Continuous positive airway pressure for children with undifferentiated respiratory distress in Ghana: an open-label, cluster, crossover trial

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Summary

Background In low-income and middle-income countries, invasive mechanical ventilation is often not available for children at risk of death from respiratory failure. We aimed to determine if continuous positive airway pressure (CPAP), a form of non-invasive ventilation, decreases all-cause mortality in children with undifferentiated respiratory distress in Ghana.

Methods This open-label, cluster crossover trial was done in two Ghanaian non-tertiary hospitals where invasive mechanical ventilation is not routinely available. Eligible participants were children aged from 1 month to 5 years with a respiratory rate of more than 50 breaths per min in children 1–12 months old, or more than 40 breaths per min in children older than 12 months, and use of accessory muscles or nasal flaring. CPAP machines were allocated to one hospital during each study block, while the other hospital served as the control site. The initial intervention site was randomly chosen using a coin toss. 5 cm of water pressure was delivered via CPAP nasal prongs. The primary outcome measure was all-cause mortality rate at 2 weeks after enrolment in patients for whom data were available after 2 weeks. We also did post-hoc regression analysis and subgroup analysis of children by malaria status, oxygen saturation, and age. This study is registered with ClinicalTrials.gov, number NCT01839474.

Findings Between Jan 20, 2014, and Dec 5, 2015, 2200 children were enrolled: 1025 at the intervention site and 1175 at the control site. Final analysis included 1021 patients in the CPAP group and 1160 patients in the control group. 2 weeks after enrolment, 26 (3%) of 1021 patients in the CPAP group, and 44 (4%) of 1160 patients in the control group, had died (relative risk [RR] of mortality 0·67, 95% CI 0·42–1·08; p=0·11). In children younger than 1 year, all-cause mortality was ten (3%) of 374 patients in the CPAP group, and 24 (7%) of 359 patients in the control group (RR 0·40, 0·19–0·82; p=0·01). After adjustment for study site, time, and clinically important variables, the odds ratio for 2-week mortality in the CPAP group versus the control group was 0·4 in children aged up to 6 months, 0·5 for children aged 12 months, 0·7 for children aged 24 months, and 1·0 for those aged 36 months. 28 patients (3%) in the CPAP group and 24 patients (2%) in the control group had CPAP-related adverse events, such as vomiting, aspiration, and nasal, skin, or eye trauma. No serious adverse events were observed.

Interpretation In the unadjusted analysis the use of CPAP did not decrease all-cause 2-week mortality in children 1 month to 5 years of age with undifferentiated respiratory distress. After adjustment for study site, time, and clinically important variables, 2-week mortality in the CPAP group versus the control group was significantly decreased in children 1 year of age and younger. CPAP is safe and improves respiratory rate in a non-tertiary setting in a lower-middle-income country.

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Introduction

Pneumonia, sepsis, and severe malaria kill more than 2 million children younger than 5 years every year.1–3 These treatable illnesses can present as undifferentiated acute respiratory distress that can progress to respiratory failure. Most of these deaths occur in low-income and middle-income countries, where diagnostic and therapeutic interventions are often severely scarce.1,4,5 Further, because of physician shortages, patients are often treated by non-physician clinicians. Interventions to improve patient outcomes in low-income and middle-income countries will have maximum effect if they do not depend on sophisticated diagnostic tests and if they can be initiated and managed by non-physician health-care providers.

Continuous positive airway pressure (CPAP) can improve survival in premature neonates with respiratory distress syndrome in low-income and middle-income countries.6,7 Results from two studies8,9 suggest that CPAP could improve survival beyond the neonatal period in children with primary pulmonary disease, although neither study was large and both were done in academic...
We aimed to evaluate the effectiveness of CPAP in a setting where nurses care for patients with limited physician oversight, and where diagnostic tests such as radiographs, microbiological cultures, and blood gas analyses are not routinely done. In this context, CPAP was associated with improved respiratory rate and decreased mortality in children with undifferentiated respiratory distress, driven by improved survival in children less than 1 year old. No serious adverse events were observed. Our findings demonstrate CPAP is effective and safe to use in district level hospitals by emergency ward nurses who work much of the day without direct supervision by a physician.

Implications of all the available evidence
Our findings show the effect of CPAP on all-cause mortality in children with respiratory distress treated outside the tertiary care setting. Results from two smaller studies in academic centres in Bangladesh and Malawi showed that CPAP was associated with improved survival in children with primary pulmonary diseases. These findings, taken collectively, support the use of non-invasive ventilation for children presenting with acute respiratory distress in low-resource settings. Our findings are a step forward in codifying best practices for treating children with undifferentiated respiratory distress in resource-limited settings.

