexamethasone) compared to placebo (Corneli et al, 2007; Plint et al., 2009; Roosevelt et al., 1996; Teeratakulpisarn et al., 2007). Four studies allowed additional treatment at the discretion of the health professional (Corneli et al., 2007; Plint et al., 2009; Roosevelt et al., 1996; Teeratakulpisarn et al., 2007), but only two of these reported the results of this (Corneli et al, 2007; Teeratakulpisarn et al., 2007).

Three trials the population only included children under 1 year of age (Plint et al, 2009 [median months: 5, IQR 3-7]; Corneli et al, 2007 [mean months: 5.1, SD ± 2.8]; Roosevelt et al, 1996 [mean months: 5.3, SD ± 3.7]), with one study including some infants over 1 year of age (Teeratakulpisarn et al., 2007 [mean months: 11.2, SD ± 5.9]). Duration of studies ranged from 10 days (Corneli et al, 2007), 14 days (Roosevelt et al., 1996), 22 days (Plint et al., 2009), to 1 month (Teeratakulpisarn et al., 2007).

Two trials were performed in outpatient settings (Corneli et al., 2007; Plint et al., 2009), most frequently paediatric emergency departments. The remaining trials were performed in inpatient settings (Roosevelt et al., 1996; Teeratakulpisarn et al., 2007). The definition of Bronchiolitis varied, with studies using presence of RSV or clinical symptoms and signs.

Treatments regimen ranged from: single oral dose (1 mL/kg (max 12 mg); oral solution (1 mg/mL) of liquid. (Corneli et al, 2007); intra-muscular injection of dexamethasone (1 mg/kg) every 24 hours for max 3 doses (Roosevelt et al., 1996); oral dose of dexamethasone (1.0 mg/kg weight (max 10 mg) then 0.6 mg/kg (max 10 mg) after ED) one dose at ED and daily dose for 5 days after. (Plint et al, 2009; and single intra-muscular injection of dexamethasone (0.6 mg/kg).(Teeratakulpisarn et al., 2007)

Two of the studies were undertaken in the USA (Corneli et al, 2007; Roosevelt et al, 1996), one in Canada (Plint et al, 2009), one in Thailand (Teeratakulpisarn et al., 2007). The sample size ranged from 90 to 800 infants.

A Cochrane review was identified that covered this area. However, it could not be used in the review as it combined inhaled and systemic corticosteroids, and did not assess all the outcomes identified by the GDG.

4.2.7.4 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 49: GRADE profile for Systemic corticosteroids compared with placebo for bronchiolitis in children.

Table 49: GRADE profile for systemic corticosteroids compared with placebo for bronchiolitis in children

Number of studies	Number of children		Effect		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
	Systemic corticosteroids	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Hospital admission rate											
Hospital admissions by day 1											
2 studies (, Corneli et al, Plint et al., 2009)	152/504	157/496	RR: 0.95 (0.80 to 1.14)[a]	NC	Low	RCT	Serious [b]	None	Serious[c]	None	None
Hospital admissions by day 7 (Includes admissions on day 1 i.e. cumulative admissions to day 7)											
2 studies, (Corneli et al, Plint et al., 2009)	184/483	184/466	RR: 0.95 (0.82 to 1.11)[a]	NC	Low	RCT	Serious[b]	None	Serious[c]	None	None
Hospital readmission rate											
Hospital readmissions within 10 to 30 days											
2 (Roosevelt et al., 1996; Teeratakulpisarn et al, X)	3/134 (2.2%)	7/138 (5.1%)	RR: 0.41 [0.11, 1.53][a]	-	Very low	RCT	Serious[d]	None	Serious[c]	Very serious[e]	None
Return healthcare visits within 10 to 30 days (inpatient studies – infants admitted to hospital)											
2 (Roosevelt et al., 1996; Teeratakulpisarn)	33/154 (21.4%)	31/138 (22.5%)	RR: 1.21 (0.3 to 4.96)[a]	NC	Very low	RCT	Serious[d]	None	Serious[c]	Very serious[e]	None
Return healthcare visits within 10 to 30 days (outpatient studies – children seen in emergency department but not admitted)											
1 (Plint et al., 2009)	106/199	86/200	RR: 1.24 [1.01, 1.52][a]	NC	Low	RCT	Serious[b]	None	Serious[c]	None	None
Length of hospital stay											
Length of hospital stay (inpatient studies – infants admitted to hospital) [better indicated by lower values]											

Number of studies	Number of children		Effect		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
	Systemic corticosteroids	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)							
1 (Teerataku lpisarn et al., 2007)	-	-	NC	MD: -0.56 [-1.01, -0.11][a]	Moderate	RCT	None	None	Serious[c]	None	none
1 (Zhang et al, 2003)	Median 6.0 (5.3 to 8.3)	Median 5.0 (4.8 to 7.5)	p = 0.70	NC	Low	RCT	Serious[f]	None	Serious[g]	None	
1 (Roosevelt et al., 1996			NC	Hazard Ratio: 1.3 (0.9 to 1.3) p = 0.22	Low	RCT	Serious[d]	None	Seriousc	None	None
Length of hospital stay (outpatient studies – children seen in emergency department but not admitted) [better indicated by lower values]											
1 (Corneli 2007)	-	-	NC	MD: 0.28 [-0.05, +0.61][a]	Low	RCT	None	None	Serious[c]	Serious[e]	None
Change in clinical scores at 3 to 10 days [better indicated by lower values]											
At 60 mins											
1(Plint et al, 2009)	-	-	NC	MD: -0.10 (-0.57 to 0.37)a	Very low	RCT	Seriousb	None	Very seriousc	Very serious[e]	None
At 3 to 6 hours											
1 (; Corneli et al, 2007)	-	-	NC	MD: -0.50 (-1.25 to 0.25)[a]	Very low	RCT	None	None	Very Serious[c]	Very serious[e]	None
Change in oxygen saturation at 3 to 6 hours [better indicated by higher values]											
At 60 minutes											
1 (; Plint et al, 2009)			NC	MD: -0.25 (-0.82 to 0.32)[a]	Very low	RCT	Very serious, [b]	None	Very Serious[c]	Serious[e]	None
At 3 to 6 hours											
1 (; Corneli et al, 2007)			NC	MD: -0.60 (-1.12 to -0.08)[a]	Low	RCT	None	None	Very Serious[c]	None	None
Duration of cough – not reported											
Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation – not reported											
Received oxygen											
1 (Teerataku	66/89	67/85	RR: 0.77 [0.38, 1.56][a]	NC	Very Low	RCT	None	None	Serious[c]	Very serious[e]	None

Number of studies	Number of children		Effect		Quality	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
	Systemic corticosteroids	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)							
Ipisarn et al, X)											
Adverse events											
Vomiting within 20 minutes of medication											
1 (Corneli et al, 2007)	17/304	14/294	NC	RR: 1.18 [0.57, 2.45][a]	Very Low	RCT	None	None	Serious[c]	Very serious[e]	None
GI bleeding, hypertension, pneumonia or complicated caricella											
2 (Corneli et al, 2007; Roosevelt et al, 1996)	20/673	17/641	NC	RR: 0.89 [0.17, 4.49][a]	Very Low	RCT	Serious[d]	None	Serious[c]	Serious[e]	None
Mortality - not reported											

NC not calculable, RCT randomised controlled trial, RR relative risk, MD mean difference, SMD standardised mean difference, p-value
a Calculated by technical team based on data reported in the article
b Plint – treatment variation within protocols
c Plint, Corneli, Roosevelt and Teeretakulpisarn allowed additional treatment, with majority of children being treated with bronchodilators.
d Roosevelt – method of randomisation and concealment not explained
e Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.
f Single blinded
g Usual care rather than placebo

4.2.7.5 Evidence statements

Hospital admission rate

Four RCTs with 1292 children found that there is no difference in admission rates, need for oxygen support or adverse events between infants treated with systemic corticosteroids compared to infants treated with placebo. The quality of evidence was low to very low.

Hospital readmission rate

Inpatient setting

Two studies with 292 children found no difference in readmission to hospital or return to health professionals in infants treated with corticosteroids compared to infants treated with placebo. The quality of the evidence was very low.

Outpatient setting

One study with 400 children found higher rates of returns to health professional with corticosteroids compared to placebo. The quality of the evidence was low.

Length of stay

Inpatient setting

One study with 174 children found that length of stay was significantly shorter in infants treated with corticosteroids compared to infants treated with placebo. The quality of the evidence was moderate. Two studies with 170 children found no difference in length of stay. The quality of the evidence was low.

Outpatient setting

One study with 600 children found no difference in length of stay in infants treated with corticosteroids compared to infants treated with placebo. The quality of the evidence was low.

Change in clinical score at 3 to 10 days

Two studies with 1000 children found no difference in clinical score at any of the time points recorded. The quality of the evidence was low.

Change in oxygen saturation at 3 to 6 hours

One study with 600 children showed oxygen saturation was reduced between 3 and 6 hours following the administration of corticosteroids. The quality of the evidence was low.

Adverse events

Two studies with 718 children found no difference in adverse events. The quality of the evidence was very low.

Duration of cough

No studies reported data on this outcome.

Need for high flow humidified oxygen, CPAP or mechanical ventilation

No studies reported data on this outcome.

4.2.7.6 Evidence to recommendations

The evidence to recommendations covering the clinical and cost effectiveness of systemic corticosteroid therapy is presented in section 4.2.10.

4.2.7.7 Recommendations

The recommendations covering the clinical and cost effectiveness of systemic corticosteroid therapy are presented in section 4.2.12.

4.2.8 Combined bronchodilator and corticosteroid therapy

4.2.8.1 Review question

What is the efficacy of combined bronchodilator and corticosteroid therapy?

4.2.8.2 Description of included studies

Eight RCTs were identified for this review (Bentur et al., 2005; Berger et al., 1998; Goebel et al., 2000; Klassen et al., 1997; Kuyucu et al., 2004; Mesquita et al., 2009; Plint et al., 2009; Schuh et al., 2002). Two studies explicitly examined combined bronchodilator and corticosteroid therapies. (Kuyucu et al., 2004; Plint et al., 2009). The other six studies randomised subjects to corticosteroid or placebo arms but additionally gave all subjects bronchodilator treatment. These studies have therefore been interpreted as combined therapy trials (Bentur et al., 2005; Berger et al., 1998; Goebel et al., 2000; Klassen et al., 1997; Mesquita et al., 2009; Schuh et al., 2002).

Of the eight RCTs identified:

- Six studies investigated combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to bronchodilator plus placebo (Berger et al., 1998; Klassen et al., 1997; Kuyucu et al., 2004; Mesquita et al., 2009; Plint et al., 2009; Schuh et al., 2002)
- One study investigated combined bronchodilator and corticosteroid therapy (both inhaled) compared to bronchodilator plus placebo (Bentur et al., 2005)
- One study investigated combined bronchodilator (systemic/inhaled, although the majority received systemic bronchodilator) and corticosteroid (systemic) therapy (Goebel et al., 2000)
- One study investigated combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to placebo (Plint et al., 2009)
- One study investigated combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to corticosteroid plus placebo (Plint et al., 2009)

The studies examined a range of combined bronchodilator and corticosteroid therapies including albuterol plus prednisolone in three studies (Berger et al., 1998; Goebel et al., 2000), dexamethasone plus epinephrine in four studies, (Bentur et al., 2005; Kuyucu et al., 2004; Mesquita et al., 2009; Plint et al., 2009) and dexamethasone plus salbutamol in three studies (Klassen et al., 1997; Kuyucu et al., 2004; Schuh et al., 2002).

Two studies allowed additional treatment at the discretion of the health professional, for example additional corticosteroids or bronchodilators (Plint et al., 2009; Schuh et al., 2002) but only one of these reported the results of this (Schuh et al., 2002).

Seven studies included children under 1 year of age (Bentur et al., 2005; Berger et al., 1998; Klassen et al., 1997; Kuyucu et al., 2004; Mesquita et al., 2009; Plint et al., 2009; Schuh et al., 2002) and one study included children up to the age of 16 months (Goebel et al., 2000). Six trials were performed in outpatient settings (Berger et al., 1998; Goebel et al., 2000; Kuyucu et al., 2004; Mesquita et al., 2009; Plint et al., 2009; Schuh et al., 2002), most

frequently paediatric emergency departments. The remaining trials were performed in inpatient settings (Bentur et al., 2005; Klassen et al., 1997). The definition of bronchiolitis was explicitly stated in 4 studies (Berger et al., 1998; Kuyucu et al., 2004; Mesquita et al., 2009; Plint et al., 2009), all of which used a definition based on the presence of clinical symptoms and signs.

Three of the studies were undertaken in Canada, (Klassen et al., 1997; Plint et al., 2009; Schuh et al., 2002), one in Turkey (Kuyucu et al., 2004), two in Israel (Bentur et al., 2005; Berger et al., 1998), one in the USA (Goebel et al., 2000) and one in Paraguay (Mesquita et al., 2009). The sample size ranged from 42 to 800 infants.

Two Cochrane reviews were identified that covered this area. However, they could not be used in the review as they undertook different comparisons from those specified by the GDG and did not assess all the outcomes specified by the GDG. The Cochrane review also included some studies which gave all subjects additional bronchodilator in the glucocorticoid versus placebo comparison instead of the combined therapy comparison.

More details on each individual study can be found in the evidence tables.

