Continuous positive airway pressure for children in resource-limited settings, effect on mortality and adverse events: systematic review and meta-analysis

Kristen L Sessions,1 Andrew G Smith,2 Peter J Holmberg,3 Brian Wahl,4 Tisungane Mvalo,5,6 Mohammad J Chisti,7 Ryan W Carroll,8 Eric D McCollum4,9

ABSTRACT
Objective Determine non-invasive ventilation with continuous positive airway pressure (CPAP) outcomes for paediatric respiratory distress in low-income and middle-income countries (LMICs).
Design Systematic review and meta-analysis.
Setting LMIC hospitals.
Patients One month to 15 years olds with respiratory distress.
Interventions We searched Medline, Embase, LILACS, Web of Science and Scopus on 7 April 2020. Included studies assessed CPAP safety, efficacy or effectiveness. All study types were included; neonatal only studies were excluded. Data were extracted by two reviewers and bias was assessed. Certainty of evidence was evaluated, and risk ratios (RR) were produced for meta-analyses. (PROSPERO protocol CRD42018084278).
Results 2174 papers were screened, 20 were included in the systematic review and 3 were included in two separate meta-analyses of mortality and adverse events. Studies suitable for meta-analysis were randomised controlled trials (RCTs) from Bangladesh, Ghana and Malawi. For meta-analyses comparing death or adverse events between CPAP and low-flow oxygen recipients, we found no clear CPAP effect on mortality (RR 0.75, 95% CI 0.33 to 1.72) or adverse events (RR 1.52, CI 0.71 to 3.26). We downgraded the certainty of evidence for both death and adverse events outcomes to ‘low’ due to design issues and results discrepancies across RCTs.
Conclusions Evidence for CPAP efficacy against mortality and adverse events has low certainty and is context dependent. Hospitals introducing CPAP need to have mechanisms in place to optimise safety in the context it is being used; this includes the location (a high dependency or intensive care area), adequate numbers of staff trained in CPAP use, close monitoring and mechanisms for escalation, daily direct physician supervision, equipment that is age appropriate and user-friendly and continuous monitoring of outcomes and quality of care.

INTRODUCTION
Significant progress has been made in reducing the global mortality burden for children during the last 20 years. Despite this, nearly 5.4 million children worldwide below 5 years old died in 2017.1 Reflecting historical mortality trends, lower respiratory infections (LRIs) are disproportionately represented, accounting for more deaths among 1–59 month olds than any other illness.1 Various efforts, including WHO treatment guidelines and the Millennium and Sustainable Development Goals, have contributed to child mortality reductions from LRIs.1 However, large respiratory mortality disparities persist in low-income and middle-income countries (LMICs).2

Current management of LRIs and respiratory distress include medical therapies in addition to respiratory support. In many LMICs, the highest level of respiratory support is conventional low-flow oxygen. Larger hospitals may have some capacity for more intensive management, including non-invasive ventilation (NIV) with continuous positive airway pressure (CPAP) and intubation with invasive mechanical ventilation (IMV), but the necessary equipment, medications and human resource capacity makes this infrequent.

CPAP NIV provides positive airway pressure to a spontaneously breathing individual to improve lung
Original research

Table 1  Search strategy

<table>
<thead>
<tr>
<th>PICO term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Patients 1 month to 15 years of age with respiratory distress including, but not limited to, pneumonia or bronchiolitis in low-income and middle-income countries</td>
</tr>
<tr>
<td>Intervention</td>
<td>Non-invasive ventilation including bCPAP, positive end-expiratory pressure and CPAP used in the acute hospital setting for treatment of respiratory distress</td>
</tr>
<tr>
<td>Comparison</td>
<td>High or low-flow oxygen therapy through nasal cannula, mechanical ventilation or no respiratory support</td>
</tr>
<tr>
<td>Outcome</td>
<td>Mortality, treatment failure, adverse events</td>
</tr>
</tbody>
</table>

bCPAP, bubble continuous positive airway pressure.

compliance, ventilation-perfusion mismatch, gas exchange and work of breathing. In high-income countries, CPAP is a standard of care for paediatric respiratory patients with respiratory distress and can reduce IMV and mortality. In LMICs, ‘bubble CPAP’ (bCPAP) may particularly benefit neonatal respiratory distress (<28 days old). bCPAP, unlike conventional CPAP, generates pressure according to the depth the circuit’s expiratory limb is submerged below water. A systematic review of neonatal bCPAP in LMICs demonstrated a 30%–50% reduction in IMV but without a mortality change. Similarly, a systematic review of high flow nasal cannula oxygen found that, when compared with CPAP, CPAP had a lower treatment failure risk among infants with younger age, hypoxemia or respiratory distress. No mortality difference was found. CPAP safety concerns include possible excessive oxygen delivery, skin and/or nasal septal damage, aspiration and, rarely, pneumothorax.

