# Bronchiolitis: diagnosis and management of bronchiolitis in children.

## Appendix J - GRADE tables

*Clinical Guideline <…>*

*Appendix J - GRADE tables*

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# Appendix A: GRADE tables

## A.1 Symptoms and signs

**Table 1: GRADE profile for typical symptoms of bronchiolitis**

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

| Number of studies | | Quality | Design | Limitations | Inconsistency | Indirect-ness | Imprecision | Other considerations |
|---|---|---|---|---|---|---|---|---|
| 1 (Tsolia et al, 2003) | Symptom: RSC+ (n = 291), RSV- (n = 182)<br>Age (months) median: 2.8, 4.5 | Very Low | Cohort | Very serious[g] | None | None | Serious[b] | None |
| **What is the typical duration of symptoms?** | | | | | | | | |
| 1 (Swingler et al, | Median duration of illness = 12 days (95% CI 11 to 14 days).<br>39% of children were still symptomatic after 14 days, 18% after 21 days and 9% after 28 days. | Very low | Prospective cohort | Serious[h] | None | Serious[i] | Serious[b] | None |
| 1 (Petruzella et al, | Median time to resolution of symptoms<br>15 days<br>25% of infants continued to be symptomatic at day 20<br>At end of follow-up period 11% of infants continued to be symptomatic | Low | Prospective cohort | Serious[j] | None | None | Serious[b] | None |
| 1 (Thompson et al, | 4 bronchiolitis studies identified - Cough<br>Patel, 2003 - RCT of 61 infants followed up until symptoms resolution. Median duration 8.4 days<br>Plint, 2009 - RCT of 201 infants followed-up for 22 days. Median duration 13.3 days (IQR 8.2 to 19.5)<br>Petruzella, 2010 - observational study of 95 infants followed-up unitl symptoms resolution. Median duration 15 days (IQR 11-20)<br>Plint, 2004 - observational study of 163 infants followed-up for 3 weeks. Median duration 12 days (IQR 8 to 20)<br><br>Pooled results<br>Time for symptoms to resolve in 50% of infants was 13 days<br>Time for symptoms to resolve in 90% of infants was 21 days (estimate) | Low | Systematic Review and meta-analysis | None | None | Serious[k] | Serious[b] | None |
| 1 (Mansbach et al, | Outcome: RSV only, RV only, RSV and RV, Other<br>Relapse within 2-weeks (%):12, 8, 15, 13<br>Duration of symptoms (days)(from onset to 2 week follow-up): 8 (4 to 10), 3 (2 to 8), 6 (2 to 9), 8 (2 to 9) | Very low | Cohort | Serious[e] | None | Serious[c] | Very Serious[b, f] | None |
| **How do symptoms change during the course of a bronchiolitis episode? – No data** | | | | | | | | |
| **When do symptoms peak? – No data** | | | | | | | | |

*a Analysis does not account for confounders*
*b Imprecision could not be calculated*
*c comparing RSV+/-*
*d no evidence of search strategy or systematic data extraction*
*e Descriptive only. Study population includes infants with previous wheeze. Duration of symptoms censored at 2 weeks*
*f Study population includes infants with previous wheeze*

*g Admission based on symptoms of Bronchiolitis. High proportion of eligible infants did not have RSV test. Reliability assessing outcomes not reported*
*h High loss to follow-up not explained (26.5%) or analysed*
*I Limited to mild Bronchiolitis only*
*j truncated follow-up*
*k Study focused on cough as a general symptom for respiratory conditions.*

# A.2 Risk factors

## A.2.1 Prematurity

**Table 2: GRADE profile for the association between prematurity and risk of developing severe bronchiolitis**

| | Number of children | | Effect | | | | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | Quality | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **History of prematurity** | | | | | | | | | | | |
| **Risk of bronchiolitis/respiratory syncytial virus (rsv) hospitalisation** | | | | | | | | | | | |
| **Association between ≤28 weeks of gestational age (reference not reported) and RSV hospitalisation[a]** | | | | | | | | | | | |
| 1 (Boyce et al., 2000) | NR | NR | Adjusted IRR: 2.4 (1.8 to 3.3)[b] | - | Very low | Retrospective cohort | Very serious[c] | None | Serious[d] | None | None |
| **Association between ≤28 weeks gestational age (vs ≥37 weeks) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Rietveld et al., 2006) | NR | NR | Adjusted OR: 3.2 (2.1 to 4.8)e | - | Very low | Retrospective cohort | Very serious[f] | None | Serious[g] | None | None |
| **Association between 29 to 32 weeks gestational age (vs ≥37 weeks) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Rietveld et al., 2006) | NR | NR | Adjusted OR: 2.8 (2.1 to 3.8)[e] | - | Very low | Retrospective cohort | Very serious[f] | None | Serious[g] | None | None |
| **Association between 29 to 33 weeks of gestational age (reference not reported) and RSV hospitalisation[a]** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Boyce et al., 2000) | NR | NR | Adjusted IRR: 2.2 (1.8 to 2.7)b | - | Very low | Retrospective cohort | Very seriousc | None | Seriousd | None | None |
| **Association between ≤32 weeks of gestational age (vs ≥40 weeks) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Nielsen et al., 2003) | 49/1250 (3.9%) | 54/5959 (0.9%) | Adjusted OR: 3.88 (2.74 to 7.75)[h] | - | Low | Retrospective, matched case-control | Very serious[i] | None | None | None | None |
| **Association between <33 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis** | | | | | | | | | | | |
| 1 (Paranjothy et al, 2013) | NR | NR | Adjusted HR: 3.89 (3.55 to 4.25)[j] | - | Low | Retrospective cohort | Very serious[k] | None | None | None | None |
| **Association between 33 to 34 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis** | | | | | | | | | | | |
| 1 (Paranjothy et al, 2013) | NR | NR | Adjusted HR: 2.45 (2.21 to 2.71)[j] | - | Low | Retrospective cohort | Very serious[k] | None | None | None | None |
| **Association between 33 to 34 weeks of gestational age (vs ≥38 weeks) and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Lanari et al., 2013) | 54/737 (7.3%) | 25/706 (3.5%) | Adjusted HR: 2.1 (1.3 to 3.4)[l] | - | Moderate | Longitudinal multicentre cohort study | Serious[m] | None | None | None | None |
| **Association between 33 to 34 weeks gestational age (vs ≥37 weeks) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Rietveld et al., 2006) | NR | NR | Adjusted OR: 2.3 (1.8 to 3.0)e | - | Very low | Retrospective cohort | Very serious[f] | None | Serious[g] | None | None |
| **Association between 33 to 35 weeks of gestational age (vs ≥40 weeks) and RSV hospitalisation** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Nielsen et al., 2003) | 61/1250 (4.9%) | 139/5959 (2.3%) | Adjusted OR: 1.73 (1.20 to 2.82)[h] | - | Very low | Retrospective, matched case-control | Very serious[i] | None | None | Serious[n] | None |
| **Association between 33 to <36 weeks of gestational age (reference not reported) and RSV hospitalisation[a]** | | | | | | | | | | | |
| 1 (Boyce et al., 2000) | NR | NR | Adjusted IRR: 1.8 (1.6 to 2.1)[b] | - | Very low | Retrospective cohort | Very serious[c] | None | Serious[d] | None | None |
| **Association between 35 to 36 weeks gestational age (vs ≥37 weeks) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Rietveld et al., 2006) | NR | NR | Adjusted OR: 1.6 (1.3 to 1.9)[e] | - | Very low | Retrospective cohort | Very serious[f] | None | Serious[g] | None | None |
| **Association between 35 to 36 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis** | | | | | | | | | | | |
| 1 (Paranjothy et al, 2013) | NR | NR | Adjusted HR: 1.89 (1.75 to 2.03)[j] | - | Low | Retrospective cohort | Very serious[k] | None | None | None | None |
| **Association between 35 to 37 weeks of gestational age (vs ≥38) and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Lanari et al, 2013) | 41/767 (5.3%) | 25/706 (3.5%) | Adjusted HR: 1.5 (0.9 to 2.5)[l] | - | Low | Longitudinal multicentre cohort study | Serious[m] | None | None | Serious[n] | None |
| **Association between 35 to 37 weeks of gestational age (vs ≥40 weeks) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Nielsen et al., 2003) | 119/1250 (9.5%) | 393/5959 (6.6%) | Adjusted OR: 1.43 (1.10 to 1.97)[h] | - | Very low | Retrospective, matched case-control | Very serious[i] | None | None | Serious[n] | None |
| **Association between <37 weeks gestational age (vs ≥37 weeks) and bronchiolitis hospitalisation** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Grimwood et al., 2008) | 32/141 (22.7%) | 1178/11270 (10.5%) | Adjusted OR: 2.29 (1.48 to 3.56)[o] | p≤0.0005 | Low | Retrospective cohort | Very serious[p] | None | None | None | None |
| **Association between <37 weeks gestational age (vs ≥37 weeks) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Cilla et al., 2006) | NR | NR | Adjusted OR: 1.61 (1.07 to 2.42)[q] | p=0.022 | Very low | Retrospective cohort | Very serious[r] | None | None | Seriousn | None |
| 1 (Kristensen et al., 2009) | 49/313 (15.7%) | 49/313 (15.7%) | Adjusted OR: 1.03 (0.65 to 1.64)[s] | - | Very low | Retrospective matched case-control | Very serious[t] | None | Very serious[q] | Very serious[n] | None |
| 1 (Papenburg et al., 2012) | 57/460 (12.4%) | 16/141 (11.4%) | Adjusted OR: 1.29 (0.68 to 2.43)[u] | - | Very low | Prospective cohort | None | None | Very serious[v] | Very serious[n] | None |
| **Association between <37 weeks (vs born at term) and bronchiolitis hospital admission** | | | | | | | | | | | |
| 1 (Murray et al., 2014) | NR | NR | Adjusted relative risk: 1.89 (1.77 to 2.02)[w] | - | Moderate | Prospective cohort | Serious[x] | None | None | None | None |
| **Association between 37 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis** | | | | | | | | | | | |
| 1 (Paranjothy et al, 2013) | NR | NR | Adjusted HR: 1.59 (1.49 to 1.71)[j] | - | Low | Retrospective cohort | Very serious[k] | None | None | None | None |
| **Association between 38 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis** | | | | | | | | | | | |
| 1 (Paranjothy et al, 2013) | NR | NR | Adjusted HR: 1.33 (1.26 to 1.40)[j] | - | Low | Retrospective cohort | Very serious[k] | None | None | None | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Association between 39 weeks of gestational age (vs 40 to 42 weeks) and emergency admission for acute bronchiolitis** | | | | | | | | | | | |
| 1 (Paranjothy et al, 2013) | NR | NR | Adjusted HR: 1.16 (1.10 to 1.21)[j] | - | Very low | Retrospective cohort | Very serious[k] | None | None | Serious[n] | None |
| **Association between 37 to 39 weeks of gestational age (vs ≥40 weeks) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Nielsen et al., 2003) | 419/1250 (33.5%) | 1890/5959 (31.7%) | Adjusted OR: 1.18 (1.00 to 1.40)[h] | - | Very low | Retrospective, matched case-control | Very serious[l] | None | None | Serious[n] | None |
| **Association between gestational age per 1 week less and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Pezzotti et al., 2009) | NR | NR | Adjusted IRR: 0.97 (0.88 to 1.07)[y] | p=0.58 | Very low | Retrospective cohort | Very serious[z] | None | Seriousa[a] | None | None |
| **Association between prematurity (not defined) and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Al-Shehri et al., 2005) | NR | NR | Adjusted OR: 3.44 (2.27 to 4.33)[ab] | - | Low | Prospective, matched case-control | Seriousa[c] | None | Serious[ad] | None | None |
| **RISK OF RSV REHOSPITALISATION** | | | | | | | | | | | |
| **Association between 23 to 32 weeks of gestational age (vs 33 to 36 weeks) and RSV rehospitalisation** | | | | | | | | | | | |
| 1 (Joffe et al., 1999) | NR<br>Number hospitalised for RSV/total 23 to 32 weeks gestation: 32/438 (7.3%) | NR<br>Number hospitalised for RSV/total 33 to 36 weeks gestation: 23/1283 (1.8%) | Adjusted OR: 2.6 (1.4 to 5.1)[ae] | p= 0.003 | Very low | Retrospective cohort | Very serious[af] | | Very serious[ag] | None | None |
| **Association between increasing gestational age and RSV rehospitalisation** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Carbonell-estrany et al., 2000) | NR | NR | Adjusted OR: 0.85 (0.72 to 0.99)[ah] | p<0.047 | Very low | Prospective cohort | Serious[ai] | None | Serious[aj] | Serious[n] | None |
| 1 (Carbonell-estrany et al., 2001) | NR | NR | Adjusted OR: 0.87 (0.77 to 0.97)[ak] | p=0.019 | Low | Prospective cohort | Serious[al] | None | Seriousa[m] | None | None |
| **RISK OF SEVERE RSV DISEASE/BRONCHIOLITIS – BASED ON DISEASE SEVERITY SCORES** | | | | | | | | | | | |
| **Association between <36 weeks of gestational age (reference not reported) and severe RSV disease - severity score ≥3[an]** | | | | | | | | | | | |
| 1 (Bockova et al., 2002) | 5/45 (11.1%) | 58/831 (7.0%) | Adjusted OR: 1.8 (0.7 to 5.1)[ao] | - | Very low | Prospective cohort | Serious[ap] | None | Serious[aq] | Very serious[n] | None |
| **Association between <36 weeks of gestational age (reference not reported) and respiratory distress - moderate or severe RDAI scoream** | | | | | | | | | | | |
| 1 (Chan et al.,1999) | NR | NR | Adjusted OR: 5.1 (1.0 to 25.0)[ar] | p=0.02 | Very low | Retrospective cohort | Very serious[as] | None | None | Serious[n] | None |
| **Association between <37 weeks gestational age (reference category not reported) and severe bronchiolitis (bronchiolitis clinical score ≥11)** | | | | | | | | | | | |
| 1 (Ricart et al., 2013) | 21/82 (25.6%) | 41/328 (12.5%) | Adjusted OR: 2.6 (1.3 to 5.1)[at] | p=0.005 | Moderate | Prospective cohort | Serious[ap] | None | None | None | None |
| **Association between <37 weeks gestational age (≥37 weeks) and severe RSV disease - disease severity score ≥2[au]** | | | | | | | | | | | |
| 1 (Papenburg et al., 2012) | NR | NR | Adjusted OR: 3.08 (1.63 to 5.83)av | - | Low | Prospective cohort | None | None | Very serious[aw] | None | None |
| **RISK OF ICU ADMISSION** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Association between <32 weeks of gestational age (reference not reported) and ICU admission in non RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Hervas et al., 2012) | NR | NR | Adjusted OR: 5.6 (1.89 to 16.59)[ax] | p<0.01 | Low | Retrospective review | Very serious[ay] | None | None | None | None |
| **Association between <32 weeks of gestational age (reference not reported) and ICU admission in RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Hervas et al., 2012) | NR | NR | Adjusted OR: 4.92 (1.95 to 12.40)[ax] | p<0.001 | Low | Retrospective review | Very serious[ay] | None | None | None | None |
| **Association between birth before gestational age of 32 weeks (vs reference not reported) and intensive care requirement in RSV infection** | | | | | | | | | | | |
| 1 (Simon et al., 2007) | NR | NR | Adjusted OR: 2.80 (1.58 to 5.00)[az] | p=0.0001 | Moderate | Prospective cohort | Serious[as] | None | None | None | None |
| **Association between <32 weeks gestational age (vs reference not reported and ICU admission in RSV infection** | | | | | | | | | | | |
| 1 (Dotan et al., 2013) | NR | NR | Adjusted OR: 10.58 (3.25 to 34.54)[aaa] | - | Low | Retrospective cohort | Very serious[aab] | None | None | None | None |
| **Association between born before gestational age of 32 weeks and intensive care requirement in RSV infection** | | | | | | | | | | | |
| 1 (Wilkesmann et al., 2007) | NR | NR | Adjusted OR: 2.80 (1.58 to 5.00)[aac] | p<0.001 | Moderate | Prospective cohort | Serious[aad] | None | None | None | None |
| **Association between <37 weeks gestational age (reference not reported) and PICU admission in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 1.63 (1.29 to 2.05)[aae] | p<0.0001 | Low | Retrospective cohort | Very serious[aaf] | None | None | None | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Association between prematurity <37 weeks gestation (vs term) and intensive care requirement in RSV infection** | | | | | | | | | | | |
| 1 (Simon et al., 2007) | NR | NR | Adjusted OR: 1.73 (1.08 to 2.72)[az] | p=0.0218 | Low | Prospective cohort | Serious[aag] | None | None | Serious[n] | None |
| **Association between prematurity (not defined) and intensive care requirement in RSV infection** | | | | | | | | | | | |
| 1 (Wilkesmann et al., 2007) | NR | NR | Adjusted OR: 1.73 (1.08 to 2.72)[aac] | p=0.022 | Low | Prospective cohort | Serious[aad] | None | None | Serious[n] | None |
| 1 (Zhang et al., 2014) | NR | NR | Adjusted OR: 2.46 (0.81 to 7.47)[aah] | p=0.113 | Very low | Retrospective chart review | Very serious[aai] | None | None | Serious[n] | None |
| **RISK OF OXYGEN REQUIREMENT** | | | | | | | | | | | |
| **Association between <37 weeks gestational age (reference not reported) and oxygen requirement in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 1.36 (1.17 to 1.59)[aae] | p<0.0001 | Very low | Retrospective cohort | Very serious[aaf] | None | None | Serious[n] | None |
| **Association between <37 weeks gestational age (vs ≥37 weeks) and oxygen supplementation in infants admitted for bronchiolitis** | | | | | | | | | | | |
| 1 (Semple et al., 2011) | 54/241 (23%) | 18/86 (21%) | Adjusted OR: 1.01 (0.94 to 1.08)[aaj] | p=0.843 | Moderate | Prospective cohort | Serious[aak] | None | None | None | None |
| **Association between gestational age <37 weeks (vs term) and need for supplemental oxygen** | | | | | | | | | | | |
| 1 (Kristensen et al., 2009) | NR | NR | Adjusted relative risk: 1.88 (1.16 to 3.04)[aal] | - | Very low | Retrospective matched case-control | Very serious[t] | None | Very serious[q] | Serious[n] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **RISK OF MECHANICAL VENTILATION** | | | | | | | | | | | |
| **Association between <37 weeks gestational age (reference not reported) and intubation requirement in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 1.54 (1.02 to 2.33)[aae] | p=0.04 | Very low | Retrospective cohort | Very serious[aaf] | None | None | Serious[n] | None |
| **Association between <37 weeks gestational age (reference not reported) and respiratory failure - requiring intubation and positive pressure ventilation in RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Chan et al., 2002) | 4/7 (57.1%) | 21/ 209 (10.0%) | Adjusted OR: 1.14 (1.02 to 2.07)[aam] | p=0.02 | Very low | Retrospective cohort | Very serious[aan] | None | None | Serious[n] | None |
| **Association between <37 weeks gestational age (vs ≥37 weeks) and mechanical ventilation in infants admitted for bronchiolitis** | | | | | | | | | | | |
| 1 (Semple et al., 2011) | 27/51 (53%) | 18/86 (21%) | Adjusted OR: 0.99 (0.89 to 1.11)[aaj] | p=0.868 | Moderate | Prospective cohort | Serious[aak] | None | None | None | None |
| **Association between <37 weeks gestational age (vs ≥37 weeks) and severe bronchiolitis - assisted ventilation or continuous positive airway pressure** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 5/34 (14.7%) | 27/107 (25.2%) | Adjusted OR: 0.58 (0.19 to 1.78)[aao] | - | Very low | Retrospective cohort | Very serious[aap] | None | None | Very serious[n] | None |
| **RISK FOR HYPOXEMIA** | | | | | | | | | | | |
| **Association between <37 weeks gestational age (reference not reported) and hypoxemia (SpO2 <90% in room air) in RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Chan et al., 2002) | 11/31 (35.5%) | 14/185 (7.6%) | Adjusted OR: 1.17 (1.06 to 1.55)[aam] | p<0.01 | Very low | Retrospective cohort | Very serious[aan] | None | None | Serious[n] | None |
| **RISK OF RESPIRATORY FAILURE (not defined)** | | | | | | | | | | | |
| **Association between prematurity (not defined) and respiratory failure** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Wilkesmann et al., 2007) | NR | NR | Adjusted OR: 4.73 (1.96 to 11.94)[aac] | p=0.001 | Moderate | Prospective cohort | Serious[aad] | None | None | None | None |

*NR not reported, OR odds ratio, IRR incidence rate ratio, HR hazard ratio, P probability*
*a RSV hospitalisation defined as hospitalisation caused by RSV infection or bronchiolitis. Both of these outcomes based on ICD-9 codes - overall 6.3% of RSV associated hospitalisations were coded specifically for RSV and 93.7% were coded as bronchiolitis.*
*b Adjusted for BPD, CHD, number of siblings, presence of other conditions, male sex, white race, rural residence, maternal smoking and maternal education <12 years.*
*c Retrospective study design, outcome (RSV/bronchiolitis hospitalisation) based on reliability of coding systems. Gestational age missing for ~15% of children - if gestational age was missing from the birth certificate, this was estimated from birth weight with the use of the race and calendar-year specific distributions of gestational age in the population. Exclusion criteria not reported, reference not reported.*
*d Database used for this study contains information only on children enrolled in Medicaid therefore may not be generalizable.*
*e Adjusted for gender, birth weight, age, BPD, age.*
*f Retrospective study design, number of controls not reported and unclear whether controls were tested for RSV.*
*g Bronchiolitis or pneumonia were diagnosed in 93% whereas most of the remaining hospitalised children were diagnosed with upper respiratory tract infection.*
*h Adjusted for birthweight, number of older siblings, smoking in pregnancy, anti RSV titre.*
*I Retrospective study design, overlapping group intervals (eg: 33-35 weeks, 35-37 weeks), no indication that controls have been tested for RSV.*
*j Adjusted for maternal age, parity, Townsend score quintile for social deprivation, gender, major or minor congenital anomaly, multiple birth, breastfeeding, Apgar score at 5 min, neonatal admission to hospital and season of birth*
*k Retrospective study design, inclusion and exclusion criteria not reported*
*l Adjusted for gender and gestational age*
*m Bronchiolitis hospitalisation based on reliability of coding systems*
*n Wide confidence interval spans multiple interpretations*
*o Adjusted for gender, ethnicity, multiple birth, mother smoking during pregnancy, month of birth and deprivation score.*
*p Retrospective study design, no indication that controls have been tested for RSV, exclusion criteria not reported, 66.5% of eligible participants (admitted during weekdays) were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregivers.*
*q Adjusted for haemodynamically unstable heart disease, maternal age, period of birth, birth weight and rural/urban residence.*
*r Retrospective study design, no indication that controls have been tested for RSV.*
*s Adjusted for underlying condition, type of heart disease and haemodynamic significance.*
*t Retrospective study design, inclusion based on reliability of coding systems.*
*u Adjusted for age <6 months, history or breast feeding, ≥3 children in the household, presence of comorbidity and viral coinfection.*
*v 34.5% of infants hospitalised for RSV were diagnosed with pneumonia, included children less than 3 years of age however mean age of cases and controls was 8 and 12.5 months.*
*w Adjusted for cystic fibrosis, congenital heart disease, chronic lung disease, immunodeficiency, nervous system congenital anomalies, down's syndrome, cerebral palsy*
*x Risk factor and bronchiolitis diagnoses based on reliability of coding systems*

*y Adjusted for age of mother, parity, years of education, birth country of mother, gender, calendar year, age, epidemic period, birth weight, apgar score, broncho-dysplasia and congenital heart disease.*
*z Retrospective study design, bronchiolitis hospitalisation (including bronchiolitis due to RSV and other or unknown etiologies) based on reliability of ICD-9 coding system, exclusion criteria not reported.*
*aa All infants premature (<36 weeks gestation).*
*ab Adjusted for congenital heart defects, chronic lung disease, atopic child, atopic father, atopic mother, atopic parents, breastfeeding, history of exposure to smoking, age.*
*ac Exclusion criteria not reported, prematurity not defined -unclear how this was determined.*
*ad Included children ≤5 years however mean age of cases and controls 7.6 and 8.8 months respectively.*
*ae Unclear what confounders were adjusted for.*
*af Retrospective study design, inclusion based on reliability of coding system.*
*ag All premature infants and also inclusion was based on the presence of ICD codes which included a broad range of conditions such as acute bronchitis and bronchiolitis, pneumonia, other diseases of lung.*
*ah Adjusted for gestational age, birth weight, family history of asthma, clinical risk index for babies, month of discharge, chronic lung disease and siblings at school age.*
*ai Identification of a causative pathogen was attempted in 89 (75.4%) of all hospital admissions; therefore not all subjects tested, increasing gestational age not defined*
*aj All premature infants <33 weeks.*
*ak Adjusted for gestational age, weight at birth, family history of asthma, CRIB index, age at entry RSV season, month of discharge, CLD, multiple births, heart disease, breast-feeding, smoke exposure, attendance at daycare and siblings at school age in the model.*
*al 10% of admissions not tested for RSV - because 10% of admissions were not tested for RSV, the overall hospitalisation rate for RSV illness was calculated by applying the RSV positive rate in tested patients (63%) to all respiratory hospitalisations (207) and dividing it by the total number of study patients (999), 54/207 lost to follow up (26%), increasing gestational age not defined*
*am All premature infants.*
*an Severity based on a previously published severity index (McConnochie et al., 1990), 1 point each was assigned for apnea, pH <7.35, PC02 >45, oxygen saturation <87% and length of stay >5 days, 2 points were assigned for mechanical ventilation. Severity index for each subject was the sum of the points, the maximum score is 7.*
*ao Adjusted for age, gender, underlying conditions (CHD, CLD of prematurity, reactive airway disease, 2 or more previous hospitalisations for respiratory infection, history of mechanical ventilation, or immunodeficiency).*
*ap Reference not reported.*
*aq Included children with mild respiratory symptoms or apnea.*
*ar Adjusted for <3 months of age, family history of asthma and underlying illness.*
*as Retrospective study design, exclusion criteria not reported, reference category not reported.*
*at Adjusted for BPD, hemodynamically significant CHD, temperature >38 degrees, age at admission, human rhinovirus (HRV), human respiratory syncytial virus (HRSV).*
*au Patients given 1 point for each of the following: admission to PICU, hospitalised for >5 days, require supplemental oxygen therapy (fraction of inhaled oxygen ≥0.3)*
*av Adjusted for age <6 months and viral coinfection*
*aw 34.5% of infants hospitalised for RSV were diagnosed with pneumonia, included children less than 3 years however mean age of cases and controls was 8 and 12.5 months.*
*ax Adjusted for nebulized epinephrine, nebulized salbutamol, year, congenital heart disease, atelectasis/condensation, age, gender.*
*ay Retrospective study design, diagnosis of bronchiolitis based on reliability of coding systems, reference not reported.*
*az Adjusted for CLD, CHD*
*aaa Adjusted for young age, male gender and twin birth*
*aab Retrospective study design, data sources not reported*
*aac Adjusted for CLDplus, congenital heart disease and neuromuscular impairment*
*aad Exclusion criteria not reported, prematurity not defined*
*aae Adjusted for RSV, weight, age at hospitalisation, gender, race, congenital heart defects, chronic lung disease, trisomy 21, congenital syndromes.*
*aaf Retrospective study design, inclusion of subjects based on reliability of ICD coding system , reference not reported.*
*aag Exclusion criteria not reported*
*aah Adjusted for sex, age and CHD*

*aai Retrospective, exclusion criteria not reported*
*aaj Adjusted for birth weight, sex, family history of atopy, index of deprivations, corrected age on admission, weight on admission and household tobacco smoker.*
*aak Infants both admitted and discharged on Saturdays and Sundays were not recruited and some infants admitted on weekdays for less than 24 hours were missed.*
*aal Adjusted for age, cardiac decompensation.*
*aam Unclear what factors were adjusted for.*
*aan Retrospective study design, very small number of cases, exclusion criteria not reported, unclear what confounders were adjusted for, reference not reported.*
*aao Adjusted for year, gender, month of birth, age at admission, mother smoking during pregnancy, ethnicity, number of other children living in the house.*
*aap Retrospective study design, exclusion criteria not reported, 66.5% of eligible participants (admitted during weekdays) were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregive*

## A.2.2 Bronchopulmonary dysplasia /Chronic lung disease of prematurity

### Table 3: GRADE profile for the association between BPD and risk of developing severe bronchiolitis

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

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Association between bronchopulmonary dysplasia (defined by Jobe and Bancalari – criteria not reported) and severe bronchiolitis - bronchiolitis clinical score ≥11** | | | | | | | | | | | |
| 1 (Ricart et al., 2013) | 6/82 (7.3%) | 4/328 (1.2%) | Adjusted OR: 7.2 (1.2 to 43.3)[k] | p=0.031 | Moderate | Prospective cohort | None | None | None | Serious[j] | None |

*NR not reported, p-value, IRR incidence rate ratio, OR odds ratio*
*a Boyce: RSV hospitalisation defined as hospitalisation caused by RSV infection or bronchiolitis. Both of these outcomes based on ICD-9 codes - overall 6.3% of RSV associated hospitalisations were coded specifically for RSV and 93.7% were coded as bronchiolitis.*
*b Adjusted for congenital heart disease, gestational age, other conditions*, number of siblings, sex, race, rural residence, maternal smoking and maternal education <12 years. * (other conditions identified included asthma, previous respiratory hospitalisation, cystic fibrosis, cancer, human immunodeficiency virus infection, immunodeficiency, use of chronic oral steroids, chronic renal disease, diabetes, congenital anomalies of the respiratory system, tracheoesophageal fistula, esophageal atresia and stenosis, neonatal respiratory distress syndrome and other respiratory conditions of the fetus and newborn).*
*c Retrospective study design, both risk factor (BPD) and outcome (RSV/bronchiolitis hospitalisation) based on reliability of coding systems, gestational age missing for ~15% of children (hence estimated from birth weight with the use of the race and calendar-year specific distributions of gestational age in the population), exclusion criteria not reported.*
*d Database used for this study contains information only on children enrolled in Medicaid therefore may not be generalizable.*
*e Unclear what confounders were adjusted for.*
*f Retrospective study design, both presence of risk factor (BPD) and outcome (RSV hospitalisation) based on reliability of coding systems, number of cases and controls not explicitly reported, all variables were entered into 1 final multivariable model with no variable selection procedures.*
*g Adjusted for age of mother, parity, years of education, birth country of mother, gender, calendar year, age, epidemic period, birth weight, gestational age, apgar score and CHD.*
*h Retrospective study design, both bronchopulmonary-dysplasia and bronchiolitis hospitalisation (including bronchiolitis due to RSV and other or unknown etiologies) based on reliability of ICD-9 coding system, exclusion criteria not reported.*
*I All infants premature (<36 weeks gestation).*
*j ~~Confidence interval spans multiple interpretations.~~*
*k Adjusted for hemodynamically significant congenital heart disease, gestational age <37 weeks, temperature >38 degrees, age at admission, human rhinovirus (HRV) and human respiratory syncytial virus (HRSV).*

### Table 4: GRADE profile for the association between chronic lung disease and risk of developing severe bronchiolitis

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Chronic lung disease** | | | | | | | | | | | |
| **RISK OF BRONCHIOLITIS HOSPITALISATION** | | | | | | | | | | | |
| **Association between chronic lung diseases (not defined) and bronchiolitis hospitalisation** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Al-Shehri et al., 2005) | NR | NR | Adjusted OR: 3.12 (2.19 to 3.78)[a] | - | Low | Prospective, matched case-control | Serious[b] | None | Serious[c] | None | None |
| 1 (Murray et al., 2014) | NR | NR | Adjusted relative risk: 1.61 (1.42 to 1.82)[d] | - | Moderate | Prospective cohort | Serious[e] | None | None | None | None |
| **RISK OF RSV REHOSPITALISATION** | | | | | | | | | | | |
| **Association between chronic lung disease (oxygen requirement at 36 weeks postconceptional age) and RSV rehospitalisation in premature infants ≤32 weeks gestation** | | | | | | | | | | | |
| 1 (Carbonell-Estrany et al., 2000) | 8/53 (15%) | 27/509 (5.3%) | Adjusted OR: 3.1 (1.22 to 7.91)[f] | p<0.016 | Very low | Prospective cohort study | Serious[g] | None | Serious[h] | Serious[i] | None |
| **Association between chronic lung disease (oxygen requirement beyond 36 weeks post-conceptional age) and RSV rehospitalisation in premature infants ≤35 weeks gestation** | | | | | | | | | | | |
| 1 (Liese et al., 2003) | 8/37 (21.6%) | 45/680 (6.6%) | Adjusted OR: 3.99 (1.4 to 11.2)[j] | p=0.009 | Very low | Retrospective cohort | Very serious[k] | None | Very serious[l] | None | None |
| **RISK OF OXYGEN REQUIREMENT** | | | | | | | | | | | |
| **Association between chronic lung disease (not defined) and oxygen requirement in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 3.27 (2.14 to 5.00)[m] | p<0.0001 | Low | Retrospective cohort | Very serious[n] | None | None | None | None |
| **RISK OF PICU REQUIREMENT** | | | | | | | | | | | |
| **Association between chronic lung disease (not defined) and PICU requirement in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 1.80 (1.12 to 2.89)[m] | p=0.01 | Very low | Retrospective cohort | Very serious[n] | None | None | Serious[l] | None |
| **RISK OF RESPIRATORY FAILURE** | | | | | | | | | | | |
| **Association between CLDplus (chronic lung disease of prematurity and treatment within the last 6 months before diagnosis of the RSV infection) and respiratory failure** | | | | | | | | | | | |
| 1 (Wilkesmann et al., 2007) | NR | NR | Adjusted OR: 5.42 (2.00 to 14.17)[o] | p=0.0008 | Moderate | Prospective cohort | Serious[p] | None | None | None | None |