4.2.8.3 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

Five GRADE profiles have been produced for this review:

- Table 50: GRADE profile for comparison of combined bronchodilator (inhaled) and corticosteroid (systemic) therapy with bronchodilator and placebo
-
- Table ***51***: GRADE profile for comparison of combined bronchodilator and corticosteroid therapy (both inhaled) with bronchodilator and placebo
- Table 52: GRADE profile for comparison of combined bronchodilator (systemic/inhaled) and corticosteroid therapy (systemic) with bronchodilator and placebo
- Table 53: GRADE profile for comparison of combined bronchodilator (inhaled) and corticosteroid (systemic) therapy with placebo
- Table 54: GRADE profile for comparison of combined bronchodilator (inhaled) and corticosteroid (systemic) therapy with corticosteroid and placebo

Table 50: GRADE profile for comparison of combined bronchodilator (inhaled) and corticosteroid (systemic) therapy with bronchodilator and placebo

	Number of children		Effect				Quality assessment				
Number of studies	Combined bronchodilator (inhaled) + corticosteroid (systemic) therapy	Bronchodilator + placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Hospital admissions (outpatients)											
Day 1											
5 studies (Berger et al., 1998; Kuyucu et al., 2004; Mesquita et al., 2009; Plint et al., 2009; Schuh et al., 2002)	43/312 (13.8%)	53/294 (18.0%)	RR: 0.80 (0.49 to 1.33)[a]	-	Very low	RCT	Very serious[b]	None	Very serious[c,d]	Very serious[e]	None
Day 7 (Includes admissions on day 1, i.e. cumulative admissions to day 7)											
3 (Alansari et al., 2013; Bawazeer et al., 2014; Plint et al., 2009)	58/385 (20.4%)	70/366 (25.4%)	RR: 0.80 (0.59 to 1.09)[a]	-	Very low	RCT	None	None	Very serious[c]	Serious[f]	None
Day 22 (Includes admissions on day 1 and 7, i.e. cumulative admissions to day 22)											
1 (Plint et al., 2009)	37/200 (18.5%)	50/199 (25.1%)	RR: 0.74 (0.51 to 1.07)[a]	-	Low	RCT	None	None	Serious[c]	Serious[f]	None
Hospital re-admissions (inpatients)											
1 (Klassen et al., 1997)	4/35 (11.4%)	1/32 (3.1%)	RR: 3.66 (0.43 to 31.03)[a]	p=0.36g	Very low	RCT	Serious[h]	None	None	Very serious[e]	None
Length of hospital stay in days (outpatients)											
1 (Berger et al., 1998)	n=5 Mean (SD): 5 (2.105)	n=2 Mean (SD): 8 (2.828)	-	MD: -3.00 (-7.33 to 1.33)[a]	Very low	RCT	Serious[i]	None	None	Very serious[j]	None
Reported as geometric mean time (95%CI) to readiness for discharge in hours											

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Combined bronchodilator (inhaled) + corticosteroid (systemic) therapy	Bronchodilator + placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1 (Alansari et al., 2013)	n=100 Geometric mean time (95%CI): 18.6 (14.9 to 23.1)	n=90 Geometric mean time (95%CI): 27.1 (21.8 to 33.8)	Ratio of geometric means: 0.69 (0.51 to 0.93)	p=0.015	Low	RCT	None	None	Serious[c]	Serious[f]	None
Length of hospital stay in hours (inpatients)											
1 (Klassen et al., 1997)	n=35 Median (95%CI): 57 (38 to 76)	n=32 Median (95%CI): 48 (42 to 54)	-	p=0.19[g]	Moderate	RCT	Serioush	None	None	NC	None
Change in disease severity score (outpatients)											
30 minutes											
1 (Plint et al., 2009)	n=199 Mean (SD): -1.62 (2.23)	n=198 Mean (SD): -1.44 (1.94)	-	MD: -0.18 (-0.59 to 0.23)[a]	High	RCT	None	None	None	None	None
60 minutes											
2 studies (Mesquita et al., 2009; Plint et al., 2009)	n=232	n=230	-	SMD: -0.02 (-0.20 to 0.16)[a]	High	RCT	None	None	None	None	None
120 minutes											
1 (Kuyucu et al., 2004)	n=46	n=23	-	MD: 0.00 (-0.50 to 0.50)[a]	Moderate	RCT	Serious[k]	None	None	None	None
4 hours											
3 studies (Bawazeer et al., 2014; Mesquita et al., 2009; Schuh et al., 2002)	n=154	n=143	-	SMD: -0.25 (-0.66 to 0.16)[a]	Very low	RCT	Serious[l]	Serious[m]	Serious[n]	Serious[o]	None
24 hours											
1 (Kuyucu et al., 2004)	n=46	n=23	-	MD: -0.49 (-0.99 to 0.02)[a]	Low	RCT	Serious[k]	None	None	Serious[o]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Combined bronchodilator (inhaled) + corticosteroid (systemic) therapy	Bronchodilator + placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
3 to 10 days											
3 studies (Berger et al., 1998; Kuyucu et al., 2004; Schuh et al., 2002)	n=101	n=73	-	SMD: -0.24 (-0.55 to 0.07)[a]	Very low	RCT	Serious[l,k]	Very serious[p]	Serious[n]	Serious[o]	None
Change in disease severity score (inpatients)											
12 hours											
1 (Klassen et al., 1997)	n=35 Mean (SD): -1.3 (2.0)	n=31 Mean (SD): -1.0 (1.8)	-	MD: -0.30 (-1.22 to 0.62)a p=0.51[g]	Low	RCT	Serious[h]	None	None	Serious[o]	None
24 hours											
1 (Klassen et al., 1997)	n=33 Mean (SD): -1.4 (2.0)	n=28 Mean (SD): -1.6 (2.3)	-	MD: 0.20 (-0.89 to 1.29)[a] p=0.74	Low	RCT	Serioush	None	None	Serious[q]	None
Change in oxygen saturation (outpatients)											
30 minutes											
1 (Plint et al., 2009)	n=199 Mean (SD): -0.35 (2.61)	n=198 Mean (SD): 0.17 (2.09)	-	MD: -0.52 (-0.99 to -0.05)[a]	High	RCT	None	None	None	None	None
1 hour											
2 studies (Mesquita et al., 2009; Plint et al., 2009)	n=232	n=230	-	SMD: -0.24 (-0.48 to 0.01)a	High	RCT	None	None	None	None	None
4 hours											
3 studies (Bawazeer et al., 2014; Mesquita et al., 2009;	n=154	n=143	-	SMD: 0.08 (-0.15 to 0.316)[a]	Low	RCT	Serious[l]	None	Serious[n]	None	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Combined bronchodilator (inhaled) + corticosteroid (systemic) therapy	Bronchodilator + placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Schuh et al., 2009)											
24 to 72 hours											
1 (Berger et al., 1998)	n=20 Mean (SD): 1 (0.5)	n=18 Mean (SD): 0.8 (0.3)	-	MD: 0.20 (-0.06 to 0.46)[a]	Low	RCT	Serious[i]	None	None	Serious[q]	None
Change in oxygen saturation (inpatients)											
12 hours											
1 (Klassen et al., 1997)	n=35 Mean (SD): 0.7 (2.5)	n=31 Mean (SD): 1.4 (2.8)	-	MD: -0.70 (-1.99 to 0.59)[a] p=0.29[g]	Low	RCT	Serious[h]	None	None	Serious[o]	None
24 hours											
1 (Klassen et al., 1997)	n=33 Mean (SD): 1.0 (3.6)	n=28 Mean (SD): 1.9 (3.1)	-	MD: -0.90 (-2.58 to 0.78)[a] p=0.28[g]	Low	RCT	Serious[h]	None	None	Serious[o]	None
Need for high flow humidified oxygen, CPAP or mechanical ventilation (outpatients)											
Reported as need for supplemental oxygen											
1 (Berger et al., 1998)	5/20 (25%)	2/18 (11.1%)	RR: 2.25 (0.50 to 10.20)a	-	Very low	RCT	Seriousi	None	None	Very serious[e]	None
Adverse events											
Pneumonia											
1 (Klassen et al., 1997)	1/35 (2.9%)	1/32 (3.1%)	RR: 0.91 (0.06 to 14.02)[a]	-	Very low	RCT	Serious[h]	None	None	Very serious[e]	None
Tremor											
1 (Plint et al., 2009)	4/199 (2.0%)	4/198 (2.0%)	RR: 0.99 (0.25 to 3.92)[a]	-	Very low	RCT	None	None	Serious[c]	Very serious[e]	None
Pallor											
1 (Plint et al., 2009)	23/199 (11.6%)	22/198 (11.1%)	RR: 1.04 (0.60 to 1.80)[a]	-	Very low	RCT	None	None	Serious[c]	Very serious[e]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Combined bronchodilator (inhaled) + corticosteroid (systemic) therapy	Bronchodilator + placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Vomiting											
1 (Plint et al., 2009)	2/199 (1.0%)	4/198 (2.0%)	RR: 0.50 (0.09 to 2.69)[a]	-	Very low	RCT	None	None	Serious[c]	Very serious[e]	None
Dark stools											
1 (Plint et al., 2009)	17/199 (8.5%)	14/198 (7.1%)	RR: 1.21 (0.61 to 2.38)[a]	-	Very low	RCT	None	None	Serious[c]	Very serious[e]	None
Hypertension											
1 (Plint et al., 2009)	0/199 (0%)	1/198 (0.5%)	RR: 0.33 (0.01 to 8.09)a	-	Very low	RCT	None	None	Seriousc	Very seriouse	None
Hyperkalaemia											
1 (Plint et al., 2009)	0/199 (0%)	0/198 (0%)	NC	-	Moderate	RCT	None	None	Seriousc	NC	None

NA not applicable, NC not calculable, RCT randomised controlled trial, p-value, RR risk ratio, MD mean difference, SMD standardised mean difference, SD standard deviation
a Calculated by the NCC-WCH technical team from data reported in the article
b Berger: randomisation not described, 4 drop-outs – unclear which arm they were assigned to, Kuyucu- randomisation not described, allocation concealment not clearly described, 21 lost to follow up - unclear which group they were assigned to, Schuh- 920/1464 children not approached because the research nurse was not present
c Plint: physician allowed to provide co-interventions after 90 minutes, Alansari: Population includes patients with asthma risk, as determined by eczema or a family history of asthma in a first degree relative
d Schuh: Additional treatment given at discretion of the physician
e Very serious imprecision when 95% CI crosses two default MID.
f Serious imprecision when 95% CI crosses one default MID.
g As reported in the study
h Bronchiolitis not clearly defined
I Berger: randomisation not described, 4 drop-outs – unclear which arm they were assigned to
j Very serious imprecision when 95% CI crosses two default MID.
k Randomisation not described, allocation concealment not clearly described, 21 lost to follow up- unclear which group they were assigned to
l Schuh: 920/1464 children in one study not approached because the research nurse was not present, bronchiolitis not defined
m High heterogeneity: I2= 765%
n Schuh: Additional treatment given at discretion of the physician
o Serious imprecision when 95% CI crosses one default MID.
p High heterogeneity: I2= 70%
q Serious imprecision when 95% CI crosses one default MID.

Table 51: GRADE profile for comparison of combined bronchodilator and corticosteroid therapy (both inhaled) with bronchodilator and placebo

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Combined bronchodilator and corticosteroid therapy (both inhaled)	Bronchodilator + placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Hospital re-admissions (inpatients)											
1 (Bentur et al., 2005)	12/29 (41.3%)	14/32 (43.8%)	RR: 0.95 (0.53 to 1.70)[a]	p=NSb	Very low	RCT	Serious[c]	None	None	Very serious[d]	None
Length of hospital stay in days (inpatients)											
Premature infants											
1 (Bentur et al., 2005)	n=6 Mean (SD): 6.5 (4.2)	n=7 Mean (SD): 9.1 (5.0)	-	MD: -2.60 (-7.60 to 2.40)a p=0.018[b]	Very low	RCT	Serious[c]	None	None	Very serious[e]	None
Full-term infants											
1 (Bentur et al., 2005)	n=23 Mean (SD): 5.2 (8.6)	n=25 Mean (SD): 5.5 (9.5)	-	MD: -0.30 (-5.43 to 4.83)[a] p=NS[b]	Very low	RCT	Serious[c]	None	None	Very serious[e]	None
Change in disease severity score (inpatients)											
Clinical score at discharge (endpoint)											
1 (Bentur et al., 2005)	n=29 Mean (SD): 2.1 (2.7)	n=32 Mean (SD): 2.2 (2.3)	-	MD: -0.10 (-1.35 to 1.15)[a] p=NSb	Low	RCT	Serious[c]	None	None	Seriousf	None
Need for/use of feeding support – tube feeding, IV fluids (inpatients)											
Reported as duration of IV fluids in hours											
1 (Bentur et al., 2005)	n=29 Mean (SD): 78.6 (213.8)	n=32 Mean (SD): 88.5 (201.4)	-	MD: -9.90 (-114.41 to 94.61)[a] p=NS[b]	Low	RCT	Serious[c]	None	None	Serious[f]	None

NA not applicable, RCT randomised controlled trial, RR risk ratio, MD mean difference, SMD standardised mean difference, SD standard deviation, p-value, NS Non Significant at p = 0.05
a Calculated by the NCC-WCH technical team from data reported in the article
b As reported in the study
c Bronchiolitis not defined, some outcomes specified in methods not reported in results (eg: oxygen saturation)
d Very serious imprecision when 95% CI crosses two default MID.e Very serious imprecision when 95% CI crosses two default MID.
f Serious imprecision when 95% CI crosses one default MID.