Evidence before this study
We searched PubMed and Cochrane databases with the search terms “child” OR “pediatric” OR “infant” AND any combination of “bubble CPAP” OR “bubble continuous positive airway pressure” OR “nasal CPAP”. We also searched these databases with the terms “developing country” or “low or middle income country”, and “efficacy” OR “survival” OR “treatment outcomes”. The reports we identified that were published before our study were either based in neonatal intensive care units focusing on the neonatal period, or did not look at mortality as an outcome measure. Before the start of this trial, we found no studies evaluating the effect of continuous positive airway pressure (CPAP) on mortality in children aged from 1 month to 5 years, presenting with undifferentiated acute respiratory distress in non-tertiary hospitals in a low-income or middle-income country. In a previously published randomised clinical trial, we showed feasibility and safety of nurse-administered CPAP for children with respiratory distress in four non-tertiary hospitals in Ghana. That study showed that CPAP lowers respiratory rate at 1 h, but it was not powered to detect a difference in mortality. This study was an open-label cluster crossover trial done in two non-tertiary hospitals in Ghana. The aim of the study was to determine whether the use of CPAP decreases all-cause 2-week mortality in children aged 1 month up to 5 years old, presenting with undifferentiated acute respiratory distress.

Methods
Study design
This study was an open-label, prospective, cluster, crossover trial that was done at two non-tertiary hospitals in Ghana. The aim was to determine whether the application of CPAP decreased all-cause 2-week mortality in children aged from 1 month to 5 years who presented with undifferentiated acute respiratory distress.

Added value of this study
The study protocol was approved by the Columbia University Medical Center Institutional Review Board.
and local institutional review boards at the Kwame Nkrumah University of Science and Technology and Ghana Health Services, and by the leadership of each hospital. The Ghana Food and Drug Authority provided regulatory oversight.

CPAP was delivered according to a previously published protocol.10

Participants
All children presenting to the hospitals’ emergency departments with fast breathing were screened for study eligibility. Inclusion criteria were age 1 month to 5 years, respiratory rate of more than 50 breaths per min in children 1–12 months old or more than 40 breaths per min in children older than 12 months, and use of accessory muscles or nasal flaring. Exclusion criteria included skin breakdown around the nose or mouth, facial trauma, inability to protect the airway, persistent emesis, unresponsiveness or coma, poor respiratory effort requiring positive pressure ventilation, known or suspected pneumothorax, asthma, upper airway obstruction, or cardiac instability (systolic blood pressure less than the fifth percentile for age). Research staff were available 24 h a day, 7 days a week to enrol patients. CPAP was applied and managed by the existing hospital staff nurses, who were trained by study investigators. Written documentation of informed consent was obtained after the participants’ guardians reviewed the consent form written in English, or had it translated verbally into their spoken language.

Randomisation and masking
CPAP machines were allocated to one hospital (intervention site) for each study block, while the other hospital served as the control site. The initial intervention site was randomly chosen with a coin toss. CPAP was available at Mampong Hospital for the first 6 months, then at Kintampo Hospital for the subsequent 12 months, and then back to Mampong for the final 6 months. Each site thus served as an intervention site and control site for 12 months, covering every calendar month to control for seasonal variability. There was no masking.

Procedures
CPAP was delivered with the DeVilbiss IntelliPAP CPAP machine (Somerset, PA, USA) using a previously published protocol.10 5 cm of water pressure was delivered regardless of age, oxygen saturation, or clinical presentation. Seven CPAP machines were provided to each site and this was a sufficient number throughout the study. Three sizes of single-use Hudson RCI nasal prongs (Durham, NC, USA) were available as the interface. Size selection was determined by best fit in the nares and obtaining a complete seal. Delivered pressure was locked at 5 cm of water and confirmed by observing bubbles in the expiratory bottle of the closed system. Wall oxygen or concentrators were used to administer the minimal amount of oxygen needed to maintain an oxygen saturation of at least 92% as measured by pulse oximetry, either through the CPAP circuit or via a non-rebreather facemask in the control group. Because the enrolled patients might have been suffering from severe anaemia or severe sepsis, and they were critically ill with very fast breathing, we used 92% as the cutoff to avoid being too close to the steep part of the oxygen dissociation curve. Since physicians are not usually present in the emergency ward at the study hospitals, emergency ward nurses were responsible for the initiation and management of CPAP. CPAP was continued until the patient had a normal respiratory rate for their age (at which time it was immediately removed), was unable to tolerate the device, developed a nasal or facial skin injury, transferred to another facility, or died. The treating clinician could elect to remove CPAP at any time. Patients were treated per local care and physicians’ orders. Every 6 months, the local research staff received refresher training on the use of CPAP and the management of critically ill children.

