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

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2021-323041).

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Received 18 August 2021
Accepted 17 November 2021
Published Online First
8 December 2021

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 year 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.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

⇒ Lower respiratory infections (LRIs) like pneumonia are the leading infectious cause of paediatric death globally despite antibiotics and oxygen treatment.

⇒ Non-invasive ventilation (NIV) with continuous positive airway pressure (CPAP) is an accepted paediatric treatment modality in high-income countries and for severely ill neonates in low-income and middle-income countries (LMICs).

⇒ The most up-to-date research evaluating the efficacy, effectiveness and safety of CPAP NIV for severe LRI of non-neonates has been reported but not systematically assessed and evaluated by meta-analysis.

WHAT THIS STUDY ADDS?

⇒ This systematic review and meta-analysis synthesises the most updated body of evidence for non-neonates treated with CPAP NIV in LMICs.

⇒ We provide key evidence-based recommendations for hospitals in LMICs who have already implemented CPAP NIV for the management of non-neonates with severe respiratory illnesses like LRIs.

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 compliance, ventilation-perfusion mismatch, gas exchange and work of breathing.[3] In high-income

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To cite: Sessions KL, Smith AG, Holmberg PJ, *et al*. *Arch Dis Child* 2022;**107**:543–552.

Table 1 Search strategy

PICO term	Description
Population	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
Intervention	Non-invasive ventilation including bCPAP, positive end-expiratory pressure and CPAP used in the acute hospital setting for treatment of respiratory distress
Comparison	High or low-flow oxygen therapy through nasal cannula, mechanical ventilation or no respiratory support
Outcome	Mortality, treatment failure, adverse events

bCPAP, bubble continuous positive airway pressure.

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.[3] A systematic review of neonatal bCPAP in LMICs demonstrated a 30%–50% reduction in IMV but without a mortality change.[4] 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.[5] No mortality difference was found. CPAP NIV 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.[6] 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 olds with respiratory distress in LMICs.

METHODS

The development and reporting of this work are per the Preferred Reporting Items for Systematic Reviews (PRISMA) statement.[7] 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.

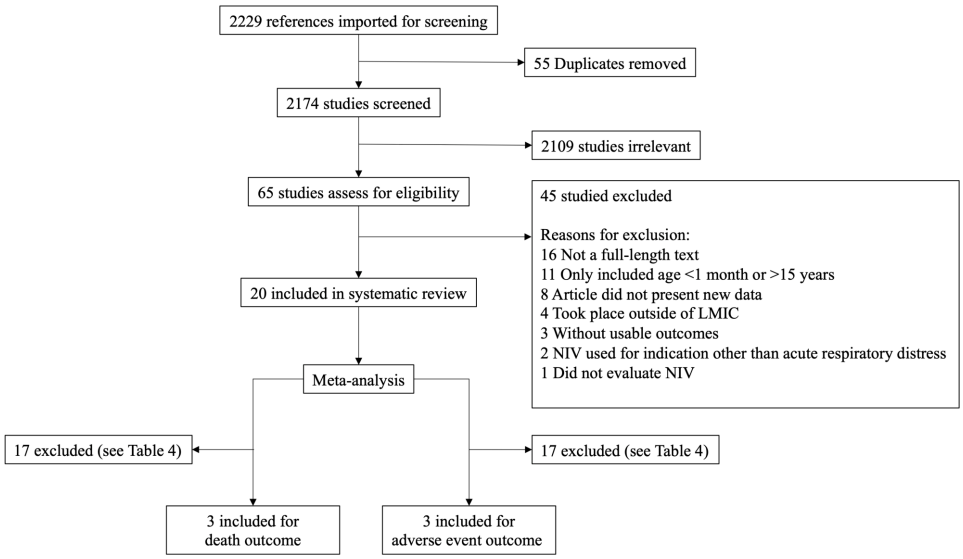

Figure 1 Study selection. LMICs, low-income and middle-income countries; NIV, non-invasive ventilation.

