

## REVIEW

# Helium–oxygen in bronchiolitis—A systematic review and meta-analysis

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## Abstract

**Introduction:** Bronchiolitis is common reason for infant hospitalization. The aim of our systematic review and meta-analysis was to evaluate helium–oxygen (heliox) in bronchiolitis.

**Methods:** We screened 463 studies, assessed 22 of them, and included six randomized controlled trials. Primary outcomes were the need for continuous positive airway pressure (CPAP) or intubation, hospitalization duration, and change in the modified Woods Clinical Asthma Scale (M-WCAS). We calculated mean differences with 95% confidence intervals (CIs) for continuous outcomes and risk ratios (RRs) for dichotomous outcomes.

**Results:** Six studies (five double- and one single-blinded) with 560 infants were included. The risk of bias was high in one, moderate in four, and low in one. The RR for the need for CPAP (three studies) was 0.87 (CI: 0.56–1.35), and for intubation (four studies) was 1.39 (CI: 0.53–3.63), heliox compared to air–oxygen. The hospital stay (four studies) was 0.25 days longer (CI: –0.22 to 0.71) in the heliox group. The mean decrease in M-WCAS from the baseline (three studies) was 1.90 points (CI: 1.46–2.34) greater in the heliox group.

**Conclusion:** We found low-quality evidence that heliox does not reduce the need for CPAP, intubation, or length of hospitalization for bronchiolitis. Based on the M-WCAS scores, heliox seems to relieve respiratory distress symptoms rapidly after its initiation. The included studies had high heterogeneity in their methods and included relatively mild cases of bronchiolitis. A larger randomized controlled trial with more severe cases of bronchiolitis with enough power to analyze the need for intubation is needed in the future.

## KEYWORDS

bronchiolitis, helium–oxygen, intensive care, respiratory syncytial virus

Ilari Kuitunen and Panu Kiviranta shared their first authorship.

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## 1 | INTRODUCTION

Bronchiolitis is a common viral lower respiratory tract infection in infants. The diagnosis is clinical, and the main symptoms are rhinorrhea, coughing, tachypnea, wheezing, rales, and increased respiratory effort. The most severe and typical form of the disease occurs in infants fewer than 6 months old.<sup>1</sup> The most frequent causative pathogen, respiratory syncytial virus (RSV), is estimated to cause over 30 million cases and over 3 million hospitalizations in children under 5 years of age annually.<sup>2</sup>

Previous studies have shown that the following treatments have been ineffective in treating infant bronchiolitis: bronchodilators,<sup>3</sup> chest physiotherapy,<sup>4</sup> systematic or inhaled glucocorticoids,<sup>5</sup> magnesium sulfate,<sup>6</sup> and antibiotics.<sup>7</sup> The current treatment strategy focuses on breathing support. Both high-flow nasal cannula<sup>8</sup> and continuous positive airway pressure (CPAP) methods have been shown to be effective in treating bronchiolitis.<sup>9</sup>

Helium has been shown to reduce both airway resistance and respiratory effort in prospective, nonrandomized studies.<sup>10,11</sup> Therefore, an inhaled helium–oxygen mixture (heliox) has been studied as a treatment for bronchiolitis. However, the results have been controversial; while improvements have been seen in respiratory parameters,<sup>12–14</sup> heliox has not reduced the length of stay in hospital or the need for invasive ventilation.<sup>14,15</sup>

A previous meta-analysis conducted in 2015 stated that heliox does not increase the rate of discharge from the emergency department, decrease the rates of intubation, but it may decrease the length of stay in infants severe respiratory distress and receiving CPAP, but it must be noted that the quality of the included studies was classified as low and the meta-analysis included both parallel and crossover designed studies.<sup>16</sup> Since then, other studies on the use of heliox as a treatment for bronchiolitis<sup>17,18</sup> have been published. Thus, we decided to update the evidence summary. Bronchiolitis treatment strategies are a timely topic, as the 2021–2022 winter season has been predicted to have a high number of bronchiolitis cases since previous RSV seasons were interrupted by the pandemic restrictions.<sup>19–23</sup>

To further clarify the present role of heliox treatment in infant bronchiolitis, we summarized current evidence by conducting a systematic review and meta-analysis.

## 2 | METHODS

### 2.1 | Search strategy

The databases searched in this systematic review were PubMed (MEDLINE), the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus. The literature search was conducted on November 5, 2021. The following phrases were used in the search: “helium” or “helium–oxygen” or “heliox” AND “bronchiolitis” or “bronchitis” or “wheezing” or “respiratory syncytial virus” or “RSV.” We used neither language nor time restrictions. The results were uploaded to Covidence software (Covidence).

### 2.2 | Inclusion and exclusion criteria

All randomized controlled trials (RCTs), regardless of blinding, were included. The reports focused on heliox use in infants aged less than 24 months at the time of the bronchiolitis episode. We had no prespecified criteria for bronchiolitis diagnosis, and we decided to include both positive and negative RSV cases. We had no exclusion criteria regarding prematurity or birthweight in our review.