While neonatal bCPAP in LMICs is widely considered beneficial and safe, CPAP efficacy, effectiveness and safety for non-neonates in LMICs has been a recent focus. A systematic review of the literature through 2018 concluded bCPAP was safe and effective in LMICs. However, recent research has raised new questions regarding CPAP for non-neonates. This study’s main objective was to systematically review the literature to determine through meta-analyses if CPAP is efficacious, effective, and safe for 1 month to 15 years old with respiratory distress in LMICs.

METHODS
The development and reporting of this work are per the Preferred Reporting Items for Systematic Reviews (PRISMA) statement. The protocol was registered on PROSPERO (CRD42018084278).

Data sources and search strategies
A search of Medline, Embase, LILACS, Web of Science and Scopus was performed on 7 April 2020 (table 1). There were no language, age, publication date or type restrictions. The World Bank LMIC classification was applied. The search strategy was facilitated by a medical reference librarian (online supplemental appendix 1). The references of included studies were also searched.

Inclusion and exclusion criteria for systematic review
All studies published in peer-reviewed journals on NIV efficacy, effectiveness or safety in the population of interest were included. We defined NIV as bCPAP or CPAP. Editorials, letters, narratives, systematic reviews and errata were excluded. Included studies assessed hospital CPAP efficacy, effectiveness or safety for 1 month to 15 years old with respiratory distress in LMICs. Studies on neonates (<28 days old) only were excluded.

Data collection and extraction for systematic review
Search keywords are in online supplemental appendix 1. The online Covidence platform for data extraction and quality assessments was used. Two independent reviewers screened each study by title and abstract. Eligible studies underwent a full review. Disagreements at the title and abstract stage were resolved by a third blinded author; disagreements at the manuscript review stage were resolved by consensus. A data extraction tool was created in Covidence to collect author, funding, setting, study design, population, interventions and outcomes data.

