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Bubble continuous positive airway pressure in the treatment of severe pediatric pneumonia in Malawi: a cost-effectiveness analysis

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ABSTRACT

Objective: Pneumonia is the largest infectious cause of death in children under five globally, and limited resource settings bear an overwhelming proportion of this disease burden. Bubble continuous positive airway pressure (bCPAP), an accepted supportive therapy, is often thought of as cost-prohibitive in these settings. We hypothesize that bCPAP is a cost-effective intervention in a resource-limited setting. The main objective of this study is to determine the cost-effectiveness of bCPAP, using Malawi as an example.

Design: This is a cost-effectiveness analysis.

Setting: Malawi district and central hospitals

Participants: Children one-month to five years with severe pneumonia.

Interventions: We constructed a decision tree for the treatment of severe pediatric pneumonia. We compared standard of care (including low-flow oxygen) to standard of care plus bCPAP in terms of costs, clinical outcomes, and averted disability-adjusted-life-years (DALYs). We assigned input values from a review of the literature, including applicable clinical trials.

Main outcome measure: We calculated an incremental cost-effectiveness ratio (ICER) and conducted one-way and multi-way probabilistic sensitivity analyses.

Results: In the base case analysis, the cost of bCPAP per patient was $15 per day and $41 per hospitalization, with an incremental net cost of $64 per pneumonia episode. BCPAP averts 5.0 DALYs per child treated, with an ICER of $12.88 per DALY averted compared to standard of care. In one-way sensitivity analyses, the most influential uncertainties were case fatality rates (ICER range $9-32 per DALY averted). In a multi-way sensitivity analysis, the median ICER was $12.97 per DALY averted (90% CI, $12.77-$12.99).

Conclusions: BCPAP is a cost-effective intervention for severe pediatric pneumonia in Malawi. These results may be used to inform policy decisions, including support for widespread use of bCPAP in similar settings.

STRENGTHS and LIMITATIONS of this STUDY

Strengths

- Only cost-effectiveness analysis evaluating the use of bubble continuous airway pressure (bCPAP) for pediatric pneumonia.
- We chose an example low-income country (Malawi) where costing and outcomes data exist.
- In general, we used conservative estimates that would over-estimate bCPAP costs and under-estimate benefits, and the intervention was still cost-effective.
- Because of extensive sensitivity analyses, we are confident that our results are robust.

Limitations

- Cost-effectiveness analyses are inherently limited by the data available.
    - Most individual inputs are based on a single study, generally with a small sample size.
    - The case fatality rate for standard of care and bCPAP came from a randomized controlled trial in Bangladesh, though supported by results from prospective cohort studies conducted in Malawi.
    - The cost of long-term sequelae is a rough estimate based on the cost of lifelong treatment, which likely overestimates the cost considerably.

INTRODUCTION

In 2015, over 5.9 million children worldwide died before their fifth birthday; the majority of these deaths were preventable or treatable with simple, inexpensive interventions.[3] The leading infectious cause of death in children under age five is pneumonia, accounting for 15% of pediatric deaths worldwide, and resource-limited resource settings bear a disproportionate share of mortality and disease burden._ENREF_4_ENREF_1[4] Pneumonia frequently causes respiratory distress and hypoxia in children, which can lead to respiratory failure and cardiac arrest in severe or untreated cases. _ENREF_7_ENREF_7The highest case fatality rate (CFR) occurs in children with severe pneumonia (Table 1).[5,6] Even a small improvement in the management of pneumonia could result in a significant decrease in childhood morbidity and mortality.

Effective bubble continuous positive airway pressure (bCPAP) reduces the need for invasive methods of respiratory support (intubation, mechanical ventilation),[7,8] and has been shown to improve clinical outcomes in several resource-limited settings: India, Malawi, Ghana, Vietnam, and Bangladesh to name a few.[1,8-12] However, bCPAP is not universally available despite compelling evidence of its benefits, possibly because it is deemed too expensive for resource-limited settings.

Malawi is a low-income, HIV-endemic country in southern Africa with limited resources and a high burden of disease: 43,000 under-five children died in 2012 alone,[4] and pneumonia continues to be the leading cause of childhood death with a 24.3% annual incidence rate[6] and a CFR of 23.1% in children with very severe/severe pneumonia.[5,13,14]

Our review of the literature yielded few cost-effectiveness analyses of bCPAP in the treatment of pneumonia in resource-limited settings, and no analyses of bCPAP in severe pneumonia in a pediatric, non-neonatal, population. This study addresses this gap in knowledge with the following aims: (1) to quantify the clinical benefits of bCPAP in the treatment of severe pediatric pneumonia in Malawi as measured by mortality rates and Disability Adjusted Life Years (DALYs), (2) to assess the costs associated with implementation of bCPAP in Malawi, and, (3) to determine the incremental cost-effectiveness ratio (ICER) of bCPAP as compared to standard of care.

METHODS

Overview

The focus of this study is children under age five, excluding neonates, in Malawi with severe pneumonia, by World Health Organization (WHO) criteria.[15] We constructed a decision tree with *Microsoft Excel for Mac* 2011, version 14.4.3 comparing current standard of care with standard of care plus bCPAP (Figure 1). The standard of care in Malawi for the treatment of severe pediatric pneumonia includes hospitalization at a district or central hospital with a dedicated pediatric ward, antibiotic therapy, and oxygen therapy via an oxygen concentrator and nasal cannula in a high-dependency unit.[13]

Intervention

Treatment for severe pediatric pneumonia ideally includes six elements: provider knowledge to appropriately manage pneumonia; oxygen; antibiotics; non-invasive positive pressure ventilation (such as bCPAP); non-invasive monitoring (continuous pulse oximetry); and nasopharyngeal (NP) suctioning. The first three are part of standard of care in Malawi. For bCPAP delivery, we modeled our analysis on a basic, modified nasal prong and oxygen concentrator model,[16] a bCPAP system previously shown to be effective in treating severe pneumonia in children in resource-limited

settings.[1,9] For bCPAP, we also included the costs of provider training, pulse oximetry and NP suction as these are integral to the intervention.

Analytic approach

We took the perspective of a Malawian government hospital, encompassing all (i.e. societal) direct medical costs, with a lifelong horizon in terms of morbidity and mortality. The benefit of averted mortality is the discounted average of life expectancy, while the cost of long-term sequelae is the discounted cost of lifelong therapy.

Inputs and assumptions

Cost inputs came from published values in the literature or vendors (Table 2). We identified resources required for bCPAP from prior micro-costing studies in Malawi.[2,13] Specific indirect provider training costs are allocated for the implementation of bCPAP and based on published costs associated with the Child Lung Health Programme (CLHP) in Malawi. The CLHP trained providers in the diagnosis and treatment of pneumonia and the use of oxygen therapy.[5,14] CLHP also supplied oxygen concentrators and essential supplies to 25 pediatric wards around the country.[13] We included the cost of essential capital equipment: an additional oxygen concentrator, pulse oximeter and NP suctioning device. We assumed the oxygen concentrator would be used for bCPAP for 90 days out of the year, and assumed no additional benefit when not in use for bCPAP. The entire bCPAP system, including the concentrator, reusable components, pulse oximeter, NP suction device, and spare parts, have a lifespan of 5 years.

We did not include extra personnel time in the bCPAP intervention as there are no data on the extra time required, and based on conversations with providers from this setting, we assume it to be minimal and prior analysts have made the same assumption.[2,17] We used activity unit costs and relied on data from WHO-CHOICE to determine the average cost per bed day in a public teaching hospital in Malawi.[18] In addition to bed-day costs, we included the cost of antibiotics, a chest radiograph, and laboratory investigations in the cost of hospitalization. The range for vendor costs used in sensitivity analysis was set at +/- 50%.

Survival and sequelae probabilities were determined through review of the literature. CFRs for both bCPAP and standard of care came from a single, randomized controlled trial (RCT) conducted in Bangladesh with three treatment arms: low-flow oxygen, high-flow oxygen, and bCPAP.[1] In this RCT, patients who failed low-flow oxygen were then randomized to high-flow oxygen or bCPAP therapy.[1] In Malawi, neither high-flow oxygen nor bCPAP are routinely available as rescue therapies. For this reason, we chose to use treatment failure rates as a proxy for mortality. When reliable studies were unavailable, educated assumptions were made and noted as estimates. We used the WHO and Global Burden of Disease published disability weights for treated or untreated lower respiratory tract infection (LRTI) for children[19] and accounted for the risk of long-term sequelae in survivors.[20] All costs are reported in United States Dollars (USD) adjusted for inflation based on the Consumer Price Index. We discounted health outcomes (death and DALYs) and costs by 3%.

We calculated DALYs following a patient from birth with an average age of onset of severe pneumonia of one year[5] and an average life expectancy if one survives to age five of 65.4 years.[21] Long-term sequelae of pneumonia include: restrictive lung disease, obstructive lung disease, bronchiectasis, chronic bronchitis, asthma, and abnormal pulmonary function or chronic respiratory disease not otherwise specified.[20] Most of these conditions are chronically controlled with a combination of an inhaled steroid and a β_2-agonist. The Global Asthma Network recommends

beclomethasone (steroid) and salbutamol (β_2-agonist) in resource-limited settings,[22] and both are listed in the Malawian Standard Treatment Guidelines published by the Ministry of Health.[23] We assumed that sequelae are life-long and non-progressive and an affected person would require daily medications to control symptoms and prevent acute exacerbations. We used data from resource-limited settings for length of stay (LOS) for pneumonia survivors and non-survivors with bCPAP[1,9] and without,[1,5,24] as well as for average duration of bCPAP therapy.[1,8]

We assigned baseline values and ranges to each health outcome and cost input based on confidence intervals or plausible ranges as determined from review of the literature (Table 3). Each input is an estimate based on the best sources available. We used a series of deterministic one-way (*Microsoft Excel*) and multi-way probabilistic (*@Risk* Palisade software, version 6.3.1: Industrial version) sensitivity analyses, assuming uniform distributions and extreme, but plausible values, for the parameters of all inputs, to evaluate the effect of uncertainty on each of the model's important cost and health inputs on the ICER.

RESULTS

BCPAP costs $15 per patient day and $41 per hospitalization. The increased probability of survival resulted in added hospital days. The base case analysis shows that the cost of treating one child with severe pneumonia is $88 for standard of care, and $152 for standard of care plus bCPAP. This yields an overall incremental net cost of $64 per use of bCPAP compared to standard of care and an ICER of $12.88 per DALY averted (Table 4). Standard of care and bCPAP incur an average of 7.4 and 2.4 DALYs per child treated, respectively, a difference of 5.0 DALYs.

A series of 1-way sensitivity analyses were performed to test key inputs across the range of input values. Variation in costs associated with bCPAP and their effect on the ICER are shown in Figure 2, while variations in the CFRs for standard of care and bCPAP are shown in Figure 3.

We ranked inputs in order of effect on the median ICER; the inputs causing the greatest variability were CFRs for standard of care and bCPAP, cost per day for bCPAP, and bCPAP duration. All inputs, including those pertaining to the intervention – CFR for bCPAP, duration of bCPAP, cost of bCPAP per day, one-time costs for bCPAP – influenced the median ICER between $9 and $40 per DALY averted (Figure 4). The multi-way probabilistic analysis resulted in a median ICER of $12.97 per DALY averted (90% CI, $12.77-$12.99; Figure 5).

