PREDICT

Paediatric Research in Emergency Departments International Collaborative

AUSTRALASIAN BRONCHIOLITIS

GUIDELINE

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A Guideline Advisory Group was initially established from PREDICT and convened a multidisciplinary Guideline Development Committee with expert knowledge and skills within the fields of Emergency and Paediatric Medicine. This multidisciplinary Development Committee complement the skills and knowledge of the Guideline Advisory Group. This ensured stakeholder engagement and representation from specific specialty areas to ensure broad relevance of the guideline.

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SUMMARY

PURPOSE/AIM

This guideline has been developed to provide an evidence-based clinical framework for the management of infants (0–12 months) with bronchiolitis treated in Australasian emergency departments (EDs) or general paediatric wards. Application of these guidelines for children over 12 months may be relevant but there is less diagnostic certainty in the 12–24 month age group.

(All references to age within this guideline refer to chronological age unless stated otherwise.)

DIAGNOSIS

Viral bronchiolitis is a clinical diagnosis, based on typical history and examination. Peak severity is usually at around day two to three of the illness with resolution over 7–10 days. The cough may persist for weeks. Bronchiolitis most commonly occurs in the winter months, but can be seen all year round.

FEATURES

Bronchiolitis typically begins with an acute upper respiratory tract infection followed by onset of respiratory distress and fever and one or more of:

- Cough
- Tachypnoea
- Retractions
- Widespread crackles or wheeze

Bronchiolitis is usually self-limiting, often requiring no treatment or interventions.

RISK FACTORS FOR MORE SERIOUS ILLNESS

- Gestational age less than 37 weeks
- Chronological age at presentation less than 10 weeks
- Post-natal exposure to cigarette smoke
- Breast fed for less than two months
- Failure to thrive
- Chronic lung disease
- Congenital heart disease
- Chronic neurological conditions
- Indigenous ethnicity

Infants with any of these risk factors are more likely to deteriorate rapidly and require escalation of care. Consider hospital admission even if presenting early in illness with mild symptoms.

INITIAL ASSESSMENT

This table is meant to provide guidance in order to stratify severity. The more symptoms the infant has in the mod-severe categories, the more likely they are to develop severe disease.

	MILD	MODERATE	SEVERE
Behaviour	Normal	Some/intermittent irritability	Increasing irritability and/or lethargy Fatigue
Respiratory rate	Normal – mild tachypnoea	Increased respiratory rate	Marked increase or decrease in respiratory rate
Use of accessory muscles	Nil to mild chest wall retraction	Moderate chest wall retractions Tracheal tug Nasal flaring	Marked chest wall retractions Marked tracheal tug Marked nasal flaring
Oxygen saturation/ oxygen requirement	O_2 saturations greater than 92% (in room air)	O_2 saturations 90 – 92% (in room air)	O_2 saturations less than 90% (in room air) Hypoxemia, may not be corrected by O_2
Apnoeic episodes	None	May have brief apnoea	May have increasingly frequent or prolonged apnoea
Feeding	Normal	May have difficulty with feeding or reduced feeding	Reluctant or unable to feed

INITIAL MANAGEMENT

The main treatment of bronchiolitis is supportive.
This involves ensuring appropriate oxygenation and fluid intake.

	MILD	MODERATE	SEVERE
Likelihood of admission	Suitable for discharge Consider risk factors	Likely admission, may be able to be discharged after a period of observation Management should be discussed with a local senior physician	Requires admission and consider need for transfer to an appropriate children's facility/PICU Threshold for referral is determined by local escalation policies but should be early
Observations **Vital signs (respiratory rate, heart rate, O_2 saturation, temperature)**	Adequate assessment in ED prior to discharge (minimum of two recorded measurements or every four hours as per local hospital guidelines and EWT)	Hourly – dependent on condition (as per local hospital guidelines and EWT)	Hourly with continuous cardiorespiratory (including oximetry) monitoring and close nursing observation – dependent on condition (as per local hospital guidelines and EWT)
Hydration/nutrition	Small frequent feeds	If not feeding adequately (less than 50% over 12 hours), administer NG or IV hydration	If not feeding adequately (less than 50% over 12 hours), or unable to feed, administer NG or IV hydration
Oxygen saturation/oxygen requirement	Nil requirement	Administer O_2 to maintain saturations greater than or equal to 92%	Administer O_2 to maintain saturations greater than or equal to 92%
Respiratory support		Consider HFNC if a trial of NPO_2 is ineffective	Consider HFNC or CPAP
Disposition/ escalation	Consider further medical review if early in the illness and any risk factors are present or if child develops increasing severity after discharge	Decision to admit should be supported by clinical assessment, social and geographical factors and phase of illness	Consider escalation if severity does not improve Consider ICU review/ admission or transfer to local centre with paediatric HDU/ICU capacity if: • Severity does not improve • Persistent desaturations • Significant or recurrent apnoeas associated with desaturations
Parental education	Provide advice on the expected course of illness and when to return (worsening symptoms and inability to feed adequately)	Provide advice on the expected course of illness and when to return (worsening symptoms and inability to feed adequately)	Provide advice on the expected course of illness
	Provide Parent Information sheet	Provide Parent Information sheet	Provide Parent Information sheet

PICU = paediatric intensive care unit, **EWT** = early warning tool, **NG** = nasogastric, **IV** = intravenous, **NPO_2** = nasal prong oxygen, **HFNC** = heated humidified high flow oxygen/air via nasal cannulae, **CPAP** = continuous positive airway pressure, **HDU** = high dependency unit.

INVESTIGATIONS

In most infants presenting to hospital and/or hospitalised with bronchiolitis, no investigations are required.

Chest X-ray (CXR)

- Is not routinely indicated in infants presenting with bronchiolitis and may lead to unnecessary treatment with antibiotics with subsequent risk of adverse events

Blood tests (including full blood count (FBC), blood cultures)

- Have no role in management

Virological testing (nasopharyngeal swab or aspirate)

- Has no role in management of individual patients

Urine microscopy and culture

- May be considered to identify urinary tract infection if a temperature over 38 degrees in an infant less than two months of age with bronchiolitis

MANAGEMENT

Respiratory support

- Oxygen therapy should be instituted when oxygen saturations are persistently less than 92%
- It is appreciated that infants with bronchiolitis will have brief episodes of mild/moderate desaturations to levels less than 92%. These brief desaturations are not a reason to commence oxygen therapy.
- Oxygen should be discontinued when oxygen saturations are persistently greater than or equal to 92%.
- Heated humidified high flow oxygen/air via nasal cannulae (HFNC) can be considered in the presence of hypoxia (oxygen saturation less than 92%) and moderate to severe recessions. Its use in infants without hypoxia should be limited to the randomised controlled trial (RCT) setting only

Monitoring

- Observations as per local hospital guidelines and Early Warning Tools (EWTs)
- Continuous oximetry should not be routinely used to dictate medical management unless disease is severe

Hydration/nutrition

- When non-oral hydration is required either intravenous (IV) or nasogastric (NG) hydration are appropriate
- If IV fluid is used it should be isotonic (0.9% Sodium Chloride with Glucose or similar)
- The ideal volume of IV or NG fluids required to maintain hydration remains unknown; between 60% to 100% of maintenance fluid is an appropriate volume to initiate

Medication

- Beta 2 agonists — Do not administer beta 2 agonists (including those with a personal or family history of atopy)
- Corticosteroids — Do not administer systemic or local glucocorticoids (nebulised, oral, intramuscular (IM) or IV)
- Adrenaline — Do not administer adrenaline (nebulised, IM or IV) except in peri-arrest or arrest situation
- Hypertonic Saline — Do not administer nebulised hypertonic saline
- Antibiotics — Including Azithromycin are not indicated in bronchiolitis
- Antivirals — Are not indicated

Nasal suction

- Nasal suction is not routinely recommended. Superficial nasal suction may be considered in those with moderate disease to assist feeding
- Nasal saline drops may be considered at time of feeding

Chest physiotherapy

- Is not indicated

ONGOING MANAGEMENT

- HFNC or Nasal CPAP therapy may be considered in the appropriate ward setting

DISCHARGE PLANNING AND COMMUNITY-BASED MANAGEMENT

- Infants can be discharged when oxygen saturations are greater than or equal to 92% and feeding is adequate
- Infants younger than 8 weeks of age are at an increased risk of representation
- Discharge on home oxygen can be considered after a period of observation in selected infants as per local policies, if appropriate community short term oxygen therapy is available
- Follow-up and review as per local practice

EDUCATION (PARENT/CARE-GIVER)

- A Bronchiolitis Parent Information Sheet should be provided
- Parents should be educated about the illness, the expected progression and when and where to seek further medical care

SAFETY INITIATIVES

- Use simple infection control practices such as hand washing
- Cohorting of infants (based on virological testing) has not been shown to improve outcomes

To download this summary only, please see the *Bedside Clinical Guideline* at:
http://www.predict.org.au/download/Australasian-bronchiolitis-bedside-clinical-guideline.pdf

CLINICAL RECOMMENDATIONS

DIAGNOSIS

1. Infants can be diagnosed with bronchiolitis if they have an upper respiratory tract infection followed by onset of respiratory distress with fever, and one or more of: cough, tachypnoea, retractions and diffuse crackles or wheeze on auscultation.
(NHMRC: C, GRADE: Weak)

2. Clinicians should consider as risk factors for more serious illness: gestational age less than 37 weeks; chronological age at presentation less than 10 weeks; exposure to cigarette smoke; breast feeding for less than two months; failure to thrive; having chronic lung disease; having chronic heart and/or chronic neurological conditions; being Indigenous ethnicity, and should take these into account when managing infants with bronchiolitis.
(NHMRC: C, GRADE: Conditional)

3. Routine CXR is not recommended as it does not improve management in infants presenting with simple bronchiolitis, and may lead to treatments of no benefit.
(NHMRC: D, GRADE: Conditional)

4. There is no role for blood tests in managing infants presenting to hospital and hospitalised with bronchiolitis. Routine bacteriological testing of blood and urine is not recommended.
(NHMRC: D, GRADE: Conditional)

In infants less than two months of age presenting to hospital or hospitalised with bronchiolitis with a temperature over 38 degrees, there is a low risk of urinary tract infection (UTI). If clinical uncertainty exists clinicians may consider collecting a urine sample for microscopy, culture and sensitivity looking for the concurrent presence of UTI.

5 In infants with bronchiolitis, routine use of viral testing is not recommended for any clinically relevant end-points, including cohorting of bronchiolitis patients.
(NHMRC: C, GRADE: Conditional

MANAGEMENT

6. For infants presenting to hospital or hospitalised with bronchiolitis, there is insufficient evidence to recommend the use of a scoring system to predict need for admission or hospital length of stay.
(NHMRC: D, GRADE: Weak)

7. Oxygen saturations, adequacy of feeding, age (infants younger than eight weeks), and lack of social support should be considered at the time of discharge as a risk for representation. There is insufficient evidence to recommend absolute discharge criteria for infants attending the ED, or hospitalised with bronchiolitis
(NHMRC: Practice Point, GRADE: Weak)

8a. Do not administer beta 2 agonists to infants, less than or equal to 12 months of age, presenting to hospital or hospitalised with bronchiolitis.
(NHMRC: A, GRADE: Strong)

8b. Do not administer beta 2 agonists to infants, less than or equal to 12 months of age, presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy.
(NHMRC: D, GRADE: Weak)

9. Do not administer adrenaline/epinephrine to infants presenting to hospital or hospitalised with bronchiolitis.
(NHMRC: B, GRADE: Strong)

10. Do not administer nebulised hypertonic saline in infants presenting to hospital or hospitalised with bronchiolitis.
(NHMRC: D, GRADE: Conditional)

11a. Do not administer systemic or local glucocorticoids to infants presenting to hospital or hospitalised with bronchiolitis.
(NHMRC: B, GRADE: Strong)

11b. Do not administer systemic or local glucocorticoids to infants presenting to hospital or hospitalised with bronchiolitis, with a positive response to beta 2 agonists.
(NHMRC: D, GRADE: Weak)

11c. Do not administer a combination of systemic or local glucocorticoids and adrenaline/epinephrine to infants presenting to hospital or hospitalised with bronchiolitis.
(NHMRC: D, GRADE: Weak)

12a. Consider the use of supplemental oxygen in the treatment of hypoxic (oxygen saturations less than 92%) infants with bronchiolitis.
(NHMRC: C, GRADE: Conditional)

12b. In uncomplicated bronchiolitis oxygen supplementation should be commenced if the oxygen saturation level is sustained at a level less than 92%. At oxygen saturation levels of 92% or greater, oxygen therapy should be discontinued.
(NHMRC: C, GRADE: Conditional)

MANAGEMENT

14. High Flow Nasal Cannulae Oxygen (HFNC) in bronchiolitis can be considered in the inpatient setting on infants with bronchiolitis with hypoxia (oxygen saturations less than 92%). Its use in children without hypoxia should be limited to the RCT setting only.
(NHMRC: C, GRADE: Conditional)

15. Chest physiotherapy is not recommended for routine use in infants with bronchiolitis.
(NHMRC: B, GRADE: Strong)

16a. Nasal suction is not recommended as routine practice in the management of infants with bronchiolitis. Superficial nasal suction may be considered in those with moderate disease to assist feeding.
(NHMRC: D, GRADE: Conditional)

16b. Deep nasal suction for the management of bronchiolitis is not recommended.
(NHMRC: D, GRADE: Conditional)

17. Routine nasal saline drops are not recommended. Trial of intermittent saline drops may be considered at time of feeding.
(NHMRC: Practice Point, GRADE: Weak)

18. Nasal CPAP therapy for infants with bronchiolitis may be considered for the management of infants.
(NHMRC: C, GRADE: Conditional)

19. After a period of observation, infants at low risk for severe bronchiolitis can be considered for discharge on home oxygen as part of an organised 'Home Oxygen Program' which has clear 'Return to Hospital' advice.
(NHMRC: C, GRADE: Conditional)

20a. Do not use antibiotics to treat infants with bronchiolitis.
(NHMRC: B, GRADE: Conditional)

20b. Do not use azithromycin for treatment of infants admitted to hospital with bronchiolitis.
(NHMRC: B, GRADE: Conditional)

20c. Do not use azithromycin for treatment of infants admitted to hospital with bronchiolitis who are at risk of developing bronchiectasis.
(NHMRC: C, GRADE: Conditional)

21a. Supplemental hydration is recommended for infants who cannot maintain hydration orally.
(NHMRC: Practice Point, GRADE: Weak)

21b. Both NG and IV routes are acceptable means for non-oral hydration in infants admitted to hospital with bronchiolitis.
(NHMRC: B, GRADE: Strong)

21c. There is insufficient evidence to recommend a specific proportion of maintenance fluid. There is a risk of fluid overload therefore judicious and vigilant use of hydration fluid is and regular clinical review is recommended. Isotonic fluid is recommended.
(NHMRC: Practice Point, GRADE: Weak)

22. Hand hygiene is the most effective intervention to reduce hospital acquired infections and is recommended. There is inadequate evidence for benefits in cohorting infants with bronchiolitis.
(NHMRC: D, GRADE: Weak)

METHODOLOGY

The aim of this project was to formulate an evidence-based, clinical practice guideline for infants with bronchiolitis presenting to, and admitted into Australasian hospitals.

The scope was to examine the evidence for the diagnosis and management for the purpose of improving health outcomes. The guideline addresses the emergency department and general ward management of bronchiolitis, recognising that in order to influence management for the majority of patients who present to hospital with bronchiolitis, these two areas are critical to in-hospital management. Management in primary care and in intensive care units is excluded (as only a small proportion of patients admitted to hospital with bronchiolitis require intensive care management) (1). The guideline excludes public health prevention as this is outside the scope of Australasian hospital based care.

The Australasian Bronchiolitis Guideline has been developed utilising both the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (2) and the National Health and Medical Research Council (NHMRC) Grading System methodology (3). A Guideline Development Committee was formed comprising of 22 individuals including; General Paediatricians, Paediatric Respiratory Physicians, Paediatric Emergency Medicine Physicians, Emergency Physicians, Paediatric Intensive Care Physicians, Paediatric Nurse Practitioners, Paediatric Nurses, and Emergency Nurses from a mixture of metropolitan and non-metropolitan centres, from both New Zealand and Australia (including representatives from seven of the eight States and Territories). The Guideline Development Committee conducted a face-to-face meeting in which guideline methodology was agreed on, current State and Tertiary Children's Hospitals Bronchiolitis guidelines (4-7) were reviewed and 33 key PICOt questions relevant to the management of bronchiolitis were formulated.

An evidence search from 1 January 2000 to 1 May 2015 was conducted of the following electronic databases: Ovid Medline, Ovid Embase, PubMed, Cinahl, Cochrane Review library and Cochrane Database of Systematic Reviews (CDSR) (search strategy available in appendix). One of five members of the Guideline Development Committee reviewed the title and abstracts of the 7955 titles identified in the literature search. Articles relevant to 33 PICOt questions and the proposed guideline were included. Where screening by title and abstract was insufficient to make a decision as to relevance, a copy of the complete article was sourced and reviewed. Selected articles were then divided into the relevant PICOt question groups. If a high-quality Cochrane systematic review relevant to the PICOt question existed only systematic reviews and RCTs subsequent to the year of the documented search date in the Cochrane systematic review were included.

Two members of the Guideline Development Committee independently reviewed articles relevant to each PICOt question utilising the GRADE (2) and NHMRC Grading System (3) to assess methodological quality, data synthesis and development of recommendations. The GRADE system entails an assessment of the quality of a body of evidence for each individual outcome, including consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. The GRADE method is recognised internationally as a reliable method of reviewing the quality of evidence and is a structured process for developing and presenting evidence summaries for systematic reviews. The process is transparent and includes comprehensive criteria for downgrading and upgrading quality of evidence ratings for the development of recommendations (2). The NHMRC process is Australian specific and addresses the evidence to support clinical questions such as intervention, diagnosis, prognosis, aetiology and screening which are specifically related to guideline development (3). The NHMRC process for evidence review includes rating the five key components of the 'body of evidence' for each recommendation. These components are: the evidence base, in terms of the number of studies, level of evidence and quality of studies (risk of bias), consistency of the study results, potential clinical impact of the proposed recommendation, generalisability of the body of evidence to the target population and the applicability of the body of evidence to the Australian healthcare context (8). Any disagreements that arose between the first two reviewers were resolved through discussion with a third reviewer. Evidence tables and summaries of evidence were prepared for each PICOt question.

Where possible the evidence presented in these guidelines is based on systematic reviews and RCTs. Where there was only low quality indirect supportive evidence, clinical care statements outlining current accepted practise points were included.

A draft guideline, and the recommendations and evidence tables for the 33 PICOt was reviewed by the Guideline Development Committee. Consensus was sought using nominal group technique principles to formulate the clinical practice recommendations and practice points for the draft guideline.

A second literature search was performed on the 17th of December 2015 of the same electronic databases, using the same search strategy, to identify any subsequent literature at the time of the draft guideline development (7 months since initial search). A further 764 articles were identified and these were reviewed utilising the same process as used for the first literature search.

The draft guideline was sent to key stakeholders within Australia and New Zealand. Feedback was incorporated into the final guideline.

NHMRC STRENGTH OF RECOMMENDATION DEFINITIONS (3)

A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

GRADE QUALITY OF EVIDENCE DEFINITIONS (9)

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

PICOt QUESTIONS

NUMBER	QUESTION
1	In infants presenting to hospital what factors in history and physical examination contribute to a differential diagnosis of bronchiolitis?
2	In infants presenting to hospital with bronchiolitis, what are the risk factors for admission or severe disease (e.g. prolonged length of hospital stay, intensive care unit (ICU) admission, and death)?
3	In infants presenting to hospital or hospitalised with bronchiolitis, does performing a CXR beneficially change medical management or clinically relevant end-points?
4	In infants presenting to hospital or hospitalised with bronchiolitis, does performing laboratory tests (blood and/or urine) beneficially change medical management or clinically relevant end-points?
5	In infants presenting to hospital or hospitalised with bronchiolitis, does performing virological investigations beneficially change medical management or clinically relevant end-points?
6	For infants presenting to hospital or hospitalised with bronchiolitis, does use of a bronchiolitis scoring system beneficially change medical management or clinically relevant end-points?
7	For infants presenting to hospital or hospitalised with bronchiolitis, what criteria should be used for safe discharge?
8a. i)	In infants presenting to hospital or hospitalised with bronchiolitis, does administration of Beta2 Agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?
8a. ii)	In older infants presenting to hospital or hospitalised with bronchiolitis, does administration of Beta2 Agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?
8b. i)	In infants presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy, does administration of Beta2 Agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?
8b. ii)	In older infants presenting to hospital or hospitalised with bronchiolitis, with a second or subsequent episode/s of bronchiolitis or wheeze, does administration of Beta2 Agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?
9	In infants presenting to hospital or hospitalised with bronchiolitis, does administration of adrenaline / epinephrine (nebulisation, IM or IV) improve clinically relevant end-points?
10	In infants presenting to hospital or hospitalised with bronchiolitis, does administration of nebulised hypertonic saline improve clinically relevant end-points?
11a.	In infants presenting to hospital or hospitalised with bronchiolitis, does administration of systemic or local glucocorticoids (nebulisation, oral, IM or IV) improve clinically relevant end-points?
11b.	In infants presenting to hospital or hospitalised with bronchiolitis, with a positive response to Beta2 Agonists, does administration of systemic or local glucocorticoids (nebulisation, oral, IM or IV) improve clinically relevant end-points?

NUMBER	QUESTION
11c.	In infants presenting to hospital or hospitalised with bronchiolitis, does administration of the combination of systemic or local glucocorticoids (nebulisation, oral, IM or IV) and adrenaline improve clinically relevant end-points?
12a.	In infants presenting to hospital or hospitalised with bronchiolitis, does administration of supplemental oxygen improve clinically relevant end-points?
12b.	In infants presenting to hospital or hospitalised with bronchiolitis, what level of oxygen saturation should lead to commencement or discontinuation of supplemental oxygen to improve clinically relevant end-points?
13.	In infants hospitalised with bronchiolitis does continuous monitoring of pulse oximetry beneficially change medical management or clinically relevant end-points?
14.	In infants hospitalised with bronchiolitis does the use of heated humidified high flow oxygen, or air, via nasal cannula improve clinically relevant end-points?
15.	In infants hospitalised with bronchiolitis, does chest physiotherapy improve clinically relevant end-points?
16a.	In infants hospitalised with bronchiolitis, does suctioning of the nose or naso pharynx improve clinically relevant end-points?
16b.	In infants hospitalised with bronchiolitis, does deep suctioning in comparison to superficial suctioning beneficially improve clinically relevant end-points?
17	In infants hospitalised with bronchiolitis, does the use of nasal saline drops improve clinically relevant end-points?
18.	In infants hospitalised with bronchiolitis, does the use of bubble CPAP improve clinically relevant end-points?
19.	In infants hospitalised with bronchiolitis, is provision of home oxygen a safe alternative for management?
20a.	In infants presenting to hospital or hospitalised with bronchiolitis, does the use of antibiotic medication improve clinically relevant end-points?
20b.	In infants presenting to hospital or hospitalised with bronchiolitis, does the use azithromycin medication improve clinically relevant end-points?
20c.	In infants presenting to hospital or hospitalised with bronchiolitis, does the use of antibiotic medication in infants who are at risk of developing bronchiectasis, improve clinically relevant end-points?
21a.	In infants presenting to hospital or hospitalised with bronchiolitis, does the use of non-oral hydration improve clinically relevant end-points?
21b.	In infants presenting to hospital or hospitalised with bronchiolitis, what forms of non-oral hydration improve clinically relevant end-points
21c.	In infants presenting to hospital or hospitalised with bronchiolitis, does limiting the volume of non-oral hydration impact on clinical relevant end-points?
22	In infants presenting to hospital or hospitalised with bronchiolitis, does infection control practises improve clinically relevant end-points?

CLINICAL RECOMMENDATIONS EVIDENCE SUMMARIES

1. Infants can be diagnosed with bronchiolitis if they have an upper respiratory tract infection followed by onset of respiratory distress with fever, and some of: cough, tachypnoea, retractions and diffuse crackles or wheeze on auscultation.

Strength of recommendation:

NHMRC C

GRADE WEAK

A systematic review and guideline (10) and two prospective observational studies (11, 12) provide recent evidence for the clinical features that make the diagnosis of bronchiolitis likely. The major factors which were predictive were fever, cough, tachypnoea, retractions and wheeze. Other major international guidelines support the clinical diagnosis of bronchiolitis (10, 13).

2. Clinicians should consider as risk factors for more serious illness: gestational age less than 37 weeks; chronological age at presentation less than 10 weeks; exposure to cigarette smoke; breast feeding for less than two months; failure to thrive; having chronic lung disease; having chronic heart and/or neurological conditions; being an indigenous infant, and should take these into account when managing infants with bronchiolitis.

Strength of recommendation:

NHMRC C

GRADE CONDITIONAL

Twenty-two observational studies and two matched case control studies (14-37) provided a diverse patient population and methods, but provide consistent outcomes highlighting chronological age, breast feeding for less than 2 months, poor nutrition, exposure to tobacco smoke, and existing lung disease as being risk factors for more severe bronchiolitis. Two observational studies identify indigenous infants of Australia and New Zealand as being at higher risk (16, 22).

3. Routine CXR is not recommended as it does not improve management in infants presenting with bronchiolitis, and may lead to treatments of no benefit.

Strength of recommendation:

NHMRC D

GRADE CONDITIONAL

Key data on the clinical utility of CXR in infants presenting to or admitted to hospital with bronchiolitis comes from two systematic reviews (Bordley et al (38), including 13 RCTs and three prospective observational studies; Williams et al (39), including five prospective observational studies, one cohort study and two retrospective studies); a systematic review and guideline (10); a qualitative review of the literature (40); two prospective observational studies (41, 42), with Yong et al (42) also including an economic evaluation. Despite the heterogeneity of the studies, outcomes consistently confirm that CXR is not of clinical value in typical bronchiolitis, adds cost, and increases the risk of unnecessary antibiotic use.

4. There is no role for blood tests in managing infants presenting to hospital and hospitalised with bronchiolitis. Routine bacteriological testing of blood and urine is not recommended.

In infants less than two months of age presenting to hospital or hospitalised with bronchiolitis with a temperature over 38 degrees, there is a low risk of UTI. If clinical uncertainty exists clinicians may consider collecting a urine sample for microscopy, culture and sensitivity looking for the concurrent presence of UTI.

Strength of recommendation:

NHMRC D

GRADE CONDITIONAL

A systematic review (38) (which assessed 82 studies) found that studies did not define clear indications for testing or the impact of testing on patient outcomes. A systematic review and guideline (10) found no utility in routine testing. Studies assessing the utility of blood tests in infants with bronchiolitis (38, 43-45) have assessed a variety of markers with none demonstrating clinical benefit.