Figure 1  Study selection. LMICs, low-income and middle-income countries; NIV, non-invasive ventilation.
### Table 2 Characteristics of included studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country and setting</th>
<th>Study design</th>
<th>Sample size and population</th>
<th>Intervention and equipment</th>
<th>Comparison</th>
<th>Outcomes of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cam, 20022</td>
<td>Vietnam Referral hospital Intensive care unit</td>
<td>Randomised control trial</td>
<td>N=37 Age 0–15 years, dengue shock syndrome with respiratory failure despite nasal canula oxygen</td>
<td>CPAP (n=18) Via Beneveniste valve</td>
<td>Oxygen mask (n=19)</td>
<td>Mortality Adverse events Success of treatment at 30 min* and 24 hours</td>
</tr>
<tr>
<td>Chisti, 20151</td>
<td>Bangladesh Center for Diarrhoeal Disease Research Intensive care unit</td>
<td>Randomised control trial</td>
<td>N=225 Age 0–5 years, severe pneumonia and hypoxemia</td>
<td>Locally constructed bCPAP (n=79) Low flow oxygen (n=67) High flow oxygen (n=79)</td>
<td>Mortality treatment failure* (clinical failure, mechanical ventilation or death) Duration of hospital stay Duration of symptoms</td>
<td></td>
</tr>
<tr>
<td>Lal, 20181</td>
<td>India Referral hospital</td>
<td>Randomised control trial</td>
<td>N=72 Age 1–12 months, acute bronchiolitis with wheezing</td>
<td>bCPAP via Gregory circuit (n=36) Standard of care with oxygen mask (n=36)</td>
<td>Mortality Adverse events Need for mechanical ventilation Change in vital signs* and MPSNZ-55 and SA score*</td>
<td></td>
</tr>
<tr>
<td>McCollum, 20191,12</td>
<td>Malawi District Hospital General ward</td>
<td>Randomised control trial</td>
<td>N=644 Age 1–59 months, severe pneumonia and one or more high risk conditions (HIV infection or exposure, Hypoxemia, severe malnutrition)</td>
<td>bCPAP via Fisher and Paykel healthcare CPAP system (n=321) Low-flow oxygen (n=323)</td>
<td>Mortality* Adverse events Duration of respiratory support</td>
<td></td>
</tr>
<tr>
<td>Morales, 20041-13</td>
<td>Mexico National Institute of Respiratory Disease Intensive care unit</td>
<td>Prospective comparative study4</td>
<td>N=26 Age 0–14 years, acute respiratory failure, Glasgow Coma Score &gt;8</td>
<td>NIV via quantum ventilator (n=14) Orotracheal intubation (n=12)</td>
<td>Mortality Adverse events Treatment success* (vital sign stabilisation after 2 hours) Vital sign changes Duration of hospital stay</td>
<td></td>
</tr>
<tr>
<td>Wilson, 20131,14</td>
<td>Ghana Four district hospitals General wards</td>
<td>Crossover randomised control trial</td>
<td>N=69 Age 3 months to 5 years, tachypnoea and retractions or nasal flaring</td>
<td>Hudson RCI CPAP nasal cannula and DeVilviss IntelliPAP CPAP machine Immediate CPAP use (n=31) delayed CPAP use (n=38)</td>
<td>Mortality Change in vital signs*</td>
<td></td>
</tr>
<tr>
<td>Wilson, 20171,15</td>
<td>Ghana District hospital and Municipal hospital General wards</td>
<td>Crossover cluster Randomised control trial</td>
<td>N=2200 Age 1 month–5 years, tachypnoea and retractions or nasal flaring</td>
<td>Hudson RCI CPAP nasal cannula and DeVilviss IntelliPAP CPAP machine (n=1025) Oxygen via non-rebreather face mask (n=1175)</td>
<td>Mortality* Adverse events Duration of CPAP</td>
<td></td>
</tr>
<tr>
<td>Balfour-Lynn, 20141-16</td>
<td>Ghana District hospital General ward</td>
<td>Observational implementation study19</td>
<td>N=106 Age 0–5 years, respiratory distress based on respiratory rate, SpO2, intercostal retractions and grunting</td>
<td>NIV via Nippy Junior paediatric pressure controlled portable ventilator</td>
<td>N/A Mortality* Adverse events</td>
<td></td>
</tr>
<tr>
<td>Bjorkland, 20191,17</td>
<td>Uganda Referral hospital Acute care unit</td>
<td>Prospective, non-blinded, non-randomised interventional study</td>
<td>N=83 Age 30 days – 5 years, moderate or severe respiratory distress based on a calculated respiratory score (Tal score &gt;3) or hypoxia despite low-flow oxygen</td>
<td>SEAL-bCPAP with nasal prong adaptation from ear plug material</td>
<td>N/A Mortality* Adverse events* Change in respiratory rate, oxygen saturation and Tal score†</td>
<td></td>
</tr>
<tr>
<td>Bonora, 20111,18</td>
<td>Argentina Referral hospital Intensive care unit</td>
<td>Retrospective observational study</td>
<td>N=154 Age 1–18 years, patients needing NIV for &gt;30 min to attempt to avoid intubation</td>
<td>Neumovent graph, neumovent graph net or harmony devices for NIV</td>
<td>N/A Mortality Need for intubation* Duration of NIV Duration of hospital stay</td>
<td></td>
</tr>
<tr>
<td>Brown, 20131,19</td>
<td>Malawi Referral hospital</td>
<td>Case report</td>
<td>N=1 Age 6 months, respiratory distress</td>
<td>Low cost bCPAP device developed by authors</td>
<td>N/A Mortality Adverse events Vital sign changes after 1 hour Length of hospital stay</td>
<td></td>
</tr>
</tbody>
</table>

Continued
Data extraction and risk of bias assessments were performed by two independent reviewers and discrepancies were adjudicated by consensus. Comparative studies, including all randomised control trials (RCTs), were evaluated using Cochrane recommended criteria. Studies with no comparator group were evaluated using criteria proposed by Murad et al to evaluate selection, ascertainment, causality and reporting domains.

**Risk of bias assessment for studies included in systematic review**

Data extraction and risk of bias assessments were performed by two independent reviewers and discrepancies were adjudicated by consensus. Comparative studies, including all randomised control trials (RCTs), were evaluated using Cochrane recommended criteria. Studies with no comparator group were evaluated using criteria proposed by Murad et al to evaluate selection, ascertainment, causality and reporting domains.