DISCUSSION

Our base case analysis demonstrated an ICER of $12.88 per DALY averted, which is highly cost-effective by most standards. National immunization programs in resource-limited settings cost approximately $7-438 per DALY averted.[25] Multi-way sensitivity analyses produced a median ICER close to the base case, and a narrow confidence interval. The inputs that caused the greatest median ICER variability were CFRs for standard of care and bCPAP, daily bCPAP costs, and LOS. LOS directly impacted the cost of hospitalization and indirectly affected the cost of bCPAP; bCPAP lengthened LOS through increased survival for children that would otherwise have died, which was accounted for in this model. BCPAP therapy would need to extend LOS considerably longer than standard of care to create an unfavorable ICER, and there is no evidence for this in the literature.

CFRs were highly influential in this model. We used treatment failure rates from Chisti, et al., as a surrogate for mortality.[1] The CFR for standard of care was consistent with data from Malawi reported by Enarson, et al., though higher than reported in an observational study by Lazzerini, et al. (CFR for

severe pneumonia by WHO criteria was 21.9-23.1% and 11.8%, respectively).[5,26] If we used the published CFRs by Chisti, et al., (3.8% for bCPAP and 14.9% for low-flow), or using the standard of care CFR from Lazzerini, et al., then the base case ICER would be $22.50 or $33.30 per DALY averted, respectively; still cost-effective by most standards.

Our findings are consistent with past studies of similar interventions. In Papua New Guinea, oxygen therapy was cost-effective with an ICER of $50 per DALY averted,[27] and in Malawi, bCPAP was cost-effective for neonates with an ICER of $4.20 per life year gained.[2] The latter study, by Chen, et al., appears more favorable than our results, but there are several notable differences in cost inputs: we accounted for training costs, maintenance costs, the cost of pulse oximetry, and the cost for NP suction. When these additional costs are taken into account, our results are consistent with Chen, et al.

There are several limitations to this analysis. Most individual inputs are based on a single study, generally with a small sample size. The CFR for standard of care and bCPAP came from an RCT in Bangladesh,[1] and though the standard of care CFR is supported by results from prospective cohort studies conducted in Malawi,[5,26] similar corroborating results do not exist for the CFR for bCPAP. The cost of long-term sequelae is a rough estimate based on the cost of lifelong treatment with a recommended inhaled steroid and a β_2-agonist; however, our estimate likely overestimates the cost as not all patients with sequelae will need or be prescribed therapy, and overall access to affordable medications in Malawi is poor.[28] Extensive sensitivity analyses were performed in an attempt to account for the imprecision in the model, and our finding of excellent cost-effectiveness is robust.

In general, we used conservative estimates that would over-estimate bCPAP costs and under-estimate benefits. This includes the assumption that bCPAP would be used for 90 days out of the year and only for the treatment of pneumonia. BCPAP is also an effective supportive therapy for sepsis, anemia, dengue, and shock,[12] which are not accounted for in this model. Added use of bCPAP would disperse fixed costs more widely. We modeled the cost of training, but no additional benefit, though skilled providers identify and manage patients more effectively.[29] Much of the overall cost of bCPAP can be attributed to additional hospital costs and, in part, to long-term sequelae due to increased survival. Overall, we believe that bCPAP may be more cost-effective than our model shows.

It is far more meaningful to estimate costs and effectiveness within the local context of disease burden and available resources[30] as opposed to assigning an arbitrary cost-effectiveness threshold. This analysis indicates that bCPAP for severe pediatric pneumonia can be life saving and cost-effective in resource-limited settings similar to that of Malawi. An estimated 95% of all episodes of clinical pneumonia are in resource-limited settings: if every child under five with severe pneumonia had access to effective bCPAP, the worldwide pneumonia mortality rate would decrease by 33%.[1,4]

When considering whether to introduce a new bCPAP device as compared to using an oxygen concentrator,[16] we were concerned about a possible unintended consequence; one oxygen concentrator with tubing can be "split" to provide low-flow oxygen for up to four children at once. If the concentrator is used instead for bCPAP, which requires higher flow rates, only one patient can receive treatment per concentrator, leaving potentially three other patients without oxygen. We do not recommend that oxygen concentrators be used for bCPAP at the expense of children needing low-flow oxygen; this would deny children standard of care. This is why we included the cost of an oxygen concentrator in our model, though we recognize that this does not completely eliminate this allocation dilemma in settings with an insufficient number of concentrators.

Much of the current global health funding is devoted to the research and development of new technologies, as opposed to focusing on implementing effective, inexpensive therapies already available. We feel that bCPAP is not only appropriate, but also cost-effective and life saving for the treatment of severe pneumonia in resource-limited settings. The results of this study support widespread implementation of bCPAP in resource-limited settings, similar to Malawi, which could greatly decrease childhood morbidity and mortality globally.

Authors' contributions
T Kortz, JG Kahn, and E Marseille designed the study. T Kortz collected the data, performed the literature search and constructed the decision tree. T Kortz and B Herzel performed the sensitivity analyses. All authors interpreted the data. T Kortz and B Herzel wrote the manuscript and generated the figures and tables, which were edited by JG Kahn and E Marseille. All authors were involved in the decision to submit the manuscript for publication

Data access
All authors had full access to all of the data (including decision trees, sensitivity analyses, graphs and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement
The authors have nothing to disclose.

Transparency declaration
I, Teresa Bleakly Kortz, the lead author and manuscript guarantor affirm that the manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted; and that any discrepancy from the study as planned has been explained.

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Ethics committee approval and patient consent
Not required.

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Data sharing statement
No additional data available.

***Table 1*: WHO classification of pneumonia for children ages 2-59 months by severity of disease** _ENREF_14[15]

Diagnosis	Presenting Signs and Symptoms
Pneumonia	Fast breathing (≥50 ages 2–11 months, ≥ 40 ages 1-5 years) Chest indrawing
Severe Pneumonia	Cough or difficulty in breathing with: ▪ Oxygen saturation < 90% or central cyanosis ▪ Severe respiratory distress (eg. grunting, very severe chest indrawing) ▪ Signs of pneumonia with a general danger sign (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions)

***Figure 1*: Decision tree depicting the two treatment options (standard of care and standard of care plus bCPAP) for very severe pediatric pneumonia in Malawi**

Table 2: **Detailed cost inputs including relevant adjustments and assumptions**

	Net Present Value* (2016 USD)	Source	Assumptions/Comments
One Time Costs for bCPAP per Patient Hospitalization			
Nasal prongs	$8.82	Hospital supplier (Chen 2014)	
Stockinette hat	$0.16	Hospital supplier (Chen 2014)	
Glass bottle	$1.00	Vendor	
Suction catheter	$0.59	Hospital supplier (Chen 2014)	
Total One Time Cost	**$10.57**		
Daily Costs for bCPAP per Patient Day			
Oxygen concentrator	$1,484.30	Vendor	WHO certified device, delivers up to 10 LPM
Shipping and handling	$605.04	Enarson 2008	
Nasopharyngeal suction machine	$439.99	Vendor	
Pulse oximeter and reusable probes	$1,966.00	Vendor	
Gross particle filter (15)	$89.06	Vendor	WHO recommended 5-year supply
Intake product filter (5)	$89.06	Vendor	WHO recommended 5-year supply
Firebreak device	$9.80	Vendor	
Spare parts for ongoing maintenance and repair (filters, tubing, valve kits, sieve beds)	$461.14	Enarson 2008	Electrical Engineering Department created in 2005 for Child Lung Health Programme in Malawi
Surge prevention device	$107.00	Vendor	
Provider training (per site)	$1,774.96	Enarson 2008	Training per site
Total Daily Cost	**$15.41**		System life 5 years, used 3 mo/year
Hospital Costs per Patient Day			
Hospital bed day	$2.49	WHO-CHOICE	
Antibiotics (ampicillin, gentamicin)	$1.99	MSH 2015	
Total Daily Hospital Cost	**$4.48**		
One Time Hospital Costs per Patient Hospitalization			
Chest radiograph	$2.00	Ayieko 2009	
Laboratory investigations	$3.10	Ayieko 2009	Adjusted by GDP ratio
Total One-Time Hospital Costs	**$5.10**		
Other Costs			
Cost of long-term sequealae (per lifetime)Ŧ	**$656.43**	MSH 2015	Median buyer's price of daily beclomethasone and salbutamol

* Net present value based on Consumer Price Index (2016 US$)
Ŧ Discounted cost (3%)

***Table 3*: Base case input values and ranges as supported by the literature and used in the decision tree analysis**

Input	Base Case Value	Published Range	Sensitivity Parameter Estimate (Min, Max)	Source
Health Input				
Standard of Care Case Fatality Rate	**0.24**	0.12-0.24	(0.12, 0.36)	Chisti 2015 Enarson 2014 Lazzerini 2016
bCPAP Case Fatality Rate	**0.06**	0.04-0.12	(0.01, 0.12)	Chisti 2015
Risk of Long-Term Sequelae	**0.14**	0.06–0.21	(0.06, 0.21)	Edmond 2012
Disability Weight per Episode of Treated/Untreated LRTI for Children	**0.28**	n/a	(0.14, 0.42)	WHO 2015
Disability Weight for Chronic Sequelae of Treated/Untreated LRTI for Children	**0.1**	n/a	(0.05, 0.15)	WHO 2015
Cost Input [Ŧ]				
Daily Costs for bCPAP (USD/per patient day)	**$15.41**	n/a	(7.70, 23.11)	Composite
One Time Costs for bCPAP[§] (USD/per patient hospitalization)	**$10.57**	n/a	(5.29, 15.86)	Composite
Daily Cost of Inpatient Hospital Care (USD/per patient day)	**$4.48**	n/a	(2.24, 6.72)	WHO-CHOICE MSH 2015
One Time Costs of Inpatient Hospital Care (USD/per patient hospitalization)	**$5.10**	0-6.64	(2.55, 7.65)	Ayieko 2009
Cost of Long-Term Sequelae (USD/per episode)	**$656.43**	n/a	(328.22, 984.65)	MSH 2015
Length of Stay if Patient Dies: Low-Flow Oxygen (days)	**1**	1-2	(0, 2)	Chisti 2015
Length of Stay if Patient Dies: bCPAP (days)	**2**	1-3	(1, 3)	Chisti 2015
Length of Stay If Patient Survives: Low-Flow Oxygen (days)	**4**	3-6	(2, 6)	Chisti 2015 Chola 2009 Enarson 2014
Length of Stay If Patient Survives: bCPAP (days)	**5**	3-7	(3, 8)	Chisti 2015 Jayashree 2015
bCPAP Duration (days)	**2**	1-3	(1, 3)	Chisti 2015 Kinikar 2011

[Ŧ] Net Present Value is the total adjusted cost based on the Consumer Price Index (2015 USD$) with discounting (3%) when appropriate

Sensitivity analysis parameters are 0.5 (min) and 1.5 (max) times the base case value

***Table 4*: Cost-effectiveness results by treatment course**

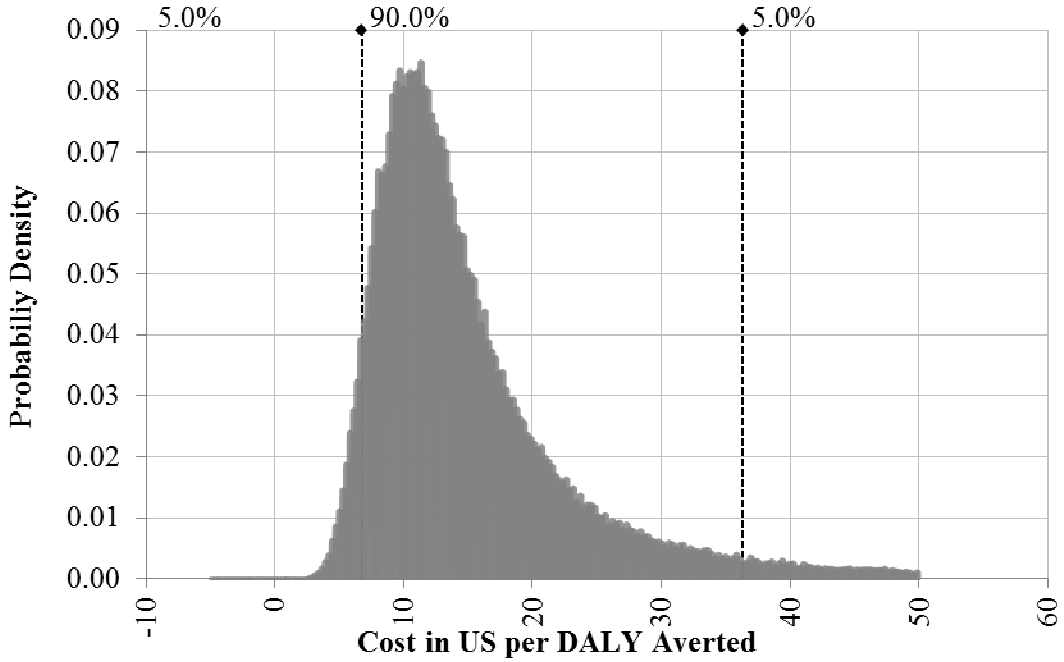
Treatment Course	Cost (USD)	Delta Cost (USD)	DALYs Incurred	DALYs Averted	ICER (USD per DALY averted)
Standard of care	$88	--	7.4	--	--
bCPAP	$152	$64	2.4	5.0	$12.88
Costs and DALYs are per patient treated					

***Figure 2*:** Variation in ICER values across a range of bCPAP treatment costs. Base case values demarcated with a triangle.