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

## A.2.3 Congenital heart disease

**Table 5: GRADE profile for the association between congenital heart disease and risk of developing severe bronchiolitis**

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

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Murray et al., 2014) | NR | NR | Adjusted OR: 3.35 (2.92 (3.84)[p] | - | Moderate | Prospective cohort | Serious[q] | None | None | None | None |
| **RISK OF OXYGEN REQUIREMENT** | | | | | | | | | | | |
| **Association between congenital heart disease and oxygen requirement in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 1.88 (1.32 to 2.67)[r] | p=0.0005 | Low | Retrospective cohort | Very serious[s] | None | None | None | None |
| **RISK OF ICU ADMISSION** | | | | | | | | | | | |
| **Association between congenital heart disease and PICU admission in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 2.77 (1.89 to 4.05)[r] | p<0.0001 | Low | Retrospective cohort | Very serious[s] | None | None | None | None |
| **Association between congenital heart disease and ICU admission in RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Hervas et al., 2012) | NR | NR | Adjusted OR: 3.08 (1.14 to 8.3)[t] | P<0.0001 | Very low | Retrospective review | Very serious[u] | None | Serious[v] | Serious[d] | None |
| **Association between congenital heart disease and intensive care requirement in RSV infection** | | | | | | | | | | | |
| 1 (Simon et al., 2007) | NR | NR | Adjusted OR: 2.97 (1.81 to 4.82)[w] | p<0.001 | Moderate | Prospective cohort | Serious[x] | None | None | None | None |
| 1 (Wilkesman n et al., 2007) | NR | NR | Adjusted OR: 2.97 (1.81 to 4.82)[y] | p<0.001 | Moderate | Prospective cohort | Serious[z] | None | None | None | None |
| 1 (Zhang et al., 2014) | NR | NR | Adjusted OR: 8.20 (3.10 to 21.70)a[a] | p<0.001 | Low | Retrospective chart review | Very serious[ab] | None | None | None | None |
| **RISK OF SEVERE RSV-LRI - OXYGEN SUPPLEMENTATION OR MECHANICAL VENTILATION** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Association between congenital heart disease and severe RSV-LRI (oxygen supplementation or mechanical ventilation)** | | | | | | | | | | | |
| 1 (Kaneko et al., 2001) | 6/20 (30%) | 1/137 (0.7%) | Adjusted OR: 99.2 (8.5 to 1160.1)[ac] | p<0.0005 | Very low | Retrospective chart review | Very serious[ad] | None | Serious[ae] | None | None |
| **RISK OF SEVERE BRONCHIOLITIS - DEFINED BY A BRONCHIOLITIS CLINICAL SCORE** | | | | | | | | | | | |
| **Association between hemodynamically significant congenital heart disease (defined either by the use of medication to control congestive heart failure, infants with moderate to severe pulmonary hypertension or with cyanotic heart disease) and severe bronchiolitis- bronchiolitis clinical score ≥11** | | | | | | | | | | | |
| 1 (Ricart et al., 2013) | 5/82 (6.1%) | 7/328 (2.1%) | Adjusted OR: 4.7 (1.1 to 19.9)[af] | p=0.038 | Moderate | Prospective cohort | None | None | None | Serious[d] | None |

*NR not reported, OR odds ratio, IRR incidence rate ratio, P p-value*
*a Adjusted for prematurity, chronic lung disease, atopic child, atopic father, atopic mother, atopic parents, breastfeeding, history of exposure to smoking, age.*
*b Exclusion criteria not reported, unclear how congenital heart defects was identified (definition not reported).*
*c Included children ≤5 yrs but mean age of cases and controls 7.6 and 8.8 months respectively.*
*d Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID. ~~Confidence interval spans multiple interpretations~~.*
*e Adjusted for age of mother, parity, years of education, birth country of mother, gender, calendar year, age, epidemic period, birth weight, gestational age, apgar score, bronchopulmonary-dysplasia.*
*f Retrospective study design, bronchiolitis hospitalisation (including bronchiolitis due to RSV and other or unknown aetiologies) based on reliability of ICD-9 coding system, exclusion criteria not reported, CHD identified from hospital discharge database (no other details reported).*
*g All infants premature (<36 weeks gestation).*
*h Boyce: RSV hospitalisation defined as hospitalisation caused by RSV infection or bronchiolitis. Both of these outcomes based on ICD-9 codes - overall 6.3% of RSV associated hospitalisations were coded specifically for RSV and 93.7% were coded as bronchiolitis.*
*I Unclear what confounders were adjusted for.*
*j Retrospective study design, both presence of risk factor (CHD) and outcome (RSV hospitalisation) based on reliability of coding systems, number of cases and controls not explicitly reported, all variables were entered into 1 final multivariable model with no variable selection procedures.*
*k Adjusted for BPD, gestational age, number of siblings, presence of other conditions, male sex, white race, rural residence, maternal smoking and maternal education <12 years.*
*l Retrospective study design, both risk factor (CHD) and outcome (RSV/bronchiolitis hospitalisation) based on reliability of coding systems, gestational age missing for ~15% of children (if gestational age was missing from the birth certificate, this was estimated from birth weight with the use of the race and calendar-year specific distributions of gestational age in the population), exclusion criteria not reported.*
*m Database used for this study contains information only on children enrolled in Medicaid therefore may not be generalizable.*
*n Adjusted for gestational age, maternal age, period of birth, birth weight and rural/urban residence.*
*o Retrospective study design, no indication that controls have been tested for RSV, CHD identified from medical records, no other details reported.*
*p Adjusted for premature birth, cystic fibrosis, chronic lung disease, immunodeficiency, nervous system congenital anomalies, down's syndrome, cerebral palsy*
*q Risk factor and bronchiolitis diagnoses based on reliability of coding systems*

*r Adjusted for RSV, weight, age at hospitalisation, gender, race, prematurity, chronic lung disease, trisomy 21, congenital syndromes.*
*s Retrospective study design, inclusion of subjects based on reliability of ICD coding system*
*t Adjusted for nebulized epinephrine, nebulized salbutamol, year, atelectasis/condensation, age, male sex, gestational age.*
*u Retrospective study design, diagnosis of bronchiolitis based on reliability of coding systems, CHD identified from medical records (no other details reported).*
*v Includes children with ICD codes of acute bronchiolitis, RSV bronchiolitis, RSV pneumonia and RSV not otherwise specified.*
*w Adjusted for prematurity, CLD.*
*x Exclusion criteria not reported, unclear how data on CHD was obtained – details not reported*
*y Adjusted for prematurity, CLDplus, neuromuscular impairment and nosocomial infection*
*z Exclusion criteria not reported*
*aa Adjusted for sex, young age, prematurity*
*ab Exclusion criteria not reported, retrospective*
*ac Adjusted for age <3 months.*
*ad Retrospective study design, CHD identified from review of patient records (no other details reported).*
*ae Included children younger than 4 years although the mean age of each of the study groups ranged from 1.3 to 21.3 months.*
*af Adjusted for BPD, gestational age <37 weeks, temperature >38 degrees, age at admission, human rhinovirus (HRV), human respiratory syncytial virus (HRSV).*

## A.2.4 Cystic fibrosis

**Table 6: GRADE profile for the association between cystic fibrosis and risk of developing severe bronchiolitis**

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

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

## A.2.5 Immunodeficiency

**Table 7: GRADE findings for the association between immunodeficiency and risk of developing severe bronchiolitis**

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

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

## A.2.6 Non breast-fed

**Table 8: GRADE profile for the association between non- breast fed and risk of developing severe bronchiolitis**

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

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Bulkow et al., 2002) | 103/195 (53%) | 245/327 (75%) | Adjusted OR: 0.38[g] | p=0.001 | Very low | Retrospective, matched case-control | Very serious[h] | None | Serious[i] | ~~NA~~[j]NC[j] | None |
| **Association between infants ever breastfed more than half of feedings (vs no breastfeeding) and RSV hospitalisation (infants <6 months)** | | | | | | | | | | | |
| 1 (Bulkow et al., 2002) | NR | NR | Adjusted OR: 0.33[g] | p=0.001 | Low | Retrospective, matched case-control | Very serious[h] | None | None | ~~NA~~[j]NC[j] | None |
| **Association between breastfed within 8 weeks of age of admission (vs no breastfeeding) and RSV hospitalisation (complete data set)** | | | | | | | | | | | |
| 1 (Bulkow et al., 2002) | 65/204 (32%) | 171/338 (51%) | Adjusted OR: 0.44[g] | p=0.004 | Very low | Retrospective, matched case-control | Very serious[h] | None | Serious[i] | ~~NA~~[j]NC[j] | None |
| **Association between breastfed within 8 weeks of age of admission (vs no breastfeeding) and RSV hospitalisation (infants ≥6 months)** | | | | | | | | | | | |
| 1 (Bulkow et al., 2002) | NR | NR | Adjusted OR: 0.27[k] | p=0.004 | Very low | Retrospective, matched case-control | Very serious[h] | None | Serious[i] | ~~NA~~[j]NC[j] | None |
| **Association between infants ever breastfed (vs no breastfeeding) and RSV hospitalisation (infants ≥6 months)** | | | | | | | | | | | |
| 1 (Bulkow et al., 2002) | 128/204 (63%) | 272/337 (81%) | Adjusted OR: 0.25[k] | p=0.001 | Very low | Retrospective, matched case-control | Very serious[h] | None | Serious[i] | ~~NA~~[j]NC[j] | None |
| **Association between breast-feeding ≤2 months (vs >2 months) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Figueras-Aloy et al., 2004) | 159/186 (85.5%) | 251/371 (67.6%) | Adjusted OR: 3.26 (1.96 to 5.42)[l] | - | Low | Prospective case-control | Serious[m] | None | Serious[n] | None | None |
| **Association between a history of breast-feeding (yes vs no) and RSV hospitalisation** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Papenburg et al., 2012) | 341/460 (74.1%) | 25/141 (17.7%) | Adjusted OR: 0.55 (0.33 to 0.92)[o] | - | Low | Prospective cohort | None | None | Very serious[p] | None | None |
| **Association between lack of breastfeeding and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Lanari et al., 2013) | 42/482 (8.7%) | 78/1728 (4.5%) | Adjusted HR: 1.8 (1.2 to 2.6)[q] | - | Low | Longitudinal multicentre cohort study | Serious[r] | None | None | Serious[d] | None |

*NR not reported, HRR hazard rate ratio, OR odds ratio, P p-value*
*a Adjusted for prematurity, congenital heart defects, chronic lung diseases, atopic child, father, mother, parents, history of exposure to smoking, age (one year or less).*
*b Exclusion criteria not reported, reference category not reported.*
*c Included children ≤5 years but mean age of cases and controls 7.6 and 8.8 months respectively.*
*d Serious imprecision when 95% CI crosses one default MID. ~~Confidence interval spans multiple interpretations.~~*
*e Adjusted for gender, maternal age, maternal education, maternal smoking during pregnancy, First Nations status, older siblings, birth weight, congenital anomalies.*
*f Retrospective study design, bronchiolitis diagnosis based on reliability of coding systems.*
*g Adjusted for high risk infant, ≥4 others aged <12 years in household and ≥2 persons/room in household.*
*h Retrospective study design, confidence intervals not presented therefore imprecision could not be assessed.*
*I Complete data set includes children <3 years- case patients age ranged from <1 month to 34 months (median: 5.9 months).*
*j Could not be assessed due to the way results were presented (no confidence intervals reported).*
*k Adjusted for high risk infant, shares bed ≥1 other.*
*l Adjusted for medical centre, absolute chronologic age, school age siblings, residents and/or visitors at home ≥4, history of wheezing in the family.*
*m Current age of subjects not reported, data sources not reported.*
*n All subjects premature and previously hospitalised for prematurity.*
*o Adjusted for age <6 months, prematurity (<37 weeks), ≥3 children in the household, presence of comorbidity and viral coinfection.*
*p 34.5% of infants hospitalised for RSV were diagnosed with pneumonia, also included children less than 3 years of age however mean age of cases and controls was 8 and 12.5 months.*
*q Adjusted for gender, gestational age, treatment with corticosteroids, cigarette smoke exposure, singleton delivery, respiratory diseases, surfactant therapy, siblings, crowding, humidity, exposed to epidemic RSV season*
*r Bronchiolitis hospitalisation based on reliability of coding systems*

## A.2.7 Young infants

**Table 9: GRADE profile for the association between young infants and risk of developing severe bronchiolitis**

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

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalised | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Pezzotti et al., 2009) | NR | NR | Adjusted IRR: 14.54 (6.75 to 31.35)[j] | p<0.01 | Very low | Retrospective cohort | Very serious[k] | None | Serious[l] | None | None |
| **Association between infants <6 months of age (vs 18 to 36 months) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Papenburg et al., 2012) | 270/460 (58.6%) | 30/141 (21.3%) | Adjusted OR: 4.63 (2.94 to 7.28)[m] | - | Low | Prospective cohort | None | None | Very serious[n] | None | None |
| **Association between infants 6 to 11 months of age (vs ≥12 months) and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Pezzotti et al., 2009) | NR | NR | Adjusted IRR: 5.98 (2.68 to 13.35)[j] | p<0.01 | Very low | Retrospective cohort | Very serious[k] | None | Serious[l] | None | None |
| **Association between chronological age at the beginning of RSV season 6 to 11 months of age (vs ≥12 months) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Rossi et al., 2011) | 31/145 (21.4%) | 98/292 (33.6%) | Adjusted OR: 2.467 (0.879 to 6.925)[h] | | Low | Prospective, case-control | None | None | Serious[l] | Serious[o] | None |
| **Association between infants ≤1 year of age (reference not reported) and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Al-Shehri et al., 2005) | 33/51 (65%) | 57/115 (49.5%) | Adjusted OR: 3.44 (2.27 to 4.33)[p] | - | Low | Prospective, matched case-control | Serious[q] | None | Serious[r] | None | None |
| **RISK OF RSV REHOSPITALISATION** | | | | | | | | | | | |
| **Association between age at entry RSV season >3 months of age (vs <3 months) and RSV rehospitalisation** | | | | | | | | | | | |
| 1 (Carbonell-Estany et al., 2001) | 24/309 (7.7%) | 285/309 (92.2%) | Adjusted OR: 0.44 (0.25 to 0.77)[s] | p=0.004 | Low | Prospective cohort | Serious[t] | None | Serious[u] | None | None |
| **RISK OF SEVERE RSV DISEASE – BASED ON DISEASE SEVERITY SCORES** | | | | | | | | | | | |
| **Association between infants <3 months of age (reference not reported) and respiratory distress - moderate or severe RDAI score** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalised | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Chan et al., 1999) | 21/68 (31%) | 12/117 (10%) | Adjusted OR: 4.5 (1.2 to 17.6)[v] | p=0.001 | Very low | Retrospective cohort | Very serious[w] | None | None | Serious[x] | None |
| **Association between infants <6 months of age (reference not reported) and severe RSV disease - severity score ≥3y** | | | | | | | | | | | |
| 1 (Bockova et al., 2002) | 37/45 (82.2%) | 377/831 (45.4%) | Adjusted OR: 6.6 (3.0 to 14.4)[z] | - | Moderate | Prospective cohort | None | None | Seriousa[a] | None | None |
| **Association between infants <6 months of age (vs 18 to 36 months) and severe RSV disease - severity score ≥2ab** | | | | | | | | | | | |
| 1 (Papenburg et al., 2012) | NR | NR | Adjusted OR: 2.26 (1.31 to 3.89)[m] | - | Low | Prospective cohort | None | None | Very serious[n] | None | None |
| **RISK OF SEVERE RSV-LRI - REQUIRING OXYGEN OR MECHANICAL VENTILATION** | | | | | | | | | | | |
| **Association between infants <3 months of age (reference not reported) and severe RSV-LRI - requiring oxygen supplementation or mechanical ventilation** | | | | | | | | | | | |
| 1 (Kaneko et al., 2001) | 13/20 (65%) | 6/137 (4.4%) | Adjusted OR: 59.9 (14.7 to 244.0)[ac] | p<0.0001 | Very low | Retrospective chart review | Very serious[ad] | None | Serious[ae] | None | None |
| **RISK OF SEVERE RSV BRONCHIOLITIS - ASSISTED VENTILATION OR CPAP** | | | | | | | | | | | |
| **Association between age at admission <2 months of age (vs ≥2 months) and severe RSV bronchiolitis - assisted ventilation or CPAP** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 13/34 (38.2%) | 22/107 (20.6%) | Adjusted OR: 2.50 (0.98 to 6.39)[af] | - | Very low | Retrospective cohort | Very serious[ag] | None | None | Serious[x] | None |
| **RISK OF LENGTH OF STAY ≥5 DAYS** | | | | | | | | | | | |
| **Association between age at admission <2 months of age (vs ≥2 months) and length of stay ≥5 days in RSV positive children hospitalised with bronchiolitis** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 22/64 (34.4%) | 38/77 (49.4%) | Adjusted OR: 1.92 (0.63 to 5.83)[ah] | - | Very low | Retrospective cohort | Very serious[ag] | None | None | Very serious[x] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalised | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **RISK OF ICU ADMISSION** | | | | | | | | | | | |
| **Association between postnatal age <30 days of age (reference not reported) and PICU admission for infants with bronchiolitis** | | | | | | | | | | | |
| 1 (Papoff et al., 2009) | NR | NR | Adjusted OR: 8.382 (2.352 to 29.864)[ai] | p=0.001 | Moderate | Prospective cohort | Serious[aj] | None | None | None | None |
| **Association between young age <42 days and ICU admission in RSV infection** | | | | | | | | | | | |
| 1 (Dotan et al., 2013) | NR | NR | Adjusted OR: 3.39 (1.46 to 7.9)[ak] | - | Low | Retrospective cohort | Very serious[al] | None | none | None | None |
| **Association between infants <2 months of age (≥12 months) and ICU admission in children with bronchiolitis** | | | | | | | | | | | |
| 1 (Damore et al., 2008) | 27/50 (53%) | 138/533 (26%) | Adjusted OR: 4.14 (2.05 to 8.34)[am] | p<0.001 | Moderate | Prospective cohort | Serious[an] | None | None | None | None |
| **Association between ≤6 months and ICU admission in RSV disease** | | | | | | | | | | | |
| 1 (Zhang et al., 2014) | NR | NR | Adjusted OR: 2.81 (1.36 to 5.80)[ao] | p=0.005 | Low | Retrospective chart review | Very serious[ap] | None | None | None | None |

*NR not reported, OR odds ratio, IRR incidence rate ratio, p-value*
*a Adjusted for medical centre, breast feeding, school age siblings, residents and/or visitors at home ≥4 (without school age siblings and the subject him/herself), history of wheezing in the family*
*b Current age of subjects not reported, data sources not reported, reference category not reported*
*c All subjects premature and previously hospitalised for prematurity*
*d Adjusted for school age siblings or day care attendance and tobacco smoking during pregnancy*
*e Current age of subjects not reported*
*f Adjusted for preschool-aged non-multiple birth siblings, exposure to smoking and multiple birth*
*g Imprecision could not be assessed as confidence intervals not reported, control group not defined*
*h Adjusted for birth weight category and birth order*
*I Included infants ≤4 years of age, median age=5 months*

*j Adjusted for age of mother, parity, years of education, birth country of mother, gender, calendar year, epidemic period, birth weight, gestational age, apgar score, bronchopulmonary-dysplasia and congenital heart disease*
*k Retrospective study design, bronchiolitis hospitalisation (including bronchiolitis due to RSV and other or unknown etiologies) based on reliability of ICD-9 coding system, exclusion criteria not reported*
*l All infants premature (<36 weeks gestation)*
*m Adjusted for prematurity (<37 weeks) and viral coinfection*
*n 34.5% of infants hospitalised for RSV were diagnosed with pneumonia, included children less than 3 years of age however mean age of cases and controls was 8 and 12.5 months respectively*
*o Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID. ~~Confidence interval spans multiple interpretations~~*
*p Adjusted for prematurity, congenital heart defects, chronic lung disease, atopic child, atopic father, atopic mother, atopic parents, breastfeeding, history of exposure to smoking*
*q Exclusion criteria not reported, reference category not reported*
*r Included children ≤5 years of age however mean age of cases and controls 7.6 and 8.8 months respectively*
*s Adjusted for: gestational age, weight at birth, CRIB index, month of discharge, smoke exposure and siblings at school age in the model*
*t 10% of admissions not tested for RSV - because 10% of admissions were not tested for RSV, the overall hospitalisation rate for RSV illness was calculated by applying the RSV positive rate in tested patients (63%) to all respiratory hospitalisations (207) and dividing it by the total number of study patients (999), 54/207 lost to follow up (26%)*
*u All premature infants*
*v Adjusted for prematurity (<36 weeks), family history of asthma and underlying illness*
*w Retrospective study design, exclusion criteria not reported, reference category not reported*
*x Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID. ~~Confidence interval spans multiple interpretations~~*
*y Severity based on a previously published severity index (McConnochie et al., 1990), 1 point each was assigned for apnea, pH <7.35, PC02 >45, oxygen saturation <87% and length of stay >5 days, 2 points were assigned for mechanical ventilation. Severity index for each subject was the sum of the points, the maximum score is 7.*
*z Adjusted for prematurity, gender, underlying conditions (congenital heart disease, chronic lung disease of prematurity, reactive airway disease, 2 or more previous hospitalisations for respiratory infection, history of mechanical ventilation, or immunodeficiency)*
*aa Included children with mild respiratory symptoms or apnea*
*ab Patients given 1 point for each of the following: admission to PICU, hospitalised for >5 days, require supplemental oxygen therapy (fraction of inhaled oxygen ≥0.3)*
*ac Adjusted for CHD*
*ad Retrospective study design, reference category not stated*
*ae Included children younger than 4 years although the mean age of each of the study groups ranged from 1.3 to 21.3 months*
*af Adjusted for year, gender, month of birth, mother smoking during pregnancy, ethnicity, number of other children living in the house and gestational age*
*ag Retrospective study design, no indication that controls have been tested for RSV, exclusion criteria not reported, 66.5% of eligible participants were enrolled, the main reason for non-participation was discharge from hospital before research staff were able to approach their caregivers*
*ah Adjusted for year, gender, multiple birth, ethnicity, number of other children, birth weight*
*ai Adjusted for birth weight, RSV infection, lymphocytes, pulmonary consolidation and CRP*
*aj Reference not reported*
*ak Adjusted for gestational age, male gender and being a twin*
*al Retrospective study design, data sources not reported*
*am Adjusted for emergency department visit during past week, moderate/severe retractions and oral intake (adequate, inadequate, unknown)*
*an Some infants have a history of wheezing (26% of cases and 27% of controls) - unclear whether this might be family history of wheezing*
*ao Adjusted for sex, congenital heart disease and prematurity*
*ap Exclusion criteria not reported, retrospective*

## A.2.8 Sex (Male)

**Table 10~~12~~: GRADE profile for the association between sex (male) and risk of developing severe bronchiolitis**

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

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| | | | (1.2 to 1.4)r | | | | | | | | |
| 1 (Gavin et al., 2007) | NR | NR | Adjusted OR: 1.07 (0.70 to 1.64)u | - | Very low | Retrospective cohort | Very serious[v] | None | Very serious[w] | Very serious[d] | None |
| 1 (Kristensen et al., 2009) | 165/313 (52.7%) | 158/313 (50.5%) | Adjusted OR: 1.14 (0.81 to 1.59)x | - | Very low | Retrospective matched case-control | Very serious[y] | None | Very serious[z] | Serious[d] | None |
| 1 (Law et al., 2004) | NR<br>Number hospitalised/total ale: 46/961 (4.8%) | NR<br>Number hospitalised/Total female: 20/796 (2.5%) | Adjusted OR: 1.91 (1.10 to 3.31)[aa] | p=0.02 | Very low | Prospective cohort | Serious[ab] | None | Serious[ac] | Serious[d] | None |
| 1 (Lanari et al., 2013) | 76/1150 (6.6%) | 44/1060 (4.2%) | Adjusted HR: 1.6 (1.1 to 2.4)[ad] | - | Low | Longitudinal multicentre cohort study | Serious[ae] | None | None | Serious[d] | None |
| **RISK OF RSV REHOSPITALISATION** | | | | | | | | | | | |
| **Association between male gender and RSV rehospitalisation** | | | | | | | | | | | |
| 1 (Liese et al., 2003) | 33/37 (89.2%) | 342/680 (50.3%) | Adjusted OR: 8.7 (2.6 to 29.1)[af] | p<0.001 | Very low | Retrospective cohort | Very serious[ag] | None | Very serious[ah] | None | None |
| **RISK OF SEVERE RSV DISEASE – BASED ON DISEASE SEVERITY SCORE** | | | | | | | | | | | |
| **Association between male gender and severe RSV disease - severity score ≥3ai** | | | | | | | | | | | |
| 1 (Bockova et al., 2002) | 25/45 (55.6%) | 418/831 (50.3%) | Adjusted OR: 1.2 (0.6 to 2.2)[aj] | - | Very low | Prospective cohort | None | None | Serious[ak] | Very serious[d] | None |
| **RISK OF OXYGEN REQUIREMENT** | | | | | | | | | | | |
| ***** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 0.80 (0.71 to 0.91)[al] | p<0.0005 | Very low | Retrospective cohort | Very serious[am] | None | None | Serious[d] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Association between male gender and oxygen requirement in children with non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Hervas et al., 2012) | NR | NR | Adjusted OR: 0.68 (0.51 to 0.91)[an] | p<0.001 | Very low | Retrospective review | Very serious[ao] | None | None | Serious[d] | None |
| **Association between male gender and oxygen supplementation in children admitted with bronchiolitis** | | | | | | | | | | | |
| 1 (Semple et al., 2001) | 140/241 (58%) | 44/86 (51%) | Adjusted OR: 0.77 (0.43 to 1.38)[ap] | p=0.374 | Very low | Prospective cohort | Serious[aq] | None | None | Very serious[d] | None |
| **RISK OF MECHANICAL VENTILATION** | | | | | | | | | | | |
| **Association between male gender and mechanical ventilation in children admitted with bronchiolitis** | | | | | | | | | | | |
| 1 (Semple et al., 2001) | 31/51 (61%) | 44/86 (51%) | Adjusted OR: 1.28 (0.52 to 3.13)[ar] | p=0.592 | Very low | Prospective cohort | Serious[as] | None | None | Very serious[d] | None |
| **Association between male gender and severe RSV bronchiolitis – severe defined as the need for assisted ventilation or CPAP in hospitalised children** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 18/34 (52.9%) | 64/107 (59.8%) | Adjusted OR: 0.79 (0.34 to 1.85)at | - | Very low | Retrospective cohort | Very seriousau | None | None | Very seriousd | None |
| **RISK OF LENGTH OF STAY ≥5 DAYS** | | | | | | | | | | | |
| **Association between male gender and length of stay ≥5 days in RSV positive children hospitalised with bronchiolitis** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 40/64 (62.5%) | 42/77 (54.5%) | Adjusted OR: 2.25 (0.85 to 6.00)[av] | - | Very low | Retrospective cohort | Very serious[au] | None | None | Serious[d] | None |
| **ICU ADMISSION** | | | | | | | | | | | |
| **Association between male gender and ICU admission in RSV infection** | | | | | | | | | | | |
| 1 (Dotan et al., 2013) | NR | NR | Adjusted OR: 1.97 (1.05 to 3.69)[aw] | - | Very low | Retrospective cohort | Very serious[ax] | None | None | Serious[d] | None |

*NR not reported, p-value, RR rate ratio, CPAP continuous positive airway pressure, IRR incidence rate ratio, OR odds ratio*
*a Adjusted for race, ethnicity, insurance status, metropolitan statistical areas, region, season, urgent/emergent visit.*
*b Retrospective study design, bronchiolitis diagnosis based on reliability of coding system, exclusion criteria not reported, sample size unclear.*
*c Study is ED based therefore generalizability questionable, bronchiolitis cases were identified using an ICD code which captures both bronchiolitis and bronchitis - 70% of the final sample had code for acute bronchiolitis.*
*d Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.~~Confidence interval spans multiple interpretations.~~*

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

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

### A.2.9 Previous hospitalisation

No evidence was identified for this review.

### A.2.10 Ethnicity

**Table 1110: GRADE profile for the association between ethnicity and risk of developing severe bronchiolitis**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Ethnicity** | | | | | | | | | | | |
| **RISK OF RSV/BRONCHIOLITIS HOSPITALISATION** | | | | | | | | | | | |
| **Association between white race (reference not reported) and RSV hospitalisationa** | | | | | | | | | | | |
| 1 (Boyce et al., 2000) | NR | NR | Adjusted IRR: 1.3 (1.2 to 1.4)[b] | - | Very low | Retrospective cohort | Very serious[c] | None | Serious[d] | Serious[e] | None |
| **Association between Māori ethnicity (vs European, Pakeha) and RSV positive bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 49/141 (34.8%) | 1533/11270 (13.6%) | Adjusted rate ratio: 3.64 (2.27 to 5.85)[f] | p≤0.0001 | Low | Retrospective cohort | Very serious[g] | None | None | None | None |
| **Association between Pacific ethnicity (vs European, Pakeha) and RSV positive bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 37/141 (26.2%) | 1207/11270 (10.7%) | Adjusted rate ratio: 3.60 (2.14 to 6.06)[f] | p≤0.0001 | Low | Retrospective cohort | Very serious[g] | None | None | None | None |
| **Association between Hispanic ethnicity (vs non-hispanic) and bronchiolitis hospitalisation from the emergency department** | | | | | | | | | | | |
| 1 (Mansbach et al., 2005) | NR | NR | Adjusted OR: 2.3 | p=0.029 | Very low | Retrospective cohort | Very seriousi | None | Serious[j] | Serious[e] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| | | | (1.1 to 5.0)h | | | | | | | | |
| **Association between black race (vs white race) and bronchiolitis hospitalisation from the emergency department** | | | | | | | | | | | |
| 1 (Mansbach et al., 2005) | NR | NR | Adjusted OR: 1.6 (0.9 to 3.2)[k] | p=0.132 | Very low | Retrospective cohort | Very serious[i] | None | Serious[j] | Serious[e] | None |
| **RISK OF MECHANICAL VENTILATION** | | | | | | | | | | | |
| **Association between Māori ethnicity (vs European, Pakeha) and severe RSV bronchiolitis - assisted ventilation or continuous positive airway pressure** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 12/34 (35.3%) | 37/107 (34.6%) | Adjusted OR: 1.34 (0.42 to 4.28)[l] | - | Very low | Retrospective cohort | Very serious[m] | None | None | Very serious[e] | None |
| **Association between Pacific ethnicity (vs European, Pakeha) and severe RSV bronchiolitis - assisted ventilation or continuous positive airway pressure** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 9/34 (26.5%) | 28/107 (26.2%) | Adjusted OR: 1.42 (0.36 to 5.52)[l] | - | Very low | Retrospective cohort | Very serious[m] | None | None | Very serious[e] | None |
| **Association between black race (vs white race) and intubation requirement in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 1.73 (0.93 to 3.19)[n] | p=0.999 | Very low | Retrospective cohort | Very serious[o] | None | None | Serious[e] | None |
| **Association between Hispanic race (vs white race) and intubation requirement in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 2.17 (1.32 to 3.58)n | p=0.136 | Low | Retrospective cohort | Very serious[o] | None | None | None | None |
| **RISK OF LENGTH OF STAY ≥5 DAYS** | | | | | | | | | | | |
| **Association between Māori ethnicity (vs European, Pakeha) and length of stay ≥5 days in RSV positive children hospitalised with bronchiolitis** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 22/64 (34.4%) | 27/77 (35.1%) | Adjusted OR: 1.44 | - | Very low | Retrospective cohort | Very serious[m] | None | None | Very serious[e] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| | | | (0.38 to 5.51)[p] | | | | | | | | |
| **Association between Pacific ethnicity (vs European, Pakeha) and length of stay ≥5 days in RSV positive children hospitalised with bronchiolitis** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 19/64 (29.7%) | 18/77 (23.4%) | Adjusted OR: 2.21 (0.49 to 10.02)[p] | - | Very low | Retrospective cohort | Very serious[m] | None | None | Very serious[e] | None |
| **RISK OF OXYGEN REQUIREMENT** | | | | | | | | | | | |
| **Association between black race (vs white race) and oxygen requirement in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 0.49 (0.41 to 0.60)[n] | p<0.001 | Low | Retrospective cohort | Very serious[o] | None | None | None | None |
| **Association between Hispanic race (vs white race) and oxygen requirement in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 1.12 (0.96 to 1.31)[n] | p=0.149 | Very low | Retrospective cohort | Very serious[o] | None | None | Serious[e] | None |
| **RISK OF PICU REQUIREMENT** | | | | | | | | | | | |
| **Association between black race (vs white race) and PICU requirement in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 0.89 (0.65 to 1.23)[n] | p=0.486 | Very low | Retrospective cohort | Very serious[o] | None | None | Serious[e] | None |
| **Association between Hispanic race (vs white race) and PICU requirement in RSV/non-RSV bronchiolitis** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 1.01 (0.79 to 1.31)[n] | p=0.917 | Very low | Retrospective cohort | Very serious[o] | None | None | Serious[e] | None |

*NR not reported, p-value, OR odds ratio, IRR incidence rate ratio*
*a Boyce: RSV hospitalisation defined as hospitalisation caused by RSV infection or bronchiolitis. Both of these outcomes based on ICD-9 codes - overall 6.3% of RSV associated hospitalisations were coded specifically for RSV and 93.7% were coded as bronchiolitis.*