**Data synthesis, assessment of reporting biases and assessment of heterogeneity**

The feasibility of meta-analyses was assessed using clinical and methodological characteristics for all study designs. Random-effects models summarised study findings using an inverse variance method. For dichotomous outcomes, risk ratios (RR) or ORs and 95% CIs estimated the treatment effect. We used difference in means for continuous outcomes. We created and evaluated a funnel plot to evaluate for reporting biases. We estimated...
### Table 3 Outcomes for randomised control trials

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Total sample size</th>
<th>Mortality</th>
<th>Findings</th>
<th>Adverse events</th>
<th>Reported limitations</th>
<th>Reported conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cam, 2002</td>
<td>37</td>
<td>CPAP: 4/18 (22%) Oxygen: 0/19 (0%)</td>
<td>Stabilisation of patient with PaO₂ &gt;80 mm Hg after 30 min: CPAP: 14/18 (78%) Oxygen: 6/19 (32%) 13/19 oxygen patients were transitioned to CPAP after failure on oxygen, all improved</td>
<td>0 (0%)</td>
<td>Small sample size compared with calculated sample size</td>
<td>Nasal CPAP is useful in improving management of acute respiratory failure in children with dengue shock syndrome</td>
</tr>
<tr>
<td>Chisti, 2015</td>
<td>225</td>
<td>bCPAP: 3/79 (4%) Low-flow oxygen: 10/67 (15%) High-flow oxygen: 10/79 (13%) Total: 23/225 (10%)</td>
<td>Treatment failure: bCPAP: 5/79 (6%) Low-flow oxygen: 16/67 (24%) High-flow oxygen: 10/79 (13%) Length of hospital stay (days; median (IQR)): bCPAP: 5 (3–7) Low-flow oxygen: 4 (3–7) High-flow oxygen: 5 (3–7)</td>
<td>bCPAP: 17/79 (22%) Oxygen: 14/67 (21%) AE included abdominal distension, and newly recognised heart failure.</td>
<td>Trial was stopped early before full recruitment</td>
<td>Bubble CPAP therapy could be beneficial in hospitals in developing countries where the only respiratory support is standard flow oxygen.</td>
</tr>
<tr>
<td>Lal, 2018</td>
<td>72</td>
<td>Not reported</td>
<td>Decrease in RR at 1 hour (mean, SD): bCPAP: 8 (6) Supplemental oxygen via facemask or hood: 5 (4) Need for mechanical ventilation: CPAP: 1/36 (3%) Standard of care: 1/36 (3%)</td>
<td>0 (0%)</td>
<td>Study duration was only 1 hour, functional outcomes including need for invasive ventilation and duration of hospital stay were not evaluated</td>
<td>CPAP significantly decreases respiratory rate in patients with acute bronchiolitis in the first hour of treatment</td>
</tr>
<tr>
<td>Morales, 2004</td>
<td>26</td>
<td>0 (0%)</td>
<td>Duration of Hospital stay (days, mean (SD)): NIV: 8.2 (2.8) Intubation: 19 (11) Success of intervention: NIV: 12 (86%) Intubation: 12 (100%)</td>
<td>NIV: 11 (79%) Intubation: 11 (92%) Complications included aerophagia, erythema, septal necrosis, pericardial effusions, infections</td>
<td>Limitations not reported</td>
<td>NIV is useful in reducing the possibility of orotracheal intubation and decreases the length of hospital stay compared with mechanical ventilation</td>
</tr>
<tr>
<td>McCollum, 2019</td>
<td>644</td>
<td>bCPAP: 53/321 (17%) Oxygen: 35/323 (11%)</td>
<td>Duration of respiratory support (days, mean (SD)): bCPAP: 4.5 (1.9) oxygen: 3.9 (2.1)</td>
<td>bCPAP: 11/321 (3%) Oxygen: 1/323 (&lt;1%) AE included aspiration events, probable pneumothorax and skin breakdown</td>
<td>Trial stopped early before full recruitment, no access to radiographic imaging, designed to reflect real-world setting but staff augmented,</td>
<td>BCPAP in a paediatric ward without daily physician supervision did not reduce mortality among high-risk Malawian children with severe pneumonia, compared with oxygen.</td>
</tr>
<tr>
<td>Wilson, 2013</td>
<td>70</td>
<td>Immediate CPAP: 3/31 (10%) Delayed CPAP: 0/38 (0%)</td>
<td>Decrease in RR at 1 hour (mean (CI)): Immediate CPAP: 16 (10, 21) Delayed CPAP: 1 (-2, 5) Percent change in RR at 2 hours: Immediate CPAP: data missing Delayed CPAP: 13 (8, 19)</td>
<td>Not reported</td>
<td>Study design not powered to evaluate mortality, Active study was only 2 hours long, not blinded, 100% consent rate, limited diagnostic testing</td>
<td>CPAP is a safe and effective method to decrease respiratory rates in children presenting with nonspecific respiratory distress</td>
</tr>
<tr>
<td>Wilson, 2017</td>
<td>2200</td>
<td>CPAP: 26/995 (3%) Control: 44/1160 (4%)</td>
<td>Duration of CPAP (median (IQR)): CPAP: 12 (7.2–19.8) Control: 0 (0)</td>
<td>CPAP related AE: CPAP: 28/1021 (3%) Control: 24/1160 (2%) CPAP related AE included vomiting, nasal trauma, skin trauma, aspiration and eye trauma Other AE: CPAP: 70/1021 (7%) Control: 85/1160 (7%) Other AE included fever, cough, diarrhoea, rash, skin or mucosal complaints, respiratory distress, rhinitis, swelling, seizure, anaemia or malaria</td>
<td>Allocation by site rather than patient leading to concealment and enrolment bias, limited diagnostic abilities, possibly underpowered</td>
<td>CPAP did not decrease all-cause 2-week mortality in children 1 month to 5 years with undifferentiated respiratory distress. After adjustments for key variables, 2-week mortality in CPAP group vs control group was decreased for children under 1 year of age. CPAP improved respiratory rate.</td>
</tr>
</tbody>
</table>