### 2.3 | Review process

Two authors (I.K. and P.K.) individually screened the abstracts, and conflicts were resolved by a third author or through mutual consensus. Full texts were then assessed by the two authors, and data were extracted using the Covidence 2.0 data extraction templates. The risk of bias was assessed according to Cochrane tool 2.0 for assessment by one author (I.K.), and a senior author (M.R.) was consulted if needed.<sup>24</sup> The risk of bias is reported in the Cochrane Risk of Bias 2.0 table, and it is presented by generating plots using the robvis package.<sup>25</sup> Reporting quality was assessed using the Grading of Recommendations Assessment, Development and Evaluation methodology.<sup>26</sup> Background information on the studies and study populations is presented in Tables 1–3. A flow chart of the study process is presented in Figure 1, and the six selected studies are summarized in Table 1. We have reported this study as suggested in the preferred reporting items for reviews and meta-analyses (PRISMA) guidelines.<sup>27</sup>

### 2.4 | Outcome measures

Our primary outcomes were (1) the need for CPAP, (2) the need for endotracheal intubation, (3) the length of stay in the intensive care unit or pediatric ward, and (4) the change in the modified Woods Clinical Asthma Scale (M-WCAS). Furthermore, we assessed the adverse events as secondary outcomes (mortality or possible other side effects, if the information was available).

### 2.5 | Subgroup analyses

We planned, depending on the available data, to perform a subgroup analysis in preterm neonates and in infants with RSV bronchiolitis.

### 2.6 | Statistics

Review Manager version 5.4 (The Cochrane Collaboration) was used for the meta-analysis. Data analyses were performed according to the Cochrane Handbook for Systematic Review guidelines.<sup>28</sup> We calculated the mean differences (MDs) for the continuous outcomes, as all the included studies used the same continuous outcome measurements. For dichotomous outcomes, we calculated the risk

TABLE 1 Background information of included studies

| Study                 | Country          | Study period | Participants Blinding (N) | Intervention          | Control                 | Admission route                              | Setting              | Main outcome   | Secondary outcomes   | Funding                | Conflicts of interest   | Sponsoring                  |
|-----------------------|------------------|--------------|---------------------------|-----------------------|-------------------------|--|----------------------|--|--|------------------------|---|-----------------------------|
| Liet et al. 2005      | Canada           | 2000–2003    | Double 39                 | Helium 78% oxygen 22% | Nitrogen 78% oxygen 22% | Inflatable head hood                         | PICU                 | Need for intubation  | Clinical scores, oxygen requirement, progression of blood CO <sub>2</sub> , the duration of study gas administration, or PICU stay | Received and reported. | Not reported  | Sponsored by heliox company |
| Cambonie et al. 2006  | France           | 1999–2002    | Double 19                 | Helium 79% oxygen 21% | Nitrogen 79% oxygen 21% | Airhood                                      | PICU                 | M-WCAS at 30 min and at 60 min   | Successful weaning, gas mixture treatment duration, need for intubation, treatment duration  | Received and reported  | Not reported  | Sponsored by heliox company |
| Kim et al. 2011       | USA              | 2004–2008    | Single 69                 | Helium 70% oxygen 30% | Nitrogen 70% oxygen 30% | Face mask of high-flow nasal cannula         | ED                   | M-WCAS for 240 min (at 60-min intervals)                                 |  | Received and reported  | Dr Corcoran was a paid consultant for Praxair Corporation. Others had no COI                | Sponsored by heliox company |
| Chowdhury et al. 2013 | UK and Australia | 2005–2008    | Double 281                | Helium 79% oxygen 21% | Nitrogen 79% oxygen 21% | Face mask or high-flow nasal cannula or CPAP | ED and standard ward | Treatment duration to alleviate hypoxia and respiratory distress for 1 h | Need for CPAP. M-WCAS change   | Received and reported  | Dr Bland was a Clinical Director of British Oxygen Company (BOC) medical. Others had no COI | Sponsored by heliox company |
| Sellem et al. 2018    | Egypt            | 2013–2015    | Double 48                 | Helium 70% oxygen 30% | Nitrogen 70% oxygen 30% | High-flow nasal cannula                      | PICU                 | Improvement of arterial PaO <sub>2</sub>                                 | M-WCAS at 2 h and 24 h   | Not reported           | The authors declared none   | Not reported                |

TABLE 1 (Continued)

| Study              | Country | Study period | Participants |                  | Admission route        | Setting       | Main outcome         | Secondary outcomes  | Funding      | Conflicts of interest     | Sponsoring   |
|--------------------|---------|--------------|--------------|------------------|------------------------|---------------|----------------------|---|--------------|---------------------------|--------------|
|                    |         |              | Blinding (N) | Participants (N) |                        |               |                      |   |              |                           |              |
| Seliem et al. 2019 | Egypt   | 2015–2016    | Double       | 104              | Low-flow nasal cannula | Standard ward | M-WCAS at 2 and 24 h | Total duration of treatment required to improve respiratory distress for a period of 1 h. Need for supplemental oxygen or respiratory support | Not reported | The authors declared none | Not reported |

Abbreviations: COI, conflict of interest; ED, emergency department; M-WCAS, modified Woods Clinical Asthma Scale; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus.

ratios (RRs) with confidence intervals (CIs). Forest plots are presented for the primary outcomes. Inconsistency index statistic  $I^2$  for heterogeneity was used, and if  $I^2 > 50\%$ , a random-effect model was used. If heterogeneity was low ( $<50\%$ ), the fixed effect model was chosen.