Studies assessing the incidence of UTI in infants hospitalised with bronchiolitis included a systematic review of infants less than 90 days of age with bronchiolitis (46) including 11 studies (six prospective and five retrospective) and a prospective cohort study of infants with bronchiolitis between 2 and 12months of age (47). The incidence of UTI in infants under 90 days was 3.3% and those aged 2 to 12 months was 2% (48). All studies excluded infants who were severely unwell.

5. In infants with bronchiolitis, routine use of viral testing is not recommended for any clinically relevant end-points, including cohorting of bronchiolitis patients.

Strength of recommendation:

NHMRC C

GRADE CONDITIONAL

Data was obtained from one systematic review (38) which included 82 trials (17 were primary articles on diagnosis of bronchiolitis and 65 were reports of treatment or prevention trials); one systematic review and guideline (10); one controlled clinical trial; and nine prospective observational studies (18, 49-57). The viral panels used were not consistent. There is non-uniformity of study design and outcomes, few studies look at clinical outcomes and where they did, there is lack of evidence of any benefit to clinically relevant outcomes, and routine viral testing cannot be recommended.

6. For infants presenting to hospital or hospitalised with bronchiolitis, there is insufficient evidence to recommend the use of a scoring system to predict need for admission or hospital length of stay.

Strength of recommendation:

NHMRC D

GRADE WEAK

The evidence is based on eight prospective observational cohort studies and two cross sectional observational studies (58-64) which were conducted using a variety of scoring systems (including Kristjansson Respiratory Score, modified Wood's Clinical Asthma Score (M-WCAS) and Tal severity Score, modified Tal, Respiratory Distress Assessment Instrument (RDAI) and the Children's Hospital of Wisconsin Respiratory Score (CHWRS) in addition to the use of specific identified clinical parameters as a scoring system). Limitations to the studies included low number of patients, single centre based studies, unique clinical settings and varied use/comparison of multiple scoring systems across the eight studies. Outcome measures were most often inter-rater reliability, with only a few clinically relevant outcomes used. None of the studies showed benefit for any clinically relevant outcomes (such as need for admission, length of hospital stay, need for ICU admission and representation after discharge from the ED).

7. Oxygen saturations, adequacy of feeding, age (infants younger than eight weeks), and social support should be considered at the time of discharge as a risk for representation. There is insufficient evidence to recommend absolute discharge criteria for infants attending the ED, or hospitalised with bronchiolitis.

Strength of recommendation:

NHMRC PRACTICE POINT

GRADE WEAK

The evidence base for discharge criteria comes from three systematic reviews and guidelines (10, 65, 66) and two multi-centre prospective observational studies (67, 68) involving over 3000 infants. There is insufficient evidence to determine absolute criteria for safe discharge from hospital or the ED, of infants with bronchiolitis, but recommend oxygen saturations and adequacy of feeding are the most important criteria.

8a. Do not administer beta 2 agonists to infants, less than or equal to 12 months of age, presenting to hospital or hospitalised with bronchiolitis.

Strength of recommendation:

NHMRC A

GRADE STRONG

8b. Do not administer beta 2 agonists to infants, less than or equal to 12 months of age, presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy.

Strength of recommendation:

NHMRC D

GRADE WEAK

Data regarding the administration of beta 2 agonists (with the exclusion of adrenaline) in infants presenting to hospital or hospitalised with bronchiolitis comes from one Cochrane systematic review (69) (30 RCTs, n=1992) and three systematic reviews and guidelines (10, 13, 65). Subsequent to the meta-analysis there has been one further small RCT (70) (n= 56) which does not change the findings of the meta-analysis.

Infants with bronchiolitis administered beta 2 agonists do not have any change in rate of hospitalisation (11.9% in beta 2 agonist group vs. 15.9% in placebo group, Odds ratio (OR) 0.75, 95% confidence interval (CI) 0.46 to 1.21, n=710), length of stay (mean difference (MD) 0.06 days,

95% CI -0.27 days to 0.39 days, n=349), or oxygen saturation (MD -0.43%, 95% CI -0.92% to 0.06%, n=1,242). Administration of beta 2 agonists results in a statistical improvement in short term clinical severity scores (standard MD (SMD) -0.30, 95% CI -0.54 to -0.05, n=1,086). However, this marginal change is not associated with any clinically relevant improvement.

Administration of beta 2 agonists in RCTs resulted in the following adverse events tachycardia, hypertension, decreased oxygen saturation, flushing, hyperactivity, prolonged cough, and tremor.

There is no good quality evidence evaluating the effect of beta 2 agonists in infants with bronchiolitis and a personal or family history of atopy. Given the high quality (NHMRC A, GRADE strong) recommendation not to use beta 2 agonists in infants presenting to or hospitalised with bronchiolitis, beta 2 agonists should only be used in infants with a personal or family history of atopy as part of an RCT.

Previously trials of beta 2 agonists have been suggested as a clinical option. However, given the high level of evidence (NHMRC A, GRADE strong) demonstrating no benefit of beta 2 agonists in infants presenting to or hospitalised with bronchiolitis, and that there is no well-established way to determine an "objective method of response" to beta 2 agonists in bronchiolitis, this option is no longer recommended. Although it is true that a small subset of children with bronchiolitis may have reversible airway obstruction resulting from smooth muscle constriction, attempts to define a subgroup of responders have not been successful to date. If a clinical trial of bronchodilators is undertaken, clinicians should note that the variability of the disease process, the host's airway, and the clinical assessments, particularly scoring, would limit the clinician's ability to observe a clinically relevant response to bronchodilators (13).

The sensitivity analysis of the Cochrane systematic review showed no significant subgroup effect in studies involving inpatients versus outpatients (infants in the outpatient studies tended to be older). Limiting the analysis to infants aged less than or equal to 12 months did not improve heterogeneity. Furthermore, infants less than or equal to 12 months of age are included in the Cochrane systematic meta-analysis for the critical outcomes of rate of hospitalisation and length of stay.

A smaller under-powered Cochrane systematic meta-analysis (71) (eight studies, n=281) of short acting beta 2 agonists for recurrent wheeze in children under two years of age has also found that there is no current clinical benefit.

The high quality (NHMRC A, GRADE strong) recommendation not to use beta 2 agonists in infants presenting to or hospitalised with bronchiolitis should be extended to infants less than or equal to 12 months of age.

9. Do not administer adrenaline/epinephrine to infants presenting to hospital or hospitalised with bronchiolitis.

Strength of recommendation:

NHMRC	B
GRADE	STRONG

Data regarding the administration of adrenaline/epinephrine in infants presenting to hospital or hospitalised with bronchiolitis comes from one Cochrane systematic review (72) (19 RCTs, n=2,256) and two systematic reviews and guidelines (13, 65). Subsequent to the Cochrane systematic review there have been three further RCTs comparing adrenaline/epinephrine to a nasal decongestant or beta-2-agonists (Livni et al (73), n=65; Modaressi et al (74), n=40; Simsek-Kiper et al (75), n=75), or to placebo in ambulatory (Sarrell et al (76), n=330) and inpatient settings (Skjerven et al (77), n=404), that have not changed the findings of the meta-analysis.

Infants with bronchiolitis administered adrenaline/epinephrine in ambulatory settings have a significant reduction in rate of hospitalisation within the first 24 hours after initiation of treatment (risk ratio (RR) 0.67, 95% CI 0.50 to 0.89, n=995). However this is not the case when only trials at low risk of bias are analysed (RR 0.77, 95% CI 0.56 to 1.07, n=842), in the most recent study (Sarrell et al (76), n=330), or when hospitalization is analysed over the first seven days after initiating treatment (RR 0.81, 95% CI 0.63 to 1.03, n=875).

Evidence from the Cochrane meta-analysis and the recent high quality RCT (Skjerven et al (77), n=404) do not suggest that administering adrenaline/epinephrine in inpatients with bronchiolitis changes hospital length of stay or readmission rates.

Administration of adrenaline/epinephrine in RCTs resulted in the adverse events of tachycardia, hypertension, pallor, vomiting and tremor.

10. Do not administer nebulised hypertonic saline in infants presenting to hospital or hospitalised with bronchiolitis.

Strength of recommendation:

NHMRC D

GRADE CONDITIONAL

Data regarding the administration of nebulised hypertonic saline in infants presenting to hospital or hospitalised with bronchiolitis is based on one Cochrane systematic review of 11 RCTs (78) and a further nine additional RCTs (79-87). Subsequent to the Cochrane systematic review there have been three further systematic reviews (88-90) and the newer trials have been included in an updated systematic review by the Cochrane authors (91) and a live meta-analysis (92).

Infants admitted to hospital with bronchiolitis and administered nebulised hypertonic saline have a reduced length of stay of 0.45 of a day (95% CI -0.74 to -0.14 days; 15 studies, n=1,922). However there is considerable heterogeneity in this overall result (I2=78%). Removal of two studies with overall length of stay considerably longer than current clinical practice in Australia and New Zealand, and with a primary outcome definition considerably different than that used in Australia and New Zealand for discharge (no respiratory signs or symptoms for 12 hours), partially explains the heterogeneity and results in a pooled estimate suggesting no effect. Furthermore, analysis restricted to the four largest trials, all at lower risk of bias, again suggests no benefit (89). A number of studies included in the meta-analysis also appear to be unbalanced with regards to duration of illness prior to treatment in the hypertonic saline arms.

Infants presenting to hospital with bronchiolitis and administered nebulised hypertonic saline in the ED have a reduced admission rate into hospital of 20% (RR 0.80, 95% CI 0.67 to 0.96; 7 RCTs, n=951). The seven RCTs reporting this outcome included a range of regimens, strengths and added medications. Furthermore, subgroup analysis suggests that nebulised hypertonic saline is not effective in the studies using just one to two doses compared with those using three or more (one to two doses RR 0.93, 95% CI 0.73 to 1.20, 4 RCTs, n=358; three or more doses RR 0.67, 95% CI 0.52 to 0.87, 3 RCTs, n=593; p value for subgroup comparison = 0.07).

In infants receiving nebulised hypertonic saline there appears to be no increased risk of adverse events or change in readmission rates following discharge from EDs.

Evidence from the largest individual studies, and from the meta-analysis, does not consistently provide evidence of improved length of stay following the use of nebulised hypertonic saline. While there is weak evidence of reduced admission rates following the use of nebulised hypertonic saline, there is heterogeneity in the treatment regimens used, and a suggestion that one to two dose regimens are ineffective. Given the lack of long term effect of nebulised hypertonic saline on length of stay the routine use of nebulised hypertonic saline in the ED to reduce admissions is not supported by the current evidence base and nebulised hypertonic saline should only be used in infants with bronchiolitis as part of an RCT.

11a. Do not administer systemic or local glucocorticoids to infants presenting to hospital or hospitalised with bronchiolitis.

Strength of recommendation:

NHMRC B

GRADE Strong

11b. Do not administer systemic or local glucocorticoids to infants presenting to hospital or hospitalised with bronchiolitis, with a positive response to beta 2 agonists.

Strength of recommendation:

NHMRC D

GRADE WEAK

11c. Do not administer a combination of systemic or local glucocorticoids and adrenaline/epinephrine to infants presenting to hospital or hospitalised with bronchiolitis.

Strength of recommendation:

NHMRC D

GRADE WEAK

Data regarding the administration of systemic or local glucocorticoids (nebulisation, oral, IM or IV) in infants presenting to hospital or hospitalised with bronchiolitis comes from one Cochrane systematic review (Fernandes et al (93),17 RCTs, n=2,596) and three systematic reviews

and guidelines (10, 13, 65). Subsequent to the Cochrane systematic review there have been two further RCTs (Alansari et al (94), n=200; Jartti et al (95), n=79).

Infants with bronchiolitis administered glucocorticoids do not have different rates of hospitalisation (day one RR 0.92, 95% CI 0.78 to 1.08, n=1,762; day seven RR 0.86, 95% CI 0.70 to 1.06, n=1,530) or clinically significant differences in length of stay (mean difference -0.18, 95% CI -0.39 to 0.04, n=633).

There is no good quality evidence evaluating the effect of glucocorticoids in infants with bronchiolitis and a positive response to beta 2 agonists. Furthermore there is no good quality evidence evaluating the effect of glucocorticoids in infants with a personal or family history of atopy. Given the high quality (NHMRC B, GRADE strong) recommendation not to use glucocorticoids in infants presenting to or hospitalised with bronchiolitis, glucocorticoids should only be used in infants with a positive response to beta 2 agonists as part of an RCT.

Adrenaline/epinephrine is not recommended for use in infants presenting to or hospitalised with bronchiolitis (NHMRC B, GRADE strong). This recommendation is based on one Cochrane systematic review (Hartling et al (72), 19 RCTs, n=2,256), three systematic reviews and guidelines (10, 13, 65) and seven subsequent RCTs (73-77, 96, 97).

Evidence for the administration of the combination of glucocorticoids and adrenaline/epinephrine in infants presenting to or hospitalised with bronchiolitis comes from a single multi-centre RCT conducted in eight EDs in Canada (Plint et al (98), n=800). This trial compared adrenaline and high dose dexamethasone in a factorial design. Admission rates in unadjusted analysis suggested a possible benefit in the combination arm (adrenaline/epinephrine and glucocorticoid admission on day of enrolment (RR 0.65, 95% CI 0.41 to 1.04; day 7 RR 0.65, 95% CI 0.45 to 0.95). However when adjusted for multiple comparisons in the factorial design this was no longer significant (adrenaline/epinephrine and glucocorticoid admission on day of enrolment RR 0.65, 95% CI 0.37 to 1.15; day 7 RR 0.65, 95% CI 0.41 to 1.03).

Given the evidence base for the single interventions, and the exploratory nature of the findings in the Plint trial (98) combination treatment with glucocorticoids and adrenaline/epinephrine should only be used in infants with bronchiolitis as part of an RCT.

12a. Consider the use of supplemental oxygen in the treatment of hypoxic (oxygen saturations less than 92%) infants with bronchiolitis.

Strength of recommendation:

NHMRC C

GRADE CONDITIONAL

12b. In uncomplicated bronchiolitis oxygen supplementation should be commenced if the oxygen saturation level is sustained at a level less than 92%. At oxygen saturation levels of greater than or equal to 92%, oxygen therapy should be discontinued.

Strength of recommendation:

NHMRC C

GRADE CONDITIONAL

In evaluating the effect of oxygen administration for infants with bronchiolitis the evidence is based on a systematic review (99), a systematic review and guideline (13), a prospective observational case series of 68 infants(100) and a retrospective observational cohort study of 127 infants (101). There was low to very low level evidence for the use supplemental oxygen although the evidence based guideline formed a weak recommendation based on low level evidence and reasoning from first principles (13). There was no evidence of the effect of oxygen therapy on readmission to hospital or on feeding difficulties. There is no evidence of the benefit of oxygen in children without hypoxia.

The benefit of supplemental oxygen therapy has not been specifically studied - rather there is an assumption about the benefits of oxygen and the observational studies have principally looked at length of time of administration and feeding difficulties as a gauge of effectiveness. Therefore oxygen therapy is based on practice by first principles and low to very low-grade evidence. The evidence is applicable to the Australian and New Zealand setting.

The evidence relating to the role of oxygen saturations in patient management is based on two systematic reviews (99, 102), a systematic review and guideline (13) and two RCTs of 828 infants (103, 104). Additional evidence is from a prospective observational case series of 68 infants (100) and three retrospective observational studies (101, 105, 106). The absolute level of oxygen saturation for supplemental oxygen therapy to commence with the threshold has ranged in these studies from 90 - 94%.

For the critical outcome of admission to hospital there is moderate evidence that oxygen saturation levels affects the decision to admit independently of other factors including signs of respiratory distress.

For the critical outcome of length of stay in hospital there is low level evidence that oxygen saturation targets prolong length of stay with a target of less than 92% established as a need for commencement of oxygen supplementation.

For the important outcome of readmission there is high level evidence that oxygen level saturations do not affect readmissions to hospital.

For the important outcome of feeding difficulties there is very low evidence for the impact of oxygen saturation targets.

To date, neither of the RCTs have reported long-term neurodevelopmental outcomes.

13. Routine use of continuous pulse oximetry is not required for medical management of non-hypoxic (saturations greater than or equal to 92%) infants not receiving oxygen, or stable infants receiving oxygen.

Strength of recommendation:

NHMRC C

GRADE CONDITIONAL

The evidence is based on two high quality evidence reviews (13, 99). In addition, there was one randomised, double-blind, parallel-group trial (104) involving 213 infants, one randomised, parallel-group, superiority clinical trial (107) of 161 infants to either continuous vs. intermittent pulse oximetry and one prospective observational study (100) of 68 patients evaluating discharge oxygen saturation levels. A further three retrospective studies (101, 105, 106) involved 439 infants.

For the critical outcome of length of stay there is moderate evidence that continuous monitoring of pulse oximetry increases hospital length of stay. A prospective observational study (108) subjects with bronchiolitis demonstrated significantly lower nocturnal baseline SpO2 than control infants without lung disease or upper airway obstruction on admission which recovered during hospitalisation.

For the critical outcome threshold for discharge oxygen saturations there is low quality evidence on the comparative effect of different discharge oxygen saturation thresholds. For the critical outcome frequency of nocturnal desaturations there is very low quality evidence to indicate that the frequency of nocturnal desaturations prolongs length of stay. For the important outcome of feeding there is very low quality evidence that the disease course or hospital length of stay is altered by maintaining feeding. For the important outcome of cost there was no evidence of reduced cost savings in those infants admitted with bronchiolitis on continuous oximetry monitoring.

14. HFNC in bronchiolitis can be considered in the inpatient setting in children with bronchiolitis with hypoxia (oxygen saturations less than 92%). Its use in children without hypoxia should be limited to the RCT setting only.

Strength of recommendation:

NHMRC C

GRADE CONDITIONAL

There have been limited studies on HFNC in children with bronchiolitis during inpatient stay outside of the paediatric ICU (PICU). A Cochrane systematic review (109) one systematic review and guideline (13), one RCT (110), two prospective studies (111, 112), four non-systematic reviews (113-116) and one retrospective cohort review (117) all provide low to very low level evidence for the benefit of HFNC. A prospective interventional study of 14 infants with bronchiolitis demonstrates reduction in work of breathing receiving HFNC (118).

There are insufficient studies and patients investigated to recommend HFNC as a standard therapy in a general paediatric unit.

For the critical outcome of length of stay in hospital there is low quality evidence that HFNC oxygen improves length of stay in hospital.

For the critical outcome for rate of PICU admission there is low quality evidence that HFNC oxygen reduces PICU admission rates.

For the important outcome of adverse events there is very low evidence that HFNC oxygen is safe.

For the important outcome of cost there is very low evidence that oxygen administered via HFNC may reduce overall health care cost, with the potential to reduce patient transfers both between hospitals and to the PICU.

15. Chest physiotherapy is not recommended for routine use in infants with bronchiolitis.

Strength of recommendation:

NHMRC B

GRADE STRONG

There is one Cochrane systematic review (119) with nine clinical trials including 891 patients on the topic. In addition there is one low quality RCT (120) two prospective clinical trials (121, 122) and three observational trials (123-125) of very low quality and one systematic review and guideline (10). For the critical outcome of change in severity status of bronchiolitis there is moderate evidence that physiotherapy does not alter severity. For the critical outcome of time to recovery/ clinical stability there is high quality evidence that physiotherapy does not improve recovery or stability. For the critical outcome of oxygen saturation levels there is very low level evidence of physiotherapy improving this outcome. For the important outcome of duration of oxygen supplementation there is high quality evidence that duration is not altered by physiotherapy. For the important outcome of length of hospital stay there is high level evidence that length of stay is not altered by physiotherapy. For the important outcome of complications of therapy there is high-level evidence of minimal adverse effects resulting from physiotherapy. For the important outcome of heart rate variability there is very low level evidence that heart rate variability is modified by physiotherapy.

16a. Nasal suction is not recommended as routine practice in the management of infants with bronchiolitis. Superficial suction may be considered to assist with feeding.

Strength of recommendation:

NHMRC D

GRADE CONDITIONAL

16b. Deep nasal suction for the management of bronchiolitis is not recommended.

Strength of recommendation:

NHMRC D

GRADE CONDITIONAL

There is only one retrospective comparative study (125) of 740 patients examining suction types and frequency. Three non-systematic reviews or guidelines refer to the use of suction but without provision of references and are rated very low. For the critical outcome of length of hospital stay there is low level evidence that the use of deep nasal suction increases length of hospital stay while non-invasive frequent suction may decrease length of stay. There was low level evidence for the important outcome of increased adverse events.

17. Routine nasal saline drops are not recommended. Trial of intermittent saline drops may be considered at time of feeding.

Strength of recommendation:

NHMRC PRACTICE POINT

GRADE WEAK

There is no Cochrane review. Two RCTs use administration of nasal saline as the control therapy in chest physiotherapy techniques (120) or phenylephrine nasal drops (126). A guideline (127) and a review article (128) recommend nasal saline as a practice point. Nasal saline drops have not been demonstrated to improve outcomes in bronchiolitis but may be considered for use particularly prior to feeding (breast or bottle). No evidence is available to demonstrate benefit or harm.

18. Nasal CPAP therapy for infants with bronchiolitis may be considered for the management of infants.

Strength of recommendation:

NHMRC C

GRADE CONDITIONAL

One Cochrane systematic review (129) analysed two RCTs with a total of 50 patients with low level of evidence and high risk of biases. Relevant clinical outcomes, such as intubation rates, were addressed and a trend towards reduction in intubations was shown. A recent prospective observational study (130) of low quality evaluated general paediatric ward administration of nCPAP. A retrospective study (131) of very low quality compared HFNC to nCPAP

in the ICU setting only. Two recent systematic reviews (116, 132) analysed the use of nCPAP for bronchiolitis. All studies are inconsistent as they evaluated different populations (PICU vs. ward) and interventions (HFNC, nCPAP). There was no evidence for the effect of nCPAP on the important outcome of duration of ED length of stay.

19. After a period of observation, infants at low risk for severe bronchiolitis can be considered for discharge on home oxygen as part of an organised 'Home Oxygen Program' which has clear 'Return to Hospital' advice.

Strength of recommendation:

NHMRC C

GRADE CONDITIONAL

There have been no systematic reviews on this question. The evidence is based on two RCTs of 136 infants both with methodological flaws. One trial (133) was stopped before the enrolment of the desired number of patients in their sample-size calculation was achieved and one trial (134) had very low numbers to compare the two groups in terms of evaluating the cost savings plus the patients were recruited over a single bronchiolitis season. Additional evidence comes from one prospective observational study (135) one retrospective comparative study (136) and three retrospective chart reviews (137-139). For the critical outcome of length of stay in hospital there is very low quality evidence of a reduced length of stay in those treated with home oxygen therapy and there is very low evidence for the critical outcome of the total length of oxygen therapy. For the important outcome of cost savings there is very low quality evidence of reduced costs in those treated with home oxygen therapy. For the critical outcome of readmission within seven days there is very low quality evidence of a reduced readmission rate in those treated with home oxygen therapy. For the important outcome of adverse events there is very low quality evidence of no increase in adverse events in those treated with home oxygen therapy. All studies have had exclusions of infants with factors that place them at risk of severe disease and the evidence to date has indicated no increased risk of harm in infants treated. However, the studies have been underpowered or only observational with risk of imprecision and inconsistency. The true effect on harm has not been established.

20a. Do not use antibiotics to treat infants with bronchiolitis.

Strength of recommendation:

NHMRC B

GRADE CONDITIONAL

20b. Do not use azithromycin for treatment of infants admitted to hospital with bronchiolitis.

Strength of recommendation:

NHMRC B

GRADE CONDITIONAL

20c. Do not use azithromycin for treatment of infants admitted to hospital with bronchiolitis who are at risk of developing bronchiectasis.

Strength of recommendation:

NHMRC C

GRADE CONDITIONAL

Two Cochrane systematic reviews (140, 141) and a single RCT of 40 infants (142) showed no benefit of antibiotics for treating bronchiolitis, in terms of hospital length of stay and hospital readmission rates (140) or persisting symptoms (141). The risk of secondary bacterial infection in bronchiolitis is very low and there is potential harm of antibiotics use from adverse reactions and increased antibiotic resistance.

One Cochrane systematic review containing three RCTS (140) shows that there is no difference in length of stay, PICU admission, or symptom resolution for those treated with azithromycin versus placebo for infants hospitalised with bronchiolitis.

There is low quality evidence (140) that there is no difference in length of stay, PICU admission, or symptom resolution for those treated with azithromycin versus placebo for infants hospitalised with bronchiolitis.

One RCT of azithromycin versus placebo, once a week for three weeks, in 219 indigenous infants enrolled in Australia and New Zealand found no difference in length of hospital stay, symptoms at 21 days, adverse events or readmission rates at six months (143). There are no reports on bronchiectasis as an outcome.

21a. Supplemental hydration is recommended for infants who cannot maintain hydration orally.

Strength of recommendation:

NHMRC PRACTICE POINT

GRADE WEAK

A Cochrane systematic review(144) of benefit versus harm from advice to increase fluid intake for treating acute respiratory infections was unable to identify any evidence from RCTs in the primary care or outpatient setting.

21b. Both NG and IV routes are acceptable means for non-oral hydration in infants admitted to hospital with bronchiolitis.

Strength of recommendation:

NHMRC B

GRADE STRONG

A large RCT(145) of 759 infants showed no difference in mean length of stay for infants with bronchiolitis treated with IV hydration vs. NG feeds; however there was a higher likelihood of success of first insertion of NG tubes versus IV cannulae.

21c. There is insufficient evidence to recommend a specific proportion of maintenance fluid. There is a risk of fluid overload and judicious and vigilant use of hydration fluid is recommended. Isotonic fluid is recommended.

Strength of recommendation:

NHMRC PRACTICE POINT

GRADE WEAK

Serious concerns about risk of hyponatraemia in moderate bronchiolitis (146) have prompted caution about use of hypotonic IV fluids in infants with bronchiolitis. Regimens of fluid volumes, from restricted to liberal, have been used with little evidence supporting their use.

22. Hand hygiene is the most effective intervention to reduce hospital acquired infections and is recommended. There is inadequate evidence for the benefits of cohorting bronchiolitic patients.

Strength of recommendation:

NHMRC B

GRADE WEAK

The current evidence is derived from observational studies (147-150). No RCT on containing common viral infections such as RSV by different infection control practices in ED or general paediatric ward setting is available. The Cochrane systematic review (151) on this topic focuses on different pandemic viral infections affecting a range of population in a variety of settings. This evidence could be extrapolated as indirect evidence for infants with bronchiolitis secondary to common respiratory viral infections for the outcome of nosocomial infection rates.