AE, adverse events; bCPAP, bubble continuous positive airway pressure; CPAP, continuous positive airway pressure; RR, respiratory rate in breaths per minute.
### Table 4: Outcomes for non-randomised control trials

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Total sample size</th>
<th>Mortality</th>
<th>Additional findings</th>
<th>Adverse events</th>
<th>Reported limitations</th>
<th>Reported conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balfour-Lynn, 2014</td>
<td>106</td>
<td>2 (2%)</td>
<td>N/A</td>
<td>0 (0%)</td>
<td>Possibility of missing data</td>
<td>NIPPV can be a simple and cost-effective way to treat patients with acute respiratory failure</td>
</tr>
<tr>
<td>Bjorklund, 2019</td>
<td>83</td>
<td>8 (10%)</td>
<td>Patients with severe illness based on TAL score: 0 hours: 64/83 (77%) 2 hours: 12/83 (15%)</td>
<td>Severe: 0 Mild: 5 (6%) Mild AE included nasal tissue irritation and abdominal distension</td>
<td>Evaluations for complications based only on clinical exam, not powered to evaluate effectiveness, differences in pretrial and trial patients</td>
<td>SEAL-bCPAP is safe for treatment of respiratory distress in non-neonatal children in LMIC with a trend towards decreased mortality</td>
</tr>
<tr>
<td>Bonora, 2011</td>
<td>154</td>
<td>Avoided intubation: 3.8% Required intubation: 38.8%</td>
<td>No need for intubation: 80/154 (52%) Duration of NIV (days, median (IQR)): Avoided intubation: 4 (2.25–6) Required intubation: 2 (1–4) Duration of hospital stay (days, median (IQR)): Avoided intubation: 6 (5–9) Required intubation: 13 (9–24)</td>
<td>Skin breakdown noted but number of adverse events not reported</td>
<td>Retrospective study design with no control group, no rigid protocol to determine when therapies should be escalated or discontinued</td>
<td>NIV avoided mechanical ventilation in a high proportion of children</td>
</tr>
<tr>
<td>Brown, 2013</td>
<td>1</td>
<td>0 (0%)</td>
<td>Duration of bCPAP: 4 days Duration of hospital stay: 6 days</td>
<td>0 (0%)</td>
<td>Limitations not reported</td>
<td>A low-cost bCPAP could reduce child mortality in Africa</td>
</tr>
<tr>
<td>Figueroa, 2017</td>
<td>120</td>
<td>Not reported</td>
<td>Success of bCPAP: 72% Duration of bCPAP (hours, mean (CI)): 75 (65–85) Duration of ICU stay (days, mean (CI)): 10 (6–11)</td>
<td>4 (3%) Complications included abdominal bloating and pneumothorax</td>
<td>Limitations not reported</td>
<td>A reduction in respiratory rate, heart rate and TAL scores at 2 hours after starting intervention were predictors of success</td>
</tr>
<tr>
<td>Ghiggi, 2000</td>
<td>42</td>
<td>2 (5%)</td>
<td>Duration of nasopharyngeal CPAP (days, mean (SD)): 4.12 (3.71) Need for mechanical ventilation: 13/42 (31%)</td>
<td>8 (19%) Complications included tube obstructions and apnoea due to excessive sedation</td>
<td>Small sample size</td>
<td>Nasopharyngeal CPAP was useful to avoid mechanical ventilation</td>
</tr>
<tr>
<td>Kinikar, 2011</td>
<td>36</td>
<td>0 (0%)</td>
<td>Duration of ICU stay (days, median (range)): 2 (2–5) Duration of hospital stay (days, median (range)): 7 (6–11) Decrease in mean RR after 6 hours: H1N1 positive: 20 H1N1 negative: 17</td>
<td>0 (0%)</td>
<td>Limitations not reported</td>
<td>Indigenous NB-CPAP improves hypoxemia and signs and symptoms in hemodynamically stable children with acute respiratory failure due to influenza-like injury</td>
</tr>
<tr>
<td>Lum, 2011</td>