Table 52: GRADE profile for comparison of combined bronchodilator (systemic/inhaled) and corticosteroid therapy (systemic) with bronchodilator and placebo

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Combined bronchodilator and corticosteroid therapy (both inhaled)	Bronchodilator + placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Hospital admissions (outpatients)											
1 (Goebel et al., 2000)	4/24 (16.7%)	2/24 (8.3%)	RR: 2.00 (0.40 to 9.91)[a]	-	Very low	RCT	Seriousb	None	Serious[d]	Very serious[e]	None
Length of hospital stay in days (outpatients)											
1 (Goebel et al., 2000)	n=4 Mean (SD): 2.3 (1.7)	n=2 Mean (SD): 2.5 (1.7)	-	MD: -0.20 (-3.09 to 2.69)[a]	Very low	RCT	Serious[b]	None	Serious[d]	Very serious[f]	None
Change in disease severity score (outpatients)											
Clinical score on day 2 (endpoint)											
1 (Goebel et al., 2000)	n=17 Mean (SD): 2.6 (1.5)	n=15 Mean (SD): 3.9 (1.5)	-	MD: -1.30 (-2.34 to -0.26)a	Very low	RCT	Very serious[b,c]	None	Serious[d]	Serious[g]	None
Adverse events											
Appearing jittery											
1 (Goebel et al., 2000)	1/24 (4.2%)	0/24 (0%)	RR: 3.00 (0.13 to 70.16)[a]	-	Very low	RCT	Serious[b]	None	Serious[d]	Very serious[e]	None

NA not applicable, RCT randomised controlled trial, RR risk ratio, MD mean difference, SD standard deviation
a Calculated by the NCC-WCH technical team from data reported in the article
b Bronchiolitis not clearly defined
c 7 subjects in the combined therapy group and 9 subjects in the bronchodilator + placebo group had missing outcome data
d Mixed routes of administration: though the majority of subjects received bronchodilator by mouth (systemic), a small number of hospitalised subjects and one outpatient received bronchodilator by the use of a nebuliser (exact numbers not reported and no subgroup analysis presented)
e Very serious imprecision when 95% CI crosses two default MID.
f Very serious imprecision when 95% CI crosses two default MID.
g Serious imprecision when 95% CI crosses one default MID.

Table 53: GRADE profile for comparison of combined bronchodilator (inhaled) and corticosteroid (systemic) therapy with placebo

Number	Number of children	Effect	Quality	Design	Quality assessment

of studies	Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Hospital admissions (outpatients)											
Day 1											
1 study (; Plint et al., 2009)	23/200 (11.5%)	36/201 (17.9%)	RR: 0.64 (0.40 to 1.04)[a]	-	Very low	RCT	None	None	Serious[b]	Serious[c]	None
Day 7 (Includes admissions on day 1, i.e. cumulative admissions to day 7)											
1 (Plint et al., 2009)	34/200 (17.0%)	53/201 (26.4%)	RR: 0.64 (0.44 to 0.95)[a]	-	Low	RCT	None	None	Serious[b]	Serious[c]	None
Day 22 (Includes admissions on day 1 and 7, i.e. cumulative admissions to day 22)											
1 (Plint et al., 2009)	37/200 (18.5%)	54/201 (26.9%)	RR: 0.69 (0.48 to 1.00)[a]	-	Low	RCT	None	None	Serious[b]	Serious[c]	None
Length of hospital stay in hours (outpatients)											
Reported as time to discharge – time between the triage time at enrolment visit and the time of discharge from the last emergency department visit or the last hospitalisation for each patient within the next 7 days											
1 (Plint et al., 2009)	n=199 Median (interquartile range): 4.6 (3.5 to 7.0)	n=200 Median (interquartile range): 5.3 (3.8 to 21)	-	p=0.94[e]	Moderate	RCT	None	None	Serious[b]	NA	None
Change in disease severity score (outpatients)											
30 minutes											
1 (Plint et al., 2009)	n=199 Mean (SD): -1.62 (2.23)	n=200 Mean (SD): -1.06 (2.16)	-	MD: -0.56 (-0.99 to -0.13)[a]	High	RCT	None	None	None	None	None
60 minutes											
1 (Plint et al., 2009)	n=199	n=200	-	MD: -0.85 (-1.34 to -0.36)[a]	Low	RCT	None	None	None	Serious[e]	None
	n=15 Mean (SD): 4.40 (2.75)	n=15 Mean (SD): 4.80 (2.54)	-	MD: -0.4 (-2.29 to 1.49)[a]	Very low	RCT	None	None	None	Very serious[f]	None
	n=15 Mean (SD): 4.08 (3.25)	n=15 Mean (SD): 5 (2.31)	-	MD: -0.92 (-2.94 to 1.10)[a]	Low	RCT	None	None	None	Serious[e]	None
Change in oxygen saturation (outpatients)											

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
30 minutes											
1 (Plint et al., 2009)	n=199 Mean (SD): -0.35 (2.61)	n=200 Mean (SD): -0.24 (2.77)	-	MD: -0.11 (-0.64 to 0.42)[a]	High	RCT	None	None	None	None	None
60 minutes											
1 study (; Plint et al., 2009)	n=214	n=215	-	MD: 0.04 (-0.53 to 0.61)[a]	Moderate	RCT	None	None	None	None	None
	n=15 Mean (SD): 95.47 (1.88)	n=15 Mean (SD): 95.6 (1.95)	-	MD: -0.13 (-1.5 to 1.24)[a]	Very low	RCT	None	None	None	Very serious[f]	None
	n=15 Mean (SD): 95.08 (1.75)	n=15 Mean (SD): 95.62 (1.89)	-	MD: -0.54 (-1.84 to 0.76)a	Low	RCT	None	None	None	Seriousf	None
Duration of cough (outpatients)											
Reported as number of days with no coughing											
1 (Plint et al., 2009)	n=NR Median (interquartile range): 12.6 (7.8 to 18.5)	n=NR Median (interquartile range): 13.3 (8.2 to 19.5)	Mean ratio: 0.94 (0.84 to 1.07)	-	Moderate	RCT	None	None	Serious[b]	None	None
Adverse events											
Tremor											
1 (Plint et al., 2009)	4/199 (2.0%)	2/201 (1%)	RR: 2.02 (0.37 to 10.90)[a]	-	Very low	RCT	None	None	Serious[b]	Very serious[g]	None
Pallor											
1 (Plint et al., 2009)	23/199 (11.6%)	16/201 (8%)	RR: 1.45 (0.79 to 2.66)[a]	-	Low	RCT	None	None	Serious[b]	Serious[h]	None
Vomiting											
1 (Plint et al., 2009)	2/199 (1.0%)	3/201 (1.5%)	RR: 0.67 (0.11 to	-	Very low	RCT	None	None	Serious[b]	Very serious[g]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy	Placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
			3.99)[a]								
Dark stools											
1 (Plint et al., 2009)	17/199 (8.5%)	16/201 (8.0%)	RR: 1.07 (0.56 to 2.06)[a]	-	Very low	RCT	None	None	Serious[b]	Very serious[g]	None
Hypertension											
1 (Plint et al., 2009)	0/199 (0%)	0/201 (0%)	NC	-	Moderate	RCT	None	None	Serious[b]	NA	None
Hyperkalaemia											
1 (Plint et al., 2009)	0/199 (0%)	0/201 (0%)	NC	-	Moderate	RCT	None	None	Serious[b]	NA	None
Need for/use of feeding support (tube feeding, IV fluids)											
Reported as number of days with normal feeding											
1 (Plint et al., 2009)	Median (interquartile range): 0.6 (0.2 to 1.3)	Median (interquartile range): 0.9 (0.3 to 2.1)	Mean ratio (95%CI): 0.63 (0.50 to 0.80)[i]	-	Low	RCT	None	None	Serious[b]	Serious[c]	None

NA not applicable, NC not calculable, RCT randomised controlled trial, p-value, RR risk ratio, MD mean difference, SMD standardised mean difference, SD standard deviation
a Calculated by the technical team from data reported in the article
b Plint: physician allowed to provide co-interventions after 90 minutes
c Serious imprecision when 95% CI crosses one default MID.d As reported in study, adjusted for multiple comparisons
e Serious imprecision when 95% CI crosses one default MID.
f Very serious imprecision when 95% CI crosses two default MID.
g Very serious imprecision when 95% CI crosses two default MID.
h Serious imprecision when 95% CI crosses one default MID.
i As reported in the study

Table 54: GRADE profile for comparison of combined bronchodilator (inhaled) and corticosteroid (systemic) therapy with corticosteroid and placebo

Number	Number of children	Effect	Quality	Design	Quality assessment

of studies	Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy	Corticosteroid + placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Hospital admissions (outpatients)											
Day 1											
1 (Plint et al., 2009)	23/200 (11.5%)	31/200 (15.5%)	RR: 0.74 (0.45 to 1.23)a	-	Low	RCT	None	None	Serious[b]	Serious[c]	None
Day 7											
1 (Plint et al., 2009)	34/200 (17%)	51/200 (25.5%)	RR: 0.67 (0.45 to 0.98)[a]	-	Low	RCT	None	None	Serious[b]	Serious[c]	None
Day 22											
1 (Plint et al., 2009)	37/200 (18.5%)	53/200 (26.5%)	RR: 0.70 (0.48 to 1.01)[a]	-	Low	RCT	None	None	Serious[b]	Serious[c]	None
Change in disease severity score (outpatients)											
30 minutes											
1 (Plint et al., 2009)	n=199 Mean (SD): -1.62 (2.23)	n=199 Mean (SD): -0.98 (2.07)	-	MD: -0.64 (-1.06 to -0.22)[a]	High	RCT	None	None	None	None	None
60 minutes											
1 (Plint et al., 2009)	n=199 Mean (SD): -2.50 (2.58)	n=199 Mean (SD): -1.75 (2.4)	-	MD: -0.75 (-1.24 to -0.26)a	High	RCT	None	None	None	None	None
Change in oxygen saturation (outpatients)											
30 minutes											
1 (Plint et al., 2009)	n=199 Mean (SD): -0.35 (2.61)	n=199 Mean (SD): -0.52 (2.45)	-	MD: 0.17 (-0.33 to 0.67)[a]	High	RCT	None	None	None	None	None
60 minutes											
1 (Plint et al., 2009)	n=199 Mean (SD): -0.73 (2.56)	n=199 Mean (SD): -1.02 (2.57)	-	MD: 0.29 (-0.21 to 0.79)[a]	High	RCT	None	None	None	None	None
Adverse events											
Tremor											
1 (Plint et al., 2009)	4/199 (2.0%)	5/199 (2.5%)	RR: 0.80 (0.22 to 2.94)[a]	-	Very low	RCT	None	None	Serious[b]	Very serious[d]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy	Corticosteroid + placebo	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Pallor											
1 (Plint et al., 2009)	23/199 (11.6%)	15/199 (7.5%)	RR: 1.53 (0.82 to 2.85)[a]	-	Low	RCT	None	None	Serious[b]	Serious[e]	None
Vomiting											
1 (Plint et al., 2009)	2/199 (1%)	5/199 (2.5%)	RR: 0.40 (0.08 to 2.04)[a]	-	Very low	RCT	None	None	Serious[b]	Very serious[d]	None
Dark stools											
1 (Plint et al., 2009)	17/199 (8.5%)	12/199 (6.0%)	RR: 1.42 (0.69 to 2.89)[a]	-	Very low	RCT	None	None	Seriousb	Very serious[d]	None
Hypertension											
1 (Plint et al., 2009)	0/199 (0%)	1/199 (0.5%)	RR: 0.33 (0.01 to 8.13)[a]	-	Very low	RCT	None	None	Serious[b]	Very serious[d]	None
Hyperkalaemia											
1 (Plint et al., 2009)	0/199 (0%)	1/199 (0.5%)	RR: 0.33 (0.01 to 8.13)[a]	-	Very low	RCT	None	None	Serious[b]	Very serious[d]	None

NA not applicable, RCT randomised controlled trial, p-value, RR risk ratio, MD mean difference, SD standard deviation
a Calculated by the NCC-WCH technical team from data reported in the article
b Physician allowed to provide co-interventions after 90 minutes
c Serious imprecision when 95% CI crosses one default MID.
d Very serious imprecision when 95% CI crosses two default MID.
e Serious imprecision when 95% CI crosses one default MID.

4.2.8.4 Evidence statements

Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy versus bronchodilator plus placebo

Hospital admissions

Eight RCTs, seven of which were in outpatients including around 1000 children and one in inpatients including 67 children found that there is no difference in admission (outpatients) or readmission (inpatients) rates in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with bronchodilator plus placebo. The quality of evidence was low to very low.

Length of stay

Two RCTs, one of which was in outpatients including 38 children and one in inpatients including 67 children found that there is no difference in length of hospital stay in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with bronchodilator plus placebo. The quality of evidence was moderate to very low. One other outpatient study including 298 children found length of stay (reported as time ready for discharge) was shorter in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with bronchodilator plus placebo. The quality of evidence was low.

Change in disease severity score

Three studies (outpatients) with 928 children found that clinical score was better at 4 hours in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with bronchodilator plus placebo. The quality of evidence for this finding was very low. However, two of these studies plus three other studies showed no difference between the groups at any other time points that were recorded. The quality of evidence was high to very low.

One RCT in inpatients including 67 children found no difference in clinical score at both 12 and 24 hours in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with bronchodilator plus placebo. The quality of evidence was low.

Change in oxygen saturation

One study (outpatients) with 397 children found that oxygen saturation at 30 minutes showed a bigger decrease in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with bronchodilator plus placebo. The quality of the evidence was high. The same study plus 4 other studies including 335 children found no difference in oxygen saturation at any of the other time points recorded. The quality of evidence was high to low.

One study (inpatients) including 67 children found no difference in oxygen saturation at both 12 and 24 hours in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with bronchodilator plus placebo. The quality of the evidence was low.

Need for high flow humidified oxygen, CPAP or mechanical ventilation

One study (outpatients) including 38 children found no difference in need for high flow humidified oxygen (reported as need for supplemental oxygen) in infants treated with

combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with bronchodilator plus placebo. The quality of evidence was very low.