***Figure 3*:** Variation in ICER as CFR varies in the two treatment arms: standard of care and standard of care plus bCPAP. The CFR in one arm is held constant while the other is varied. Base case values demarcated with a triangle.

***Figure 4*:** Tornado plot for the multi-way probabilistic sensitivity analysis demonstrating inputs with the greatest impact on median ICER value variability.

Figure 5: Multi-way probabilistic sensitivity analysis displaying distribution of ICER values



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CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
Results		
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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Bubble continuous positive airway pressure in the treatment of severe pediatric pneumonia in Malawi: a cost-effectiveness analysis

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Bubble continuous positive airway pressure in the treatment of severe pediatric pneumonia in Malawi: a cost-effectiveness analysis

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ABSTRACT

Background Pneumonia is the largest infectious cause of death in children under five globally, and limited resource settings bear an overwhelming proportion of this disease burden. Bubble continuous positive airway pressure (bCPAP), an accepted supportive therapy, is often thought of as cost-prohibitive in these settings. This study addresses the cost-effectiveness of bCPAP, using Malawi as an example.

Methods We constructed a decision tree for the treatment of severe pediatric pneumonia for children one month to five years. We compared standard of care (including low flow oxygen) to standard of care plus bCPAP in terms of costs, clinical outcomes, and averted disability-adjusted-life-years (DALYs). We assigned input values from a review of the literature, including applicable clinical trials, and calculated an incremental cost-effectiveness ratio (ICER). We conducted one-way and multi-way probabilistic sensitivity analyses.

Findings In the base case analysis, the cost of bCPAP per patient was $15 per day and $41 per hospitalization, with an incremental net cost of $64 per pneumonia episode. BCPAP averts 5.0 DALYs per child treated, with an ICER of $12.88 per DALY averted compared to standard of care. In one-way sensitivity analyses, the most influential uncertainties were case fatality rates (ICER range $9-32 per DALY averted). In a multi-way sensitivity analysis, the median ICER was $12.97 per DALY averted (90% CI, $12.77-$12.99).

Interpretation BCPAP is a cost-effective intervention for severe pediatric pneumonia in Malawi. These results may be used to inform policy decisions, including support for widespread use of bCPAP in similar settings.

Funding None

STRENGTHS and LIMITATIONS of this STUDY

Strengths

- Only cost-effectiveness analysis evaluating the use of bubble continuous airway pressure (bCPAP) for pediatric pneumonia.
- We chose an example low-income country (Malawi) where costing and outcomes data exist.
- In general, we used conservative estimates that would over-estimate bCPAP costs and under-estimate benefits, and the intervention was still cost-effective.
- Because of extensive sensitivity analyses, we are confident that our results are robust.

Limitations

- Cost-effectiveness analyses are inherently limited by the data available.
    - Most individual inputs are based on a single study, generally with a small sample size.
    - The case fatality rate for standard of care and bCPAP came from a randomized controlled trial in Bangladesh and were determined using the proxy of treatment failure rates as opposed to reported mortality rates given Malawi's more limited resources. The case fatality/treatment failure rates from the Bangladeshi trial are supported by results from prospective cohort studies conducted in Malawi.
    - The cost of long-term sequelae is a rough estimate based on the cost of lifelong treatment, which likely overestimates the cost considerably.

INTRODUCTION

In 2015, over 5.9 million children worldwide died before their fifth birthday; the majority of these deaths were preventable or treatable with simple, inexpensive interventions.[3] The leading infectious cause of death in children under age five is pneumonia, accounting for 15% of pediatric deaths worldwide, and resource-limited resource settings bear a disproportionate share of mortality and disease burden.[4] Pneumonia frequently causes respiratory distress and hypoxia in children, which can lead to respiratory failure and cardiac arrest in severe or untreated cases. The highest case fatality rate (CFR) occurs in children with severe pneumonia (Table 1).[5,6] Even a small improvement in the management of pneumonia could result in a significant decrease in childhood morbidity and mortality.

Effective bubble continuous positive airway pressure (bCPAP) reduces the need for invasive methods of respiratory support (intubation, mechanical ventilation),[7,8] and has been shown to improve clinical outcomes in several resource-limited settings: India, Malawi, Ghana, Vietnam, and Bangladesh to name a few.[1,8-12] However, bCPAP is not universally available despite compelling evidence of its benefits, possibly because it is deemed too expensive for resource-limited settings.

Malawi is a low-income, HIV-endemic country in southern Africa with limited resources and a high burden of disease: 43,000 under-five children died in 2012 alone,[4] and pneumonia continues to be the leading cause of childhood death with a 24.3% annual incidence rate[6] and a CFR of 23.1% in children with very severe/severe pneumonia.[5,13,14]

Our review of the literature yielded few cost-effectiveness analyses of bCPAP in the treatment of pneumonia in resource-limited settings, and no analyses of bCPAP in severe pneumonia in a pediatric, non-neonatal, population. This study addresses this gap in knowledge with the following aims: (1) to quantify the clinical benefits of bCPAP in the treatment of severe pediatric pneumonia in Malawi as measured by mortality rates and Disability Adjusted Life Years (DALYs), (2) to assess the costs associated with implementation of bCPAP in Malawi, and, (3) to determine the incremental cost-effectiveness ratio (ICER) of bCPAP as compared to standard of care.

METHODS

Overview

The focus of this study is children under age five, excluding neonates, in Malawi with severe pneumonia, by World Health Organization (WHO) criteria.[15] We constructed a decision tree with *Microsoft Excel for Mac* 2011, version 14.4.3 comparing current standard of care with standard of care plus bCPAP (Figure 1, detailed decision tree available in supplemental material as Figure 1A). The standard of care in Malawi for the treatment of severe pediatric pneumonia includes hospitalization at a district or central hospital with a dedicated pediatric ward, antibiotic therapy, and oxygen therapy via an oxygen concentrator and nasal cannula in a high-dependency unit.[13]

Intervention

Treatment for severe pediatric pneumonia ideally includes six elements: provider knowledge to appropriately manage pneumonia; oxygen; antibiotics; non-invasive positive pressure ventilation (such as bCPAP); non-invasive monitoring (continuous pulse oximetry); and nasopharyngeal (NP) suctioning. The first three are part of standard of care in Malawi. For bCPAP delivery, we modeled our analysis on a basic, modified nasal prong and oxygen concentrator model,[16] a bCPAP system

previously shown to be effective in treating severe pneumonia in children in resource-limited settings.[1,9] For bCPAP, we also included the costs of provider training, pulse oximetry and NP suction as these are integral to the intervention.

Analytic approach

We took the perspective of a Malawian government hospital, encompassing all (i.e. societal) direct medical costs, with a lifelong horizon in terms of morbidity and mortality. The benefit of averted mortality is the discounted average life expectancy, while the cost of long-term sequelae is the discounted cost of lifelong therapy.

Inputs and assumptions

Cost inputs came from published values in the literature or vendors (Table 1A in supplemental material). We identified resources required for bCPAP from prior micro-costing studies in Malawi.[2,13] Specific indirect provider training costs are allocated for the implementation of bCPAP and based on published costs associated with the Child Lung Health Programme (CLHP) in Malawi. The CLHP trained providers in the diagnosis and treatment of pneumonia and the use of oxygen therapy.[5,14] CLHP also supplied oxygen concentrators and essential supplies to 25 pediatric wards around the country.[13] We included the cost of essential capital equipment: an additional oxygen concentrator, pulse oximeter and NP suctioning device. We assumed the oxygen concentrator would be used for bCPAP for 90 days out of the year, and assumed no additional benefit when not in use for bCPAP. The entire bCPAP system, including the concentrator, reusable components, pulse oximeter, NP suction device, and spare parts, has a lifespan of 5 years.

We did not include extra personnel time in the bCPAP intervention as there are limited data on the extra time required, and based on conversations with providers from this setting, we assume it is minimal. Prior analysts have made the same assumption.[2,17] We used activity unit costs and relied on data from WHO-CHOICE to determine the average cost per bed day in a public teaching hospital in Malawi.[18] In addition to bed-day costs, we included the cost of antibiotics, a chest radiograph, and laboratory investigations in the cost of hospitalization. The range for vendor costs used in sensitivity analysis was set at +/- 50%.

Survival and sequelae probabilities were determined through review of the literature. CFRs for both bCPAP and standard of care came from a single, randomized controlled trial (RCT) conducted in Bangladesh with three treatment arms: low-flow oxygen, high-flow oxygen, and bCPAP.[1] In this RCT, patients who failed low-flow oxygen were then randomized to high-flow oxygen or bCPAP therapy, and those that failed bCPAP or high-flow oxygen were intubated and mechanically ventilated.[1] In Malawi, neither high-flow oxygen, bCPAP, and mechanical intubation are not routinely available as rescue therapies. For this reason, we chose to use treatment failure rates as a proxy for mortality. When reliable studies were unavailable, educated assumptions were made and noted as estimates. We used the WHO and Global Burden of Disease published disability weights for treated or untreated lower respiratory tract infection (LRTI) for children[19] and accounted for the risk of long-term sequelae in survivors.[20] Complication rates of bCPAP in prior studies have been reported as "negligent" or non-existent; therefore, we did not include an input for bCPAP-related complications.[21-24] All costs are reported in United States Dollars (USD) adjusted for inflation based on the Consumer Price Index. We discounted health outcomes (death and DALYs) and costs by 3%.