GRADE & NHMRC EVIDENCE TABLES

Question 1. GRADE Evidence Summary

Considered Judgement - Strength of recommendation							
Question 1: In infants presenting to hospital what factors in the history and physical examination contribute to a differential diagnosis of bronchiolitis?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
	HIGH	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Diagnosis of bronchiolitis			**x**		**x**		
O_2 Sensitivity and specificity			**x**		**x**		
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement A systematic review and guideline and two prospective observational studies provide recent evidence for the clinical features that make the diagnosis of bronchiolitis likely. The major factors which were predictive were fever, tachypnoea, retractions and wheeze. Other major international guidelines support the clinical diagnosis of bronchiolitis. Major guidelines all suggest a clinical picture of bronchiolitis but site no supportive evidence for the predictive value of these clinical findings.							
3. What benefit will the proposed intervention/action have?							
Evidence statement The combination of cough, wheeze and retractions demonstrate RSV positive bronchiolitis (as opposed to bronchiolitis from other viruses) with a sensitivity of 0.8.				**Quality of evidence** **LOW**			
Judging the benefits in context The evidence is applicable and generalizable to the New Zealand and Australian health settings.							
4. What harm might the proposed intervention/action do?							
Evidence statement Single observational study with limited numbers.				**Quality of evidence** **VERY LOW**			
Judging the harms in context Risks of missing diagnosis of other serious conditions such as cardiac failure remains, but evidence for other clinical or test features for diagnoses these in this context are missing.							
5. What is the likely balance between good and harm?							
Evidence statement Clinical diagnosis is reasonably accurate but awareness of differential diagnoses needs to be maintained.				**Overall quality of evidence** **VERY LOW**			
Judging the balance of benefits and harms in context Given the wealth of clinical experience within the bronchiolitis working party, I am confident that clear guidelines around diagnosis of bronchiolitis will be able to be made around consensus of opinion.							
Benefits clearly outweigh harms	Recommend			STRONG			
Benefits probably outweigh harms	Consider			CONDITIONAL			
Not known	**Make a recommendation for research (see 8 below)**			**WEAK**			
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against			CONDITIONAL			
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against			STRONG			
6. Is the intervention/action implementable in the New Zealand and Australian context?							
Summary statement This evidence is directly transferrable to the Australasian population.							
Yes	**Recommend/consider**						
Not known	Consider economic evaluation						
No	Recommend/consider against						
7. Final recommendation							
Infants can be diagnosed with bronchiolitis if they have an upper respiratory tract infection followed by onset of respiratory distress with fever, and one or more of cough, tachypnoea, retractions and diffuse crackles or wheeze on auscultation.				**Strength of recommendation** STRONG CONDITIONAL **WEAK**			
8. Recommendations for research							
Research defining the positive and negative predictive values of clinical criteria for diagnosing bronchiolitis is needed. Especially that that gives strength to the ability to refute the diagnosis of bronchiolitis when other conditions are present (e.g. cardiac failure, immunodeficiency).							

Question 1. NHMRC Evidence Summary

Question 1: In infants presenting to hospital what factors in the history and physical examination contribute to a differential diagnosis of bronchiolitis.	**Evidence table ref:** Amat 2014, Corneli 2012, Drolia 2009, Durani 2008, McLellan 2014, Ralston 2014, Ricci 2015 (10-13, 21, 152, 153).

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

A systematic review and guideline and two prospective observational studies provide recent evidence for the clinical features that make the diagnosis of bronchiolitis likely. The major factors which were predictive were fever, cough, tachypnoea, retractions and wheeze. Other major international guidelines support the clinical diagnosis of bronchiolitis. Major guidelines all suggest a clinical picture of bronchiolitis but cite no supportive evidence for the predictive value of these clinical findings.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	**Not applicable (one study only)**

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

Well conducted prospective study	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

Evidence in children under 36 months not entirely generalizable to infants under one year of age.	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

Studies were undertaken in the USA but the evidence is applicable to children in Australia and New Zealand with bronchiolitis.	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	**Evidence applicable to Australian/New Zealand healthcare context with few caveats**
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	**Not applicable (one study only)**
3. Clinical Impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats

EVIDENCE STATEMENT

There is one prospective cohort study from USA assessing clinical predictors of RSV bronchiolitis infection in infants and children less than 36 months of age. One hundred and ninety seven patients were admitted to hospital with suspected RSV infection – all had viral testing.
They identified cough, fever, wheeze, and retractions as independent predictors.

Major guidelines all suggest a clinical picture of bronchiolitis but site no supportive evidence for the predictive value of these clinical findings.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Infants can be diagnosed with bronchiolitis if they have an upper respiratory tract infection followed by onset of respiratory distress with fever, and one or more of: cough, tachypnoea, retractions and diffuse crackles or wheeze on auscultation.	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	**Body of evidence provides some support for recommendations(s) but care should be taken in its application**
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

Further research should concentrate on risk factors for other conditions that may masquerade as bronchiolitis including immunodeficiency, congenital lung disease and cardiac anomalies.

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 2. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 2: In infants presenting to hospital with bronchiolitis, what are the risk factors for admission or severe disease (e.g. prolonged length of hospital stay, ICU admission, death)?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Admission to hospital			X			X	
O_2 Admission to ICU			X		X		
O_3 Prolonged hospital length of stay			X			X	
O_4 Death			X		X		

2. Is there sufficient evidence to make a recommendation?

Evidence statement:
Twenty two observational studies and two matched case control studies provided a diverse patient population and methods, but provide consistent outcomes. Two observational studies included indigenous Australians and New Zealanders. Many studies focussed on individual risk factors (e.g. prematurity, cigarette smoke exposure, chronological age at presentation) with diverse inclusion criteria and outcomes. Despite the number of studies there are only a few studies supporting each risk factor, but findings were consistent. Significant inconsistency was demonstrated in the role of RSV infection as a risk factor.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
Gestational age less than 37 weeks; chronological age at presentation less than 10 weeks; postnatal exposure to cigarette smoke; breast feeding for less than two months; failure to thrive; being of indigenous origin; having chronic lung disease should all be considered as risk factors for more serious illness.	**LOW**

Judging the benefits in context
Benefit of ensuring clinicians think about the management more carefully in those thought to be at high risk. No harms in applying this.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
Clinicians should consider the presence of any of the risk factors when making management decisions in infants with bronchiolitis.	**LOW**

Judging the harms in context
No harms.

5. What is the likely balance between good and harm?

Evidence statement	Overall quality of evidence
Reducing discharge of infants likely to deteriorate must be weighed against the risks of inpatient hospital stay.	**LOW**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	**Consider**	**CONDITIONAL**
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Implementable in Australia and New Zealand.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Clinicians should consider; gestational age less than 37 weeks; chronological age at presentation less than 10 weeks; postnatal exposure to cigarette smoke; breast feeding for less than two months; failure to thrive; having chronic lung disease; being an indigenous infant all as risk factors for more serious illness and should take these into account when managing infants with bronchiolitis.	**Strength of recommendation** STRONG **CONDITIONAL** WEAK

8. Recommendations for research

Large cohort studies are needed to define the relative risk of particular factors and to define subpopulations with increased risk or other risk factors.

Question 2. NHMRC Evidence Summary

Question 2: Question 2: In infants presenting to hospital with bronchiolitis, what are the risk factors for admission or severe disease (e.g. prolonged hospital stay, ICU admission, death)?	**Evidence table ref:** Al-Sheri 2005, Alvarez 2013, Bailey 2009, Bradley 2005, Brand 2012, Chan 2002, Chatzimichael 2007, Corneli 2012, Craig 2008, Damore2008, DiFranza 2012, Figueras 2004, Garcia 2010, Gouyon 2013, Hasegawa 2015, Helfrich 2015, Holman 2003, Marlais 2011, Papoff 2011, Sala 2015, Somech 2006, Stagliano 2015, Trefny 2000, Voets 2006 (14-37).

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Twenty two observational studies and two matched case control studies provided a diverse patient population and methods, but provide consistent outcomes. Two observational studies included indigenous Australians and New Zealanders. Many studies focussed on individual risk factors (e.g. prematurity, cigarette smoke exposure, chronological age at presentation) with diverse inclusion criteria and outcomes. Despite the number of studies there are only a few studies supporting each risk factor, but most findings were consistent. Significant inconsistency was demonstrated in the role of RSV infection as a risk factor.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

Some inconsistency in outcome measures and patient populations making comparison across studies difficult.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	Evidence is not consistent
	NA	Not applicable (one study only)

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

Risk factors for more severe disease in bronchiolitis are elucidated and will help clinicians make informed decisions.	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

Should be generalisable but study populations were heterogeneous.	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	**Evidence not directly generalisable to target population but could be sensibly applied**
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	**Evidence applicable to Australian/New Zealand healthcare context with few caveats**
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		
Component	**Rating**	**Description**
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical Impact	C	Moderate
4. Generalisability	C	Evidence not directly generalisable to target population but could be sensibly applied
5. Applicability	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
Evidence statement Multiple observational studies with inconsistencies in design and outcomes but consistency of findings. Evidence applicable to Australian and New Zealand settings and should guide practice with consideration to local ad patient factors.		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Clinicians should consider; gestational age less than 37 weeks; chronological age at presentation less than 10 weeks; postnatal exposure to cigarette smoke; breast feeding for less than 2 months; failure to thrive; having chronic lung disease; being an indigenous infant all as risk factors for more serious illness and should take these into account when managing infants with bronchiolitis.	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	**Body of evidence provides some support for recommendations(s) but care should be taken in its application**
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care? Currently little adrenaline/epinephrine are used in clinical practice in Australia and New Zealand, this is in contrast to North American practice.	YES **NO**
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

Question 3. GRADE Evidence Summary

Considered Judgment - Strength of recommendation

Question 3: In infants presenting to hospital or hospitalised with bronchiolitis, does performing CXR beneficially change medical management or clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcomein making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Diagnostic accuracy				X	X		
O_2 Cost savings (without compromise of diagnostic accuracy of alternate diagnoses)				X		X	
O_3 Indicator for administration of antibiotics				X	X		
O_4 Readmission				X		X	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

Key data on the clinical utility of CXR in infants presenting to or admitted to hospital with bronchiolitis comes from two systematic reviews (Bordley et al (38), including 13 RCTs and three prospective observational studies; Williams et al (39), including five prospective observational studies, one cohort study and two retrospective studies); a systematic review and guideline (10); a qualitative review of the literature (40); two prospective observational studies (41, 42), with Yong et al (42) also including an economic evaluation. Despite the heterogeneity of the studies, outcomes consistently confirm that CXR is not of clinical value in typical bronchiolitis, adds cost and increases the risk of unnecessary antibiotic use.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
For the critical outcome of diagnostic accuracy, there is low quality evidence of a reduced length of stay in those patients who receive a CXR. For the important outcome of cost saving, evidence of low quality indicates that avoiding CXR saves money. For the important outcome on indication for administration of antibiotics, there is low quality evidence that suggests CXR is not useful in confirming the diagnosis of bronchiolitis, and that it leads to unnecessary antibiotic use	**VERY LOW**

Judging the benefits in context

The evidence is applicable and generalisable to the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
For the important outcome of readmission rate there is low quality evidence of improved diagnostic accuracy in the infants who had a CXR taken.	**VERY LOW**

Judging the harms in context

Evidence to date indicates no direct increased risk of harm in infants receiving a CXR, but with some increased risk of unnecessary antibiotic use. However the majority of studies have only been in mild or moderately unwell infants, and so the risk in severely unwell infants is unknown.

5. What is the likely balance between good and harm?

Evidence statement	Overall quality of evidence
Harms are likely to outweigh benefits.	**VERY LOW**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms **Harms probably outweigh benefits**	**Consider against**	**CONDITIONAL**
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

The evidence is implementable in Australia and New Zealand

Yes	Recommend/consider
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Routine CXR does not improve management in infants presenting with simple bronchiolitis, and may lead to treatments of no benefit.	**Strength of recommendation** STRONG **CONDITIONAL** WEAK

Recommendation for research

Studies on children with more severe bronchiolitis are needed to define the role of CXR in this population.

Question 3. NHMRC Evidence Summary

Question 3. In infants presenting to hospital or hospitalised with bronchiolitis, does performing CXR beneficially change medical management or clinically relevant end-points?		**Evidence table ref:** Bordley 2004, Caiulo 2011, Farah 2002, Kern 2001, Kneyber 2001, Offer 2000, Quintero 2007, Ricci 2015, Schuh 2007, Williams 2012, Yong 2009 (10, 38-42, 154-158).
1. Evidence base (number of studies, level of evidence and risk of bias in the included studies)		
Key data on the clinical utility of CXR in infants presenting to or admitted to hospital with bronchiolitis comes from two systematic reviews (Bordley et al (38), including 13 RCTs and three prospective studies; Williams et al (39), including five prospective observational studies, one cohort study and two retrospective studies); a systematic review and guideline (10); a qualitative review of the literature (40); two prospective observational studies (41, 42), with Yong et al (42) also including an economic evaluation. Despite the heterogeneity of the studies, outcomes consistently confirm that CXR is not of clinical value in typical bronchiolitis, adds cost and increases the risk of unnecessary antibiotic use.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency (if only one study was available, rank this component as 'not applicable')		
Evidence regarding the use of CXRs is not consistent, due to the heterogeneity of the studies. Outcomes from Bordley et al (38) suggests that in mild disease, CXRs offer no information that is likely to affect treatment and should not routinely be performed. Data from two studies (41, 42) demonstrate that CXRs may lead to the use of antibiotics. Therefore more likely to be inappropriate use than to improve clinical outcomes and insufficient data exists to show that CXR films reliably distinguish between viral and bacterial disease or predict severity of disease. Yong et al (42) concludes that for infants with typical bronchiolitis, omitting radiography is cost saving without compromising diagnostic accuracy of alternate diagnoses and of associated pneumonia. Schuh et al (41) suggests that radiographs in children with typical bronchiolitis have limited value in children without severe distress or significant hypoxia.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	**Evidence is not consistent**
	NA	Not applicable (one study only)
3. Clinical impact (indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)		
That radiographs in children with typical bronchiolitis have no proven value in children with bronchiolitis outside the ICU setting, and may lead to treatments that are of no benefit.	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted
4. Generalisability (how well does the body of evidence match the population and clinical settings being targeted by the guideline?)		
Studies were conducted in a number of countries including the USA, Canada, Europe and Israel using populations that are directly generalizable to patients with bronchiolitis seen in Australia and New Zealand.	**A**	**Evidence directly generalisable to target population**
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability (is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)

The results are applicable to the Australian and New Zealand health care context with few caveats.	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	**Evidence applicable to Australian/New Zealand healthcare context with few caveats**
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX (summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)

Component	Rating	Description
1. Evidence base	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency	D	**Evidence is not consistent**
3. Clinical Impact	C	**Moderate**
4. Generalisability	A	**Evidence directly generalisable to target population**
5. Applicability	B	**Evidence applicable to Australian/New Zealand healthcare context with few caveats**

Evidence statement

For the critical outcome of diagnostic accuracy, there is low quality evidence of a reduced length of stay in those patients who receive a CXR.

For the important outcome of cost saving, evidence of low quality suggests that avoiding CXR saves money

For the important outcome on indication for administration of antibiotics, there is low quality evidence that suggests CXR is not useful in confirming the diagnosis of bronchiolitis, and that it leads to unnecessary antibiotic use

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Routine CXR does not improve management in infants presenting with simple bronchiolitis, and may lead to treatments of no benefit.	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	**Body of evidence is weak and recommendation must be applied with caution**
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care? Some clinicians are currently using routine CXR.	**YES** NO
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

Question 4. GRADE Evidence Summary

Considered Judgement - Strength of recommendation							
Question 4: In infants presenting to hospital and hospitalized with bronchiolitis, does performing pathology tests (blood and urine) beneficially change medical management or clinically relevant end points.							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
	HIGH	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Length of stay				**X**	**X**		
O_2 Length of stay in ICU				**X**		**X**	
O_3 Death in ICU				**X**		**X**	
O_4 Diagnosis of bacterial co-infection				**X**		**X**	
O5 Diagnosis of pneumonia				**X**		**X**	
O6 Diagnosis of UTI		**X**				**X**	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

Evidence for diagnostic testing comes from a systematic review (38) that identified 82 studies. Bordley et al (38) found that studies did not define clear indications for testing or the impact of testing on patient outcomes.

Subsequent studies have indicated some risk of UTI in younger infants (47).

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
There is evidence from two cohort studies, one prospective and one retrospective, demonstrating that in febrile infants with a diagnosis of bronchiolitis, one from 2-12 months of age and the other in infants less than eight weeks (with RSV positive bronchiolitis) that the rate of UTI is 2% and 1.4% respectively. Another study with low evidence rating demonstrated that in febrile infants under 60 days of age with a diagnosis of bronchiolitis, the rate of UTI was 3.3%. There is very low quality and inconsistent evidence that procalcitonin can predict the presence of co-infection in an infant with bronchiolitis. The clinical role of procalcitonin is yet to be defined. With regards to length of stay, there was one study demonstrating that length of stay is not affected by measurement of CRP.	**LOW**

Judging the benefits in context

This is applicable to infants in Australia and New Zealand.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Evidence has not suggested any adverse harm in children having a urine sample tested for UTI. There is a theoretical risk there will be false positives and therefore unnecessary antibiotics given. The evidence for doing blood tests to look for co-infection is very low and of unknown clinical importance. There is pain and discomfort associated with blood tests and invasive urine testing.	**LOW**

Judging the harms in context

For otherwise well febrile children with bronchiolitis the harms of blood testing and urine testing probably outweigh the benefits.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence LOW**
It is likely that testing urine in infants with bronchiolitis will not cause any harm, but needs to be confined to the patients at highest risk.	

Judging the balance of benefits and harms in context

The benefits are likely to outweigh the harm

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	**Consider against**	**CONDITIONAL**
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
There is no role for blood tests in managing infants presenting to hospital and hospitalised with bronchiolitis. Routine bacteriological testing of urine or blood is not indicated. **In infants less than 2 months of age who are hospitalised or in hospital for bronchiolitis with a temperature over 38 degrees, there is a low risk of UTI. If clinical uncertainty exists clinicians may consider collecting a urine sample for microscopy, culture and sensitivity looking for the concurrent presence of UTI.**	**Strength of recommendation** STRONG **CONDITIONAL** WEAK
8. Recommendations for research	
More research needs to look into whether febrile (greater than 38^{0}C) infants (less than or equal to 12 months) with a clear diagnosis of bronchiolitis have a concurrent UTI as this not only has implications for immediate treatment but also for further imaging of the urinary tract. Research on the clinical role of new markers of bacterial infection is needed to define any role for them in the clinical environment.	

Question 4. NHMRC Evidence Summary

Question 4: In infants presenting to hospital and hospitalized with bronchiolitis, does performing blood tests (blood and urine) beneficially change medical management or clinically relevant end points?		**Evidence table ref:** Bordley 2004, Dayan 2004, Elkhunovich 2015, Fares 2011, Laham 2014, Luu 2013, Ralston 2011, Ricci 2015, Titus 2003 (10, 38, 43-48, 159).
1. Evidence base (number of studies, level of evidence and risk of bias in the included studies)		
Evidence for diagnostic testing comes from a systematic review (38) that identified 82 studies. They found that studies did not define clear indications for testing or the impact of testing on patient outcomes. A systematic review and Guideline (10) recommends against routine diagnostic testing. Studies assessing the incidence of UTI in infants hospitalised with bronchiolitis included a systematic review of infants under 90 days of age with bronchiolitis (46) including 11 studies (6 prospective and 5 retrospective) a prospective cohort study of infants with bronchiolitis between 2 and 12 months of age (47).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency (if only one study was available, rank this component as 'not applicable')		
In the studies looking at urine, different age groups were looked at – less than 60days (48), less than 8 weeks (159) and 2-12 months (47). In the studies looking for bacterial co infection using blood tests, one study looked at procalcitonin and one looked CRP, FBC and ESR and therefore no comment can be made on consistency.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact (indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)		
There is moderate evidence from two cohort studies, one prospective and one retrospective, demonstrating that in febrile children with a diagnosis of bronchiolitis, one from 2-12 months of age and the other in infants less than 8 weeks (with RSV positive bronchiolitis) that the rate of UTI is 2% and 1.4% respectively. Another study with low evidence rating demonstrated that in febrile children under 60 days of age with a diagnosis of bronchiolitis, the rate of UTI was 3.3%. There is moderate evidence that blood tests do not impact clinical outcomes.	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted
4. Generalisability (how well does the body of evidence match the population and clinical settings being targeted by the guideline?)		
They are mainly applicable to this guideline.	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

Study outcomes are applicable in Australia and NZ	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	**Evidence applicable to Australian/New Zealand healthcare context with few caveats**
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors (indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)

In the study designs on measuring urines, it is not always clear exactly how bronchiolitis was diagnosed and therefore the question arises as to whether the children had a primary diagnosis of bronchiolitis or UTI.

EVIDENCE STATEMENT MATRIX (summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical Impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian healthcare context with few caveats

Evidence statement

There is evidence from two cohort studies, one prospective and one retrospective, demonstrating that in febrile infants with a diagnosis of bronchiolitis, one from 2-12 months of age and the other in infants less than 8 weeks (with RSV positive bronchiolitis) that the rate of UTI is 2% and 1.4% respectively. Another study with low evidence rating demonstrated that in febrile infants under 60 days of age with a diagnosis of bronchiolitis, the rate of UTI was 3.3%.

There is no consistency of the evidence relating to blood tests with a systematic review highlighting that there has been no evidence to suggest benefit to clinically relevant outcomes There is very low quality and inconsistent evidence that procalcitonin can predict the presence of co-infection in an infant with bronchiolitis. The clinical role of procalcitonin is yet to be defined.

Regarding length of stay, one study demonstrated that length of stay is not affected by measurement of CRP.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
There is no role for blood tests in managing infants presenting to hospital and hospitalized with bronchiolitis.	**C**	**Body of evidence provides some support for recommendations(s) but care should be taken in its application**
	D	Body of evidence is weak and recommendation must be applied with caution
In infants less than two months of age who are hospitalised or in hospital for bronchiolitis with a temperature over 38 degrees, there is a low risk of UTI. If clinical uncertainty exists clinicians may consider collecting a urine sample for microscopy, culture and sensitivity looking for the concurrent presence of UTI.	PP	Practice Point

UNRESOLVED ISSUES (If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)

IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)

Will this recommendation result in changes in usual care?	**YES**
	NO
Are there any resource implications associated with implementing this recommendation?	**YES**
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 5. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 5. In infants presenting to hospital or hospitalised with bronchiolitis, does performing virological investigations beneficially change medical management or clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Hospital Admission			X		X		
O_2 Hospital Length of stay			X			X	
O_3 ICU admission			X		X		
O_4 Death			N/A		X		

2. Is there is insufficient evidence to make a recommendation?

Evidence statement
Systematic review (38) reviewed 82 trials (17 reports on diagnosis of bronchiolitis and 65 reports of treatment or prevention) for utility of diagnostic testing in bronchiolitis and found no clear indications for testing nor impact on clinical outcomes. An RCT (56) has subsequently shown that clinician knowledge of viral study results at 12 hours does not influence clinical care over knowledge at four weeks. Eight prospective observational studies have looked at a variety of viral panels and outcomes with inconsistent results about the influence of RSV on disease severity or hospital length of stay. There is heterogeneity of study design and outcome measures but studies consistently show lack of influence on clinician management, or improved clinical outcomes due to patient cohorting by virus (RSV). A systematic review and guideline (10) recommends against routine viral testing.

3. What benefit will the proposed intervention/action have?

Evidence statement:	Quality of evidence
No clinical benefit has been demonstrated.	**LOW**

Judging the benefits in context
Cost savings and reduction in discomfort.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
Potential for hospital acquired infection.	**LOW**

Judging the harms in context
No evidence of increased hospital acquired infections, and simple means to limit spread exist.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Benefits of limiting viral testing outweigh harms.	**LOW**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	**Consider against**	**CONDITIONAL**
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Fully implementable in Australia and New Zealand.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
In infants with bronchiolitis, routine use of viral testing is not recommended for any clinically relevant end-points, including cohorting of bronchiolitis patients.	STRONG **CONDITIONAL** WEAK

8. Recommendations for research

Research to determine if patient cohorting on virological results improves hospital transmission more than appropriate contact precautions is warranted.

Question 5. NHMRC Evidence Summary

Question 5: In infants presenting to hospital or hospitalised with bronchiolitis, does performing virological investigations beneficially change medical management or clinically relevant end-points?	**Evidence table ref:** Bamberger 2012, Baumer 2007, Bordley 2004, Brand 2012, Friedman 2003, Garcia-Garcia 2006, Huijskens 2012, Mackie 2001, Mansbach 2012, Nascimento 2010, Ralston 2014, Ricart 2013, Ricci 2015, Wishaupt 2011, Yu 2010 (10, 13, 18, 38, 49-57, 66, 160)

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

Systematic review (38) reviewed 82 trials for utility of diagnostic testing in bronchiolitis and found no clear indications for testing nor impact on clinical outcomes. An RCT (56) has subsequently shown that clinician knowledge of viral study results at 12 hours does not influence clinical care over knowledge at four weeks. Eight prospective observational studies have looked at a variety of viral panels and outcomes with inconsistent results about the influence of RSV on disease severity or hospital length of stay. All have consistently shown lack of influence on clinician management, or improved clinical outcomes with patient cohorting by virus (RSV).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias**
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias

2. Consistency (if only one study was available, rank this component as 'not applicable')

Results are not consistent and study methodology and viral panels are not consistent.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	Evidence is not consistent
	NA	Not applicable (one study only)

3. Clinical impact (indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)

Varied results and in consistent findings.	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted

4. Generalisability (how well does the body of evidence match the population and clinical settings being targeted by the guideline?)