Adverse effects

Two studies including 464 children found no difference in adverse events in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with bronchodilator plus placebo. The quality of evidence was moderate to very low.

Combined bronchodilator and corticosteroid therapy (both inhaled) versus bronchodilator plus placebo

One RCT (inpatients) with 61 children found that there is no difference in readmission rates, length of hospital stay (in full term but not premature infants), clinical score at discharge and the need for/use of feeding support (reported as duration of IV fluids) in infants treated with combined bronchodilator and corticosteroid therapy (both inhaled) compared to infants treated with bronchodilator plus placebo. The quality of evidence was low to very low.

Combined bronchodilator (systemic/inhaled) and corticosteroid (systemic) therapy versus bronchodilator plus placebo

One study (outpatients) with 48 children found no difference in admission rates, length of hospital stay or adverse events (appearing jittery) in infants treated with bronchodilator (systemic/inhaled) and corticosteroid (systemic) therapy compared to infants treated with placebo. The quality of evidence was very low.

Change in disease severity score

The same study found that clinical score was better on day 2 in infants treated with bronchodilator (systemic/inhaled) and corticosteroid (systemic) therapy compared to infants treated with placebo. The quality of evidence was very low.

4.2.8.4.1 Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy versus placebo

Hospital admissions

One study (outpatients) with 397 children found no difference in admission rates at day 1 in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with placebo. The quality of the evidence for this finding was very low. However, the same study found a lower admission rate at day 7 but not day 22 in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with placebo. The quality of evidence was low.

Length of stay, duration of cough, adverse events, oxygen saturation

The same study (outpatients) found no difference in length of hospital stay, duration of cough, adverse events or oxygen saturation in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with placebo. The quality of evidence was high to very low.

Change in disease severity score

The same study (outpatients) found that clinical score at 30 minutes and 60 minutes showed a bigger decrease in infants treated with combined bronchodilator (inhaled) and

corticosteroid (systemic) therapy compared to infants treated with placebo. The quality of the evidence was high and low respectively.

Need for/use of feeding support

The same study (outpatients) found that the need for/use of feeding support (reported as number of days with normal feeding) was lower in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with placebo. The quality of evidence was low.

Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy versus corticosteroid plus placebo

Oxygen saturation, adverse events

One study (outpatients) with 397 children found no difference in oxygen saturation or adverse events in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with corticosteroid plus placebo. The quality of evidence for oxygen saturation was high and for adverse events ranged from low to very low.

Hospital admissions, clinical score

The same study found a lower hospital admission rate at day 7 (but not day 1 or 22) and a bigger decrease in clinical score at both 30 and 60 minutes in infants treated with combined bronchodilator (inhaled) and corticosteroid (systemic) therapy compared to infants treated with corticosteroid plus placebo. The quality of evidence for hospital admissions and clinical score was low and high respectively.

4.2.8.5 Evidence to recommendations

The evidence to recommendations covering the clinical and cost effectiveness of combined bronchodilators and corticosteroid therapy is presented in section 4.2.10.

4.2.8.6 Recommendations

The recommendations covering the clinical and cost effectiveness of combined bronchodilator and corticosteroid therapy are presented in section 4.2.12.

4.2.9 Health economics profile

One cost-effectiveness analysis was identified for this question (Sumner et al. 2010). This analysis was based on the RCT by Plint et al. 2009. This was a Canadian study comparing nebulized epinephrine plus oral dexamethasone, nebulized epinephrine alone, oral dexamethasone alone, and no active treatment. The length of hospital stay and re-admissions were not reported separately and so it was not possible to adapt this model to the UK setting.

A decision tree model was developed in Excel based on the outcomes of the network meta-analysis (Hartling et al. 2011) published comparing bronchodilators and corticosteroids, alone and in combination, with no treatment. This network meta-analysis was excluded from the clinical review because the methods were unclear. However, the main results of the network meta-analysis were the same as the guideline clinical review. As the network meta-analysis provided comparisons of the treatments where no direct information existed it was decided that the evidence should be used to develop an economic evaluation.

The following comparisons were considered in the model:

- No treatment
- Adrenaline
- Adrenaline plus steroid
- Steroid
- Steroid plus salbutamol
- Salbutamol

The population of children being treated for bronchiolitis in the NHS was estimated using the NHS reference cost data. This data reports the number of finished consultant episodes due to bronchiolitis for paediatric care, N=33,154. As this figure includes re-admissions it has been assumed that approximately 80% of these episodes will be initial admissions, N=26,523. The admissions have been distributed over 7 days, with 70% of admissions occurring on day 1. The network meta-analysis (Harling et al. 2011) baseline risk of admission from all studies was 20%. Therefore, if N=26,523 infants are admitted for bronchiolitis, then N=132,616 will have been diagnosed with bronchiolitis.

All infants are diagnosed by a physician (in the emergency department) and so the costs of an initial diagnosis have not been included in the model. After the initial diagnosis infants may be admitted on that day, or subsequent days up to day 7. It is assumed that the treatments being compared relate only to the initial treatment given in the emergency department. The drug costs were low (£1.41 per 5ml, steroid; £1.50 per salbutamol inhaler; £4.72 per amp, adrenaline). The mean difference in length of stay was calculated by weighting the average length of stay for each finished consultant episode related to paediatric admissions for bronchiolitis (2.03 days). The mean cost per day was calculated as £516.

Using the mean inputs from the Hartling et al. 2011 network meta-analysis the base case results show that using any treatment, apart from salbutamol, could lead to reduced admissions, up to 10,958 with adrenaline and steroids when compared to no treatment when 132,616 infants are diagnosed with bronchiolitis in the emergency department.

The reduction in admissions leads to cost savings compared to no treatment, approximately £18million savings are made due to fewer admissions when adrenaline and steroids are given in the emergency department (table 55).

Table 55: Results – treatment costs, hospital stay costs, total costs and cost differences

	Treatment cost	Total cost of hospital stay	Total costs	Cost savings
Adrenaline + steroid (dexamethasone)	£1,438,353	£8,211,233	£9,649,586	
Adrenaline	£1,251,365	£15,296,031	£16,547,396	£6,897,809
Steroid	£186,989	£20,498,351	£20,685,340	£4,137,944
No treatment		£27,810,074	£27,810,074	£7,124,735
Steroid + salbutamol	£878,615	£27,737,141	£28,615,756	£805,682
Salbutamol	£691,627	£29,123,074	£29,814,700	£198,944

The results of this analysis point towards adrenaline plus steroid having the potential to reduce costs in the NHS due to fewer admissions and shorter hospital stays. However, the clinical evidence used in the analysis compares all treatments to no treatment (placebo arm), and this does not reflect current practice which is likely to vary from hospital to hospital, with some treating with these drugs and others not using the listed drugs. When a probabilistic sensitivity analysis was run adrenaline plus steroid, adrenaline alone and steroids alone were all likely to be cost saving in a high proportion of the 1,000 simulations (81%, 90%, and 82%

respectively). Steroid plus salbutamol, and salbutamol alone were cost saving in less than 50% of the 1,000 simulations (44% and 35%).

Also, the confidence intervals for difference in length of stay when using adrenaline plus steroid were -5.3 days for the lower 95% confidence interval, and plus 3.01 days for the upper confidence interval. This data is likely to be out-of-date as when the GDG discussed the clinical evidence for this question the current length of stay was reported as approximately 3 days. Therefore, the adrenaline plus steroid data may be overestimating the benefit of reduced length of stay.

The GDG noted that the patients included in the only study for adrenaline plus steroids in the NMA were less severe than would normally be admitted in the UK. When adrenaline is given in the UK it is for the sicker infants, and these infants would always be admitted. Therefore these results should be viewed with caution and would support the need for a RCT of adrenaline plus steroid compared to no treatment with an outcome of length of stay.

More details of this evaluation can be found in the appendix.

4.2.10 Evidence to recommendations

Relative value placed on the outcomes considered

The aim of these three reviews was to determine whether bronchodilator therapy or corticosteroids used either individually or in combination are effective in the treatment of bronchiolitis. Although a separate review was undertaken for each question the GDG wanted to ensure that outcomes could be compared between treatments. Therefore, the GDG outlined the important outcomes that were common across the three reviews but due to the different duration of action between bronchodilators and corticosteroids there were some differences, and these were carried over to the combined treatment protocol. In addition, the GDG tailored the outcomes to address inpatient and outpatient settings. The GDG indicated as critical outcomes hospital admission rate for outpatients, length of stay for inpatients, and need for high flow humidified oxygen, CPAP or mechanical ventilation.

Bronchodilators

The important outcomes for bronchodilators are hospital admission rate (including readmission); length of hospital stay; change in disease severity score at 2 to 4 hours after treatment for salbutamol/ipratropium and at 30 min to 2 hours for adrenalin; change in O2 saturation; need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation; adverse effects(including mortality); need for/use of feeding support (tube feeding, IV fluids) and change in respiratory rate.

Corticosteroids

The important outcomes for corticosteroids are hospital admission rate (including readmission); length of hospital stay; change in disease severity score 1 to 7 days after starting treatment; change in O2 saturation; need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation; adverse effects(including mortality) and duration of cough

Combined bronchodilators and corticosteroid

The important outcomes for combined bronchodilators and corticosteroid therapy are hospital admission rate (including readmission); length of hospital stay; change in disease severity score 1 to 7 days after starting treatment; change in O2 saturation; need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation;

adverse effects (including mortality); need for/use of feeding support (tube feeding, IV fluids) and duration of cough.

The differences in outcomes between bronchodilators and corticosteroids reviews were:

- Different timing in the recording of the disease severity score. This is due to the fact that the physiological response to these treatments is slower with corticosteroids, so the GDG decided that any change in disease severity score would need to be recorded at 1 to 7 days after starting treatment, compared to 2 to 4 hours for corticosteroids.
- Change in respiratory rate was included for bronchodilators, as a primary reason to use this treatment is to rapidly improve respiratory distress.
- Duration of cough was included for corticosteroids as an effect of inflammation in bronchiolitis.
- Need for/use of feeding support was included for bronchodilators as the rapid action would prevent infants needing further support.

4.2.10.1 Consideration of clinical benefits and harms

The GDG discussed the results of the three reviews that were presented, and made recommendations based on the evidence and their own experience.

Inhaled adrenaline and other bronchodilators (salbutamol, albuterol, terbutaline, ipratroprium bromide) and corticosteroids (inhaled or systemic) have been used in bronchiolitis to relieve bronchospasm and improve airflow. The potential mechanisms of action of these agents differ but the intended effect is to alleviate symptoms and reduce the work of breathing. Bronchodilators might directly relieve bronchospasm through a direct effect on the airway muscle, whilst corticosteroids might reduce inflammation, thereby easing respiratory obstruction.

The reviews identified studies on a number of bronchodilators and corticosteroids, some of which were not used in the UK. The GDG focused their discussion on treatments that are currently used in the management of bronchiolitis in the UK.

None of the reviews showed a significant benefit either with bronchodilators or with corticosteroids whether used in isolation or in combination. This was in keeping with the clinical experience of GDG members. The GDG recommended that bronchodilators should not be used in the treatment of bronchiolitis. The GDG were aware however that it might sometimes be difficult to distinguish between wheeze of bronchiolitis and that of early asthma/viral induced wheeze in older infants. However, most babies with bronchiolitis have lung crackles on auscultation, so they considered that if on repeated examination there was wheeze without crackles the possibility of bronchodilator responsive wheeze (particularly if a personal or family history of atopy) should be considered.

4.2.10.2 Bronchodilator therapy

The GDG identified salbutamol as the main bronchodilator currently used in the management of bronchiolitis. The results of the review (including a network meta-analysis) could not demonstrate that salbutamol was effective compared with placebo. The GDG agreed and commented that this was consistent with their experience in that there was no clear benefit to be observed with salbutamol in clinical practice. Therefore, the GDG recommended that salbutamol should not be used to treat bronchiolitis.

The GDG examined the evidence for adrenaline. The results from pairwise meta-analysis and a network meta-analysis suggested that adrenaline would be the treatment most likely to reduce rates of admission, but found no difference between treatment and placebo for other outcomes. The GDG commented that the effect of adrenaline may be considered for its short-term benefit for severe respiratory distress with the rationale for longer term effects in

bronchiolitis being less clear. The GDG noted that the included studies did not undertake sub-group analysis by severity of disease and that this would be important to understanding the effect of adrenaline. Therefore, the GDG decided not to make a recommendation on the use of adrenaline as an emergency treatment for respiratory distress as this would apply to all respiratory conditions and was beyond the remit of the guideline. The GDG concluded that the evidence supported a recommendation that adrenaline should not be used for the general management of bronchiolitis.

The GDG noted that inhaled terbutaline is occasionally used in the UK, but again there was no evidence to support its effectiveness in bronchiolitis, and so they recommended that it should not be used.

Finally, inhaled ipratropium bromide has been proposed as a possible treatment for bronchiolitis, based on its established efficacy in bronchospasm due to asthma. However, the available evidence did not support its effectiveness in bronchiolitis and so they recommended that it should not be used.

4.2.10.3 Corticosteroid therapy

The review found no difference in effect of inhaled corticosteroids compared to placebo. The GDG considered that this was in keeping with their clinical experience.

For systemic corticosteroids (oral and intramuscular administration) the individual RCTs found this treatment was associated with a reduced length of hospital stay and reduced disease severity at certain time points but not others. Furthermore, for outcomes, such as admission to hospital, there was no difference between treatment groups. The results of a network meta-analysis found no difference between corticosteroids and placebo for rates of admission or length of stay.. For length of stay, the GDG noted that in the study showing a reduction in length of stay the average age of infants was between 10 and 11 months. This was higher than they would have expected in a population of infants with true bronchiolitis and they thought that this raised the possibility that the study may include infants with other respiratory disorders in which corticosteroids might have been effective. Therefore, the GDG was not persuaded that this finding was reliable.