Due to the included studies' diverse result reporting, we used the following adjustments and assumptions: If the included study reported only means with standard errors (SEs) instead of standard deviations (SDs), SD was calculated for the meta-analysis by multiplying the SE with the square root of the number of included participants in this treatment group, as suggested by Chapter 6.5.2.2 in the Cochrane Handbook:

$$SD = SE \times \sqrt{N}.$$

If the study did not report the SD for the change from the baseline and only reported the baseline mean with SD and the later mean with SD, we calculated the SD for the change. The following equation reported by Cambonie et al.<sup>13</sup> was used to calculate the correlation coefficient:

$$\text{Corr}_E = \frac{SD_{E,\text{baseline}}^2 + SD_{E,\text{final}}^2 - SD_{E,\text{change}}^2}{2 \times SD_{E,\text{baseline}} \times SD_{E,\text{final}}}.$$

This equation indicated 0.91 to be the correlation coefficient, and this number was inserted into the following formula to determine the SD for the change:

$$SD_{E,\text{change}} = \sqrt{SD_{E,\text{baseline}}^2 + SD_{E,\text{final}}^2 - (2 \times \text{Corr} \times SD_{E,\text{baseline}} \times SD_{E,\text{final}})}.$$

Furthermore, as one of the included studies<sup>18</sup> reported their main outcomes as medians instead of means, we decided to use the median as a substitute for the mean, as described in Chapters 6.5.2.9 and 10.5.3 of the Cochrane Handbook. As the authors did not report enough values to calculate the skewness statistic (Cochrane Handbook, Chapter 9.4.5.3), we relied on the assumption that the data were not skewed based on the other included studies. As the medians were reported with interquartile ranges (IQRs), we calculated the SD by dividing the width of the IQR by 1.35, as suggested in Cochrane Handbook Chapter 7.7.3.5. Furthermore, as two of the studies<sup>13,14</sup> reported their M-WCAS results only in figures, we used WebPlotDigitizer software to identify the desired means and SDs from those figures (<https://automeris.io/WebPlotDigitizer/>). In one study,<sup>18</sup> the M-WCAS results were presented as medians with IQRs, and when calculating the SD for change, we noticed that the SD was greater than the change, which is a strong indication of skewed distribution in the presented results. We decided to exclude this study from the final meta-analysis. One study<sup>15</sup> reported the main outcomes as means with 95% CIs, and we calculated the SD using the following formula, as suggested in Cochrane Handbook Chapter 6.5.2.2:

**TABLE 2** Inclusion and exclusion criteria and the bronchiolitis definition used in patient selection in included studies