Population consistent with Australasian population.	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

Applicable.	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	**Evidence applicable to Australian/New Zealand healthcare context with few caveats**
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX (summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical Impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats

Evidence statement

Evidence is consistent that viral testing does not improve or change clinical care, and inconsistent about the link to severity of disease, so cannot recommend use of virological testing.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* **In infants with bronchiolitis, routine use of viral testing is not recommended for any clinically relevant end-points, including cohorting of bronchiolitis patients.**	OVERALL GRADE OF RECOMMENDATION	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	**Body of evidence provides some support for recommendations(s) but care should be taken in its application**
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)

Will this recommendation result in changes in usual care? A number of sites currently undertake viral testing.	**YES** NO
Are there any resource implications associated with implementing this recommendation? Test resource savings if implemented. Increased resource usage if increased hospital transmission and infection.	**YES** NO
Will the implementation of this recommendation require changes in the way care is currently organised? Varies according to site.	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation? Cohorting practices exist in some sites based on the result of viral testing.	**YES** NO

Question 6. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 6: For infants presenting to hospital or hospitalised with bronchiolitis, does use of a bronchiolitis scoring system beneficially change medical management or clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Length of stay				X		X	
O_2 Inter rater Agreement				X		X	
O_3 Score Reliability				X		X	
O_4 Useful Predictor				X		X	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement
The evidence is based on eight prospective observational cohort studies and two cross sectional observational studies which were conducted using a variety of scoring systems (including Kristjansson Respiratory Score, modified Wood's Clinical Asthma Score (M-WCAS) and Tal Severity Score, modified Tal, Respiratory Distress Assessment Instrument (RDAI) and the Children's Hospital of Wisconsin Respiratory Score (CHWRS) in addition to the use of specific identified clinical parameters as a scoring system). Limitations to the studies included low number of patients; single centre based studies, unique clinical settings and varied use/comparison of multiple scoring systems across the 8 studies.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the important outcome of score reliability, there is low quality evidence in two studies which demonstrates the reliability of two scoring systems for the assessment of severity in bronchiolitis. For the important outcome of useful predictor, there is low quality evidence from two studies which demonstrates a correlation between score and severity of illness.	**VERY LOW**

Judging the benefits in context

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of score reliability there is low quality evidence of ability to differentiate patients requiring admission or escalation of care. Application of these scores may lead to incorrect decision making.	**VERY LOW**

Judging the harms in context
Due to minimal evidence, there are no indicators that a specific scoring system is more beneficial than clinical assessment and recording of oxygen saturation and observations when assessing, admitting or discharging a child from hospital with the diagnosis of bronchiolitis.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The benefits are not likely to outweigh the harm.	**VERY LOW**

Judging the balance of benefits and harms in context
Until further studies are conducted, the use of a scoring system does not change medical management or clinically relevant endpoints.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms	Consider against	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Current Bronchiolitis scoring systems do not change medical management or change clinically relevant end points.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

For infants presenting to hospital or hospitalised with bronchiolitis, there is insufficient evidence to recommend the use of a scoring system to predict need for admission or hospital length of stay.	**Strength of recommendation** STRONG CONDITIONAL **WEAK**

8. Recommendations for research

Further research is needed to derive and validate a bronchiolitis scoring system for infants diagnosed with bronchiolitis that is generalisable for different populations, and that has significance for patient centred outcomes.

Question 6. NHMRC Evidence Summary

Question 6: For infants presenting to hospital or hospitalised with bronchiolitis, does use of a bronchiolitis scoring system beneficially change medical management or clinically relevant end-points?		**Evidence table ref:** Chin 2004, Destino 2012, Duarte-Dorado 2013, Fernandes 2015, Gajdos 2009, Liu 2004, McCallum 2013, Mosalli 2015, Shete 2014, Walsh 2006 (58-64, 161-163).
1. Evidence base (number of studies, level of evidence and risk of bias in the included studies)		
Eight prospective observational cohort studies enrolling a total of 594 children enrolled and two cross sectional observational studies which enrolled 282 children. All studies are rated low or unclear for risk of bias.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency (if only one study was available, rank this component as 'not applicable')		
Evidence is inconsistent: There were eight different scoring systems used in the literature: 1. Chin et al (58) - Kristjansson Respiratory Score to Wang Respiratory Score 2. Destino et al (59) - Resp Distress Assessment Instrument and Children's Hospital of Wisconsin Respiratory Score in Bronchiolitis 3. Duarte-Dorado et al (60) - Modified Woods Clinical Asthma Score (M-WCAS) and the Tal et al Severity Score 4. Liu et al (61) - Clinical Parameters used for score were respiratory rate, retractions, dyspnoea and auscultation 5. Modified Resp Distress Assessment Instrument (RDAI) 6. McCallum et al (62) - Comparison of Tal and Modified Tal Scoring Systems 7. Walsh et al (64) - assessment tool used – work of breathing, dehydration and tachycardia 8. Shete et al (63) - Modified Tal's score and oxygen saturation	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	**Evidence is not consistent**
	NA	Not applicable (one study only per topic/tool)
3. Clinical impact (indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)		
Outcomes of studies concluded that RDAI score may serve as a guide to clinician in recognizing categories of patients who may require general or intensive care. The Tal and mTal scoring systems were found to be reliable for research and clinical practice in one study. Further evaluation is needed to ensure validity and consistency of the other scoring systems used in these studies. Regarding predicting admission (59)the CHWRS had a sensitivity of 0.65 and specificity of 0.65, while the RDAI is not predictive of disposition. There is a correlation between oxygen saturations and Tals score.	A	Very large
	B	Substantial
	C	Moderate
	D	**Slight/Restricted**
4. Generalisability (how well does the body of evidence match the population and clinical settings being targeted by the guideline?)		
The studies were conducted in a number of countries using populations that are directly generalisable to patients with bronchiolitis seen in Australia and New Zealand. One study was conducted in the Northern Territory of Australia and therefore relative and reflective of the indigenous population present in Australia and New Zealand.	**A**	**Evidence directly generalisable to target population**
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability (is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)		
The results are probably applicable to the Australian/New Zealand healthcare context.	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
	D	Evidence not applicable to Australian/New Zealand healthcare context
Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX (summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of
2. Consistency	D	Evidence is not consistent
3. Clinical Impact	D	Slight/Restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats

Evidence statement:
There is no clear and relevant evidence of benefits to infants with bronchiolitis for the use of a bronchiolitis scoring system. The evidence is generalizable to Australia and New Zealand.

RECOMMENDATION (What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)

For infants presenting to hospital or hospitalised with bronchiolitis, there is insufficient evidence to recommend the use of a scoring system to predict need for admission or hospital length of stay.

OVERALL GRADE OF RECOMMENDATION	
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
D	**Body of evidence is weak and recommendation must be applied with caution**
PP	Practice Point

UNRESOLVED ISSUES (If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)

Studies compared a range of different scoring systems, and the optimal scoring system is still to be determined.

IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)

Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	**NO**

Question 7. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 7: For infants presenting to hospital or hospitalised with bronchiolitis, what criteria should be used for safe discharge?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
Length of Stay				X	X		
Readmission				X	X		

2. Is there is insufficient evidence to make a recommendation?

Evidence statement
The evidence is based on two prospective cohort studies (67, 68) conducted in over 30 United States EDs and hospitals and 3 Guidelines (10, 65, 66).

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of length of stay there is low quality evidence of identified criteria that should be used for safe discharge which would lead to a reduced length of stay. For the critical outcome of readmission rate, there is low quality evidence that supports an increase or decrease in the readmission rate of children who have been discharged from hospital with a diagnosis of bronchiolitis using a specific discharge criterion.	**VERY LOW**

Judging the benefits in context
The evidence is applicable and generalisable to the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of readmission rate there is low quality evidence that supports the use of specific discharge criteria which would lead to a reduced length of stay.	**VERY LOW**

Judging the harms in context

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The benefits are not likely to outweigh the harm.	**VERY LOW**

Judging the balance of benefits and harms in context
Benefits clearly outweigh harms.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Oxygen saturations, adequacy of feeding, age (infants younger than 8 weeks), and social support should be considered at the time of discharge as a risk for representation. There is insufficient evidence to recommend absolute discharge criteria for infants attending the ED, or hospitalised with bronchiolitis.	Strength of recommendation STRONG CONDITIONAL **WEAK**

8. Recommendations for research

Research on outcomes of infants with differing levels of oxygen saturations and duration of adequate feeding at the time of discharge.

Question 7. NHMRC Evidence Summary

For infants presenting to hospital or hospitalised with bronchiolitis, what criteria should be used for safe discharge?		**Evidence table ref:** Baraldi 2014, Baumer 2007, Mansbach 2008, Mansbach 2015, Ricci 2015 (10, 65-68).
1. Evidence base (number of studies, level of evidence and risk of bias in the included studies) Two prospective multiyear cohort studies conducted at over 30 US hospitals enrolling over 3000 patients under the age of two years who were seen in ED or admitted to hospital with a diagnosis of Bronchiolitis.		
All studies are rated low or unclear for risk of bias.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency (if only one study was available, rank this component as 'not applicable')		
Evidence is inconsistent.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	**Evidence is not consistent**
	NA	Not applicable (one study only per topic/tool)
3. Clinical impact (indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)		
Outcomes of studies concluded there is insufficient data to demonstrate clearly what criteria should be used for safe discharge.	A	Very large
	B	Substantial
	C	Moderate
	D	**Slight/Restricted**
4. Generalisability (how well does the body of evidence match the population and clinical settings being targeted by the guideline?)		
The studies were conducted in the USA using populations that are directly generalisable to patients with bronchiolitis who are seen in Australia and New Zealand.	**A**	**Evidence directly generalisable to target population**
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability (is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)		
The results are probably applicable to the Australian/New Zealand healthcare context.	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
	D	Evidence not applicable to Australian/New Zealand healthcare context
Other factors (indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)		
EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of
2. Consistency	N/A	Not applicable (one study only per topic/tool)
3. Clinical Impact	D	Slight/Restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
Evidence statement: There is no clear and relevant evidence of benefits to infants with bronchiolitis. The evidence is generalisable to Australia and New Zealand.		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	OVERALL GRADE OF RECOMMENDATION	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
Oxygen saturations, adequacy of feeding, age (infants younger than 8 weeks), and social support should be considered at the time of discharge as a risk for representation. There is insufficient evidence to recommend absolute discharge criteria for infants attending the ED, or hospitalised with bronchiolitis.	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

UNRESOLVED ISSUES (If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)

IMPLEMENTATION OF RECOMMENDATION (Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)

Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	**YES**
Knowledge base	NO

Question 8a. i) GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 8a i): In infants presenting to hospital or hospitalised with bronchiolitis, does administration of beta 2 agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Rate of hospitalisation	X				X		
O_2 Length of stay	X				X		
O_3 Rate of readmission				X		X	
O_4 Adverse outcomes			X			X	

2. Is there sufficient evidence to make a recommendation?

Evidence statement

The evidence is based predominantly on one systematic review containing 30 RCTs involving 1992 infants with bronchiolitis. This review contained 11 inpatient, 10 outpatient, and 9 mixed inpatient/outpatient studies (69). Subsequently there has been one additional RCT of 56 infants (70) which does not change the findings of the review.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcomes of rate of hospitalisation and length of stay there is high quality evidence that beta 2 agonists do not affect rate of hospitalisation or length of stay.	**HIGH**

Judging the benefits in context

There is a high quality of evidence that routine use of beta 2 agonists in the treatment of infants with bronchiolitis is not associated with any clinically relevant benefit.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of rate of readmission no evidence was available. Reporting of adverse effects in the RCTs were exclusively found in the study groups receiving beta 2 agonists and included the following adverse events: tachycardia, hypertension, decreased oxygen saturation, flushing, hyperactivity, prolonged cough, and tremor. Furthermore, adverse effects of beta 2 agonists are generally well described in the literature.	**LOW**

Judging the harms in context

While the majority of the adverse events associated with beta 2 agonist use are self-limiting, given the lack of evidence to support the use of beta 2 agonists for the treatment of infants with bronchiolitis, beta 2 agonists should not be routinely used in the treatment of infants with bronchiolitis.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The lack of benefits clearly doesn't outweigh the harms.	**HIGH**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	**Recommend against**	**STRONG**
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

Studies were conducted internationally (USA, Canada, UK, Australia, Turkey, France, Saudi Arabia, Egypt, Chile and Tunisia) in populations that are generalizable to patients with bronchiolitis seen in Australia and New Zealand. Beta 2 agonists are widely used and available in Australia and New Zealand.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Do not administer beta 2 agonists to infants presenting to hospital or hospitalised with bronchiolitis.	**STRONG** CONDITIONAL WEAK

8. Recommendations for research

Previous studies should be reviewed to clarify rates of readmission in infants administered beta 2 agonists and discharged home.

Question 8a. i) NHMRC Evidence Summary

Question 8a i): In infants presenting to hospital or hospitalised with bronchiolitis, does administration of beta 2 Agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?	**Evidence table ref:** Baraldi 2014, Gadomski 2014, Kose 2014, Ralston 2014, Ricci 2015 (10, 13, 65, 69, 70).

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies*

One systematic review containing 30 RCTs (11 inpatient, 10 outpatient, and nine mixed inpatient/outpatient settings) involving 1992 infants (Level I). Most studies are rated low or unclear for risk of bias; sensitivity analysis restricted to those studies of low risk of bias confirmed the results. Subsequently there has been one additional RCT of 56 infants which did not alter the previous findings.	**A**	**One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias**
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

Evidence is consistent that beta 2 agonists are not associated with changes to hospitalisation rates or length of stay, with low levels of heterogeneity. There is considerable heterogeneity in meta-analysis of the outcomes of oxygenation and clinical severity scores. Both may represent measurement differences in that oxygenation levels are not reported at consistent times, and a number of clinical severity scores are used.	A	All studies consistent
	B	**Most studies consistent and inconsistency can be explained**
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

Infants with bronchiolitis administered beta 2 agonists do not have any change in rate of hospitalisation (OR 0.75, 95% CI 0.46 to 1.21), length of stay (MD 0.06 days, 95% CI -0.27 days to 0.39 days), or oxygen saturation (MD -0.43%, 95% CI -0.92% to 0.06%). Administration of beta 2 agonists results in a statistical improvement in short term clinical severity scores (SMD -0.30, 95% CI -0.54 to -0.05). However, this marginal change is not associated with any clinically relevant improvement. Administration of beta 2 agonists results in the following adverse events: tachycardia, hypertension, decreased oxygen saturation, flushing, hyperactivity, prolonged cough, and tremor.	A	Very large
	B	**Substantial**
	C	Moderate
	D	Slight/Restricted

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

Studies were completed in a wide range of countries (USA, Canada, UK, Australia, Turkey, France, Saudi Arabia, Egypt, Chile and Tunisia) using populations that are directly generalisable to patients with bronchiolitis seen in Australia and New Zealand. No studies have been done specifically looking at Maori/Pacific Island or Aboriginal infants who do have a high disease burden with bronchiolitis.	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

The results are directly applicable to the Australian/New Zealand healthcare context. Beta 2 agonists are readily available in Australia and New Zealand.	**A**	**Evidence directly applicable to Australian/New Zealand healthcare context**
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	B	Substantial
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	A	Evidence applicable to Australian/New Zealand healthcare context

Evidence statement

There is clear evidence of no clinically relevant benefits to infants with bronchiolitis administered beta 2 agonists.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* **Do not administer beta 2 agonists to infants presenting to hospital or hospitalised with bronchiolitis.**	**OVERALL GRADE OF RECOMMENDATION**	
	A	**Body of evidence can be trusted to guide practice**
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*	
IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*	
Will this recommendation result in changes in usual care? There is no evidence that the use of bronchodilators is effective in treating first time wheezing infants with bronchiolitis. Often trials of beta agonists therapy are done in this population and potential treatment risks outweighs the body of evidence that suggests that beta agonist use in bronchiolitis is not useful.	**YES** NO
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

Question 8a. ii) GRADE Evidence Summary

Considered Judgement - Strength of recommendation							
Question 8a ii): In older infants presenting to hospital or hospitalised with bronchiolitis, does administration of Beta 2 agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
	HIGH	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Rate of hospitalisation	**X**				**X**		
O_2 Length of stay	**X**				**X**		
O_3 Rate of readmission				**X**		**X**	
O_4 Adverse outcomes			**X**			**X**	

2. Is there sufficient evidence to make a recommendation?

Evidence statement:
The evidence is based predominantly on one systematic review containing 30 RCTs involving 1992 infants with bronchiolitis. This review contained 11 inpatient and 10 outpatient studies (69). Subsequently there has been one additional RCT of 56 infants (70) which does not change the findings of the review.

The sensitivity analysis of the Cochrane systematic meta-analysis showed no significant subgroup effect in studies involving inpatients vs. outpatients (infants in the outpatient studies tended to be older). Limiting the analysis to infants aged less than or equal to 12 months did not improve heterogeneity. Furthermore, infants less than or equal to 12 months of age are included in the Cochrane systematic meta-analysis for the critical outcomes of rate of hospitalisation and length of stay.

A smaller under-powered Cochrane systematic meta-analysis (Chavasse et al (71), 8 studies, n=281) of short acting beta 2 agonists for recurrent wheeze in children under two years of age has also found that there is no current clinical benefit.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcomes of rate of hospitalisation and length of stay there is high quality evidence that beta 2 agonists do not affect rate of hospitalisation or length of stay.	**HIGH**

Judging the benefits in context
There is a high quality of evidence that routine use of beta 2 agonists in the treatment of infants with bronchiolitis is not associated with any clinically relevant benefit.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of rate of readmission no evidence was available. Reporting of adverse effects in the RCTs were exclusively found in the study groups receiving beta 2 agonists and included the following adverse events: tachycardia, hypertension, decreased oxygen saturation, flushing, hyperactivity, prolonged cough, and tremor. Furthermore, adverse effects of beta 2 agonists are generally well described in the literature.	**LOW**

Judging the harms in context
While the majority of the adverse events associated with beta 2 agonist use are self-limiting, given the lack of evidence to support the use of beta 2 agonists for the treatment of infants with bronchiolitis, beta 2 agonists should not be routinely used in the treatment of infants with bronchiolitis.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The lack of benefits clearly doesn't outweigh the harms.	**HIGH**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	**Recommend against**	**STRONG**
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Studies were conducted internationally (USA, Canada, UK, Australia, Turkey, France, Saudi Arabia, Egypt, Chile and Tunisia) in populations that are generalizable to patients with bronchiolitis seen in Australia and New Zealand. Beta 2 agonists are widely used and available in Australia and New Zealand. Infants less than or equal to 12 months of age are included in the Cochrane systematic meta-analysis for the critical outcomes of rate of hospitalisation and length of stay.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Do not administer beta 2 agonists to infants, less than or equal to 12 months of age, presenting to hospital or hospitalised with bronchiolitis.	**Strength of recommendation** **STRONG** CONDITIONAL WEAK
8. Recommendations for research	
Previous studies should be reviewed to clarify the effects of beta 2 agonists in infants aged between 6 and 12 months of age.	

Question 8a. ii) NHMRC Evidence Summary

Question 8a ii): In older infants presenting to hospital or hospitalised with bronchiolitis, does administration of beta 2 Agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?		**Evidence table ref:** Baraldi 2014, Chavasse 2002, Gadomski 2014, Kose 2014, Ralston 2014, Ricci 2015 (10, 13, 65, 69-71).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One systematic review containing 30 RCTs (11 inpatient, 10 outpatient, and nine mixed inpatient/outpatient settings) involving 1992 infants (Level I). Most studies are rated low or unclear for risk of bias; sensitivity analysis restricted to those studies of low risk of bias confirmed the results. Subsequently there has been one additional RCT of 56 infants which did not alter the previous findings. A smaller under-powered Cochrane systematic meta-analysis (Chavasse et al (71), eight studies, n=281) of short acting beta 2 agonists for recurrent wheeze in children under two years of age has also found that there is no current clinical benefit.	**A**	**One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias**
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Evidence is consistent that beta 2 agonists are not associated with changes to hospitalisation rates or length of stay, with low levels of heterogeneity. There is considerable heterogeneity in meta-analysis of the outcomes of oxygenation and clinical severity scores. Both may represent measurement differences in that oxygenation levels are not reported at consistent times, and a number of clinical severity scores are used. The sensitivity analysis of the Cochrane systematic meta-analysis showed no significant subgroup effect in studies involving inpatients vs. outpatients (infants in the outpatient studies tended to be older). Limiting the analysis to infants aged less than or equal to 12 months did not improve heterogeneity. Furthermore, infants less than or equal to 12 months of age are included in the Cochrane systematic meta-analysis for the critical outcomes of rate of hospitalisation and length of stay.	A	All studies consistent
	B	**Most studies consistent and inconsistency can be explained**
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Infants with bronchiolitis administered beta 2 agonists do not have any change in rate of hospitalisation (OR 0.75, 95% CI 0.46 to 1.21), length of stay (MD 0.06 days, 95% CI -0.27 days to 0.39 days), or oxygen saturation (MD -0.43%, 95% CI -0.92% to 0.06%). Administration of beta 2 agonists results in a statistical improvement in short term clinical severity scores (SMD -0.30, 95% CI -0.54 to -0.05). However, this marginal change is not associated with any clinically relevant improvement. Administration of beta 2 agonists results in the following adverse events: tachycardia, hypertension, decreased oxygen saturation, flushing, hyperactivity, prolonged cough, and tremor.	A	Very large
	B	**Substantial**
	C	Moderate
	D	Slight/Restricted

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

Studies were completed in a wide range of countries (USA, Canada, UK, Australia, Turkey, France, Saudi Arabia, Egypt, Chile and Tunisia) using populations that are directly generalisable to patients with bronchiolitis seen in Australia and New Zealand. No studies have been done specifically looking at Maori/Pacific Island or Aboriginal infants who do have a high disease burden with bronchiolitis.	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

The results are directly applicable to the Australian/New Zealand healthcare context. Beta 2 agonists are readily available in Australia and New Zealand.	**A**	**Evidence directly applicable to Australian/New Zealand healthcare context**
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	B	Substantial
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	A	Evidence applicable to Australian/New Zealand healthcare context

Evidence statement
There is clear evidence of no clinically relevant benefits to infants with bronchiolitis administered beta 2 agonists.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Do not administer beta 2 agonists to infants, less than or equal to 12 months of age, presenting to hospital or hospitalised with bronchiolitis.	**A**	**Body of evidence can be trusted to guide practice**
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care? **There is no evidence that the use of bronchodilators is effective in treating first time wheezing infants with bronchiolitis. Often trials of beta agonist therapy are done in older infants yet there are potential treatment risks and the body of evidence that suggests that beta agonist use in bronchiolitis is not useful. Previous research in Australasia shows that a considerable proportion of infants with bronchiolitis are exposed to ineffective beta 2 agonist therapy.**	**YES** NO
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation?	**YES** NO

Question 8b. i) GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 8b i): In infants presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy, does administration of beta 2 agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Rate of hospitalisation				X	X		
O_2 Length of stay				X	X		
O_3 Rate of readmission				X		X	
O_4 Adverse outcomes			X			X	

2. Is there sufficient evidence to make a recommendation?

Evidence statement
In the Gadomski et al (69) review none of the 30 RCTs specifically addresses the evidence for beta 2 agonist use in infants presenting to hospital or hospitalised with bronchiolitis with a personal or family history of atopy.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
There is no specific evidence for this subgroup. In general, for infants with bronchiolitis for the critical outcomes of rate of hospitalisation and length of stay there is high quality evidence that beta 2 agonists do not affect rate of hospitalisation or length of stay.	**VERY LOW**

Judging the benefits in context
There is no randomised controlled evidence of benefit for this subgroup.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
For the important outcome of rate of readmission no evidence was available. Reporting of adverse effects in general studies of beta 2 agonists vs. placebo were exclusively found in the study groups receiving beta 2 agonists and included the following adverse events: tachycardia, hypertension, decreased oxygen saturation, flushing, hyperactivity, prolonged cough, and tremor. Furthermore, adverse effects of beta 2 agonists are generally well described in the literature.	**LOW**

Judging the harms in context
While the majority of the adverse events associated with beta 2 agonist use are self-limiting, given the lack of evidence to support the use of beta 2 agonists for the treatment of infants with bronchiolitis, beta 2 agonists should not be routinely used in the treatment of infants with bronchiolitis, with a personal or family history of atopy.

5. What is the likely balance between good and harm?

Evidence statement	Overall quality of evidence
There is no good evidence to support the trial of beta 2 agonists in infants with personal or family history of atopy.	**VERY LOW**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Beta 2 agonists are widely used and available in Australia and New Zealand.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Do not administer beta 2 agonists to infants presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy.	**Strength of recommendation** STRONG CONDITIONAL **WEAK**

8. Recommendations for research

Studies of the use of beta 2 agonists in infants presenting to hospital or hospitalised with bronchiolitis and a personal or family history of atopy are needed.

Question 8b. i) NHMRC Evidence Summary

Question 8b i): In infants presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy, does administration of Beta 2 agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?		**Evidence table ref:** Baraldi 2014, Gadomski 2014, Ralston 2014, Ricci 2015 (10, 13, 65, 69).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No studies have addressed this question.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	**Not applicable (one study only)**
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	**Slight/Restricted**
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	**Evidence not directly generalisable to target population and hard to judge whether sensible to apply**
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	**Evidence not applicable to Australian/New Zealand healthcare context**

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

There is no good quality evidence evaluating the effect of beta 2 agonists in infants with bronchiolitis and a personnel or family history of atopy.

Previously trials of beta 2 agonists have been suggested as a clinical option. However, given the high level of evidence (NHMRC A, GRADE strong) demonstrating no benefit of beta 2 agonists in infants presenting to or hospitalised with bronchiolitis, and that there is no well-established way to determine an "objective method of response" to beta 2 agonists in bronchiolitis, this option is no longer recommended. Although it is true that a small subset of children with bronchiolitis may have reversible airway obstruction resulting from smooth muscle constriction, attempts to define a subgroup of responders have not been successful to date. If a clinical trial of bronchodilators is undertaken, clinicians should note that the variability of the disease process, the host's airway, and the clinical assessments, particularly scoring, would limit the clinician's ability to observe a clinically relevant response to bronchodilators (13).

Administration of beta 2 agonists has resulted in the following adverse events: tachycardia, hypertension, decreased oxygen saturation, flushing, hyperactivity, prolonged cough, and tremor.

Beta 2 agonists should only be used in infants with a personal or family history of atopy as part of an RCT in order to establish a better evidence base.

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical Impact	D	Slight/Restricted
4. Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability	D	Evidence not applicable to Australian healthcare context

Evidence statement

There is no good evidence to support the trial of beta 2 agonists in infants with personal or family history of atopy.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Do not administer beta 2 agonists to infants presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy.	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	**Body of evidence is weak and recommendation must be applied with caution**
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care?	**YES**
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 8b. ii) GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 8b ii): In older infants presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy, does administration of Beta 2 agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Rate of hospitalisation				X	X		
O_2 Length of stay				X	X		
O_3 Rate of readmission				X		X	
O_4 Adverse outcomes			X			X	

2. Is there sufficient evidence to make a recommendation?

Evidence statement
In the Gadomski et al (69) review none of the 30 RCTs specifically addresses the evidence for beta 2 agonist use in infants presenting to hospital or hospitalised with bronchiolitis with a personal or family history of atopy.

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
There is no specific evidence for this subgroup. In general, for infants with bronchiolitis for the critical outcomes of rate of hospitalisation and length of stay there is high quality evidence that beta 2 agonists do not affect rate of hospitalisation or length of stay.	**VERY LOW**

Judging the benefits in context
There is no randomised controlled evidence of benefit for this subgroup.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
For the important outcome of rate of readmission no evidence was available. Reporting of adverse effects in general studies of beta 2 agonists vs. placebo were exclusively found in the study groups receiving beta 2 agonists and included the following adverse events: tachycardia, hypertension, decreased oxygen saturation, flushing, hyperactivity, prolonged cough, and tremor. Furthermore, adverse effects of beta 2 agonists are generally well described in the literature.	**LOW**

Judging the harms in context
While the majority of the adverse events associated with beta 2 agonist use are self-limiting, given the lack of evidence to support the use of beta 2 agonists for the treatment of infants with bronchiolitis, beta 2 agonists should not be routinely used in the treatment of infants with bronchiolitis, with a personal or family history of atopy.