The GDG noted that in two studies the use of corticosteroids was associated with reduced oxygen saturation levels three to six hours later. This was an unexpected observation and if true would clearly be a cause for concern. The GDG also noted that there is no information about possible effect of inhaled corticosteroids on cough and wheeze.

The GDG considered the fact that corticosteroids can cause various adverse effects, including impaired resistance to infection, growth retardation, adrenal suppression, altered bone metabolism, and others.

The GDG therefore made recommendation that neither inhaled nor systemic corticosteroids should be given to treat bronchiolitis.

4.2.10.4 Combined bronchodilator and corticosteroid therapy

The review identified various combinations of an inhaled bronchodilator and either inhaled or systemic corticosteroid treatment. The evidence did not show a consistent benefit from such combined therapy compared to placebo. Individual RCTs found differences for individual outcomes, such as oxygen saturation, but other studies failed to confirm this finding and even within individual studies there was inconsistency at different time-points. Results from a network meta-analysis found no difference in admission rates or length of stay, in infants treated with combined bronchodilators and corticosteroids compared to infants treated with placebo.

The uncertainty of the effectiveness of combination therapy was consistent with GDG members' experience. The GDG commented that parents and carers are often less concerned about inhaled rather than systemic corticosteroid therapy because the risk of adverse effects is lower. However, the GDG believed the evidence was insufficient to recommend that a combination of bronchodilators and corticosteroids should be used.

4.2.10.5 Consideration of health benefits and resource uses

The GDGs experience was that bronchodilators or corticosteroids were frequently used to manage bronchiolitis, but that there was a wide variation in practise across the UK. Given that the evidence showed little or no benefit of bronchodilators or corticosteroids compared to placebo, this means resources are being wasted on treatments that do not benefit the patient.

4.2.10.6 Quality of evidence

A common set of biases were identified across the reviews, these were focused on lack of a clear definition of bronchiolitis, inclusion of different age-groups, different study settings, high imprecision in outcomes that did not allow clear conclusions (linked to small sample sizes and heterogeneity). Furthermore, studies often allowed additional treatments which were likely to affect outcomes.

A network meta-analysis was also available for this question, and was based on the results of existing Cochrane reviews. Whilst the methodology used to undertake the network analysis was of good quality, the data used within the network could not be verified and the GDG were concerned about the inclusion of low quality evidence and that this resulted in considerable uncertainty in the results. In particular, the use of an RCT by Barlas et al, 1998, which used mist tents as a placebo, led the decision of the GDG to not use the network meta-analysis.

4.2.10.7 Other considerations

The GDG did not identify any equality issues in relation to these questions.

The GDG also pointed out that the use of steroids should be avoided if the child has HIV infection, or is suspected of having tuberculosis infection, or has been exposed to varicella in the previous three weeks (because of the risk of disseminated fatal varicella).

4.2.11 Recommendations

The recommendations for this section are in 4.2.12.

4.2.12 Research recommendations

5. What is the efficacy of combined bronchodilator and corticosteroid therapy?

Why this is important

5.1. There are no effective therapies for the treatment of bronchiolitis. One study reported that infants provided with both nebulised adrenaline and systemic steroids had improved clinical outcomes. This was a subgroup analysis, so was not anticipated in the trial design and consequently the analysis was not adequately powered to answer this question. A multicentre RCT that assesses the clinical and cost effectiveness of combined adrenaline and corticosteroids treatment for bronchiolitis is needed.

4.2.13 Montelukast

4.2.13.1 Review question

What is the efficacy of Montelukast?

Further details on the protocol for this review question are provided in Appendix E.

4.2.13.2 Introduction

Montelukast is a leukotriene receptor antagonist and was developed as a prophylactic treatment for asthma (and associated rhinitis). It has a license from 6 months of age in the UK for this purpose. Montelukast targets the cysteinyl leukotriene inflammatory pathway, specifically leukotriene D4. Blocking the leukotriene receptor reduces airway inflammation and associated airway bronchoconstriction and wheeze. Montelukast has not demonstrated benefit for the management of acute asthma. Response to Montelukast is considered to be under genetic variance, and from a clinical perspective there are responders and non-responders to treatment in children with asthma. Leuktotriene genes, in particular ALOX5, are under investigation to understand whether genetic variance explains treatment response.

Compared with children without respiratory illness, cysteinyl leukotrienes are increased in the nasal and lower airway of infants with bronchiolitis during acute infection, though to a lesser degree than in children with acute asthma. This observation has prompted consideration as to whether Montelukast might be valuable in reducing airway inflammation in bronchiolitis and its associated wheeze. Montelukast has been considered as a possible therapy for both symptoms of acute disease or chronic symptoms post bronchiolitis (off-license). This review considers whether Montelukast has a role in the management of acute bronchiolitis.

4.2.13.3 Description of included studies

Two RCTs were included in this review (Amirav et al, 2008; Zedan et al, 2010). One study was undertaken in Israel (Amirav et al, 2008) and the other in Egypt (Zedan et al, 2010). The studies used the same study protocol: children up to the age of 24 months were included, Montelukast (in sodium salt form) 4 mg, daily until discharge from unit. One study included 55 children (Amirav et al, 2008) and the other 85 children (Zedan et al, 2010).

The clinical definition of bronchiolitis was similar between the studies: First episode of wheezing or shortness of breath, prodromal rhinorrhoea and cough, followed by at least 2 of the following signs: chest recession, tachypnoea, wheezing, or rales. (Amirav et al, 2008). Respiratory distress preceded by flu-like symptoms resulting in an obstructive–like condition with wheezes and inconstant rales (Zedan et al, 2010).

The outcomes identified by the GDG for this review were:

- Change in O2 saturation
- Duration of cough
- Length of hospital stay
- Change in respiratory rate
- Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
- Hospital admission rate
- Adverse effects (including mortality)

Data was only available for one of these outcomes: length of stay. The technical team also extracted evidence on a clinical score. This was not specified by the GDG but was considered to be relevant to the review.

More details on each individual study can be found in the evidence tables in Appendix I.

4.2.13.4 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 56: GRADE profile for comparison of Montelukast with placebo for the management of bronchiolitis

Table 56: GRADE profile for comparison of Montelukast with placebo for the management of bronchiolitis

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Length of stay (days)											
2 studies (Amirav et al, 2008; Zedan et al, 2010)	-	-	-	-0.91 [-1.69, -0.13]*	Very Low	RCT	None	Very serious[a]	Serious[b]	None	Yes[c]
Clinical score (clinical score by Wang et al, 1992)											
2 studies (Amirav et al, 2008; Zedan et al, 2010)	-	-	-	-0.18 [-0.52, 0.15]*	Very Low	RCT	None	Very serious[a]	Serious[b]	None	Yes[c]

NC not calculable, NR not reported, RCT randomised controlled trial, p-value, RR relative risk
** Calculated by the NCC-WCH technical team from data reported in the article. Based on a fixed-effect model.*
a High heterogeneity between studies (I2 = 85%)
b Both studies included children up to the age of 24 months. The GDG believe that these older children are unlikely to have bronchiolitis and could potentially have asthma, which Montelukast was developed to treat.
c Zeden et al, 2010 uses the same design and methodology as Amirav et al, 2008. However, no link is mentioned between the studies

4.2.13.4.1 Evidence statements

Change in O2 saturation

No studies reported data on this outcome.

Duration of cough

No studies reported data on this outcome.

Length of hospital stay

One RCT with 55 children found no difference in length of stay between children who were treated with Montelukast and those who received the placebo. The quality of evidence was very low. Another RCT with 85 children found that length of stay was significantly reduced in children treated with Montelukast compared to those who were treated with the placebo. The quality of evidence was very low.

Change in respiratory rate

No studies reported data on this outcome.

Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation

No studies reported data on this outcome.

Hospital admission rate

No studies reported data on this outcome.

Adverse effects (including mortality)

No studies reported data on this outcome.

Clinical score

Two RCTs with 140 children found no significant difference in the clinical score at discharge of children with bronchiolitis who were treated with Montelukast compared to children with bronchiolitis who were treated with placebo. The quality of evidence for this finding was very low.

Health economics profile

No published economic evaluations were identified for this question. As the evidence was limited, developing an economic evaluation would not be useful for decision-making.

4.2.13.4.2 Evidence to recommendations

4.2.13.5 Relative value placed on the outcomes considered

The GDG indicated admission rates, length of stay, and need for high flow humidified oxygen, CPAP or mechanical ventilation as critical outcomes for this review. Other important

outcomes were: change in O_2 saturation, duration of cough, change in respiratory rate and adverse effects (including mortality). Of the eight outcomes outlined by the GDG, evidence was available only for length of hospital stay. For this reason, evidence related to clinical score was also taken in to consideration by the GDG in making their recommendation.

4.2.13.6 Consideration of clinical benefits and harms

The aim of this question was to determine the efficacy of Montelukast in children with bronchiolitis. Montelukast was developed as a treatment for asthma. However, due to its anti-inflammatory and mucolytic action it is hypothesised that Montelukast can be useful in the treatment of bronchiolitis. Whilst Montelukast is not currently used in the UK as a treatment for bronchiolitis and it is not licensed for young children under 6 months, the GDG were aware that its use is being suggested and therefore wanted the evidence on its efficacy to be reviewed.

The GDG was satisfied that the evidence presented in the review was complete and they were not aware of any relevant studies that had not been identified. However, the GDG felt that the available evidence was limited, with only two RCTs with small sample sizes available providing data on disease severity and length of hospital stay. Also, the GDG highlighted that the study populations included children up to the age of 24 months and older children in this age range were more likely to have a diagnosis of asthma rather than bronchiolitis. The GDG concluded that for these reasons the usefulness of the findings was limited.

The GDG discussed the evidence showing no difference in disease severity score between children treated with Montelukast and children treated with placebo. It was highlighted that children would only be discharged when their symptoms had improved, which explained the fact there was no difference in disease severity at discharge in either study. When results for specific time points were examined the two studies found different results with a trend to placebo being better in the Amirav study and a trend to Montelukast being better in the Zedan study. However, it was noted that neither study accounted for the effect of children being discharged from hospital on the average disease severity score. For this reason, the GDG was concerned that the rapid decline in clinical score reported in the Zedan study was difficult to explain as this effect would be attenuated by children being discharged from hospital.

The GDG discussed the finding that length of stay was shorter for children with bronchiolitis, who were treated with Montelukast, compared to children with bronchiolitis who were treated with placebo. However, this result was reported in only one RCT and not replicated from the other study. The GDG also noted that the length of stay in the Montelukast group in both studies was longer than that achieved in their own units, and significantly longer than that achieved in standard UK practice. The GDG were concerned about the reporting of length of stay results in the Zedan study. The study reported data on several sub-groups, but these figures showed little variation from the main findings, which the GDG found surprising as given the small sample size it would be expected that variation between sub-groups would be greater.

The GDG also discussed the administration of Montelukast to children on feeding support might be difficult because Montelukast for paediatric use in young children is formulated in granular form and the granules should not be dissolved, but mixed with cold or room temperature soft foods. Moreover, the full dose must be administered immediately after the opening of the packet. The presence of the granules and the fact that Montelukast cannot be dissolved prior to ingestion could be the cause feeding tubes obstruction.

The GDG concluded the results of the Amirav study were most valid, and that until suitable evidence was available that it should not be used to treat Bronchiolitis.

4.2.13.7 Consideration of health benefits and resource uses

As there appeared to be no health benefits from the use of Montelukast compared to placebo it would not be a good use of resources.

4.2.13.8 Quality of evidence

The main source of bias was the inclusion of children up to the age of 24 months in the studies. The GDG has highlighted that study populations of these studies could include children with asthma. The GDG also noted inconsistency in the evidence reported between studies. In addition, no time-series analysis was undertaken on the primary outcome of long of stay. The level of evidence was of very low quality.

4.2.13.9 Other considerations

No equality issues were identified for this question.

4.2.13.9.1 Key conclusions

Due to the limited and contradictory evidence the GDG recommended that Montelukast not be used as a treatment of bronchiolitis in children. However, they recognised that there is the need for more research on its use and suggested that research should be performed comparing Montelukast and placebo to treat bronchiolitis in children younger than 12 months.

4.2.13.10 Recommendations

The recommendations for Montelukast are in section 4.2.12.

4.2.13.11 Research recommendations

6. What is the efficacy of Montelukast in the treatment of acute bronchiolitis in infants and children?

Why this is important

6.1. Montelukast is a leukotriene receptor antagonist that has proven effectiveness in the treatment of asthma in infants and children. The inflammatory mediators known as leukotrienes are known to be increased in infants and children with bronchiolitis. Existing trials have been inconsistent in their findings with regard to the efficacy of Montelukast in bronchiolitis. A multi-centre RCT is required comparing the clinical and cost effectiveness of Montelukast with placebo for the treatment of bronchiolitis. Important outcomes would include hospital admission rate, duration of symptoms and hospital length of stay.

4.2.14 Recommendations

34. Do not use any of the following to treat bronchiolitis in children:

- antibiotics
- hypertonic saline
- adrenaline (nebulised)
- salbutamol
- Montelukast
- ipratropium bromide
- systemic or inhaled corticosteroids

- a combination of systemic corticosteroids and nebulised adrenaline

4.3 Heliox

4.3.1 Review question

What is the efficacy of heliox?

Further details on the protocol for this review question are provided in Appendix E.