Respiratory rate, oxygen saturation, heart rate, blood pressure, and temperature were recorded at baseline, 4 h, 8 h, 12 h, and 24 h. Study staff were trained to count respiratory rate for 60 s, either continuously or in two 30 s blocks using a stopwatch or the second hand of a timepiece, according to WHO recommendations.5 General Electric Dinamap V100 (Fairfield, CT, USA) automated patient monitors were provided by the study group to measure oxygen saturation, heart rate, non-invasive blood pressure, and axillary temperature.

Haemoglobin was measured with each hospital’s existing full blood count machine. Plasmodium falciparum malaria was tested using rapid antigen detection with either Standard Diagnostics HRP-II (Gyeonggi-do, South Korea) or Premier Medical Corporation HRP-2 (Gujarat, India). Adverse events were recorded on case report forms, which included specific prompts to report any vomiting; aspiration; or nasal, skin, or eye trauma. A hospital visit, home visit, or phone call was used to document the status of the patient from 2 weeks after enrolment. Data from the paper case report forms were transferred via double data entry to an electronic Microsoft Access database.

Outcomes
The primary outcome was all-cause mortality 2 weeks after enrolment. Secondary outcomes were change in respiratory rate at 24 h, rate of adverse events, and proportion of patients requiring supplemental oxygen for oxygen saturations lower than 92%. Safety analysis included all adverse events and serious adverse events for both groups.

Statistical analysis
A sample size of 906 participants in each group was calculated to detect a 3% absolute reduction in mortality.
2200 enrolled

286 excluded
  246 ineligible
  40 declined to participate

1025 enrolled at CPAP site*  
  652 Kintampo  
  373 Mampong

372 Mampong  
653 Kintampo

15 excluded
  2 withdrew consent
  9 lost to 2-week follow-up
  1 lost case report form
  3 enrolled but did not meet age criteria

1175 enrolled at control site*  
  515 Kintampo  
  660 Mampong

515 Kintampo  
660 Mampong

1021 included in primary analysis  
1160 included in primary analysis

Figure 1: Trial profile  
CPAP=continuous positive airway pressure. *CPAP was available at Mampong Hospital for the first 6 months, then at Kintampo Hospital for the next 12 months, and then back at Mampong for the final 6 months. All patients enrolled at the intervention site received CPAP, and no patients at the control site received CPAP. †Participant was younger than 1 month old at enrolment, removed from final analyses.

The results reported here are based on complete cases. Multiple imputation was used for missing values (n=512, haemoglobin; n=18, rapid malaria; n=1, oxygen saturation), and the results were similar to the results obtained using the observed data. We used the multivariate imputation by chained equations method, which considers full conditional specifications, for multiple imputation. This method is based on an iterative Markov Chain Monte Carlo method. At each iteration, a variable is chosen from the variable list in the order provided and a regression model is fitted using all the other variables in the list as predictors. The missing values in the dependent variable are then imputed. The method continues until the maximum number of iterations is reached. The results were similar to the ones obtained with the available data. In this paper we only present the results using the original data. We used SAS version 9.4 for the analyses.

We also did post-hoc analysis of children by malaria status, oxygen saturation, and age. The analysis based on age subgroups was not performed as post-hoc in this Article. The subgroup analysis. We chose the conservative approach of describing it as post-hoc in this Article.

The outcome variable was binary (dead or alive at 2 weeks), therefore we fitted a multivariate logistic regression model with the predictors study arm, study site, study month, age, respiratory rate, and oxygen saturation. Since there were only two study sites, we included this variable as a fixed effect to adjust by site. A quadratic term for study month was considered to allow non-linear association with the outcome. Interaction effects of age with study arm, and age with study site, were also included.