5. What is the likely balance between good and harm?

Evidence statement	Overall quality of evidence
There is no good evidence to support the trial of beta 2 agonists in infants with personal or family history of atopy.	**VERY LOW**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Beta 2 agonists are widely used and available in Australia and New Zealand.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Do not administer beta 2 agonists to infants, less than or equal to 12 months of age, presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy.	**Strength of recommendation** STRONG CONDITIONAL **WEAK**

8. Recommendations for research

Studies of the use of beta 2 agonists in infants presenting to hospital or hospitalised with bronchiolitis and a personal or family history of atopy are needed.

Question 8b. ii) NHMRC Evidence Summary

Question 8b ii): In older infants presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy, does administration of Beta 2 agonists (nebulisation, aerosol, oral or IV) improve clinically relevant end-points?		**Evidence table ref:** Baraldi 2014, Chavasse 2002, Gadomski 2010, Ralston 2014, Ricci 2015 (10, 13, 65, 69, 71).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No studies have addressed this question.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	**Not applicable (one study only)**
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	**Slight/Restricted**
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	**Evidence not directly generalisable to target population and hard to judge whether sensible to apply**
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	**Evidence not applicable to Australian/New Zealand healthcare context**
Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

There is no good quality evidence evaluating the effect of beta 2 agonists in infants with bronchiolitis and a personnel or family history of atopy.

Previously trials of beta 2 agonists have been suggested as a clinical option. However, given the high level of evidence (NHMRC A, GRADE strong) demonstrating no benefit of beta 2 agonists in infants presenting to or hospitalised with bronchiolitis, and that there is no well-established way to determine an "objective method of response" to beta 2 agonists in bronchiolitis, this option is no longer recommended. Although it is true that a small subset of children with bronchiolitis may have reversible airway obstruction resulting from smooth muscle constriction, attempts to define a subgroup of responders have not been successful to date. If a clinical trial of bronchodilators is undertaken, clinicians should note that the variability of the disease process, the host's airway, and the clinical assessments, particularly scoring, would limit the clinician's ability to observe a clinically relevant response to bronchodilators (13).

Administration of beta 2 agonists has resulted in the following adverse events: tachycardia, hypertension, decreased oxygen saturation, flushing, hyperactivity, prolonged cough, and tremor.

Beta 2 agonists should only be used in infants with a personal or family history of atopy as part of an RCT in order to establish a better evidence base.

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical Impact	D	Slight/Restricted
4. Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability	D	Evidence not applicable to Australian healthcare context

Evidence statement

Do not administer beta 2 agonists to infants presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*

Do not administer beta 2 agonists to infants, less than or equal to 12 months of age, presenting to hospital or hospitalised with bronchiolitis, with a personal or family history of atopy.

OVERALL GRADE OF RECOMMENDATION	
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care?	**YES**
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 9. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 9: In infants presenting to hospital or hospitalised with bronchiolitis, does administration of adrenaline/epinephrine (nebulisation, IM or IV) improve clinically relevant end-points?

9. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Rate of hospitalisation			x		x		
O_2 Length of stay	x				x		
O_3 Rate of readmission		x				x	
O_4 Adverse outcomes			x			x	

10. Is there sufficient evidence to make a recommendation?

Evidence statement:
The evidence is based predominantly on one Cochrane systematic review containing 19 RCTs involving 2,256 infants with bronchiolitis (72). Subsequently there have been five additional RCTs of 914 infants which support the findings of the review.

11. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of rate of hospitalisation there is low quality evidence that Infants with bronchiolitis administered adrenaline/epinephrine in ambulatory settings have a significant reduction in rate of hospitalisation within the first 24 hours after initiation of treatment (RR 0.67, 95% CI 0.50 to 0.89, n=995). However this is not the case when only trials at low risk of bias are analysed (RR 0.77, 95% CI 0.56 to 1.07, n=842), in the most recent study (Sarrell et al (76), n=330), or when hospitalization is analysed over the first seven days after initiating treatment (RR 0.81, 95% CI 0.63 to 1.03, n=875). For the critical outcome of length of stay there is high quality of evidence (mean difference -0.25, 95% CI -0.62 to 0.13, n=696) that adrenaline/epinephrine administration does not affect length of stay.	**LOW/HIGH**

Judging the benefits in context
There is a moderate quality of evidence that routine use of adrenaline/epinephrine in the treatment of infants with bronchiolitis is not associated with any consistent clinically relevant benefit.

12. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of rate of readmission there is moderate quality evidence that adrenaline/epinephrine administration does not affect readmission rate. Administration of adrenaline/epinephrine in RCTs resulted in the following adverse events; tachycardia, hypertension, pallor, vomiting and tremor.	**LOW/MODERATE**

Judging the harms in context
While the majority of the adverse events associated with adrenaline/epinephrine use are self-limiting, given the lack of evidence to support the use of adrenaline/epinephrine for the treatment of infants with bronchiolitis, adrenaline/epinephrine should not be routinely used in the treatment of infants with bronchiolitis.

13. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The lack of benefits clearly doesn't outweigh the harms.	**MODERATE**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	**Recommend against**	**STRONG**
Harms clearly outweigh benefits		

14. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Studies were conducted internationally (USA, Canada, UK, Australia, Norway, Turkey, Iran, Israel, Jordan, Chile, India, Bangladesh) in populations that are generalizable to patients with bronchiolitis seen in Australia and New Zealand. Adrenaline/epinephrine is widely used and available in Australia and New Zealand.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

15. Final recommendation	
Do not administer adrenaline/epinephrine to infants presenting to hospital or hospitalised with bronchiolitis.	**Strength of recommendation** **STRONG** CONDITIONAL WEAK
16. Recommendations for research	
Nil.	

Question 9. NHMRC Evidence Summary

Question 9: In infants presenting to hospital or hospitalised with bronchiolitis, does administration of adrenaline/epinephrine (nebulisation, IM or IV) improve clinically relevant end-points?		**Evidence table ref:** Baraldi 2014, Hartling 2011, Hartling 2011, Livni 2010, Modaressi 2012, Ralston 2014, Ricci 2015 Sarrell 2010, Simsek-Kiper 2010, Skjerven 2013 (10, 13, 65, 72-76, 164).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One systematic review (Hartling et al (72), 19 studies, n=2,256) (level I). Subsequent to this there has been three further RCTs comparing adrenaline/epinephrine to a nasal decongestant or beta-2-agonists (Livni et al (73), n=65, Modaressi et al (74), n=40, Simsek-Kiper et al (75), n=75) or to placebo in ambulatory (Sarrell et al (76), n=330) and inpatient settings (Skjerven et al (77), n=404) that have not changed the findings of the meta-analysis. Infants with bronchiolitis administered adrenaline/epinephrine in ambulatory settings have a significant reduction in rate of hospitalisation within the first 24 hours after initiation of treatment (RR 0.67, 95% CI 0.50 to 0.89, n=995). However this is not the case when only trials at low risk of bias are analysed (RR 0.77, 95% CI 0.56 to 1.07, n=842), in the most recent study (Sarrell et al (76), n=330), or when hospitalization is analysed over the first seven days after initiating treatment (RR 0.81, 95% CI 0.63 to 1.03, n=875).	**A**	**One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias**
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There is inconsistency in evidence regarding rate of hospitalisation. The evidence regarding length of stay, adverse events and readmissions is consistent.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Evidence regarding hospitalisation discussed above. Evidence from the Cochrane meta-analysis and the recent high quality RCT (Skjerven et al (77), n=404) do not suggest that administering adrenaline/epinephrine in inpatients with bronchiolitis changes hospital length of stay or readmission rates. Administration of adrenaline/epinephrine in RCTs resulted in the following adverse events tachycardia, hypertension, pallor, vomiting and tremor.	A	Very large
	B	**Substantial**
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
Studies were conducted internationally (USA, Canada, UK, Australia, Norway, Turkey, Iran, Israel, Jordan, Chile, India, Bangladesh) in populations that are generalizable to patients with bronchiolitis seen in Australia and New Zealand. Adrenaline/epinephrine is widely used and available in Australia and New Zealand. No studies have been done specifically looking at Maori/Pacific Island or Aboriginal infants who do have a high disease burden with bronchiolitis.	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

The results are directly applicable to the Australian/New Zealand healthcare context. Adrenaline/epinephrine is readily available in Australia and New Zealand.	**A**	**Evidence directly applicable to Australian/New Zealand healthcare context**
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical Impact	B	Substantial
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	A	Evidence applicable to Australian/New Zealand healthcare context

Evidence statement

There is clear evidence of no clinically relevant benefits to infants with bronchiolitis administered beta 2 agonists.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*

Do not administer adrenaline/epinephrine to infants presenting to hospital or hospitalised with bronchiolitis.

	OVERALL GRADE OF RECOMMENDATION
A	Body of evidence can be trusted to guide practice
B	**Body of evidence can be trusted to guide practice in most situations**
C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care? Currently little adrenaline/epinephrine are used in clinical practice in Australia and New Zealand, this is in contrast to North American practice.	YES **NO**
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

Question 10. GRADE Evidence Summary

Considered Judgement - Strength of recommendation							
Question 10: In infants presenting to hospital or hospitalised with bronchiolitis, does administration of nebulised hypertonic saline improve clinically relevant end-points?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
	HIGH	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Length of stay				**X**	**X**		
O_2 Admission rate			**X**		**X**		
O_3 Readmission rate			**X**			**X**	
O_4 Adverse events			**X**			**X**	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

The evidence is based on one Cochrane systematic review of 11 RCTs (78) and a further nine additional RCTs (79-87). Subsequent to the Cochrane review there have been three further systematic reviews (88-90) and the newer trials have been included in an updated systematic review by the Cochrane authors (91) and a live meta-analysis (92).

3. What benefit will the proposed intervention/action have?

Evidence statement

Quality of evidence VERY LOW

For the critical outcome of length of stay there is very low quality evidence of a reduced length of stay in infants treated with nebulised hypertonic saline (mean difference -0.44 days, 95% CI -0.74 to -0.14 days; 15 studies, n=1,922). However there is considerable heterogeneity in the overall result (I2=78%). Removal of two studies with overall length of stay considerably longer than current clinical practice in Australia and New Zealand, and with a primary outcome definition considerably different than that used in Australia and New Zealand for discharge (no respiratory signs or symptoms for 12 hours), partially explains the heterogeneity and results in a pooled estimate suggesting no effect. Furthermore, analysis restricted to the four largest trials, all at lower risk of bias, again suggests no benefit (89). A number of studies included in the meta-analysis also appear to be unbalanced with regards to duration of illness prior to treatment in the hypertonic saline arms.

For the critical outcome of admission rate there is very low quality evidence of a reduced admission rate in infants treated with nebulised hypertonic saline (RR 0.80, 95% CI 0.67 to 0.96; 7 RCTs, n=951). The seven RCTs reporting this outcome included a range of regimens, strengths and added medications. Furthermore, subgroup analysis suggests that nebulised hypertonic saline is not effective in the studies using just one to two doses compared with those using three or more (one to two doses RR 0.93, 95% CI 0.73 to 1.20, 4 RCTs, n=358; three or more doses RR 0.67, 95% CI 0.52 to 0.87, 3 RCTs, n=593; p value for subgroup comparison = 0.07).

Judging the benefits in context

There are two positive studies with overall length of stay considerably longer than current clinical practice in Australia and New Zealand, and with a primary outcome definition considerably different than that used in Australia and New Zealand for discharge (no respiratory signs or symptoms for 12 hours), removal of these studies partially explains the heterogeneity in the length of stay analysis and results in a pooled estimate suggesting no effect. The remaining studies appear applicable and generalisable to the Australian and New Zealand health settings.

4. What harm might the proposed intervention/action do?

Evidence statement

Quality of evidence LOW

For the important outcome of readmission rate there is low quality evidence of no increase in readmission rate in those treated with nebulised hypertonic saline.

For the important outcome of adverse events there is low quality evidence of no increase in adverse events in those treated with nebulised hypertonic saline.

Judging the harms in context

Evidence to date indicates no increased risk of harm in infants treated. However the majority of studies have only been in mild or moderately unwell infants, and so the risk in severely unwell infants is unknown.

5. What is the likely balance between good and harm?

Evidence statement

Overall quality of evidence VERY LOW

Evidence from the largest individual studies, and from the meta-analysis, do not consistently provide evidence of improved length of stay following the use of nebulised hypertonic saline. While there is weak evidence of reduced admission rates following the use of hypertonic saline, there is heterogeneity in the treatment regimens used, and a suggestion that one to two dose regimens are ineffective. Given the lack of long term effect of nebulised hypertonic saline on length of stay the routine use of nebulized hypertonic saline in the ED to reduce admissions is not supported by the current evidence base outside of a RCT.

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	**Consider against**	**CONDITIONAL**
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?	
Summary statement Hypertonic saline is readily available in Australia and New Zealand, although use is currently confined to patients with bronchiectasis and cystic fibrosis.	
Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Do not administer nebulised hypertonic saline in infants presenting to hospital or hospitalised with bronchiolitis.	**Strength of recommendation** STRONG **CONDITIONAL** WEAK

8. Recommendations for research
Further research is required to determine the optimum strength and frequency of this treatment. Further large multicenter trials are required to confirm the overall benefits of nebulized hypertonic saline in ED settings with regards to effects on admission into hospital. To date, research studies conducted in regard to the use of nebulised hypertonic saline have included a range of regimens, strengths and added medications. Further research is required to determine the optimum strength and frequency of this treatment.

Question 10. NHMRC Evidence Summary

Question 10: In infants presenting to hospital or hospitalised with bronchiolitis, does administration of nebulised hypertonic saline improve clinically relevant end-points?		**Evidence table ref:** Badgett 2015, Chen 2014, Everard 2014, Florin 2014, Jacobs 2014, Khanal 2015, Maguire 2015, Mitchell 2013, Ojha 2015, Sharma 2013, Silver 2015, Teunissen 2015, Wu 2014, Zhang 2013, Zhang 2015 (78-92).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
The evidence is based on one Cochrane systematic review of 11 RCTs (78) and a further nine additional RCTs (79-87). Subsequent to the Cochrane review there have been three further systematic reviews (88-90) and the newer trials have included in an updated systematic review by the Cochrane authors (91) and a live meta-analysis (92). Use of hypertonic saline is associated with a reduced length of stay in infants treated with nebulised hypertonic saline (mean difference -0.44 days, 95% CI -0.74 to -0.14 days; 15 RCTs, n=1,944) and a reduced admission rate (RR 0.80, 95% CI 0.67 to 0.96; 7 RCTs, n=951).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Studies reporting length of stay have considerable heterogeneity in the overall result (I2=78%). Removal of two studies with overall length of stay considerably longer than current clinical practice in Australia and New Zealand, and with a primary outcome definition considerably different than that used in Australia and New Zealand for discharge (no respiratory signs or symptoms for 12 hours), partially explains the heterogeneity and results in a pooled estimate suggesting no effect. Furthermore, analysis restricted to the four largest trials, all at lower risk of bias, again suggests no benefit (89). A number of studies included in the meta-analysis also appear to be unbalanced with regards to duration of illness prior to treatment in the hypertonic saline arms. Studies reporting admission rates included a range of regimens, strengths and added medications. Furthermore, subgroup analysis suggests that nebulised hypertonic saline is not effective in the studies using just one to two doses compared with those using three or more (one to two doses RR 0.93, 95% CI 0.73 to 1.20, 4 RCTs, n=358; three or more doses RR 0.67, 95% CI 0.52 to 0.87, 3 RCTs, n=593; p value for subgroup comparison = 0.07).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	**Evidence is not consistent**
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Length of stay for patients admitted to hospital receiving nebulised hypertonic saline is reduced by 0.45 of a day (95% CI -0.82 to -0.08). Admission rates to hospital for patients receiving nebulised hypertonic saline in the ED are reduced by 20% (RR 0.80, 95% CI 0.67 to 0.96). There appears to be no increase in adverse events or change in readmission rates following discharge from EDs.	A	Very large
	B	Substantial
	C	Moderate
	D	**Slight/Restricted**

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
Studies were conducted internationally (USA, Canada, UK, Netherlands, Turkey, Tunis, Israel, Qatar, Dhabi, India, Argentina, Nepal, Italy, China) in populations that are generalizable to patients with bronchiolitis seen in Australia and New Zealand. No studies have been done specifically looking at Maori/Pacific Island or Aboriginal infants who do have a high disease burden with bronchiolitis.	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
There are two positive studies with overall length of stay considerably longer than current clinical practice in Australia and New Zealand, and with a primary outcome definition considerably different than that used in Australia and New Zealand for discharge (no respiratory signs or symptoms for 12 hours), removal of these studies partially explains the heterogeneity in the length of stay analysis and results in a pooled estimate suggesting no effect. The remaining studies appear applicable Australian/New Zealand healthcare context. Hypertonic saline is readily available in Australia and New Zealand, although use is currently confined to patients with bronchiectasis and cystic fibrosis.	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	D	Evidence is not consistent
3. Clinical Impact	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats

Evidence statement

Studies were conducted internationally (USA, Canada, UK, Netherlands, Turkey, Tunis, Israel, Qatar, Dhabi, India, Argentina, Nepal, Italy, China) in populations that are generalizable to patients with bronchiolitis seen in Australia and New Zealand. Hypertonic saline is readily available in Australia and New Zealand, although use is currently confined to patients with bronchiectasis and cystic fibrosis.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* **Do not administer nebulised hypertonic saline in infants presenting to hospital or hospitalised with bronchiolitis.**	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	**Body of evidence is weak and recommendation must be applied with caution**
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

Effect of nebulised hypertonic saline on admission rates when given in the ED remains uncertain. Studies used different regimens of nebulised hypertonic saline, and the optimal regime is still to be determined.

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 11a. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 11a: In infants presenting to hospital or hospitalised with bronchiolitis, does administration of systemic or local glucocorticoids (nebulisation, oral, IM or IV) improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Rate of hospitalisation	X				X		
O_2 Length of stay		X			X		
O_3 Rate of readmission		X				X	
O_4 Adverse outcomes			X			X	

2. Is there sufficient evidence to make a recommendation?

Evidence statement:
The evidence is based predominantly on one Cochrane systematic review containing 17 RCTs involving 2,596 infants with bronchiolitis (93). Subsequently there has been two further RCTs (Alansari et al (94), n=200; Jartti et al (95), n=79).

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
For the critical outcome of rate of hospitalisation there is high quality evidence that glucocorticoids do not effect rate of hospitalisation at either one day (RR 0.92, 95% CI 0.78 to 1.08, n=1,762) or seven days (RR 0.86, 95% CI 0.70 to 1.06, n=1,530). For the critical outcome of length of stay evidence from the most recent Cochrane meta-analysis does not suggest that glucocorticoids effects length of stay (mean difference -0.18, 95% CI -0.39 to 0.04, n=633). Data from the subsequent RCT conducted by Alansari found a significant difference in geometric mean length of stay between those treated with glucocorticoids and those not (favouring shorter length of stay with glucocorticoids). Unfortunately published data is not available to allow this to be combined with the eight RCTs included in the meta-analysis. Regardless of the inability to combine data, the current effect size of glucocorticoids on length of stay (-0.18, 95% CI -0.39 to 0.04) remains of marginal clinical significance.	**HIGH**

Judging the benefits in context
There is a high quality of evidence that routine use of glucocorticoids in the treatment of infants with bronchiolitis is not associated with any consistent clinically relevant benefit.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
For the important outcome of rate of readmission there is moderate quality evidence that glucocorticoid administration does not affect readmission rate. Administration of glucocorticoids in the RCTs did not result in excess adverse events. However, the long-term effects of glucocorticoids have not been studied, the number of participants is not adequate for very rare adverse events to be evident and adverse events were not systematically measured across the RCTs.	**MODERATE**

Judging the harms in context
While glucocorticoids do not appear to have an excess of short term adverse events the long-term adverse events are unknown. Given the lack of evidence to support the use of glucocorticoids in the treatment of infants with bronchiolitis, glucocorticoids should not be routinely used in the treatment of infants with bronchiolitis.

5. What is the likely balance between good and harm?

Evidence statement	Overall quality of evidence
The lack of benefits clearly doesn't outweigh the harms.	**HIGH**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	**Recommend against**	**STRONG**
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?	
Summary statement Studies were conducted internationally (USA, Canada, UK, Belgium, Brazil, Turkey, Israel, Thailand, Mexico, Paraguay) in populations that are generalizable to patients with bronchiolitis seen in Australia and New Zealand. Glucocorticoids are widely used and available in Australia and New Zealand.	
Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Do not administer local or systemic glucocorticoids to infants presenting to hospital or hospitalised with bronchiolitis.	**Strength of recommendation** **STRONG** CONDITIONAL WEAK
8. Recommendations for research	
Studies of long-term effects are required.	

Question 11a. NHMRC Evidence Summary

Question 11a: In infants presenting to hospital or hospitalised with bronchiolitis, does administration of systemic or local glucocorticoids (nebulisation, oral, IM or IV) improve clinically relevant end-points?		**Evidence table ref:** Alansari 2013, Baraldi 2014, Fernandes 2013, Jartti 2015, Ralston 2014, Ricci 2015 (10, 13, 65, 93-95).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One systematic review (Fernandes et al (93), 17 RCTs, n=2,596) (level I). Subsequent to this there have been two further RCTs (Alansari et al (94), n=200; Jartti et al (95), n=79).	**A**	**One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias**
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
There is possible inconsistency in evidence regarding length of stay. The evidence regarding hospitalisations, adverse events and readmissions is consistent.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	**Substantial**
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
Studies were conducted internationally (USA, Canada, UK, Belgium, Brazil, Turkey, Israel, Thailand, Mexico, Paraguay) in populations that are generalizable to patients with bronchiolitis seen in Australia and New Zealand. Glucocorticoids are widely used and available in Australia and New Zealand. No studies have been done specifically looking at Maori/Pacific Island or Aboriginal infants who do have a high disease burden with bronchiolitis.	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

The results are directly applicable to the Australian/New Zealand healthcare context. Glucocorticoids are readily available in Australia and New Zealand.	**A**	**Evidence directly applicable to Australian/New Zealand healthcare context**
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical Impact	B	Substantial
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	A	Evidence applicable to Australian/New Zealand healthcare context

Evidence statement

There is clear evidence of no clinically relevant benefits to infants with bronchiolitis administered glucocorticoids.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Do not administer local or systemic glucocorticoids to infants presenting to hospital or hospitalised with bronchiolitis.	A	Body of evidence can be trusted to guide practice
	B	**Body of evidence can be trusted to guide practice in most situations**
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care? There is some use of glucocorticoids in clinical practice in Australia and New Zealand.	**YES** NO
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

Question 11b. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 11b: In infants presenting to hospital or hospitalised with bronchiolitis, with a positive response to beta 2 agonists, does administration of systemic or local glucocorticoids (nebulisation, oral, IM or IV) improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Rate of hospitalisation				X	X		
O_2 Length of stay				X	X		
O_3 Rate of readmission				X		X	
O_4 Adverse outcomes			X			X	

2. Is there sufficient evidence to make a recommendation?

Evidence statement
In the Fernandes et al (93) review none of the 17 RCTs specifically addresses the evidence for glucocorticoid use in infants presenting to hospital or hospitalised with a positive response to beta 2 agonists, or those with a personal or family history of atopy.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
There is no specific evidence for this subgroup. In general, for infants with bronchiolitis for the critical outcomes of rate of hospitalisation and length of stay there is high quality evidence that glucocorticoids do not effect rate of hospitalisation or length of stay.	**VERY LOW**

Judging the benefits in context
There is no randomised controlled evidence of benefit for this subgroup.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of rate of readmission no evidence is available. Administration of glucocorticoids in the RCTs did not result in excess adverse events. However, the long-term effects of glucocorticoids has not been studied, the number of participants is not adequate for very rare adverse events to be evident and adverse events were not systematically measured across the RCTs.	**LOW**

Judging the harms in context
Given the lack of evidence to support the use of glucocorticoids for the treatment of infants with bronchiolitis, glucocorticoids should not be routinely used in the treatment of infants with bronchiolitis, with a positive response to beta 2 agonists.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
There is no good evidence to support glucocorticoids in infants with bronchiolitis and a positive response to beta 2 agonists.	**VERY LOW**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Beta 2 agonists are widely used and available in Australia and New Zealand.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Do not administer systemic or local glucocorticoids to infants presenting to hospital or hospitalised with bronchiolitis, with a positive response to beta 2 agonists.	**Strength of recommendation** STONG CONDITIONAL **WEAK**

8. Recommendations for research

Studies of the use of glucocorticoids in infants presenting to hospital or hospitalised with bronchiolitis and with a positive response to beta 2 agonists are needed.

Question 11b. NHMRC Evidence Summary

Question 11b: In infants presenting to hospital or hospitalised with bronchiolitis, with a positive response to beta 2 agonists, does administration of systemic or local glucocorticoids (nebulisation, oral, IM or IV) improve clinically relevant end-points?	**Evidence table ref:** Baraldi 2014, Fernandes 2013, Gadomski 2014, Ralston 2014, Ricci 2015 (10, 13, 65, 69, 93).

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

No studies have addressed this question.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	**Not applicable (one study only)**

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

	A	Very large
	B	Substantial
	C	Moderate
	D	**Slight/Restricted**

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	**Evidence not directly generalisable to target population and hard to judge whether sensible to apply**

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	**Evidence not applicable to Australian/New Zealand healthcare context**

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

There is no good quality evidence evaluating the effect of glucocorticoids in infants with bronchiolitis and a positive response to beta 2 agonists.

Previously individual patient trials of beta 2 agonists have been suggested as a clinical option. However, given the high level of evidence (NHMRC A, GRADE strong) demonstrating no benefit of beta 2 agonists in infants presenting to or hospitalised with bronchiolitis, and that there is no well-established way to determine an "objective method of response" to beta 2 agonists in bronchiolitis, this option is no longer recommended. Although it is true that a small subset of children with bronchiolitis may have reversible airway obstruction resulting from smooth muscle constriction, attempts to define a subgroup of responders have not been successful to date. If a clinical trial of bronchodilators is undertaken, clinicians should note that the variability of the disease process, the host's airway, and the clinical assessments, particularly scoring, would limit the clinician's ability to observe a clinically relevant response to bronchodilators (13).

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical Impact	D	Slight/Restricted
4. Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply
5. Applicability	D	Evidence not applicable to Australian healthcare context

Evidence statement

Do not administer systemic or local glucocorticoids to infants presenting to hospital or hospitalised with bronchiolitis, with a positive response to beta 2 agonists.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
Do not administer systemic or local glucocorticoids to infants presenting to hospital or hospitalised with bronchiolitis, with a positive response to beta 2 agonists.	**D**	**Body of evidence is weak and recommendation must be applied with caution**
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care? This practice is used by some clinicians.	**YES** NO
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

Question 11c. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 11c: In infants presenting to hospital or hospitalised with bronchiolitis, does administration of the combination of systemic or local glucocorticoids (nebulisation, oral, IM or IV) and adrenaline improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Rate of hospitalisation			X		X		
O_2 Length of stay			X		X		
O_3 Rate of readmission				X		X	
O_4 Adverse outcomes			X			X	

2. Is there sufficient evidence to make a recommendation?

Evidence statement

The evidence for the administration of glucocorticoids in bronchiolitis is based on **one Cochrane systematic** meta-analysis (Fernandes et al (93), 17 RCTs, n=2,596) and three systematic reviews (10, 13, 65). The evidence for the administration of adrenaline in bronchiolitis is based on **one Cochrane systematic** meta-analysis (Hartling et al (72), 19 RCTs, n=2,256), three systematic reviews (10, 13, 65) and seven subsequent RCTs (73-77, 96, 97).