We calculated DALYs following a patient from birth with an average age of onset of severe pneumonia of one year[5] and an average life expectancy if one survives to age five of 65.4 years.[25]

Long-term sequelae of pneumonia include: restrictive lung disease, obstructive lung disease, bronchiectasis, chronic bronchitis, asthma, and abnormal pulmonary function or chronic respiratory disease not otherwise specified.[20] Most of these conditions are chronically controlled with a combination of an inhaled steroid and a β_2-agonist. The Global Asthma Network recommends beclomethasone (steroid) and salbutamol (β_2-agonist) in resource-limited settings,[26] and both are listed in the Malawian Standard Treatment Guidelines published by the Ministry of Health.[27] We assumed that sequelae are life-long and non-progressive and an affected person requires daily medications to control symptoms and prevent acute exacerbations. We used data from resource-limited settings for length of stay (LOS) for pneumonia survivors and non-survivors with bCPAP[1,9] and without,[1,5,28] as well as for average duration of bCPAP therapy.[1,8]

We assigned baseline values and ranges to each health outcome and cost input based on confidence intervals or plausible ranges as determined from review of the literature (Table 2). Each input is an estimate based on the best sources available. We used a series of deterministic one-way (*Microsoft Excel*) and multi-way probabilistic (*@Risk* Palisade software, version 6.3.1: Industrial version) sensitivity analyses, assuming uniform distributions and extreme, but plausible values, for the parameters of all inputs, to evaluate the effect of uncertainty on each of the model's important cost and health inputs on the ICER.

RESULTS

BCPAP costs $15 per patient day and $41 per hospitalization. The increased probability of survival resulted in added hospital days. The base case analysis shows that the cost of treating one child with severe pneumonia is $88 for standard of care, and $152 for standard of care plus bCPAP. This yields an overall incremental net cost of $64 per use of bCPAP compared to standard of care and an ICER of $12.88 per DALY averted (Table 4). Standard of care and bCPAP incur an average of 7.4 and 2.4 DALYs per child treated, respectively, a difference of 5.0 DALYs.

A series of 1-way sensitivity analyses were performed to test key inputs across the range of input values. Variation in costs associated with bCPAP and their effect on the ICER are shown in Figure 2, while variations in the CFRs for standard of care and bCPAP are shown in Figure 3.

We ranked inputs in order of effect on the median ICER; the inputs causing the greatest variability were CFRs for standard of care and bCPAP, cost per day for bCPAP, and bCPAP duration. All inputs, including those pertaining to the intervention – CFR for bCPAP, duration of bCPAP, cost of bCPAP per day, one-time costs for bCPAP – influenced the median ICER between $9 and $40 per DALY averted (Figure 4). The multi-way probabilistic analysis resulted in a median ICER of $12.97 per DALY averted (90% CI, $12.77-$12.99; Figure 2A in supplemental material).

DISCUSSION

Our base case analysis demonstrated an ICER of $12.88 per DALY averted, which is highly cost-effective by most standards. National immunization programs in resource-limited settings cost approximately $7-438 per DALY averted.[29] Multi-way sensitivity analyses produced a median ICER close to the base case, and a narrow confidence interval. The inputs that caused the greatest median ICER variability were CFRs for standard of care and bCPAP, daily bCPAP costs, and LOS. LOS directly impacted the cost of hospitalization and indirectly affected the cost of bCPAP; bCPAP lengthened LOS through increased survival for children that would otherwise have died, which was accounted for in this model. BCPAP therapy would need to extend LOS considerably longer than standard of care to create an unfavorable ICER, and there is no evidence for this in the literature.

CFRs were highly influential in this model. We used treatment failure rates from Chisti, et al., as a surrogate for mortality.[1] The CFR for standard of care was consistent with data from Malawi reported by Enarson, et al., though higher than reported in an observational study by Lazzerini, et al. (CFR for severe pneumonia by WHO criteria was 21.9-23.1% and 11.8%, respectively).[5,30] If we used the published CFRs by Chisti, et al., (3.8% for bCPAP and 14.9% for low-flow), or using the standard of care CFR from Lazzerini, et al., then the base case ICER would be $22.50 or $33.30 per DALY averted, respectively; still cost-effective by most standards.

Our findings are consistent with past studies of similar interventions. In Papua New Guinea, oxygen therapy was cost-effective with an ICER of $50 per DALY averted,[31] and in Malawi, bCPAP was cost-effective for neonates with an ICER of $4.20 per life year gained.[2] The latter study, by Chen, et al., appears more favorable than our results, but there are several notable differences in cost inputs: we accounted for training costs, maintenance costs, the cost of pulse oximetry, and the cost for NP suction. When these additional costs are taken into account, our results are consistent with Chen, et al.

There are several limitations to this analysis. Most individual inputs are based on a single study, generally with a small sample size. The CFR for standard of care and bCPAP came from an RCT in Bangladesh,[1] we chose to use failure rates as a proxy for mortality due to treatment arm crossover and a lack of rescue therapies, namely mechanical ventilation, in Malawi. It is possible that the failure rates overestimate the CFR in both arms; however, the standard of care CFR is supported by results from prospective cohort studies conducted in Malawi,[5,30] though similar corroborating results do not exist for the bCPAP CFR in Malawi. Our sensitivity analyses examined wide ranges for both mortality rates and included rates beyond what is currently published. The cost of long-term sequelae is a rough estimate based on the cost of lifelong treatment with a recommended inhaled steroid and a β_2-agonist; however, our estimate likely overestimates the cost as not all patients with sequelae will need or be prescribed therapy, and overall access to affordable medications in Malawi is poor.[32] Extensive sensitivity analyses were performed in an attempt to account for the imprecision in the model, and our finding of excellent cost-effectiveness is robust.

In general, we used conservative estimates that would over-estimate bCPAP costs and under-estimate benefits. This includes the assumption that bCPAP would be used for 90 days out of the year and only for the treatment of pneumonia. BCPAP is also an effective supportive therapy for sepsis, anemia, dengue, and shock,[12] which are not accounted for in this model. Added use of bCPAP would disperse fixed costs more widely. We modeled the cost of training, but no additional benefit, though skilled providers identify and manage patients more effectively.[33] Much of the overall cost of bCPAP can be attributed to additional hospital costs and, in part, to long-term sequelae due to increased survival. Overall, we believe that bCPAP may be more cost-effective than our model shows.

It is far more meaningful to estimate costs and effectiveness within the local context of disease burden and available resources[34] as opposed to assigning an arbitrary cost-effectiveness threshold. This analysis indicates that bCPAP for severe pediatric pneumonia can be life saving and cost-effective in resource-limited settings similar to that of Malawi. An estimated 95% of all episodes of clinical pneumonia are in resource-limited settings: if every child under five with severe pneumonia had access to effective bCPAP, the worldwide pneumonia mortality rate would decrease by 33%.[1,4]

When considering whether to introduce a new bCPAP device as compared to using an oxygen concentrator,[16] we were concerned about a possible unintended consequence; one oxygen

concentrator with tubing can be "split" to provide low-flow oxygen for up to four children at once. If the concentrator is used instead for bCPAP, which requires higher flow rates, only one patient can receive treatment per concentrator, leaving potentially three other patients without oxygen. We do not recommend that oxygen concentrators be used for bCPAP at the expense of children needing low-flow oxygen; this would deny children standard of care. This is why we included the cost of an oxygen concentrator in our model, though we recognize that this does not completely eliminate this allocation dilemma in settings with an insufficient number of concentrators.

The CEA is an analytical tool that adds data – in this instance favorable data – to support the next steps of research and implementation. Ideally, future studies should measure the real-life application, generalizability, accessibility, and sustainability of bCPAP in a variety of settings, which will be critical in determining bCPAP's long-term success in resource-limited settings.

Much of the current global health funding is devoted to the research and development of new technologies, as opposed to focusing on implementing effective, inexpensive therapies already available. We feel that bCPAP is not only appropriate, but also cost-effective and life saving for the treatment of severe pneumonia in resource-limited settings. The results of this study support widespread implementation of bCPAP in resource-limited settings, similar to Malawi, which could greatly decrease childhood morbidity and mortality globally.

Authors' contributions
T Kortz, JG Kahn, and E Marseille designed the study. T Kortz collected the data, performed the literature search and constructed the decision tree. T Kortz and B Herzel performed the sensitivity analyses. All authors interpreted the data. T Kortz and B Herzel wrote the manuscript and generated the figures and tables, which were edited by JG Kahn and E Marseille. All authors were involved in the decision to submit the manuscript for publication

Data access
All authors had full access to all of the data (including decision trees, sensitivity analyses, graphs and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement
The authors have nothing to disclose.

Transparency declaration
I, Teresa Bleakly Kortz, the lead author and manuscript guarantor affirm that the manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted; and that any discrepancy from the study as planned has been explained.

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Ethics committee approval and patient consent
Not required.

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Data sharing statement
No additional data available.

***Table 1*: WHO classification of pneumonia for children ages 2-59 months by severity of disease**[15]

Diagnosis	Presenting Signs and Symptoms
Pneumonia	Fast breathing (≥50 ages 2–11 months, ≥ 40 ages 1-5 years) Chest indrawing
Severe Pneumonia	Cough or difficulty in breathing with: ▪ Oxygen saturation < 90% or central cyanosis ▪ Severe respiratory distress (eg. grunting, very severe chest indrawing) ▪ Signs of pneumonia with a general danger sign (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions)

***Figure 1*: Decision tree depicting the two treatment options (standard of care and standard of care plus bCPAP) for severe pediatric pneumonia in Malawi**

***Table 2*: Base case input values and ranges as supported by the literature and used in the decision tree analysis**

Input	Base Case Value	Published Range	Sensitivity Parameter Estimate (Min, Max)	Source
Health Input				
Standard of Care Case Fatality Rate	**0.24**	0.12-0.24	(0.12, 0.36)	Chisti 2015 Enarson 2014 Lazzerini 2016
bCPAP Case Fatality Rate	**0.06**	0.04-0.12	(0.01, 0.12)	Chisti 2015
Risk of Long-Term Sequelae	**0.14**	0.06–0.21	(0.06, 0.21)	Edmond 2012
Disability Weight per Episode of Treated/Untreated LRTI for Children	**0.28**	n/a	(0.14, 0.42)	WHO 2015
Disability Weight for Chronic Sequelae of Treated/Untreated LRTI for Children	**0.1**	n/a	(0.05, 0.15)	WHO 2015
Cost Input [Ŧ]				
Daily Costs for bCPAP (USD/per patient day)	**$15.41**	n/a	(7.70, 23.11)	Composite
One Time Costs for bCPAP[§] (USD/per patient hospitalization)	**$10.57**	n/a	(5.29, 15.86)	Composite
Daily Cost of Inpatient Hospital Care (USD/per patient day)	**$4.48**	n/a	(2.24, 6.72)	WHO-CHOICE MSH 2015
One Time Costs of Inpatient Hospital Care (USD/per patient hospitalization)	**$5.10**	0-6.64	(2.55, 7.65)	Ayieko 2009
Cost of Long-Term Sequelae (USD/per episode)	**$656.43**	n/a	(328.22, 984.65)	MSH 2015
Length of Stay if Patient Dies: Low-Flow Oxygen (days)	**1**	1-2	(0, 2)	Chisti 2015
Length of Stay if Patient Dies: bCPAP (days)	**2**	1-3	(1, 3)	Chisti 2015
Length of Stay If Patient Survives: Low-Flow Oxygen (days)	**4**	3-6	(2, 6)	Chisti 2015 Chola 2009 Enarson 2014
Length of Stay If Patient Survives: bCPAP (days)	**5**	3-7	(3, 8)	Chisti 2015 Jayashree 2015
bCPAP Duration (days)	**2**	1-3	(1, 3)	Chisti 2015 Kinikar 2011

[Ŧ] Net Present Value is the total adjusted cost based on the Consumer Price Index (2015 USD$) with discounting (3%) when appropriate
Sensitivity analysis parameters are 0.5 (min) and 1.5 (max) times the base case value

***Table 3*: Cost-effectiveness results by treatment course**

Treatment Course	Cost (USD)	Delta Cost (USD)	DALYs Incurred	DALYs Averted	ICER (USD per DALY averted)
Standard of care	$88	--	7.4	--	--
bCPAP	$152	$64	2.4	5.0	$12.88

Costs and DALYs are per patient treated

***Figure 2*:** Variation in ICER values across a range of bCPAP treatment costs. Base case values demarcated with a triangle.