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

## A.2.11 Down's syndrome

**Table 12~~11~~: GRADE profile for the association between Down's syndrome and risk of developing severe bronchiolitis**

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

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Murray et al., 2014) | NR | NR | Adjusted relative risk: 2.53 (1.72 to 3.72)[f] | - | Moderate | Prospective cohort | Serious[g] | None | None | None | None |

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

## A.2.12 Family smoking

**Table 1312: GRADE profile for the association between family smoking and risk of developing severe bronchiolitis**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalised | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Family smoking** | | | | | | | | | | | |
| **RISK OF BRONCHIOLITIS/RSV HOSPTALISATION** | | | | | | | | | | | |
| **Association between history of exposure to smoking and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Al-Shehri et al., 2005) | Passive smoking: 19/51 (37%) | Passive smoking: 15/115 (13%) | Adjusted OR: 2.51 (2.11 to 3.73)[a] | - | Low | Prospective matched case-control | Serious[b] | None | Serious[c] | None | None |
| **Association between passive cigarette smoke exposure and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Lanari et al., 2013) | 8/108 (7.4%) | 112/2102 (5.3%) | Adjusted HR: 1.5 (0.7 to 3.1)[d] | - | Very low | Longitudinal multicentre cohort study | Serious[e] | None | None | Very serious[f] | None |
| **Association between ≥2 smokers in the household (vs factor not present) and RSV hospitalisation** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalised | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Law et al., 2004) | NR<br>Number hospitalised/Total with ≥2 smokers in the household: 20/321 (6.2%) | NR<br>Number hospitalised/Total without ≥2 smokers in the household: 46/1437 (3.2%) | Adjusted OR: 1.71 (0.97 to 3.00)[g] | p=0.064 | Very low | Prospective cohort | Serious[h] | None | Seriousi | Serious[j] | None |
| **RISK OF RSV REHOSPITALISATION** | | | | | | | | | | | |
| **Association between tobacco smoke exposure and RSV rehospitalisation** | | | | | | | | | | | |
| 1 (Carbonell-Estrany et al., 2001) | 45/87 (51.7%) | 269/812 (33.1%) | Adjusted OR: 1.63 (1.05 to 2.56)[k] | p=0.031 | Very low | Prospective cohort study | SeriousI | None | Serious[m] | Serious[j] | None |
| **RISK OF OXYGEN SUPPLEMENTATION** | | | | | | | | | | | |
| **Association between household tobacco smoker (yes vs no) and oxygen supplementation in infants admitted with bronchiolitis** | | | | | | | | | | | |
| 1 (Semple et al., 2001) | 154/241 (64%) | 41/86 (48%) | Adjusted OR: 2.23 (1.21 to 4.10)[n] | p=0.01 | Low | Prospective cohort | Serious[o] | None | None | Serious[j] | None |
| **RISK OF MECHANICAL VENTILATION** | | | | | | | | | | | |
| **Association between household tobacco smoker (yes vs no) and mechanical ventilation in infants admitted with bronchiolitis** | | | | | | | | | | | |
| 1 (Semple et al., 2001) | 32/51 (63%) | 41/86 (48%) | Adjusted OR: 7.19 (2.28 to 22.60)[n] | p=0.001 | Moderate | Prospective cohort | Serious[o] | None | None | None | None |

*NR not reported, p-value, OR odds ratio*
*a Adjusted for prematurity, congenital heart defects, chronic lung disease, atopic child, father, mother, parents, breastfeeding, age.*
*b Exclusion criteria not reported, unclear how exposure to smoking was determined.*
*c Included children ≤5 years but mean age of cases and controls 7.6 and 8.8 months respectively.*
*d Adjusted for gender and gestational age*
*e Bronchiolitis hospitalisation based on reliability of coding systems*
*f Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID. ~~Confidence interval spans multiple zones~~*
*g Adjusted for born in November, December or January, gender, small for gestational age, subject attending day care, any preschool age siblings, >5 individuals in the home, eczema in 1st degree relative.*
*h Controls not tested for RSV.*
*I All premature infants.*
*j Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID. ~~Confidence interval spans multiple interpretations.~~*
*k Adjusted for gestational age, birth weight, clinical risk index for babies, age at entry to RSV season, month of discharge, siblings at school age*

*l 10% of admissions not tested for RSV - because 10% of admissions were not tested for RSV, the overall hospitalisation rate for RSV illness was calculated by applying the RSV positive rate in tested patients (63%) to all respiratory hospitalisations (207) and dividing it by the total number of study patients (999), 54/207 lost to follow up (26%).*
*m All infants born prematurely.*
*n Adjusted for gestation, birth weight, sex, family history of atopy, index of multiple deprivations 2004, corrected age on admission, weight on admission.*
*o Infants both admitted and discharged on Saturdays and Sundays were not recruited and some infants admitted on weekdays for less than 24 hours were missed.*

## A.2.13 Multiple birth

**Table 1413: GRADE profile for the association between multiple birth and risk of developing severe bronchiolitis**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Multiple birth** | | | | | | | | | | | |
| **RISK OF BRONCHIOLITIS/RSV HOSPITALISATION** | | | | | | | | | | | |
| **Association between multiple birth (yes vs no) and RSV positive bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 10/141 (7.1%) | 524/11270 (4.6%) | Adjusted RR: 1.25 (0.62 to 2.54)[a] | - | Very low | Retrospective cohort | Very serious[b] | None | None | Very serious[c] | None |
| **Association between multiple birth (yes vs no) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Ambrose et al., 2014) | NR | NR | Adjusted HR: 0.48d | p=0.043 | Moderate | Prospective cohort | Serious[e] | None | None | ~~Not assessed~~NC | None |
| **Association between singleton delivery and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Lanari et al., 2013) | 97/1673 (5.8%) | 23/537 (4.3%) | Adjusted HR: 1.8 (1.1 to 2.9)[f] | - | Low | Longitudinal multicentre cohort study | Serious[g] | None | None | Serious[c] | None |
| **RISK OF LENGTH OF STAY ≥5 DAYS** | | | | | | | | | | | |
| **Association between multiple birth (yes vs no) and length of stay ≥5 days in RSV positive children hospitalised with bronchiolitis** | | | | | | | | | | | |
| 1 (Grimwood et al., 2008) | 8/64 (12.5%) | 2/77 (2.6%) | Adjusted OR: 6.52 (0.89 to 47.96)[h] | - | Very low | Retrospective cohort | Very serious[b] | None | None | Serious[c] | None |

*RR rate ratio, OR odds ratio, p-value*
*a Adjusted for gender, month of birth, mother smoking during pregnancy, ethnicity, deprivation score and gestational age*

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

## A.2.14 Neuromuscular disorders

**Table 15~~14~~: GRADE profile for the association between neurodisability and risk of developing severe bronchiolitis**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Neuromuscular disorders** | | | | | | | | | | | |
| **RISK OF INTENSIVE CARE REQUIREMENT** | | | | | | | | | | | |
| **Association between neuromuscular impairmenta and intensive care** | | | | | | | | | | | |
| 1 (Wilkesmann et al., 2007) | NR | NR | Adjusted OR: 4.94 (2.69 to 8.94)[b] | p<0.001 | Moderate | Prospective cohort | Serious[c] | None | None | None | None |
| **Association between neuromuscular disorders (not defined) and PICU requirement** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 2.79 (1.43 to 5.46)[d] | p=0.003 | Low | Retrospective cohort | Very serious[e] | None | None | None | None |
| **RISK OF RESPIRATORY FAILURE** | | | | | | | | | | | |
| **Association between neuromuscular impairmenta and respiratory failure** | | | | | | | | | | | |
| 1 (Wilkesmann et al., 2007) | NR | NR | Adjusted OR: 3.85 (1.28 to 10.22)[b] | p=0.017 | Moderate | Prospective cohort | Serious[c] | None | None | None | None |
| **RISK OF RSV/BRONCHIOLITIS HOSPITALISATION** | | | | | | | | | | | |
| **Association between neurologic problemsf and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Doering et al., 2006) | NR | NR | Adjusted OR: 3.6 | p=0.01 | Very low | Retrospective cohort | Very serious[h] | None | Very serious[i] | None | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| | | | (1.3 to 9.9)g | | | | | | | | |
| **Association between encephalocele (based on ICD code) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Kristensen et al., 2012) | NR<br>Number with RSV hospitalisation/Total number with encephalocele: 58/542 (10.7%) | NR | Adjusted IRR: 1.54 (1.14 to 2.08)[j] | p=0.005 | Very low | Retrospective cohort | Very serious[k] | None | None | Serious[l] | None |
| **Association between spina bifida and malformations of the spinal cord (based on ICD code) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Kristensen et al., 2012) | NR<br>Number with RSV hospitalisation/Total number with spina bifida and malformations of the spinal cord: 17/172 (9.9%) | NR | Adjusted IRR: 2.16 (1.31 to 3.55)j | p=0.002 | Low | Retrospective cohort | Very serious[k] | None | None | None | None |
| **Association between spinal muscular atrophy (based on ICD code) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Kristensen et al., 2012) | NR<br>Number with RSV hospitalisation/Total number with spinal muscular atrophy: 2/39 (5.1%) | NR | Adjusted IRR: 1.02 (0.24 to 4.27)[j] | p=0.983 | Very low | Retrospective cohort | Very serious[k] | None | None | Very serious[l] | None |
| **Association between muscular dystrophy (based on ICD code) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Kristensen et al., 2012) | NR<br>Number with RSV hospitalisation/Total number with muscular dystrophy: 13/82 (15.9%) | NR | Adjusted IRR: 2.49 (1.36 to 4.56)j | p=0.003 | Low | Retrospective cohort | Very serious[k] | None | None | None | None |
| **Association between congenital disturbances of muscle tonus, peripheral nerve disease, congenital myasthenia (based on ICD code) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Kristensen et al., 2012) | NR<br>Number with RSV hospitalisation/Total number with congenital disturbances of muscle tonus, peripheral nerve disease, congenital myasthenia: 23/344 (6.7%) | NR | Adjusted IRR: 1.21 (0.78 to 1.88)j | p=0.4 | Very low | Retrospective cohort | Very serious[k] | None | None | Serious[l] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Association between cerebral palsy (based on ICD code) and RSV hospitalisation** | | | | | | | | | | | |
| 1 (Kristensen et al., 2012) | NR<br>Number with RSV hospitalisation/Total number with cerebral palsy: 93/905 (10.3%) | NR | Adjusted IRR: 1.59 (1.27 to 1.99)[j] | p<0.001 | Low | Retrospective cohort | Very serious[k] | None | None | None | None |
| **Association between cerebral palsy and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Murray et al., 2014) | NR | NR | Adjusted relative risk: 2.43 (1.48 to 3.99)[m] | - | Moderate | Prospective cohort | Serious[n] | None | None | None | None |
| **Association between nervous system congenital anomalieso and bronchiolitis hospitalisation** | | | | | | | | | | | |
| 1 (Murray et al., 2014) | NR | NR | Adjusted relative risk: 1.73 (1.26 to 2.36)[p] | - | Moderate | Prospective cohort | Serious[n] | None | None | None | None |
| **RISK OF HOSPITALISATION >9 DAYS** | | | | | | | | | | | |
| **Association between severe motor intellectual disabilities (SMID)q and hospitalisation > 9 days in RSV infection** | | | | | | | | | | | |
| 1 (Onoyama et al., 2013) | NR | NR | Adjusted OR: 2.544 (0.677 to 10.294)[r] | p=0.172 | Very low | Retrospective case-control | Very serious[s] | None | None | Very serious[l] | None |
| **RISK OF OXYGEN REQUIREMENT** | | | | | | | | | | | |
| **Association between neuromuscular disorders (not defined) and oxygen requirement** | | | | | | | | | | | |
| 1 (Garcia et al., 2010) | NR | NR | Adjusted OR: 1.52 (0.87 to 2.64)[d] | p=0.139 | Very low | Retrospective cohort | Very serious[e] | None | None | Serious[l] | None |
| **RISK OF MECHANICAL VENTILATION** | | | | | | | | | | | |
| **Association between severe motor intellectual disabilities (SMID)q and mechanical ventilation in RSV infection** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With severe bronchiolitis eg: hospitalisation | Without severe bronchiolitis eg: sent home | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Onoyama et al., 2013) | NR | NR | Adjusted OR: 5.100 (0.769 to 46.473)[t] | p=0.104 | Very low | Retrospective case-control | Very serious[s] | None | None | Serious[l] | None |

*NR not reported, p-valuerobability, OR odds ratio, IRR incidence rate ratio*
*a NMI was an item to be checked in the primary database by the local nurse and the attending physician. Information obtained from free text fields (admission note, discharge summary) was also used to identify all RSV-infected children with NMI. The NMI group included children with: hydrocephalus n=3, cerebral palsy and central hypoventilation syndromes n=41, genetic defects/chromosomal abnormalities n=8, neuromuscular disorders n=8, severe developmental delay n=5, peripheral nerve defects n=2, other NMI as CNS neoplasia or epilepsy n=3.*
*b Adjusted for prematurity (not defined), born before gest. wk 32, CLDplus, congenital heart disease and nosocomial infection.*
*c Exclusion criteria not reported*
*d Adjusted for RSV, weight, age at hospitalisation, male gender, race, prematurity, CHD, CLD, trisomy 21, congenital syndromes, respiratory tract abnormalities*
*e Retrospective study design, inclusion of subjects based on reliability of ICD coding system.*
*f The presence of 1 or more of the following diagnoses: intracranial hemorrhage (ICH), grade III or IV (periventricular hemorrhage), cystic periventricular leukomalacia (cPVL), cerebral infarction, hydrocephalus or other symptomatic neurologic conditions.*
*g Adjusted for male gender, presence of older sibling and discharge from October to December*
*h Retrospective study design, only 31 of 57 children had laboratory proven RSV hospitalisation. Among 26 of 57 children classified as probable RSV-H, 21 were not tested for RSV infection.*
*I All infants were preterm (29 to 35 weeks gestational age) and also an additional clinical case definition for RSV hospitalisation was used: children hospitalised between October and May with a clinical diagnosis of obstructive bronchitis, bronchiolitis, apnea or a diagnosis of pneumonia in the presence of wheezing were classified as suffering from a probable RSV infection.*
*j Unclear what factors were adjusted for, all variables were entered into 1 final multivariable model with no variable selection procedures*
*k Retrospective study design, both presence of risk factor and outcome based on reliability of coding systems, number of cases and controls not explicitly reported, all variables were entered into 1 final multivariable model with no variable selection procedures.*
*l Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID. ~~Confidence interval spans multiple interpretations~~*
*m Adjusted for premature birth, cystic fibrosis, congenital heart disease, chronic lung disease, immunodeficiency, downs syndrome and congenital anomalies*
*n Risk factor and bronchiolitis diagnoses based on reliability of coding systems*
*o incorporates conditions such as spina bifida, anencephaly, and other congenital malformations of the nervous system*
*p Adjusted for premature birth, cystic fibrosis, congenital heart disease, chronic lung disease, immunodeficiency, downs syndrome and cerebral palsy*
*q SMID was diagnosed according to the classical criteria (Oshima's criteria)*
*r Adjusted for mechanical ventilation and duration of supplemental oxygen*
*s Retrospective study design, exclusion criteria not reported*
*t Adjusted for duration of hospitalisation and duration of supplemental oxygen >7 days*

# A.3 Predictors of deterioration

**Table 1615: GRADE profile for association between clinical features and risk for progressing to severe bronchiolitis**

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

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With Bronchiolitis deterioration: e.g. Hospitalization | Without deterioration: e.g. Discharge | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Respiratory rate 50-59 breaths/min k** | | | | | | | | | | | |
| 1. Schroeder et al., 2013 | N = 16/108 | N = 348/2048 | Adjusted OR l: 1.29 (0.66-2.51) | P=0.46 | Low | Prospective multicentre cohort study | Serious [m] | None | Serious [n] | Very Serious [d] | None |
| **Respiratory rate 60-69 breaths/min k** | | | | | | | | | | | |
| 1. Schroeder et al., 2013 | N = 15/108 | N = 389/2048 | Adjusted OR l: 1.06 (0.62-1.81) | P=0.84 | Low | Prospective multicentre cohort study | Serious [m] | None | Serious [n] | Very Serious [d] | None |
| **Respiratory rate >70 breaths/min k** | | | | | | | | | | | |
| 1. Schroeder et al., 2013 | N = 14/108 | N = 205/2048 | Adjusted OR l: 2.26 (1.03-4.95) | P=0.04 | Low | Prospective multicentre cohort study | Serious m | None | Serious n | Serious d | None |
| **MAJOR MEDICAL INTERVENTION o – vs. no MMI** | | | | | | | | | | | |
| **Respiratory rate ≥ 60 breaths/min** | | | | | | | | | | | |
| 1. Parker et al., 2009 | N = 25/52 | N = 32/260 | Adjusted OR p: 1.85 (0.97-3.54) | - | Low | Prospective cohort study | Serious [q] | None | Serious [r] | Serious [d] | None |
| **Oxygen Saturation** | | | | | | | | | | | |
| **ADMISSION TO HOSPITAL – vs. discharge** | | | | | | | | | | | |
| **Initial oximetry value < 94%** | | | | | | | | | | | |
| 1. Corneli et al. 2012 | SpO2, % Admitted=95.7 | SpO2, % Discharged=97.2 | Adjusted OR s: 5.5 (2.9-10.2) | P<0.0001 | Low | Secondary analysis of a multicentre randomized trail | Very Serious [g] | None | Serious [h] | None | Some [i] |
| **SpO2 < 95%** | | | | | | | | | | | |
| 1. Corrard et al., 2013 | N = 11/17 | N = 4/154 | Adjusted OR t: - | P<0.0001 | Very Low | Prospective multicentre observational study | Very Serious [u] | None | Serious v | ~~Very Serious~~NC [w] | None |
| **Pulse oximetry < 93%** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With Bronchiolitis deterioration: e.g. Hospitalization | Without deterioration: e.g. Discharge | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1. Yusuf et al., 2012 | N = 8/85 * | N = 5/240 * | Adjusted OR x: 4.72 (1.47-15.18) | P=0.009 | Low | Retrospective cohort study | Serious [y] | None | Serious [z] | None | None |
| **APNOEA j – vs. no apnoea** | | | | | | | | | | | |
| **Lowest documented oxygen saturation over entire preadmission visit <90%** | | | | | | | | | | | |
| 1. Schroeder et al., 2013 | N = 44/108 | N = 573/2048 | Adjusted OR aa: 1.60 (1.03-2.46) | P=0.04 | Low | Prospective multicentre cohort study | Serious [m] | None | Serious [n] | Serious [d] | None |
| **CPAP/INTUBATION – vs. no cpap/intubation** | | | | | | | | | | | |
| **Oxygen saturation <85%** | | | | | | | | | | | |
| 1. Mansbach et al., 2012 | N = 17/161 | N = 3/1998 | Adjusted OR bb: 3.28 (2.02-4.82) | - | Moderate | Prospective multicentre cohort study | Serious [cc] | None | Serious [dd] | None | None |
| **Oxygen saturation 85-87,9%** | | | | | | | | | | | |
| 1. Mansbach et al., 2012 | N = 6/161 | N = 3/1998 | Adjusted OR bb: 1.34 (0.57-3.43) | - | Low | Prospective multicentre cohort study | Serious [cc] | None | Serious [dd] | Very serious [d] | None |
| **Oxygen saturation 88-89,9%** | | | | | | | | | | | |
| 1. Mansbach et al., 2012 | N = 6/161 | N = 4/1998 | Adjusted OR bb: 1.91 (0.79-3.80) | - | Low | Prospective multicentre cohort study | Serious [cc] | None | Serious [dd] | Serious [d] | None |
| **Oxygen saturation 90-93.9%** | | | | | | | | | | | |
| 1. Mansbach et al., 2012 | N = 16/161 | N = 17/1998 | Adjusted OR bb: 1.15 (0.70-1.52) | - | Low | Prospective multicentre cohort study | Serious [cc] | None | Serious [dd] | Very serious [d] | None |
| **MAJOR MEDICAL INTERVENTION o – vs. no MMI** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | With Bronchiolitis deterioration: e.g. Hospitalization | Without deterioration: e.g. Discharge | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Oxygen saturation ≤92%** | | | | | | | | | | | |
| 1. Parker et al., 2009 | N = 9/52 | N = 16/260 | Adjusted OR [p]: 2.41 (0.96-6.14) | - | Low | Prospective cohort study | Serious [q] | None | Serious [r] | Serious [d] | None |
| **Ability to feed** | | | | | | | | | | | |
| **ADMISSION TO HOSPITAL – vs. discharge** | | | | | | | | | | | |
| **24h Food Intake <50%** | | | | | | | | | | | |
| 1. Corrard et al., 2013 | N = 9/17 | N = 15/150 | Adjusted OR ee: 10.6 (3.0-37.3) | - | Low | Prospective multicentre observational study | Very Serious [u] | None | Serious [v] | None | None |
| **CPAP/INTUBATION – vs. no cpap/intubation** | | | | | | | | | | | |
| **Inadequate oral intake** | | | | | | | | | | | |
| 1. Mansbach et al., 2012 | N = 63/161 | N = 41/1998 | Adjusted OR [ff]: 2.51 (1.34-4.26) | - | Moderate | Prospective multicentre cohort study | Serious [cc] | None | Serious [dd] | None | Some [gg] |
| **ICU ADMISSION – compared to regular floor admissions** | | | | | | | | | | | |
| **Inadequate oral intake** | | | | | | | | | | | |
| 1. Damore et al., 2008 | N = 26/50 * | N = 165/533 * | Adjusted OR [hh:] 3.31 (1.55-7.07) | P=0.002 | Moderate | Prospective multicentre cohort study | Serious [ii] | None | Serious [jj] | None | None |

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

*d. Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID. ~~Wide confidence interval spans multiple interpretations.~~*
*e. Disposition was reviewed by a consultant paediatrician within 24 h. A substantial number are discharged at this initial review. Therefore, authors defined "need for admission" as a hospital stay of more than 24 h, retrospectively categorizing those who were discharged on initial consultant review as fit for discharge.*
*f. Adjusted for initial oximetry value and RDAI score.*
*g. The study excluded children with risk factors, premature infants, infants with bronchiolitis complications (apnoea), and those younger than 2 months; unclear timing of baseline measurements. Also, no significance level for included variables in the multivariate model is specified; retrospective study design.*
*h. Very small children excluded from the study (younger than 2 months).*
*i. In the original trial, patients were randomized to receive either oral dexamethasone or placebo (no treatment effect demonstrated in the original trial); 22 patients were subsequently hospitalized during the 7 days after ED discharge and their data were not treated as admission in the analysis.*
*j. To examine inpatient apnoea among children admitted to the hospital with bronchiolitis, authors identified all children who experienced apnoea at any time during their hospitalization.*
*k. Respiratory rate recorded at preadmission visit (ED)*
*l. Adjusted for age, gender, race, birth weight and lowest documented oxygen saturation over entire preadmission visit <90%; reference = Respiratory rate 40-49.*
*m. Patients enrolled in academic medical centres, and therefore results may not be generalizable to community medical centres; ED and daily hospital data were obtained by chart review.*
*n. Children aged up to 2 years (The GDG has specified that it is likely that older children will not have bronchiolitis).*
*o. MMI defined as oxygen administration for 30 min or more for saturation <90% in room air, IV fluid bolus of 20ml/kg or more, any treatment for apnoea, or admission to Critical Care Unit.*
*p. Adjusted for decreased dehydration, accessory muscle score ≥6/9, oxygen saturation/respiratory rate, age, prolonged stay>12 hr.*
*q. Premature infants and those younger than 2 months were excluded from the study; overall population baseline characteristics not reported; some data were obtained through retrospective chart review.*
*r. Children aged up to 23 months (The GDG has specified that it is likely that older children will not have bronchiolitis).*
*s. Adjusted for respiratory rate and RDAI score.*
*t. Adjusted for age<2months, food intake <50%, intercostal retractions.*
*u. The study excluded patients with risk factors (prematurity, chronic lung or heart disease) and breast-fed children; the statistical analysis is unclear about how they constructed the regression model (no significance level reported); incomplete results; ORs not adjusted for other relevant clinical signs reported in the study like respiratory rate and temperature.*
*v. Only infants aged 0-6 months were considered for the study.*
*w. it was not possible to assess imprecision because of the lack of information provided (No OR and CI reported).*
*x. Adjusted for IVF in ED.*
*y. Not reported how prognostic factors were measured; authors report that primary reason for admission from the EDOU was sometimes absent from the chart; univariate association table difficult to interpret because of the way results are reported (patients demographics only reported as the admitted frequency); patients received treatments (i.e. oxygen supplementation) while in the ED, before disposition; retrospective study design.*
*z. Children aged up to 2 years (The GDG has specified that it is likely that older children will not have bronchiolitis).*
*aa. Adjusted for respiratory rate, age, gender, race, birth weight.*
*bb.Adjusted for age, gender, race, birth weight, mother smoked during pregnancy, difficulty breathing, presence of apnoea, retractions, oral intake. Reference = oxygen saturation ≥94%.*
*cc. Patients enrolled in academic medical centres, and therefore results may not be generalizable to community medical centres; variations in the use of CPAP/intubation by institution not explained nor explored; ED and daily hospital data obtained by chart review.*
*dd. Children aged up to 2 years (The GDG has specified that it is likely that older children will not have bronchiolitis).*
*ee. Adjusted for age<2 months, intercostal retractions, and NOT for oxygen saturation. When SpO2 is introduced in the model, 24 FI becomes no longer significant.*
*ff. Adjusted for age, gender, race, birth weight, mother smoked during pregnancy, difficulty breathing, presence of apnoea, retractions, oxygen saturation. Reference = adequate oral intake.*
*gg. Adjusted OR calculated for missing data for Oral Intake (see evidence table for details).*

*hh. Adjusted for age < 2 months, ED visit during the past week, moderate/severe retractions, duration of symptoms >4 d*

# A.4 Criteria for referral

**Table 1716: GRADE profile for criteria for admission and discharge**

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

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Admitted to hospital from the emergency department | Discharged from the emergency department | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Mansback et al, 2008) | N=619 | N=837 | Adjusted OR: 2.02 (1.46 to 2.80) [d] | P<0.001 | Low | Prospective cohort | Serious [e] | None | Serious [f] | None | None |
| **Dehydration** | | | | | | | | | | | |
| **Association between dehydration in the emergency department and admission to hospital k** | | | | | | | | | | | |
| 1 (Walsh et al, 2004) (Derivation set) | N=62 | N=37 | Adjusted OR: 2.54 (1.34 to 4.82) [l] | P=0.004 | Very low | Retrospective review | Very serious [m] | None | Serious [n] | None | None |
| 1 (Walsh et al, 2004) (Validation set) | N=43 | N=139 | Adjusted OR: 10.97 (4.00 to 30.08) [l] | P<0.001 | Very low | Retrospective review | Very serious [o] | None | Serious [n] | None | None |
| **Difficulty feeding** | | | | | | | | | | | |
| **Association between adequate oral intake (reference: inadequate) and discharge from the emergency department** | | | | | | | | | | | |
| 1 (Mansback et al, 2008) | N=619 | N=837 | Adjusted OR: 6.02 (3.87 to 9.35) d | P<0.001 | Low | Prospective cohort | Serious [e] | None | Serious [f] | None | None |
| **Association between unknown oral intake (reference: inadequate) and discharge from the emergency department** | | | | | | | | | | | |
| 1 (Mansback et al, 2008) | N=619 | N=837 | Adjusted OR: 3.80 (1.89 to 7.63) d | P<0.001 | Low | Prospective cohort | Serious [e] | None | Serious [f] | None | None |
| **Association between receiving intravenous fluids in the emergency department observation unit and admission to hospital** | | | | | | | | | | | |
| 1 (Yusuf et al, 2012) | N=85 | N=240 | Adjusted OR: 2.51 (1.43 to 4.41) [g] | P=0.001 | Low | Retrospective cohort | Serious [h] | None | Serious [i] | None | None |
| **Difficulty breathing** | | | | | | | | | | | |
| **Association between mild retractions (reference: moderate/severe) and discharge from the emergency department** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Admitted to hospital from the emergency department | Discharged from the emergency department | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Mansback et al, 2008) | N=619 | N=837 | Adjusted OR: 2.78 (1.91 to 4.06) d | P<0.001 | Low | Prospective cohort | Serious [e] | None | Serious [f] | None | None |
| **Association between increased work of breathing in the emergency department and admission to hospital p** | | | | | | | | | | | |
| 1 (Walsh et al, 2004) (Derivation set) | N=62 | N=37 | Adjusted OR: 3.39 (1.29 to 8.92) [l] | P=0.013 | Very low | Retrospective review | Very serious [m] | None | Serious [n] | None | None |
| 1 (Walsh et al, 2004) (Validation set) | N=43 | N=139 | Adjusted OR: 6.94 (3.04 to 15.84) [l] | P<0.001 | Very low | Retrospective review | Very serious [o] | None | Serious [n] | None | None |

*OR odds ratio, RCT randomised controlled trial, p-value*
*a Corneli et al., 2012 adjusted for: initial oxygen saturation <94%, respiratory rate >60/min and RDAI score >11.*
*b Corneli et al., 2012 risk of bias: Infants were diagnosed by a trained study clinicians, but their diagnosis appears to be based on the inclusion criteria. It is unclear from the methods how measurements were timed and included in the model. The population is taken from a RCT for dexamethasone, therefore the original study exclusion and inclusion criteria apply here.*
*c Corneli et al., 2012 indirectness: Do not predefine criteria for admission to hospital.*
*d Mansback et al., 2008 adjusted for: age ≥2 months, female, non-white race/ethnicity, ≥1 parent with asthma, no history of intubation, eczema, duration of symptoms >7 days, respiratory rate less than normal for age, number of β-receptor agonists and epinephrine treatments during the first hour Initial room air oxygen saturation ≥94%, respiratory rate less than normal for age, retractions, oral intake and no ED visit during the past week.*
*e Mansback et al., 2008 risk of bias: The final model includes 1012 infants with complete data (444 without complete data) but they do not report how many of those infants were admitted or discharged. Only 1459 out of 2129 (68%) of the eligible infants were enrolled, the remaining were missed by site personnel (89%) or other reasons such as refusal to participate. Infants were diagnosed by the attending physician, diagnostic criteria are not reported.*
*f Mansback et al., 2008 indirectness: Many infants covered by Medicaid insurance: admitted group 59%, discharged group 63%. Infants up to 24 months of age included. Do not predefine criteria for admission to hospital.*
*g Yusuf et al., 2012 adjusted for: oxygen saturation <93% and intravenous fluids in the ED.*
*h Yusuf et al., 2012 risk of bias: Infants diagnosed by the emergency room physician, diagnostic criteria is not reported. Patient demographics are only reported as the admitted frequency. The primary reason for admission from the emergency department observation unit was sometimes absent from the chart. Retrospective study design.*
*i Yusuf et al., 2012 indirectness: Infants received treatment in the ED before the disposition decision was reached. Infants up to 24 months of age included. Do not predefine criteria for admission to hospital.*
*j Normal respiratory values for age: 0 to 1.9 months 45 breaths/min; 2 to 5.9 months 43 breaths/min; 6 to 23.9 months 40 breaths/min.*
*k Dehydration determined either explicitly when documented or implicitly by the reviewer using the criteria described in Berhman & Orernstein 2000 and Baker & Ruddy 2000, classified on an ordinal scale as none, mild, moderate or severe.*
*l Walsh et al., 2004 adjusted for: increased work of breathing, tachycardia, age and dehydration.*

*m Walsh et al., 2004 risk of bias (derivation set): Demographics only reported for the three category model (fit for discharge, LOS 2 to 3 days, LOS ≥4 days) not the two-category model (discharged or admitted). 23 of the 99 patients were excluded because of missing data, it is then unclear how many analysed infants (n=76) in the derivation phase were admitted or discharged. Include infants who are readmitted in the 'need for admission' group. Return visits that did not lead to admission were also counted as discharges. Infants diagnosed by attending paediatrician, diagnostic criteria not reported. The calculation for age was unclear. Demographics are based on the number of episodes of bronchiolitis, not the number of patients. Unclear how the model was 'trimmed', no significance level is discussed. Unclear which treatments were received in the ED. Retrospective study design.*
*n Walsh et al., 2004 indirectness: Infants up to 24 months of age included (the GDG has specified that it is likely that older children will not have bronchiolitis). Do not predefine the criteria for admission to hospital.*
*o Walsh et al., 2004 risk of bias (validation set): Demographics only reported for the entire validation set, demographics are not reported separately for infants admitted or discharged. Include infants who are readmitted in the 'need for admission' group. Return visits that did not lead to admission were also counted as discharges. Infants diagnosed by attending paediatrician, diagnostic criteria not reported. The calculation for age was unclear. Demographics are based on the number of episodes of bronchiolitis, not the number of patients. Unclear how the model was 'trimmed', no significance level is discussed. Unclear which treatments were received in the ED.*
*p Increased work of breathing determined by implicit review, but required at least more than one mild recession to be noted on the chart.*

**Table 18~~17~~: GRADE profile for comparison of true oximetry values with altered (elevated) oximetry values**

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

*NA not applicable NC not calculable, NR not reported, RCT randomised controlled trial, P probability-value, OR odds ratio*
** Calculated by the NCC-WCH technical team from data reported in the article*
*a The two groups were comparable at baseline although there was a limited number of patients presenting with low oxygen saturation levels which in the end did not allow to determine a specific threshold for admission; also, there was a high number of refusals (but 0 lost at follow-up or discontinued the intervention).*
*b The comparison used in the study is different from what indicated in the review protocol as no specific threshold is applied.*
*c Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.~~Wide 95% CI crossing +/- 0.25 around the line of no effect.~~*