Table 2 Characteristics of included studies

Author, Year	Country and setting	Study design	Sample size and population	Intervention and equipment	Comparison	Outcomes of interest
Randomised control trials						
Cam, 2002[9]	Vietnam Referral hospital Intensive care unit	Randomised control trial	N=37 Age 0–15 years, dengue shock syndrome with respiratory failure despite nasal canula oxygen	CPAP (n=18) Via Beneveniste valve	Oxygen mask (n=19)	Mortality Adverse events Success of treatment at 30 min* and 24 hours
Chisti, 2015[10]	Bangladesh Center for Diarrhoeal Disease Research Intensive care unit	Randomised control trial	N=225 Age 0–5 years, severe pneumonia and hypoxemia	Locally constructed bCPAP (n=79)	Low flow oxygen (n=67) High flow oxygen (n=79)	Mortality treatment failure* (clinical failure, mechanical ventilation or death) Duration of hospital stay Duration of symptoms
Lal, 2018[11]	India Referral hospital	Randomised control trial	N=72 Age 1–12 months, acute bronchiolitis with wheezing	bCPAP via Gregory circuit (n=36)	Standard of care with oxygen mask (n=36)	Mortality Adverse events Need for mechanical ventilation Change in vital signs* and MPSNZ-SS+ and SA score+
McCollum, 2019[12]	Malawi District Hospital General ward	Randomised control trial	N=644 Age 1–59 months, severe pneumonia and one or more high risk conditions (HIV infection or exposure, Hypoxemia, severe malnutrition)	bCPAP via Fisher and Paykel healthcare CPAP system (n=321)	Low-flow oxygen (n=323)	Mortality* Adverse events Duration of respiratory support
Morales, 2004[15]	Mexico National Institute of Respiratory Disease Intensive care unit	Prospective comparative study‡	N=26 Age 0–14 years, acute respiratory failure, Glasgow Coma Score >8	NIV via quantum ventilator (n=14)	Orotracheal intubation (n=12)	Mortality Adverse events Treatment success* (vital sign stabilisation after 2 hours) Vital sign changes Duration of hospital stay
Wilson, 2013[13]	Ghana Four district hospitals General wards	Crossover randomised control trial	N=69 Age 3 months to 5 years, tachypnoea and retractions or nasal flaring	Hudson RCI CPAP nasal cannula and DeVilviss IntelliPAP CPAP machine	Immediate CPAP use (n=31) delayed CPAP use (n=38)	Mortality Change in vital signs*
Wilson, 2017[14]	Ghana District hospital and Municipal hospital General wards	Crossover cluster Randomised control trial	N=2200 Age 1 month-5 years, tachypnoea and retractions or nasal flaring	Hudson RCI CPAP nasal cannula and DeVilviss IntelliPAP CPAP machine (n=1025)	Oxygen via non-rebreather face mask (n=1175)	Mortality* Adverse events Duration of CPAP
Non-comparative studies						
Balfour-Lynn, 2014[16]	Ghana District hospital General ward	Observational implementation study[20]	N=106 Age 0–5 years, respiratory distress based on respiratory rate, SpO_2, intercostal retractions and grunting	NIV via Nippy Junior paediatric pressure controlled portable ventilator	N/A	Mortality* Adverse events
Bjorkland, 2019[17]	Uganda Referral hospital Acute care unit	Prospective, non-blinded, non-randomised interventional study	N=83 Age 30 days - 5 years, moderate or severe respiratory distress based on a calculated respiratory score (Tal score >3) or hypoxia despite low-flow oxygen	SEAL-bCPAP with nasal prong adaptation from ear plug material	N/A	Mortality* Adverse events* Change in respiratory rate, oxygen saturation and Tal score†
Bonora, 2011[18]	Argentina Referral hospital Intensive care unit	Retrospective observational study	N=154 Age 1–18 years, patients needing NIV for >30 min to attempt to avoid intubation	Neumovent graph, neumovent graph net or harmony devices for NIV	N/A	Mortality Need for intubation* Duration of NIV Duration of hospital stay
Brown, 2013[27]	Malawi Referral hospital	Case report	N=1 Age 6 months, respiratory distress	Low cost bCPAP device developed by authors	N/A	Mortality Adverse events Vital sign changes after 1 hour Length of hospital stay