4.3.2 Introduction

Heliox is a gas that is a mixture of oxygen (21%) and Helium (79%). It is an inert gas with an excellent safety profile. The components of atmospheric air consist mainly of oxygen (21%) and Nitrogen (79%).

Heliox is thought to be able to reduce the work of breathing. As heliox is lighter than air or oxygen, it promotes laminar flow in areas of turbulence or airways narrowing. Heliox has a higher binary diffusion coefficient for CO2 and O2 and is therefore thought to reduce respiratory system resistance.

4.3.3 Description of included studies

Six RCTs were included in this review, four studies used a parallel design (Cambonie et al., 2006; Chowdhury et al., 2013; Kim et al., 2010; Liet et al., 2005) and two studies used a cross-over design (Hollman et al., 1998; Torres et al., 2008). One study was a multi-centre trial involving three hospitals in Canada and one hospital in France (Liet 2005), another multi-centre trial involved two hospitals in the United Kingdom and two hospitals in Australia (Chowdhury et al., 2013). Two studies were conducted in the USA (Holman et al., 1998; Kim et al., 2011) and the remaining studies were conducted in France (Cambonie et al., 2006) and Spain (Torres 2008). In addition, the results from an existing systematic review (Liet et al., 2010) were included in this review. The systematic review included four of the six identified RCTs (Cambonie et al., 2006; Hollman et al., 1998; Kim et al., 20110; Liet et al., 2005).

Four trials (Cambonie et al., 2006; Holman et al., 1998; Liet et al., 2005; Torres et al., 2008) recruited infants from paediatric intensive care units (PICU) and two trials (Chowdhury et al., 2013; Kim et al., 2010) recruited infants from the emergency department. The sample size ranged from 12 (Torres et al., 2008) to 281 (Chowdhury et al., 2013).

Four trials included infants who tested positive for RSVbronchiolitis. Two trials (Chowdhury et al., 2013; Kim et al., 2011) diagnosed bronchiolitis based on the presence of symptoms. One trial (Kim et al., 2011) used the following criteria: tachypnea, cough, prolonged expiratory phase, wheezing, rales, chest recession, and hyperinflation of lungs on chest radiography. The other trial (Chowdhury et al., 2013) used the following criteria: history of upper respiratory tract infection followed by wheezing, coughing, breathing difficulty, or chest crackles on auscultation.

Two studies recruited infants up to 24 months of age (Hollman et al., 1998; Torres et al., 2008), two studies recruited infants less than 12 months (Chowdhury et al., 2013; Kim et al., 2010) and the remaining studies recruited infants less than 9 months (Liet et al., 2005) and 3 months (Cambione et al., 2006).

The outcomes listed by the GDG were:

- Change in CO2 after 24 hours of heliox treatment
- Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation

- Time to return to oral feeding
- Length of hospital stay (including duration of treatment required)
- Change in disease severity score at 1 to 4 hours after treatment
- Change in O2 saturation
- Adverse effects (including mortality)

The studies did not report data on all these outcomes and in some situations other outcomes are presented.

More details on each individual study can be found in the evidence table in Appendix I.

A Cochrane review (Liet et al, 2010) was available for this question. Where possible the results of this were included, however, it was found that the Cochrane review mixed results from parallel and cross-over studies in meta-analysis.

4.3.4 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

One GRADE profile has been produced for this review:

- Table 57: GRADE profile for comparison of heliox with oxygen (control)

Table 57: GRADE profile for comparison of heliox with oxygen (control)

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Heliox	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
1.Change in C02 after 24 hours of heliox treatment (increased severity indicated by higher values)											
Change in C02 (PC02 mmHg) within the first hour after starting treatment											
1 (Cambonie et al., 2006)	N=10	N=9	-	MD -0.10 (-0.88, 0.68)*	Very low	RCT	Serious [a]	None	None [b]	Very serious [c, d]	-
Change in C02 (tcPC02 mmHg) 30 minutes after starting treatment											
1 (Torres et al., 2008)	N=12	N=12	-	MD -4.30 (-6.38, -2.22)*	Low	RCT Crossover	Very serious [e]	None	None [f]	None	-
Change in C02 (PC02 mmHg) after 24 hours of starting treatment											
1 (Liet et al., 2005)	N=18	N=21	-	MD 3.00 (2.37, 3.63)*	Moderate	RCT	None	None	Serious [h]	None	-
2. Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation											
Rate of (endotracheal) intubation											
1 (Liet et al., 2010)	5/28	4/30	RR 1.38 (0.41, 4.56)	-	Very low	Meta-analysis of RCTs	Serious [a]	None [i]	Serious [b, h]	Very serious [j]	-
Need for mechanical ventilation											
1 (Liet et al., 2010)	5/28	5/30	RR 1.11 (0.36, 3.38)	-	Very low	Meta-analysis of RCTs	Serious [a]	None [i]	Serious [b, h]	Very serious [j]	Yes [k]
Required >50% oxygen, helium-oxygen and intubation											
1 (Kim et al., 2011)	1/35	0/35	RR 3.00 (0.13, 71.22)*	-	Very low	RCT	Serious [l]	None	Serious [m]	Very serious [j]	Yes [n]
Need for CPAP											
1 (Chowdhury et al., 2013)	24/140	27/141	RR 0.90 (0.54, 1.47)*	P=0.78	Very low	RCT	None [o]	Serious [p]	None [q]	Very serious [j]	-
3. Time to return to oral feeding											
Not reported											
4. Length of hospital stay											
Length of PICU stay, days											
1 (Liet et al., 2010)	N=27	N=31	-	MD -0.15 (-0.92, 0.61)	Very low	Meta-analysis of RCTs	Serious [a]	None [i]	Serious [b, h]	Very serious [c, d]	-

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Heliox	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Hours until "readiness to discharge" from the emergency department											
1 (Kim et al., 2011)	N=34	N=35	-	P=0.87[r]	Low	RCT	Serious[l]	None	Serious[m]	NC [g]	-
Length of treatment (total LoT to alleviate hypoxia (SpO2 ≥ 93% in room air) and respiratory distress (minimal work of breathing)). days [s]											
1 (Chowdhury et al., 2013)	N=141	N=140	-	MD -0.22 [-0.63, 0.19]*	Moderate	RCT	None[o]	Serious[p]	None[q]	None[d]	-
Length of treatment (total LoT to alleviate hypoxia (SpO_2 ≥ 93% in room air) and respiratory distress (minimal work of breathing)) for infants receiving treatment (Heliox or Airox) via a facemask, days s											
1 (Chowdhury et al., 2013)	N=44	N=40	-	MD -0.70 (-1.26, -0.14)*	High	RCT	None[o]	None	None[q]	None[d]	-
Length of treatment ((total LoT to alleviate hypoxia (SpO_2 ≥ 93% in room air) and respiratory distress (minimal work of breathing)) for infants receiving treatment (Heliox or Airox) via nasal cannula, days s											
1 (Chowdhury et al., 2013)	N=40	N=47	-	MD -0.34 (-1.22, 0.53)*	Moderate	RCT	None[o]	None	None[q]	Serious[c, d]	-
5. Change in disease severity score at 1 to 4 hours after treatment (increased severity indicated by higher values)											
Change in M-WCAS within the first hour after starting treatment											
2 (Cambonie et al., 2006; Hollman et al., 1998)	N=23	N=22	-	SMD -2.26 (-3.04, -1.48)*	Very low	Meta-analysis of RCTs	Very serious[a, t]	None[i]	Serious[b, u]	None	-
Change in M-WCAS within the first hour after starting treatment											
1 (Torres et al., 2008)	N=12	N=12	-	MD -1.04 (-1.45, -0.63)*	Low	RCT Crossover	Very Serious[e]	None	None[f]	None	-
Change in RDAI score after 24 hours											
1 (Liet et al., 2005)	N=18	N=21	-	P=0.76[v]	Moderate	RCT	None	None	Serious [h]	NC [g]	-
Mean change in M-WCAS 240 minutes after treatment or discharge											
1 (Kim et al., 2011)	N=34	N=35	-	P<0.001[w]	Low	RCT	Serious[l]	None	Serious[m]	NC [g]	-
Heliox effect relative to Airox over time calculated using regression analysis based on M-WCAS											
1 (Chowdhury et al., 2013)	N=140	N=141	RR 20.13 (20.20, 20.06)	P<0.001	Moderate	RCT	None[o]	Serious[p]	None[q]	None	Yes[y]
6. Change in 02 saturation (increased severity indicated by higher values)											
1 (Torres et al., 2008)	N=12	N=12	-	MD 1.10 (-1.90, 4.10)*	Very low	RCT Crossover	Very Serious[e]	None	None[f]	Very serious[d]	-
7. Adverse effects											

Number of studies	Number of infants		Effect		Quality	Design	Quality assessment				
	Heliox	Comparator	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Mortality											
1 (Liet et al., 2005)	0/18	1/21	RR 0.39 (0.02, 8.93)*	-	Very low	RCT	None	None	Serious[h]	Very serious[i]	-

MD mean difference, M-WCAS modified Wood's clinical asthma score, p-value, RCT randomised controlled trial, RDAI respiratory distress assessment instrument, RR relative risk, SMD standard mean difference,

** Calculated by the NCC-WCH technical team from data reported in the article*

a. Cambonie et al., 2006 (risk of bias): Small sample size and long study period (3 years) to recruit only 20 infants. Randomisation not described (Cochrane contacted reported computerised random listing and sealed envelopes). Oxygen saturation ≥90% for inclusion appears restrictive

b. Cambonie et al., 2006 (indirectness): Supplemental oxygen to maintain oxygen saturation >90%, all infants <3 months of age

c. Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.

d. Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.

e. Torres et al., 2008 (risk of bias): Not blinded. Inadequate randomisation (sequential allocation). Small sample size - 12 out of 40 infants met inclusion criteria. Did not describe infants with a previous history of wheeze in inclusion/exclusion criteria

f. Torres et al., 2008 (indirectness): Nebulised epinephrine at study entry, then at the discretion of physician

g. It was not possible to assess imprecision due to lack of information reported in the paper.

h. Liet et al., 2005 (indirectness): Inhaled corticosteroids were used once in the control group and never in the heliox group p=NS. Inhaled bronchodilator therapy was administered in 17 infants in the control group and 13 infants in the heliox group p=NS. FI02 was reduced to the lowest level that allowed for adequate oxygenation (oxygen saturation ≥92%)

i. I2=0% (0-40% may represent unimportant heterogeneity)j. Very serious imprecision when 95% CI crosses two default MID.k. Liet et al., 2005 report positive pressure ventilation (invasive or noninvasive). Cambonie et al., 2006 infants who required intubation also received mechanical ventilation

l. Kim et al., 2010 (risk of bias): Emergency department physicians were unmasked during the emergency department visit

m. Kim et al., 2010 (indirectness): Infants initially received nebulised albuterol treatment driven by 100% oxygen. After randomisation received 11.25mg racemic epinephrine via a face mask

n. One infant in the heliox group required >50% oxygen, helium-oxygen and intubation (this infant was found to have a lobar pneumonia on chest radiography)

o. Chowdhury et al., 2013 (risk of bias): 35 infants did not complete treatment. Heliox group were younger at presentation

p. 87 infants received treatment via a nasal cannula and 84 infants received treatment via a facemask

q. Chowdhury et al., 2013 (indirectness): Additional oxygen allowed if oxygen saturation <93% or worsening respiratory distress

r. Mean "readiness to discharge" for admitted infants: heliox group 41.6 hours, control group 43 hours

s. Total LoT to alleviate hypoxia (SpO_2 ≥ 93% in room air) and respiratory distress (minimal work of breathing). Length of treatment was calculated from the start to successful stop of the trial gas defined by clinical stability (minimal work of breathing and SpO_2 >93%) for 1 hour breathing room air

t. Hollman et al., 1998 (risk of bias): Small sample size, 18 infants enrolled. 5 infants were not randomised because they had severe bronchiolitis. Only those 13 infants who were randomised are included in this analysis. Three eligible infants were not enrolled in the study because of agitation related to the face mask and technical difficulties. Did not describe infants with a previous history of wheeze in inclusion/exclusion criteria

u Hollman et al., 1998 (indirectness): After enrolment oxygen saturation maintained ≥93%. 17 out of 18 enrolled infants received bronchodilators before admission to ICU and received nebulised albuterol as standard therapy

v –Mean change in RDAI 24 hours after treatment: heliox group -2 (SEM 0), control group -2 (SEM 0)

w Mean change in MWCAS from baseline to 240 minutes or emergency department discharge: heliox group 1.84, control group 0.31

x Time MWCAS was measured over not described

4.3.5 Evidence statements

Change in CO2 after 24 hours of heliox treatment

One RCT study with 39 children showed that 24 hours after treatment the change in CO2 was less in children treated with heliox compared to children treated with placebo. The quality of the evidence was moderate.

One RCT study with 12 children found at 30 minutes after treatment the change in CO2 was higher in children treated with heliox compared to children treated with placebo. The quality of the evidence was very low.

One RCT study with 20 children found one hour after treatment there was no difference in change in CO2 in children treated with heliox compared to children treated with placebo. The quality of the evidence was very low.

Need for high flow humidified oxygen, CPAP or mechanical ventilation

Three studies with 475 children (including a meta-analysis) did not report a difference in need for oxygen support in children treated with heliox compared to children treated with placebo. The quality of the evidence was very low.

Time to return to oral feeding

No studies reported data on this outcome.

Length of hospital stay

Two studies (including a meta-analysis) with 156 children did not report a difference in length of hospital stay in children treated with heliox compared to children treated with placebo. The quality of this evidence was very low.