Evidence for the administration of the combination of glucocorticoids and adrenaline comes from a single high quality multi-centre RCT conducted in eight EDs in Canada (Plint et al (98), n=800). This trial compared adrenaline and high dose dexamethasone in a factorial design.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of hospitalisation there is low quality evidence in support of the combination of glucocorticoids and adrenaline. Admission rates in unadjusted analysis of the Plint trial (98) suggested a possible benefit in the combination arm (adrenaline and glucocorticoid admission on day of enrolment RR 0.65, 95% CI 0.41 to 1.04; day 7 RR 0.65, 95% CI 0.45 to 0.95). However when adjusted for multiple comparisons in the factorial design this was no longer significant (adrenaline and glucocorticoid admission on day of enrolment RR 0.65, 95% CI 0.37 to 1.15; day 7 RR 0.65, 95% CI 0.41 to 1.03). For the critical outcome of length of stay the combination of glucocorticoids and adrenaline is no better than placebo.	**LOW**

Judging the benefits in context

Given the evidence base for the single interventions, and the exploratory nature of the finding in the Plint trial (98), combination treatment with glucocorticoids and adrenaline should only be used in infants with bronchiolitis as part of an RCT.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of rate of readmission no evidence is available. Adverse events were uncommon and generally self-limiting in the Plint study (98).	**LOW**

Judging the harms in context

Given the lack of evidence to support the use of glucocorticoids or adrenaline in isolation for the treatment of infants with bronchiolitis, and the exploratory nature of the findings suggesting possible benefit with combination of glucocorticoids and adrenaline, combination treatment of glucocorticoids and adrenaline should not be routinely used in the treatment of infants with bronchiolitis.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
There is no good evidence to support the combination of glucocorticoids and adrenaline treatment in infants with bronchiolitis.	**LOW**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

Glucocorticoids and adrenaline are widely available in Australia and New Zealand, but rarely used in combination.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Do not administer a combination of systemic or local glucocorticoids and adrenaline to infants presenting to hospital or hospitalised with bronchiolitis.	**Strength of recommendation** STRONG CONDITIONAL **WEAK**
8. Recommendations for research	
Studies of the use of a combination of glucocorticoids and adrenaline in infants presenting to hospital or hospitalised with bronchiolitis are needed.	

Question 11c. NHMRC Evidence Summary

Question 11c: In infants presenting to hospital or hospitalised with bronchiolitis, does administration of the combination of systemic or local glucocorticoids (nebulisation, oral, IM or IV) and adrenaline improve clinically relevant end-points?		**Evidence table ref:** Baraldi 2014, Fernandes 2013, Hartling 2011, Livni 2010, Modaressi 2012, Plint 2009, Ralston 2014, Ricci 2015, Sarrell 2010, Simsek-Kiper 2011, Skjerven 2013 (10, 13, 65, 72-77, 93, 98).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	**Not applicable (one study only)**
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	**Substantial**
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
Single study from Canada.	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	**Evidence applicable to Australian/New Zealand healthcare context with few caveats**
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Given the lack of evidence to support the use of glucocorticoids or adrenaline in isolation for the treatment of infants with bronchiolitis, and the exploratory nature of the findings suggesting possible benefit with combination of glucocorticoids and adrenaline, combination treatment of glucocorticoids and adrenaline should not be routinely used in the treatment of infants with bronchiolitis.

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable
3. Clinical Impact	B	Substantial
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats

Evidence statement

Do not administer a combination of systemic or local glucocorticoids and adrenaline to infants presenting to hospital or hospitalised with bronchiolitis.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*

Do not administer a combination of systemic or local glucocorticoids and adrenaline/epinephrine to infants presenting to hospital or hospitalised with bronchiolitis.

OVERALL GRADE OF RECOMMENDATION	
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
D	**Body of evidence is weak and recommendation must be applied with caution**
PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 12a. GRADE Evidence Summary

Considered Judgement - Strength of recommendation							
Question 12a: In infants presenting to hospital or hospitalised with bronchiolitis, does administration of supplemental oxygen improve clinically relevant end-points?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
	HIGH	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Admission to hospital			**x**		**x**		
O_2 Length of stay in hospital			**x**		**x**		
O_3 Oxygen saturation target			**x**			**x**	
O_4 Feeding difficulties				**x**		**x**	
O_5 Readmission				**x**		**x**	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement:
The evidence is based on a systematic review (99), an evidence based guideline (13), a prospective observational case series (100) and a retrospective observational cohort study (101). There was low - very low level evidence for the use supplemental oxygen although the evidence based guideline formed a weak recommendation based on low level evidence and reasoning from first principles. There was no evidence of the effect of oxygen therapy on readmission to hospital.

3. What benefit will the proposed intervention/action have?

Evidence statement:	**Quality of evidence**
For the critical outcome of admission to hospital there is low evidence that administration of supplemental oxygen increases the rate of hospital admission. For the critical outcome of length of stay in hospital there is low grade evidence that administration of oxygen prolongs hospital length of stay. For the important outcome of oxygen saturation target there is low grade evidence for the appropriate oxygen saturation target for supplemental oxygen.	**LOW**

Judging the benefits in context
The evidence is applicable and generalisable to the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of feeding difficulties there is very low grade evidence that oxygen therapy affects feeding.	**VERY LOW**

Judging the harms in context
There is little evidence to determine the effect of oxygen therapy on feeding difficulties.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The benefit of supplemental oxygen therapy has not been specifically studied - rather an assumption about the benefits has been made and observational studies have looked at length of time of administration and feeding difficulties as a gauge of effectiveness.	**VERY LOW**

Judging the balance of benefits and harms in context
Benefits probably outweigh harms.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	**Consider**	**CONDITIONAL**
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Oxygen therapy has been based on practice by first principles and low to very low grade evidence. The evidence is applicable to the Australian and New Zealand setting.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Consider the use of supplemental oxygen in the treatment of hypoxic (saturations less than 92%) infants with bronchiolitis.	**Strength of recommendation** **Conditional**
8. Recommendations for research	
Large randomised controlled studies with pre-defined indications and protocols for supplemental oxygen are required to determine the effect on hospital admission, length of stay, oxygen saturation targets and effect on feeding difficulties.	

Question 12a. NHMRC Evidence Summary

Question 12a: In infants presenting to hospital or hospitalised with bronchiolitis, does administration of supplemental oxygen improve clinically relevant end-points?		**Evidence table ref:** Cunningham 2012, Mitchell 2013, Ralston 2014, Unger 2008 (13, 99-101).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One systematic review (Level I study) with a high risk of bias and one evidence based guideline (Level I study) with a moderate risk of bias. There have been no RCTs. There has been one prospective observational case series of 68 infants (Level IV) and one retrospective observational cohort study of 102 infants (Level IV). All studies are rated moderate for risk of bias.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias**
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All studies recommend the use of supplemental oxygen but there is no direct comparison with withholding therapy. Outcomes have been limited to length of stay in hospital and oxygen saturation targets with limited evaluation of other outcomes including no evidence for readmission.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	**Evidence is not consistent**
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
The use of supplemental oxygen therapy on increasing admission rate and prolonging admissions has not been evaluated. The impact on these parameters has significant impact on wellbeing of infants as well as cost implications for health services.	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
Current limited evidence has been obtained from similar health systems and can be generalised to Australian and New Zealand setting.	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
Relevant to Australian and New Zealand setting.	**A**	**Evidence directly applicable to Australian/New Zealand healthcare context**
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context
Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
Administration of oxygen is used by reason of first principles.		

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		
Component	**Rating**	**Description**
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
2. Consistency	D	Evidence is not consistent
3. Clinical Impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	A	Evidence directly applicable to Australian/New Zealand healthcare context

Evidence statement:

Supplemental oxygen therapy is used by reasoning of first principles and there is weak evidence for its effect on hospital admission, length of stay, oxygen saturation targets, or effect on feeding difficulties.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Consider the use of supplemental oxygen in the treatment of hypoxic (oxygen saturations less than 92%) infants with bronchiolitis.	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	**Body of evidence provides some support for recommendations(s) but care should be taken in its application**
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

Consistent definition of oxygen saturation target demonstrating hypoxia and need for administration of oxygen

Process of weaning the oxygen therapy

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care? **The practice of starting oxygen without hypoxia is unsupported.**	**YES** NO
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation? **Nurse led commencement of oxygen without physician input**	**YES** NO

Question 12b. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 12b: In infants presenting to hospital or hospitalised with bronchiolitis, what level of oxygen saturation should lead to commencement or discontinuation of supplemental oxygen to improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Admission to hospital		X			X		
O_2 Length of stay in hospital			X		X		
O_3 Oxygen saturation target		X			X		
O_4 Feeding difficulties			X			X	
O_5 Readmission to hospital		X				X	

2. Is there is insufficient evidence to make a recommendation?

The evidence relates to the role of saturations in patient management and is based on 2 systematic reviews (99, 102), an evidence based guideline (13) and two RCTs (103, 104). Additional evidence was from a prospective observational case series (100) and three retrospective observational studies (101, 105, 106).

3. What benefit will the proposed intervention/action have?

Evidence statement	Quality of evidence
For the critical outcome of admission to hospital there is moderate evidence that lower oxygen saturation levels increases the rate of admission independently of other factors. For the critical outcome of length of stay in hospital there is low level evidence that lower oxygen saturations prolong length of stay. For the critical outcome of oxygen saturation target there is moderate evidence in uncomplicated bronchiolitis that saturations less than 92% is an acceptable absolute target for supplemental oxygen.	**MODERATE**

Judging the benefits in context

The evidence is applicable and generalisable to the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	Quality of evidence
For the important outcome of readmission there is high level evidence that oxygen level saturations do not affect readmissions to hospital. For the important outcome of feeding difficulties there is very low evidence for the impact of oxygen saturations on resolution.	**MODERATE**

Judging the harms in context

Oxygen saturation targets less than 92% do not impact on reducing feeding difficulties or readmissions.

5. What is the likely balance between good and harm?

Evidence statement:	Overall quality of evidence
The harms probably outweigh the benefits.	**MODERATE**

Judging the balance of benefits and harms in context

Not known

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms **Harms probably outweigh benefits**	**Consider against**	**CONDITIONAL**
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

Oxygen saturation level has been demonstrated to influence admission and length of stay. The level at which oxygen therapy should commence or be discontinued has been established less than 92%.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
In uncomplicated bronchiolitis oxygen supplementation should be commenced if the oxygen saturation level is sustained at a level less than 92%. At oxygen saturation levels of 92% or greater oxygen therapy should be discontinued.	**Strength of recommendation** STRONG **CONDITIONAL** WEAK
8. Recommendations for research	
Further randomised controlled studies are needed to confirm the level of oxygen saturations to establish oxygen therapy. The effect of sustained hypoxia on long term development needs to be measured. Further research is needed in determining an appropriate oxygen saturation level at which to consider discharge of an infant from hospital with bronchiolitis.	

Question 12b. NHMRC Evidence Summary

Question 12b: In infants presenting to hospital or hospitalised with bronchiolitis, what level of oxygen saturation should lead to commencement or discontinuation of supplemental oxygen to improve clinically relevant end-points?		**Evidence table ref:** Choi 2006, Cunningham 2012, Cunningham 2015, Hendaus 2015, Mitchell 2013, Ralston 2014, Schroder 2004, Schuh 2014, Unger 2008 (13, 99-106).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
The evidence relates to the role of saturations in patient management and is based on two systematic reviews (99, 102), an evidence based guideline (13) and two RCTs (103, 104). Additional evidence was from a prospective observational case series (100) and three retrospective observational studies (101, 105, 106). Recent RCTs have established the absolute level of oxygen saturation for oxygen therapy to commence or be discontinued.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	**One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias**
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Two Level II RCTs relating to question and moderate to high grade evidence based systematic reviews demonstrating limited evidence addressing the question.	A	All studies consistent
	B	**Most studies consistent and inconsistency can be explained**
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Saturations measurement will modify current practice	A	Very large
	B	**Substantial**
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	**Evidence not directly generalisable to target population but could be sensibly applied**
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No direct evidence to address the question of oxygen saturation level for commencing or discontinuing oxygen supplementation

EVIDENCE STATEMENT MATRIX (summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	B	Substantial
4. Generalisability	C	Evidence not directly generalisable to target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats

Evidence statement:

For the critical outcome of admission to hospital there is moderate evidence that lower oxygen saturation levels increases the rate of admission independently of other factors.

For the critical outcome of length of stay in hospital there is low level evidence that lower oxygen saturations prolong length of stay.

For the critical outcome of oxygen saturation target there is moderate evidence in uncomplicated bronchiolitis that saturations less than 92% is an acceptable target for supplemental oxygen

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*

In uncomplicated bronchiolitis oxygen supplementation should be commenced if the oxygen saturation level is sustained at a level less than 92%. At oxygen saturation levels of 92% or greater oxygen therapy should be discontinued.

OVERALL GRADE OF RECOMMENDATION	
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	**Body of evidence provides some support for recommendations(s) but care should be taken in its application**
D	Body of evidence is weak and recommendation must be applied with caution
PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care? **Consideration of decreasing admission rates and potential for earlier discharge for infants with bronchiolitis**	**YES** NO
Are there any resource implications associated with implementing this recommendation? **Reduced health care costs relating to inpatient care**	**YES** NO
Will the implementation of this recommendation require changes in the way care is currently organised? **Education and guidelines to support changes in oxygen saturation levels to determine admission to hospital and discharge from care**	**YES** NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

Question 13. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 13: In infants hospitalised with bronchiolitis does continuous monitoring of pulse oximetry beneficially change medical management or clinically relevant end-points.

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Length of stay in hospital		x			x		
O_2 Thresholds for discharge oxygen saturations			x			x	
O_3 Frequency of nocturnal desaturations				x		x	
O_4 Maintenance of feeding				x		x	
O_5 Cost savings				x			x

2. Is there is insufficient evidence to make a recommendation?

The evidence is based on a systematic review and two high quality evidence reviews containing nine guidelines five systematic reviews and primary literature searches involving Medline, EMBASE and Cochrane. In addition, there was one randomised, double-blind, parallel-group trial involving 213 infants, one randomised, parallel-group, superiority clinical trial of 161 infants to continuous vs intermittent pulse oximetry and one prospective observational studies of 68 patients evaluating discharge oxygen saturation levels. A further three retrospective studies involved 439 infants.

3. What benefit will the proposed intervention/action have?

Evidence statement:	**Quality of evidence**
For the critical outcome of length of stay there is moderate quality evidence that continuous monitoring of pulse oximetry does not reduce hospital length of stay in non-hypoxic (saturations greater than or equal to 92%) infants. For the critical outcome of threshold for discharge oxygen saturations, there is low quality evidence on the comparative effect of different discharge oxygen saturations thresholds. For the critical outcome frequency of nocturnal desaturations there is very low quality evidence to indicate that the frequency of nocturnal desaturations influences length of stay.	**MODERATE**

Judging the benefits in context

The evidence is applicable and can be generalised to all acute health care facilities caring for bronchiolitic infants in the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of maintenance of feeding there is very low quality evidence that continuous monitoring does not affect feeding during the course of the disease. For the important outcome of cost there was no evidence of reduced cost savings in those infants admitted with bronchiolitis on continuous oximetry monitoring.	**VERY LOW**

Judging the harms in context

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The current evidence does not support continuous pulse oximetry monitoring.	**LOW**

Judging the balance of benefits and harms in context

Not Known

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	**Consider against**	**CONDITIONAL**
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

The benefit of continuous pulse oximetry in bronchiolitis has not been established and requires additional research to support its routine use in all settings.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Routine use of continuous oximetry is not required for medical management of non-hypoxic (saturations greater than or equal to 92%) infants not receiving oxygen, or stable infants receiving oxygen.	**Strength of recommendation** STRONG **CONDITIONAL** WEAK
8. Recommendations for research	
Randomised controlled studies are needed to establish use of continuous oximetry in the setting of hypoxic infants with bronchiolitis. Further studies are needed to determine what effect continuous oximetry monitoring has on time to discharge.	

Question 13. NHMRC Evidence Summary

Question 13: In infants hospitalised with bronchiolitis does continuous Monitoring of pulse oximetry beneficially change medical management or clinically relevant end-points.	**Evidence table ref:** Choi 2006, Cunningham 2012, Hendaus 2015, Kaditis 2015, McCulloch 2015, Mitchell 2013, Ralston 2014, Schroeder 2004, Schuh 2014, Unger 2008 (13, 99-102, 104-108).	
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
One systematic review (level I) and two evidence reviews (level II-a) with moderate to low risk of bias, one randomised, double-blind, parallel-group trial involving 213 infants (level II) rated low risk of bias, one randomised, parallel-group, superiority clinical trial of 161 patients (Level II) with low risk of bias and one prospective observational study (level III) with high risk of bias involving 68 infants and three retrospective studies involving 439 infants, (level III-2) with a high risk of bias.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias**
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Evidence is inconsistent that in infants hospitalised with bronchiolitis that continuous monitoring of pulse oximetry either at admission, at several key points during admission and during the weaning phase of oxygen beneficially changes medical management and/or clinically relevant end-points such as length of stay.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	**Evidence is not consistent**
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Pulse oximetry and oxygen thresholds determines the length of stay in hospital coupled with the return of feeding, thereby reducing the costs. There is low to moderate clinical evidence on the benefit of continuous oximetry for infants who have been hospitalized with bronchiolitis. Adverse events and the effect of low oxygen saturations on the patient appear unaffected by continuous vs intermittent oximetry.	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
All studies matched the population and clinical settings and can be generalised to Australia and New Zealand; two European studies, two United Kingdom studies, three USA studies and one study conducted in Western Australia.	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
The results are directly applicable to the Australasian Healthcare context. Oximeters are used in all hospital settings.	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	**Evidence applicable to Australian/New Zealand healthcare context with few caveats**
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context
Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
No direct evidence to address the question of oxygen saturation level.		

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		
Component	**Rating**	**Description**
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
2. Consistency	D	Evidence is not consistent
3. Clinical Impact	C	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats

Evidence statement:
There is low grade evidence demonstrating that there is no consistent benefit for the use of continuous pulse oximetry above intermittent oximetry for stable, non-hypoxic infants on admission, days on oxygen, discharge or hospital length of stay.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Routine use of continuous oximetry is not required for medical management of non-hypoxic (saturations greater than or equal to 92%) infants not receiving oxygen, or stable infants receiving oxygen.	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	**Body of evidence provides some support for recommendations(s) but care should be taken in its application**
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care? **Reduce the use of continuous oximetry**	**YES** NO
Are there any resource implications associated with implementing this recommendation? **Reduce admission length of stay and costs associated**	**YES** NO
Will the implementation of this recommendation require changes in the way care is currently organised? **Education and guidelines to support change in practice**	**YES** NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

Question 14. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 14: In infants hospitalised with bronchiolitis does the use of heated humidified high flow oxygen, or air, via nasal cannula improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Length of stay in hospital			X		X		
O_2 Rate of PICU admission			X		X		
O_3 Adverse Events				X		X	
O_4 Cost				X		X	

2. Is there is insufficient evidence to make a recommendation?

There have been limited studies on HFNC in children with bronchiolitis during inpatient stay outside of the PICU. A Cochrane systematic review (109), one evidence based guideline (13), one RCT (110), two prospective studies (111, 112), four non-systematic reviews (113-116), and one retrospective cohort review (117) all provide low to very low level evidence for the benefit of HFNC. A prospective interventional study of 14 infants with bronchiolitis demonstrates reduction in work of breathing receiving HFNC (118).
There are insufficient studies and patients investigated to recommend HFNC as a standard therapy in a general paediatric unit.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of length of stay in hospital there is low quality evidence that HFNC improves length of stay in hospital. For the critical outcome for rate of PICU admission there is low quality evidence that HFNC reduces PICU admission rates.	**LOW**

Judging the benefits in context
The evidence is applicable and can be generalised to all acute health care facilities caring for bronchiolitic infants in the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of adverse events there is very low evidence that HFNC is safe. For the important outcome of cost there is very low evidence that HFNC results in less health care cost overall.	**VERY LOW**

Judging the harms in context
The evidence is applicable and can be generalised to all acute health care facilities caring for bronchiolitic infants in the New Zealand and Australian health settings.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The benefits of HFNC therapy probably outweigh harm.	**LOW**

Judging the balance of benefits and harms in context
Benefit probably outweigh harms

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	**Consider**	**CONDITIONAL**
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
HFNC in bronchiolitis is feasible therapy in the inpatient setting although the benefits have yet to be demonstrated to outweigh the harms.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
HFNC in bronchiolitis can be considered in the inpatient setting in children with bronchiolitis with hypoxia (oxygen saturations 90-92%). Its use in children without hypoxia should be limited to the RCT setting only.	STRONG **CONDITIONAL** WEAK

8. Recommendations for research

Large RCT comparing HFNC with standard oxygen therapy including sub groups of infants with hypoxia and respiratory distress without hypoxia outside of the PICU setting.

Question 14. NHMRC Evidence Summary

Question 14: In infants hospitalised with bronchiolitis does the use of heated humidified high flow oxygen, or air, via nasal cannula improve clinically relevant end-points?		**Evidence table ref:** Beggs 2014, Bressan 2013, Bueno Campana 2014, Da Dalt 2013, Hanlon 2014, Haq 2014, Kelly 2013, Lee 2013, Mayfield 2014, Pham 2015, Ralston 2014, Sinha 2015 (13, 109-118, 165).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
A Cochrane systematic review (109) identified only one RCT with very low quality evidence of benefit. Further RCT (110) provides more evidence that HFNC is feasible and two prospective (111, 112) and one retrospective study (117) provide further very low level evidence of possible benefit. A prospective interventional study of 14 infants with bronchiolitis demonstrates reduction in work of breathing receiving HFNC (118). There are four non-systematic reviews (113-116).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias**
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
The RCT (110) compared HFNC to non-standardised therapy. No studies have compared to routine care.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
HFNC is gaining in popularity despite the paucity of evidence for its use. This seems to be driving the uptake of this therapy which is independent of the available study qualities.	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	**Evidence not directly generalisable to target population but could be sensibly applied**
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
	D	Evidence not applicable to Australian/New Zealand healthcare context
Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		
Component	**Rating**	**Description**
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical Impact	C	Moderate
4. Generalisability	C	Evidence not directly generalisable to target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
Evidence statement: The benefits of HFNC therapy probably outweigh harm.		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
HFNC in bronchiolitis can be considered in the inpatient setting in children with bronchiolitis with hypoxia (oxygen saturations 90-92%). Its use in children without hypoxia should be limited to the RCT setting only.	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	**Body of evidence provides some support for recommendations(s) but care should be taken in its application**
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care?	**YES**
	NO
Are there any resource implications associated with implementing this recommendation? Introduction of HFNC requires special equipment and training of staff. Successful implemental may reduce transfers to tertiary care.	**YES**
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	**YES**
	NO

Question 15. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 15: In infants hospitalised with bronchiolitis, does chest physiotherapy improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Change in severity status of bronchiolitis		X			X		
O_2 Time to recovery/clinical stability	X				X		
O_3 Oxygen saturation levels				X	X		
O_4 Duration of oxygen supplementation	X					X	
O_5 Length of Hospital Stay	X					X	
O_6 Complications of therapy	X					X	
O_7 Heart rate variability			X			X	

2. Is there is insufficient evidence to make a recommendation?

There is one Cochrane review (119) with nine clinical trials including 891 patients on the topic. In addition there is one low quality RCT (120), two prospective clinical trials (121, 122), three observational trials (123-125) of very low quality, and a further systematic review and guideline (10).

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of change in severity status of bronchiolitis there is moderate evidence that physiotherapy does not alter severity. For the critical outcome of time to recovery/clinical stability there is high quality evidence that physiotherapy does not improve recovery or stability. For the critical outcome of oxygen saturation levels there is very low level evidence of physiotherapy affecting oxygen saturation. For the important outcome of duration of oxygen supplementation there is high quality evidence that duration of oxygen supplementation is not altered by physiotherapy. For the important outcome of length of hospital stay there is high level evidence that length of stay is not altered by physiotherapy.	**HIGH**

Judging the benefits in context
The evidence is probably applicable and generalisable to the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of complications of therapy there is high level evidence of minimal adverse effects resulting from physiotherapy. For the important outcome of heart rate variability there is very low level evidence that heart rate variability is modified by physiotherapy.	**MODERATE**

Judging the harms in context
The evidence is probably applicable and generalisable to the New Zealand and Australian health settings.

5. What is the likely balance between good and harm?

Evidence statement:	**Overall quality of evidence**
The benefits are not demonstrated to improve outcomes.	**HIGH**

Judging the balance of benefits and harms in context: Benefits clearly don't outweigh harms

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	**Recommend against**	**STRONG**
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement: The evidence is probably applicable and generalisable to the New Zealand and Australian health settings.

Yes	Recommend/consider
Not known	Consider economic evaluation
No	**Recommend/consider against**

7. Final recommendation	
Chest physiotherapy is not recommended for routine use in infants with bronchiolitis.	**Strength of recommendation** **STRONG** CONDITIONAL WEAK
8. Recommendations for research	
Further research into newer specific techniques to determine the use in specific patient cohorts.	

Question 15. NHMRC Evidence Summary

Question 15: In infants hospitalised with bronchiolitis, does chest physiotherapy improve clinically relevant end-points?		**Evidence table ref:** Figuls 2012, Gomes 2012; Goncalves 2014, Jacinto 2013, Mussman 2013; Pupin 2009, Remondini 2014, Ricci 2015, Roqué i (10, 119-125).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
There is one Cochrane review (119) with nine clinical trials including 891 patients on the topic. In addition there is one low quality RCT (120), two prospective clinical trials (121, 122), three observational trials (123-125) of very low quality, and a further systematic review and guideline (10).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	**One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias**
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	**Most studies consistent and inconsistency can be explained**
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
	D	Evidence not applicable to Australian/New Zealand healthcare context
Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX (summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)		
Component	**Rating**	**Description**
1. Evidence base	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats

Evidence statement:
The benefits of chest physiotherapy are not demonstrated to improve outcomes.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Chest physiotherapy is not recommended for routine use in infants with bronchiolitis.	A	Body of evidence can be trusted to guide practice
	B	**Body of evidence can be trusted to guide practice in most situations**
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 16a. GRADE Evidence Summary

Considered Judgement - Strength of recommendation							
Question 16a: In infants hospitalised with bronchiolitis, does suctioning of the nose or naso pharynx improve clinically relevant end-points?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
	HIGH	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Length of Stay in hospital			**x**		**x**		
O_2 Adverse events				**x**		**x**	

2. Is there is insufficient evidence to make a recommendation?

There is only one retrospective comparative study (125) of 740 patients examining both suction type and suction frequency. Three non-systematic reviews or guidelines refer to suction but without provision of references and are rated very low.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of length of stay in hospital there is moderate level evidence that deep nasal suctioning increases length of stay but frequent non-invasive superficial suctioning decreases length of stay.	**LOW**

Judging the benefits in context

The evidence is applicable and generalisable to the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of the occurrence of adverse events there is very low level evidence.	**VERY LOW**

Judging the harms in context

The evidence is applicable and generalisable to the New Zealand and Australian health settings.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The benefits probably don't outweigh harms.	**LOW**

Judging the balance of benefits and harms in context

Benefits probably don't outweigh harms.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	**Consider against**	**CONDITIONAL**
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

The use of deep suctioning in bronchiolitis appears to lengthen hospital stay while non-invasive suctioning may decrease length of stay.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Nasal suction is not recommended as routine practice in the management of infants with bronchiolitis. Superficial suction may be considered to assist with feeding.	STRONG **CONDITIONAL** WEAK

8. Recommendations for research

RCTs using pre-set protocols are needed.