Continued

Table 2 Continued

Author, Year	Country and setting	Study design	Sample size and population	Intervention and equipment	Comparison	Outcomes of interest
Figuera, 2017[19]	Argentina Provincial hospital Intermediate care unit	Retrospective descriptive study	N=120 Age 1–24 months, weight <12 kg, Tal score >5	Hudson RCI-CPAP	N/A	Mortality Adverse events Success of CPAP (15% decrease in RR) Changes in vital signs and Tal score† Duration of NIV Duration of ICU stay
Ghiggi, 2000[20]	Argentina Referral hospital Intensive care unit	Prospective observational study	N=42 Age 1 month- 5 years, Acute respiratory failure from pulmonary cause with indication for mechanical ventilation	Nasopharyngeal CPAP via Sechrist IV100 B respirators	N/A	Mortality Adverse events Need for mechanical ventilation* Change in vital signs Duration of NIV
Kinikar, 2011[21]	India Referral hospital Intensive care unit	Case-control study	N=36 Age 0–12 years, influenza like illness, moderate to severe respiratory distress or respiratory failure	Locally constructed nasal bubble CPAP	N/A	Mortality Adverse events Changes in vital signs in first 6 hours*
Lum, 2011[22]	Malaysia Referral hospital Intensive care unit	Prospective observational study	N=129 Age 0–16 years, patients deemed likely to require intubation based on vital signs and work of breathing	NIV via Mapleson F breathing system	N/A	Mortality Adverse events Length of NIV Length of PICU stay Treatment success* (intubation avoided) Vital Sign changes
Machen, 2015[23]	Malawi Referral hospital Acute care unit	Prospective observational study	N=79 Weight<10 kg, respiratory distress, bCPAP deemed appropriate by physician	bCPAP	N/A	Mortality* Duration of bCPAP Duration of hospital stay Change in RISC score†
McCollum, 2011[28]	Malawi Referral hospital	Case report	N=1 3 month old, respiratory distress	Hudson RCI -bCPAP	N/A	Mortality Adverse events Duration of bCPAP Change in vital signs
Myers, 2019[24]	Malawi Referral hospital Critical care zone, emergency zone	Prospective observational study	N=117 Age 0–59 months, severe respiratory distress	Diamedica "Baby CPAP"	N/A	Mortality* Adverse events
Pulsan, 2019[25]	Papua New Guinea Referral hospital Intensive care unit, Special care nursery	Prospective observational study	N=64 Children with severe acute lower respiratory infection, with hypoxaemia or severe respiratory distress despite standard oxygen therapy	Diamedica-modified Airsep intensity bCPAP	N/A	Mortality Change in respiratory distress score*†
Walk, 2016[26]	Malawi Referral hospital High dependency unit, emergency ward	Prospective observational study	N=77 Age 1 week to 14 years, progressive acute respiratory failure despite oxygen and antimicrobial therapy	Locally constructed CPAP	N/A	Mortality* Adverse events Treatment failure (death or intubation) Duration of CPAP Changes in vital signs

*Primary outcome.
†Scoring tool to evaluate illness severity
‡Non-randomised comparative study.
bCPAP, bubble continuous positive airway pressure; CPAP, continuous positive airway pressure; HIV, immunodeficiency virus; ICU, intensive care unit; MPSNZ-SS, Modified paediatric society of New Zealand severity score; NIV, non-invasive ventilation; PICU, paediatric intensive care unit; RICS score, respiratory index of severity in children.

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 trails (RCTs), were evaluated using Cochrane recommended criteria.[8] Studies with no comparator group were evaluated using criteria proposed by Murad *et al* to evaluate selection, ascertainment, causality and reporting domains.[9]

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.