| Study                 | Inclusion criteria  | Bronchiolitis definition   | Exclusion criteria   |
|-----------------------|---|--|--|
| Liet et al. 2005      | <ul style="list-style-type: none"> <li>- Age &lt;9 months.</li> <li>- Weight &lt;10.</li> <li>- PICU admission.</li> <li>- First episode of RSV bronchiolitis.</li> <li>- Signs of respiratory failure.</li> </ul>                          | <ul style="list-style-type: none"> <li>- Presence of at least two of the following criteria: tachypnea, chest retractions, wheezing, and hyperinflation on chest radiograph.</li> <li>- Respiratory failure: saturation &lt;92% in room air or PaO<sub>2</sub> &lt;40 mmHg.</li> </ul> | <ul style="list-style-type: none"> <li>- Pneumothorax or pneumomediastinum.</li> <li>- Cystic fibrosis, uncorrected cyanotic congenital heart disease, cardiac failure, neuromuscular disease, or bronchopulmonary dysplasia.</li> <li>- mechanical ventilation already initiated.</li> </ul>  |
| Cambonie et al. 2006  | <ul style="list-style-type: none"> <li>- Age &lt;3 months.</li> <li>- first bronchiolitis episode.</li> <li>- M-WCAS 5, indicating severe respiratory distress.</li> </ul>  | <ul style="list-style-type: none"> <li>- RSV-positive disease with respiratory distress.</li> </ul>  | <ul style="list-style-type: none"> <li>- Underlying cardiopulmonary disease.</li> <li>- Pneumothorax.</li> <li>- Corticosteroid or bronchodilator treatment within 2 h of study enrollment.</li> </ul>   |
| Kim et al. 2011       | <ul style="list-style-type: none"> <li>- Age: 2–12 months of age.</li> <li>- M-WCAS 3 or higher.</li> <li>- Clinically confirmed bronchiolitis.</li> </ul>  | <ul style="list-style-type: none"> <li>- Tachypnea</li> <li>- Cough.</li> <li>- Prolonged expiratory phase.</li> <li>- Wheezing, rales, or chest retractions.</li> <li>- Hyperinflation of lungs on chest radiograph.</li> </ul>   | <ul style="list-style-type: none"> <li>- Pneumonia, croup, foreign body aspiration, pre-existing lung disease.</li> <li>- Supraventricular tachycardia is secondary to albuterol or racemic epinephrine administration.</li> <li>- Bronchodilator treatment within 2 h.</li> <li>- Systematic corticosteroids within the preceding 72 h.</li> <li>- Persistent airway hyperreactivity in the 3 months before the study.</li> </ul> |
| Chowdhury et al. 2013 | <ul style="list-style-type: none"> <li>- Age &lt;12 month, (corrected age if premature).</li> <li>- Clinically confirmed bronchiolitis.</li> </ul>  | <ul style="list-style-type: none"> <li>- History of upper respiratory tract infection followed by wheezing, coughing, breathing difficulty, or chest crackles on auscultation.</li> <li>- Respiratory distress or hypoxia: oxygen saturation &lt;93% in room air).</li> </ul>          | <ul style="list-style-type: none"> <li>- Imminent intubation; saturation &lt;93% despite 15 L/min O<sub>2</sub> via face mask; participation in another study in the previous 4 weeks; salbutamol, epinephrine, or ipratropium therapy within 1 h or systemic steroids within 4 h; bronchiolitis readmission within 24 h.</li> </ul>   |
| Seliem et al. 2018    | <ul style="list-style-type: none"> <li>- Age: 1 month to 2 years.</li> <li>- PICU admission.</li> <li>- RSV acute bronchiolitis.</li> <li>- Oxygen saturation &lt;93% in room air and required supplemental oxygen on admission.</li> </ul> | <ul style="list-style-type: none"> <li>- Cough, increased respiratory rate, chest retraction, prolongation of expiratory time, sibilant rhonchi, and hyperinflated lungs on chest X-ray.</li> <li>- RSV etiology confirmed.</li> </ul>   | <ul style="list-style-type: none"> <li>- Required mechanical ventilation.</li> <li>- Had a hemodynamically significant congenital heart defect.</li> <li>- Chronic lung disease, including bronchopulmonary dysplasia, and those previously diagnosed with hyperreactive airway diseases were also excluded.</li> </ul>  |
| Seliem et al. 2019    | <ul style="list-style-type: none"> <li>- Age: 1 month to 2 years.</li> <li>- Ward admission.</li> <li>- RSV bronchiolitis.</li> <li>- Oxygen saturations &gt;92% with room air.</li> </ul>  | <ul style="list-style-type: none"> <li>- Cough, increased respiratory rate, chest retraction, prolongation of expiratory time, sibilant rhonchi, and hyperinflated lungs on chest X-ray.</li> <li>- RSV etiology confirmed.</li> </ul>   | <ul style="list-style-type: none"> <li>- Required supplemental oxygen or mechanical ventilation.</li> <li>- Congenital heart defects.</li> <li>- Known chronic lung disease, bronchopulmonary dysplasia or diseases manifesting with airway hyperresponsiveness.</li> </ul>  |

Abbreviations: COI, conflict of interest; M-WCAS, modified Woods Clinical Asthma Scale; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus.

$$SD = \sqrt{N} \times (\text{upper limit} - \text{lower limit})/3.92.$$

Furthermore, one study<sup>14</sup> reported only means without SDs for the treatment duration outcome; thus, we used the SD reported by Cambonie et al.<sup>13</sup> in the meta-analysis, as suggested in Chapter 6.5.2.7 of the Cochrane Handbook.

## 2.7 | Protocol registration

The protocol has been registered in Prospero. The registration number is CRD42021289591, and the protocol is available at

[https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=289591](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=289591).

## 3 | RESULTS

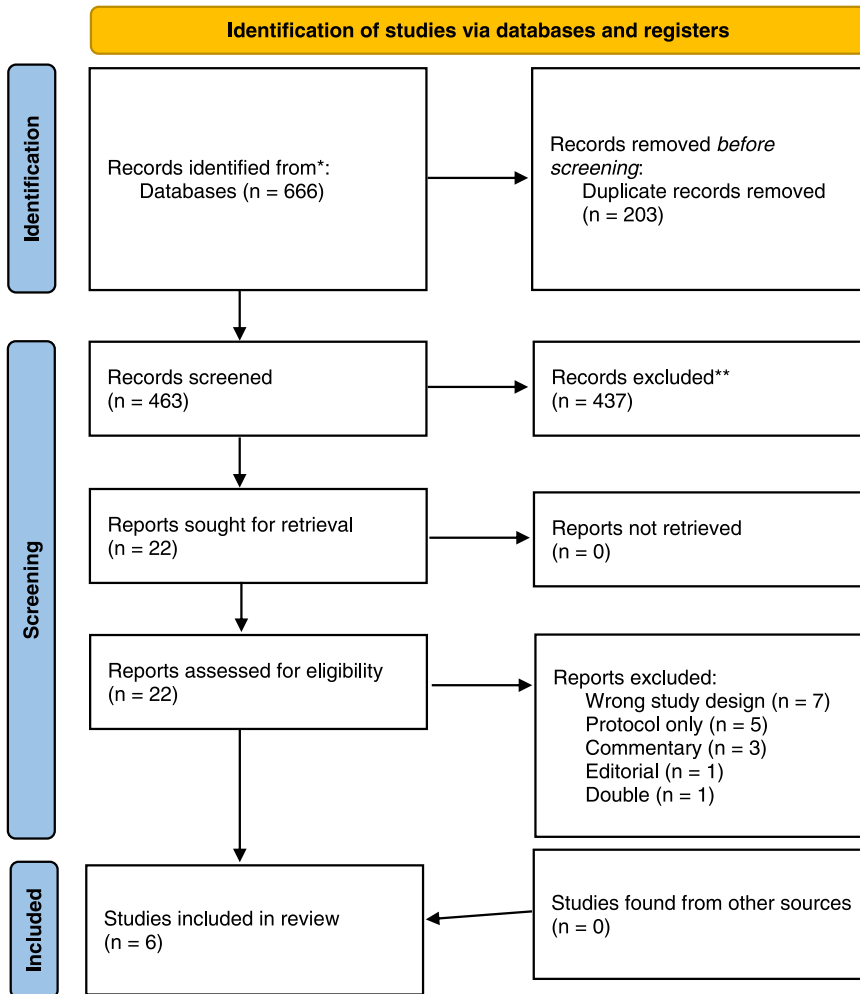
The initial search retrieved 666 studies, and after the duplicates were removed, we screened the abstracts of 463 of them. Of these, 22 were further assessed in the full-text phase. Six RCTs were found,<sup>12–15,17,18</sup> and all of these were included in the final analysis. We did not find any additional studies from other sources to be included (the references of the included studies were checked; see Figure 1).