One study with 319 children did not report a difference in length of treatment (defined as time on treatment required to alleviate hypoxia SpO_2 ≤93% in room air) and respiratory distress (minimal work of breathing) in children treated with heliox compared to children treated with placebo, when treatment was delivered via a nasal cannula. The quality of this evidence was moderate.

One study with 319 children reported that the length of treatment was reduced in children treated with heliox compared to children treated with placebo when treatment was delivered via a facemask. The quality of this evidence was high.

Change in disease severity score at 1 to 4 hours after treatment

Five studies with 436 children found that the disease severity score (MWCAS) was lower in children treated with heliox compared to children treated with placebo. The quality of the evidence was moderate to low.

One study with 39 children found that there was no difference in the disease severity score (RDAI) in children treated with heliox compared to children treated with placebo. The quality of the evidence was moderate to low.

Change in O2 saturation

One RCT study with 12 children did not establish a difference change in O2 saturation in children treated with heliox compared to children treated with placebo. The quality of this evidence was very low.

Adverse effects (including mortality)

One RCT study with 39 children did not establish a difference in adverse effects in children treated with heliox compared to placebo. The quality of this evidence was very low.

4.3.6 Health economics profile

This question was prioritised for economic evaluation. As the evidence of effectiveness was limited and equivocal, a cost-effectiveness analysis based on this evidence would not provide useful evidence.

4.3.7 Evidence to recommendations

4.3.7.1 Relative value placed on the outcomes considered

The GDG considered that the critical outcomes for this evidence review were: length of hospital stay; and need for high flow humidified oxygen, CPAP or mechanical ventilation. Other important outcomes indicated by the GDG were: change in CO_2 after 24 hours of heliox treatment, time to return to oral feeding, change in disease severity score at 1 to 4 hrs after treatment, change in O_2 saturation, and adverse effects (including mortality).The studies did not report data on all the outcomes chosen by the GDG. While length of hospital stay was a critical outcome, evidence regarding the linked outcome of length of treatment was considered. The GDG was interested in understanding the possible differences between Heliox delivered by nasal cannula or facemask and studies reporting length of treatment with these two modalities were therefore included in the evidence review.

4.3.7.2 Consideration of clinical benefits and harms

The GDG commented that heliox treatment is not currently in widespread use in the UK. They noted that there are difficulties in relation to its use. The GDG concluded that there was no compelling evidence to either support or refute recommending heliox treatment.

With regard to the outcome of change in disease severity score the GDG noted that several studies indicated some benefit and the evidence in support of this varied from very low to moderate quality. One study found no such benefit. The GDG also noted that there was no evidence to indicate that the use of heliox influenced the length of hospital stay although one study reported that the length of treatment required to alleviate hypoxia and respiratory distress was reduced by the use of heliox delivered by face mask. They noted that in that study the numbers completing heliox treatment was reduced suggesting to them that there may have been difficulties with tolerating the face mask. Finally, the GDG noted that a study reporting O2 saturation as an outcome did not report evidence of benefit with heliox.

The GDG noted that one study (very low quality) reported a death in the heliox group.

The GDG concluded that there was no compelling evidence to either support or refute recommending heliox treatment.

4.3.7.3 Consideration of health benefits and resource uses

Heliox has been reported to be five times the cost of oxygen. The costs could be reduced by piping heliox but this would require changes in the hospital infrastructure. New hospitals are

built with oxygen piped to the beds, but not heliox as it is not commonly used in the UK. Given the limited and equivocal evidence for heliox compared to airox it is not possible to predict whether the additional cost of providing heliox would be a good use of NHS resources.

In order to consider the cost-effectiveness of heliox the outcomes of importance are length of stay, need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation and adverse events. The clinical evidence did not establish a difference in need for oxygen support in children treated with heliox compared to children treated with placebo , though in some studies the interface to provide heliox to infants was poorly tolerated. And also no difference was found in adverse effects in children treated with heliox compared to placebo. No difference was found in length of stay between children treated with heliox compared to children treated with airox. Although a difference was reported for length of treatment with heliox compared to airox when a facemask was used, it is not clear the reason for the difference as no difference in need for CPAP was identified.

4.3.7.4 Quality of evidence

The main sources of bias were: small sample sizes and the variation in the administration of bronchodilators between groups. These biases meant outcomes were mainly of very low quality. In addition, several studies did not report outcomes in a form that could be assessed using GRADE. For example, raw data or confidence intervals (but p-values only) were often unreported, and therefore it was not possible to calculate relative effects or to give a rating to imprecision.

4.3.7.5 Other considerations

No further considerations identified for this question.

4.3.8 Key conclusions

Due to the limited and contradictory evidence on this treatment, the GDG did not recommend the use of heliox but concluded that research is required comparing heliox and placebo to treat bronchiolitis in children with avoidance of CPAP and of mechanical ventilation as important outcomes. The GDG also suggested that the health economics relating to heliox should be reviewed.

4.3.9 Research recommendations

7. What is the efficacy of heliox?

Why this is important

7.1. There is some evidence that heliox therapy may reduce the need for CPAP in infants and children with severe bronchiolitis. The evidence is however inconclusive. Moreover, heliox is administered using a tight-fitting face mask and there may be difficulties with patient tolerance. A multi-centre RCT of the clinical and cost effectiveness of this treatment is required. Provision of heliox through a hospital piped supply is not widely available and has cost implication.

5 Supportive treatment

5.1 Oxygen supplementation

5.1.1 Review question

What is the efficacy of oxygen supplementation (non-humidified, humidified and high flow) and of continuous positive airway pressure CPAP?

Further details on the protocol for this review question are provided in Appendix E.

5.1.2 Introduction

It is widely recognised that oxygen should be used to treat children and infants with hypoxia in bronchiolitis. Although arterial blood gases are the gold standard for measuring hypoxia, another way to indicate the oxygen level is the measurement of oxygen saturations.

Oxygen therapy provides the child with a concentration of oxygen greater than that of room air, with the aim of treating the symptoms of hypoxia, and decreasing the work of breathing.

When oxygen saturation is too low, oxygen supplementation can be provided by a variety of means including non-rebreathing masks, nasal cannulae, incubators, head boxes, and in children oxygen is often wafted near their face if compliance is an issue. It may be humidified for patient comfort, so that it does not dry the patient's mouth or nose. This may also be useful if children are requiring regular suction so that the nasal secretions do not become dry and more difficult to remove (but no evidence to support this)

The mechanism by which oxygen is delivered may be via low flow devices, high flow, CPAP or via an endotracheal tube.

Oxygen is a drug and can have potentially serious side-effects. Use of high concentration of oxygen has been found to cause retinopathy of prematurity

5.1.3 Description of included studies

Three RCT studies were included in this review. Two compared CPAP with standard oxygen supplementation using either nasal cannulas or a face mask (Thia et al, 2008; Milesi et al, 2013), while the third one compared high flow humidified nasal cannula oxygen with head-box oxygen (Hilliard et al., 2012). Two studies were undertaken in the UK (Thia et al, 2008; Hilliard et al., 2012) and one in France (Milesi et al, 2013). The samples sizes were 29 infants (Thia et al, 2008), 19 infants (Milesi et al, 2013) and 19 infants (Hilliard et al., 2012). The diagnosis of bronchiolitis was based on clinical criteria in one study (Thia et al, 2008) and on RSV testing in one study (Milesi et al, 2013). All of the children included in the studies were less than 12 months old, with the mean average being between 2 and 3 months old.

Study details from Hilliard et al., 2012 were found in a recent Cochrane review as the reviewers contacted authors directly to request additional information. However, missing raw data were not provided.

The outcomes chosen by the GDG were:

- Change in O2 saturation
- Change in arterial or capillary carbon dioxide levels
- Change in disease severity score
- Length of hospital stay
- Change in respiratory rate

- Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation
- Need for/use of feeding support (tube feeding, IV fluids)
- Adverse effects (including mortality)

No comparative data was found for other forms of oxygen supplementation.

5.1.4 Evidence profile

Study quality was assessed using the GRADE methodology. Randomised controlled trials (RCTs) were the most appropriate study design for addressing this question, so were initially assigned high quality and downgraded based on potential sources of bias.

Two GRADE profiles have been produced for this review.

- Table 58 GRADE profile for CPAP compared with standard oxygen support for children with bronchiolitis
- Table 59: GRADE profile for comparison of High Flow Humidified oxygen via nasal cannula with comparator oxygen support (head-box oxygen)

Table 58: GRADE profile for comparison of CPAP with comparator oxygen support

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	CPAPa	Standard oxygen supportb	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Change in O2 saturation											
Pulse oximetry (%)											
1 (Milesi et al, 2013)	0.7 (SEM 1)*	2.4 (SEM 3) *	NS	-	Very low	RCT	Very Serious[c]	None	None	Very serious[d]	None
Fraction of inspired oxygen (%)											
1 (Milesi et al, 2013)	7 (SEM 3) *	-5 (SEM 5) *	P < 0.05	-	Very low	RCT	Very Serious[c]	None	None	Very serious[d]	None
Change in arterial or capillary carbon dioxide levels											
Partial pressure of CO2 measured on capillary blood gas sampling (torr)											
1 (Milesi et al, 2013)	6 (SEM 2) *	4 (SEM 4) *	NS	-	Very low	RCT	Very Serious[c]	None	None	Very serious[d]	None
1 (Thia et al, 2007)	-0.92 (NR)	+0.04 (NR)	P<0.015	-	Very low	Crossover RCT	Serious[e]	None	Very serious[f]	None	None
1 (Thia et al, 2007) (0 to 12 hours)	As first treatment : -1.35 (SD 1.37)	As first treatment: -0.53 (SD 1.25)	-0.82 [-1.78, 0.14]	-	Low	Crossover RCT	Serious[e]	None	None	Very serious[d]	None
1 (Thia et al, 2007) (12 to 24 hours)	After standard therapy: -0.41 (SD 0.87)	After CPAP: 0.5 (SD 0.9)	NR	-	Very Low	Crossover RCT	Serious[e]	None	Very serious[f]	None	None
Change in disease severity score											
Modified Wood's clinical asthma score											
1 (Milesi et al, 2013)	2.4 (SEM 0.4) *	0.5 (SEM 0.4) *	P < 0.05	-	Very low	RCT	Very Serious[c]	None	None	Very serious[d]	None
Length of hospital stay (days)											
1 (Milesi et al, 2013)	5 (SEM 0.5) *	5 (SEM 0.5) *	NS	-	Very low	RCT	Very Serious[c]	None	None	Very serious[d]	None
Change in respiratory rate (breaths/min)											
1 (Milesi et al, 2013)	7 (SEM 4) *	1.3 (SEM 4) *	NS	-	Very low	RCT	Very Serious[c]	None	None	Serious[g]	None
Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation – `											
Intubated											
1 (Milesi et al, 2013)	0 of 10	0 of 9	NS	-	Very low	RCT	Very Serious[c]	None	None	None	None
Mechanical ventilation											
1 (Thia et al, 2007)	0 of 16	1 of 15	NS	-	Moderate	Crossover RCT	Serious[e]	None	None	None	None
Need for/Use of feeding support (tube feeding, IV fluids) – Not reported											
Adverse effects (including mortality)											

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	CPAPa	Standard oxygen supportb	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Need to switch treatment groups because of a >30% worsening of clinical score:											
1 (Milesi et al, 2013)	4 of 9	0 of 10	P = 0.032	-	Very low	RCT	Very Serious[c]	None	None	Serious[g]	None
Required one dose of triclofos to tolerate CPAP											
1 (Thia et al, 2007)	9 of 29	0 of 29	NC	-	Moderate	RCT	Serious[e]	None	None	None	None

NS Not statistically significant at p = 0.05 NC not calculable, NR not reported, RCT randomised controlled trial, p-value, RR relative risk
** graphs in paper suggest that direction of change should be reversed.*
a Both Milesi and Thai use nasal continuous positive airway pressure
b Both Milesi and Thai use oxygen via nasal cannula or face mask, although Milesi used humidified oxygen.
c Milesi – randomisation used sequentially number envelopes. Small sample size of 19 infants. 4 of 9 in control group were switched to experimental group.
d Very serious imprecision when 95% CI crosses two default MID.e Thai – small sample size of 29; Identified differences between cross-over groups. Two infants in control group withdrawn before start of treatment.
f Examines change in period after crossover, so each group had different managed in period before cross-over. No washout period reported.
g Serious imprecision when 95% CI crosses one default MID.

Table 59: GRADE profile for comparison of High Flow Humidified oxygen via nasal cannula with comparator oxygen support (head-box oxygen)

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	HHHFNC	HBO	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Change in O2 saturation											
SpO_2% at 8 hours											
1 (Hilliard et al., 2012)	Median = 100% (94-100)	96% (93-100)	-	P = 0.04	Low	RCT	Very Serious [a]	None	None	NC [b]	None
SpO_2% at 12 hours											
1 (Hilliard et al., 2012)	Median = 99% (96-100)	96% (93-99)	-	P = 0.04	Low	RCT	Very Serious [a]	None	None	NC [b]	None
SpO_2% at 24 hours											
1 (Hilliard et al., 2012)	NR	NR	-	NS	Low	RCT	Very Serious [a]	None	None	NC [b]	None
Change in disease severity score											
Combined bronchiolitis severity score											
1 (Hilliard et al., 2012)	NR	NR	-	NS	Low	RCT	Very Serious a	None	None	NC[b]	None
Length of hospital stay (hours)											
1 (Hilliard et al.,	Median = 162 (96-300)	Median = 164 (84-	-	P = 0.7	Low	RCT	Very Serious a	None	None	NC[b]	None

Number of studies	Number of children		Effect		Quality	Design	Quality assessment				
	HHHFNC	HBO	Relative (95% CI)	Absolute (95% CI)			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
2012)		233)									
Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation											
1 (Hilliard et al., 2012)	0/11	0/8	NC	-	Low	RCT	Very Serious a	None	None	NC [b]	None
Adverse effects (including mortality) – not reported											
Change in respiratory rate (breaths/min) – not reported											
Change in arterial or capillary carbon dioxide levels – not reported											
Need for/Use of feeding support (tube feeding, IV fluids) – not reported											

NA not assessable; NS Not statistically significant at p = 0.05, NC not calculable, NR not reported, RCT randomised controlled trial, p-value, RR relative risk
a.Risk of bias was unclear as the method to generate the sequence was not reported; not blind; one participant was changed from the control to intervention group due to "clinical reasons", but no details were provided; weaning protocols have been reported to be different, and these differences could have biased outcomes like length of stay and time to discharge; small trial, authors reported that to show even a large reduction in the need for further respiratory support would need a study with over 100 patients in each arm.
b.It was not possible to grade for imprecision due to lack of information (95%CI were not reported).