Table 3 Outcomes for randomised control trials

Author, year	Total sample size	Mortality	Findings	Adverse events	Reported limitations	Reported conclusions
Cam, 2002[9]	37	CPAP: 4/18 (22%) Oxygen: 0/19 (0%)	Stabilisation of patient with PaO_2 >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	0 (0%)	Small sample size compared with calculated sample size	Nasal CPAP is useful in improving management of acute respiratory failure in children with dengue shock syndrome
Chisti, 2015[10]	225	bCPAP: 3/79 (4%) Low-flow oxygen: 10/67 (15%) High-flow oxygen: 10/79 (13%) Total: 23/225 (10%)	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)	bCPAP: 17/79 (22%) Oxygen: 14/67 (21%) AEs included abdominal distension, and newly recognised heart failure.	Trial was stopped early before full recruitment	Bubble CPAP therapy could be beneficial in hospitals in developing countries where the only respiratory support is standard flow oxygen.
Lal, 2018[11]	72	Not reported	Decrease in RR at 1 hour (mean, SD): bCPAP: 8 (6) Supplemental oxygen via facemask or hood: 5 (4) Need for mechanical ventilation: bCPAP: 2/36 (5%) Standard of care: 1/36 (3%)	0 (0%)	Study duration was only 1 hour, functional outcomes including need for invasive ventilation and duration of hospital stay were not evaluated	CPAP significantly decreases respiratory rate in patients with acute bronchiolitis in the first hour of treatment
Morales, 2004[15]	26	0 (0%)	Duration of Hospital stay (days, mean (SD)): NIV: 8.2 (2.8) Intubation: 19 (11) Success of intervention: NIV: 12 (86%) Intubation: 12 (100%)	NIV: 11 (79%) Intubation: 11 (92%) Complications included aerophagia, erythema, septal necrosis, pericardial effusions, infections	Limitations not reported	NIV is useful in reducing the possibility of orotracheal intubation and decreases the length of hospital stay compared with mechanical ventilation
McCollum, 2019[12]	644	bCPAP: 53/321 (17%) Oxygen: 35/323 (11%)	Duration of respiratory support (days, mean (SD)): bCPAP: 4.5 (1.9) oxygen: 3.9 (2.1)	bCPAP: 11/321 (3%) Oxygen: 1/323 (<1%) AE included aspiration events, probable pneumothorax and skin breakdown	Trial stopped early before full recruitment, no access to radiographic imaging, designed to reflect real-world setting but staff augmented,	bCPAP in a paediatric ward without daily physician supervision did not reduce mortality among high-risk Malawian children with severe pneumonia, compared with oxygen.
Wilson, 2013[13]	70	Immediate CPAP: 3/31 (10%) Delayed CPAP: 0/38 (0%)	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)	Not reported	Study design not powered to evaluate mortality, Active study was only 2 hours long, not blinded, 100% consent rate, limited diagnostic testing	CPAP is a safe and effective method to decrease respiratory rates in children presenting with nonspecific respiratory distress
Wilson, 2017[14]	2200	CPAP: 26/995 (3%) Control: 44/1160 (4%)	Duration of CPAP (median (IQR)): CPAP: 12 (7.2–19.8) Control: 0 (0)	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	Allocation by site rather than patient leading to concealment and enrolment bias, limited diagnostic abilities, possibly underpowered	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.