# A.5 Fluids and nutritional support

**Table 19~~18~~: GRADE profile for comparison of intravenous fluids with comparator gastric tube feeding**

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

*NC not calculable, p-value, MD mean difference, SD standard deviation*
*a As reported in the study*
*b Calculated by the NCC-WCH technical team from data reported in the article*
*c Method of randomisation and allocation concealment not described, small sample size (based on sample size calculation reported in study, sufficient numbers not reached)*
*d Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.~~Serious imprecision – confidence intervals of SMD crosses -0.5 and no treatment effect, based on Cohen's effect size criteria~~*
*e it was not possible to assess imprecision because of the lack of information reported in the paper. ~~Poor reporting, therefore imprecision could not be calculated~~*

**Table 2019: GRADE profile for comparison of nasogastric hydration with comparator intravenous hydration**

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

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Nasogastric hydration | Intravenous hydration | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Oakley et al., 2013) | 9/336 (3%) | 1/342 (0.3%) | OR: 9.39 (1.18 to 74.49)[a] | - | Very low | Multicentre open randomised trial | None | None | Very serious[c] | Serious[d] | None |
| **Intravenous line-site soreness** | | | | | | | | | | | |
| 1 (Oakley et al., 2013) | 0/336 (0%) | 9/342 (3%) | OR: 0.05 (0.00 to 0.90)[a] | - | Very low | Multicentre open randomised trial | None | None | Very serious[c] | Serious[d] | None |
| **Epistaxis** | | | | | | | | | | | |
| 1 (Oakley et al., 2013) | 4/336 (1%) | 1/342 (0.3%) | OR: 4.11 (0.46 to 36.95[]a] | - | Very low | Multicentre open randomised trial | None | None | Very serious[c] | Very serious[d] | None |
| **Any sign nasal trauma** | | | | | | | | | | | |
| 1 (Oakley et al., 2013) | 3/336 (1%) | 0/342 (0%) | OR: 7.19 (0.37 to 139.71)[a] | - | Very low | Multicentre open randomised trial | None | None | Very serious[c] | Very serious[d] | None |
| **Intravenous line-site infection** | | | | | | | | | | | |
| 1 (Oakley et al., 2013) | 0/336 (0%) | 0/342 (0%) | NC | - | Low | Multicentre open randomised trial | None | None | Very serious[c] | NCA | None |
| **Other[e]** | | | | | | | | | | | |
| 1 (Oakley et al., 2013) | 11/336 (3%) | 11/342 (3%) | OR: 1.02 (0.44 to 2.38)[a] | - | Very low | Multicentre open randomised trial | None | None | Very serious[c] | Very serious[d] | None |

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

# A.6 Pulse oximetry monitoring

**Table 21~~20~~: GRADE profile for comparison of pre-intervention (no pulse oximetry monitoring) with post-intervention (pulse oximetry monitoring added to ED)**

| Number of studies | Number of patients | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-intervention | Post-intervention | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Admission rates** | | | | | | | | | | | |
| 1. (Choi et al., 2006) | N= 32/159 (20%) | N= 16/89 (18%) | RR = 0.89 95%CI (0.52-1.53) * | P=0.61 | Very Low | Retrospective ~~case-control~~cohort | Very Serious [a] | None | Serious [b] | Very serious [c] | None |
| **Duration of admission** | | | | | | | | | | | |
| **Reported as triage to disposition time (either to home or to an inpatient bed)** | | | | | | | | | | | |
| 1. (Choi et al., 2006) | N=159 259 min | N=89 249 min | - | P=0.033 | Very Low | Retrospective ~~case-control~~cohort | Very Serious [d] | None | Serious [e] | ~~Not assessed~~NC [f] | None |

*NA not applicable, NC not calculable, NR not reported, RCT randomised controlled trial, p-value, RR relative risk*
** Calculated by the NCC-WCH technical team from data reported in the article*
*a Cases and controls are taken from comparable populations: poorly addressed (population characteristics poorly reported); participants and non-participants are compared to establish their similarities and differences: not reported; main potential confounders are identified and taken into account: not addressed; the paper used a retrospective design.*
*b Outcome: triage to disposition time, rather than actual duration of admission.*
*c Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID ~~Very serious imprecision (95% CI crosses +/- 0.25 around the line of no effect).~~*
*d Cases and controls are taken from comparable populations: poorly addressed (population characteristics poorly reported); participants and non-participants are compared to establish their similarities and differences: not reported; Main potential confounders are identified and taken into account: not addressed. Also, confidence intervals and means were not reported, therefore it was not possible to grade imprecision (study has been downgraded because of this).*
*e Outcome: triage to disposition time rather than actual duration of admission.*
*f it was not possible to assess imprecision because of the lack of information reported in the paper (CI and means not reported). Confidence intervals and means were not reported, therefore it was not possible to grade imprecision.*

# A.7 Chest radiography

**Table 2221: GRADE profile for the diagnostic value of chest radiography vs. no chest radiography in identifying alternative diagnoses to bronchiolitis.**

| Number. of studies | Number of patients | Measure of diagnostic accuracy | | | | | | Quality | Quality assessment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Sensitivity (95% confidence interval) | Specificity (95% confidence interval) | Positive likelihood ratio (95% confidence interval) | Negative likelihood ratio (95% confidence interval) | Positive Predictive Value (95% confidence interval) | Negative Predictive Value (95% confidence interval) | | Design | Limita-tions | Inconsist-ency | Indirect-ness | Impreci-sion | Other considera-tions |
| **Identification of additional or alternate diagnosis** | | | | | | | | | | | | | | |
| **Detection of alternate diagnoses (lobar consolidation, cardiomegaly, congenital lung anomaly, pleural effusion, and mediastinal or parenchymal mass) pre-radiography** | | | | | | | | | | | | | | |
| 1 (Yong et al,2009) | 265 | 0% (0-0.84)[a] | 97% (94-98) [a] | 0 (0-0.18∞) [a] | 1.03 (1.021-1.046) [a] | 0% (0-0.330) [a] | 99% (978-100) [a] | Very low | Economic Evaluation | Serious [b, c, g] | None | Serious [m] | Serious [h] | None Some [v] |
| **Detection of alternate diagnoses (lobar consolidation, cardiomegaly, congenital lung anomaly, pleural effusion, and mediastinal or parenchymal mass) post-radiography** | | | | | | | | | | | | | | |
| 1 ( Yong et al, 2009) | 265 | 0% (0-0.84) [a] | 89% (845-92) [a] | 0 (0-0.06∞) [a] | 1.13 (1.08-1.17) [a] | 0% (0-0.11) [a] | 99% (968-100) [a] | Very low | Economic Evaluation | Serious [b, c, g] | None | Serious [m] | Serious [j] | None |
| **Detection of cases of pneumonia, pre-radiography** | | | | | | | | | | | | | | |
| 1 ( Yong et al, 2009) | 265 | 12% (3-27) [a] | 89% (85-93) [a] | 1.12 (0.29-4.34) [a] | 0.98 (0.82-1.18) [a] | 7% (2-16) [a] | 94% (91-97) [a] | Very low | Economic Evaluation | Very serious b, c, g[h] | None | Serious [m] | Serious [j] | None |
| **Detection of cases of pneumonia, post-radiography** | | | | | | | | | | | | | | |
| 1 ( Yong et al, 2009) | 265 | 41% (17-64) a | 84% (79 - 88) [a] | 2.55 (1.35-4.82) [a] | 0.70 (0.47-1.05) [a] | 15% (4 - 25) [a] | 95% (93 - 98) [a] | Very low | Economic Evaluation | Serious [b, c, g] | None | Serious [m] | Serious [k] | NoneSome [v] |
| **Detection of severe cases of bronchiolitis (atelectasis on chest x-ray)** | | | | | | | | | | | | | | |
| 1 (Shaw et al, 1991) | 213 | 21% (12-30) [a] | 98% (95-100) a | 10.47 (3.01-36.37) [a] | 0.81 (0.71-0.91) [a] | 82% (68-100) [a] | 70% (63-76) [a] | Very Low | Cross-sectional | Very serious [b, d, f] | None | None | Very Serious [k] | Some [e] |

*a Calculated by the NCC-WCH technical team from data reported in the article*
*b Lack of a gold standard*
*c The researchers excluded premature infants (selection bias)*

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*d- No clear method of diagnosis stated and severity of illness may have been lower than in other studies*
*e Unclear applicability ("history of previous upper tract respiratory infection" inclusion criterion)*
*f Infants in the mild disease group and those in the severe disease group are significantly different in terms of baseline characteristics historical information (gestational age, perinatal complications, URI symptoms, exposure to a smoker in the family, whether the baby had been breastfed, family history of wheezing) and no control for confounding*
*g The study radiologist knew the patients were suspected of having bronchiolitis*
*h Thresholds used: <74% low, 75-89% moderate, >90% high (for sensitivity, specificity and predictive values); <5 not useful, 5-10 moderately useful, >10 very useful (for positive likelihood ratio); >0.5 not useful, 0.1-0.5 moderately useful, 0-0.1 very useful (for negative likelihood ratio). In this case: low sensitivity, high specificity, low PPV, high NPV, not useful to inf +LR, not useful –LR (one of them spans over two or more thresholds).*
*I In this case: low sensitivity, moderate to high specificity, low PPV, high NPV, not useful to inf +LR and not useful –LR (two measures cross the thresholds).*
*j In this case: low sensitivity, moderate to high specificity, low PPV, high NPV, not useful +LR, and not useful to moderately useful –LR (two measures cross the thresholds).*
*k In this case: low sensitivity, high specificity, low to high PPV, low to moderate NPV, not useful to very useful +LR, not useful –LR (three measures cross thresholds).*
*l In this case: low sensitivity, moderate specificity, low PPV, high NPV, not useful +LR, and moderately useful to very useful –LR (one measure crosses thresholds).*
*m Included infants up to 23 months of age. The GDG has specified that it is likely that older children will not have bronchiolitis.~~a Calculated by the technical team from data reported in the article~~*
*~~b Lack of a gold standard~~*
*~~c The researchers excluded premature infants (selection bias)~~*
*~~d No clear method of diagnosis stated and severity of illness may have been lower than in other studies~~*
*~~e Data collected retrospectively~~*
*~~f Unclear applicability ("history of previous upper tract respiratory infection" inclusion criterion)~~*
*~~g Infants in the mild disease group and those in the severe disease group are significantly different in terms of baseline characteristics historical information (gestational age, perinatal complications, URI symptoms, exposure to a smoker in the family, whether the baby had been breastfed, family history of wheezing) and no control for confounding~~*
*~~h The study radiologist knew the patients were suspected of having bronchiolitis~~*
*~~I Method of diagnosis and inclusion/exclusion criteria reported elsewhere~~*
*~~j Baseline information about the two groups are not reported~~*
*~~k Information on how the index test was performed are not reported~~*
*~~l Statistical analyses controlled for confounders~~*
*~~m Confidence Intervals does not cross the line of no effect~~*
*~~n Thresholds used: <74% low, 75-89% moderate, >90% high (for sensitivity, specificity and predictive values); <5 not useful, 5-10 moderately useful, >10 very useful (for positive likelihood ratio); >0.5 not useful, 0.1-0.5 moderately useful, 0-0.1 very useful (for negative likelihood ratio). In this case: low sensitivity, high specificity, low PPV, high NPV, not useful to inf +LR, not useful –LR (one of them spans over two or more thresholds).~~*
*~~o In this case: low sensitivity, moderate to high specificity, low PPV, high NPV, not useful to inf +LR and not useful –LR (two measures cross the thresholds).~~*
*~~p In this case: low sensitivity, moderate to high specificity, low PPV, high NPV, not useful +LR, and not useful to moderately useful –LR (two measures cross the thresholds).~~*
*~~q In this case: low sensitivity, high specificity, low to high PPV, low to moderate NPV, not useful to very useful +LR, not useful –LR (three measures cross thresholds).~~*
*~~r In this case: low sensitivity, moderate specificity, low PPV, high NPV, not useful +LR, and moderately useful to very useful –LR (one measure crosses thresholds).~~*
*~~s Wide confidence interval crossing +0.25 around line of no effect~~*
*~~t Imprecision could not be investigated due to way the results have been reported (no confidence intervals)~~*
*~~u SMD cannot be calculated due to way the results have been reported (no mean differences for both control and intervention group), therefore imprecision could not be evaluated~~*
*~~v This study also reports that the interpretation of chest X-ray by ED physicians resulted in a fivefold increase in the rate of antibiotic therapy after radiography, from 2.6% to 14.7%. A study by Schuh et al., which uses the same study participants, presents the raw data for antibiotic administration: 7/265 pre radiography vs. 39/265 post radiography respectively.~~*
*~~w Included infants up to 23 months of age. The GDG has specified that it is likely that older children will not have bronchiolitis.~~*
*~~x Included infants up to 22 months of age. The GDG has specified that it is likely that older children will not have bronchiolitis.~~*

**Table 2322: GRADE profile for the effect that chest radiography has on the management of bronchiolitis.**

| Number of studies | Number of patients | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Identification of additional or alternate diagnosis – association between radiograph findings and severe bronchiolitis** | | | | | | | | | | | |
| **Atelectasis and disease severity** | | | | | | | | | | | |
| 1 (Shaw et al, 1991) | Mild disease: 3 of 139 with Atelectasis | Severe 16 of 74 had atelectasis | RR 2.70 (1.97-3.70) | P<0.001 | Very low | Cross-sectional | Very serious [a, b, e] | None | None | None | Some [d] |
| **Hyperaeration and disease severity** | | | | | | | | | | | |
| 1 (Shaw et al, 1991) | Mild disease: 52 of 139 showed hyperaeration | Severe disease: 69 of 74 had hyperaeration | RR 1.58 (1.03-2.42) | P<0.05 | Very low | Cross-sectional | Very serious [a, b, e] | None | None | Serious [k] | Some [d] |
| **Radiological change and disease severity** | | | | | | | | | | | |
| 1 (Dawson et al, 1990) | - | - | Chi-square 9.92 | P<0.10 | Very Low | Cross-sectional | Serious [a, g, f] | None | Serious [n] | NC [l] | None |
| 1 (Dawson et al, 1990) | - | - | Chi-square 4.56 | P<0.10 | Very Low | Cross-sectional | Serious [a, g, f] | None | Serious [n] | NC [l] | None |
| 1 (Dawson et al, 1990) | - | - | Chi-square 6.55 | P<0.10 | Very Low | Cross-sectional | Serious [a, g , f] | None | Serious [n] | NC [l] | None |
| **Antibiotic administration – with radiograph compared to no radiograph** | | | | | | | | | | | |
| **Children aged less than 3 months** | | | | | | | | | | | |
| 1 (Christakis et al, 2005) | - | - | Adjusted OR 1.11 (0.96-1.28) | P>0.05 | Very low | Retrospective cohort study | Very serious [a, c, h] | None | None | Serious [k] | Some [i, j] |
| **Children aged 3 months or more** | | | | | | | | | | | |
| 1 (Christakis et al, 2005) | - | - | Adjusted OR 1.22 | P<0.001 | Very low | Retrospective cohort study | Very serious [a, c, h] | None | None | Serious [k] | Some [i, j] |

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

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

* Calculated by the NCC-WCH technical team from data reported in the article

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

## A.8 Capillary blood gas testing

No evidence was identified for this review.

## A.9 Chest physiotherapy

**Table 2423: GRADE profile for comparison of slow and long expiration techniques + assisted cough + bronchodilator with bronchodilator only**

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Clinical score** | | | | | | | | | | | |
| **Proportion of patients discharged a (comparator: salbutamol)** | | | | | | | | | | | |
| 1. Castro-Rodriguez et al. 2014 | N = 23/25 (92%) | N = 20/23 (87%) | RR 1.06 (0.87-1.29) * | P=0.66 | Low | RCT | Serious [b] | None | Serious [c] | Serious [d] | None |
| **Tal's clinical score e (comparator: salbutamol)** | | | | | | | | | | | |
| 1. Castro-Rodriguez et al. 2014 | Mean (95% CI): 2.8 (2.2-3.3) N = 25 | Mean (95% CI): 3.4 (2.8-4.1) N = 23 | NC | MD -0.60 (-1.40 to 0.20) * ns | Low | RCT | Serious [b] | None | Serious [c] | None [f] | None |
| **Wang's total clinical score (comparator: albuterol) at 30 min** | | | | | | | | | | | |
| 1. Postiaux et al., 2011 | Mean ±SD: 3.6 ±2.3 N =12, 31 sessions | Mean ±SD: 5.1 ±2.6 N =8, 27 sessions | NC | MD -1.50 (-3.72 to 0.72) * P=0.02 | Moderate | RCT | Serious [g] | None | None | Serious h | None |
| **Wang's total clinical score (comparator: albuterol) at 150 min** | | | | | | | | | | | |
| 1. Postiaux et al., 2011 | Mean ±SD: 3.7 ±2.7 N =12, 31 sessions | Mean ±SD: 4.6 ±2.9 N =8, 27 sessions | NC | MD -0.90 (-2.35 to 0.55) * P=0.21 | Low | RCT | Serious [g] | None | None | Very Serious [i] | None |
| **Respiratory rate section of Wang's clinical score at 30 min (comparator: albuterol)** | | | | | | | | | | | |
| 1. Postiaux et al., 2011 | Mean ±SD: 1.3 ±0.9 N =12, 31 sessions | Mean ±SD: 2.0 ±0.7 N =8, 27 sessions | NC | MD - 0.70 (-1.11 to -0.29) * P=0.001 | Moderate | RCT | Serious [g] | None | None | Serious [n] | None |
| **Respiratory rate section of Wang's clinical score at 150 min (comparator: albuterol)** | | | | | | | | | | | |
| 1. Postiaux et al., 2011 | Mean ±SD: 1.3 ±0.8 N =12 | Mean ±SD: 1.7 ±0.7 N =8 | NC | MD - 0.40 (-0.78 to -0.01) * P=0.06 | Moderate | RCT | Serious [g] | None | None | Serious [o] | None |
| **O2 Saturation , %** | | | | | | | | | | | |
| **Comparator: salbutamol** | | | | | | | | | | | |
| 1. Castro-Rodriguez et al., 2014 | Mean (95% CI): 96.4 (95.7-97.1) N = 25 | Mean (95% CI): 96.0 (94.9-96.5) N = 23 | NC | MD 0.40 (-0.83 to 1.63) * ns | Very Low | RCT | Serious [b] | None | Serious [c] | Very Serious [j] | None |
| **Measurement at 30 min, comparator: albuterol** | | | | | | | | | | | |

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1. Postiaux et al., 2011 | Mean±SD: 95 ±3<br>N =12, 31 sessions | Mean±SD: 95 ±3<br>N =8, 27 sessions | NC | MD 0.00 (-2.68 to 2.68) *<br>P=0.61 | Low | RCT | Serious [g] | None | None | Very Serious [k] | None |
| **Measurement at 150 min, comparator: albuterol** | | | | | | | | | | | |
| 1. Postiaux et al., 2011 | Mean±SD: 96 ±2<br>N =12, 31 sessions | Mean±SD: 96 ±2<br>N =8, 27 sessions | NC | MD 0.00 (-1.03 to 1.03) *<br>p=0.83 | Low | RCT | Serious [g] | None | None | Very Serious [i] | None |
| **Respiratory rate** | | | | | | | | | | | |
| **Comparator: salbutamol** | | | | | | | | | | | |
| 1. Castro-Rodriguez et al., 2014 | Mean ±SD: 43.0 ±11<br>N = 25 | Mean±SD: 48.9 ±9<br>N = 23 | NC | MD - 5.90 (-11.57 to -0.23) * ns | Low | RCT | Serious [b] | None | Serious [c] | Serious [m] | None |

*MD Mean Difference, SD standard deviation, NC not calculable, NR not reported, Ns non-significant, RCT randomised controlled trial, p-value, RR relative risk*
** Calculated by the NCC-WCH technical team from data reported in the article*
*a. primary outcome was defined as the proportion of patients discharged after the first hour of treatment if clinical score ≤5/12 and SpO2≥93%*
*b. performance bias: not reported if physiotherapists administering the intervention were aware of treatment allocation; detection bias: investigators not blind to confounding and prognostic factors*
*c. "most infants were under one year of age" and some of the participants had previous wheezy episodes*
*d. Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID. ~~Wide confidence intervals crossing +/-0.25 around the line of no effect~~*
*e. Tal's clinical score e (min 0 – max 12) assessing respiratory rate, wheeze, cyanosis and accessory respiratory muscle utilization*
*f. SMD calculation by NCC-WCH: SMD (95%CI) = -0.60 (-1.88 to -0.68). (Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID)., ~~No imprecision, based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*
*g. Selection bias: concealment of allocation not described, as well as the random sequence generation is not reported*
*h. SMD calculation by NCC-WCH: SMD (95%CI) = -1.50 (-2.77 to -0.22). Serious imprecision when 95% CI crosses one default MID. ~~Serious imprecision, based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*
*i. SMD calculation by NCC-WCH: SMD (95%CI) = -0.90 (-2.35 to 0.55). Very serious imprecision when 95% CI crosses two default MID ~~Very Serious imprecision, based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*
*j. SMD calculation by NCC-WCH: SMD (95%CI) = 0.40 (-0.83 to 1.63). Very Serious imprecision, when 95% CI crosses two default MID~~based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*
*k. SMD calculation by NCC-WCH: SMD (95%CI) = 0.00 (-0.55 to 1.55). Very Serious imprecision, when 95% CI crosses two default MID~~based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*
*l. SMD calculation by NCC-WCH: SMD (95%CI) = 0.00 (-0.03 to 1.03). Very Serious imprecision, when 95% CI crosses two default MID ~~based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*
*m. SMD calculation by NCC-WCH: SMD (95%CI) = -5.90 (-11.56 to -0.23). Serious imprecision, when 95% CI crosses one default MID.~~based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*

*n. SMD calculation by NCC-WCH: SMD (95%CI) = -0.70 (-1.11 to -0.28). Serious imprecision, when 95% CI crosses one default MID. ~~based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*
*o. SMD calculation by NCC-WCH: SMD (95%CI) = -0.40 (-0.78 to -0.01). Serious imprecision, when 95% CI crosses one default MID. ~~based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*

*Table 25~~24~~: GRADE profile for comparison of increased exhalation/expiration techniques + assisted cough + upper airways suction with suction only*

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Clinical score** | | | | | | | | | | | |
| **Wang's total clinical score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 4.0 (2-7) N =10 | Median (range) = 7.0 (4-10) N =10 | NC | ns | Very Low | RCT | Very Serious [a] | None | Serious [b] | ~~NA~~ NC [c] | None |
| **Wheezing section of Wang's score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 0.0 (0-1) N =10 | Median (range) = 0.0 (0-2) N =10 | NC | ns | Very Low | RCT | Very Serious [a] | None | Serious [b] | ~~NA~~ NC [c] | None |
| **Respiratory rate section of Wang's score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 2.0 (0-3) N =10 | Median (range) = 2.0 (1-3) N =10 | NC | ns | Very Low | RCT | Very Serious [a] | None | Serious [b] | ~~NA~~ NC [c] | None |
| **Retractions section of Wang's score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 1.0 (0-2) N =10 | Median (range) = 1.0 (0-3) N =10 | NC | ns | Very Low | RCT | Very Serious [a] | None | Serious [b] | ~~NA~~ NC [c] | None |
| **General condition section of Wang's score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 3.0 (0-3) N =10 | Median (range) = 3.0 (0-3) N =10 | NC | ns | Very Low | RCT | Very Serious [a] | None | Serious [b] | ~~NA~~ NC [c] | None |
| **O2 saturation** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Mean±s.d. = 89 ±4.47 N =10 | Mean±s.d. = 90.3 ±2.62 N =10 | NC | MD = -1.30 (-4.51 to 1.91) * ns | Very Low | RCT | Very Serious [a] | None | Serious [b] | Very Serious [d] | None |
| **Time to recovery [e]** | | | | | | | | | | | |
| **Overall population** | | | | | | | | | | | |
| 1. Gajdos et al., 2010 | Median, days (95%CI): 2.02 (1.96-2.34) N = 246 | Median, days (95%CI): 2.31 (1.97-2.73) N = 250 | HR = 1.09 (0.91-1.31) | P=0.33 | Moderate | RCT | Low risk [f] | None | Serious [g] | Serious [h] | None |
| **< 2 months (n=238)** | | | | | | | | | | | |

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1. Gajdos et al., 2010 | Median, days (95%CI): 2.47 (1.98-3.31) | Median, days (95%CI): 2.64 (2.25-3.08) | HR = 1.09 (0.84-1.41) | P=0.51 | Moderate | RCT | Low risk [f] | None | Serious [g] | Serious [h] | None |
| **≥ 2 months (n=258)** | | | | | | | | | | | |
| 1. Gajdos et al., 2010 | Median, days (95%CI): 2.00 (1.51-2.25) | Median, days (95%CI): 2.01 (1.65-2.44) | HR = 1.09 (0.85-1.40) | P=0.48 | Moderate | RCT | Low risk [f] | None | Serious [g] | Serious [h] | None |
| **Reported side effects** | | | | | | | | | | | |
| **Bradycardia with desaturation** | | | | | | | | | | | |
| 1. Gajdos et al., 2010 | N = 3/246 (1.2%) | N = 3/250 (1.2%) | RR = 1.0 (0.2-5.00) | P=1.00 | Low | RCT | Low risk [f] | None | Serious [g] | Very Serious [h] | None |
| **Bradycardia without desaturation** | | | | | | | | | | | |
| 1. Gajdos et al., 2010 | N = 7/246 (2.8%) | N = 2/250 (0.8%) | RR = 3.6 (0.7-16.9) | P=0.10 | Low | RCT | Low risk [f] | None | Serious [g] | Very Serious [h] | None |
| **Vomiting** | | | | | | | | | | | |
| 1. Gajdos et al., 2010 | N = 10/246 (4.1%) | N = 1/250 (0.4%) | RR = 10.2 (1.3-78.8) | P=0.005 | Moderate | RCT | Low risk [f] | None | Serious [g] | None | None |
| **Respiratory destabilization** | | | | | | | | | | | |
| 1. Gajdos et al., 2010 | N = 16/246 (6.5%) | N = 3/250 (1.2%) | RR = 5.4 (1.6-18.4) | P=0.002 | Moderate | RCT | Low risk [f] | None | Serious [g] | None | None |
| **Hypotonia** | | | | | | | | | | | |
| 1. Gajdos et al., 2010 | N = 2/246 (0.8%) | N = 0/250 (0.0%) | RR = 5.08 (0.24-105.29) | P=0.24 | Low | RCT | Low risk [f] | None | Serious [g] | Very Serious [h] | None |
| **Need for ventilation** | | | | | | | | | | | |
| 1. Gajdos et al., 2010 | N = 5/246 (2.0%) | N = 2/250 (0.8%) | RR = 2.5 (0.5-13.0) | P=0.29 | Low | RCT | Low risk [f] | None | Serious g | Very Serious [h] | None |

*MD Mean Difference, SD standard deviation, NA not applicable, NC not calculable, NR not reported, Ns non-significant, RCT randomised controlled trial, p-value, RR relative risk*

** Calculated by the technical team from data reported in the article*

*a. Selection bias: method of randomization and concealment of allocation were not reported; performance bias: the third group (suction) didn't receive the same techniques as G1 and G2 during hospitalization; blinding of those who administered the treatment was not described; attrition bias: the third group did not receive assessment at follow up (low risk); detection bias: low risk of bias. Also, the study was downgraded because imprecision was not assessable (see footnote c).*
*b. Children aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis), authors excluded infants without RSV.*
*c. It was not possible to grade for imprecision due to lack of information (95%CI were not reported).*
*d. SMD calculation by NCC-WCH: SMD (95%CI) = -1.30 (-4.51 to 1.91). Very serious imprecision when 95% CI crosses two default MID~~Very Serious imprecision, based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*
*e. Time to recovery: an infant was considered to be cured if no oxygen supplementation had been given for 8 h, and the child had minimal or no chest recession and was ingesting more than two-thirds of daily needs.*
*f. Selection bias: low risk; performance bias: low risk; attrition bias: low risk; detection bias: low risk.*
*g. Infants aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis)*
*h. Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.~~Wide confidence intervals crossing +/-0.25 around the line of no effect (same imprecision rules as for RR and OR).~~*

**Table 26~~25~~: GRADE profile for comparison of percussion and vibration techniques + suction with suction only**

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Clinical score** | | | | | | | | | | | |
| **Webb's total clinical score a** | | | | | | | | | | | |
| 1. Nicholas et al., 1999 | NR N = 26 | NR N = 24 | NC | ns | Very Low | RCT | Very Serious [b] | None | None | NC~~A~~ [c] | None |
| **Wang's total clinical score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 5.5 (1-7) N =10 | Median (range) = 7.0 (4-10) N =10 | NC | ns | Very Low | RCT | Very Serious [d] | None | Serious [e] | ~~NA~~ NC [f] | None |
| **Wheezing section of Wang's score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 0.0 (0-1) N =10 | Median (range) = 0.0 (0-2) N =10 | NC | ns | Very Low | RCT | Very Serious [d] | None | Serious [e] | ~~NA~~ NC [f] | None |
| **Respiratory rate section of Wang's score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 2.0 (1-2) N =10 | Median (range) = 2.0 (1-3) N =10 | NC | ns | Very Low | RCT | Very Serious [d] | None | Serious [e] | ~~NA~~ NC [f] | None |
| **Retractions section of Wang's score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 1.0 (0-2) N =10 | Median (range) = 1.0 (0-3) N =10 | NC | P<0.05 | Very Low | RCT | Very Serious [d] | None | Serious [e] | ~~NA~~ NC [f] | None |
| **General condition section of Wang's score** | | | | | | | | | | | |

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1. Gomes et al., 2012 | Median (range) = 3.0 (0-3) N =10 | Median (range) = 3.0 (0-3) N =10 | NC | ns | Very Low | RCT | Very Serious [d] | None | Serious [e] | ~~NA~~ NC [f] | None |
| **O2 saturation** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Mean±s.d. = 93 ±4.05 N =10 | Mean±s.d. = 90.3 ±2.62 N =10 | NC | MD = 2.70 (-0.29 to 5.69) * Ns | Very Low | RCT | Very Serious [d] | None | Serious [e] | Serious [g] | None |
| **Length of stay** | | | | | | | | | | | |
| 1. Nicholas et al., 1999 | Mean, days (range) = 6.7 (3-9.5) | Mean, days (range) = 6.6 (2.3-11.5) | NC | ns | Very Low | RCT | Very Serious [b] | None | None | ~~NA~~ NC [c] | None |
| **Provision of inspired O2 and requirement of nasogastric feeding** | | | | | | | | | | | |
| 1. Nicholas et al., 1999 | Mean, h = 86 N = 26 | Mean, h = 92 N = 24 | NC | ns | Very Low | RCT | Very Serious [b] | None | None | ~~NA~~ NC [c] | None |

*MD Mean Difference, SD standard deviation, NA not applicable, NC not calculable, NR not reported, NS non-significant, RCT randomised controlled trial, p-value, RR relative risk*

** Calculated by the NCC-WCH technical team from data reported in the article*

*a. Clinical score: a score of 0 to 3 was allocated for each of ten clinical signs (heart rate, respiratory rate, hyperinflation, use of respiratory muscles, recession, rhinitis, wheeze, cough, ~~crepitations~~crackles, and ronchi)*

*b. Selection bias: allocation concealment not described, performance bias: blinding not reported, attrition bias: not clear how data were treated, detection bias: description of the outcomes not appropriately reported, blinding not described. Also, the study was downgraded because imprecision was not assessable (see footnote c).*

*c. It was not possible to grade for imprecision due to lack of information (95%CI were not reported).*

*d. Selection bias: method of randomization and concealment of allocation were not reported; performance bias: the third group (suction) didn't receive the same techniques as G1 and G2 during hospitalization; blinding of those who administered the treatment was not described; attrition bias: the third group did not receive assessment at follow up (low risk); detection bias: low risk of bias.*

*e. Children aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis), authors excluded infants without RSV.*

*f. It was not possible to grade for imprecision due to lack of information (95%CI were not reported).*

*g. SMD calculation by NCC-WCH: SMD (95%CI) = 2.70 (-0.29 to 5.69). Very serious imprecision when 95% CI crosses two default MID ~~Serious imprecision, based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*

**Table 27~~26~~: GRADE profile for comparison of prolonged slow expiration techniques with percussion and vibration techniques**

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Clinical score** | | | | | | | | | | | |
| **Wang's total clinical score** | | | | | | | | | | | |

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| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1. Gomes et al., 2012 | Median (range) = 4.0 (2-7) N =10 | Median (range) = 5.5 (1-7) N =10 | NC | ns | Very Low | RCT | Very Serious [a] | None | Serious [b] | ~~NA~~ NC [c] | None |
| **Wheezing section of Wang's score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 0.0 (0-1) N =10 | Median (range) = 0.0 (0-1) N =10 | NC | ns | Very Low | RCT | Very Serious [a] | None | Serious [b] | ~~NA~~ NC [c] | None |
| **Respiratory rate section of Wang's score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 2.0 (0-3) N =10 | Median (range) = 2.0 (1-2) N =10 | NC | ns | Very Low | RCT | Very Serious [a] | None | Serious [b] | ~~NA~~ NC [c] | None |
| **Retractions section of Wang's score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 1.0 (0-2) N =10 | Median (range) = 1.0 (0-2) N =10 | NC | P<0.05 | Very Low | RCT | Very Serious [a] | None | Serious [b] | ~~NA~~ NC [c] | None |
| **General condition section of Wang's score** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Median (range) = 3.0 (0-3) N =10 | Median (range) = 3.0 (0-3) N =10 | NC | ns | Very Low | RCT | Very Serious [a] | None | Serious [b] | ~~NA~~ NC [c] | None |
| **O2 saturation** | | | | | | | | | | | |
| 1. Gomes et al., 2012 | Mean±s.d. = 89 ±4.47 N =10 | Mean±s.d. = 93 ±4.05 N =10 | NC | MD = -4.00 (-7.74 to -0.26) * ns | Very Low | RCT | Very Serious [a] | None | Serious [b] | Serious [d] | None |