Table 1: Baseline characteristics of the intention-to-treat population

<table>
<thead>
<tr>
<th></th>
<th>CPAP (n=1025)</th>
<th>Control (n=1175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>455 (44%)</td>
<td>515 (44%)</td>
</tr>
<tr>
<td>Male</td>
<td>570 (56%)</td>
<td>660 (56%)</td>
</tr>
<tr>
<td>Age (months)</td>
<td>16.7 (8-22.9)</td>
<td>18.3 (10.1-30.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>9.6 (7.4-11)</td>
<td>9.6 (7.5-12)</td>
</tr>
<tr>
<td>Respiratory rate (breaths per min)</td>
<td>56 (50-62)</td>
<td>55 (48-62)</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>98% (96-99)</td>
<td>98% (97-100)</td>
</tr>
<tr>
<td>Patients with oxygen saturation &lt;92%</td>
<td>74% (7%)</td>
<td>69% (6%)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>153 (140-165)</td>
<td>152 (138-166)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.6 (36.8-38.5)</td>
<td>37.6 (36.8-38.4)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>101 (95-110)</td>
<td>102 (95-115)</td>
</tr>
<tr>
<td>Median haemoglobin (g/dL)</td>
<td>8.5 (6.4-9.9)</td>
<td>8.0 (6.1-9.6)</td>
</tr>
<tr>
<td>Malaria positive by rapid antigen detection</td>
<td>689/1015 (68%)</td>
<td>856/1148 (75%)</td>
</tr>
</tbody>
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Data are n (%) or median (IQR). All continuous variables were found to be normally distributed when performing the Kolmogorov-Smirnov test, with p values approximately 0.0001. The medians and IQRs are reported for continuous variables and the relative frequency shown for the categorical variables. CPAP=continuous positive airway pressure. *One participant in the control group did not have an oxygen saturation recorded (n=12 patients did not have a haemoglobin test performed (n=179 for CPAP; n=333 for control). (18 participants had invalid or no malaria rapid diagnostic test results (n=6 for CPAP; n=12 for control).
Role of the funding source
The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Between Jan 20, 2014 and Dec 5, 2015, 2486 children were screened. 246 were found to be ineligible, and 40 did not have parental approval to participate. 2200 participants were enrolled, 1025 in the CPAP group, and 1175 in the control group. In the control group, two patients withdrew consent and one patient was lost to follow-up in the CPAP group. The parents of three patients withdrew consent, nine were lost to follow-up, one case report form was lost, and three children were less than 1 month of age. 2181 participants were included in the final analysis (1021 in the CPAP group and 1160 in the control group; figure 1).

Compared with children in the control group, children in the CPAP group were younger and had similar respiratory rates and haemoglobin levels. Children in the CPAP group also had a lower prevalence of positive malaria rapid antigen detection (table 1).

All patients enrolled at a CPAP site received the intervention, and none in the control group were managed with CPAP. The median duration of CPAP use was 12 h (range 0·08–98, IQR 7·2–19·8). CPAP was managed with CPAP. The median duration of CPAP use intervention, and none in the control group were

Table 3: Participant age (months) and adjusted odds ratios for all-cause mortality

<table>
<thead>
<tr>
<th>Study site</th>
<th>Odds ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Kintampo vs Mampong</td>
<td>0·36 (0·023)</td>
</tr>
<tr>
<td>Month of study enrolment</td>
<td>0·72 (0·0003)</td>
</tr>
<tr>
<td>Respiratory rate (breaths per min)</td>
<td>1·04 (0·0001)</td>
</tr>
<tr>
<td>Age (months)</td>
<td>0·96 (0·065)</td>
</tr>
<tr>
<td>Age x study arm†</td>
<td>1·03 (0·17)</td>
</tr>
<tr>
<td>Age x study site‡</td>
<td>1·05 (0·0295)</td>
</tr>
</tbody>
</table>

We fitted a logistic multivariate regression model. CPAP=continuous positive airway pressure. *Exp(Est)=exponentiated parameter estimate. †Interaction effects.