**TABLE 3** Study population baseline characteristics in the included studies

| Study                              | No. of participants |         | Patient age      |                 | Ex. preterm  |             | Gestational age  |                 | Weight           |                 | Viral etiology RSV |             | Respiratory rate beginning |                 | Saturation beginning |                 | M-WCAS           |                 | pH beginning     |                 | Baseline PaO <sub>2</sub> mmHg |                 |
|------------------------------------|---------------------|---------|------------------|-----------------|--------------|-------------|------------------|-----------------|------------------|-----------------|--------------------|-------------|----------------------------|-----------------|----------------------|-----------------|------------------|-----------------|------------------|-----------------|--------------------------------|-----------------|
|                                    | Heliox n            | Airox n | Heliox mean (SD) | Airox mean (SD) | Heliox n (%) | Airox n (%) | Heliox mean (SD) | Airox mean (SD) | Heliox mean (SD) | Airox mean (SD) | Heliox n (%)       | Airox n (%) | Heliox mean (SD)           | Airox mean (SD) | Heliox mean (SD)     | Airox mean (SD) | Heliox mean (SD) | Airox mean (SD) | Heliox mean (SD) | Airox mean (SD) | Heliox mean (SD)               | Airox mean (SD) |
| Liet et al. 2005                   | 18                  | 21      | 1.1 (0.2)        | 1.0 (0.2)       | 6 (37)       | 5 (24)      | 37.8 (0.7)       | 38.8 (0.8)      | 4.3 (0.3)        | 4.2 (0.3)       | 18 (100)           | 21 (100)    | 59 (1)                     | 53 (1)          | N/A                  | N/A             | N/A              | N/A             | 7.29             | 7.28            | N/A                            | N/A             |
| Cambonie et al. 2006               | 10                  | 9       | 1.0 (0.2)        | 1.0 (0.3)       | N/A          | N/A         | N/A              | N/A             | 3.5 (0.5)        | 3.8 (0.2)       | 10 (100)           | 9 (100)     | 59 (6)                     | 65 (6)          | N/A                  | N/A             | 5.4 (0.2)        | 5.6 (0.2)       | 7.30             | 7.33            | 59.7                           | 64.3            |
| Kim et al. 2011                    | 34                  | 35      | 5.1 (NA)         | 6.1 (NA)        | N/A          | N/A         | N/A              | N/A             | N/A              | N/A             | 23 (68)            | 17 (49)     | N/A                        | N/A             | N/A                  | N/A             | 3.9 (na)         | 3.67 (na)       | N/A              | N/A             | N/A                            | N/A             |
| Chowdhury et al. 2013 <sup>a</sup> | 140                 | 141     | 2.5 mo           | 4.1 mo          | N/A          | N/A         | 39               | 40              | 5.7 kg           | 5.7 kg          | 27 (19)            | 31 (22)     | 56                         | 53              | 93                   | 92              | 3                | 3               | N/A              | N/A             | N/A                            | N/A             |
| Sellem et al. 2018                 | 24                  | 24      | 6.5 (1.3)        | 6.6 (1.1)       | N/A          | N/A         | N/A              | N/A             | N/A              | N/A             | 24 (100)           | 24 (100)    | 63 (5)                     | 64 (3)          | 87 (4)               | 88 (5)          | 5.5 (0.6)        | 5.4 (0.6)       | N/A              | N/A             | 42 (6)                         | 41 (4)          |
| Sellem et al. 2019 <sup>a</sup>    | 52                  | 52      | 11.7 mo          | 12.1 mo         | N/A          | N/A         | N/A              | N/A             | 10.4 kg          | 10.8 kg         | 52 (100)           | 52 (100)    | 66                         | 65              | 95                   | 95              | 4.2 (na)         | 4.3 (na)        | N/A              | N/A             | 56.8                           | 57.1            |

Abbreviations: M-WCAS, modified Woods Clinical Asthma Scale; RSV, respiratory syncytial virus.

<sup>a</sup>Medians presented instead of means.