***Figure 3*:** Variation in ICER as CFR varies in the two treatment arms: standard of care and standard of care plus bCPAP. The CFR in one arm is held constant while the other is varied. Base case values demarcated with a triangle.

***Figure 4*:** Tornado plot for the multi-way probabilistic sensitivity analysis demonstrating inputs with the greatest impact on median ICER value variability.

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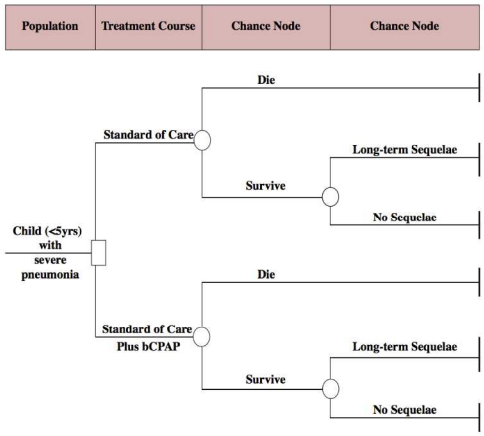

Figure 1: Decision tree depicting the two treatment options (standard of care and standard of care plus bCPAP) for severe pediatric pneumonia in Malawi

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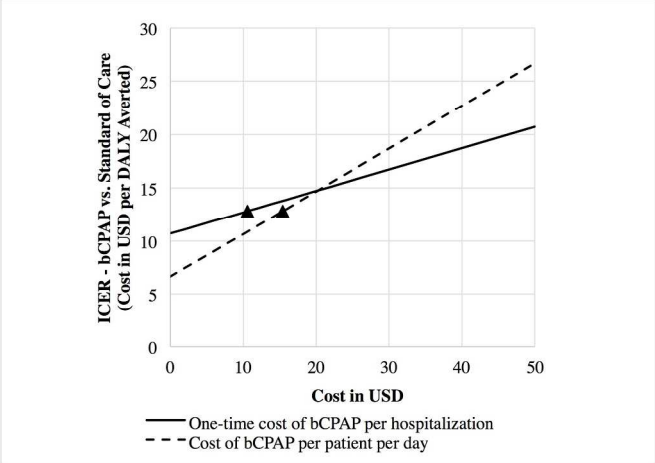

Figure 2: Variation in ICER values across a range of bCPAP treatment costs. Base case values demarcated with a triangle.

215x279mm (300 x 300 DPI)

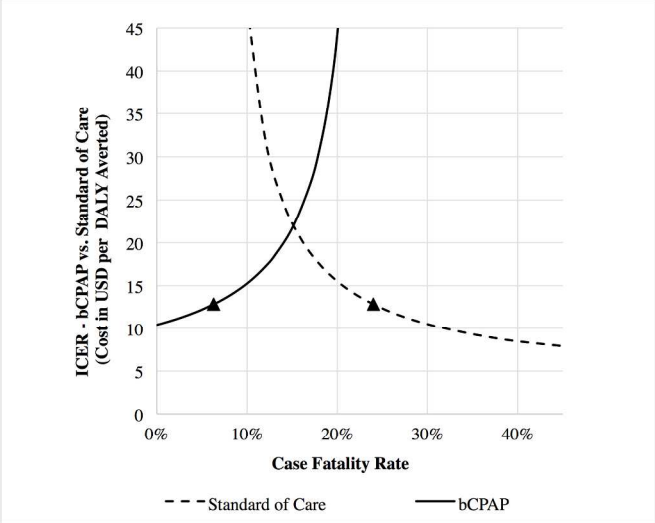

Figure 3: Variation in ICER as CFR varies in the two treatment arms: standard of care and standard of care plus bCPAP. The CFR in one arm is held constant while the other is varied. Base case values demarcated with a triangle.

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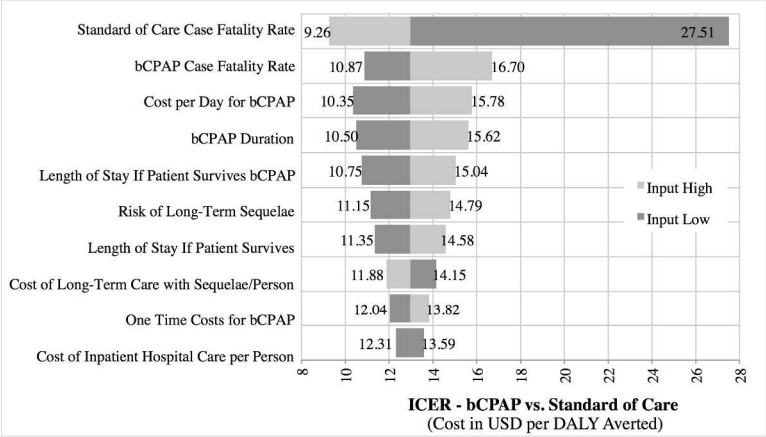


Figure 4: Tornado plot for the multi-way probabilistic sensitivity analysis demonstrating inputs with the greatest impact on median ICER value variability.

215x279mm (300 x 300 DPI)

Figure 1A: **Detailed decision tree depicting the two treatment options (standard of care and standard of care plus bCPAP) for severe pediatric pneumonia in Malawi**

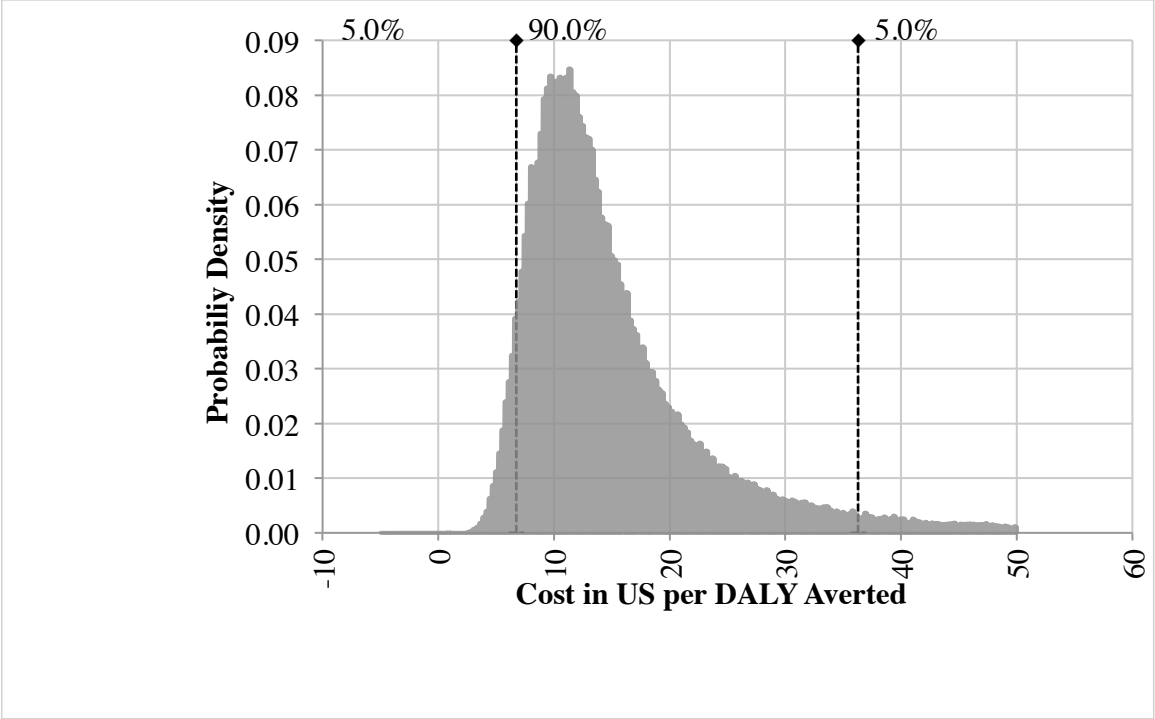
Decision Tree						DALYs				Costs									
Population	Treatment Course of Action	Survival	Sequelae	Path Probability	# in path	Per episode	Per outcome	Total per person	Total given # in path	Number of days receiving bCPAP	Cost for bCPAP per day	One time costs per person for bCPAP	Total cost of bCPAP per person	Number of hospital days	Cost per hospital day	One time hospital costs	Hospital costs per person	Cost of long-term sequelae	Total costs given # in path
		Die																	
		0.24		0.24	24.00	0	28.88	28.88	693.12	0	$0.00	$0.00	$0.00	1	$4.48	$5.10	$9.58	$0.00	$229.92
			Long-term Sequelae																
	Standard of Care		0.136	0.103	10.34	0.28	2.86	3.13	32.40	0	$0.00	$0.00	$0.00	4	$4.48	$5.10	$23.02	$656.43	$7,022.80
		Survive																	
Children with		0.76	No Long-term Sequelae																
severe pneumonia			0.864	0.657	65.66	0.28	0	0.28	18.12	0	$0.00	$0.00	$0.00	4	$4.48	$5.10	$23.02	$0.00	$1,511.59
n=100				**1.00**	**100.00**				**743.64**										**$8,764**
		Die																	
		0.063		0.063	6.30	0	28.88	28.88	181.94	2	$15.41	$10.57	$41.39	2	$4.48	$5.10	$14.06	$0.00	$349.34
	Combined bCPAP																		
			Long-term Sequelae																
			0.136	0.127	12.74	0.28	2.86	3.13	39.95	2	$15.41	$10.57	$41.39	5	$4.48	$5.10	$27.50	$656.43	$9,242.90
		Survive																	
		0.937	No Long-term Sequelae																
			0.864	0.810	80.96	0.28	0	0.28	22.34	2	$15.41	$10.57	$41.39	5	$4.48	$5.10	$27.50	$0.00	$5,577.11
				1.00	**100.00**				**244.23**										**$15,169**

Table 1A: **Detailed cost inputs including relevant adjustments and assumptions**

	Net Present Value* (2016 USD)	Source	Assumptions/Comments
One Time Costs for bCPAP per Patient Hospitalization			
Nasal prongs	$8·82	Hospital supplier (Chen 2014)	
Stockinette hat	$0·16	Hospital supplier (Chen 2014)	
Glass bottle	$1·00	Vendor	
Suction catheter	$0·59	Hospital supplier (Chen 2014)	
Total One Time Cost	**$10·57**		
Daily Costs for bCPAP per Patient Day			
Oxygen concentrator	$1,484·30	Vendor	WHO certified device, delivers up to 10 LPM
Shipping and handling	$605·04	Enarson 2008	
Nasopharyngeal suction machine	$439·99	Vendor	
Pulse oximeter and reusable probes	$1,966·00	Vendor	
Gross particle filter (15)	$89·06	Vendor	WHO recommended 5-year supply
Intake product filter (5)	$89·06	Vendor	WHO recommended 5-year supply
Firebreak device	$9·80	Vendor	
Spare parts for ongoing maintenance and repair (filters, tubing, valve kits, sieve beds)	$461·14	Enarson 2008	Electrical Engineering Department created in 2005 for Child Lung Health Programme in Malawi
Surge prevention device	$107·00	Vendor	
Provider training (per site)	$1,774·96	Enarson 2008	Training per site
Total Daily Cost	**$15·41**		System life 5 years, used 3 mo/year
Hospital Costs per Patient Day			
Hospital bed day	$2·49	WHO-CHOICE	
Antibiotics (ampicillin, gentamicin)	$1·99	MSH 2015	
Total Daily Hospital Cost	**$4·48**		
One Time Hospital Costs per Patient Hospitalization			
Chest radiograph	$2·00	Ayieko 2009	
Laboratory investigations	$3·10	Ayieko 2009	Adjusted by GDP ratio
Total One-Time Hospital Costs	**$5·10**		
Other Costs			
Cost of long-term sequealae (per lifetime)Ŧ	**$656·43**	MSH 2015	Median buyer's price of daily beclomethasone and salbutamol

* Net present value based on Consumer Price Index (2016 US$)
Ŧ Discounted cost (3%)

Figure 2A: Multi-way probabilistic sensitivity analysis displaying distribution of ICER values. *Median ICER: $12.97 per DALY averted. Interquartile range: $9.83 to $18.15 per DALY averted.*



CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	

		11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.
Measurement and valuation of preference based outcomes		12	If applicable, describe the population and methods used to elicit preferences for outcomes.
Estimating resources and costs		13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
		13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
Currency, price date, and conversion		14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
Choice of model		15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.
Assumptions		16	Describe all structural or other assumptions underpinning the decision-analytical model.
Analytical methods		17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
Results			
Study parameters		18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.
Incremental costs and outcomes		19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.
Characterising uncertainty		20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

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Bubble continuous positive airway pressure in the treatment of severe pediatric pneumonia in Malawi: a cost-effectiveness analysis

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ABSTRACT

Background Pneumonia is the largest infectious cause of death in children under five globally, and limited resource settings bear an overwhelming proportion of this disease burden. Bubble continuous positive airway pressure (bCPAP), an accepted supportive therapy, is often thought of as cost-prohibitive in these settings. This study addresses the cost-effectiveness of bCPAP, using Malawi as an example.