Question 16a. NHMRC Evidence Summary

Question 16a: In infants hospitalised with bronchiolitis, does suctioning of the nose or naso pharynx improve clinically relevant end-points?	**Evidence table ref:** Mussman 2013 (125).

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

There is only one clinical trial - retrospective comparative trial examining suctioning techniques and frequency (125).

A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

A	All studies consistent
B	Most studies consistent and inconsistency can be explained
C	Some inconsistency, reflecting genuine uncertainty around question
D	Evidence is not consistent
NA	**Not applicable (one study only)**

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

A	Very large
B	Substantial
C	Moderate
D	**Slight/Restricted**

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

A	Evidence directly generalisable to target population
B	**Evidence directly generalisable to target population with some caveats**
C	Evidence not directly generalisable to target population but could be sensibly applied
D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

A	Evidence directly applicable to Australian/New Zealand healthcare context
B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical Impact	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats

Evidence statement:
There is no evidence to support the use of superficial nasal suction.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* **Nasal suction is not recommended as routine practice in the management of infants with bronchiolitis. Superficial suction may be considered to assist with feeding.**	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	**Body of evidence is weak and recommendation must be applied with caution**
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*	
IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*	
Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 16b. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 16b: In infants hospitalised with bronchiolitis, does deep suctioning in comparison to superficial suctioning beneficially improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Length of Stay in hospital			x		**x**		
O_2 Adverse events				**x**		**x**	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement:
There is only one retrospective comparative study (125) of 740 patients examining both suction type and suction frequency.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of length of stay in hospital there is low level evidence that deep suctioning increases length of stay in comparison to superficial suctioning.	**LOW**

Judging the benefits in context
The evidence is applicable and generalisable to the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of adverse events there is very low level evidence that deep suction increases adverse events.	**VERY LOW**

Judging the harms in context
The evidence is applicable and generalisable to the New Zealand and Australian health settings.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Harms probably outweigh benefits of deep suctioning in comparison with superficial suctioning.	**LOW**

Judging the balance of benefits and harms in context
Benefits clearly don't outweigh harms.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms **Harms probably outweigh benefits**	**Consider against**	**CONDITIONAL**
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
The use of deep suctioning in bronchiolitis appears to lengthen hospital stay in comparison to superficial suctioning.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	**Recommend/consider against**

7. Final recommendation

	Strength of recommendation
Deep nasal suction for the management of bronchiolitis is not recommended.	STRONG **CONDITIONAL** WEAK

8. Recommendations for research

RCTs using pre-set protocols on use of nasal suction are needed.

Question 16b. NHMRC Evidence Summary

Question 16b: In infants hospitalised with bronchiolitis, does deep suctioning in comparison to superficial suctioning beneficially improve clinically relevant end-points?	**Evidence table ref:** Mussman 2013 (125).

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

There is only one clinical trial - retrospective comparative trial of 740 patients (125).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	**Not applicable (one study only)**

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

	A	Very large
	B	Substantial
	C	Moderate
	D	**Slight/Restricted**

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical Impact	D	Slight/Restricted
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats

Evidence statement:
There is limited evidence that does not support the use of deep suctioning in comparison of superficial suctioning of the nose or naso-pharynx.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* **Deep nasal suction for the management of bronchiolitis is not recommended.**	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	**Body of evidence is weak and recommendation must be applied with caution**
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*	
IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*	
Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 17. GRADE Evidence Summary

Considered Judgement - Strength of recommendation							
Question 17: In infants hospitalised with bronchiolitis, does the use of nasal saline drops improve clinically relevant end-points?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
	HIGH	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 O_2 saturations				**x**	**x**		
O_2 Retractions				**x**	**x**		
O_3 Dyspnoea				**x**		**x**	

2. Is there is insufficient evidence to make a recommendation?

There is no Cochrane review. Two RCTs use administration of nasal saline as the control therapy in use of chest physiotherapy (120) or phenylephrine nasal drops (126). A guideline (127) and a review article (128) recommend nasal saline as a practice point.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of O_2 saturations there is very low evidence of effectiveness. For the critical outcome of retractions there is very low evidence of improvement in work of breathing. For the important outcome of dyspnoea there is very low evidence of improvement.	**VERY LOW**

Judging the benefits in context

The evidence is applicable and generalisable to the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement:	**Quality of evidence**
Not assessed.	**N/A**

Judging the harms in context

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The benefits are not known.	**VERY LOW**

Judging the balance of benefits and harms in context

Benefits probably outweigh harms.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

Evidence applicable to Australia and New Zealand practice.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Routine nasal saline drops are not recommended. Trial of intermittent saline drops may be considered at time of feeding.	**Strength of recommendation** STRONG CONDITIONAL **WEAK**

8. Recommendations for research

RCTs with pre-set protocols to establish the benefit or harm of nasal saline drops are needed.

Question 17. NHMRC Evidence Summary

Question 17: In infants hospitalised with bronchiolitis, does the use of nasal saline drops improve clinically relevant end-points?	**Evidence table ref:** Gomes 2012, Soleimani 2014, Turner 2008, Verma 2013 (120, 126-128).

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

There are no Cochrane or systematic reviews on the question. Two clinical trials have used nasal saline drops as the control group for unrelated interventions: physiotherapy and phenylephrine drops (120, 126). Nasal saline is recommended in guidelines and consensus statements as practice points.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	**Evidence is not consistent**
	NA	Not applicable (one study only)

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

The intervention has not been specifically investigated so the clinical impact cannot be determined.	A	Very large
	B	Substantial
	C	Moderate
	D	**Slight/Restricted**

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	**Evidence not directly generalisable to target population and hard to judge whether sensible to apply**

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

No specific studies to evaluate the intervention.

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	D	Evidence is not consistent
3. Clinical Impact	D	Slight/Restricted
4. Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats

Evidence statement:
There is no evidence to guide the use of nasal saline solution in the infant of bronchiolitis.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* **Routine nasal saline drops are not recommended. Trial of intermittent saline drops may be considered at time of feeding.**	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*	
IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*	
Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 18. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 18: In infants hospitalised with bronchiolitis, does the use of nasal/bubble CPAP improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Need for mechanical ventilation				X	X		
O_2 Duration of ED stay				X		X	
O_3 Need for ICU admission				X		X	
O_4 Adverse events				X		X	

2. Is there is insufficient evidence to make a recommendation?

One Cochrane systematic review (129) analysed two RCTs with a total of 50 patients with low level of evidence and high risk of biases. Relevant clinical outcome such as intubation rates was addressed and a trend towards reduction in intubations shown with a lack of high-level significance. A recent prospective observational study (130) of low quality evaluated general paediatric ward administration of nCPAP. A retrospective study (131) compared HFNC to nCPAP in the ICU setting only and was of very low quality. Two systematic reviews (116, 132) analysed the use of nCPAP for bronchiolitis.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
There is very low level evidence that nCPAP reduces the need for mechanical ventilation. There is no evidence that nCPAP affects the duration of ED stay. There is very low level evidence that nCPAP affects the need for ICU admission.	**VERY LOW**

Judging the benefits in context

The evidence is applicable and generalisable to the New Zealand and Australian health systems in relation to therapy outside of the ICU setting.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
There is very low level evidence that nCPAP affects the rate of adverse events.	**VERY LOW**

Judging the harms in context

The evidence is probably applicable and generalisable to the New Zealand and Australian health systems in relation to therapy outside of the ICU setting.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Benefits probably outweigh harms.	**VERY LOW**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	**Consider**	**CONDITIONAL**
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

The use of nCPAP outside of the paediatric intensive care in infants with bronchiolitis can be considered.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Nasal CPAP therapy for infants with bronchiolitis may be considered for the management of infants	**Strength of recommendation** STRONG **CONDITIONAL** WEAK

8. Recommendations for research

Large RCT in paediatric wards and paediatric intensive care is needed. Direct comparison of HFNC and CPAP needs to be done.

Question 18. NHMRC Evidence Summary

Question 18: In infants hospitalised with bronchiolitis, does the use of bubble CPAP improve clinically relevant end-points?		**Evidence table ref:** Metge 2014, Palanivel 2009, Oymar 2014, Kana 2015, Evans 2012, Sinha 2015 (116, 129-132, 166).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
In the non-PICU setting there has been one low quality prospective study investigating nCPAP (130). A Cochrane review (129) of 2 low quality studies of 50 patients on nCPAP in the PICU setting with unclear conclusions on the benefit. One retrospective study of low quality (131) compared HFNC to nCPAP and there are two low quality systematic reviews (116, 132).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias**
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
All studies are inconsistent as they evaluated different populations (PICU vs ward) and interventions (HFNC, nCPAP).	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	**Evidence is not consistent**
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	**Evidence not directly generalisable to target population but could be sensibly applied**
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
	D	Evidence not applicable to Australian/New Zealand healthcare context
Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
2. Consistency	D	Evidence is not consistent
3. Clinical Impact	C	Moderate
4. Generalisability	C	Evidence not directly generalisable to target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats

Evidence statement:
There is low level quality evidence for the use of nasal continuous positive airway pressure in the ward inpatient setting.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* **Nasal CPAP therapy for infants with bronchiolitis may be considered for the management of infants.**	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	**Body of evidence provides some support for recommendations(s) but care should be taken in its application**
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point
UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*		
IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*		
Will this recommendation result in changes in usual care? Increase in ward based respiratory support.	**YES**	
	NO	
Are there any resource implications associated with implementing this recommendation? Appropriate training and support for ward staff.	**YES**	
	NO	
Will the implementation of this recommendation require changes in the way care is currently organised?	**YES**	
	NO	
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES	
	NO	

Question 19. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 19: In infants hospitalised with bronchiolitis, is provision of home oxygen a safe alternative for management?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Length of stay in hospital				X	X		
O_2 Readmission rate in seven days				X		X	
O_3 Length of oxygen therapy				X		X	
O_4 Adverse events				X		X	
O_5 Cost savings				X		X	

2. Is there is insufficient evidence to make a recommendation?

There have been no systematic reviews on this question. The evidence is based on two RCTs both with significantly methodological flaws, Bajaj et al's study (133) was stopped before the enrolment of the desired number of patients in their sample-size calculation was achieved and Tie et al (134) had very low numbers to compare the two groups in terms of evaluating the cost savings and the patients were recruited over a single Australian bronchiolitis season. Additional evidence came from one prospective observational study (135), one retrospective comparative study (136) and three retrospective chart reviews (137-139).

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of length of stay in hospital there is very low quality evidence of a reduced length of stay in those treated with home oxygen therapy. For the critical outcome of total length of oxygen therapy there is very low quality evidence of a reduced length of oxygen therapy in those treated with home oxygen therapy. For the important outcome of cost savings there is very low quality evidence of a reduced cost saving in those treated with home oxygen therapy.	**VERY LOW**

Judging the benefits in context

The evidence is applicable and can be generalised to most acute tertiary and metropolitan health care facilities caring for bronchiolitic infants with the intention of supplying home oxygen in the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the critical outcome of readmission in seven days there is very low quality evidence of a reduced readmission rate in those treated with home oxygen therapy. For the important outcome of adverse events there is very low quality evidence of no increase in adverse events in those treated with home oxygen therapy.	**VERY LOW**

Judging the harms in context

Evidence to date indicates no increased risk of harm in infants treated. However the studies have been underpowered or only observational with risk of imprecision and inconsistency. The true effect on harm has not been established.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The benefits are likely to outweigh the harms.	**VERY LOW**

Judging the balance of benefits and harms in context

Benefits probably outweigh harms.

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	**Consider**	**CONDITIONAL**
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

Home oxygen therapy has been implemented in at least one Australian centre and with appropriate resourcing has potential to be more widely implemented.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
After a period of observation, infants at low risk for severe bronchiolitis can be considered for discharge on home oxygen as part of an organised 'Home Oxygen Program' which has clear 'Return to Hospital' advice.	**Strength of recommendation** STRONG **CONDITIONAL** WEAK
8. Recommendations for research	
Large randomised controlled study with pre-defined outcomes and use of oxygen therapy is required to establish the position of this therapy in bronchiolitis.	

Question 19. NHMRC Evidence Summary

Question 19: In infants hospitalised with bronchiolitis, is provision of home oxygen a safe alternative for management?		**Evidence table ref:** Bajaj 2006, Flett 2014, Gauthier 2012, Halstead 2012, Sandweiss 2013, Tie 2009, Zappia 2013 (133-139).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
No systematic reviews. Two RCTs involving 136 infants (Level III-1). Both studies are rated high for risk of bias. There has been one additional prospective observational study of 112 infants (Level IV) a retrospective historical control study of 692 infants and three retrospective chart reviews of 1060 children (Level III-3 - IV). All studies are rated low for risk of bias.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias**
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Evidence is consistent that home oxygen therapy reduces length of stay in hospital. However, studies are variable in quality and reporting of all outcomes.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Length of stay in hospital for the individual patient is reduced but no study has compared the total length of care for patients both in hospital and at home while receiving oxygen therapy. There is potential for cost savings and positive patient satisfaction but only one study has looked at resource implications for community practice. There appears to be no increase in adverse events or change in readmission rates following discharge.	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
The majority of the studies were conducted in North America in an elevated altitude where home oxygen therapy is used frequently. 2 studies were from Australia and hence generalizable to Australia and New Zealand.	A	Evidence directly generalisable to target population
	B	**Evidence directly generalisable to target population with some caveats**
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
The results are directly applicable to the Australian/New Zealand healthcare context. The provision of home oxygen services would require some individual health services to provide appropriate equipment and follow up not currently available.	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
	D	Evidence not applicable to Australian/New Zealand healthcare context
Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		
Component	**Rating**	**Description**
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
2. Consistency	C	Some inconsistency, reflecting genuine uncertainty around question
3. Clinical Impact	C	Moderate
4. Generalisability	B	Evidence directly generalisable to target population with some caveats
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
Evidence statement: There is some evidence of benefits to infants with bronchiolitis being considered for home oxygen therapy after a suitable period of observation in hospital. The evidence is likely to be generalizable to many health services in Australia and New Zealand.		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* **After a period of observation, infants at low risk for severe bronchiolitis can be considered for discharge on home oxygen as part of an organised 'Home Oxygen Program' which has clear 'Return to Hospital' advice.**	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	**Body of evidence provides some support for recommendations(s) but care should be taken in its application**
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*
Studies were inconsistent in determining the length of time before patients were deemed suitable for discharge home on oxygen and after being sent home how the oxygen was weaned. Studies were underpowered.

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*	
Will this recommendation result in changes in usual care?	**YES**
	NO
Are there any resource implications associated with implementing this recommendation? Easily accessible home oxygen service is required.	**YES**
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	**YES**
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 20a. GRADE Evidence Summary

Considered Judgment - Strength of recommendation							
Question 20a: In infants presenting to hospital or hospitalized with bronchiolitis, does the use of antibiotic medication improve clinically relevant endpoints.							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
	HIGH	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Length of hospital stay		**X**			**X**		
O_2 Hospital readmission within 6 months		**X**				**X**	
O_3 Adverse effects			**X**			**X**	
O_4 PICU admission			**X**		**X**		
O_5 Persistent respiratory symptoms			**X**			**X**	

2. Is there is insufficient evidence to make a recommendation?

The evidence is based on two Cochrane systematic reviews. The first review (140) contains seven RCTs involving 824 participants. In the second systematic review (141) only a single study of 30 infants met inclusion criteria. Subsequently there have been a two further RCTs of 40 (142) and 219 (143) infants.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of length of stay there is moderate quality evidence of no benefit of antibiotics compared to placebo. For the critical outcome of PICU admission there is low quality evidence of reduced PICU admission in antibiotic treatment with one study (157) of 71 infants with only one admission to PICU. For the important outcome of persistent respiratory symptoms there is low quality evidence that there is no benefit of antibiotics.	**MODERATE**

Judging the benefits in context

The evidence is applicable and generalizable to the New Zealand and Australian setting.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of adverse effects there was no difference found in adverse gastro-intestinal effects with antibiotic use in a study of 40 infants (167) and a study of 219 infants (143). There were no deaths reported in any of the included studies. For the important outcome of hospital re-admission within 6 months there is moderate quality evidence of no benefit compared to placebo.	**MODERATE**

Judging the harms in context

Bronchiolitis is a viral infection and the low risk of secondary bacterial infection needs to be balanced with the significant harms of antibiotic use, including rash, diarrhoea, vomiting as well as increased hospital and community antibiotic resistance.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Harms probably outweigh the benefits.	**MODERATE**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms **Harms probably outweigh benefits**	**Consider against**	**CONDITIONAL**
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

There is insufficient evidence to support the use of antibiotics for infants with bronchiolitis. Although macrolide antibiotics have both antibiotic and anti-inflammatory properties their use for treatment of viral bronchiolitis is not justified.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	**Recommend/consider against**

7. Final recommendation	
Do not use antibiotics to treat infants with bronchiolitis.	**Strength of recommendation** STRONG **CONDITIONAL** WEAK
8. Recommendations for research	
Studies on subgroups of high risk patients who may benefit from antibiotics, including those admitted to ICU with severe bronchiolitis are needed. The optimal treatment regime (single dose to 14 days) and timing (acute versus post-acute) is yet to be established.	

Question 20a. NHMRC Evidence Summary

Question 20a: In infants presenting to hospital or hospitalised with bronchiolitis, does the use of antibiotic medication improve clinically relevant end-points?		**Evidence table ref:** Beigleman 2014, Farley 2014, Kneyber 2008, Mazumder 2009, McCallum 2012, McCallum 2013, McCallum 2015, Pinto 2012, Tahan 2007 (140-143, 167-171)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
The evidence is based on two Cochrane systematic reviews and an RCT. The first review (140) contains seven RCTs involving 824 participants comparing antibiotics to placebo or other. In the second systematic review for persistent symptoms following acute bronchiolitis (141) only a single study of 30 infants met inclusion criteria. Subsequently there have been a two further RCTs of 40 (142) and 219 (143) infants. Two studies with a high risk of bias showed reduced hospital admission (167) or mixed results for effects on wheeze (169).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	**One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias**
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
For length of stay, data from three studies was combined (141, 157, 171) and showed no difference between azithromycin and placebo (pooled MD -0.58, 95% CI -1.18 to 0.02) with acceptable statistical heterogeneity. This result was further supported by a subsequent RCT of 219 infants (143). Two studies providing data to compare hospital readmissions showed no significant difference but data was not pooled due to risk of heterogeneity (142). This result was further supported by a subsequent RCT of 219 infants (143).	A	All studies consistent
	B	**Most studies consistent and inconsistency can be explained**
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
There is no evidence of benefit of antibiotics and there are real concerns of potential harm caused by adverse effects such as gastrointestinal upset, rash and impact on community and hospital antibiotic resistance.	A	Very large
	B	**Substantial**
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
Two studies were conducted in Bangladesh, while three studies were conducted in high income countries (140). One study was conducted in indigenous infants in Australia and New Zealand (143). All studies included participants who were hospitalised and only one recruited from an outpatients department.	**A**	**Evidence directly generalisable to target population**
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
Use of antibiotics for hospitalised febrile young infants is common but the evidence supports the low incidence of serious bacterial infection in infants with a clinical diagnosis of bronchiolitis. One study was conducted in indigenous infants in Australia and New Zealand (143).	**A**	**Evidence directly applicable to Australian/New Zealand healthcare context**
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context
Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		
Bronchiolitis is a clinical diagnosis, caused by viral infection with extremely low rates of secondary bacterial infection, other than PICU population.		

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		
Component	**Rating**	**Description**
1. Evidence base	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian/New Zealand healthcare context
Evidence statement There is evidence to support not using antibiotics for treating infants with a clinical diagnosis of bronchiolitis.		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* Do not use antibiotics to treat infants with bronchiolitis.	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	**Body of evidence can be trusted to guide practice in most situations**
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*
Sub-populations of high risk groups with severe bronchiolitis require further study.

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*	
Will this recommendation result in changes in usual care? A number of infants with bronchiolitis in Australia and New Zealand receive antibiotics.	**YES** NO
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

Question 20b. GRADE Evidence Summary

Considered Judgment - Strength of recommendation							
Question 20b: In Infants presenting to hospital or hospitalised with bronchiolitis, does the use of azithromycin medication improve clinically relevant end points?							
1. Outcome measures:	**Quality of evidence**				**Importance of outcome in making a decision**		
	HIGH	**MOD**	**LOW**	**V. LOW**	**Critical**	**Important**	**Not Important**
O_1 Length of stay		**X**			**X**		
O_2 Hospital readmission		**X**				**X**	
O_3 Duration of fever		**X**				**X**	
O_4 Occurrence of recurrent wheeze			**X**			**X**	
O_5 Adverse effects			**X**			**X**	
O_6 PICU admission			**X**		**X**		
2. Is there is insufficient evidence to make a recommendation?							
Evidence statement The evidence is based on one systematic review containing three RCTs that compared azithromycin to placebo, involving 353 hospitalised infants (140). Subsequently there has been two RCTs, one of 40 infants (142), and one of 219 infants (143).							
3. What benefit will the proposed intervention/action have?							
Evidence statement For the critical outcome of length of stay there is moderate quality evidence of no difference in length of stay for those treated with azithromycin versus placebo. For the critical outcome of PICU admission there is low quality evidence of no difference in admission rate for those treated with azithromycin versus placebo. For symptom resolution, including duration of fever, there is moderate quality evidence that treatment with azithromycin has no benefit over placebo. For the occurrence of recurrent wheeze, there is low quality evidence that azithromycin results in prolonged time to third wheezing episode.					**Quality of evidence** **MODERATE**		
Judging the benefits in context The evidence is applicable and generalizable to the Australian and New Zealand health settings.							
4. What harm might the proposed intervention/action do?							
Evidence statement For the important outcome of hospital readmission there is moderate quality evidence of no increase in readmission rate in those treated with azithromycin. For the important outcome of adverse effects there is low quality evidence of no difference in reported gastrointestinal side effects in those treated with azithromycin.					**Quality of evidence** **MODERATE**		
Judging the harms in context Evidence shows no increase in harms but the lack of beneficial effect must be weighed against the possibility of adverse effects, increasing antibiotic resistance and cost of treatment.							
5. What is the likely balance between good and harm?							
Evidence statement The harms probably outweigh the benefits.					**Overall quality of evidence MODERATE**		
Judging the balance of benefits and harms in context							
Benefits clearly outweigh harms	Recommend				STRONG		
Benefits probably outweigh harms	Consider				CONDITIONAL		
Not known	Make a recommendation for research (see 8 below)				WEAK		
Benefits probably don't outweigh harms **Harms probably outweigh benefits**	**Consider against**				**CONDITIONAL**		
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against				STRONG		

6. Is the intervention/action implementable in the New Zealand and Australian context?	
Summary statement Azithromycin is currently used for treatment of children with bronchiectasis and cystic fibrosis; however the anti-inflammatory effects have not been shown to benefit infants with bronchiolitis.	
Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	**Recommend/consider against**
7. Final recommendation	
Do not use azithromycin for treatment of infants admitted to hospital with bronchiolitis.	**Strength of recommendation** STRONG **CONDITIONAL** WEAK
8. Recommendations for research	
Nil.	

Question 20b. NHMRC Evidence Summary

Question 20b: In Infants presenting to hospital or hospitalised with bronchiolitis, does the use of azithromycin medication improve clinically relevant end points?		**Evidence table ref:** Beigelman 2014, Farley 2014, Macias 2015, McCallum 2015 (140, 142, 143, 172)
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
The evidence is based on one systematic review containing three RCTs that compared azithromycin to placebo, involving 353 hospitalised infants (140). All studies are rated are rated low or unclear risk of bias. Subsequently there has been two RCTs, one of 40 infants (142), and one of 219 infants (143).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	**One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias**
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Evidence is consistent that the use of azithromycin for treatment of bronchiolitis did not reduce length of stay, hospital readmission rates and PICU admission.	A	All studies consistent
	B	**Most studies consistent and inconsistency can be explained**
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Rates of antibiotic use in bronchiolitis have been reported as high (17 – 43% for inpatients in a multicentre observational study)(172). The use of azithromycin in variable dosing regimens has no clinical benefit and possible harms.	A	Very large
	B	**Substantial**
	C	Moderate
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
Three studies were conducted in high income countries and one study was conducted in Brazil (140, 142). One study of 219 infants was conducted in indigenous infants in Australia and New Zealand (143). The patients are directly generalisable to those seen in Australia and New Zealand.	**A**	**Evidence directly generalisable to target population**
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

The results are applicable to the Australian/ New Zealand healthcare context with a few caveats. One study of 219 infants was conducted in indigenous infants in Australia and New Zealand (143).	**A**	**Evidence directly applicable to Australian/New Zealand healthcare context**
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian/New Zealand healthcare context

Evidence statement

Currently there is no evidence of benefit.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Do not use azithromycin for treatment of infants admitted to hospital with bronchiolitis.	A	Body of evidence can be trusted to guide practice
	B	**Body of evidence can be trusted to guide practice in most situations**
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care?	**YES**
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 20c. GRADE Evidence Summary

Considered Judgment - Strength of recommendation

Question 20c: In infants presenting to hospital or hospitalised with bronchiolitis, does the use of antibiotic medication in infants who are at risk of developing bronchiectasis, improve clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Hospital readmission		X				X	
O_2 Recurrent symptoms				X		X	
O_3 Prolonged symptoms		X				X	
O_4 Bronchiectasis				X	X		

2. Is there is insufficient evidence to make a recommendation?

Evidence statement
One RCT of azithromycin versus placebo, once a week for three weeks, in 219 indigenous infants enrolled in Australia and New Zealand found no difference in length of hospital stay, symptoms at 21 days, adverse events or readmission rates at six months (143).