**FIGURE 1** PRISMA flow chart of the review process. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

The six studies included 560 infants under 24 months of age. All six studies compared heliox to a standard air–oxygen mixture. Three of the studies were conducted in intensive care units, two in pediatric wards, and one in the emergency department (Table 1). The patients' inclusion and exclusion criteria were heterogeneous and relied on different clinical diagnostic criteria of bronchiolitis (Table 2). Funding sources were not reported in two of the studies, and conflicts of interest were also not reported in two of the studies. Four of the studies had gained financial support from companies that provide heliox (Table 1). The ages of the included patients were highly varied (Table 3). Only two studies reported gestational ages, and only one study presented the ratio of infants born preterm, before gestation week 37 (11).

### 3.1 | Risk of bias

The risk of bias was assessed in five domains and overall. All the studies had some concerns, at least in one domain, in the risk of bias assessment. One study had a high risk of bias due to the outcome measurement. Another study was single-blinded, and the blinding process had not been described precisely enough. All the included studies reported their adverse events vaguely and lacked key

| Study                 | Risk of bias domains |    |    |    |    | Overall |
|-----------------------|----------------------|----|----|----|----|---------|
|                       | D1                   | D2 | D3 | D4 | D5 |         |
| Liet et al. 2005      | +                    | +  | +  | -  | -  | -       |
| Cambonie et al. 2006  | +                    | +  | +  | ⊗  | -  | ⊗       |
| Kim et al. 2011       | -                    | +  | +  | -  | -  | -       |
| Chowdhury et al. 2013 | +                    | +  | +  | +  | -  | +       |
| Seliem et al. 2018    | +                    | +  | +  | -  | -  | -       |
| Seliem et al. 2019    | +                    | +  | +  | -  | -  | -       |

Domains:  
 D1: Bias arising from the randomization process.  
 D2: Bias due to deviations from intended intervention.  
 D3: Bias due to missing outcome data.  
 D4: Bias in measurement of the outcome.  
 D5: Bias in selection of the reported result.

Judgement  
 ⊗ High  
 - Some concerns  
 + Low

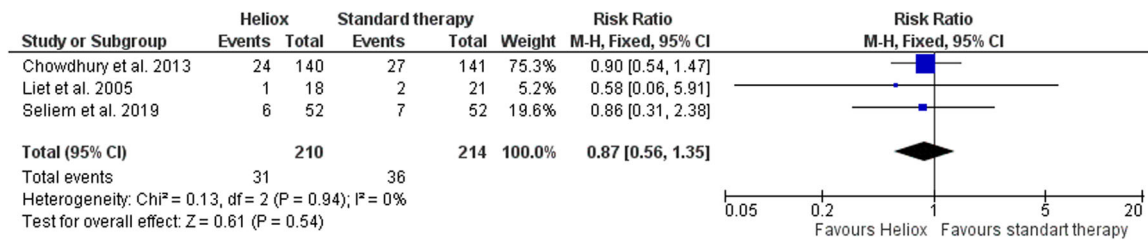
**FIGURE 2** Risk of bias assessment of the included studies. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

information on primary outcomes, which led to concerns about bias in the selection of the reported results (Figure 2).

### 3.2 | Need for CPAP

Three studies (424 infants) reported the need for the initiation of CPAP. In the heliox group, 31 (14.7%) of the 210 children needed





**FIGURE 3** Need for initiation of continuous positive airway pressure (CPAP) treatment. Heliox treatment compared to standard therapy. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

CPAP, and in the standard therapy group, 36 (16.8%) of the 214 infants needed CPAP. The heterogeneity was low, and the RR for the heliox group compared to the air–oxygen group in the fixed model was 0.87 (CI: 0.56–1.35; Figure 3). We ranked the quality of evidence as moderate (Table 4).

### 3.3 | Need for endotracheal intubation

Four studies (313 infants) reported the need for intubation. In the heliox group, 8 (7.0%) of the 114 infants needed to be intubated compared to 6 (5.1%) of the 117 infants in the standard treatment group. The heterogeneity was low, and the RR for intubation in the heliox group compared to the air–oxygen group in the fixed model was 1.39 (CI: 0.53–3.63; Figure 4). We ranked the quality of evidence as low (Table 4).

### 3.4 | Length of hospitalization

Four studies (408 infants) reported the overall duration of the stay in the intensive care unit or in the ward. The length of hospitalization showed high variation between the studies. The observed heterogeneity was high. The weighted MD in the length of stay in the random effect model was 0.25 days (CI: 0.22–0.71), favoring the standard therapy group (Figure 5). We ranked the overall quality of evidence as low (Table 4).

### 3.5 | Change in M-WCAS

Three studies (136 infants) reported the M-WCAS scores at the start of the treatment and later. The reported time periods selected for the analysis varied from between 1 and 4 h. The observed heterogeneity was high. The MD for the change in the M-WCAS from the baseline in the random effects analysis was –1.90 points (CI: –2.34 to –1.46), clearly favoring the heliox group (Figure 6). We ranked the quality of the evidence as low (Table 4).

### 3.6 | Possible side effects and adverse outcomes

None of the studies discussed possible unexpected side effects. Only one study included mortality information; it reported one death in the heliox group out of the nine included patients, and no deaths were observed in the control group.<sup>13</sup> Only one of the studies reported follow-up after discharge, and they did not find differences in the readmission rate between the heliox and control groups.