Methods We constructed a decision tree for the treatment of severe pediatric pneumonia for children one month to five years. We compared standard of care (including low flow oxygen) to standard of care plus bCPAP in terms of costs, clinical outcomes, and averted disability-adjusted-life-years (DALYs). We assigned input values from a review of the literature, including applicable clinical trials, and calculated an incremental cost-effectiveness ratio (ICER). We conducted one-way and multi-way probabilistic sensitivity analyses.

Findings In the base case analysis, the cost of bCPAP per patient was $15 per day and $41 per hospitalization, with an incremental net cost of $64 per pneumonia episode. BCPAP averts 5.0 DALYs per child treated, with an ICER of $12.88 per DALY averted compared to standard of care. In one-way sensitivity analyses, the most influential uncertainties were case fatality rates (ICER range $9-32 per DALY averted). In a multi-way sensitivity analysis, the median ICER was $12.97 per DALY averted (90% CI, $12.77-$12.99).

Interpretation BCPAP is a cost-effective intervention for severe pediatric pneumonia in Malawi. These results may be used to inform policy decisions, including support for widespread use of bCPAP in similar settings.

Funding None

STRENGTHS and LIMITATIONS of this STUDY

Strengths

- Only cost-effectiveness analysis evaluating the use of bubble continuous airway pressure (bCPAP) for pediatric pneumonia.
- We chose an example low-income country (Malawi) where costing and outcomes data exist.
- In general, we used conservative estimates that would over-estimate bCPAP costs and under-estimate benefits, and the intervention was still cost-effective.
- Because of extensive sensitivity analyses, we are confident that our results are robust.

Limitations

- Cost-effectiveness analyses are inherently limited by the data available.
    - Most individual inputs are based on a single study, generally with a small sample size.
    - The case fatality rate for standard of care and bCPAP came from a randomized controlled trial in Bangladesh and were determined using the proxy of treatment failure rates as opposed to reported mortality rates given Malawi's more limited resources. The case fatality/treatment failure rates from the Bangladeshi trial are supported by results from prospective cohort studies conducted in Malawi.
    - The cost of long-term sequelae is a rough estimate based on the cost of lifelong treatment, which likely overestimates the cost considerably.

INTRODUCTION

In 2015, over 5.9 million children worldwide died before their fifth birthday; the majority of these deaths were preventable or treatable with simple, inexpensive interventions.[1] The leading infectious cause of death in children under age five is pneumonia, accounting for 15% of pediatric deaths worldwide, and resource-limited resource settings bear a disproportionate share of mortality and disease burden.[2] Pneumonia frequently causes respiratory distress and hypoxia in children, which can lead to respiratory failure and cardiac arrest in severe or untreated cases. The highest case fatality rate (CFR) occurs in children with severe pneumonia (Table 1).[3,4] Even a small improvement in the management of pneumonia could result in a significant decrease in childhood morbidity and mortality.

Effective bubble continuous positive airway pressure (bCPAP) reduces the need for invasive methods of respiratory support (intubation, mechanical ventilation),[5,6] and has been shown to improve clinical outcomes in several resource-limited settings: India, Malawi, Ghana, Vietnam, and Bangladesh to name a few.[6-11] However, bCPAP is not universally available despite compelling evidence of its benefits, possibly because it is deemed too expensive for resource-limited settings.

Malawi is a low-income, HIV-endemic country in southern Africa with limited resources and a high burden of disease: 43,000 under-five children died in 2012 alone,[2] and pneumonia continues to be the leading cause of childhood death with a 24.3% annual incidence rate[4] and a CFR of 23.1% in children with very severe/severe pneumonia.[3,12,13]

Our review of the literature yielded few cost-effectiveness analyses of bCPAP in the treatment of pneumonia in resource-limited settings, and no analyses of bCPAP in severe pneumonia in a pediatric, non-neonatal, population. This study addresses this gap in knowledge with the following aims: (1) to quantify the clinical benefits of bCPAP in the treatment of severe pediatric pneumonia in Malawi as measured by mortality rates and Disability Adjusted Life Years (DALYs), (2) to assess the costs associated with implementation of bCPAP in Malawi, and, (3) to determine the incremental cost-effectiveness ratio (ICER) of bCPAP as compared to standard of care.

METHODS

Overview

The focus of this study is children under age five, excluding neonates, in Malawi with severe pneumonia, by World Health Organization (WHO) criteria.[14] We constructed a decision tree with *Microsoft Excel for Mac* 2011, version 14.4.3 comparing current standard of care with standard of care plus bCPAP (Figure 1, detailed decision tree available in supplemental material as Figure 1A). The standard of care in Malawi for the treatment of severe pediatric pneumonia includes hospitalization at a district or central hospital with a dedicated pediatric ward, antibiotic therapy, and oxygen therapy via an oxygen concentrator and nasal cannula in a high-dependency unit.[12]

Intervention

Treatment for severe pediatric pneumonia ideally includes six elements: provider knowledge to appropriately manage pneumonia; oxygen; antibiotics; non-invasive positive pressure ventilation (such as bCPAP); non-invasive monitoring (continuous pulse oximetry); and nasopharyngeal (NP) suctioning. The first three are part of standard of care in Malawi. For bCPAP delivery, we modeled our analysis on a basic, modified nasal prong and oxygen concentrator model,[15] a bCPAP system

previously shown to be effective in treating severe pneumonia in children in resource-limited settings.[7,8] For bCPAP, we also included the costs of provider training, pulse oximetry and NP suction as these are integral to the intervention.

Analytic approach

We took the perspective of a Malawian government hospital, encompassing all (i.e. societal) direct medical costs, with a lifelong horizon in terms of morbidity and mortality. The benefit of averted mortality is the discounted average life expectancy, while the cost of long-term sequelae is the discounted cost of lifelong therapy.

Inputs and assumptions

Cost inputs came from published values in the literature or vendors (Table 1A in supplemental material). We identified resources required for bCPAP from prior micro-costing studies in Malawi.[12,16] Specific indirect provider training costs are allocated for the implementation of bCPAP and based on published costs associated with the Child Lung Health Programme (CLHP) in Malawi. The CLHP trained providers in the diagnosis and treatment of pneumonia and the use of oxygen therapy.[3,13] CLHP also supplied oxygen concentrators and essential supplies to 25 pediatric wards around the country.[12] We included the cost of essential capital equipment: an additional oxygen concentrator, pulse oximeter and NP suctioning device. We assumed the oxygen concentrator would be used for bCPAP for 90 days out of the year, and assumed no additional benefit when not in use for bCPAP. The entire bCPAP system, including the concentrator, reusable components, pulse oximeter, NP suction device, and spare parts, has a lifespan of 5 years.

We did not include extra personnel time in the bCPAP intervention as there are limited data on the extra time required, and based on conversations with providers from this setting, we assume it is minimal. Prior analysts have made the same assumption.[16,17] We used activity unit costs and relied on data from WHO-CHOICE to determine the average cost per bed day in a public teaching hospital in Malawi.[18] In addition to bed-day costs, we included the cost of antibiotics, a chest radiograph, and laboratory investigations in the cost of hospitalization. The range for vendor costs used in sensitivity analysis was set at +/- 50%.

Survival and sequelae probabilities were determined through review of the literature. CFRs for both bCPAP and standard of care came from a single, randomized controlled trial (RCT) conducted in Bangladesh with three treatment arms: low-flow oxygen, high-flow oxygen, and bCPAP.[7] In this RCT, patients who failed low-flow oxygen were then randomized to high-flow oxygen or bCPAP therapy, and those that failed bCPAP or high-flow oxygen were intubated and mechanically ventilated.[7] In Malawi, neither high-flow oxygen, bCPAP, and mechanical intubation are not routinely available as rescue therapies. For this reason, we chose to use treatment failure rates as a proxy for mortality. When reliable studies were unavailable, educated assumptions were made and noted as estimates. We used the WHO and Global Burden of Disease published disability weights for treated or untreated lower respiratory tract infection (LRTI) for children[19] and accounted for the risk of long-term sequelae in survivors.[20] Complication rates of bCPAP in prior studies have been reported as negligible or non-existent; therefore, we did not include an input for bCPAP-related complications.[21-24] All costs are reported in United States Dollars (USD) adjusted for inflation based on the Consumer Price Index. We discounted health outcomes (death and DALYs) and costs by 3%.

We calculated DALYs following a patient from birth with an average age of onset of severe pneumonia of one year[5] and an average life expectancy if one survives to age five of 65.4 years.[25]

Long-term sequelae of pneumonia include: restrictive lung disease, obstructive lung disease, bronchiectasis, chronic bronchitis, asthma, and abnormal pulmonary function or chronic respiratory disease not otherwise specified.[20] Most of these conditions are chronically controlled with a combination of an inhaled steroid and a β_2-agonist. The Global Asthma Network recommends beclomethasone (steroid) and salbutamol (β_2-agonist) in resource-limited settings,[26] and both are listed in the Malawian Standard Treatment Guidelines published by the Ministry of Health.[27] We assumed that sequelae are life-long and non-progressive and an affected person requires daily medications to control symptoms and prevent acute exacerbations. We used data from resource-limited settings for length of stay (LOS) for pneumonia survivors and non-survivors with bCPAP[1,9] and without,[3,7,28] as well as for average duration of bCPAP therapy.[6,7]

We assigned baseline values and ranges to each health outcome and cost input based on confidence intervals or plausible ranges as determined from review of the literature (Table 2). Each input is an estimate based on the best sources available. We used a series of deterministic one-way (*Microsoft Excel*) and multi-way probabilistic (*@Risk* Palisade software, version 6.3.1: Industrial version) sensitivity analyses, assuming uniform distributions and extreme, but plausible values, for the parameters of all inputs, to evaluate the effect of uncertainty on each of the model's important cost and health inputs on the ICER.

RESULTS

BCPAP costs $15 per patient day and $41 per hospitalization. The increased probability of survival resulted in added hospital days. The base case analysis shows that the cost of treating one child with severe pneumonia is $88 for standard of care, and $152 for standard of care plus bCPAP. This yields an overall incremental net cost of $64 per use of bCPAP compared to standard of care and an ICER of $12.88 per DALY averted (Table 3). Standard of care and bCPAP incur an average of 7.4 and 2.4 DALYs per child treated, respectively, a difference of 5.0 DALYs.