<td>129</td>
<td>19 (15%)</td>
<td>Duration of NIV (days, median (IQR)): 4 (2–8) Duration of PICU stay (days, median (IQR)): 4.5 (2–9) Avoided mechanical ventilation for ≥5 days: 98 (76%)</td>
<td>29 (22%) Complications included pneumonia while on NIV, pressure from mask and problems with mask fitting</td>
<td>Not an RCT, no routine use of blood gas sampling, shortage of NIV machines</td>
<td>NIV represents a viable strategy that provided effective respiratory support and prevented intubation in majority of patients</td>
</tr>
<tr>
<td>Machen, 2015</td>
<td>79</td>
<td>23 (29%)</td>
<td>Duration of CPAP (days, mean): 3.12 Duration of hospitalisation (days, mean): 8.41 Had lower RISC score after 24 hours: 63 (80%)</td>
<td>Not reported</td>
<td>Clinical diagnoses could have led to misclassification</td>
<td>bCPAP was most beneficial to patients with bronchiolitis</td>
</tr>
<tr>
<td>McCollum, 2011</td>
<td>1</td>
<td>0 (0%)</td>
<td>Duration of bCPAP (days): 7</td>
<td>0 (0%)</td>
<td>Limitations not reported</td>
<td>bCPAP was successful in treating an infant with PJP pneumonia secondary to HIV infection</td>
</tr>
<tr>
<td>Myers, 2019</td>
<td>117</td>
<td>38 (33%)</td>
<td>Required intubation: 15/115 (13%) Duration of treatment (hours, median (IQR)): 24 (24–60)</td>
<td>13 (11%) Complications included blocked nostrils or nasal prongs, interruption of oxygen supply, nasal septum lesions and aspiration</td>
<td>Observational study design, small sample size, limited human resources and some missing data points</td>
<td>It is feasible to use bCPAP in the hospital management of critically ill children in resource-limited settings</td>
</tr>
</tbody>
</table>

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Table continued...
statistical heterogeneity using the $\chi^2$ test and the $I^2$ statistic. The latter describes the proportion of variation across studies due to heterogeneity rather than sampling error. All statistical analyses were done using Stata V.16.1 (Stata, College Station, Texas, USA).

Certainty of evidence assessment

For studies contributing data to meta-analyses, we used GRADEpro GDT software (GRADEpro GDT 2015) to apply the Cochrane-recommended GRADE domains of study limitations, consistency of effect, imprecision, indirectness and publication bias to evaluate evidence quality.10 When appropriate limitations were identified, we downgraded evidence according to guidelines.

Role of the funding source

There was no direct funding. The corresponding author had full access to all study data and final responsibility for submission.

RESULTS

Systematic review

A total of 2174 studies were screened and 20 were included in the systematic review (figure 1). These included 5 RCTs,11–15 1 cluster RCT,16 1 non-randomised comparative study,17 and 13 observational studies18–28 (table 2). Most studies evaluated bCPAP or conventional CPAP and were small. Ten studies also included neonates. Sixteen studies were at tertiary referral or provincial hospitals and included intensive care or high acuity units. Four studies, including RCTs in Malawi14 and Ghana,16 were at district hospitals in a general paediatric ward. The Ghana RCT had daily physician oversight while the Malawi RCT did not. Mortality was the primary endpoint in seven studies. In the Bangladesh RCT, bCPAP was delivered in an intensive care unit (ICU) under paediatric intensive care physician supervision.12