## 4 | DISCUSSION

### 4.1 | Summary of main results

Six RCTs with 560 infants with bronchiolitis demonstrated that heliox treatment did not have an impact on clinically important endpoints, such as the need for CPAP or invasive mechanical ventilation. It also did not have an effect on the duration of hospitalization. However, heliox seems to reduce symptoms, as shown by a decrease in the M-WCAS score measured after the initiation of therapy, although the minimal important difference in the M-WCAS has not been studied. The results of this study are in line with a previously published meta-analysis.<sup>16</sup>

### 4.2 | Implications for clinical practice

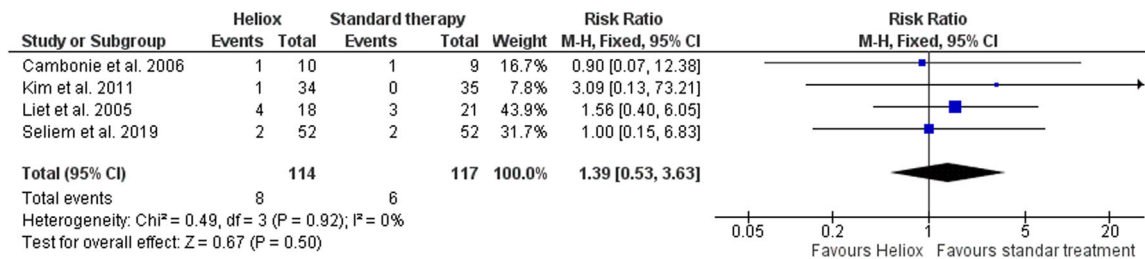
Based on these results, we conclude that it is not justified to continue using heliox to treat bronchiolitis outside of RCTs to avoid escalation of care or to shorten the hospital stay. It is possible that some subpopulations with low respiratory capacity might benefit from the reduced breathing work, although the initiation of heliox should never delay intubation when required. It must be noted that one study found that heliox was only beneficial if it was given with a tight-fitted face mask instead of a nasal cannula.<sup>15</sup> However, as this was the only study that addressed differences in administration routes, a meta-analysis stratified by the delivery device was not possible.



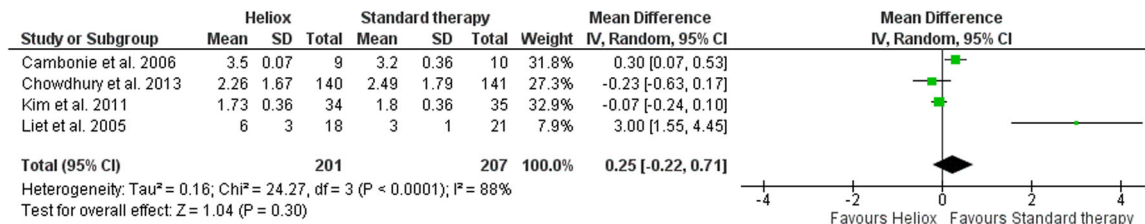
TABLE 4 Body of evidence for main outcomes assessed by the GRADE methodology

| Outcome        | Quality assessment |        | Summary of findings  |                         |              |                                    |                  | Effect       |           | Quality of evidence     |   |               |
|----------------|--------------------|--------|--|-------------------------|--------------|------------------------------------|------------------|--------------|-----------|-------------------------|---|---------------|
|                | No. of studies     | Design | Risk of bias   | Inconsistency           | Indirectness | Imprecision                        | Publication bias | Intervention | Control   |                         | Relative risk (95% CI)                                  | Absolute risk |
| CPAP           | 3                  | RCT    | No serious limitations.  | No serious limitations. | Direct       | Serious limitations: CI includes 0 | Undetected       | 31 of 210    | 36 of 214 | 0.87 (CI: 0.56 to 1.35) | 2.1% (-4.9% to 9.0%)                                    | Moderate      |
| Intubation     | 4                  | RCT    | Some limitations: 1 study was single blinded.  | No serious limitations  | Direct       | Serious limitations: CI includes 0 | Undetected       | 8 of 114     | 6 of 117  | 1.39 (CI: 0.53 to 3.63) | -1.9% (-8.1% to 4.3%)                                   | Low           |
| Length of stay | 4                  | RCT    | Some limitations: 1 study was single blinded.  | No serious limitations  | Direct       | Serious limitations: CI includes 0 | Undetected       |              |           |                         | 0.25 days (-0.22 to 0.71), favors standard therapy      | Low           |
| M-WCAS         | 3                  | RCT    | Serious limitations: 1 study was single blinded.<br>2 studies presented results only in graphs.<br>1 study did not report standard deviations. | No serious limitations  | Direct       | No serious limitations             | Undetected       |              |           |                         | -1.90 points (CI: -2.34 to -1.46) favors heliox therapy | Low           |