A series of 1-way sensitivity analyses were performed to test key inputs across the range of input values. Variation in costs associated with bCPAP and their effect on the ICER are shown in Figure 2, while variations in the CFRs for standard of care and bCPAP are shown in Figure 3.

We ranked inputs in order of effect on the median ICER; the inputs causing the greatest variability were CFRs for standard of care and bCPAP, cost per day for bCPAP, and bCPAP duration. All inputs, including those pertaining to the intervention – CFR for bCPAP, duration of bCPAP, cost of bCPAP per day, one-time costs for bCPAP – influenced the median ICER between $9 and $40 per DALY averted (Figure 4). The multi-way probabilistic analysis resulted in a median ICER of $12.97 per DALY averted (90% CI, $12.77-$12.99; Figure 2A in supplemental material).

DISCUSSION

Our base case analysis demonstrated an ICER of $12.88 per DALY averted, which is highly cost-effective by most standards. National immunization programs in resource-limited settings cost approximately $7-438 per DALY averted.[29] Multi-way sensitivity analyses produced a median ICER close to the base case, and a narrow confidence interval. The inputs that caused the greatest median ICER variability were CFRs for standard of care and bCPAP, daily bCPAP costs, and LOS. LOS directly impacted the cost of hospitalization and indirectly affected the cost of bCPAP; bCPAP lengthened LOS through increased survival for children that would otherwise have died, which was accounted for in this model. BCPAP therapy would need to extend LOS considerably longer than standard of care to create an unfavorable ICER, and there is no evidence for this in the literature.

CFRs were highly influential in this model. We used treatment failure rates from Chisti, et al., as a surrogate for mortality.[7] The CFR for standard of care was consistent with data from Malawi reported by Enarson, et al., though higher than reported in an observational study by Lazzerini, et al. (CFR for severe pneumonia by WHO criteria was 21.9-23.1% and 11.8%, respectively).[3,30] If we used the published CFRs by Chisti, et al., (3.8% for bCPAP and 14.9% for low-flow), or using the standard of care CFR from Lazzerini, et al., then the base case ICER would be $22.50 or $33.30 per DALY averted, respectively; still cost-effective by most standards.

Our findings are consistent with past studies of similar interventions. In Papua New Guinea, oxygen therapy was cost-effective with an ICER of $50 per DALY averted,[31] and in Malawi, bCPAP was cost-effective for neonates with an ICER of $4.20 per life year gained.[16] The latter study, by Chen, et al., appears more favorable than our results, but there are several notable differences in cost inputs: we accounted for training costs, maintenance costs, the cost of pulse oximetry, and the cost for NP suction. When these additional costs are taken into account, our results are consistent with Chen, et al.

There are several limitations to this analysis. Most individual inputs are based on a single study, generally with a small sample size. The CFR for standard of care and bCPAP came from an RCT in Bangladesh,[7] we chose to use failure rates as a proxy for mortality due to treatment arm crossover and a lack of rescue therapies, namely mechanical ventilation, in Malawi. It is possible that the failure rates overestimate the CFR in both arms; however, the standard of care CFR is supported by results from prospective cohort studies conducted in Malawi,[3,30] though similar corroborating results do not exist for the bCPAP CFR in Malawi. Our sensitivity analyses examined wide ranges for both mortality rates and included rates beyond what is currently published. The cost of long-term sequelae is a rough estimate based on the cost of lifelong treatment with a recommended inhaled steroid and a β_2-agonist; however, our estimate likely overestimates the cost as not all patients with sequelae will need or be prescribed therapy, and overall access to affordable medications in Malawi is poor.[32] Extensive sensitivity analyses were performed in an attempt to account for the imprecision in the model, and our finding of excellent cost-effectiveness is robust.

In general, we used conservative estimates that would over-estimate bCPAP costs and under-estimate benefits. This includes the assumption that bCPAP would be used for 90 days out of the year and only for the treatment of pneumonia. BCPAP is also an effective supportive therapy for sepsis, anemia, dengue, and shock,[11] which are not accounted for in this model. Added use of bCPAP would disperse fixed costs more widely. We modeled the cost of training, but no additional benefit, though skilled providers identify and manage patients more effectively.[33] Much of the overall cost of bCPAP can be attributed to additional hospital costs and, in part, to long-term sequelae due to increased survival. Overall, we believe that bCPAP may be more cost-effective than our model shows.

It is far more meaningful to estimate costs and effectiveness within the local context of disease burden and available resources[34] as opposed to assigning an arbitrary cost-effectiveness threshold. This analysis indicates that bCPAP for severe pediatric pneumonia can be life saving and cost-effective in resource-limited settings similar to that of Malawi. An estimated 95% of all episodes of clinical pneumonia are in resource-limited settings: if every child under five with severe pneumonia had access to effective bCPAP, the worldwide pneumonia mortality rate would decrease by 33%.[2,7]

When considering whether to introduce a new bCPAP device as compared to using an oxygen concentrator,[16] we were concerned about a possible unintended consequence; one oxygen

concentrator with tubing can be "split" to provide low-flow oxygen for up to four children at once. If the concentrator is used instead for bCPAP, which requires higher flow rates, only one patient can receive treatment per concentrator, leaving potentially three other patients without oxygen. We do not recommend that oxygen concentrators be used for bCPAP at the expense of children needing low-flow oxygen; this would deny children standard of care. This is why we included the cost of an oxygen concentrator in our model, though we recognize that this does not completely eliminate this allocation dilemma in settings with an insufficient number of concentrators.

The CEA is an analytical tool that adds data – in this instance favorable data – regarding the value of the implementation of interventions in relevant settings (for bCPAP, resource-limited contexts similar to Malawi). Much of the current global health funding is devoted to the introduction of new technologies, as opposed to focusing on wide implementation of already available, effective, and inexpensive therapies. We found that the existing bCPAP technology is not only appropriate, but also cost-effective and life saving for the treatment of severe pneumonia in resource-limited settings. Malawi is primed for a nationwide roll out of bCPAP with modest investment from a donor or the Ministry of Health given the existing equipment, training and infrastructure. BCPAP applicability in other countries will need to be assessed, and implementation tailored to available resources and priorities. The results of this study support widespread implementation of bCPAP in Malawi, and potentially in similar resource-limited settings, which could greatly decrease childhood morbidity and mortality globally.

Authors' contributions
T Kortz, JG Kahn, and E Marseille designed the study. T Kortz collected the data, performed the literature search and constructed the decision tree. T Kortz and B Herzel performed the sensitivity analyses. All authors interpreted the data. T Kortz and B Herzel wrote the manuscript and generated the figures and tables, which were edited by JG Kahn and E Marseille. All authors were involved in the decision to submit the manuscript for publication

Data access
All authors had full access to all of the data (including decision trees, sensitivity analyses, graphs and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement
The authors have nothing to disclose.

Transparency declaration
I, Teresa Bleakly Kortz, the lead author and manuscript guarantor affirm that the manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted; and that any discrepancy from the study as planned has been explained.

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Ethics committee approval and patient consent
Not required.

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Data sharing statement
No additional data available.

***Table 1*: WHO classification of pneumonia for children ages 2-59 months by severity of disease**[15]

Diagnosis	Presenting Signs and Symptoms
Pneumonia	Fast breathing (≥50 ages 2–11 months, ≥ 40 ages 1-5 years) Chest indrawing
Severe Pneumonia	Cough or difficulty in breathing with: ▪ Oxygen saturation < 90% or central cyanosis ▪ Severe respiratory distress (eg. grunting, very severe chest indrawing) ▪ Signs of pneumonia with a general danger sign (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions)

***Figure 1*: Decision tree depicting the two treatment options (standard of care and standard of care plus bCPAP) for severe pediatric pneumonia in Malawi**

***Table 2*: Base case input values and ranges as supported by the literature and used in the decision tree analysis**

Input	Base Case Value	Published Range	Sensitivity Parameter Estimate (Min, Max)	Source
Health Input				
Standard of Care Case Fatality Rate	**0.24**	0.12-0.24	(0.12, 0.36)	Chisti 2015 Enarson 2014 Lazzerini 2016
bCPAP Case Fatality Rate	**0.06**	0.04-0.12	(0.01, 0.12)	Chisti 2015
Risk of Long-Term Sequelae	**0.14**	0.06–0.21	(0.06, 0.21)	Edmond 2012
Disability Weight per Episode of Treated/Untreated LRTI for Children	**0.28**	n/a	(0.14, 0.42)	WHO 2015
Disability Weight for Chronic Sequelae of Treated/Untreated LRTI for Children	**0.1**	n/a	(0.05, 0.15)	WHO 2015
Cost Input [Ŧ]				
Daily Costs for bCPAP (USD/per patient day)	**$15.41**	n/a	(7.70, 23.11)	Composite
One Time Costs for bCPAP[§] (USD/per patient hospitalization)	**$10.57**	n/a	(5.29, 15.86)	Composite
Daily Cost of Inpatient Hospital Care (USD/per patient day)	**$4.48**	n/a	(2.24, 6.72)	WHO-CHOICE MSH 2015
One Time Costs of Inpatient Hospital Care (USD/per patient hospitalization)	**$5.10**	0-6.64	(2.55, 7.65)	Ayieko 2009
Cost of Long-Term Sequelae (USD/per episode)	**$656.43**	n/a	(328.22, 984.65)	MSH 2015
Length of Stay if Patient Dies: Low-Flow Oxygen (days)	**1**	1-2	(0, 2)	Chisti 2015
Length of Stay if Patient Dies: bCPAP (days)	**2**	1-3	(1, 3)	Chisti 2015
Length of Stay If Patient Survives: Low-Flow Oxygen (days)	**4**	3-6	(2, 6)	Chisti 2015 Chola 2009 Enarson 2014
Length of Stay If Patient Survives: bCPAP (days)	**5**	3-7	(3, 8)	Chisti 2015 Jayashree 2015
bCPAP Duration (days)	**2**	1-3	(1, 3)	Chisti 2015 Kinikar 2011

[Ŧ] Net Present Value is the total adjusted cost based on the Consumer Price Index (2015 USD$) with discounting (3%) when appropriate

Sensitivity analysis parameters are 0.5 (min) and 1.5 (max) times the base case value

***Table 3*: Cost-effectiveness results by treatment course**

Treatment Course	Cost (USD)	Delta Cost (USD)	DALYs Incurred	DALYs Averted	ICER (USD per DALY averted)
Standard of care	$88	--	7.4	--	--
bCPAP	$152	$64	2.4	5.0	$12.88

Costs and DALYs are per patient treated

***Figure 2*:** Variation in ICER values across a range of bCPAP treatment costs. Base case values demarcated with a triangle.

***Figure 3*:** Variation in ICER as CFR varies in the two treatment arms: standard of care and standard of care plus bCPAP. The CFR in one arm is held constant while the other is varied. Base case values demarcated with a triangle.

***Figure 4*:** Tornado plot for the multi-way probabilistic sensitivity analysis demonstrating inputs with the greatest impact on median ICER value variability.