5.1.5 Evidence statements

The evidence statements outlined below are based on data comparing CPAP and standard oxygen supplementation. No comparative data was found for other forms of oxygen supplementation.

Change in O2 saturation

One RCT with 19 children found no difference in change in O2 saturation (using pulse oximetry) in children treated with CPAP compared to children treated with standard oxygen therapy. The quality of the evidence was very low. However, the same RCT found the change in fraction of inspired oxygen was greater in children treated with CPAP compared to children treated with standard oxygen therapy. The quality of the evidence was very low.

One RCT of 19 patients found that infants who received high flow humidified O2 via nasal cannula had a lower oxygen saturation compared to those who were given head-box oxygen. The findings were significant at 8 and 12 hours after randomisation, but not significant at 24 hours. The quality of the evidence was low.

Change in arterial or capillary blood carbon dioxide levels

One RCT with 31 children found the reduction in CO2 was greater in children treated with CPAP compared to children treated with standard oxygen therapy. The quality of the evidence was very low. Another RCT with 19 children found no difference in change in CO2 in children treated with CPAP compared to children treated with standard oxygen therapy using a different measure CO2. The quality of the evidence was low.

Change in disease severity score

One RCT with 19 children found change in disease severity score was better in children treated with CPAP compared to children treated with standard oxygen therapy. The quality of the evidence was very low. One RCT of 19 patients found no difference in disease severity score in infants treated with high flow humidified oxygen via nasal cannula and those treated with head-box oxygen. The quality of the evidence was low.

Length of hospital stay

One RCT with 19 children found no difference in length of stay in children treated with CPAP compared to children treated with standard oxygen therapy. The quality of the evidence was very low. One RCT of 19 patients found no difference in total length of stay in infants treated with high flow humidified oxygen via nasal cannula and those treated with head-box oxygen. The quality of the evidence was low.

Change in respiratory rate

One RCT with 19 children found no difference in change in respiratory rates in children treated with CPAP compared to children treated with standard oxygen therapy. The quality of the evidence was very low.

Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation

Two RCT with 50 children found no difference need for additional support in children treated with CPAP compared to children treated with standard oxygen therapy. The quality of the evidence was moderate to very low.

One RCT of 19 patients reported that no infant required additional respiratory support. The quality of the evidence was low.

Need for/Use of feeding support (tube feeding, IV fluids)

No studies reported data on this outcome.

Adverse effects (including mortality)

One RCT with 19 children found requirement for additional treatment was lower (better) in children treated with CPAP compared to children treated with standard oxygen therapy. The quality of the evidence was very low.

Another RCT with 31 children found that the need for sedation was higher in children treated with CPAP compared to children treated with standard oxygen therapy. The quality of the evidence was moderate.

One RCT of 19 patients reported that all participants tolerated the treatment well.

5.1.6 Health economics profile

This question was prioritised for economic evaluation, for no oxygen supplementation compared to oxygen supplementation. No clinical evidence was identified for this comparison. A costing analysis of high flow oxygen and CPAP was developed at the request of the GDG.

The cost per use, equipment plus consumables, for high flow oxygen was calculated as £84 per use, CPAP was between £28 and £66 per use. If the staff ratio for CPAP is two nurses per infant, and a nurse is required to do a ten minute check every hour, then this would cost an additional £164 per 24hours.

If CPAP is given only in intensive care, rather than the normal ward then this would add £275 to £601 per day in hospital. The weighted cost per day for acute bronchiolitis taken from the NHS reference costs (2012/13) is £516. High dependency care and intensive care is more expensive (£791 and £1,118 respectively).

5.1.7 Evidence to recommendations

5.1.7.1 Relative value placed on the outcomes considered

The GDG considered that critical outcomes for this evidence review were length of stay and need for high flow humidified oxygen, CPAP or mechanical ventilation. Other important outcomes indicated by the GDG were: change in O2 saturation, change in arterial or capillary blood carbon dioxide levels, change in disease severity score, change in respiratory rate, need for feeding support (either tube feeding or intravenous fluids) and the occurrence of adverse effects (including mortality). They were particularly concerned to examine the effect blood carbon dioxide levels which can indicate respiratory failure. Another outcome that was of particular interest was the potential effect on length of stay in hospital. Evidence was available for seven of the eight outcomes chosen by the GDG. The only outcome that was not reported in the included studies for this review was need for or use of feeding support (tube feeding, IV fluids).

5.1.7.2 Consideration of clinical benefits and harms

- The aim of this evidence review was to determine the effectiveness of oxygen supplementation for children with bronchiolitis, and to determine which of the following is the optimal method of treatment

- Oxygen, unhumidified
- Oxygen humidified
- High flow humidified oxygen
- CPAP

O2 supplementation is commonly used in children presenting to secondary care with bronchiolitis. The GDG considered that the use of oxygen supplementation in such children might prevent the need for more invasive methods of respiratory support such as mechanical ventilation.

The GDG noted that the evidence was limited across the reported outcomes. In particular the evidence of benefit for the use of CPAP was very limited, with either no change or small improvements for oxygen saturation, change in carbon dioxide and disease severity scores reported across trials.

The GDG considered that oxygen can potentially have adverse effects – for example it can lead to retinopathy in the premature infant. For this and for other reasons (cost and convenience) oxygen should not be given to all with bronchiolitis. However, clinically significant hypoxia is clearly potentially or actually hazardous. The GDG considered that in determining the level oxygen saturation that should be used as a threshold for starting oxygen supplementation it was essential to consider the sinusoidal nature of the oxygen saturation curve. The curve drops sharply below about 90% saturation with the oxygen carriage below such levels falling rapidly. On consideration they considered that by recommending that oxygen be given if the saturation was persistently below 93% there was a built in safety margin between 90 and 93% and so the risk of a marked reduction in oxygen carriage would be reduced.

5.1.7.3 Consideration of health benefits and resource uses

The GDG believed that cost of using CPAP is higher than other simpler methods of delivering oxygen, but they recognised that they did not have sufficient information to discriminate between these methods in making recommendations.

5.1.7.4 Quality of evidence

This review was limited to three RCTS. The studies identified had small sample sizes and so there was very serious imprecision. In addition, one of the two studies did not specify the washout period. Study quality therefore ranged from very low to low.

5.1.7.5 Other considerations

Any other relevant considerations such as those related to equalities

5.1.8 Key conclusions

The GDG concluded that the evidence presented in this review was not sufficient to determine the optimal target saturation for safe and effective care in bronchiolitis, however they agreed that oxygen supplementation should be given to children if the oxygen saturation is persistently 92% or less.

The GDG could not identify the best method to deliver oxygen to a child with bronchiolitis (standard nasal cannula or high flow nasal cannula),The GDG also agreed that there is the need for further research comparing standard care with CPAP and/or high flow humidified O2.

5.1.9 Recommendations

35. Give oxygen supplementation to children with bronchiolitis if their oxygen saturation is persistently 92% or less.

36. Consider continuous positive airway pressure (CPAP) in children with bronchiolitis who have impending respiratory failure (see recommendation 31)

5.1.10 Research recommendations

8. What is the clinical and cost effectiveness of high-flow humidified oxygen versus standard supplemental oxygen?

Why this is important

8.1. Providing oxygen (typically by nasal cannula) is standard care for bronchiolitis. Newly-developed medical devices can now deliver high-flow humidified oxygen that is thought to provide more comfortable and effective delivery of gases while retaining airway humidity. The use of this medical device is becoming widespread without demonstration of additional efficacy. A multicentre RCT comparing high-flow humidified oxygen and standard supplemental oxygen would be of benefit, as would including weaning strategies for high-flow humidified oxygen.

5.2 Nasal suctioning

5.2.1 Review question

What is the efficacy of suction to remove secretions from the upper respiratory tract?

Further details on the protocol for this review question are provided in Appendix E.

5.2.2 Introduction

Some infants with bronchiolitis are known to produce secretions which may settle in their nasal passages. Small infants are obligatory nasal breathers and so suction is used to remove excess secretions in order to maintain a patent airway. This is thought to lessen the work of breathing and facilitate easier feeding. It is usually an invasive, blind procedure, with uncertain outcome. It does have undesirable side effects (such as mechanical trauma from poor technique or excessive suction pressures) which may affect the patient's recovery, but these can be minimised by careful practice

5.2.3 Description of included studies

No studies meeting the specified inclusion criteria were identified.

5.2.4 Evidence to recommendations

5.2.4.1 Relative value placed on the outcomes considered

The aim of this review was to determine the efficacy nasal suction in children with bronchiolitis. The GDG indicated length of hospital stay and oral feed toleration as critical outcomes to be considered. Other important outcomes were: need for oxygen supplementation, hospital admission rates, readmission rates, and adverse effects (including mortality).

5.2.4.2 Consideration of clinical benefits and harms

The GDG noted that nasal suctioning is a long-standing and widely used technique in children with bronchiolitis. They wished to examine the evidence regarding this practice.

The GDG noted that no evidence was identified for this review. Therefore, the GDG considered the use of suctioning based on their experience and knowledge in relation to the outcomes that they had specified.

The GDG recognised that in managing bronchiolitis in children possible relief of breathing difficulties and maintenance of adequate oral fluid intake are important objectives. They noted that infants are often obligatory nasal breathers and that the increase in upper airway and nasal mucus production associated with bronchiolitis can interfere with their breathing and consequently may contribute to feeding difficulties. They were aware that in the UK it is sometimes practice to perform nasal suctioning routinely prior to feeding infants with bronchiolitis and also prior to giving inhaled therapies. They agreed however that excessive secretions did not necessarily cause difficulty in every affected child and moreover nasal suction may cause distress to the child and may be upsetting for parents and carers.

The GDG acknowledged that removing secretions from the upper respiratory tract via nasal suction, is a temporary measure used to diminish the effort that the child has to do for breathing, but it is not a treatment for bronchiolitis. Moreover, it can be distressing for the child, parents and carers. The GDG was concerned that frequent suctioning, the use of excessively powerful suction pressures, or an incorrect or forceful technique could cause injury to the tissues of the nose or upper airway. They observed that there are no widely accepted guidelines on good technique and indeed a lack of evidence to support such guidance.

The GDG agreed that suctioning should not be routinely performed in children with bronchiolitis. However, in their experience when used selectively in children in whom excessive secretions appeared to be causing breathing difficulties or feeding difficulties upper airway suctioning could be beneficial. In children with bronchiolitis who present with apnoea they agreed that airway secretions could be an unrecognised contributing factor and given the serious and urgent nature of this complication they advised that upper airway suctioning would be appropriate

5.2.4.3 Consideration of health benefits and resource uses

The GDG acknowledged that suctioning uses resources and because suctioning equipment is not usually available other than in the hospital setting its use might prolong length of hospital stay. However, there was no comparative data to assess whether benefits justified the resources used. The main cost will be a nurse’s time. If it takes 10 minutes for a nurse to perform nasal suctioning and this is done before each feed, approximately every 4 hours, this would be 1 hour of a nurse’s time per 24 hours. The mean cost for a nurse on a 24 hour ward is £41 per hour (Curtis 2013). The GDG discussed that suctioning can prolong length of stay. However, there was no comparative data to assess any associated health benefits to justify the resources used or demonstrate any difference in length of stay.

5.2.4.4 Other considerations

The GDG were not aware of any equality issues in relation to these questions.

5.2.5 Key conclusions

In the absence of evidence the GDG consensus was that upper airway suctioning should not be routinely performed in children with bronchiolitis but that upper airway suctioning can be considered to alleviate distress due to upper airway blockage and help with feeding difficulties.

The GDG also recommended the use of upper airway suctioning in children with bronchiolitis with apnoea even if the upper airways do not show obvious sign of mucus obstruction.

The GDG recognised that the role of upper airway suctioning in the management of bronchiolitis is largely unknown so they recommended research on the effect of upper airway suctioning in children presenting with bronchiolitis.

5.2.6 Recommendations

37. Do not routinely perform upper airway suctioning in children with bronchiolitis.

38. Consider upper airway suctioning in children who have respiratory distress or feeding difficulties because of upper airway secretions.

39. Perform upper airway suctioning in children with bronchiolitis presenting with apnoea even if there are no obvious upper airway secretions.

5.2.7 Research recommendations

9. What is the clinical and cost effectiveness of suction to remove secretions from the upper respiratory tract compared with minimal handling?

Why this is important

9.1. Suction is a commonly used therapy in bronchiolitis. Infants are obligate nasal breathers, so removal of secretions is thought to relieve respiratory distress. However, suction is distressing to infants and parents. Methods vary and there is no evidence on which approach, if any, is most effective. In some trials it appears that minimal handling is more effective than therapies. A multicentre RCT comparing the clinical and cost effectiveness of suction (also covering different suction strategies, for example superficial versus deep) with minimal handling is needed.

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