*MD Mean Difference, SD standard deviation, NA not applicable, NC not calculable, NR not reported, Ns non-significant, RCT randomised controlled trial, p-value, RR relative risk*

** Calculated by the NCC-WCH technical team from data reported in the article*

*a. Selection bias: method of randomization and concealment of allocation were not reported; performance bias: the third group (suction) didn't receive the same techniques as G1 and G2 during hospitalization; blinding of those who administered the treatment was not described; attrition bias: the third group did not receive assessment at follow up (low risk); detection bias: low risk of bias. Also, the study was downgraded because imprecision was not assessable (see footnote c).*

*b. Children aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis), authors excluded infants without RSV.*

*c. It was not possible to grade for imprecision due to lack of information (95%CI were not reported).*

*d. SMD calculation by NCC-WCH: SMD (95%CI) = -4.00 (-7.74 to 0.26). Serious imprecision when 95% CI crosses one default MID. ~~Serious imprecision, based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*

**Table 2827: GRADE profile for comparison of prolonged slow expiration techniques + slow accelerated expiratory flow + induced cough with no intervention**

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Time to clinical stability [a]** | | | | | | | | | | | |
| 1. Rochat et al., 2012 | Mean ±sd, days = 2.9 ±2.1<br>N = 50 | Mean ±sd, days = 3.2 ±2.8<br>N = 49 | NC | MD -0.30 (-1.27 to 0.67) *<br>P=0.45 | Low | RCT | Serious [b] | None | None | Very Serious [c] | None |
| **Clinical score** | | | | | | | | | | | |
| **Clinical state [d]** | | | | | | | | | | | |
| 1. Rochat et al., 2012 | points/day measured as daily changes =<br>-0.12 (-0.08 to -0.15) | points/day measured as daily changes =<br>-0.09 (-0.06 to -0.13) | NC | MD -0.03 (-0.08 to 0.02) *<br>P=0.37 | Moderate | RCT | Serious [b] | None | None | None [e] | None |
| **Respiratory score [f]** | | | | | | | | | | | |
| 1. Rochat et al., 2012 | points/day measured as daily changes = -1.6 (-1.4 to -1.8) | points/day measured as daily changes =<br>-1.3 (-1.1 to -1.5) | NC | MD -0.30 (-0.57 to -0.02) *<br>P=0.04 | Low | RCT | Serious [b] | None | None | Serious [g] | None |
| **O2 Saturation** | | | | | | | | | | | |
| 1. Rochat et al., 2012 | %/day measured as daily changes = 1.0 (0.7-1.2) | %/day measured as daily changes = 1.0 (0.8-1.2) | NC | MD 0.00 (-0.35 to 0.35) *<br>P=0.85 | Moderate | RCT | Serious [b] | None | None | None [h] | None |
| **Respiratory rate** | | | | | | | | | | | |
| 1. Rochat et al., 2012 | rate/day measured as daily changes =<br>-1.1 (-0.6 to -1.7) | rate/day measured as daily changes = -0.7 (-0.2 to -1.2) | NC | MD -0.40 (-1.6 to 0.36) *<br>P=0.24 | Low | RCT | Serious [b] | None | None | Serious [i] | None |

*MD Mean Difference, SD standard deviation, NC not calculable, NR not reported, RCT randomised controlled trial, p-value, RR relative risk*
** Calculated by the NCC-WCH technical team from data reported in the article*
*a. Time to clinical stability: based on feeding more than 50% of the required amount, the absence of vomiting, undisrupted sleep and SpO2≥92% for more than 10 h*
*b. This was an open trial: all children underwent daily clinical evaluations performed by a physiotherapist who was different from the one administering the treatment (performance and detection bias)*

*c. SMD calculation by NCC-WCH: SMD (95%CI) = -0.30 (-1.27 to 0.67). Very serious imprecision when 95% CI crosses two default MID~~Very Serious imprecision, based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*
*d. Clinical state measured by a general score made of three well-being items (feeding, vomiting and quality of sleep).*
*e. SMD calculation by NCC-WCH: SMD (95%CI) = -0.03 (-0.08 to -0.02). (Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID)~~No imprecision, based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*
*f. Change in respiratory state measured by a respiratory score made of seven items: respiratory rate, SpO2, presence and severity of retractions, adventitious respiratory sounds, presence of vesicular murmur, thoracic distension.*
*g. SMD calculation by NCC-WCH: SMD (95%CI) = -0.30 (-0.57 to -0.02). Serious imprecision, based on Cohen's effect size criteria of crossing -/+0.5 the line of effect. Serious imprecision when 95% CI crosses one default MID*
*h. SMD calculation by NCC-WCH: SMD (95%CI) = 0.00 (-0.35 to 0.35). (Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID)~~No imprecision, based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*
*i. SMD calculation by NCC-WCH: SMD (95%CI) = -0.40 (-1.16 to 0.36). ~~Serious~~Serious imprecision when 95% CI crosses one default MID. ~~s imprecision, based on Cohen's effect size criteria of crossing -/+0.5 the line of effect.~~*

**Table 29~~28~~: GRADE profile for comparison of chest percussion in 5 drainage positions + assisted cough + oropharyngeal suction with no intervention**

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Clinical score [a]** | | | | | | | | | | | |
| **After 1 day** | | | | | | | | | | | |
| 1. Webb et al., 1985 | Median (range) = 7 (2-24) N = 42 | Median (range) = 10 (2-27) N = 45 | NC | Ns | Very low | RCT | Very Serious [b] | None | Serious [c] | NA [d] | None |
| **After 2 days** | | | | | | | | | | | |
| 1. Webb et al., 1985 | Median (range) = 7 (2-21) N = 38 | Median (range) = 8 (2-17) N = 39 | NC | Ns | Very low | RCT | Very Serious [b] | None | Serious [c] | NA [d] | None |
| **After 3 days** | | | | | | | | | | | |
| 1. Webb et al., 1985 | Median (range) = 7 (3-28) N = 28 | Median (range) = 6 (2-21) N = 31 | NC | Ns | Very low | RCT | Very Serious [b] | None | Serious [c] | NA d | None |
| **After 4 days** | | | | | | | | | | | |
| 1. Webb et al., 1985 | Median (range) = 4 (2-18) N = 16 | Median (range) = 6 (2-17) N = 21 | NC | Ns | Very low | RCT | Very Serious [b] | None | Serious [c] | NA [d] | None |
| **After 5 days** | | | | | | | | | | | |
| 1. Webb et al., 1985 | Median (range) = 6 (3-10) N = 11 | Median (range) = 5 (1-11) N = 18 | NC | Ns | Very low | RCT | Very Serious [b] | None | Serious [c] | NA [d] | None |

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Length of stay, days** | | | | | | | | | | | |
| 1. Webb et al., 1985 | Median, (range) = 4 (2-11) N = 44 | Median, (range) = 14 (4-27) N = 46 | NC | Ns | Very low | RCT | Very Serious [b] | None | Serious [c] | NA [d] | None |
| **Total length of illness, days** | | | | | | | | | | | |
| 1. Webb et al., 1985 | Median, (range) = 13 (7-26) N = 44 | Median, (range) = 14 (4-27) N = 46 | NC | Ns | Very low | RCT | Very Serious [b] | None | Serious [c] | NA [d] | None |

*NA not applicable, NC not calculable, NR not reported, Ns non-significant, RCT randomised controlled trial, p-value, RR relative risk*
** Calculated by the NCC-WCH technical team from data reported in the article*
*a. Clinical score: a score of 0 to 3 was allocated for each of ten clinical signs (heart rate, respiratory rate, hyperinflation, use of respiratory muscles, recession, rhinitis, wheeze, cough, crepitations, and ronchi)*
*b. Selection bias: randomization method was not described, concealment of allocation was not reported; performance bias: blinding was reported not to be possible; attrition bias: a follow-up of two weeks has been described in the article, but data of such assessment are not reported. Also, 90 patients were analysed, but not clear how many were randomized and if there was attrition of patients; detection bias: unclear. Also, the study was downgraded because imprecision was not assessable (see footnote d).*
*c. children aged up to 15 months (the GDG has specified that it is likely that older children will not have bronchiolitis)*
*d. It was not possible to grade for imprecision due to lack of information (95%CI were not reported).*

# A.10 Antibiotics

**Table 30~~29~~: GRADE profile for oral antibiotics compared with placebo for bronchiolitis in children**

| Number of studies | Number of children | | Effect | | Quality | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Antibiotics | Placebo | Relative (95% confidence interval) | Absolute (95% confidence interval) | | | | | | | |
| **Durartion of cough** | | | | | | | | | | | |
| **Total duration of symptoms (days)** | | | | | | | | | | | |
| 1 study (Kneyber et al., 2008) | 4.94 ± 3.78 (n=32) | 4.62 ± 2.05 (n=39) | NC | MD 0.32 higher (1.14 lower to 1.78 higher) | Moderate | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | Serious[c] | Yes[a] |
| **Length of hospital stay (days)** | | | | | | | | | | | |
| 3 studies (Kabir et al., 2009; Kneyber et al., | - | - | NC | MD 0.01 [-0.97, 1.00] | Very low | Meta-analysis of RCT | no serious risk of bias | very serious [b] | no serious indirectness | serious[c] | Yes [d] |

| Number of studies | Number of children | | Effect | | Quality | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Antibiotics | Placebo | Relative (95% confidence interval) | Absolute (95% confidence interval) | | | | | | | |
| 2008; Pinto et al., et al, 2013)) | | | | | | | | | | | |
| **Change in O2 saturation** | | | | | | | | | | | |
| **Oxygen use** | | | | | | | | | | | |
| 1 study (Kneyber et al., 2008) | 20/32 (62.5%) | 31/39 (79.5%) | OR 0.43 (0.15 to 1.24) | 170 fewer per 1000 (from 427 fewer to 33 more) | Low | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | ~~S~~very ~~s~~erious[e] | none |
| **Duration of oxygen use (days)** | | | | | | | | | | | |
| 2 studies (Kneyber et al., 2008; Pinto et al., et al, 2013) | - | - | NC | MD -0.05 [-0.64, 0.55] | Moderate | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | ~~No serious imprecision~~None | Yes[g] |
| **Hospital admission rate** | | | | | | | | | | | |
| **PICU admission** | | | | | | | | | | | |
| 1 study (Kneyber et al., 2008) | 0/32 (0%) | 1/39 (2.6%) | OR 0.39 (0.02 to 10.03) | 15 fewer per 1000 (from 25 fewer to 183 more) | Low | RCT | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[e] | none |
| **Re-admission for wheezing within 6 months of discharge** | | | | | | | | | | | |
| 1 study (Tahan et al., 2007) | 1/12 (8.3%) | 4/9 (44.4%) | OR 0.11 (0.01 to 1.29) | 364 fewer per 1000 (from 437 fewer to 63 more) | Very low | RCT | very serious [f] | no serious inconsistency | no serious indirectness | very serious [e] | none |
| **Change in respiratory rate – not reported** | | | | | | | | | | | |
| **Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation – not reported** | | | | | | | | | | | |
| **Adverse events** | | | | | | | | | | | |
| **Mortality** | | | | | | | | | | | |
| 4 study (Field et al., 1966; Kneyber et al., 2008; Pinto et al., et al, 2013; Tahan et al., 2007) | - | - | - | No reported deaths | Low | RCT | very serious [f] | no serious inconsistency | no serious indirectness | ~~no serious imprecision~~None | none |

*NC not calculable, SD standard deviation, RCT randomised controlled trial, MD mean difference, OR odds ratio*

*a Cochrane review by Spurling included data from a second study (Tahan et al., 2007) was presented in forest plot but SD not reported so data not meta-analysed (mean for antibiotic group 9.54 (n=28), mean for placebo group 9.4 (n=24)). Unclear what "symptoms" were included in the outcome. Cochrane author confirmed that this is outcome data and not baseline data (as we suspected from study report); they had access to additional data from this trial.*
*b I2 = 78%*
*c Calculated on SMD (Serious imprecision when 95% CI crosses one default MID ~~SMD crosses line of no effect and large effect (+0.5)~~*
*d Cochrane review by Spurling included two studies excluded from this meta-analysis. One of the studies was underpowered to detect a difference in length of hospital stay. Data from a second study (Tahan et al., 2007 was presented in forest plot but SD not reported so the data does not contribute to pooled effect estimate (mean for antibiotic group was 2.13 (n=12), mean for placebo group = 3.67 (n=9))*
*e Very wide confidence intervalf Method of randomisation Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID and allocation concealment unclear. 9/30 ((30%) children randomised were excluded as they received corticosteroid therapy*
*f Information on death was not explicitly reported.*

**Table 31~~30~~: Oral or parenteral antibiotics compared with supportive treatment for bronchiolitis in children**

| Number of studies | Number of children | | Effect | | Quality | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Antibiotics | Placebo | Relative (95% confidence interval) | Absolute (95% confidence interval) | | | | | | | |
| Length of hospital stay (days) | | | | | | | | | | | |
| 1 study (Rasul et al., 2008) | 6.49 ± 1.32 (n=45) | 6.2 ± 1.4 (n=15) | NC | MD 0.29 higher (0.52 lower to 1.10 higher) | Low | RCT | serious[a] | no serious inconsistency | no serious indirectness | seriousb | none |
| **Change in O2 saturation** | | | | | | | | | | | |
| **Oxygen saturation (<96%) on day 3** | | | | | | | | | | | |
| 1 study (Mazumder et al., 2009) | 15/61 (24.6%) | 5/43 (11.6%) | OR 2.48 (0.83 to 7.44) | 130 more per 1000 (from 18 fewer to 378 more) | Very low | RCT | very serious[c] | no serious inconsistency | no serious indirectness | seriousf | none |
| **Oxygen saturation (<96%) on day 5** | | | | | | | | | | | |
| 1 study (Mazumder et al., 2009) | 5/61 (8.2%) | 2/43 (4.7%) | OR 1.83 (0.34 to 9.91) | 35 more per 1000 (from 30 fewer to 279 more) | Very low | RCT | very serious[c] | no serious inconsistency | no serious indirectness | very serious[d] | none |
| **Duration of cough** | | | | | | | | | | | |
| **Cough on day 3** | | | | | | | | | | | |
| 1 study (Rasul et al., 2008) | 10/45 (22.2%) | 4/15 (26.7%) | OR 0.79 (0.21 to 3.01) | 44 fewer per 1000 (from 196 fewer to 256 more) | Very low | RCT | serious[a] | no serious inconsistency | no serious indirectness | very serious[d] | none |
| **Cough on day 7** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Antibiotics | Placebo | Relative (95% confidence interval) | Absolute (95% confidence interval) | | | | | | | |
| 1 study (Kabir et al., 2009) | 19/198 (9.6%) | 3/97 (3.1%) | OR 3.33 (0.96 to 11.53) | 65 more per 1000 (from 1 fewer to 238 more) | Low | RCT | serious[e] | no serious inconsistency | no serious indirectness | serious[f] | none |
| **Hospital admission rate - not reported** | | | | | | | | | | | |
| **Change in Respiratory rate – not reported** | | | | | | | | | | | |
| **Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation - not reported** | | | | | | | | | | | |
| **Adverse events** | | | | | | | | | | | |
| **Mortality** | | | | | | | | | | | |
| 1 study (Rasul et al., 2008; Kabir et al., 2009) | - | - | - | No reported deaths | Very low | RCT | very seriousg | no serious inconsistency | no serious indirectness | ~~none~~NC | none |

*NC not calculable, RCT randomised controlled trial, MD mean difference, OR odds ratio*
*a Unclear whether participants, clinicians or outcome assessors were blinded to intervention and unclear whether any children were withdrawn from the trial due to deterioration in condition*
*b Calculated on SMD (Serious imprecision when 95% CI crosses one default MID)~~Confidence interval larger than half of combined SD~~*
*c Inadequate method of randomisation, unclear method of allocation concealment, blinding and losses to follow up not reported*
*d Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID. ~~Very wide confidence interval~~*
*e Unclear allocation concealment, blinding not reported, Cochrane review authors assessed study as being at high risk of reporting bias (selective reporting)*
*f Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.~~Wide confidence interval~~*
*g Information on death was not explicitly reported.*

# A.11 Hypertonic saline

**Table 32~~31~~: GRADE profile for comparison of hypertonic saline (HS) (and bronchodilators) with 0.9% saline (and bronchodilators) in all settings**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention Hypertonic saline (HS) | Comparator 0.9% Normal saline (NS) | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Hospital admission rate** | | | | | | | | | | | |
| **All concentrations HS vs. 0.9% NS** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention Hypertonic saline (HS) | Comparator 0.9% Normal saline (NS) | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 8 (Anil et al., 2010; Grewal et al., 2009; Ipek et al., 2011; Kuzik et al., 2010; Sarrell et al., 2002; Jacobs et al., 2014; Florin et al., 2014; Wu et al., 2014) | 123/486 | 156/460 | RR 0.79 (0.66, 0.95) * | - | Very low | RCT | Very serious a, b, c, d, e, r, s, t | Serious u | Serious g, h, i, j, k, v, w, x | Serious y | Yes l, m, n, o, p, q, z, aa, ab |
| **Hospital readmission rate** | | | | | | | | | | | |
| **HS~~hypertonic saline~~ vs. 0.9% saline** | | | | | | | | | | | |
| 3 (Anil et al., 2010; Al-Ansari et al., 2010; Grewal et al., 2009) | 32/213 | 22/153 | RR = 1.04 (0.62, 1.76) * | - | Very low | RCT | Serious a, e, ac | None aj | Serious g, k, af | Very ~~S~~serious ag | Yes m, o, ah, ai, aj |
| **Length of stay** | | | | | | | | | | | |
| **All concentrations HS vs. 0.9% NS** | | | | | | | | | | | |
| 10 (Al-Ansari et al., 2010; Del Giudice et al., 2012; Kuzik et al., 2007; Luo et al., 2010; Luo et al., 2011; Mandelberg et al., 2003; Tal et al., 2006; Wu et al., 2014; Sharma et al., 2013; | 607 | 558 | - | SMD -0.45 (-0.71, -0.19) * | Very low | RCT | Very serious ac, al, am, an, ao, ap, t, a~~k~~v, r | Very serious a~~w~~v | Very serious af, aq, ar, as, at, v, x, a~~y~~z | Serious ad | Yes o, p ,ai, av, au, ak, z, ae |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention Hypertonic saline (HS) | Comparator 0.9% Normal saline (NS) | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| Jacobs et al., 2014) | | | | | | | | | | | |
| **Disease severity score at 60 minutes (increased severity indicated by higher values)** | | | | | | | | | | | |
| **All concentrations HS vs. 0.9% NS** | | | | | | | | | | | |
| 4 (Anil et al., 2010; Ipek et al., 2011; Kuzik et al., 2010; Florin et al., 2014) | 191 | 186 | - | SMD 0.11 (-0.21 to 0.43) * | Very low | RCT | Very serious b, e, c, s | Serious ~~bb~~av | Serious h, i, k, w | None ~~au, bq~~ | Yes m, n, p, ah, aa |
| **Disease severity score at 120 minutes (increased severity indicated by higher values)** | | | | | | | | | | | |
| **3% ~~hypertonic saline vs~~HS. 0.9% saline** | | | | | | | | | | | |
| 2 (Anil et al., 2010; Gewal et al., 2009) | 98 | 97 | - | SMD 0.31 (-0.21, 0.83) * | Very low | RCT | Serious a, e | Serious ~~bc, bd~~ba | Serious g, k | Serious ~~aw, be~~bb | Yes m, o, aj |
| **Disease severity score at 24 hours/1 day (increased severity indicated by higher values)** | | | | | | | | | | | |
| **All concentrations HS vs. 0.9% NS** | | | | | | | | | | | |
| 7 (Al-Ansari et al., 2010; Del Giudice et al., 2012; Luo et al., 2010; Luo et al., 2011; Mandelberg et al., 2003; Tal et al., 2006; Jacobs et al., 2014) | 374 | 302 | - | SMD -0.51 (-0.83, -0.19) * | Very low | RCT | Very serious ac, al, am, an, ao, ap, r | Very serious b~~cf~~ | Serious or more af, aq, ar, as, v | None ~~ba~~ | Yes o, p, ai, ~~av~~au, ~~bc~~az, z, ak |
| **Respiratory rate** | | | | | | | | | | | |
| **All concentrations HS vs. 0.9% NS** | | | | | | | | | | | |
| 2 (Ipek et al., 2011; Florin et al., 2014) | 91 | 91 | - | SMD 0.10 (-0.47 to 0.67) * | Very low | RCT | Serious b, s | Very serious ~~bh~~be | Serious h, w | Serious bi | Yes n, ~~bg~~bd, aa |
| **02 saturation (improvement indicated by higher values)** | | | | | | | | | | | |
| **60 minutes, 3% ~~hypertonic saline~~HS vs. 0.9% saline** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention Hypertonic saline (HS) | Comparator 0.9% Normal saline (NS) | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 2 (Anil et al., 2010; Ipek et al., 2011) | 135 | 134 | - | SMD 0.00 (-0.24, 0.24)* | Low | RCT | Serious b, e | None f | Serious h, k | None ~~aw, ba~~ | Yes m, n, ah |
| **120 minutes, 3% ~~hypertonic saline~~HS vs. 0.9% saline** | | | | | | | | | | | |
| 2 (Anil et al., 2010; Grewal et al., 2009) | 98 | 97 | - | SMD -0.22 (-0.50, 0.06)* | Low | RCT | None a, e | None f | Serious g, k | Serious aw, bc | Yes m, o, ah |
| **Need for mechanical ventilation** | | | | | | | | | | | |
| 1 (Mandelberg et al., 2003) | 0/27 | 2/26 | RR 0.19 (0.01, 3.84) | - | Very low | RCT | Serious al | NA | Serious ar | Very serious ag | Yes o, bj |
| **Need for tube feeding** | | | | | | | | | | | |
| **3% ~~Hypertonic Saline~~HS vs. 0.9% Normal Saline** | | | | | | | | | | | |
| 1. Teunissen et al., 2014 | 29/84 | 22/80 | - | RR = 1.26 (0.79, 1.99) * | Low | RCT | Serious bk | NA | Serious bl | Serious bm | Yes bn |
| **6% ~~Hypertonic Saline~~HS vs. 0.9% Normal Saline** | | | | | | | | | | | |
| 1. Teunissen et al., 2014 | 31/86 | 22/80 | - | RR = 1.31 (0.83, 2.06) * | Low | RCT | Serious bk | NA | Serious bl | Serious bm | Yes bo |
| **Adverse effects** | | | | | | | | | | | |
| 1 (Grewal et al., 2012) | 4/23 (3 vomiting, 1 diarrhoea) | 0/23 | RR 9.00 (0.51, 158.17) * | - | Very low | RCT | None a | None | Serious g | Very serious ag | Yes o, ah |

*RCT randomised controlled trial, RR relative risk, SMD standard mean difference, NA not applicable.*
** Calculated by the NCC-WCH technical team from data reported in the article*

*a Grewal et al., 2009 - Restricted recruitment times, usually 4pm to 2am when research assistant available (included infants with mild to moderate bronchiolitis presented to the emergency department)*
*b Ipek et al., 2011 - Randomisation unclear (assigned to one of four groups according to consecutive order of admission). Blinding unclear (only study physician described as blinded)*
*c Kuzik et al., 2010 - Longer duration of illness before presentation in NS group p=0.06*
*d Sarrell et al., 2002 - Randomisation not described (Cochrane reports randomisation in blocks of 4 using an online randomiser). Inclusion criteria unclear. Five patients hospitalised and excluded*

*e Anil et al., 2010 - Enrollment between 8am and 5pm in the emergency department (severe cases may present outside of these hours). Randomisation unclear (random number table generated by a computer). Four infants from HS group did not complete RDAI scoring*
*f I2=0 (0-40% represents no heterogeneity)*
*g Grewal et al., 2009 - Additional interventions and second dose of study drug at physician's discretion (second dose received by 13 HS group patients and 11 NS group patients)*
*h Ipek et al., 2011 - Additional corticosteroid administration (group 1: 8[26.7%], group 2: 7[23.3%], group 3: 7[23.3%], group 4: 11[37.7%]) when clinical score deteriorated and/or arterial oxygen saturation detected <85% on room air after treatment*
*I Kuzik et al., 2010 - Included infants presented to the emergency department with moderately severe viral bronchiolitis, 38 out of 88 infants had a previous history of wheezing. Data from the subgroup containing infants without a previous history of wheeze is presented here. Patients received supplemental oxygen if necessary*
*j Sarrell 2002 - Excluding infants with oxygen saturation <96% in room air appears restrictive*
*k Anil et al., 2010 - Additional treatments included oxygen to maintain 90-92%, nasal suction if nose blocked and antipyretics to stabilise if necessary*
*l. All of the studies were performed in the emergency department, except Sarrell et al., 2002 which was performed in an outpatient setting*
*m. Anil et al., 2010 – 5 groups: hypertonic 3% saline & salbutamol vs. normal 0.9% saline & salbutamol vs. hypertonic 3% saline & epinephrine vs. normal 0.9% saline & epinephrine vs normal 0.9% saline*
*n. Ipek et al., 2011 – 4 groups: hypertonic 3% saline & salbutamol vs. normal 0.9% saline & salbutamol vs. hypertonic 3% saline vs. normal 0.9% saline*
*o. Hypertonic 3% saline & epinephrine vs. normal 0.9% saline & epinephrine: Grewal et al., 2009; Mandelberg et al., 2003; Del Giudice et al., 2012; Tal et al., 2006*
*p. Hypertonic 3% saline & salbutamol vs. normal 0.9% saline & salbutamol: Kuzik et al., 2010; Luo et al., 2010*
*q. Sarrell et al., 2002 - hypertonic 3% saline & terbutaline vs. normal 0.9% saline & terbutaline*
*r. Jacobs et al., 2014 – groups statically different at baseline with regards to family history of atopy; the study reported that any co-interventions were at the discretion of the clinician, but no data are reported that specify the different treatments received by the groups.*
*s. Florin et al., 2014 – additional therapies were requested at the discretion of the study physician, but not recorded nor specified in the study; patients with risk factors for more severe bronchiolitis were excluded from the study.*
*t. Wu et al., 2014 – an additional 39 patients were enrolled after admission and not included in the analysis, however they have been included in the descriptive analysis and no reason nor explanation has been provided in the article; not reported whether investigators were kept blind to important confounding and prognostic factors; "medical readiness" was used as a criterion for discharge; admission and discharge were at discretion of the attending physician; the study failed to achieve the planned sample size; children with risk factors for severe bronchiolitis were excluded from the study.*
*u. I2 = 43% (41-69% may represent substantial heterogeneity)*
*v. Jacobs et al., 2014 – children aged up to 18 months; those with risk factors for severe bronchiolitis were excluded.*
*w. Florin et al., 2014 – children aged 2-24 months (the GDG has specified that it is likely that older children will not have bronchiolitis).*
*x. Wu et al., 2014 – children aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis).*
*y. Serious imprecision when 95% CI crosses one default MID.~~Wide 95% CI crossing +/-0.25 around the line of no effect.~~*
*z. Jacobs et al., 2014 – 7% HS and racemic epinephrine vs. 0.9% NS and racemic epinephrine.*
*aa. Florin et al., 2014 – 3% HS and albuterol vs. 0.9% NS and albuterol.*
*ab. Wu et al., 2014 – 3% HS and albuterol vs. 0.9% NS and albuterol.*
*ac. Al-Ansari et al., 2010 - Discharge frequently determined by social factors, such as availability and consensus of family members. Three infants were lost to follow-up after discharge, two in the HS group and one in the NS group*
*ad. Wide 95% CI crossing +/-0.50 around the line of no effect.*
*ae. Al-Ansari et al., 2010 readmission within 2 days, Anil et al., 2010 short-stay readmission, Grewal et al., 2009 returns to the emergency department*
*af. Al-Ansari et al., 2010 - Additional treatments at discretion of physician included nebulised epinephrine 5ml and supplementary oxygen*
*ag. Very serious imprecision when 95% CI crosses two default MID.~~Wide confidence intervals crossing +/-0.25 around the line of no effect~~*
*ah. Emergency department setting*
*ai. Al-Ansari et al., 2010 – hypertonic 3% saline & epinephrine vs. normal 0.9% saline & epinephrine*
*aj. I 2 = 0% (0-40% represents no heterogeneity)*
*ak. Al-Ansari et al., 2010 B - hypertonic 5% saline & epinephrine vs. 0.9% normal saline and epinephrine.*

*al. Mandelberg et al., 2003 - Randomisation unclear (Cochrane report randomisation in block of 4 using online randomiser). Results presented in figures (values taken from Cochrane)*
*am. Del Giudice et al., 2012 - Randomisation unclear (computer based randomisation programme)*
*an. Luo et al., 2010 - Randomisation unclear (infants recruited were assigned to a treatment group or a control group)*
*ao. Luo et al., 2011 - Seven patients from each group discharged within 12 hours after enrolment*
*ap. Tal et al., 2006 - Randomisation not described (Cochrane report randomisation in block of 4 using online randomiser)*
*aq. Luo et al., 2010 and Luo et al., 2011 - Patients received supportive and comprehensive treatments including sputum aspiration, water electrolyte balance maintenance and oxygen therapy*
*ar. Mandelberg et al., 2003 - Mean doses of add-on inhalation epinephrine in 0.9% saline solution needed per day: NS group 1.2 SD 0.9, HS group 0.9 SD 0.7*
*as. Tal et al., 2006 - Add-on inhalation treatments of epinephrine in 0.9% saline solution. Discharge criteria suggests supplementary oxygen and intravenous fluids may be provided*
*at. Kuzik et al., 2007 - Many additional treatments (albuterol, racemic epinephrine and steroids) at discretion of physician, treatment at SKMC was more likely to include antibiotics (p=0.002) as well as the addition of racemic epinephrine to the inhaled study solution (p=0.003)*
*~~au. Cohen's interpretation of effect size: 0.2 small, 0.5 moderate, 0.8 large~~*
*~~av~~au. All studies performed in an inpatient setting, except Al-Ansari which was performed in the emergency department*
*~~aw. Hypertonic 3% saline vs. normal 0.9% saline: Kuzik et al., 2007; Luo et al., 2011~~*
*~~ax~~av. Sharma et al., 2013 – missing data for 2 patients and no explanation provided; no mention of important confounding factors nor blinding to those prognostic factors is reported; no information provided for additional treatments; patients with risk factors for severe bronchiolitis have been excluded; figures and p-values for secondary outcomes not reported.*
*Aw . I2=78% (70-100% may represent considerable heterogeneity).*
*Ax . Sharma et al., 2013 – children aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis).*
*Ay .I2=60% (41-69% may represent substantial heterogeneity).*
*Az . Grewal et al., 2009 and Kuzik et al., 2010 use RACS which have the same relative effect but in the opposite direction, the remaining studies use Wang.*
*Ba . I2=69% (41-69% may represent substantial heterogeneity).*
*Bb . Serious imprecision when 95% CI crosses one default MID; Very serious imprecision when 95% CI crosses two default MID..*
*Bc . I2=74% (70-100% may represent considerable heterogeneity).*
*Bd . Ipek et al., 2011 – performed in an emergency department setting.*
*Be . I2=73% (70-100% may represent considerable heterogeneity).*
*Bf . Serious imprecision when 95% CI crosses one default MID; Very serious imprecision when 95% CI crosses two default MID.Bg . Mandelberg et al., 2003 – performed in an inpatient setting.*
*Bh . Teunissen et al., 2014 – the study didn't report how the randomisation sequence was prepared and concealment of allocation was unclear.*
*Bi . Teunissen et al., 2014 – patients aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis).*
*Bj . Serious imprecision when 95% CI crosses one default MID.*
*Bk . Teunissen et al., 2014 – 3% HS and salbutamol vs. 0.9% NS and salbutamol.*
*~~ay. I2=78% (70-100% may represent considerable heterogeneity).~~*
*~~az. Sharma et al., 2013 – children aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis).~~*
*~~ba. Confidence intervals do not cross the line of no effect.~~*
*~~bb. I2=60% (41-69% may represent substantial heterogeneity).~~*
*~~bc. Grewal et al., 2009 and Kuzik et al., 2010 use RACS which have the same relative effect but in the opposite direction, the remaining studies use Wang.~~*
*~~bd. I2=69% (41-69% may represent substantial heterogeneity).~~*
*~~be. Wide confidence intervals crossing the line of no effect and +0.5.~~*
*~~bf. I2=74% (70-100% may represent considerable heterogeneity).~~*
*~~bg. Ipek et al., 2011 – performed in an emergency department setting.~~*
*~~bh. I2=73% (70-100% may represent considerable heterogeneity).~~*
*~~bi. Wide 95% CI crossing +/-0.25 around the line of no effect.~~*

~~*bj. Mandelberg et al., 2003 – performed in an inpatient setting.*~~
~~*bk. Teunissen et al., 2014 – the study didn't report how the randomisation sequence was prepared and concealment of allocation was unclear.*~~
~~*bl. Teunissen et al., 2014 – patients aged up to 24 months (the GDG has specified that it is likely that older children will not have bronchiolitis).*~~
~~*bm. Wide 95% CI crossing +/-0.25 around the line of no effect.*~~
~~*bn. Teunissen et al., 2014 – 3% HS and salbutamol vs. 0.9% NS and salbutamol.*~~