Table 4: Multivariate model for all-cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group (CPAP vs control)</td>
<td>0·36 (0·023)</td>
</tr>
<tr>
<td>Study site (Kintampo vs Mampong)</td>
<td>0·34 (0·016)</td>
</tr>
<tr>
<td>Month of study enrolment</td>
<td>0·72 (0·0003)</td>
</tr>
<tr>
<td>Respiratory rate (breaths per min)</td>
<td>1·04 (0·0001)</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>0·93 (0·0001)</td>
</tr>
<tr>
<td>Age (months)</td>
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</tr>
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</tr>
<tr>
<td>Age x study site‡</td>
<td>1·05 (0·0295)</td>
</tr>
</tbody>
</table>

The analysis of the primary endpoint did not show a significant difference between study groups (table 2). Of the 2181 patients, 1958 (90%) were alive at 2 weeks at the hospital or home visit, and 153 (7%) were reported alive by a relative or community member. A total of 70 deaths
were observed (44 [4%] of 1160 patients in the control group and 26 [3%] of 1021 patients in the CPAP group; RR of mortality 0·67, 95% CI 0·42–1·08; p=0·11). The most common reported causes of death were malaria (21 deaths in the control group, ten deaths in the CPAP group), pneumonia (19 deaths in the control group, 12 deaths in the CPAP group), sepsis (18 deaths in the control group, seven deaths in the CPAP group), and anaemia (15 deaths in the control group, six deaths in the CPAP group), with most patients having multiple diagnoses. 66 deaths occurred in the hospital and four occurred after discharge from the emergency ward.

In the additional analysis by age group, more children younger than 1 year had died in the control group (24 [7%] of 359 patients) than in the CPAP group (ten [3%] of 374 patients; RR 0·40, 95% CI 0·19–0·82; p=0·010). In children aged between 1 and 5 years, there was no significant difference in mortality (RR 0·992, 0·51–1·93; p=0·977). After adjusting for study site, study month, age, respiratory rate, oxygen saturation, and interactions of age on study site and study arm, the odds ratio (OR) for 2-week mortality in the CPAP group over control group was 0·4 in children aged up to 6 months, 0·5 for children aged between 1 and 5 years, and 1·0 for children 36 months of age (table 3, table 4). Subgroup analyses by malaria status, and oxygen saturation less than 90% or 92%, showed no significant difference in mortality at 2 weeks between the CPAP and control groups.

In children at all ages, respiratory rate was significantly lower in the CPAP group at 4 h, 8 h, 12 h, and 24 h (p<0·001 at each timepoint; figure 2). All patients were monitored for vomiting, aspiration, and nasal, skin and eye trauma. In the CPAP group, 28 (3%) of 1021 patients had one or more of these events reported during the study period, compared with 24 (2%) of 1160 patients in the control group (p=0·30; table 5). Nasal trauma was
Discussion

There was no difference in all-cause mortality at 2 weeks. Nurse-initiated CPAP decreased respiratory rate in children younger than 5 years and was associated with a decrease in mortality in children less than 1 year old who presented to non-tertiary hospitals in a lower-middle-income country with undifferentiated respiratory distress. No serious adverse events attributed to CPAP were noted.

Results from previous studies have shown the effectiveness of CPAP in selected populations of children with well characterised primary pulmonary diseases who are managed at teaching hospitals in low-income and middle-income countries. By contrast, our study took place at non-tertiary hospitals where invasive mechanical ventilation is not routinely available, and diagnostic evaluations are limited in availability. Scarce access to reliable diagnostic testing is documented throughout sub-Saharan Africa, highlighting the importance of identifying interventions that are effective in undifferentiated populations. Our findings suggest that the use of CPAP in young children with respiratory insufficiency is appropriate in other parts of the developing world, where diagnostic capabilities are similarly limited.

Potential mechanisms for improved outcomes in children with primary pulmonary diseases such as pneumonia and pulmonary oedema who receive CPAP include recruitment of atelectatic alveoli, increased functional residual capacity, improved lung compliance, decreased shunting and redistribution of lung water away from gas exchange membranes. Furthermore, CPAP might decrease afterload, improve cardiac output, and unload the work of the diaphragm, contributing to improved outcomes in children with sepsis, severe malaria, and metabolic acidosis. The effectiveness of CPAP does not seem to be solely related to improved oxygen saturation. Only 6-5% of our study patients had oxygen saturations less than 92% at presentation, and the CPAP group did not have higher oxygen saturation than the control group at any time point. Further research is required to definitively determine if CPAP is associated with improved survival in children with specific non-primary pulmonary processes such as severe malaria, sepsis, or metabolic acidosis to ensure appropriate prioritisation of the technology in resource-limited settings.

Our study is unique in that CPAP was initiated and managed by emergency ward nurses who work much of the day without direct supervision by a physician. The WHO recommends redistributing health-care tasks to less highly trained individuals, when possible, to make more efficient use of limited human resources, as well as shifting the management of chest indrawing pneumonia to the community level. With a nurse to doctor ratio of 8:1 in many African nations, successful training of nurses to effectively and safely apply CPAP will be crucial for its proliferation in non-tertiary hospitals. Our study included twice-yearly CPAP refresher training for nurses caring for study patients. Further work is needed to determine how best to scale up and maintain training of non-physician providers in the use of CPAP.