<table>
<thead>
<tr>
<th>Author, year</th>
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<th>Reported conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsan, 201916</td>
<td>64</td>
<td>35 (55%)</td>
<td>RDS (mean (IQR)): Pre-CPAP: 11 (10–12) 1 hour: 9 (8–11) 84 hours: 6.5 (6–6)</td>
<td>Not reported</td>
<td>Observational study design, bCPAP only used when oxygen failed</td>
<td>bCPAP improves oxygenation and reduces respiratory distress in some children but children with comorbidities continue to do poorly</td>
</tr>
<tr>
<td>Walk, 201616</td>
<td>77</td>
<td>36 (47%)</td>
<td>Duration of treatment (days, median (IQR)): 3 (3–5)</td>
<td>13 (17%)</td>
<td>Non-randomised and uncontrolled, small sample size, underestimating missing vital sign data</td>
<td>bCPAP can be feasibly implemented into a tertiary African hospital with high-risk patients</td>
</tr>
</tbody>
</table>

AEs, adverse events; bCPAP, bubble continuous positive airway pressure; CPAP, continuous positive airway pressure; RR, respiratory rate in breaths per minute.

RCTs and mortality

For the five RCTs, CPAP mortality varied from 0% to 22% (table 3). Mortality or treatment failure served as primary endpoints for all. In the Bangladesh RCT, children on bCPAP compared with low-flow oxygen had lower mortality (4% bCPAP vs 15% oxygen: RR 0.25, 95% CI 0.07 to 0.89; $p=0.022$).12 The study was stopped early by the data safety monitoring board for benefit. A second RCT in Ghana used a cluster crossover design in which CPAP was available at one hospital at a time, while the other hospital was the control.16 Children at the intervention hospital received CPAP and at both hospitals, supplemental oxygen was provided as needed to maintain oxygenation >92%. The proportion of controls receiving oxygen was not reported. This trial found no difference in all-cause mortality between CPAP (3%) and controls (4%) (RR 0.40, 95% CI 0.19 to 0.82; $p=0.01$).16 Another RCT in Malawi comparing bCPAP to low-flow oxygen found higher mortality in the bCPAP arm (17% and 11%, RR 1.52; 95% CI 1.02 to 2.27; $p=0.036$).14 This study was stopped early due to both futility and the possibility of harm from bCPAP. In an open, prospective RCT from Vietnam involving 37 children with respiratory distress from dengue, 18 received CPAP and 19 received oxygen. Mortality was 22% after CPAP compared with 0% for controls ($p=0.03$).9

Observational studies and mortality

Among the 11 observational studies, CPAP mortality ranged from 0% to 55% (table 4). Four tertiary hospital studies reported mortality >30%,20 26–28 Mortality was the primary endpoint for five prospective observational studies and was 2%,10 29%25 33%26 and 47%.28 Results from several studies suggested multiple comorbidities may detrimentally influence outcomes. Specifically, two studies with high all-cause mortality among CPAP recipients reported fewer deaths among HIV-uninfected patients with very severe pneumonia and single organ failure.26 28

Non-fatal adverse events (AEs)

Sixteen studies reported non-fatal AEs (table 3A,B). Six of these reported no AEs. AEs in the other seven studies were 3%–22%. One study reported a 79% AE rate including infections.17 When infections were excluded, the AE rate was 22%. Most AEs were mild and included trauma to the nasal septum, skin and eyes, vomiting and abdominal distension.14 16 17 19–21 26 A few serious AEs including the development of heart failure, aspiration and pneumothorax were reported.12 14 16 21

Figure 2 Risk of bias assessment for RCT and prospective comparative studies.


Adverse events (AEs) and fatal AEs (FAEs) attributable to CPAP.
Risk of bias assessment for systematic review

Due to the inability to blind the respiratory therapy intervention, no RCT was blinded from participants, personnel or outcome assessors (figure 2). One study was not randomised and another RCT used a cluster crossover design and randomised at the hospital level. All seven studies had low risk of incomplete data or reporting bias.

Five observational studies had unclear or high risk of selection bias due to inconclusive reporting (online supplemental file). All studies were considered low risk of ascertainment bias. Due to the observational design, 10/13 studies were considered unclear or high risk of causality bias. Risk of causality bias was assigned based on potential alternate causes, presence of a challenge/rechallenge phenomenon and appropriate follow-up duration.