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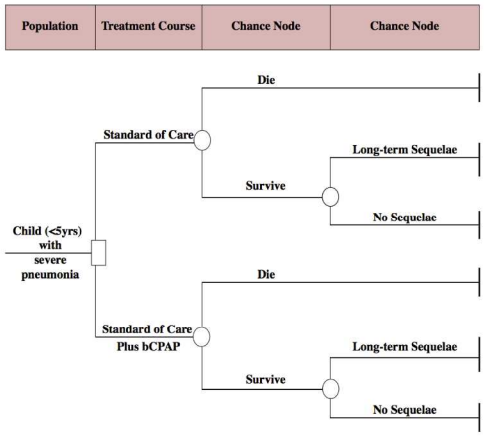

Figure 1: Decision tree depicting the two treatment options (standard of care and standard of care plus bCPAP) for severe pediatric pneumonia in Malawi

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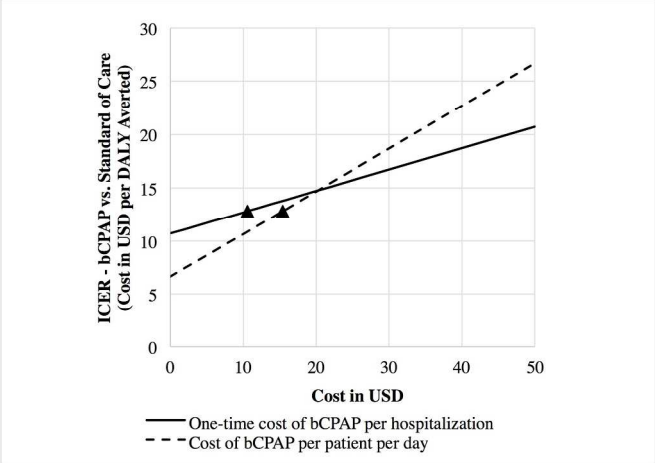

Figure 2: Variation in ICER values across a range of bCPAP treatment costs. Base case values demarcated with a triangle.

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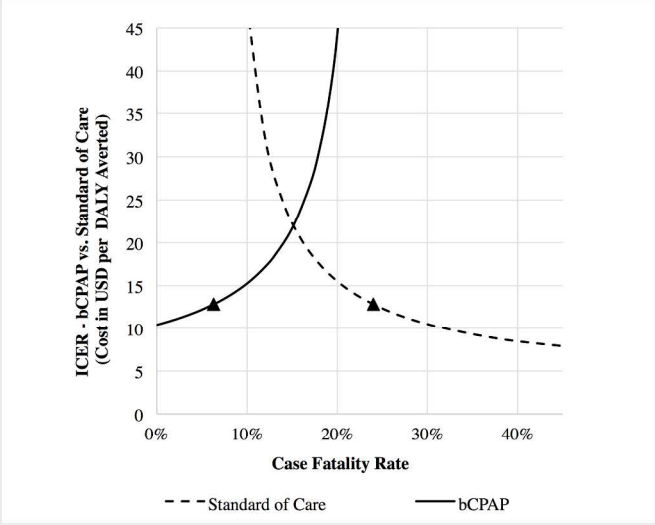

Figure 3: Variation in ICER as CFR varies in the two treatment arms: standard of care and standard of care plus bCPAP. The CFR in one arm is held constant while the other is varied. Base case values demarcated with a triangle.

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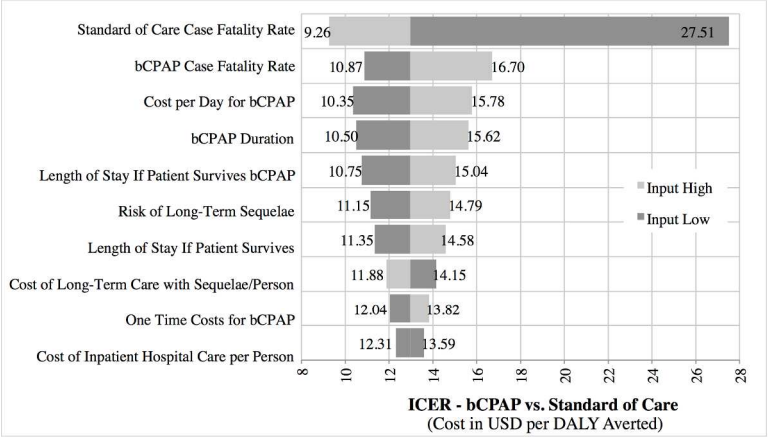


Figure 4: Tornado plot for the multi-way probabilistic sensitivity analysis demonstrating inputs with the greatest impact on median ICER value variability.

215x279mm (300 x 300 DPI)

Figure 1A: **Detailed decision tree depicting the two treatment options (standard of care and standard of care plus bCPAP) for severe pediatric pneumonia in Malawi**

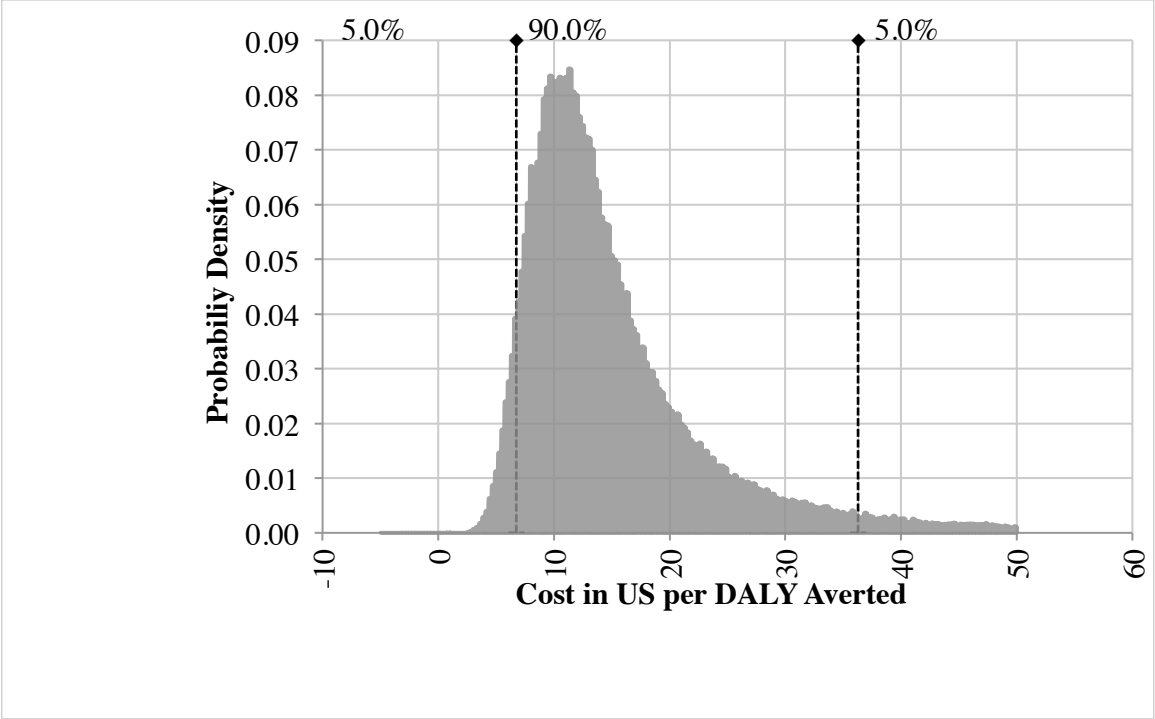
Decision Tree						DALYs				Costs									
Population	Treatment Course of Action	Survival	Sequelae	Path Probability	# in path	Per episode	Per outcome	Total per person	Total given # in path	Number of days receiving bCPAP	Cost for bCPAP per day	One time costs per person for bCPAP	Total cost of bCPAP per person	Number of hospital days	Cost per hospital day	One time hospital costs	Hospital costs per person	Cost of long-term sequelae	Total costs given # in path
		Die																	
		0.24		0.24	24.00	0	28.88	28.88	693.12	0	$0.00	$0.00	$0.00	1	$4.48	$5.10	$9.58	$0.00	$229.92
			Long-term Sequelae																
	Standard of Care		0.136	0.103	10.34	0.28	2.86	3.13	32.40	0	$0.00	$0.00	$0.00	4	$4.48	$5.10	$23.02	$656.43	$7,022.80
		Survive																	
Children with		0.76	No Long-term Sequelae																
severe pneumonia			0.864	0.657	65.66	0.28	0	0.28	18.12	0	$0.00	$0.00	$0.00	4	$4.48	$5.10	$23.02	$0.00	$1,511.59
n=100				**1.00**	**100.00**				**743.64**										**$8,764**
		Die																	
		0.063		0.063	6.30	0	28.88	28.88	181.94	2	$15.41	$10.57	$41.39	2	$4.48	$5.10	$14.06	$0.00	$349.34
	Combined bCPAP																		
			Long-term Sequelae																
			0.136	0.127	12.74	0.28	2.86	3.13	39.95	2	$15.41	$10.57	$41.39	5	$4.48	$5.10	$27.50	$656.43	$9,242.90
		Survive																	
		0.937	No Long-term Sequelae																
			0.864	0.810	80.96	0.28	0	0.28	22.34	2	$15.41	$10.57	$41.39	5	$4.48	$5.10	$27.50	$0.00	$5,577.11
				1.00	**100.00**				**244.23**										**$15,169**

Table 1A: **Detailed cost inputs including relevant adjustments and assumptions**

	Net Present Value* (2016 USD)	Source	Assumptions/Comments
One Time Costs for bCPAP per Patient Hospitalization			
Nasal prongs	$8·82	Hospital supplier (Chen 2014)	
Stockinette hat	$0·16	Hospital supplier (Chen 2014)	
Glass bottle	$1·00	Vendor	
Suction catheter	$0·59	Hospital supplier (Chen 2014)	
Total One Time Cost	**$10·57**		
Daily Costs for bCPAP per Patient Day			
Oxygen concentrator	$1,484·30	Vendor	WHO certified device, delivers up to 10 LPM
Shipping and handling	$605·04	Enarson 2008	
Nasopharyngeal suction machine	$439·99	Vendor	
Pulse oximeter and reusable probes	$1,966·00	Vendor	
Gross particle filter (15)	$89·06	Vendor	WHO recommended 5-year supply
Intake product filter (5)	$89·06	Vendor	WHO recommended 5-year supply
Firebreak device	$9·80	Vendor	
Spare parts for ongoing maintenance and repair (filters, tubing, valve kits, sieve beds)	$461·14	Enarson 2008	Electrical Engineering Department created in 2005 for Child Lung Health Programme in Malawi
Surge prevention device	$107·00	Vendor	
Provider training (per site)	$1,774·96	Enarson 2008	Training per site
Total Daily Cost	**$15·41**		System life 5 years, used 3 mo/year
Hospital Costs per Patient Day			
Hospital bed day	$2·49	WHO-CHOICE	
Antibiotics (ampicillin, gentamicin)	$1·99	MSH 2015	
Total Daily Hospital Cost	**$4·48**		
One Time Hospital Costs per Patient Hospitalization			
Chest radiograph	$2·00	Ayieko 2009	
Laboratory investigations	$3·10	Ayieko 2009	Adjusted by GDP ratio
Total One-Time Hospital Costs	**$5·10**		
Other Costs			
Cost of long-term sequealae (per lifetime)Ŧ	**$656·43**	MSH 2015	Median buyer's price of daily beclomethasone and salbutamol

* Net present value based on Consumer Price Index (2016 US$)
Ŧ Discounted cost (3%)

Figure 2A: Multi-way probabilistic sensitivity analysis displaying distribution of ICER values. *Median ICER: $12.97 per DALY averted. Interquartile range: $9.83 to $18.15 per DALY averted.*



CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	

		11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.
Measurement and valuation of preference based outcomes		12	If applicable, describe the population and methods used to elicit preferences for outcomes.
Estimating resources and costs		13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
		13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
Currency, price date, and conversion		14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
Choice of model		15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.
Assumptions		16	Describe all structural or other assumptions underpinning the decision-analytical model.
Analytical methods		17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
Results			
Study parameters		18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.
Incremental costs and outcomes		19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.
Characterising uncertainty		20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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