We found that mortality was associated with younger age, lower bodyweight, higher respiratory rate and lower oxygen saturation, which is consistent with other published data. Survival was positively associated with study month: the later in the study a patient was enrolled, the more likely he or she was to survive. We speculate that this improved survival over time was related to incremental improvements in clinical care as the study progressed. This improvement could be related to periodic training sessions, increasing comfort with patient monitoring, or variation of disease severity between study years.

CPAP significantly lowered respiratory rate throughout the 24-h monitoring period in all age groups, showing a prolonged physiological benefit. Despite this fact, a decrease in mortality was only seen among children younger than 1 year old. Younger patients might have different disease processes, a possibility that was not explored fully in this study due to limits in diagnostic evaluations. Further, the nasal prongs may have provided a better seal in younger patients. Differences in end expiratory lung volume, functional residual capacity, dead space and upper airway collapsibility may make younger patients more amenable to the benefits of CPAP compared to older patients.

This trial has several limitations. A pure, randomised control study design was not used, with allocation by site rather than by patient, and analyses were applied at the patient level. More patients in the CPAP group were enrolled from Kintampo than Mampong. The chosen study design was selected for simplicity and to maximise compliance with allocation, but it is susceptible to concealment and enrolment bias. Precise diagnoses of study participants are not known, secondary to limited capacity of the hospital laboratories. However, the study is generalisable in low-income and middle-income countries where diagnostics are very often scarce. In powering the study, we estimated a baseline mortality of 7%, but the control group had a mortality of only 3-8%. Our incorrect assumption of the baseline mortality might have lead to the study being underpowered. Our respiratory rate definitions for fast breathing were similar...
but not identical to WHO guidelines, which include three different cut-offs for defining fast breathing in children younger than 5 years;24,25 for simplicity, we chose to use two cut-offs. 27 children younger than 2 months old in our cohort met study inclusion criteria, but they would not meet WHO criteria for fast breathing. Additionally, our comparator group was not WHO standard low flow oxygen.26 Another limitation is that the malaria rapid diagnostic test detects malaria proteins, which can be present in the blood weeks after acute infection and might not reflect active disease in a malaria endemic region.27–29 Additionally, we followed up patients to 2 weeks only, so there is a possibility that deaths occurred after this period.

The study showed a significant effect in the adjusted but not the unadjusted analysis for all patients. This might be due to the fact that patients in the CPAP group were younger, and young age was significantly correlated with an increase in mortality. The finding that CPAP was shown to be beneficial in a stratified analysis adjusting for age supports this possibility. The presence of younger children with lower prevalence of malaria in the CPAP group was probably due to chance; theories for this include protective maternal antibodies, low levels of para-aminobenzoic acid in breastfed infants, less exposed skin surface area, and increased subcutaneous fat in young infants.

In conclusion, CPAP was associated with improved respiratory rate and decreased mortality in children with undifferentiated respiratory distress, with the association driven by the benefit in children younger than 1 year. There were no serious adverse events. For every 25 children under the age of 1 year treated with CPAP, one life will be saved and most will have improvements in their respiratory status. Cost-effectiveness is an important consideration in resource-poor regions of the world and has to be considered before any intervention is scaled globally.

Contributors
PTW wrote the first draft of the manuscript with input from MCM. PTW contributed to study design, provided implementation support, conducted data analysis, provided data interpretation, and contributed to the drafting, review, and editing of this manuscript. FB contributed to study design, provided implementation support, conducted data analysis and contributed to the drafting, review, and editing of this manuscript. RTM and HT contributed to study design and provided implementation support and data interpretation, in addition to contributing to the drafting, review, and editing of this manuscript. MCM contributed to study design, data analysis, provided data interpretation, and contributed to the drafting, review, and editing of this manuscript. MCM contributed to study design, data analysis, provided data interpretation, and contributed to the drafting, review, and editing of this manuscript. GA, KN-J, DP, and JS supported data acquisition and study implementation, as well as contributed to the drafting, review, and editing of this manuscript. AA-A supported data acquisition and study implementation, as well as contributed to the drafting, review and editing of this manuscript.

Declaration of interests
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