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
One RCT of azithromycin versus placebo, once a week for three weeks, in 219 indigenous infants enrolled in Australia and New Zealand found no difference in length of hospital stay, symptoms at 21 days, adverse events or readmission rates at six months (143). There are no reports on bronchiectasis as an outcome.	**LOW**

Judging the benefits in context

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
There are concerns regarding development of macrolide resistance.	**VERY LOW**

Judging the harms in context
Given the concerns of macrolide resistance, and a negative RCT in those at risk in Australia and New Zealand, there is currently no evidence to support the use of azithromycin for the prevention of bronchiectasis in those admitted with bronchiolitis.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
There is one negative RCT (143), reporting surrogate end-points for the critical outcome of bronchiectasis, and concern regarding the development of macrolide resistance.	**LOW**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research	WEAK
Benefits probably don't outweigh harms **Harms probably outweigh benefits**	**Consider against**	**CONDITIONAL**
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement
Evidence applicable.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Do not use azithromycin for treatment of infants admitted to hospital with bronchiolitis who are at risk of developing bronchiectasis.	STRONG **CONDITIONAL** WEAK

8. Recommendations for research

A RCT with longer follow-up for outcomes in at risk populations is required to determine benefit of antibiotics in infants at risk of bronchiectasis.

Question 20c. NHMRC Evidence Summary

Question 20c: In infants presenting to hospital or hospitalised with bronchiolitis, does the use of antibiotic medication in infants who are at risk of developing bronchiectasis, improve clinically relevant end-points?	**Evidence table ref:** Nil studies.

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

One RCT of azithromycin versus placebo, once a week for three weeks, in 219 indigenous infants enrolled in Australia and New Zealand found no difference in length of hospital stay, symptoms at 21 days, adverse events or readmission rates at six months (143).	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	**One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias**
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

Only one study (143) has addressed the question.	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	**Not applicable (one study only)**

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

One RCT of azithromycin versus placebo, once a week for three weeks, in 219 indigenous infants enrolled in Australia and New Zealand found no difference in length of hospital stay, symptoms at 21 days, adverse events or readmission rates at six months (143).	A	Very large
	B	Substantial
	C	Moderate
	D	**Slight/Restricted**

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

One RCT enrolled 219 indigenous infants in Australia and New Zealand (143).	**A**	**Evidence directly generalisable to target population**
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

One RCT enrolled 219 indigenous infants in Australia and New Zealand (143).	**A**	**Evidence directly applicable to Australian/New Zealand healthcare context**
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

There is one negative RCT, reporting surrogate end-points for the critical outcome of bronchiectasis, and concern regarding the development of macrolide resistance.

Component	Rating	Description
1. Evidence base	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
2. Consistency	NA	Not applicable (one study only)
3. Clinical Impact	D	Slight/Restricted
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian/New Zealand healthcare context

Evidence statement

There is no evidence to support the use of antibiotics for treating bronchiolitis in those at-risk of bronchiectasis outside of clinical research.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* **Do not use azithromycin for treatment of infants admitted to hospital with bronchiolitis who are at risk of developing bronchiectasis.**	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	**Body of evidence provides some support for recommendations(s) but care should be taken in its application**
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*	
The critical outcome of bronchiectasis is not reported.	
IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*	
Will this recommendation result in changes in usual care?	YES **NO**
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

Question 21a. GRADE Evidence Summary

Considered Judgment - Strength of recommendation

Question 21a: In infants presenting to hospital or hospitalised with bronchiolitis, does the use of non-oral rehydration improve clinically relevant end points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Length of stay				X	X		
O_2 ICU admission				X	X		

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

A retrospective cohort study of 102 infants (45) admitted to ICU with severe bronchiolitis showed that mortality, ventilator time and duration of stay in ICU was significantly different between subjects with hyponatraemia and those without. Data of the type of fluid, amount of fluid, and rate of administration were not available in this retrospective study.

A prospective cohort study of 36 infants with moderate bronchiolitis who received a standard parenteral hypotonic solution showed drop in serum sodium and osmolality compared to admission despite improvement in respiratory parameters (146). An earlier study (173) of hyponatraemia in 91 infants with severe bronchiolitis requiring ICU admission, with 4% suffering hyponatraemic seizures, showed that three of the four had received hypotonic fluids.

There is insufficient evidence to make recommendations about the use of non-oral hydration but caution about the use of hypotonic IV fluids exists.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
There is insufficient evidence to make recommendations about the use of non-oral hydration.	**VERY LOW**

Judging the benefits in context

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
There are serious concerns with the administration of hypotonic parenteral fluids to infants with bronchiolitis due to the risk of hyponatraemia and seizures.	**VERY LOW**

Judging the harms in context

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
Supplemental hydration is recommended to avoid renal failure in those not tolerating oral hydration (based on first principals). Evidence regarding the ideal volume of non-oral rehydration currently does not exist. There remains concern regarding hyponatraemia.	**VERY LOW**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

Non-oral hydration is routinely used in Australia and New Zealand.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

	Strength of recommendation
Supplemental hydration is recommended for infants who cannot maintain hydration orally.	STRONG CONDITIONAL **WEAK**

8. Recommendations for research

The ideal volume (restricted versus 100% maintenance) and type of non-oral fluids (NG rehydration solutions or milk, or type of isotonic IV solution) to give to infants with bronchiolitis has not been studied.

Question 21a. NHMRC Evidence Summary

Question: 21a: In infants presenting to hospital or hospitalised with bronchiolitis, does the use of non-oral rehydration improve clinically relevant end points?	**Evidence table ref:** Luu 2013, Rodrigues 2014 (45, 146).

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

A	All studies consistent
B	Most studies consistent and inconsistency can be explained
C	Some inconsistency, reflecting genuine uncertainty around question
D	Evidence is not consistent
NA	**Not applicable (one study only)**

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

A	Very large
B	Substantial
C	**Moderate**
D	Slight/Restricted

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

A	Evidence directly generalisable to target population
B	Evidence directly generalisable to target population with some caveats
C	**Evidence not directly generalisable to target population but could be sensibly applied**
D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

A	Evidence directly applicable to Australian/New Zealand healthcare context
B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	N/A	Not applicable (one study only)
3. Clinical Impact	C	Moderate
4. Generalisability	C	Evidence not directly generalisable to target population but could be sensibly applied
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats

Evidence statement

Supplemental hydration is recommended to avoid renal failure in those not tolerating oral hydration (based on first principals). Evidence regarding the ideal volume of non-oral rehydration currently does not exist. There remains concern regarding hyponatraemia.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* **Supplemental hydration is recommended for infants who cannot maintain hydration orally.**	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*	
The ideal volume and type of non-oral fluids to give to infants with bronchiolitis has not been studied.	
IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*	
Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	**YES**
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 21b. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 21b: In infants presenting to hospital or hospitalised with bronchiolitis, what forms of non-oral hydration improve clinically relevant end points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Length of stay		X			X		
O_2 Adverse effects		X				X	
O_3 Hospital Readmission			X			X	
O_4 Success of insertion		X				X	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

The evidence is based on one large randomized control (145) trial comparing NG and IV rehydration in 759 infants admitted to hospital with bronchiolitis and a small randomised prospective pilot study (174) of 51 infants with high dropout rate comparing IV fluids and gastric tube feeding. There have been no systematic reviews on the question.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of length of stay there is moderate level evidence that both NG and IV routes are acceptable means for non-oral hydration with no statistical difference in mean length of stay for IV rehydration 86.6 hours (SD 58.9) versus 82.2 hours (SD 58.8) for NG feeds (145).	**MODERATE**

Judging the benefits in context

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
For the important outcome of success of insertion there is moderate quality evidence to guide treatment. 85% of infants assigned NG rehydration had one insertion attempt, compared to 56% for IV hydration ($p< 0.0001$) with 20% of those with IV attempts recorded having three or more attempts. For the important outcome of adverse effects there is moderate quality evidence of no difference between IV and NG rehydration. The most common complications were NG tube pulled out (131 infants) or IV fluid extravasation (80 infants). Other adverse effects including IV line site bruising, nasal trauma occurred in 11% of those who received randomly allocated treatment (9% for NG versus 14% for IV). There were no events of clinical aspiration recorded in either study (145, 174). For the important outcome of hospital readmission for bronchiolitis there is low quality evidence regarding the difference between IV and NG rehydration due to the low numbers of patients with 1.6% for both groups.	**MODERATE**

Judging the harms in context

Non-oral hydration is essential when an infant with bronchiolitis is unable to maintain oral feeding due to severity of illness.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
NG and IV hydration appear to be similar, although IV insertion requires more attempts.	**MODERATE**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	**Recommend**	**STRONG**
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

Both IV and NG means of hydration are standard treatment for infants with bronchiolitis admitted to hospital in Australia and New Zealand.

Yes	**Recommend**/consider
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation	
Both NG and IV routes are acceptable means for non-oral hydration in infants admitted to hospital with bronchiolitis.	**Strength of recommendation** **STRONG** CONDITIONAL WEAK
8. Recommendations for research	
The use of non-oral hydration in infants less than two months has not been studied as they were excluded from published studies.	

Question 21b. NHMRC Evidence Summary

Question 21b: In infants presenting to hospital or hospitalised with bronchiolitis, what forms of non-oral hydration improve clinically relevant end points?		**Evidence table ref:** Babl 2008, Kugelman 2013, Oakley 2013 (145, 174, 175).
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
The evidence is based on one large randomised control trail (145) comparing NG and IV rehydration in 759 infants admitted to hospital with bronchiolitis and small randomised prospective pilot study (174) of 51 infants with high dropout rate.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	**One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias**
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
Both studies (145, 174) showed no difference in the primary outcome of hospital length of stay between IV hydration and NG hydration.	**A**	**All studies consistent**
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)
3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
Both means of non-oral hydration are appropriate to hydrate infants however higher success rate with fewer insertion attempts using NG tube feeding favours this method and may support change in practice.	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted
4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*		
The large multicentre RCT (Oakley 2013) enrolled infants aged 2 months to 12 months, who presented to EDs in seven hospitals in Australia and New Zealand across three bronchiolitis seasons.	**A**	**Evidence directly generalisable to target population**
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*		
Both IV and NG means of hydration are standard treatment for infants with bronchiolitis admitted to hospital in Australia and New Zealand	**A**	**Evidence directly applicable to Australian/New Zealand healthcare context**
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context
Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*		

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*		
Component	**Rating**	**Description**
1. Evidence base	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
2. Consistency	A	All studies consistent
3. Clinical Impact	C	Moderate
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	A	Evidence directly applicable to Australian/New Zealand healthcare context
Evidence statement NG and IV hydration appear to be similar, although IV insertion requires more attempts.		

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
Both NG and IV routes are acceptable means for non-oral hydration in infants admitted to hospital with bronchiolitis.	**A**	**Body of evidence can be trusted to guide practice**
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*

IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*

Will this recommendation result in changes in usual care? A survey of Australian and New Zealand emergency physicians reported 48% used NG and 52% used IV hydration in infants with bronchiolitis requiring non-oral hydration (175).	YES **NO**
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**YES** NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

Question 21c. GRADE Evidence Summary

Considered Judgement - Strength of recommendation

Question 21c: In Infants presenting to hospital or hospitalized with bronchiolitis, does limiting the volume of non-oral hydration impact on clinically relevant end-points?

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Length of stay				N/A	X		
O_2 Hyponatremia				N/A		X	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

There is insufficient evidence to make a recommendation.

A prospective cohort study of 36 infants with moderate bronchiolitis who received a standard parenteral hypotonic solution showed drop in serum sodium and osmolality compared to admission despite improvement in respiratory parameters (146).

An earlier study (173) of hyponatraemia in 91 infants with severe bronchiolitis requiring ICU admission, with 4% suffering hyponatraemic seizures showed that three of the four had received hypotonic fluids.

There is insufficient evidence to make recommendations about the use of non-oral hydration but caution about the use of hypotonic fluids.
A systematic review (144) of benefit versus harm from advice to increase fluid intake for treating acute respiratory infections in adults and children was unable to identify any evidence from RCTs in the primary care or outpatient setting.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
There is insufficient evidence to make recommendations about the use of non-oral hydration but evidence cautions the use of hypotonic fluids.	**N/A**

Judging the benefits in context

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
There is insufficient evidence to make recommendations about the use of non-oral hydration but evidence cautions the use of hypotonic fluids.	**N/A**

Judging the harms in context

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
There is insufficient evidence to make a recommendation regarding fluid restriction of infants with bronchiolitis in the non-ICU setting. The previous use of hypotonic IV fluids may have contributed to practice to restrict volumes due to risk of hyponatraemia.	**N/A**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	Consider	CONDITIONAL
Not known	**Make a recommendation for research (see 8 below)**	**WEAK**
Benefits probably don't outweigh harms Harms probably outweigh benefits	Consider against	CONDITIONAL
Benefits clearly don't outweigh harms Harms clearly outweigh benefits	Recommend against	STRONG

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

There is insufficient evidence to recommend a specific proportion of maintenance fluid. There is a risk of fluid overload and judicious and vigilant use of hydration fluid is recommended. Isotonic fluid is recommended.	**Strength of recommendation** STRONG CONDITIONAL **WEAK**

8. Recommendations for research

The use of restricted versus maintenance volumes of non-oral hydration fluids administered to infants with bronchiolitis needs to be studied in an RCT in the current era of isotonic fluid use.

Question 21c. NHMRC Evidence Summary

Question 21c: In Infants presenting to hospital or hospitalized with bronchiolitis, does limiting the volume of non-oral hydration impact on clinically relevant end-points?	**Evidence table ref:** Guppy 2011, Hanna 2003, Rodrigues 2014 (144, 146, 173)

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

There is insufficient evidence to make a recommendation	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
	D	**Level IV studies or Level I to III studies/SRs with a high risk of bias**

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	**Not applicable (one study only)**

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

	A	Very large
	B	Substantial
	C	**Moderate**
	D	Slight/Restricted

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	**Evidence not directly generalisable to target population and hard to judge whether sensible to apply**

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats
	C	**Evidence probably applicable to Australian/New Zealand healthcare context with some caveats**
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency	N/A	Not applicable (one study only)
3. Clinical Impact	C	Moderate
4. Generalisability	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply
5. Applicability	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats

Evidence statement

There is insufficient evidence to make a recommendation.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)*	**OVERALL GRADE OF RECOMMENDATION**	
There is insufficient evidence to recommend a specific proportion of maintenance fluid. **There is a risk of fluid overload and judicious and vigilant use of hydration fluid is recommended. Isotonic fluid is recommended.**	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	**Practice Point**

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*	
IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*	
Will this recommendation result in changes in usual care?	YES
	NO
Are there any resource implications associated with implementing this recommendation?	YES
	NO
Will the implementation of this recommendation require changes in the way care is currently organised?	YES
	NO
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES
	NO

Question 22. GRADE Evidence Summary

Considered Judgment - Strength of recommendation

Question 22: In infants presenting to hospital or hospitalised with bronchiolitis, does infection control practices improve clinically relevant end points??

1. Outcome measures:	Quality of evidence				Importance of outcome in making a decision		
	HIGH	MOD	LOW	V. LOW	Critical	Important	Not Important
O_1 Nosocomial infection			X		X		
O_2 Adverse Events				X		X	
O_3 Cost effectiveness				X		X	

2. Is there is insufficient evidence to make a recommendation?

Evidence statement

The current evidence is derived from five observational studies (147-150). No RCT on containing common viral infections such as RSV by different infection control practices in ED or general paediatric ward setting is available. The Cochrane review (151) focuses on different pandemic viral infections affecting a range of population in a variety of settings. This evidence could be extrapolated as indirect evidence for infants with bronchiolitis secondary to common respiratory viral infections.

3. What benefit will the proposed intervention/action have?

Evidence statement	**Quality of evidence**
For the critical outcome of nosocomial infection there is low quality evidence of a reduced rate of nosocomial infection in RSV positive infants managed with infection control procedures.	**LOW**

Judging the benefits in context

The evidence is applicable and generalizable to the New Zealand and Australian health settings.

4. What harm might the proposed intervention/action do?

Evidence statement	**Quality of evidence**
There has been no significant adverse effect of the infection control practices reported. For the important outcome of cost effectiveness of these practices, there is very little evidence in literature to support or refute these practices.	**VERY LOW**

Judging the harms in context

Evidence to date is still lacking on the cost effectiveness of different modalities of infection control measures to contain RSV infection in the hospital. It is not known whether the costs associated with isolation or cohorting the RSV positive infants significantly outweigh the benefits of preventing nosocomial RSV infections.

5. What is the likely balance between good and harm?

Evidence statement	**Overall quality of evidence**
The benefits are likely to outweigh the harms.	**LOW**

Judging the balance of benefits and harms in context

Benefits clearly outweigh harms	Recommend	STRONG
Benefits probably outweigh harms	**Consider**	**CONDITIONAL**
Not known	Make a recommendation for research (see 8 below)	WEAK
Benefits probably don't outweigh harms	Consider against	CONDITIONAL
Harms probably outweigh benefits		
Benefits clearly don't outweigh harms	Recommend against	STRONG
Harms clearly outweigh benefits		

6. Is the intervention/action implementable in the New Zealand and Australian context?

Summary statement

Infection control practices are widely adopted in Australia and New Zealand, although strong evidence on the cost effectiveness is not yet available.

Yes	**Recommend/consider**
Not known	Consider economic evaluation
No	Recommend/consider against

7. Final recommendation

Hand hygiene is the most effective intervention to reduce hospital acquired infections and is recommended. It has not been specifically looked at in patients with Bronchiolitis. There is inadequate evidence for the benefits of cohorting bronchiolitic patients.	**Strength of recommendation** STRONG CONDITIONAL **WEAK**

8. Recommendations for research

Whilst studies to date examined different regimes of infection control practices when managing infants with bronchiolitis, it could be valuable to evaluate the cost effectiveness of these procedures to prevent nosocomial viral infections such as comparing cohorting to simple hand hygiene measures. No studies have specifically looked at the practice of cohorting on the basis of virology studies in comparing outcomes.

Question 22. NHMRC Evidence Summary

Question 22: In infants presenting to hospital or hospitalised with bronchiolitis, does infection control practices improve clinically relevant end points?	**Evidence table ref:** Jefferson 2011, Mills 2011, Simon 2006, Simon 2008, Thorburn 2012 (147-151).

1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*

The current evidence is derived from five observational studies with historical controls. No RCT on containing common viral infection such as RSV by different infection control practices in ED or general paediatric ward setting is available. The Cochrane review (151) focus on different pandemic viral infection affecting a range of population in a variety of settings. This evidence could be extrapolated as indirect evidence for infants with bronchiolitis secondary to common respiratory viral infections.	A	One or more Level I studies with a low risk of bias, or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias, or SR/several Level III studies with a low risk of bias
	C	**One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias**
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias

2. Consistency *(if only one study was available, rank this component as 'not applicable')*

Most of the evidence from observation studies showed consistent reduction of nosocomial RSV infections.	A	All studies consistent
	B	**Most studies consistent and inconsistency can be explained**
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is not consistent
	NA	Not applicable (one study only)

3. Clinical impact *(indicate if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*

Risk of nosocomial infection is significantly reduced by infection control practices (pool odds ratio 0.25, 95% CI 0.16 to 0.40). No increase of significant adverse events has been reported.	A	Very large
	B	**Substantial**
	C	Moderate
	D	Slight/Restricted

4. Generalisability *(how well does the body of evidence match the population and clinical settings being targeted by the guideline?)*

Many studies were conducted in North America using populations that are directly generalisable to patients with bronchiolitis seen in Australia and New Zealand.	**A**	**Evidence directly generalisable to target population**
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether sensible to apply

5. Applicability *(is the body of evidence relevant to the Australian/New Zealand healthcare context in terms of health services / delivery of care and cultural factors?)*

The results are applicable to the Australian/New Zealand healthcare context. Infection control practices in many forms are in general universal in Australia and New Zealand, very much more so in paediatric intensive care settings.	A	Evidence directly applicable to Australian/New Zealand healthcare context
	B	**Evidence applicable to Australian/New Zealand healthcare context with few caveats**
	C	Evidence probably applicable to Australian/New Zealand healthcare context with some caveats
	D	Evidence not applicable to Australian/New Zealand healthcare context

Other factors *(indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Cost effectiveness is yet to be determined due to lack of evidence in this area.

EVIDENCE STATEMENT MATRIX *(summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account)*

Component	Rating	Description
1. Evidence base	C	One or two Level III studies with a low risk of bias or Level I or II studies with moderate risk of bias
2. Consistency	B	Most studies consistent and inconsistency can be explained
3. Clinical Impact	B	Substantial
4. Generalisability	A	Evidence directly generalisable to target population
5. Applicability	B	Evidence applicable to Australian/New Zealand healthcare context with few caveats

Evidence statement

There is low level of evidence for infection control practices to infants with bronchiolitis. These practices are widely adopted in many health care settings and no adverse events have been reported. The evidence is generalizable to Australia and New Zealand.

RECOMMENDATION *(What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible)* **Hand hygiene is the most effective intervention to reduce hospital acquired infections and is recommended. It has not been specifically looked at in patients with Bronchiolitis. There is inadequate evidence for the benefits of cohorting bronchiolitic patients.**	**OVERALL GRADE OF RECOMMENDATION**	
	A	Body of evidence can be trusted to guide practice
	B	**Body of evidence can be trusted to guide practice in most situations**
	C	Body of evidence provides some support for recommendations(s) but care should be taken in its application
	D	Body of evidence is weak and recommendation must be applied with caution
	PP	Practice Point

UNRESOLVED ISSUES *(If needed, keep a note of specific issues that arise when each recommendation is formulated and that require follow up)*	
Studies used different regimens of infection control practice. The cost analysis of each regime and the optimal regime is still to be determined.	
IMPLEMENTATION OF RECOMMENDATION *(Please indicate yes or no to the following questions. Where the answer is yes, please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines)*	
Will this recommendation result in changes in usual care?	YES **NO**
Are there any resource implications associated with implementing this recommendation?	YES **NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	YES **NO**
Are the guideline development group aware of any barriers to implementation of this recommendation?	YES **NO**

RESEARCH RECOMMENDATIONS

1. Research defining the positive and negative predictive values of clinical criteria for diagnosing bronchiolitis is needed, especially that which gives strength to the ability to refute the diagnosis of bronchiolitis when other conditions are present (e.g. cardiac failure, immunodeficiency).

2. Large cohort studies are needed to define the relative risk of particular factors and to define subpopulations with increased risk.

3. Research on infants with more severe bronchiolitis is needed to define the role of CXR.

4. Research on subpopulations at high risk for UTI when the infant is diagnosed with bronchiolitis is needed.

5. Research to determine if patient cohorting based on virological results reduces in-hospital transmission more than appropriate contact precautions is warranted.

6. Further research is needed to derive and validate a bronchiolitis scoring system for infants diagnosed with bronchiolitis that is generalizable for different populations, and that has significance for patient centred outcomes.

7. Research on outcomes of infants with differing levels of oxygen saturations and duration of adequate feeding at the time of discharge.

8. Previous studies should be reviewed to clarify rates of readmission in infants administered beta 2 agonists and discharged home.

9. Research on the use of beta 2 agonists in infants presenting to hospital or hospitalised with bronchiolitis with a personal or family history of atopy is needed.

10. Previous studies should be reviewed to clarify the effects of beta 2 agonists in infants aged between 6 and 12 months of age.

11. Studies to date have used different regimens of nebulised hypertonic saline, and the optimal regime is still to be determined. Further large multicentre trials are required to confirm the overall benefits of nebulised hypertonic saline in both inpatient and the ED settings.

12. Research on the long-term effects in infants with bronchiolitis who have received systemic or local glucocorticoids (nebulisation, oral, IM or IV) is required.

13. Research on the use of glucocorticoids in infants presenting to hospital or hospitalised with bronchiolitis and with a positive response to beta 2 agonists is needed.

14. Research on the use of a combination of glucocorticoids and adrenaline/epinephrine in infants presenting to hospital or hospitalised with bronchiolitis is needed.

15. RCTs with pre-defined indications and protocols for supplemental oxygen are required to determine the effect on hospital admission, length of stay, oxygen saturation targets and effect on feeding difficulties.

16. Further RCTs are needed to confirm the level of oxygen saturations to establish oxygen therapy.

17. Research on the effect of prolonged hypoxia (saturations less than 92%) on long term development is required.

18. Further research is needed in determining an appropriate oxygen saturation level at which to consider discharge of an infant from hospital (inpatient ward or ED) with bronchiolitis.

19. RCTs are needed to establish use of continuous oximetry in the setting of hypoxic infants with bronchiolitis.

20. Further research is needed to determine what effect continuous oximetry monitoring has on time to discharge for inpatients or ED patients.

21. RCTs comparing HFNC with standard oxygen therapy, including sub-groups of infants with hypoxia and respiratory distress without hypoxia, outside of the PICU setting are required.

22. Further research into techniques of chest physiotherapy to determine any benefit in specific patient cohorts with bronchiolitis is required.

23. RCTs using pre-set protocols are needed for use of nasal suction in infants with bronchiolitis.

24. RCTs with pre-set protocols are required to establish the benefit or harm of nasal saline drops.

25. RCTs in paediatric wards and PICUs are needed to directly compare HFNC and nasal CPAP.

26. RCTs with pre-defined indications for oxygen therapy and patient outcomes are required to establish home oxygen programmes for infants with bronchiolitis.

27. Research on subgroups of high risk patients who may benefit from antibiotics, including those admitted to PICU with severe bronchiolitis, is needed. The optimal treatment regime (single dose to 14 days) and timing (acute versus post-acute) is yet to be established.

28. A RCT with longer follow up for outcomes in at risk population is required to determine benefit of antibiotics in infants at risk of bronchiectasis

29. In infants with bronchiolitis, research on the ideal volume (restricted vs. 100% maintenance) and type of non-oral fluids (NG rehydration solutions or milk, or type of isotonic IV solution) and the effect on infants less than two months of age is needed. The use of non-oral hydration in infants less than two months has not been studied as they were excluded from published studies.

30. Research on the cost effectiveness of procedures to prevent nosocomial infections such as cohorting or hand hygiene measures is required.

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DISCLAIMER

The information set out in this publication is current at the date of first publication and is intended for use as a guide only and may or may not be relevant to patients or circumstances. This Guideline was developed for use within the inpatient wards and emergency departments of hospitals in Australia and New Zealand. The Guideline details the initial assessment and management of infants presenting with Bronchiolitis and is designed to acquaint the reader rapidly with the clinical problem and provide practical advice regarding assessment and management.

These Clinical Practice Guidelines were produced by the PREDICT research network and do not reflect the views of the NHMRC. Where possible we have achieved consensus between practicing clinicians. The recommendations contained in these guidelines do not indicate an exclusive course of action, or serve as a standard of medical care. Variations, taking individual circumstances into account, may be appropriate.

The authors of these guidelines have made considerable efforts to ensure the information upon which they are based is accurate and up to date. The authors accept no responsibility for any inaccuracies, information perceived as misleading, or the success of any treatment regimen detailed in the guidelines.

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