**Table 33~~32~~: GRADE profile for comparison of hypertonic saline (HS) with usual care.**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention 3%Hypertonic saline | Comparator Usual care | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Length of stay** | | | | | | | | | | | |
| **Time to fit for discharge (hours) a** | | | | | | | | | | | |
| 1 Everard M.L. et al., 2014 | XXX ~~XXXMean (SD) = 90.4 (73.2)~~ | XXX ~~XXXMean (SD) = 88.9 (67.9)~~ | XXX ~~XXXMD = 1.50 (-14.74, 17.74)~~ * | - | Moderate | RCT | Serious [b] | n/a | None | Very Serious [c] | None |
| **Time to actual discharge (hours)** | | | | | | | | | | | |
| 1 Everard M.L. et al., 2014 | Mean (SD) = 100.6 (76.9) | Mean (SD) = 101.3 (84.4) | MD = -0.70 (-19.24, 17.84) * | - | Moderate | RCT | Serious [b] | n/a | None | Very serious [c] | None |

*RCT randomised controlled trial, RR relative risk, MD mean difference, SD standard deviation, NA not applicable.*
** Calculated by the NCC-WCH technical team from data reported in the article*

*a. The time until the infant was assessed as being to "fit for discharge" which was defined as point at which the infant was feeding adequately (taking >755 of usual intake), and had been in air with a saturation of at least 92% for 6 hours.*
*b. Detection bias: blinding was not possible for investigators; Performance bias: the study is not blinded.*
*c. Very serious imprecision when 95% CI crosses two default MID.~~Wide confidence intervals crossing +/-0.5 around the line of no effect.~~*

# A.12 Inhaled bronchodilator therapy

**Table 34~~33~~: GRADE profile for comparison of epinephrine with placebo**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Epinephrine | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Hospital admissions (outpatients)** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Epinephrine | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **At enrolment or less than 24 hours** | | | | | | | | | | | |
| 3studies (Anil et al., 2010 3%* saline;; Khashabi et al 2005; Plint et al., 2009) | 38/261 (14.6%) | 54/262 (20.6%) | RR: 0.66 (0.37 to 1.16) [a] | - | Very low | RCT | Very serious[b] | None | None | Serious[c] | None |
| **Readmission in 2 days** | | | | | | | | | | | |
| 1 (Anil et al., 2010) 0.9%** saline and 3%* saline | 12/77 (15.6%) | 12/74 (16.2%) | RR: 0.97 (0.46 to 2.02)a | - | Low | RCT | None | None | None | Very serious [d] | None |
| **By day 7** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 47/198 (23.7%) | 53/201 (26.4%) | RR: 0.90 (0.64 to 1.26)[a] | - | Very low | RCT | None | None | Serious[f] | Very serious[d] | None |
| **By day 22** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 50/198 (25.3%) | 54/201 (26.9%) | RR: 0.94 (0.68 to 1.31)[a] | - | Very low | RCT | None | None | Serious[f] | Very serious[d] | None |
| **Hospital readmissions (inpatients)** | | | | | | | | | | | |
| **Within one month after discharge** | | | | | | | | | | | |
| 1 (Wainwright et al., 2003) | 1/99 (1.0%) | 2/95 (2.1%) | RR: 0.48 (0.04 to 5.20)[a] | - | Very low | RCT | None | None | Serious[g] | Very serious[d] | None |
| **Length of stay in hours (outpatients)** | | | | | | | | | | | |
| **Reported as time to discharge – time between the triage time at enrolment visit and the time of discharge from the last emergency department visit or the last hospitalisation for each patient within the next 7 days** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | N = 198 Median (Interquartile range): 4.9 (3.7 to 9.6) | n=200 Median (Interquartile range): 5.3 (3.8 to 21) | - | p=0.94[h] | Moderate | RCT | None | None | Seriousg | ~~NA~~NC | None |
| **Length of hospital stay in hours (inpatients)** | | | | | | | | | | | |
| 1 (Skjerven et al., 2013) | n=203 Mean (range): 78.7 (69.2 to 88.1) | n=201 Mean (range): 81.8 (72.6 to 91.0) | - | p=0.43 [h] | Moderate | RCT | Serious[i] | None | None | ~~NA~~NC | None |
| 1 (Patel et al., 2002) | n=50 Mean (SD): 59.8 (62) | n=48 Mean (SD): 63.3 (47) | - | MD (95%CI): -3.50 (-25.23 to 18.23)a | Moderate | RCT | Serious[i] | None | None | None | None |

| | Number of children | | Effect | | | | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Epinephrine** | **Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** | **Quality** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| 1 (Wainwright et al., 2003) | n=99 Mean (95%CI): 58.8 (49.4 to 70.0) | n=95 Mean (95%CI): 69.5 (59.3 to 81.4) | Ratio of means (95%CI): 0.85 (0.67 to 1.07)[i] | p=0.16i | Low | RCT | None | None | Serious[g] | Serious[c] | None |
| **Change in respiratory rate (outpatients)** | | | | | | | | | | | |
| **At 30 minutes** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=198 Mean (SD): -1.35 (8.53) | n=200 Mean (SD): -0.59 (8.34) | - | MD (95%CI): -0.76 (-2.42 to 0.90)a | High | RCT | None | None | None | None | None |
| **At 60 minutes** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=198 Mean (SD): -3.68 (8.89) | n=200 Mean (SD): -2.88 (10.2) | - | MD (95%CI): -0.80 (-2.68 to 1.08)a | High | RCT | None | None | None | None | None |
| **After treatment (endpoint, time point not reported)** | | | | | | | | | | | |
| 1 (Khashabi et al., 2005) | n=24 Mean (SD): 37.7 (7.7) | n=24 Mean (SD): 45.8 (7.7) | - | MD (95%CI): -8.10 (-12.46 to -3.74)[a] | Moderate | RCT | Serious [b] | None | None | None | None |
| **Change in disease severity score (outpatients)** | | | | | | | | | | | |
| **At 30 minutes** | | | | | | | | | | | |
| 2 studies (Plint et al., 2009; Anil et al., 2010 0.9%** saline, 3%* saline*) | n=275 | n=274 | - | SMD (95%CI): 0.09 (-0.29 to 0.48)[a] | Low | RCT | None | Very serious [l] | None | None | None |
| **At 60 minutes** | | | | | | | | | | | |
| 2 studies (Plint et al., 2009;; Anil et al., 2010 0.9%** saline, 3%* saline) | n=275 | n=274 | - | SMD (95%CI): -0.05 (-0.43 to 0.33) [a] | Very low | RCT | Very serious | Serious [m] | None | None | None |
| **At 120 minutes** | | | | | | | | | | | |
| 1 studies (Anil et al., 2010 0.9%** saline, 3%* saline) | n=92 | n=89 | - | MD (95%CI): 0.09 (-0.50 to 0.68)[a] | Very low | RCT | Very serious | Very serious [o] | None | Serious [p] | None |
| **After treatment (endpoint, time point not reported)** | | | | | | | | | | | |
| 1 (Khashabi et al., 2005) | n=24 Mean (SD): 4.9 (4) | n=24 Mean (SD): 7.9 (5.2) | - | MD (95%CI): -3.00 (-5.62 to -0.38)[a] | Moderate | RCT | Serious [b] | None | None | None | None |
| **Change in disease severity score (inpatients)** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Epinephrine | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **At 30 minutes** | | | | | | | | | | | |
| 1 (Wainwright et al., 2003) | NR | NR | - | p=0.04 (the epinephrine group had a lower respiratory-effort score than the placebo group)i | Low | RCT | Serious[k] | None | Serious[g] | ~~NA~~NC | None |
| **At 60 minutes (endpoint)** | | | | | | | | | | | |
| 1 (Wainwright et al., 2003) | n=99 Mean (95%CI): 2.44 (1.97 to 2.92) | n=95 Mean (95%CI): 3.35 (2.78 to 3.91) | - | p=0.02 | Moderate | RCT | None | None | Serious[g] | ~~NA~~NC | None |
| **Change in oxygen saturation (outpatients)** | | | | | | | | | | | |
| **At 30 minutes** | | | | | | | | | | | |
| 2 studies (Plint et al., 2009; Anil et al., 2010 0.9%** saline, 3%* saline) | n=275 | n=274 | - | SMD (95%CI): 0.12 (-0.05 to 0.29)[a] | High | RCT | None | None | None | None | None |
| **At 60 minutes** | | | | | | | | | | | |
| 2 studies (Plint et al., 2009; Anil et al., 2010 0.9%** saline, 3%* saline) | n=275 | n=274 | - | SMD (95%CI): 0.19 (0.01 to 0.38))[a] | Very low | RCT | Very serious | Serious[m] | None | None | None |
| **At 120 minutes** | | | | | | | | | | | |
| 1 studies ( Anil et al., 2010 0.9%** saline, 3%* saline) | n=77 | n=74 | - | SMD: -0.08 (-0.40 to 0.24) [a] | Very low | RCT | Very serious | Serious[n] | None | Serious [p] | None |
| **After treatment (endpoint, time point not reported)** | | | | | | | | | | | |
| 1 (Khashabi et al., 2005) | n=24 Mean (SD): 91.9 (3.5) | n=24 Mean (SD): 88.8 (3.9) | - | MD (95%CI): 3.10 (1.00 to 5.20) [a] | Moderate | RCT | Serious [b] | None | None | None | None |
| **Need for high flow humidified oxygen, CPAP or mechanical ventilation (inpatients)** | | | | | | | | | | | |
| **Reported as number requiring supplemental oxygen** | | | | | | | | | | | |
| 2 studies (Skjerven et al., 2013; Wainwright et al., 2003) | 132/291 (45.4%) | 121/284 (42.6%) | RR (95%CI): 1.07 | - | Very low | RCT | Serious[i] | None | Serious[g] | Serious[e] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Epinephrine | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| | | | (0.86 to 1.34)[a] | | | | | | | | |
| **Reported as number requiring ventilatory support** | | | | | | | | | | | |
| 1 (Skjerven et al., 2013) | 15/203 (7.4%) | 15/201 (7.5%) | RR (95%CI): 0.99 (0.50 to 1.97)[a] | - | Very low | RCT | Serious[i] | None | None | Very serious[d] | None |
| **Need for/use of feeding support (inpatients)** | | | | | | | | | | | |
| **Reported as number requiring oxygen and intravenous feeding** | | | | | | | | | | | |
| 1 (Wainwright et al., 2003) | 13/99 (13.1%) | 24/95 (25.3%) | RR (95% CI): 0.52 (0.28 to 0.96)[a] | - | Moderate | RCT | None | None | Serious [g] | None | None |
| **Reported as number requiring nasogastric tube feeding** | | | | | | | | | | | |
| 1 (Skjerven et al., 2013) | 57/201 (28.4%) | 59/199 (29.6%) | RR (95%CI): 0.96 (0.70 to 1.30)[a] | - | Very low | RCT | Serious[i] | None | None | Very serious[d] | None |
| **Need for/use of feeding support (outpatients)** | | | | | | | | | | | |
| **Reported as time to return to normal feeding in days** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=198 Median (interquartile range): 0.5 (0.2 to 1.2) | n=200 Median (interquartile range): 0.9 (0.3 to 2.1) | Mean ratio (95%CI): 0.60 (0.47 to 0.76)[h] | - | Moderate | RCT | None | None | Serious [f] | None | None |
| **Adverse events (outpatients)** | | | | | | | | | | | |
| **Tremor** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 4/198 | 2/201 | RR (95%CI): 2.03 (0.38 to 10.96)[a] | - | Very low | RCT | None | None | Serious[f] | Very serious[d] | None |
| **Pallor** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 22/198 | 16/201 | RR (95%CI): 1.40 | - | Low | RCT | None | None | Serious[f] | Serious[e] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Epinephrine | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| | | | (0.76 to 2.58)[a] | | | | | | | | |
| **Vomiting** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 4/198 | 3/201 | RR (95%CI): 1.35 (0.31 to 5.97)[a] | - | Very low | RCT | None | None | Serious [f,d] | Very serious[f] | None |
| **Varicella** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 0/198 | 0/201 | NC | - | Moderate | RCT | None | None | Serious[f] | ~~NA~~NC | None |
| **Dark stools** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 14/198 | 16/201 | RR (95%CI): 0.89 (0.45 to 1.77)[a] | - | Very low | RCT | None | None | Serious[f] | Very serious[d] | None |
| **Hypertension** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 1/198 | 0/201 | RR (95%CI): 3.05 (0.12 to 74.31)[a] | - | Very low | RCT | None | None | Serious[f] | Very serious[d] | None |
| **Hyperkalaemia** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 0/198 | 0/201 | NC | - | Moderate | RCT | None | None | Serious [f] | ~~NA~~NC | None |

*NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, p-value, RR relative risk*
** Inhalation of epinephrine, 1.5mg, diluted to 4ml with 3% saline solution*
*** Inhalation of epinephrine, 1.5mg, diluted to 4ml with 0.9% saline solution*
*a Calculated by the NCC-WCH technical team from data reported in the article*
*b Khashabi: method of randomisation not described.*
*c Serious imprecision when 95% CI crosses one default MID.*
*~~Wide confidence intervals crossing -0.25 and no treatment effect~~*
*d Very serious imprecision when 95% CI crosses two default MID.~~Wide confidence intervals crossing both +/-0.25 around no treatment effect~~*
*e Very serious imprecision when 95% CI crosses two default MID.~~Wide confidence intervals crossing +0.25 and no treatment effect~~*
*f Plint: Physician allowed to provide cointerventions after 90 minutes*
*g Wainwright: additional treatments at physician's discretion – 2 subjects in the placebo group were treated with bronchodilators other than epinephrine when their condition failed to improve*
*h As reported in the study*
*i Skjerven: 321/404 complete d the study (reasons for withdrawals reported)*
*j Patel: 10 withdrawn during the study (reasons not provided)*

*k Wainwright: numbers in each group not reported*
*l High heterogeneity: I2=70%*
*m Serious heterogeneity: I2=64%*
*n Serious heterogeneity: I2=61%*
*o Serious heterogeneity: I2=67%*
*p Serious imprecision when 95% CI crosses one default MID.~~Wide confidence intervals crossing -0.5 and no treatment effect, based on Cohen's effect size criteria~~*
*~~q Wide confidence intervals crossing -/+0.5 and no treatment effect, based on Cohen's effect size criteria~~*

**Table 3534: GRADE profile for comparison of albuterol/salbutamol with placebo**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Albuterol/Salbutamol | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Hospital admissions (outpatients)** | | | | | | | | | | | |
| **At enrolment or <24 hours** | | | | | | | | | | | |
| 2 studies (; Anil et al., 2010 0.9%* saline; Khashabi et al., 2005) | 13/60 (21.7%) | 18/61 (29.5%) | RR (95% CI): 0.69 (0.44 to 1.09) )[a] | - | Very low | RCT | Very serious[b] | None | None | Serious[c] | None |
| **Readmission in 2 days** | | | | | | | | | | | |
| 1 (Anil et al., 2010) 0.9%* saline and 3%** saline | 10/71 (14.1%) | 12/74 (16.2%) | RR (95%CI): 0.87 (0.40 to 1.90)[a] | - | Low | RCT | None | None | None | Very serious[d] | None |
| **After treatment (time point not reported)** | | | | | | | | | | | |
| 4 studies (Gadomski et al., 1994b; Schuh et al., 1990; Ipek et al., 2011; Klassen et al., 1991) | 23/114 (20.2%) | 20/108 (18.5%) | RR (95%CI): 1.11 (0.65 to 1.89)[a] | - | Very low | RCT | Very serious[e, f, g, h,] | None | Serious[i, j, k] | Very serious[d] | None |
| **Length of hospital stay (inpatients)** | | | | | | | | | | | |
| 3 studies (Patel et al., 2002; Chowdhury et al., 1995; Karadag et al., 2008) | n=95 | n=82 | - | SMD (95%CI): -0.03 (-0.33 to 0.27)[a] | Moderate | RCT | Serious [g] | None | None | None | None |
| **Reported as % of patients discharged at 24, 48 and 72 hours** | | | | | | | | | | | |
| 1 (Dobson et al., 1998) | 24 hours: 0%<br>48 hours: 17.4%<br>72 hours: 52.2% | 24 hours: 0%<br>48 hours: 24.1%<br>72 hours: 69% | - | p=0.24 [m] | Moderate | RCT | Serious [n] | None | None | ~~NA~~NC | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Albuterol/Salbutamol | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Change in respiratory rate (outpatients)** | | | | | | | | | | | |
| **After dose 1 (% decrease)** | | | | | | | | | | | |
| 1 (Schuh et al., 1990) | n=21<br>Mean (SD): -16.2 (15) | n=19<br>Mean (SD): -15.5 (15) | - | p=NSn<br><br>MD (95%CI): -1.00(-10.31 to 8.31)[a] | Very low | RCT | Serious[e] | None | Serious[i] | Very serious[o] | None |
| **After dose 2 (% decrease)** | | | | | | | | | | | |
| 1 (Schuh et al., 1990) | n=21<br>Mean (SD): -19.6 (16) | n=19<br>Mean (SD): -8 (13) | - | p=0.015n<br><br>MD (95%CI): -12.00(-21 to -3)[a] | Low | RCT | Serious[e] | None | Serious[i] | None | None |
| **At 30 minutes** | | | | | | | | | | | |
| 3 studies (Gadomski et al., 1994 and Gadomski et al., 1994b; Klassen et al., 1991) | n=95 | n=91 | - | SMD (95%CI): -0.13 (-0.49 to 0.22)[a] | Moderate | RCT | Seriousg,[h] | None | None | None | None |
| **At 60 minutes** | | | | | | | | | | | |
| 3 studies (Gadomski et al., 1994 and Gadomski et al., 1994b; Klassen et al., 1991) | n=95 | n=91 | - | SMD (95%CI): -0.09 (-0.38 to 0.20)[a] | Moderate | RCT | Serious[f, g] | None | None | None | None |
| **Post-treatment (time point not reported)** | | | | | | | | | | | |
| 2 studies (Ipek et al., 2011; Khashabi et al., 2005) | n=54 | n=54 | - | MD (95%CI): -1.66 (-4.94 to 1.61)[a] | Very low | RCT | Seriousc[g] | None | Serious[k] | Serious[p] | None |
| **Change in respiratory rate (inpatients)** | | | | | | | | | | | |
| **30 minutes (% decrease)** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Albuterol/Salbutamol | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Chevallier et al., 1995) | n=16<br>Mean (SD): -10.4 (1.6) | n=17<br>Mean (SD): -4.7 (1.5) | - | MD (95%CI): -5.70 (-6.76 to -4.64)[a] | Moderate | RCT | Seriousr | None | None | None | None |
| **150 minutes (% decrease)** | | | | | | | | | | | |
| 1 (Chevallier et al., 1995) | n=16<br>Mean (SD): -20.9 (1.5) | n=17<br>Mean (SD): -12.1 (1.4) | - | MD (95%CI): -8.80 (-9.79 to -7.81)[a] | Moderate | RCT | Serious[q] | None | None | None | None |
| **After treatment (endpoint, time point not reported)** | | | | | | | | | | | |
| 1 (Totapally et al., 2002) | n=10<br>Mean (SD): 42 (10.7) | n=9<br>Mean (SD): 41 (10.8) | - | MD (95%CI): 1.00 (-8.68 to 10.68)[a] | Very low | RCT | Serious[r] | None | None | Very serious[o] | None |
| **Change in disease severity score (outpatients)** | | | | | | | | | | | |
| **At 30 minutes** | | | | | | | | | | | |
| 4 studies (Gadomski et al., 1994 and Gadomski et al., 1994b; Can et al., 1998; Anil et al., 2010 0.9%* saline, 3%** saline) | n=177 | n=176 | - | SMD (95%CI): 0.06 (-0.45 to 0.58)[a] | Very low | RCT | Very serious[f,s] | Very serious[u] | None | Serious[u] | None |
| **At 60 minutes** | | | | | | | | | | | |
| 4 studies (; Gadomski et al., 1994 and Gadomski et al., 1994b; Can et al., 1998; Anil et al., 2010 0.9%* saline, 3%** saline) | n=177 | n=176 | - | SMD (95% CI): -0.33 (-1.11 to 0.45) [a] | Very low | RCT | Very serious [f, s] | Very serious[y] | None | Serious[p] | None |
| **At 120 minutes** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Albuterol/Salbutamol | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 studies (; Anil et al., 2010; 0.9%* saline, 3%** saline) | n=72 | n=74 | - | MD: 0.12 (-0.66 to 0.90) )[a] | Very low | RCT | Very serious | Very serious[w] | None | Serious[p] | None |
| **Average clinical score after treatment (time point not reported)** | | | | | | | | | | | |
| 4 studies (Ralston et al., 2005; Ipek et al., 2011; Khashabi et al., 2005; Klassen et al., 1991) | n=119 | n=120 | - | SMD (95%CI): -0.32 (-0.57 to -0.06)[a] | Very low | RCT | Very serious[b, g, h] | None | Serious[k] | None | None |
| **Change in disease severity score (inpatients)** | | | | | | | | | | | |
| **Day 1 (endpoint)** | | | | | | | | | | | |
| 1 (Goh et al., 1997) | n=30 Mean (SD): 7.5 (2.1) | n=29 Mean (SD): 8 (2.5) | - | MD (95%CI): -0.5 (-1.68 to 0.68)[a] | Low | RCT | Serious[x] | None | None | Serious[p] | None |
| **Day 2 (endpoint)** | | | | | | | | | | | |
| 1 (Goh et al., 1997) | n=30 Mean (SD): 4.7 (2.2) | n=29 Mean (SD): 4.4 (2.4) | - | MD (95%CI): 0.30 (-0.88 to 1.48)[a] | Low | RCT | Serious[x] | None | None | Serious[u] | None |
| **Day 3 (endpoint)** | | | | | | | | | | | |
| 1 (Goh et al., 1997) | n=30 Mean (SD): 3 (1.5) | n=29 Mean (SD): 3.1 (1.8) | - | MD (95%CI): -0.10 (-0.95 to 0.75)[a] | Low | RCT | Serious[x] | None | None | Serious[p] | None |
| **Average clinical score after treatment** | | | | | | | | | | | |
| 3 studies (Totapally et al., 2002; Patel et al., 2002; Karadag et al., 2008) | n=85 | n=69 | - | SMD (95%CI): -0.27 (-0.86 to 0.32)[a] | Very low | RCT | Serious[l, r] | Serious | None | Serious[p] | None |
| **No improvement in clinical score (dichotomous)** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Albuterol/Salbutamol | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Lines et al., 1990) | 4/26 (15.4%) | 19/23 (8.3%) | RR (95%CI): 0.19 (0.07 to 0.47)[a] | - | Moderate | RCT | Serious[z] | None | None | None | None |
| **Change in oxygen saturation (outpatients)** | | | | | | | | | | | |
| **At 30 minutes** | | | | | | | | | | | |
| 4 studies (Gadomski et al., 1994 and Gadomski et al., 1994b; Klassen et al., 1991; Anil et al., 2010 0.9%* saline, 3%** saline) | n=167 | n=165 | - | SMD (95%CI): 0.17 (-0.05 to 0.39)[a] | Moderate | RCT | Serious[f, h] | None | None | None | None |
| **At 60 minutes** | | | | | | | | | | | |
| 5 studies (; Gadomski et al., 1994 and Gadomski et al., 1994b; Can et al., 1998; Klassen et al., 1991; Anil et al., 2010 0.9%* saline, 3%** saline) | n=219 | n=217 | - | SMD: 0.02 (-0.17 to 0.21) )[a] | Low | RCT | Very serious[f,k,s] | None | None | None | None |
| **At 120 minutes** | | | | | | | | | | | |
| 1 studies (; Anil et al., 2010 0.9%* saline, 3%** saline) | n=72 | n=74 | - | MD (95%CI): 0.20 (-0.23 to 0.63) a | Low | RCT | Very serious | None | None | None | None |
| **Average after treatment (time point not reported)** | | | | | | | | | | | |
| 3 studies (Ralston et al., 2005; Ipek et al., 2011; | n=77 | n=79 | - | MD (95%CI): 0.25 (-1.07 to 1.57)[a] | Low | RCT | Serious[b, g] | None | Serious[k] | None | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Albuterol/Salbutamol | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| Khashabi et al., 2005) | | | | | | | | | | | |
| **After dose 1 (change from baseline)** | | | | | | | | | | | |
| 1 (Schuh et al., 1990) | n=21<br>Mean (SD): 0.71 (1.4) | n=19<br>Mean (SD): -0.47 (1.3) | - | p=0.01i<br>MD (95%CI): 1.18 (0.34 to 2.02)a | Low | RCT | Serious [e] | None | Serious [i] | None | None |
| **After dose 2 (change from baseline)** | | | | | | | | | | | |
| 1 (Schuh et al., 1990) | n=21<br>Mean (SD): 0.76 (0.18) | n=19<br>Mean (SD): -0.79 (3.49) | - | p=0.015i<br>MD (95%CI): 1.55 (-0.02 to 3.12)a | Very low | RCT | Serious [e] | None | Serious [i] | Serious [u] | None |
| **Change in oxygen saturation (inpatients)** | | | | | | | | | | | |
| **30 minutes (change from baseline)** | | | | | | | | | | | |
| 1 (Chevallier et al., 1995) | n=16<br>Mean (SD): 1.3 (0.2) | n=17<br>Mean (SD): -0.9 (0.1) | - | MD (95%CI): 2.20 (2.09 to 2.31)a | Moderate | RCT | Serious [q] | None | None | None | None |
| **150 minutes (change from baseline)** | | | | | | | | | | | |
| 1 (Chevallier et al., 1995) | n=16<br>Mean (SD): 1.4 (0.3) | n=17<br>Mean (SD): -1.1 (0.2) | - | MD (95%CI): 2.50 (2.32 to 2.68)a | Moderate | RCT | Serious [q] | None | None | None | None |
| **At 24 hours (endpoint)** | | | | | | | | | | | |
| 1 (Dobson et al., 1998) | n=23<br>Mean (SD): 93.2 (7.83) | n=29<br>Mean (SD): 93.5 (6.04) | - | MD (95%CI): -0.30 (-4.18 to 3.58)a | Low | RCT | Serious [n] | None | None | Serious [p] | None |
| **After treatment (time point not reported)** | | | | | | | | | | | |
| 5 studies (Totapally et al., 2002; Patel et al., 2002; Lines et al., 1990; Karadag et | n=124 | n=100 | - | MD (95%CI): 0.43 (-1.55 to 2.41)a | Very low | RCT | Very serious [l, r, z, aa] | Very serious [ab] | None | Very serious [o] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Albuterol/Salbutamol | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| al., 2008; Ho et al., 1991) | | | | | | | | | | | |
| **Adverse events (outpatients)** | | | | | | | | | | | |
| **Flushing of the face at 60 minutes** | | | | | | | | | | | |
| 1 (Gadomski et al., 1994b) | 3/19 | 0/18 | RR (95%CI): 6.65 (0.37 to 120.36)a | - | Very low | RCT | Serious [f] | None | None | Very serious [d] | None |
| **Hyperactivity** | | | | | | | | | | | |
| 1 (Gadomski et al., 1994b) | 2/19 | 0/18 | RR (95%CI): 4.75 (0.24 to 92.65)a | - | Very low | RCT | Serious [f] | None | Serious [j] | Very serious [d] | None |
| **More coughing** | | | | | | | | | | | |
| 1 (Gadomski et al., 1994b) | 0/19 | 1/18 | RR (95%CI): 0.32 (0.01 to 7.30)a | - | Very low | RCT | Serious [f] | None | Serious [j] | Very serious [d] | None |
| **Tremor** | | | | | | | | | | | |
| 1 (Gadomski et al., 1994b) | 0/19 | 0/18 | NC | - | Low | RCT | Serious [f] | None | Serious [j] | NA | None |
| **Sustained heart rate >200 beats per minute for more than 30 minutes** | | | | | | | | | | | |
| 1 (Ralston et al., 2005) | 2/23 | 0/25 | RR (95%CI): 5.42 (0.27 to 107.20)a | - | Low | RCT | None | None | None | Very serious [d] | None |

*NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, p-value, RR relative risk*
** Inhalation of salbutamol 2.5mg diluted to 4ml with 0.9% saline solution*
*** Inhalation of salbutamol 2.5mg diluted to 4ml with 3% saline solution*
*a Calculated by the NCC-WCH technical team from data reported in the article b Khashabi: method of randomisation not described*
*c Serious imprecision when 95% CI crosses one default MID.*
*d Very serious imprecision when 95% CI crosses two default MID ~~e Wide confidence intervals crossing -0.25 around no treatment effect~~*
*~~d Wide confidence intervals crossing both +/-0.25 around no treatment effect~~*
*e Schuh: unclear definition of bronchiolitis*
*f Gadomski 1994b: 5 withdrawals (reasons explained)*
*g Ipek: randomisation according to consecutive order of admission*

*h Klassen: bronchiolitis not clearly defined*
*i Schuh: 4 subjects, 3/21 from albuterol group and 1/19 from placebo group received albuterol before arrival at the emergency department*
*j Gadomski: infants whose condition did not improve after 60 mins were given additional albuterol, time point of this measurement not reported*
*k Ipek: 26.7% and 37.7% (salbutamol, placebo respectively) received corticosteroid- the decision of corticosteroid use was made when clinical score deteriorated and/or arterial oxygen saturation detected <85%on room air after treatment*
*lPatel: 10 withdrawn during the study (reasons not provided)*
*m As reported in the study*
*n Dobson: Randomisation method not described, 6 subjects with incomplete outcome data (withdrawals explained)*
*o Very serious imprecision when 95% CI crosses two default MID. ~~Confidence interval of SMD crosses both +/-0.5 around no treatment effect, based on Cohen effect size criteria~~*
*p Serious imprecision when 95% CI crosses one default MID ~~Confidence interval of SMD crosses -0.5 and no treatment effect, based on Cohen effect size criteria~~*
*q Chevallier: randomisation method and allocation concealment not described in detail*
*r Small sample size*
*s Can: randomisation and concealment not described, unclear definition of bronchiolitis*
*t Very serious heterogeneity: I2 =82%*
*u Serious imprecision when 95% CI crosses one default MID. ~~Confidence interval of SMD crosses +0.5 and no treatment effect, based on Cohen effect size criteria.~~*
*vVery serious heterogeneity: I=90%*
*w Very serious heterogeneity: I2=78%*
*x Goh: Randomisation and concealment of allocation not described in detail*
*y I2=59%*
*z Lines: randomisation method not described, unclear definition of bronchiolitis*
*aa Ho: randomisation not described, unclear definition of bronchiolitis*
*ab Very serious heterogeneity: I=91%*

**Table 36~~35~~: GRADE profile for comparison of terbutaline with placebo**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Terbutaline | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| Length of stay (inpatients) | | | | | | | | | | | |
| 1 (Tinsa et al., 2009) | n=16 Mean (SD): 3.3 (1.99) | n=19 Mean (SD): 2.57 (1.99) | - | MD (95%CI): 0.73 (-0.58 to 2.04)[ja] | Moderate | RCT | None | None | None | Serious[b] | None |
| **Respiratory rate (inpatients)** | | | | | | | | | | | |
| **30 minutes (endpoint)** | | | | | | | | | | | |
| 1 (Tinsa et al., 2009) | n=16 Mean (SD): 54.2 (13.4) | n=19 Mean (SD): 59.8 (15.5) | - | MD (95%CI): -5.6 (-15.18 to 3.98)[a] | Moderate | RCT | None | None | None | Serious[c] | None |
| 60 minutes (endpoint) | | | | | | | | | | | |
| 1 (Tinsa et al., 2009) | n=16 Mean (SD): 54.3 (13.5) | n=19 Mean (SD): 56.1 (13.3) | - | MD (95%CI): -1.8 (-10.72 to 7.12)[ja] | Low | RCT | None | None | None | Very serious[d] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Terbutaline | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **120 minutes (endpoint)** | | | | | | | | | | | |
| 1 (Tinsa et al., 2009) | n=16 Mean (SD): 50.8 (12.8) | n=19 Mean (SD): 50 (9.6) | - | MD (95%CI): 0.80 (-6.81 to 8.41)[a] | Low | RCT | None | None | None | Very serious[d] | None |
| **Clinical score (inpatients)** | | | | | | | | | | | |
| **30 minutes (endpoint)** | | | | | | | | | | | |
| 1 (Tinsa et al., 2009) | n=16 Mean (SD): 6.73 (2.5) | n=19 Mean (SD): 6.5 (0.7) | - | MD (95%CI): 0.23 (-1.03 to 1.49)[a] | Low | RCT | None | None | None | Very serious[d] | None |
| **60 minutes (endpoint)** | | | | | | | | | | | |
| 1 (Tinsa et al., 2009) | n=16 Mean (SD): 6.05 (2.8) | n=19 Mean (SD): 5.5 (1) | - | MD (95%CI): 0.55 (-0.89 to 1.99)[a] | Moderate | RCT | None | None | None | Serious[b] | None |
| **120 minutes (endpoint)** | | | | | | | | | | | |
| 1 (Tinsa et al., 2009) | n=16 Mean (SD): 4.7 (2.4) | n=19 Mean (SD): 4.6 (1.3) | - | MD (95%CI): 0.10 (-1.21 to 1.41)[a] | Low | RCT | None | None | None | Very serious[d] | None |
| **Oxygen saturation (inpatients)** | | | | | | | | | | | |
| **30 minutes (endpoint)** | | | | | | | | | | | |
| 1 (Tinsa et al., 2009) | n=16 Mean (SD): 96.1 (2.1) | n=19 Mean (SD): 95.5 (1.8) | - | MD (95%CI): 0.60 (-0.71 to 1.91)[a] | Moderate | RCT | None | None | None | Serious[b] | None |
| **60 minutes (endpoint)** | | | | | | | | | | | |
| 1 (Tinsa et al., 2009) | n=16 Mean (SD): 96.8 (1.9) | n=19 Mean (SD): 96 (2.04) | - | MD (95%CI): 0.80 (-0.51 to 2.11)[a] | Moderate | RCT | None | None | None | Serious[b] | None |
| **120 minutes (endpoint)** | | | | | | | | | | | |
| 1 (Tinsa et al., 2009) | n=16 Mean (SD): 97.2 (1.5) | n=19 Mean (SD): 97 (1.3) | - | MD (95%CI): 0.20 (-0.74 to 1.14)[a] | Low | RCT | None | None | None | Very serious[d] | None |

*NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, P p-value, RR relative risk*
*a Calculated by the technical team from data reported in the article*
*b Serious imprecision when 95% CI crosses one default MID.*
*c Serious imprecision when 95% CI crosses one default MID.*
*d Very serious imprecision when 95% CI crosses two default MID.*
~~*b Confidence interval of SMD crosses +0.5 and no treatment effect, based on Cohen effect size criteria*~~
~~*c Confidence interval of SMD crosses -0.5 and no treatment effect, based on Cohen effect size criteria*~~
~~*d Confidence interval of SMD crosses both +/-0.5 around no treatment effect, based on Cohen effect size criteria.*~~

**Table 3736: GRADE profile for comparison of ipratropium bromide with placebo**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ipratropium bromide | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Length of stay in days (inpatients)** | | | | | | | | | | | |
| 2 studies (Chowdhury et al., 1995; Karadag et al., 2008) | n=45 | n=33 | - | MD (95%CI): 0.22 (-0.37 to 0.81)[a] | Moderate | RCT | None | None | None | Serious[b] | None |
| **Change in disease severity score (inpatients)** | | | | | | | | | | | |
| **Day 1 (endpoint)** | | | | | | | | | | | |
| 1 (Goh et al., 1997) | n=30 Mean (SD): 7.3 (1.9) | n=29 Mean (SD): 8 (2.5) | - | MD (95%CI): -0.70 (-1.84 to 0.44)[a] | Low | RCT | Serious[c] | None | None | Serious[d] | None |
| **Day 2 (endpoint)** | | | | | | | | | | | |
| 1 (Goh et al., 1997) | n=30 Mean (SD): 4.6 (1.9) | n=29 Mean (SD): 4.4 (2.4) | - | MD (95%CI): 0.20 (-0.91 to 1.31)[a] | Low | RCT | Seriousc | None | None | Serious[b] | None |
| **Day 3 (endpoint)** | | | | | | | | | | | |
| 1 (Goh et al., 1997) | n=30 Mean (SD): 3.4 (1.8) | n=29 Mean (SD): 3.1 (1.8) | - | MD (95%CI): 0.30 (-0.62 to 1.22)[a] | Low | RCT | Serious[c] | None | None | Serious[b] | None |
| **No improvement in clinical score (dichotomous)** | | | | | | | | | | | |
| 1 (Lines et al., 1992) | 5/17 (29.4%) | 7/14 (50%) | RR (95%CI): 0.59 (0.24 to 1.45)[a] | - | Very low | RCT | Very serious[e] | None | None | Very serious[f] | None |
| Average clinical score after treatment (endpoint) | | | | | | | | | | | |
| 1 (Karadag et al., 2008) | n=22 Mean (SD): 4.9 (1.8) | n=11 Mean (SD): 5.3 (1.4) | - | MD (95%CI): -0.40 (-1.52 to 0.72)a | Moderate | RCT | None | None | None | Seriousd | None |
| **Oxygen saturation (inpatients)** | | | | | | | | | | | |
| **Time point not reported** | | | | | | | | | | | |
| 2 studies (Lines et a., 1992; Karadag et al., 2008) | n=39 | n=25 | - | MD (95%CI): 1.01 (0.66 to 1.36)[a] | Very low | RCT | Very serious[e] | None | None | Serious[b] | None |
| **Adverse events (inpatients)** | | | | | | | | | | | |
| **Tachycardia and persistent coughing** | | | | | | | | | | | |
| 1 (Henry et al., 1983) | 2/34 (5.9%) | 0/32 (0%) | RR (95%CI): 4.71 (0.23 to 94.58)[a] | - | Very low | RCT | Seriousg | None | None | Very serious[f] | None |

*NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, p-value, RR relative risk*
*a Calculated by the technical team from data reported in the article*
*b Serious imprecision when 95% CI crosses one default MID.~~Confidence interval of SMD crosses +0.5 and no treatment effect, based on Cohen effect size criteria~~*
*c Goh: randomisation and concealment of allocation not described in detail*
*d Serious imprecision when 95% CI crosses one default MID.~~Confidence interval of SMD crosses -0.5 and no treatment effect, based on Cohen effect size criteria~~*
*e Lines: randomisation and allocation concealment not clearly described, unclear definition of bronchiolitis*
*f ~~Wi~~Very serious imprecision when 95% CI crosses two default MID~~de confidence intervals crossing both +/-0.25 around no treatment effect~~*
*g Henry: randomisation and concealment of allocation not described*

**Table 38~~37~~: GRADE profile for comparison of salbutamol and ipratropium bromide (all subjects received both bronchodilators) with placebo**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Salbutamol and Ipratropium bromide | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Length of stay in days (inpatients)** | | | | | | | | | | | |
| 1 (Chowdhury et al., 1995) | n=24 Mean (SD): 4.6 (1.4) | n=22 Mean (SD): 4.3 (1.1) | - | MD (95%CI): 0.30 (-0.42 to 1.02)[a] | Low | RCT | None | None | Serious[b] | Serious[c] | None |

*NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, p-value, RR relative risk*
*a Calculated by the technical team from data reported in the article*
*b Combined bronchodilator treatment (salbutamol and ipratropium bromide)*
*c Serious imprecision when 95% CI crosses one default MID.~~Confidence interval of SMD crosses +0.5 and no treatment effect, based on Cohen effect size criteria~~*

**Table 39~~38~~: GRADE profile for comparison of salbutamol/ipratropium bromide/salbutamol and ipratropium bromide with placebo**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bronchodilator | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Change in disease severity score (inpatients)** | | | | | | | | | | | |
| **30 minutes (median change)** | | | | | | | | | | | |
| 1 (Chowdhury et al., 1995) | Salbutamol n= 20 Median (range): 3 (1.25 to 4.75)<br><br>Ipratropium bromide n= 23 Median (range): 2 (1 to 3) | n=22 Median (range): 2 (1 to 3) | - | p=0.23[a] | Moderate | RCT | None | None | Serious[b] | ~~NA~~NC | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bronchodilator | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| | Salbutamol and ipratropium bromide<br>n= 24<br>Median (range): 2 (1 to 3) | | | | | | | | | | |
| **60 minutes (median change)** | | | | | | | | | | | |
| 1 (Chowdhury et al., 1995) | Salbutamol<br>n= 20<br>Median (range): 2.5 (1 to 4)<br><br>Ipratropium bromide<br>n= 23<br>Median (range): 3 (1 to 4)<br><br>Salbutamol and ipratropium bromide<br>n= 24<br>Median (range): 2.5 (1.25 to 3.75) | n=22<br>Median (range): 2.5 (1 to 4) | - | p=0.93[a] | Moderate | RCT | None | None | Serious[b] | ~~NA~~NC | None |
| **6 hours (median change)** | | | | | | | | | | | |
| 1 (Chowdhury et al., 1995) | Salbutamol<br>n= 20<br>Median (range): 2.5 (1 to 4.75)<br><br>Ipratropium bromide<br>n= 23<br>Median (range): 2 (2 to 5)<br><br>Salbutamol and ipratropium bromide<br>n= 24<br>Median (range): 3 (1 to 5) | n=22<br>Median (range): 2.5 (2 to 3.25) | - | p= 0.92[a] | Moderate | RCT | None | None | Serious[b] | NA | None |
| **12 hours (median change)** | | | | | | | | | | | |
| 1 (Chowdhury et al., 1995) | Salbutamol<br>n= 20 | n=22<br>Median | - | p=0.54[a] | Moderate | RCT | None | None | Serious[b] | ~~NA~~NC | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bronchodilator | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| | Median (range): 3.5 (2 to 6)<br><br>Ipratropium bromide<br>n= 23<br>Median (range): 2 (2 to 4)<br><br>Salbutamol and ipratropium bromide<br>n= 24<br>Median (range): 4 (2 to 4.75) | (range): 2.5 (1.75 to 4.25) | | | | | | | | | |
| **24 hours (median change)** | | | | | | | | | | | |
| 1 (Chowdhury et al., 1995) | Salbutamol<br>n= 20<br>Median (range): 2.5 (1.25 to 4.5)<br><br>Ipratropium bromide<br>n= 23<br>Median (range): 4 (1 to 6)<br><br>Salbutamol and ipratropium bromide<br>n= 24<br>Median (range): 4 (2 to 4.75) | n=22<br>Median (range): 2.5 (1.75 to 4) | - | p=0.58[a] | Moderate | RCT | None | None | Serious[b] | ~~NA~~NC | None |
| **36 hours (median change)** | | | | | | | | | | | |
| 1 (Chowdhury et al., 1995) | Salbutamol<br>n= 20<br>Median (range): 4.5 (3 to 6)<br><br>Ipratropium bromide<br>n= 23<br>Median (range): 5 (2 to 7)<br><br>Salbutamol and | n=<br>Median (range): 3 (1.75 to 5) | - | p= 0.49[a] | Moderate | RCT | None | None | Serious[b] | NA | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bronchodilator | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| | ipratropium bromide n= 24 Median (range): 4 (2.25 to 5.75) | | | | | | | | | | |

*NC not calculable, NR not reported, RCT randomised controlled trial, MD mean difference, SD standard deviation, p-value, RR relative risk*
*a As reported in the study*
*b Combined bronchodilator treatment*

# A.13 Inhaled Corticosteroids

**Table 4039: GRADE profile for inhaled corticosteroids compared with placebo for bronchiolitis in children**

| Number of studies | Number of children | | Effect | | Quality | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Inhaled cortiocosteroids | Placebo | Relative (95% confidence interval) | Absolute (95% confidence interval) | | | | | | | |
| **Hospital admission rate** | | | | | | | | | | | |
| **Length of hospital stay (days)** | | | | | | | | | | | |
| 1 (Cade et al, 2000) | Median 2 (IQR 1 to 3) | Median 2 (IQR 1 to 4) | Hazard Ratio 1.10 (0.80 to 1.51)g | NC | Very low | RCT | Serious[b] | None | Serious[c] | Very serious[a] | None |
| 1 (Richter et al, 1998) | Median 2 (range 1 to 11) | Median 3 (range 1 to 7) | p = 0.65 [f] | NC | Very low | RCT | Serious[d] | None | Serious[c] | None | None |
| **Change in disease severity score at 1 to 7 days after starting treatment** | | | | | | | | | | | |
| **At 48 hours** | | | | | | | | | | | |
| 1 (Richter et al, 1998) | Median – 2.0 (-6 to +6) | Median – 1.0 (-9 to +2) | p = 0.92 [f] | NC | Low | RCT | Serious[c] | None | Serious[c] | None | None |
| **Change in O2 saturation** | | | | | | | | | | | |
| **Duration of cough – Not reported** | | | | | | | | | | | |
| **Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation – Not reported** | | | | | | | | | | | |
| **Readmission** | | | | | | | | | | | |
| **Readmission for respiratory symptoms within 12 months** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Inhaled cortiocosteroids | Placebo | Relative (95% confidence interval) | Absolute (95% confidence interval) | | | | | | | |
| 2 (Cade et al, 2000; Richter et al, 1998) | 23/102 | 16/98 | RR: 1.85 [0.36, 9.53] | NC | Very low | RCT | Serious[b, d] | Serious | Serious[c] | Very serious[a] | None |
| **Adverse effects (including mortality) – Not reported** | | | | | | | | | | | |

*NC not calculable, RCT randomised controlled trial, RR relative risk, MD mean difference, SMD Standardised Mean Difference, p-value*
*a Very serious imprecision when 95% CI crosses two default MID. ~~Wide confidence intervals crossing both +/- 0.25 around no treatment effect.~~*
*b Cade – Method of randomisation and concealment not described in detail*
*c Cade and Richter allowed additional treatment with bronchodilators*
*d Richter - Method of randomisation and concealment not described in detail*
*e Groups not balanaced at baseline*
*f As reported by authors*

# A.14 Systemic Corticosteroids

**Table 4140: GRADE profile for systemic corticosteroids compared with placebo for bronchiolitis in children**

| Number of studies | Number of children | | Effect | | Quality | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Systemic corticosteroids | Placebo | Relative (95% confidence interval) | Absolute (95% confidence interval) | | | | | | | |
| **Hospital admission rate** | | | | | | | | | | | |
| **Hospital admissions by day 1** | | | | | | | | | | | |
| 2 studies (, Corneli et al, Plint et al., 2009) | 152/504 | 157/496 | RR: 0.95 (0.80 to 1.14)[a] | NC | Low | RCT | Serious [b] | None | Serious[c] | None | None |
| **Hospital admissions by day 7 (Includes admissions on day 1 i.e. cumulative admissions to day 7)** | | | | | | | | | | | |
| 2 studies, (Corneli et al, Plint et al., 2009) | 184/483 | 184/466 | RR: 0.95 (0.82 to 1.11)[a] | NC | Low | RCT | Serious[b] | None | Serious[c] | None | None |
| **Hospital readmission rate** | | | | | | | | | | | |
| **Hospital readmissions within 10 to 30 days** | | | | | | | | | | | |
| 2 (Roosevelt et al., 1996; Teeratakulpisarn et al, X) | 3/134 (2.2%) | 7/138 (5.1%) | RR: 0.41 [0.11, 1.53][a] | - | Very low | RCT | Serious[d] | None | Serious[c] | Very serious[e] | None |
| **Return healthcare visits within 10 to 30 days (inpatient studies – infants admitted to hospital)** | | | | | | | | | | | |
| 2 (Roosevelt et al., 1996; Teeratakulpisarn) | 33/154 (21.4%) | 31/138 (22.5%) | RR: 1.21 (0.3 to 4.96)[a] | NC | Very low | RCT | Serious[d] | None | Serious[c] | Very serious[e] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Systemic corticosteroids | Placebo | Relative (95% confidence interval) | Absolute (95% confidence interval) | | | | | | | |
| **Return healthcare visits within 10 to 30 days (outpatient studies – children seen in emergency department but not admitted)** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 106/199 | 86/200 | RR: 1.24 [1.01, 1.52][a] | NC | Low | RCT | Serious[b] | None | Serious[c] | None | None |
| **Length of hospital stay** | | | | | | | | | | | |
| **Length of hospital stay (inpatient studies – infants admitted to hospital) [better indicated by lower values]** | | | | | | | | | | | |
| 1 (Teerataku lpisarn et al., 2007) | - | - | NC | MD: -0.56 [-1.01, -0.11][a] | Moderate | RCT | None | None | Serious[c] | None | none |
| 1 (Zhang et al, 2003) | Median 6.0 (5.3 to 8.3) | Median 5.0 (4.8 to 7.5) | p = 0.70 | NC | Low | RCT | Serious[f] | None | Serious[g] | None | |
| 1 (Roosevelt et al., 1996 | | | NC | Hazard Ratio: 1.3 (0.9 to 1.3) p = 0.22 | Low | RCT | Serious[d] | None | Seriousc | None | None |
| **Length of hospital stay (outpatient studies – children seen in emergency department but not admitted) [better indicated by lower values]** | | | | | | | | | | | |
| 1 (Corneli 2007) | - | - | NC | MD: 0.28 [-0.05, +0.61][a] | Low | RCT | None | None | Serious[c] | Serious[e] | None |
| **Change in clinical scores at 3 to 10 days [better indicated by lower values]** | | | | | | | | | | | |
| **At 60 mins** | | | | | | | | | | | |
| 1(Plint et al, 2009) | - | - | NC | MD: -0.10 (-0.57 to 0.37)a | Very low | RCT | Seriousb | None | Very seriousc | Very seriouse | None |
| **At 120 minutes** | | | | | | | | | | | |
| **At 3 to 6 hours** | | | | | | | | | | | |
| 1 (; Corneli et al, 2007) | - | - | NC | MD: -0.50 (-1.25 to 0.25)[a] | Very low | RCT | None | None | Very Serious[c] | Very serious[e] | None |
| **Change in oxygen saturation at 3 to 6 hours [better indicated by higher values]** | | | | | | | | | | | |
| **At 60 minutes** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Systemic corticosteroids | Placebo | Relative (95% confidence interval) | Absolute (95% confidence interval) | | | | | | | |
| 1 (; Plint et al, 2009) | | | NC | MD: -0.25 (-0.82 to 0.32)[a] | Very low | RCT | Very serious,[b] | None | Very Serious[c] | Serious[e] | None |
| **At 120 minutes** | | | | | | | | | | | |
| **At 3 to 6 hours** | | | | | | | | | | | |
| 1 (; Corneli et al, 2007) | | | NC | MD: -0.60 (-1.12 to -0.08)[a] | Low | RCT | None | None | Very Serious[c] | None | None |
| **Duration of cough – not reported** | | | | | | | | | | | |
| **Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation** | | | | | | | | | | | |
| **Received oxygen** | | | | | | | | | | | |
| 1 (Teeratakulpisarn et al, X) | 66/89 | 67/85 | RR: 0.77 [0.38, 1.56][a] | NC | Very Low | RCT | None | None | Serious[c] | Very serious[e] | None |
| **Adverse events** | | | | | | | | | | | |
| **Vomiting witin 20 minutes of medication** | | | | | | | | | | | |
| 1 (Corneli et al, 2007) | 17/304 | 14/294 | NC | RR: 1.18 [0.57, 2.45][a] | Very Low | RCT | None | None | Serious[c] | Very serious[e] | None |
| **GI bleeding, hypertension, pneumonia or complicated caricella** | | | | | | | | | | | |
| 2 (Corneli et al, 2007; Roosevelt et al, 1996) | 20/673 | 17/641 | NC | RR: 0.89 [0.17, 4.49][a] | Very Low | RCT | Serious[d] | None | Serious[c] | Serious[e] | None |
| **Mortality - not reported** | | | | | | | | | | | |

*NC not calculable, RCT randomised controlled trial, RR relative risk, MD mean difference, SMD standardised mean difference, p-value*
*a Calculated by NCC-WCH technical team based on data reported in the articleb Plint – treatment variation within protocols*
*c Plint, Corneli, Roosevelt and Teeretakulpisarn allowed additional treatment, with majority of children being treated with bronchodilators.*
*d Roosevelt – method of randomisation and concealment not explained*
*e ~~W~~Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID.~~ide confidence intervals cover +/- 0.25 effect~~ around the point of no effect*
*f Single blinded*
*g Usual care rather than placebo*

# A.15 Combined bronchodilator and corticosteroid therapy

**Table 4241: GRADE profile for comparison of combined bronchodilator (inhaled) and corticosteroid (systemic) therapy with bronchodilator and placebo**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator (inhaled) + corticosteroid (systemic) therapy | Bronchodilator + placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Hospital admissions (outpatients)** | | | | | | | | | | | |
| **Day 1** | | | | | | | | | | | |
| 5 studies (Berger et al., 1998; Kuyucu et al., 2004; Mesquita et al., 2009; Plint et al., 2009; Schuh et al., 2002) | 43/312 (13.8%) | 53/294 (18.0%) | RR: 0.80 (0.49 to 1.33)[a] | - | Very low | RCT | Very serious[b] | None | Very serious[c,d] | Very serious[e] | None |
| **Day 7 (Includes admissions on day 1, i.e. cumulative admissions to day 7)** | | | | | | | | | | | |
| 3 (Alansari et al., 2013; Bawazeer et al., 2014; Plint et al., 2009) | 58/385 (20.4%) | 70/366 (25.4%) | RR: 0.80 (0.59 to 1.09)[a] | - | Very low | RCT | None | None | Very serious[c] | Serious[f] | None |
| **Day 22 (Includes admissions on day 1 and 7, i.e. cumulative admissions to day 22)** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 37/200 (18.5%) | 50/199 (25.1%) | RR: 0.74 (0.51 to 1.07)[a] | - | Low | RCT | None | None | Serious[c] | Serious[f] | None |
| **Hospital re-admissions (inpatients)** | | | | | | | | | | | |
| 1 (Klassen et al., 1997) | 4/35 (11.4%) | 1/32 (3.1%) | RR: 3.66 (0.43 to 31.03)[a] | p=0.36g | Very low | RCT | Serious[h] | None | ~~None~~NC | Very serious[e] | None |
| **Length of hospital stay in days (outpatients)** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator (inhaled) + corticosteroid (systemic) therapy | Bronchodilator + placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Berger et al., 1998) | n=5<br>Mean (SD): 5 (2.105) | n=2<br>Mean (SD): 8 (2.828) | - | MD: -3.00 (-7.33 to 1.33)[a] | Very low | RCT | Serious[i] | None | None | Very serious[j] | None |
| **Reported as geometric mean time (95%CI) to readiness for discharge in hours** | | | | | | | | | | | |
| 1 (Alansari et al., 2013) | n=100<br>Geometric mean time (95%CI): 18.6 (14.9 to 23.1) | n=90<br>Geometric mean time (95%CI): 27.1 (21.8 to 33.8) | Ratio of geometric means: 0.69 (0.51 to 0.93) | p=0.015 | Low | RCT | None | None | Serious[c] | Serious[f] | None |
| **Length of hospital stay in hours (inpatients)** | | | | | | | | | | | |
| 1 (Klassen et al., 1997) | n=35<br>Median (95%CI): 57 (38 to 76) | n=32<br>Median (95%CI): 48 (42 to 54) | - | p=0.19[g] | Moderate | RCT | Serioush | None | None | NA | None |
| **Change in disease severity score (outpatients)** | | | | | | | | | | | |
| **30 minutes** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=199<br>Mean (SD): -1.62 (2.23) | n=198<br>Mean (SD): -1.44 (1.94) | - | MD: -0.18 (-0.59 to 0.23)[a] | High | RCT | None | None | None | None | None |
| **60 minutes** | | | | | | | | | | | |
| 2 studies (Mesquita et al., 2009; Plint et al., 2009) | n=232 | n=230 | - | SMD: -0.02 (-0.20 to 0.16)[a] | High | RCT | None | None | None | None | None |
| **120 minutes** | | | | | | | | | | | |
| 1 (Kuyucu et al., 2004) | n=46 | n=23 | - | MD: 0.00 (-0.50 to 0.50)[a] | Moderate | RCT | Serious[k] | None | None | None | None |
| **4 hours** | | | | | | | | | | | |
| 3 studies (Bawazeer et al., 2014; Mesquita et | n=154 | n=143 | - | SMD: -0.25 (-0.66 to 0.16)[a] | Very low | RCT | Serious[l] | Serious[m] | Serious[n] | Serious[o] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator (inhaled) + corticosteroid (systemic) therapy | Bronchodilator + placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| al., 2009; Schuh et al., 2002) | | | | | | | | | | | |
| **24 hours** | | | | | | | | | | | |
| 1 (Kuyucu et al., 2004) | n=46 | n=23 | - | MD: -0.49 (-0.99 to 0.02)[a] | Low | RCT | Serious[k] | None | None | Serious[o] | None |
| **3 to 10 days** | | | | | | | | | | | |
| 3 studies (Berger et al., 1998; Kuyucu et al., 2004; Schuh et al., 2002) | n=101 | n=73 | - | SMD: -0.24 (-0.55 to 0.07)[a] | Very low | RCT | Serious[l,k] | Very serious[p] | Serious[n] | Serious[o] | None |
| **Change in disease severity score (inpatients)** | | | | | | | | | | | |
| **12 hours** | | | | | | | | | | | |
| 1 (Klassen et al., 1997) | n=35 Mean (SD): -1.3 (2.0) | n=31 Mean (SD): -1.0 (1.8) | - | MD: -0.30 (-1.22 to 0.62)a p=0.51[g] | Low | RCT | Serious[h] | None | None | Serious[o] | None |
| **24 hours** | | | | | | | | | | | |
| 1 (Klassen et al., 1997) | n=33 Mean (SD): -1.4 (2.0) | n=28 Mean (SD): -1.6 (2.3) | - | MD: 0.20 (-0.89 to 1.29)[a] p=0.74 | Low | RCT | Serioush | None | None | Serious[q] | None |
| **Change in oxygen saturation (outpatients)** | | | | | | | | | | | |
| **30 minutes** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=199 Mean (SD): -0.35 (2.61) | n=198 Mean (SD): 0.17 (2.09) | - | MD: -0.52 (-0.99 to -0.05)[a] | High | RCT | None | None | None | None | None |
| **1 hour** | | | | | | | | | | | |
| 2 studies (Mesquita et | n=232 | n=230 | - | SMD: -0.24 (- | High | RCT | None | None | None | None | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator (inhaled) + corticosteroid (systemic) therapy | Bronchodilator + placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| al., 2009; Plint et al., 2009) | | | | 0.48 to 0.01)a | | | | | | | |
| **4 hours** | | | | | | | | | | | |
| 3 studies (Bawazeer et al., 2014; Mesquita et al., 2009; Schuh et al., 2009) | n=154 | n=143 | - | SMD: 0.08 (-0.15 to 0.316)[a] | Low | RCT | Serious[l] | None | Serious[n] | None | None |
| **24 to 72 hours** | | | | | | | | | | | |
| 1 (Berger et al., 1998) | n=20 Mean (SD): 1 (0.5) | n=18 Mean (SD): 0.8 (0.3) | - | MD: 0.20 (-0.06 to 0.46)[a] | Low | RCT | Serious[i] | None | None | Serious[q] | None |
| **Change in oxygen saturation (inpatients)** | | | | | | | | | | | |
| **12 hours** | | | | | | | | | | | |
| 1 (Klassen et al., 1997) | n=35 Mean (SD): 0.7 (2.5) | n=31 Mean (SD): 1.4 (2.8) | - | MD: -0.70 (-1.99 to 0.59)[a] p=0.29[g] | Low | RCT | Serious[h] | None | None | Serious[o] | None |
| **24 hours** | | | | | | | | | | | |
| 1 (Klassen et al., 1997) | n=33 Mean (SD): 1.0 (3.6) | n=28 Mean (SD): 1.9 (3.1) | - | MD: -0.90 (-2.58 to 0.78)[a] p=0.28[g] | Low | RCT | Serious[h] | None | None | Serious[o] | None |
| **Need for high flow humidified oxygen, CPAP or mechanical ventilation (outpatients)** | | | | | | | | | | | |
| **Reported as need for supplemental oxygen** | | | | | | | | | | | |
| 1 (Berger et al., 1998) | 5/20 (25%) | 2/18 (11.1%) | RR: 2.25 (0.50 to 10.20)a | - | Very low | RCT | Seriousi | None | None | Very serious[e] | None |
| **Adverse events** | | | | | | | | | | | |
| **Pneumonia** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator (inhaled) + corticosteroid (systemic) therapy | Bronchodilator + placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Klassen et al., 1997) | 1/35 (2.9%) | 1/32 (3.1%) | RR: 0.91 (0.06 to 14.02)[a] | - | Very low | RCT | Serious[h] | None | None | Very serious[e] | None |
| **Tremor** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 4/199 (2.0%) | 4/198 (2.0%) | RR: 0.99 (0.25 to 3.92)[a] | - | Very low | RCT | None | None | Serious[c] | Very serious[e] | None |
| **Pallor** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 23/199 (11.6%) | 22/198 (11.1%) | RR: 1.04 (0.60 to 1.80)[a] | - | Very low | RCT | None | None | Serious[c] | Very serious[e] | None |
| **Vomiting** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 2/199 (1.0%) | 4/198 (2.0%) | RR: 0.50 (0.09 to 2.69)[a] | - | Very low | RCT | None | None | Serious[c] | Very serious[e] | None |
| **Dark stools** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 17/199 (8.5%) | 14/198 (7.1%) | RR: 1.21 (0.61 to 2.38)[a] | - | Very low | RCT | None | None | Serious[c] | Very serious[e] | None |
| **Hypertension** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 0/199 (0%) | 1/198 (0.5%) | RR: 0.33 (0.01 to 8.09)a | - | Very low | RCT | None | None | Seriousc | Very seriouse | None |
| **Hyperkalaemia** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 0/199 (0%) | 0/198 (0%) | NC | - | Moderate | RCT | None | None | Seriousc | ~~NA~~NC | None |

*NA not applicable, NC not calculable, RCT randomised controlled trial, p-value, RR risk ratio, MD mean difference, SMD standardised mean difference, SD standard deviation*
*a Calculated by the NCC-WCH technical team from data reported in the article*
*b Berger: randomisation not described, 4 drop-outs – unclear which arm they were assigned to, Kuyucu- randomisation not described, allocation concealment not clearly described, 21 lost to follow up - unclear which group they were assigned to, Schuh- 920/1464 children not approached because the research nurse was not present*
*c Plint: physician allowed to provide co-interventions after 90 minutes, Alansari: Population includes patients with asthma risk, as determined by eczema or a family history of asthma in a first degree relative*
*d Schuh: Additional treatment given at discretion of the physician*
*e Very serious imprecision when 95% CI crosses two default MID.*

*f Serious imprecision when 95% CI crosses one default MID.*
~~*e Wide confidence intervals crossing both +/- 0.25 around no treatment effect*~~
~~*f Wide confidence interval crossing -0.25 and no treatment effect*~~
*g As reported in the study*
*h Bronchiolitis not clearly defined*
*I Berger: randomisation not described, 4 drop-outs – unclear which arm they were assigned to*
*j Very serious imprecision when 95% CI crosses two default MID.*~~*Confidence interval of SMD crosses both +/ 0.5 around no treatment effect*~~
*k Randomisation not described, allocation concealment not clearly described, 21 lost to follow up- unclear which group they were assigned to*
*l Schuh: 920/1464 children in one study not approached because the research nurse was not present, bronchiolitis not defined*
*m High heterogeneity: I2= 765%*
*n Schuh: Additional treatment given at discretion of the physician*
*o Serious imprecision when 95% CI crosses one default MID.*~~*Confidence interval of SMD crosses -0.5 and no treatment effect, based on Cohen effect size criteria.*~~
*p High heterogeneity: I2= 70%*
*q Serious imprecision when 95% CI crosses one default MID.*~~*Confidence interval of SMD crosses +0.5 and no treatment effect, based on Cohen effect size criteria.*~~

**Table 43~~42~~: GRADE profile for comparison of combined bronchodilator and corticosteroid therapy (both inhaled) with bronchodilator and placebo**

| | Number of children | | Effect | | | | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Combined bronchodilator and corticosteroid therapy (both inhaled) | Bronchodilator + placebo | Relative (95% CI) | Absolute (95% CI) | Quality | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Hospital re-admissions (inpatients)** | | | | | | | | | | | |
| 1 (Bentur et al., 2005) | 12/29 (41.3%) | 14/32 (43.8%) | RR: 0.95 (0.53 to 1.70)[a] | p=NSb | Very low | RCT | Serious[c] | None | None | Very serious[d] | None |
| **Length of hospital stay in days (inpatients)** | | | | | | | | | | | |
| **Premature infants** | | | | | | | | | | | |
| 1 (Bentur et al., 2005) | n=6 Mean (SD): 6.5 (4.2) | n=7 Mean (SD): 9.1 (5.0) | - | MD: -2.60 (-7.60 to 2.40)a p=0.018[b] | Very low | RCT | Serious[c] | None | None | Very serious[e] | None |
| **Full-term infants** | | | | | | | | | | | |
| 1 (Bentur et al., 2005) | n=23 Mean (SD): 5.2 (8.6) | n=25 Mean (SD): 5.5 (9.5) | - | MD: -0.30 (-5.43 to 4.83)[a] p=NS[b] | Very low | RCT | Serious[c] | None | None | Very serious[e] | None |
| **Change in disease severity score (inpatients)** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator and corticosteroid therapy (both inhaled) | Bronchodilator + placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Clinical score at discharge (endpoint)** | | | | | | | | | | | |
| 1 (Bentur et al., 2005) | n=29<br>Mean (SD): 2.1 (2.7) | n=32<br>Mean (SD): 2.2 (2.3) | - | MD: -0.10 (-1.35 to 1.15)[a]<br>p=NSb | Low | RCT | Serious[c] | None | None | Seriousf | None |
| **Need for/use of feeding support – tube feeding, IV fluids (inpatients)** | | | | | | | | | | | |
| **Reported as duration of IV fluids in hours** | | | | | | | | | | | |
| 1 (Bentur et al., 2005) | n=29<br>Mean (SD): 78.6 (213.8) | n=32<br>Mean (SD): 88.5 (201.4) | - | MD: -9.90 (-114.41 to 94.61)[a]<br>p=NS[b] | Low | RCT | Serious[c] | None | None | Serious[f] | None |

*NA not applicable, RCT randomised controlled trial, RR risk ratio, MD mean difference, SMD standardised mean difference, SD standard deviation, p-value, NS Non Significant at p = 0.05*
*a Calculated by the NCC-WCH technical team from data reported in the article*
*b As reported in the study*
*c Bronchiolitis not defined, some outcomes specified in methods not reported in results (eg: oxygen saturation)*
*d Very serious imprecision when 95% CI crosses two default MID.*
*e Very serious imprecision when 95% CI crosses two default MID.*
*f Serious imprecision when 95% CI crosses one default MID.*
~~*d Wide confidence intervals crossing both +/-0.25 around no treatment effect*~~
~~*e Wide SMD confidence intervals crossing both +/-0.5 around no treatment effect, based on Cohen effect size criteria.*~~
~~*f Confidence interval of SMD crosses -0.5 and no treatment effect, based on Cohen effect size criteria.*~~