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

Author, year	Total sample size	Mortality	Additional findings	Adverse events	Reported limitations	Reported conclusions
Balfour-Lynn, 2014[16]	106	2 (2%)	N/A	0 (0%)	Possibility of missing data	NIPPV can be a simple and cost-effective way to treat patients with acute respiratory failure
Bjorklund, 2019[17]	83	8 (10%)	Patients with severe illness based on Tal score: 0 hours: 64/83 (77%) 2 hours: 12/83 (15%)	Severe: 0 Mild: 5 (6%) Mild AE included nasal tissue irritation and abdominal distension	Evaluations for complications based only on clinical exam, not powered to evaluate effectiveness, differences in pretrial and trial patients	SEAL-bCPAP is safe for treatment of respiratory distress in non-neonatal children in LMIC with a trend towards decreased mortality
Bonora, 2011[18]	154	Avoided intubation: 3.8% Required intubation: 38.8%	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)	Skin breakdown noted but number of adverse events not reported	Retrospective study design with no control group, no rigid protocol to determine when therapies should be escalated or discontinued	NIV avoided mechanical ventilation in a high proportion of children
Brown, 2013[27]	1	0 (0%)	Duration of bCPAP: 4 days Duration of hospital stay: 6 days	0 (0%)	Limitations not reported	A low-cost bCPAP could reduce child mortality in Africa
Figueroa, 2017[19]	120	Not reported	Success of bCPAP: 72% Duration of bCPAP (hours, mean (CI)): 75 (65–85) Duration of ICU stay (days, mean (CI)): 10 (9–11)	4 (3%) Complications included abdominal bloating and pneumothorax	Limitations not reported	A reduction in respiratory rate, heart rate and TAL scores at 2 hours after starting intervention were predictors of success
Ghiggi, 2000[20]	42	2 (5%)	Duration of nasopharyngeal CPAP (days, mean (SD)): 4.12 (3.71) Need for mechanical ventilation: 13/42 (31%)	8 (19%) Complications included tube obstructions and apnoea due to excessive sedation	Small sample size	Nasopharyngeal CPAP was useful to avoid mechanical ventilation
Kinikar, 2011[21]	36	0 (0%)	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	0 (0%)	Limitations not reported	Indigenous NB-CPAP improves hypoxemia and signs and symptoms in hemodynamically stable children with acute respiratory failure due to influenza-like injury
Lum, 2011[22]	129	19 (15%)	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%)	29 (22%) Complications included pneumonia while on NIV, pressure from mask and problems with mask fitting	Not an RCT, no routine use of blood gas sampling, shortage of NIV machines	NIV represents a viable strategy that provided effective respiratory support and prevented intubation in majority of patients
Machen, 2015[23]	79	23 (29%)	Duration of CPAP (days, mean): 3.12 Duration of hospitalisation (days, mean): 8.41 Had lower RISC score after 24 hours: 63 (80%)	Not reported	Clinical diagnoses could have led to misclassification	bCPAP was most beneficial to patients with bronchiolitis
McCollum, 2011[28]	1	0 (0%)	Duration of bCPAP (days): 7	0 (0%)	Limitations not reported	bCPAP was successful in treating an infant with PJP pneumonia secondary to HIV infection
Myers, 2019[24]	117	38 (33%)	Required intubation: 15/115 (13%) Duration of treatment (hours, median (IQR)): 24 (24–60)	13 (11%) Complications included blocked nostrils or nasal prongs, interruption of oxygen supply, nasal septum lesions and aspiration	Observational study design, small sample size, limited human resources and some missing data points	It is feasible to use bCPAP in the hospital management of critically ill children in resource-limited settings

Continued

Table 4 Continued

Author, year	Total sample size	Mortality	Additional findings	Adverse events	Reported limitations	Reported conclusions
Pulsan, 2019[25]	64	35 (55%)	RDS (mean (IQR)): Pre-CPAP: 11 (10–12) 1 hour: 9 (8–11) 84 hours: 6.5 (6–8)	Not reported	Observational study design, bCPAP only used when oxygen failed	bCPAP improves oxygenation and reduces respiratory distress in some children but children with comorbidities continue to do poorly
Walk, 2016[26]	77	36 (47%)	Duration of treatment (days, median (IQR)): 3 (3–5)	13 (17%)	Non-randomised and uncontrolled, small sample size, understaffing, missing vital sign data	bCPAP can be feasibly implemented into a tertiary African hospital with high-risk patients

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

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 statistical heterogeneity using the χ^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 studies[18–28] (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 Malawi[14] 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]

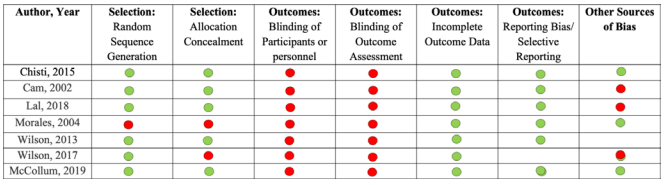

Figure 2 Risk of bias assessment for RCT and prospective comparative studies.

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 0.67, 95% CI 0.42 to 1.08; p=0.11). An exploratory adjusted analysis demonstrated decreased mortality for <1 year olds on CPAP (3%) compared with controls (7%) (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%,[18] 10%,[19] 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