Meta-analysis

The RCTs in Bangladesh, Ghana and Malawi were found suitable for inclusion in a meta-analyses for the efficacy of CPAP against mortality and adverse events (figure 1). Meta-analyses for other trial endpoints or with observational studies were not suitable due to incomparability of endpoints and populations, and high risk of bias (table 5). The combined RR of CPAP, compared with low-flow oxygen, was 0.75 (95% CI 0.33 to 1.72), indicating no conclusive mortality benefit (figure 3). We measured $I^2$ to be 82.67%, consistent with considerable heterogeneity (online supplemental appendix 2). For AEs, the combined RR of CPAP, compared with low-flow oxygen, was 1.52 (95% CI 0.71 to 3.26), which is similarly inconclusive for AE risk (figure 4). Heterogeneity was also high ($I^2$ 56.69%) (online supplemental appendix 3).

Certainty of evidence assessment

The overall certainty of evidence for the outcomes of death and adverse events was low (table 6). Evidence certainty was downgraded two levels for both outcomes due to lack of blinding of participants, personnel or during analysis, as well due to the varying RR estimates of death and also adverse events, little CI overlap and high heterogeneity.

DISCUSSION

We completed a systematic review and meta-analysis of studies on CPAP and its effect on mortality, and adverse events among 1 month to 15 year olds in LMICs. Overall, the summary estimate from the meta-analyses of three RCTs found both inconclusive
and low certainty evidence for CPAP efficacy against death and adverse events, compared with oxygen, for 1–59-month-old children with respiratory distress in LMICs. Our findings suggest that facilities in LMICs using CPAP should monitor outcomes closely and pay attention to the context in which CPAP has been most efficacious: this includes the location (a high dependency or intensive care area), adequate numbers of staff trained in CPAP use, close monitoring and mechanisms for escalation, daily direct physician supervision and equipment that is age appropriate and user-friendly.

The different contexts of the three RCTs included in these meta-analyses are important. While the Bangladesh RCT was stopped after an interim analysis showed evidence of a mortality benefit of CPAP in that context, some argued the trial’s closure was premature. In Bangladesh, the setting was an ICU with daily physician supervision and trained nurses. The Ghana RCT did not demonstrate any difference in the primary mortality outcome. However, in an exploratory analyses of the outcomes for children less than 1 year of age, the authors observed a mortality benefit for CPAP compared with controls. It was unclear what proportion of controls received oxygen and the low hypoxemia prevalence suggests it is few. Severity of illness and comorbidity is an important case-mix difference in the three RCTs, as in the other two trials oxygen was administered to all controls. The Ghana RCT was also conducted under physician oversight in a district hospital emergency department. Finally, the Malawi RCT was stopped early for both futility and potential harm from CPAP. This trial enrolled sicker children than in Ghana (all participants had at least one comorbidity or hypoxemia), and the trial was conducted in a district paediatric ward hospital with trained staff but without daily physician oversight.

When reviewing all AEs, excluding mortality, we found them to be rare and generally minor, although meta-analysis findings were inconclusive. Significant AEs were even rarer and included aspiration, pneumothorax and development of heart failure. Investigators from the Malawi trial postulate that aspiration or cardiopulmonary interactions leading to reduced cardiac output may have influenced their findings. While these results are inconclusive on the effect of CPAP on mortality, they still provide useful guidance for CPAP use in LMICs. We suggest that CPAP is used only with direct physician oversight in an ICU, high dependency or dedicated unit with overall patient to staff ratios no higher than 5:1.

Given this mixed evidence, further research is needed as more paediatric services in LMICs consider whether to implement CPAP. A strong understanding of which patient populations will derive maximum benefit from CPAP in resource-constrained settings is essential. In addition, as intensive care modalities become more common in LMICs, attention must be given to the impact of intensive care on resource utilisation. This is particularly important for a more resource intensive modality like CPAP where evidence remains low certainty and context specific. For example, if oxygen concentrators are used for bCPAP gas flow, then one child occupies one entire oxygen concentrator. Oxygen flow from the same concentrator could in turn simultaneously treat up to five total children requiring oxygen. Nevertheless, an understanding of the context in which CPAP safety can be optimised is needed from the three trials.

In sum, this systematic review demonstrates current data for CPAP has overall low certainty and is inconclusive on a mortality benefit, but adverse events are few. The current literature is helpful in understanding the context in which CPAP can be safe as a part of the overall management of acute respiratory infections in children.
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