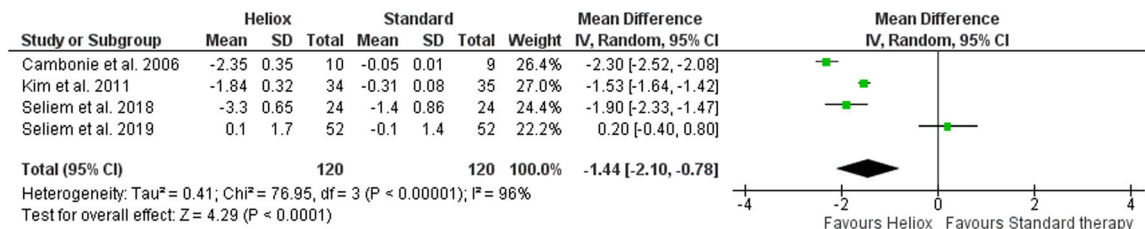
Abbreviations: CI, confidence interval; CPAP, continuous positive airway pressure; GRADE, Grading of Recommendations Assessment, Development and Evaluation; M-WCAS, modified Woods Clinical Asthma Scale; RCT, randomized controlled trial.



**FIGURE 4** Need for endotracheal intubation. Heliox treatment compared to standard therapy. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**FIGURE 5** Pediatric intensive care unit or ward treatment duration in days. Heliox treatment compared to standard therapy. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**FIGURE 6** Change in modified Woods Clinical Asthma Scale score from baseline 1 and 4 h after the initiation of treatment. Heliox treatment compared to standard therapy. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

### 4.3 | Protocol deviations

We planned to perform a subgroup analysis of patients with and without RSV. In a study by Chowdhury et al., heliox was more effective in treating RSV bronchiolitis than other viral etiologies.<sup>15</sup> Unfortunately, due to limited reporting, it was not possible to conduct this subgroup analysis as planned. Furthermore, we planned to analyze preterm or ex-preterm neonates separately; however, this information was only reported in one study.<sup>12</sup>

### 4.4 | Limitations

The limitations of the study are the heterogeneity between the original publications and the relatively high risk of bias. It is important to recognize that the patients were not uniformly ill at the time of randomization. All patients had a clinical diagnosis of bronchiolitis and respiratory distress. However, some of the studies were performed in the emergency department and all patients did not need supplemental oxygen. The majority of patients had only

mild, although clinically significant, symptoms at the time of randomization. Typical M-WCAS was 3–5, indicating relatively mild symptoms. A high percentage of patients recovering without CPAP or intubation in both groups also supported the predomination of relatively mild cases.<sup>15,17,18</sup> Another limitation was the lack of reported adverse events and readmissions in the majority of the included studies. Furthermore, it must be noted that the minimal important difference in the M-WCAS score has not been previously studied,<sup>29</sup> although M-WCAS has been validated for the assessment of bronchiolitis.<sup>30</sup>

The power calculations of the studies were designed mostly to study the length of hospital stay or reduction in M-WCAS score, and not intubation rates nor the need for CPAP. To address these relatively rare outcomes, enrollment of larger patient populations with more severe symptoms is needed, as the risk for intubation in our meta-analysis was approximately 7%. To detect a relevant absolute risk reduction of 3.5% (relative risk reduction of 50%) in the need for intubation with a 1:1 designed RCT, 650 infants per group would be needed (standard alpha 0.05 and power 0.80 in sample size calculation). In this scenario, the number needed to treat to avoid

single intubation would be 28. It remains to be seen whether infants with more severe symptoms would benefit from symptom alleviation and whether this would be associated with a reduced need for escalation of care.

An additional weakness of this meta-analysis is that in the original studies, the criteria for the initiation of CPAP and invasive mechanical ventilation were not uniformly specified. Furthermore, the design of the original publications did not allow subgroup analyses in prematurely born infants with chronic bronchopulmonary dysplasia or in infants with heart failure. This warrants future studies.

The results of this study are in line with a previously published meta-analysis.<sup>16</sup> The previous Cochrane meta-analysis included both crossover and parallel designed studies, whereas our meta-analysis included only parallel designed studies. Crossover design is prone to bias due to the possible carryover effect and therefore we decided to leave them out of our meta-analysis and especially as two of the included crossover trials were unblinded.<sup>16</sup>

In conclusion, we found low-quality evidence that heliox does not reduce the need for CPAP, intubation, or length of hospitalization in infant bronchiolitis. Although heliox seems to have short-term effects in relieving respiratory distress symptoms rapidly after its initiation, it does not have a positive effect on clinically relevant outcomes compared to standard treatment with an air-oxygen mixture. The included studies had high heterogeneity in their methods and selected outcome measures. A well-designed RCT in patients with severe bronchiolitis and proper, tight-fitting face mask administration is needed to assess whether heliox would reduce the need for CPAP or endotracheal intubation.

## AUTHOR CONTRIBUTIONS

**Ilari Kuitunen:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); writing-original draft (lead); writing-review and editing (equal). **Panu Kiviranta:** Conceptualization (equal); data curation (equal); investigation (equal); methodology (equal); writing-original draft (equal); writing-review and editing (equal). **Ulla Sankilampi:** Methodology (equal); project administration (equal); resources (equal); supervision (equal); validation (equal); writing-review and editing (equal). **Heli Salmi:** Conceptualization (equal); data curation (supporting); investigation (equal); validation (equal); writing-review and editing (equal). **Marjo Renko:** Conceptualization (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); validation (equal); writing-review and editing (equal).

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None.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

All the data generated in the review process are available from the corresponding author

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