**Table 44~~43~~: GRADE profile for comparison of combined bronchodilator (systemic/inhaled) and corticosteroid therapy (systemic) with bronchodilator and placebo**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator and corticosteroid therapy (both inhaled) | Bronchodilator + placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Hospital admissions (outpatients)** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator and corticosteroid therapy (both inhaled) | Bronchodilator + placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Goebel et al., 2000) | 4/24 (16.7%) | 2/24 (8.3%) | RR: 2.00 (0.40 to 9.91)[a] | - | Very low | RCT | Seriousb | None | Serious[d] | Very serious[e] | None |
| **Length of hospital stay in days (outpatients)** | | | | | | | | | | | |
| 1 (Goebel et al., 2000) | n=4 Mean (SD): 2.3 (1.7) | n=2 Mean (SD): 2.5 (1.7) | - | MD: -0.20 (-3.09 to 2.69)[a] | Very low | RCT | Serious[b] | None | Serious[d] | Very serious[f] | None |
| **Change in disease severity score (outpatients)** | | | | | | | | | | | |
| **Clinical score on day 2 (endpoint)** | | | | | | | | | | | |
| 1 (Goebel et al., 2000) | n=17 Mean (SD): 2.6 (1.5) | n=15 Mean (SD): 3.9 (1.5) | - | MD: -1.30 (-2.34 to -0.26)a | Very low | RCT | Very serious[b,c] | None | Serious[d] | Serious[g] | None |
| **Adverse events** | | | | | | | | | | | |
| **Appearing jittery** | | | | | | | | | | | |
| 1 (Goebel et al., 2000) | 1/24 (4.2%) | 0/24 (0%) | RR: 3.00 (0.13 to 70.16)[a] | - | Very low | RCT | Serious[b] | None | Serious[d] | Very serious[e] | None |

*NA not applicable, RCT randomised controlled trial, RR risk ratio, MD mean difference, SD standard deviation*
*a Calculated by the NCC-WCH technical team from data reported in the article*
*b Bronchiolitis not clearly defined*
*c 7 subjects in the combined therapy group and 9 subjects in the bronchodilator + placebo group had missing outcome data*
*d Mixed routes of administration: though the majority of subjects received bronchodilator by mouth (systemic), a small number of hospitalised subjects and one outpatient received bronchodilator by the use of a nebuliser (exact numbers not reported and no subgroup analysis presented)*
*e Very serious imprecision when 95% CI crosses two default MID.*
*f Very serious imprecision when 95% CI crosses two default MID.*
*g Serious imprecision when 95% CI crosses one default MID.*
~~*e Wide confidence intervals crossing both +/-0.25 around no treatment effect*~~
~~*f Wide SMD confidence intervals crossing both +/-0.5 around no treatment effect, based on Cohen effect size criteria.*~~
~~*g Confidence interval of SMD crosses -0.5 and no treatment effect, based on Cohen effect size criteria.*~~

**Table 4544: GRADE profile for comparison of combined bronchodilator (inhaled) and corticosteroid (systemic) therapy with placebo**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Hospital admissions (outpatients)** | | | | | | | | | | | |
| **Day 1** | | | | | | | | | | | |
| 1 study~~ies~~ (; Plint et al., 2009) | 23/200 (11.5%) | 36/201 (17.9%) | RR: 0.64 (0.40 to 1.04)[a] | - | Very low | RCT | None | None | Serious[b] | Serious[c] | None |
| **Day 7 (Includes admissions on day 1, i.e. cumulative admissions to day 7)** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 34/200 (17.0%) | 53/201 (26.4%) | RR: 0.64 (0.44 to 0.95)[a] | - | Low | RCT | None | None | Serious[b] | Serious[c] | None |
| **Day 22 (Includes admissions on day 1 and 7, i.e. cumulative admissions to day 22)** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 37/200 (18.5%) | 54/201 (26.9%) | RR: 0.69 (0.48 to 1.00)[a] | - | Low | RCT | None | None | Serious[b] | Serious[c] | None |
| **Length of hospital stay in hours (outpatients)** | | | | | | | | | | | |
| **Reported as time to discharge – time between the triage time at enrolment visit and the time of discharge from the last emergency department visit or the last hospitalisation for each patient within the next 7 days** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=199 Median (interquartile range): 4.6 (3.5 to 7.0) | n=200 Median (interquartile range): 5.3 (3.8 to 21) | - | p=0.94[e] | Moderate | RCT | None | None | Serious[b] | NA | None |
| **Change in disease severity score (outpatients)** | | | | | | | | | | | |
| **30 minutes** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=199 Mean (SD): -1.62 (2.23) | n=200 Mean (SD): -1.06 (2.16) | - | MD: -0.56 (-0.99 to -0.13)[a] | High | RCT | None | None | None | None | None |
| **60 minutes** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=199 | n=200 | - | MD: -0.85 (-1.34 to -0.36)[a] | Low | RCT | None | None | None | Serious[e] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| | n=15<br>Mean (SD): 4.40 (2.75) | n=15<br>Mean (SD): 4.80 (2.54) | - | MD: -0.4 (-2.29 to 1.49)[a] | Very low | RCT | None | None | None | Very serious[f] | None |
| | n=15<br>Mean (SD): 4.08 (3.25) | n=15<br>Mean (SD): 5 (2.31) | - | MD: -0.92 (-2.94 to 1.10)[a] | Low | RCT | None | None | None | Serious[e] | None |
| **Change in oxygen saturation (outpatients)** | | | | | | | | | | | |
| **30 minutes** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=199<br>Mean (SD): -0.35 (2.61) | n=200<br>Mean (SD): -0.24 (2.77) | - | MD: -0.11 (-0.64 to 0.42)[a] | High | RCT | None | None | None | None | None |
| **60 minutes** | | | | | | | | | | | |
| 1 study (; Plint et al., 2009) | n=214 | n=215 | - | MD: 0.04 (-0.53 to 0.61)[a] | Moderate | RCT | None | None | None | None | None |
| | n=15<br>Mean (SD): 95.47 (1.88) | n=15<br>Mean (SD): 95.6 (1.95) | - | MD: -0.13 (-1.5 to 1.24)[a] | Very low | RCT | None | None | None | Very serious[f] | None |
| | n=15<br>Mean (SD): 95.08 (1.75) | n=15<br>Mean (SD): 95.62 (1.89) | - | MD: -0.54 (-1.84 to 0.76)a | Low | RCT | None | None | None | Seriousf | None |
| **Duration of cough (outpatients)** | | | | | | | | | | | |
| **Reported as number of days with no coughing** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=NR<br>Median (interquartile range): 12.6 (7.8 to 18.5) | n=NR<br>Median (interquartile range): 13.3 (8.2 to 19.5) | Mean ratio: 0.94 (0.84 to 1.07) | - | Moderate | RCT | None | None | Serious[b] | None | None |
| **Adverse events** | | | | | | | | | | | |
| **Tremor** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy | Placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Plint et al., 2009) | 4/199 (2.0%) | 2/201 (1%) | RR: 2.02 (0.37 to 10.90)[a] | - | Very low | RCT | None | None | Serious[b] | Very serious[g] | None |
| **Pallor** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 23/199 (11.6%) | 16/201 (8%) | RR: 1.45 (0.79 to 2.66)[a] | - | Low | RCT | None | None | Serious[b] | Serious[h] | None |
| **Vomiting** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 2/199 (1.0%) | 3/201 (1.5%) | RR: 0.67 (0.11 to 3.99)[a] | - | Very low | RCT | None | None | Serious[b] | Very serious[g] | None |
| **Dark stools** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 17/199 (8.5%) | 16/201 (8.0%) | RR: 1.07 (0.56 to 2.06)[a] | - | Very low | RCT | None | None | Serious[b] | Very serious[g] | None |
| **Hypertension** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 0/199 (0%) | 0/201 (0%) | NC | - | Moderate | RCT | None | None | Serious[b] | NA | None |
| **Hyperkalaemia** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 0/199 (0%) | 0/201 (0%) | NC | - | Moderate | RCT | None | None | Serious[b] | NA | None |
| **Need for/use of feeding support (tube feeding, IV fluids)** | | | | | | | | | | | |
| **Reported as number of days with normal feeding** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | Median (interquartile range): 0.6 (0.2 to 1.3) | Median (interquartile range): 0.9 (0.3 to 2.1) | Mean ratio (95%CI): 0.63 (0.50 to 0.80)[i] | - | Low | RCT | None | None | Serious[b] | Serious[c] | None |

*NA not applicable, NC not calculable, RCT randomised controlled trial, p-value, RR risk ratio, MD mean difference, SMD standardised mean difference, SD standard deviation*

*a Calculated by the NCC-WCH technical team from data reported in the article*

*b Plint: physician allowed to provide co-interventions after 90 minutes*

*c Serious imprecision when 95% CI crosses one default MID. ~~Confidence interval crossing -0.25 and no treatment effect~~*

*d As reported in study, adjusted for multiple comparisons*

*e Serious imprecision when 95% CI crosses one default MID. ~~Confidence of SMD crosses -0.5 and no treatment effect , based on Cohen effect size criteria.~~*

*f Very serious imprecision when 95% CI crosses two default MID ~~Confidence interval of SMD crosses both +/- 0.5 around no treatment effect, based on Cohen effect size criteria.~~*

*g Very serious imprecision when 95% CI crosses two default MID.~~Confidence interval crossing both +/-0.25 around no treatment effect~~*
*h Serious imprecision when 95% CI crosses one default MID.~~Confidence interval crossing +/- 0.25 around no treatment effect~~*
*i As reported in the study*

**Table 46~~45~~: GRADE profile for comparison of combined bronchodilator (inhaled) and corticosteroid (systemic) therapy with corticosteroid and placebo**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy | Corticosteroid + placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Hospital admissions (outpatients)** | | | | | | | | | | | |
| **Day 1** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 23/200 (11.5%) | 31/200 (15.5%) | RR: 0.74 (0.45 to 1.23)a | - | Low | RCT | None | None | Serious[b] | Serious[c] | None |
| **Day 7** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 34/200 (17%) | 51/200 (25.5%) | RR: 0.67 (0.45 to 0.98)[a] | - | Low | RCT | None | None | Serious[b] | Serious[c] | None |
| **Day 22** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 37/200 (18.5%) | 53/200 (26.5%) | RR: 0.70 (0.48 to 1.01)[a] | - | Low | RCT | None | None | Serious[b] | Serious[c] | None |
| **Change in disease severity score (outpatients)** | | | | | | | | | | | |
| **30 minutes** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=199 Mean (SD): -1.62 (2.23) | n=199 Mean (SD): -0.98 (2.07) | - | MD: -0.64 (-1.06 to -0.22)[a] | High | RCT | None | None | None | None | None |
| **60 minutes** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=199 Mean (SD): -2.50 (2.58) | n=199 Mean (SD): -1.75 (2.4) | - | MD: -0.75 (-1.24 to -0.26)a | High | RCT | None | None | None | None | None |
| **Change in oxygen saturation (outpatients)** | | | | | | | | | | | |
| **30 minutes** | | | | | | | | | | | |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Combined bronchodilator (inhaled) and corticosteroid (systemic) therapy | Corticosteroid + placebo | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Plint et al., 2009) | n=199 Mean (SD): -0.35 (2.61) | n=199 Mean (SD): -0.52 (2.45) | - | MD: 0.17 (-0.33 to 0.67)[a] | High | RCT | None | None | None | None | None |
| **60 minutes** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | n=199 Mean (SD): -0.73 (2.56) | n=199 Mean (SD): -1.02 (2.57) | - | MD: 0.29 (-0.21 to 0.79)[a] | High | RCT | None | None | None | None | None |
| **Adverse events** | | | | | | | | | | | |
| **Tremor** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 4/199 (2.0%) | 5/199 (2.5%) | RR: 0.80 (0.22 to 2.94)[a] | - | Very low | RCT | None | None | Serious[b] | Very serious[d] | None |
| **Pallor** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 23/199 (11.6%) | 15/199 (7.5%) | RR: 1.53 (0.82 to 2.85)[a] | - | Low | RCT | None | None | Serious[b] | Serious[e] | None |
| **Vomiting** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 2/199 (1%) | 5/199 (2.5%) | RR: 0.40 (0.08 to 2.04)[a] | - | Very low | RCT | None | None | Serious[b] | Very serious[d] | None |
| **Dark stools** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 17/199 (8.5%) | 12/199 (6.0%) | RR: 1.42 (0.69 to 2.89)[a] | - | Very low | RCT | None | None | Seriousb | Very serious[d] | None |
| **Hypertension** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 0/199 (0%) | 1/199 (0.5%) | RR: 0.33 (0.01 to 8.13)[a] | - | Very low | RCT | None | None | Serious[b] | Very serious[d] | None |
| **Hyperkalaemia** | | | | | | | | | | | |
| 1 (Plint et al., 2009) | 0/199 (0%) | 1/199 (0.5%) | RR: 0.33 (0.01 to 8.13)[a] | - | Very low | RCT | None | None | Serious[b] | Very serious[d] | None |

*NA not applicable, RCT randomised controlled trial, p-value, RR risk ratio, MD mean difference, SD standard deviation*
*a Calculated by the NCC-WCH technical team from data reported in the article*

*b Physician allowed to provide co-interventions after 90 minutes*
*c Serious imprecision when 95% CI crosses one default MID.*
*d Very serious imprecision when 95% CI crosses two default MID.*
*e Serious imprecision when 95% CI crosses one default MID.* ~~*c Wide confidence intervals crossing -0.25 around no treatment effect*~~
~~*d Wide confidence intervals crossing both +/ 0.25 around no treatment effect*~~
~~*e Wide confidence interval crossing +0.25 and no treatment effect*~~

# A.16 Montelukast

**Table 47~~46~~: GRADE profile for comparison of Montelukast with placebo for the management of bronchiolitis**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Length of stay (days)** | | | | | | | | | | | |
| 2 studies (Amirav et al, 2008; Zedan et al, 2010) | - | - | - | -0.91 [-1.69, -0.13]* | Very Low | RCT | None | Very serious[a] | Serious[b] | None | Yes[c] |
| **Clinical score (clinical score by Wang et al, 1992)** | | | | | | | | | | | |
| 2 studies (Amirav et al, 2008; Zedan et al, 2010) | - | - | - | -0.18 [-0.52, 0.15]* | Very Low | RCT | None | Very serious[a] | Serious[b] | None | Yes[c] |

*NC not calculable, NR not reported, RCT randomised controlled trial, p-value, RR relative risk*
** Calculated by the NCC-WCH technical team from data reported in the article. Based on a fixed-effect model.*
*a High heterogeneity between studies (I2 = 85%)*
*b Both studies included children up to the age of 24 months. The GDG believe that these older children are unlikely to have bronchiolitis and could potentially have asthma, which Montelukast was developed to treat.*
*c Zeden et al, 2010 uses the same design and methodology as Amirav et al, 2008. However, no link is mentioned between the studies*

# A.17 Heliox

**Table 4847: GRADE profile for comparison of heliox with oxygen (control)**

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Heliox | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **1.Change in C02 after 24 hours of heliox treatment (increased severity indicated by higher values)** | | | | | | | | | | | |
| **Change in C02 (PC02 mmHg) within the first hour after starting treatment** | | | | | | | | | | | |
| 1 (Cambonie et al., 2006) | N=10 | N=9 | - | MD -0.10 (-0.88, 0.68)* | Very low | RCT | Serious [a] | None | None [b] | Very serious [c, d] | - |
| **Change in C02 (tcPC02 mmHg) 30 minutes after starting treatment** | | | | | | | | | | | |
| 1 (Torres et al., 2008) | N=12 | N=12 | - | MD -4.30 (-6.38, -2.22)* | Low | RCT Crossover | Very serious [e] | None | None [f] | None [d, g] | - |
| **Change in C02 (PC02 mmHg) after 24 hours of starting treatment** | | | | | | | | | | | |
| 1 (Liet et al., 2005) | N=18 | N=21 | - | MD 3.00 (2.37, 3.63)* | Moderate | RCT | None | None | Serious [h] | None [d, g] | - |
| **2. Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation** | | | | | | | | | | | |
| **Rate of (endotracheal) intubation** | | | | | | | | | | | |
| 1 (Liet et al., 2010) | 5/28 | 4/30 | RR 1.38 (0.41, 4.56) | - | Very low | Meta-analysis of RCTs | Serious [a] | None [i] | Serious [b, h] | Very serious [j] | - |
| **Need for mechanical ventilation** | | | | | | | | | | | |
| 1 (Liet et al., 2010) | 5/28 | 5/30 | RR 1.11 (0.36, 3.38) | - | Very low | Meta-analysis of RCTs | Serious [a] | None [i] | Serious [b, h] | Very serious [j] | Yes [k] |
| **Required >50% oxygen, helium-oxygen and intubation** | | | | | | | | | | | |
| 1 (Kim et al., 2011) | 1/35 | 0/35 | RR 3.00 (0.13, 71.22)* | - | Very low | RCT | Serious [l] | None | Serious [m] | Very serious [j] | Yes [n] |
| **Need for CPAP** | | | | | | | | | | | |
| 1 (Chowdhury et al., 2013) | 24/140 | 27/141 | RR 0.90 (0.54, 1.47)* | P=0.78 | Very low | RCT | None [o] | Serious [p] | None [q] | Very serious [j] | - |

| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Heliox | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **3. Time to return to oral feeding** | | | | | | | | | | | |
| **Not reported** | | | | | | | | | | | |
| **4. Length of hospital stay** | | | | | | | | | | | |
| **Length of PICU stay, days** | | | | | | | | | | | |
| 1 (Liet et al., 2010) | N=27 | N=31 | - | MD -0.15 (-0.92, 0.61) | Very low | Meta-analysis of RCTs | Serious [a] | None [i] | Serious [b, h] | Very serious [c, d] | - |
| **Hours until "readiness to discharge" from the emergency department** | | | | | | | | | | | |
| 1 (Kim et al., 2011) | N=34 | N=35 | - | P=0.87 [r] | Low | RCT | Serious [l] | None | Serious [m] | ~~N/A~~NC [g] | - |
| **Length of treatment (total LoT to alleviate hypoxia (SpO2 ≥ 93% in room air) and respiratory distress (minimal work of breathing)). days [s]** | | | | | | | | | | | |
| 1 (Chowdhury et al., 2013) | N=141 | N=140 | - | MD -0.22 [-0.63, 0.19]* | Moderate | RCT | None [o] | Serious [p] | None [q] | None [d] | - |
| **Length of treatment (total LoT to alleviate hypoxia (SpO2 ≥ 93% in room air) and respiratory distress (minimal work of breathing)) for infants receiving treatment (Heliox or Airox) via a facemask, days s** | | | | | | | | | | | |
| 1 (Chowdhury et al., 2013) | N=44 | N=40 | - | MD -0.70 (-1.26, -0.14)* | High | RCT | None [o] | None | None [q] | None [d] | - |
| **Length of treatment ((total LoT to alleviate hypoxia (SpO2 ≥ 93% in room air) and respiratory distress (minimal work of breathing)) for infants receiving treatment (Heliox or Airox) via nasal cannula, days s** | | | | | | | | | | | |
| 1 (Chowdhury et al., 2013) | N=40 | N=47 | - | MD -0.34 (-1.22, 0.53)* | Moderate | RCT | None o | None | None q | Serious [c, d] | - |
| **5. Change in disease severity score at 1 to 4 hours after treatment (increased severity indicated by higher values)** | | | | | | | | | | | |
| **Change in M-WCAS within the first hour after starting treatment** | | | | | | | | | | | |
| 2 (Cambonie et al., 2006; Hollman et al., 1998) | N=23 | N=22 | - | SMD -2.26 (-3.04, -1.48)* | Very low | Meta-analysis of RCTs | Very serious [a, t] | None [i] | Serious [b, u] | None ~~d, g~~ | - |
| **Change in M-WCAS within the first hour after starting treatment** | | | | | | | | | | | |
| 1 (Torres et al., 2008) | N=12 | N=12 | - | MD -1.04 (-1.45, -0.63)* | Low | RCT Crossover | Very Serious [e] | None | None [f] | None ~~d, g~~ | - |
| **Change in RDAI score after 24 hours** | | | | | | | | | | | |
| 1 (Liet et al., 2005) | N=18 | N=21 | - | P=0.76 v | Moderate | RCT | None | None | Serious [h] | ~~N/A~~NC [g] | - |

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| Number of studies | Number of infants | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Heliox | Comparator | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Mean change in M-WCAS 240 minutes after treatment or discharge** | | | | | | | | | | | |
| 1 (Kim et al., 2011) | N=34 | N=35 | - | P<0.001 w | Low | RCT | Serious l | None | Serious m | ~~N/A~~NC g | - |
| **Heliox effect relative to Airox over time calculated using regression analysis based on M-WCAS** | | | | | | | | | | | |
| 1 (Chowdhury et al., 2013) | N=140 | N=141 | RR 20.13 (20.20, 20.06) | P<0.001 | Moderate | RCT | None o | Serious p | None q | None | Yes y |
| **6. Change in 02 saturation (increased severity indicated by higher values)** | | | | | | | | | | | |
| 1 (Torres et al., 2008) | N=12 | N=12 | - | MD 1.10 (-1.90, 4.10)* | Very low | RCT Crossover | Very Serious e | None | None f | Very serious d ~~c~~ | - |
| **7. Adverse effects** | | | | | | | | | | | |
| **Mortality** | | | | | | | | | | | |
| 1 (Liet et al., 2005) | 0/18 | 1/21 | RR 0.39 (0.02, 8.93)* | - | Very low | RCT | None | None | Serious h | Very serious j | - |

*MD mean difference, M-WCAS modified Wood's clinical asthma score, p-value, RCT randomised controlled trial, RDAI respiratory distress assessment instrument, RR relative risk, SMD standard mean difference,*

** Calculated by the NCC-WCH technical team from data reported in the article*

*a - Cambonie et al., 2006 (risk of bias): Small sample size and long study period (3 years) to recruit only 20 infants. Randomisation not described (Cochrane contacted reported computerised random listing and sealed envelopes). Oxygen saturation ≥90% for inclusion appears restrictive*

*b - Cambonie et al., 2006 (indirectness): Supplemental oxygen to maintain oxygen saturation >90%, all infants <3 months of age*

*c – Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID. ~~Wide confidence interval crossing +/-0.5 around line of no effect~~*

*d - Serious imprecision when 95% CI crosses one default MID; very serious imprecision when 95% CI crosses two default MID. ~~Cohen's interpretation of effect size: 0.2 small, 0.5 moderate, 0.8 large~~*

*e - Torres et al., 2008 (risk of bias): Not blinded. Inadequate randomisation (sequential allocation). Small sample size - 12 out of 40 infants met inclusion criteria. Did not describe infants with a previous history of wheeze in inclusion/exclusion criteria*

*f - Torres et al., 2008 (indirectness): Nebulised epinephrine at study entry, then at the discretion of physician*

*g – It was not possible to assess imprecision due to lack of information reported in the paper. ~~Confidence interval does not cross line of no effect~~*

*h - Liet et al., 2005 (indirectness): Inhaled corticosteroids were used once in the control group and never in the heliox group p=NS. Inhaled bronchodilator therapy was administered in 17 infants in the control group and 13 infants in the heliox group p=NS. FI02 was reduced to the lowest level that allowed for adequate oxygenation (oxygen saturation ≥92%)*

*i - I2=0% (0-40% may represent unimportant heterogeneity)*

*j – It was not possible to assess imprecision due to lack of information reported in the paper. ~~Wide confidence interval crossing +/-0.25 around line of no effect~~*

*k –Liet et al., 2005 report positive pressure ventilation (invasive or noninvasive). Cambonie et al., 2006 infants who required intubation also received mechanical ventilation*

*l - Kim et al., 2010 (risk of bias): Emergency department physicians were unmasked during the emergency department visit*

*m - Kim et al., 2010 (indirectness): Infants initially received nebulised albuterol treatment driven by 100% oxygen. After randomisation received 11.25mg racemic epinephrine via a face mask*

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*n - One infant in the heliox group required >50% oxygen, helium-oxygen and intubation (this infant was found to have a lobar pneumonia on chest radiography)*
*o - Chowdhury et al., 2013 (risk of bias): 35 infants did not complete treatment. Heliox group were younger at presentation*
*p- 87 infants received treatment via a nasal cannula and 84 infants received treatment via a facemask*
*q - Chowdhury et al., 2013 (indirectness): Additional oxygen allowed if oxygen saturation <93% or worsening respiratory distress*
*r – Mean "readiness to discharge" for admitted infants: heliox group 41.6 hours, control group 43 hours*
*s - Total LoT to alleviate hypoxia (SpO2 ≥ 93% in room air) and respiratory distress (minimal work of breathing). Length of treatment was calculated from the start to successful stop of the trial gas defined by clinical stability (minimal work of breathing and SpO2 >93%) for 1 hour breathing room air*
*t - Hollman et al., 1998 (risk of bias): Small sample size, 18 infants enrolled. 5 infants were not randomised because they had severe bronchiolitis. Only those 13 infants who were randomised are included in this analysis. Three eligible infants were not enrolled in the study because of agitation related to the face mask and technical difficulties. Did not describe infants with a previous history of wheeze in inclusion/exclusion criteria*
*u - Hollman et al., 1998 (indirectness): After enrolment oxygen saturation maintained ≥93%. 17 out of 18 enrolled infants received bronchodilators before admission to ICU and received nebulised albuterol as standard therapy*
*v – Mean change in RDAI 24 hours after treatment: heliox group -2 (SEM 0), control group -2 (SEM 0)*
*w - Mean change in MWCAS from baseline to 240 minutes or emergency department discharge: heliox group 1.84, control group 0.31*
*x - Time MWCAS was measured over not described*

# A.18 Oxygen supplementation

**Table 4948: GRADE profile for comparison of CPAP with comparator oxygen support**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | CPAPa | Standard oxygen supportb | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Change in O2 saturation** | | | | | | | | | | | |
| **Pulse oximetry (%)** | | | | | | | | | | | |
| 1 (Milesi et al, 2013) | 0.7 (SEM 1)* | 2.4 (SEM 3) * | NS | - | Very low | RCT | Very Serious[c] | None | None | Very serious[d] | None |
| **Fraction of inspired oxygen (%)** | | | | | | | | | | | |
| 1 (Milesi et al, 2013) | 7 (SEM 3) * | -5 (SEM 5) * | P < 0.05 | - | Very low | RCT | Very Serious[c] | None | None | Very serious[d] | None |
| **Change in arterial or capillary carbon dioxide levels** | | | | | | | | | | | |
| **Partial pressure of CO2 measured on capillary blood gas sampling (torr)** | | | | | | | | | | | |
| 1 (Milesi et al, 2013) | 6 (SEM 2) * | 4 (SEM 4) * | NS | - | Very low | RCT | Very Serious[c] | None | None | Very serious[d] | None |
| 1 (Thia et al, 2007) | -0.92 (NR) | +0.04 (NR) | P<0.015 | - | Very low | Crossover RCT | Serious[e] | None | Very serious[f] | None | None |
| 1 (Thia et al, 2007) (0 to 12 hours) | As first treatment: -1.35 (SD 1.37) | As first treatment: -0.53 (SD 1.25) | -0.82 [-1.78, 0.14] | - | Low | Crossover RCT | Serious[e] | None | None | Very serious[d] | None |

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | CPAPa | Standard oxygen supportb | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| 1 (Thia et al, 2007) (12 to 24 hours) | After standard therapy: -0.41 (SD 0.87) | After CPAP: 0.5 (SD 0.9) | NR | - | Very Low | Crossover RCT | Serious[e] | None | Very serious[f] | None | None |
| **Change in disease severity score** | | | | | | | | | | | |
| **Modified Wood's clinical asthma score** | | | | | | | | | | | |
| 1 (Milesi et al, 2013) | 2.4 (SEM 0.4) * | 0.5 (SEM 0.4) * | P < 0.05 | - | Very low | RCT | Very Serious[c] | None | None | Very serious[d] | None |
| **Length of hospital stay (days)** | | | | | | | | | | | |
| 1 (Milesi et al, 2013) | 5 (SEM 0.5) * | 5 (SEM 0.5) * | NS | - | Very low | RCT | Very Serious[c] | None | None | Very serious[d] | None |
| **Change in Respiratory rate (breaths/min)** | | | | | | | | | | | |
| 1 (Milesi et al, 2013) | 7 (SEM 4) * | 1.3 (SEM 4) * | NS | - | Very low | RCT | Very Serious[c] | None | None | Seriou[sg] | None |
| **Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation – `** | | | | | | | | | | | |
| **Intubated** | | | | | | | | | | | |
| 1 (Milesi et al, 2013) | 0 of 10 | 0 of 9 | NS | - | Very low | RCT | Very Serious[c] | None | None | None | None |
| Mechanical ventilation | | | | | | | | | | | |
| 1 (Thia et al, 2007) | 0 of 16 | 1 of 15 | NS | - | Moderate | Crossover RCT | Serious[e] | None | None | None | None |
| **Need for/Use of feeding support (tube feeding, IV fluids) – Not reported** | | | | | | | | | | | |
| **Adverse effects (including mortality)** | | | | | | | | | | | |
| **Need to switch treatment groups because of a >30% worsening of clinical score:** | | | | | | | | | | | |
| 1 (Milesi et al, 2013) | 4 of 9 | 0 of 10 | P = 0.032 | - | Very low | RCT | Very Serious[c] | None | None | Serious[g] | None |
| **Required one dose of triclofos to tolerate CPAP** | | | | | | | | | | | |
| 1 (Thia et al, 2007) | 9 of 29 | 0 of 29 | NC | - | Moderate | RCT | Serious[e] | None | None | None | None |

*NS Not statistically significant at p = 0.05 NC not calculable, NR not reported, RCT randomised controlled trial, p-value, RR relative risk*
** graphs in paper suggest that direction of change should be reversed.*
*a Both Milesi and Thai use nasal continuous positive airway pressure*
*b Both Milesi and Thai use oxygen via nasal cannula or face mask, although Milesi used humidified oxygen.*
*c Milesi – randomisation used sequentially number envelopes. Small sample size of 19 infants. 4 of 9 in control group were switched to experimental group.*

*d Very serious imprecision when 95% CI crosses two default MID. ~~Very serious imprecision – SMD crosses both +/-0.5 and 0~~*
*e Thai – small sample size of 29; Identified differences between cross-over groups. Two infants in control group withdrawn before start of treatment.*
*f Examines change in period after crossover, so each group had different managed in period before cross-over. No washout period reported.*
*g ~~Serious imprecision – SMD crosses +/-0.5 and 0~~Serious imprecision when 95% CI crosses one default MID.*

**Table 50~~49~~: GRADE profile for comparison of High Flow Humidified oxygen via nasal cannula with comparator oxygen support (head-box oxygen)**

| Number of studies | Number of children | | Effect | | Quality | Design | Quality assessment | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | HHHFNC | HBO | Relative (95% CI) | Absolute (95% CI) | | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations |
| **Change in O2 saturation** | | | | | | | | | | | |
| **SpO2% at 8 hours** | | | | | | | | | | | |
| 1 (Hilliard et al., 2012) | Median = 100% (94-100) | 96% (93-100) | - | P = 0.04 | Low | RCT | Very Serious [a] | None | None | NC~~A~~ [b] | None |
| **SpO2% at 12 hours** | | | | | | | | | | | |
| 1 (Hilliard et al., 2012) | Median = 99% (96-100) | 96% (93-99) | - | P = 0.04 | Low | RCT | Very Serious [a] | None | None | ~~NA~~ NC [b] | None |
| **SpO2% at 24 hours** | | | | | | | | | | | |
| 1 (Hilliard et al., 2012) | NR | NR | - | NS | Low | RCT | Very Serious [a] | None | None | ~~NA~~ NC [b] | None |
| **Change in disease severity score** | | | | | | | | | | | |
| **Combined bronchiolitis severity score** | | | | | | | | | | | |
| 1 (Hilliard et al., 2012) | NR | NR | - | NS | Low | RCT | Very Serious a | None | None | ~~NA~~ NC b | None |
| **Length of hospital stay (hours)** | | | | | | | | | | | |
| 1 (Hilliard et al., 2012) | Median = 162 (96-300) | Median = 164 (84-233) | - | P = 0.7 | Low | RCT | Very Serious a | None | None | ~~NA~~ NC b | None |
| **Need for high flow humidified oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation** | | | | | | | | | | | |
| 1 (Hilliard et al., 2012) | 0/11 | 0/8 | NC | - | Low | RCT | Very Serious a | None | None | ~~NA~~ NC b | None |
| **Adverse effects (including mortality) – not reported** | | | | | | | | | | | |
| **Change in Respiratory rate (breaths/min) – not reported** | | | | | | | | | | | |
| **Change in arterial or capillary carbon dioxide levels – not reported** | | | | | | | | | | | |
| Need for/Use of feeding support (tube feeding, IV fluids) – not reported | | | | | | | | | | | |

*NA not assessable; NS Not statistically significant at p = 0.05, NC not calculable, NR not reported, RCT randomised controlled trial, p-value, RR relative risk*

*a.Risk of bias was unclear as the method to generate the sequence was not reported; not blind; one participant was changed from the control to intervention group due to "clinical reasons", but no details were provided; weaning protocols have been reported to be different, and these differences could have biased outcomes like length of stay and time to discharge; small trial, authors reported that to show even a large reduction in the need for further respiratory support would need a study with over 100 patients in each arm.*
*b.It was not possible to grade for imprecision due to lack of information (95%CI were not reported).*

## A.19 Nasal suctioning

No evidence was identified for this review.