Table 5 Meta-analysis study selection

Outcome	Study	Included (yes/no)	Explanation
Death	Cam (2002)[11]	No	Non-comparable age group, non-comparable case definition (dengue)
	Christi (2015)	Yes	
	Lal (2018)[13]	No	Non-comparable age group, outcome not reported
	McCollum (2019)[14]	Yes	
	Morales (2004)[17]	No	Non-comparable age group, non-comparable control group (invasive mechanical ventilation)
	Wilson (2013)[15]	No	Non-comparable age group, non-comparable study design (all participants received CPAP intervention)
	Wilson (2017)[16]	Yes	
Treatment failure	Cam (2002)[11]	No	Non-comparable age group, non-comparable case definition (dengue)
	Christi (2015)	Yes	
	Lal (2018)[13]	No	Non-comparable age group, outcome not reported
	McCollum (2019)[14]	No	Non-comparable outcome
	Morales (2004)[17]	No	Non-comparable age group, non-comparable control group (invasive mechanical ventilation)
	Wilson (2013)[15]	No	Non-comparable age group, non-comparable study design (all participants received CPAP intervention)
	Wilson (2017)[16]	No	Outcome not reported
Adverse events	Cam (2002)[11]	No	Non-comparable age group, non-comparable case definition (dengue)
	Christi (2015)	Yes	
	Lal (2018)[13]	No	Non-comparable age group
	McCollum (2019)[14]	Yes	
	Morales (2004)[17]	No	Non-comparable age group, non-comparable control group (invasive mechanical ventilation)
	Wilson (2013)[15]	No	Non-comparable age group, non-comparable study design (all participants received CPAP intervention)
	Wilson (2017)[16]	Yes	

CPAP, continuous positive airway pressure.

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]

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[17] and another RCT used a cluster crossover design and randomised at the hospital level.[15] 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 1).[18 25 27 29 30] 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.[9]

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),

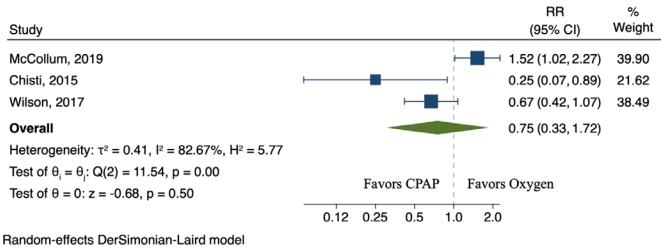

Figure 3 Meta-analysis of trials assessing CPAP against mortality in children less than 5 years. CPAP, continuous positive airway pressure.

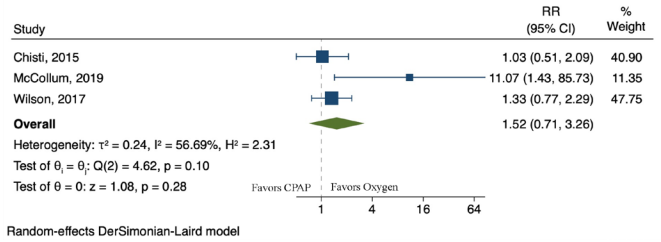

Figure 4 Meta-analysis of trials assessing CPAP against adverse events in children less than 5 years. CPAP, continuous positive airway pressure.

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.[31] 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.[32] 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.[33] Nevertheless, an understanding of the context in which CPAP safety can be optimised can be derived from the three trials.

Table 6 Certainty of evidence (GRADE)

Certainty assessment							№ of patients		Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	Usual care (oxygen)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Death												
3	Randomised trials	Serious*	Serious†	Not serious	Not serious	None	79/1395 (5.7%)	89/1550 (5.7%)	RR 0.75 (0.33 to 1.72)	14 fewer per 1000 (from 38 fewer to 41 more)	⊕⊕◯◯ Low	CRITICAL
Adverse events												
3	Randomised trials	Serious*	Serious†	Not serious	Not serious	None	17/79 (21.5%)	14/67 (20.8%)	RR 1.52 (0.71 to 3.26)	109 more per 1000 (from 61 fewer to 472 more)	⊕⊕◯◯ Low	IMPORTANT

*All trials did not mask participants or personnel to the treatment intervention and no masking was conducted during outcome analyses.
†Point estimates vary across trials, confidence intervals with minimal overlap and tests for heterogeneity significant.
RR, risk ratio.

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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Acknowledgements We would like to thank Ann Farrell, Peggy Murphy and the medical library staff at Mayo Clinic and Lurie Children's Hospital who helped with search criteria and performed the searches.

Contributors KLS and EM had full access to data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. KLS and EM conceived the study idea and designed the study. KLS and EM with the help of multiple medical librarians created the search terms and conducted the database searches. KLS and PJH extracted and analysed the data. BW conducted the meta-analysis. KLS, AGS, PJH, BW, TM, MJC, RWC and EM drafted and revised the manuscript. EDM is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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