PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
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<th>TITLE (PROVISIONAL)</th>
<th>Bubble continuous positive airway pressure in the treatment of severe pediatric pneumonia in Malawi: a cost-effectiveness analysis</th>
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<td>AUTHORS</td>
<td>Kortz, Teresa; Herzel, Benjamin; Marseille, Elliot; Kahn, James</td>
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VERSION 1 - REVIEW

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<th>REVIEWER</th>
<th>Juan Dewez</th>
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<td>REVIEW RETURNED</td>
<td>19-Dec-2016</td>
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GENERAL COMMENTS

This is a very relevant topic. Many low-and middle income countries are moving towards more advanced care in paediatrics and bubble CPAP is a quite popular candidate intervention. The objective, methods and analysis are very clear. I have minor concerns:

1. In terms of standard treatment for severe pneumonia (line 52 page 5), you don't mention pleural tap, drainage or surgical decortication. These interventions are not needed for non-severe pneumonia, but in the context of severe pneumonia, where interventions like CPAP are considered, some of the patients may need some of these interventions. Can you comment on that and on how would it affect your estimate if it would be added?

2. In terms of provider training (line 4, page 6). Does it include training of technicians in charge of repairing/maintaining the equipment? In many places technical maintenance is in principle available but not always efficient, which results in many machines to lie abandoned after few months. A robust comprehensive and sustainable training package of technicians should be part of provider training. Can you clarify this point?

3. Staffing (l29, page 6). Extra time for personnel was not included in the model. We are currently analysing data from a qualitative study in India about the views of healthcare providers on using CPAP in their units. One of the main constraints they unanimously describe is staffing. Even though your study is in children, not in neonates, providing care with CPAP is likely to increase workload in already very busy paediatric wards. I understand it is difficult to precisely estimate the increase in workload, but perhaps this should be acknowledge as a limitation of the study.

REVIEWER

Erik Jensen
CHOP. USA.

REVIEW RETURNED

21-Dec-2016

GENERAL COMMENTS

The article addresses an important question, cost effectiveness of bCPAP in resource limited settings for the treatment of pediatric
pneumonia. Unfortunately, only figure 5 was available for review. Figure 1-4 were not present in the PDF or HTML version available online. This makes it difficult to fully review the results. Other than the missing results, I have no major concerns with the results that are present. Two minor issues: (1) the methods section states that treatment failure rate on low flow support in the RCT used to inform this study was used as a proxy for mortality. I suspect that would overestimate mortality as not all babies who meet “failure” criteria will necessarily die. This is likely addressed in the sensitivity analysis, but may be a limitation. (2) The presentation of the results in Table 4 may benefit from an estimate of certainty around the ICER. While this is presented in figure 5, a numerical instead of graphical presentation in the table may help the readers.

REVIEWER
Maurizio Bonati
Head, Department of Public Health, IRCCS Mario Negri Institute, Milan, Italy
REVIEW RETURNED 27-Dec-2016

GENERAL COMMENTS
Reducing mortality, in particular in developing countries, might be achieved through improved assessment, more rigorous application of standard case management and more accurate identification and effective management of co-morbidities. These aims are essential to reduce clinical outcomes of severe pneumonia in neonates and children. This is wellknown and documented in many countries and settings. Improved oxygen systems, and the the use of a low-cost bubble CPAP device are both effective and cost-effectiveness interventions. Much has been done for neonatal pneumonia, a little less for childhood pneumonia, although by now is a WHO statement. The real issue, in the practice, is the application, generalization, access and sustainability. These should be the points to be discussed at national and local level.
In such a context, Authors chose Malawi as national example using pertinent available data and resorting to the missing data to Bangladesh setting up their model. They did a good theoretical work. However, they have failed to contextualize the results, and explain also with examples clinical and economical outcomes in the Malawian practice and elsewhere. The main suggestion is to consider the BMJ Open is not a Journal of health economics area. Tables and Figures should be reduced. References are up dated even if improved.

REVIEWER
Robert Heggie
Health Economics and Health Technology Assessment (HEHTA), University of Glasgow, United Kingdom
REVIEW RETURNED 20-Feb-2017

GENERAL COMMENTS
In my opinion, this study is of a high methodological standard. Data sources and methods are well discussed. Although the CRFs were obtained from single RCT carried out in Bangladesh, it is the nature of cost-effectiveness analysis in LMICs that local RCT data will not always be available and hence the need to be pragmatic and obtain data from the best available source, and so I think this is acceptable.
The only thing I felt was missing was a graphical representation of the decision tree model used for analysis.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1  
Reviewer Name: Juan Dewez  
Institution and Country: Liverpool School of Tropical Medicine, UK  
Comment:  
In terms of standard treatment for severe pneumonia (line 52 page 5), you don't mention pleural tap, drainage or surgical decortication. These interventions are not needed for non-severe pneumonia, but in the context of severe pneumonia, where interventions like CPAP are considered, some of the patients may need some of these interventions. Can you comment on that and on how would it affect your estimate if it would be added?

Response:  
Thank you for bringing up important adjunct therapies for severe pneumonia. Though we agree that they are components of standard of care therapy in many areas of the world, we are unaware of data to support that therapeutic thoracentesis, chest tube drainage, or thoracotomy with decortication are standard of care or widely available in Malawi. The last time I was in Malawi (August 2016), there were half a dozen pediatric surgeons in the country who presumably are trained to perform thoracotomies, though less highly trained medical personnel can place chest tubes or perform a thoracentesis. Unfortunately, despite a repeat literature search, we are unable to find data to compare the use of bCPAP with and without drainage. Likewise, we came across no evidence or clinical reasoning to suggest that drainage or thoracotomy with decortication would favor one treatment arm over the other. There is certainly a possibility that drainage or decortication may be necessary, and not only necessary, but potentially available in certain hospitals in Malawi. If required, this would increase the cost of pneumonia therapy, but in the absence of data or clinical reasoning to support the idea that treatment arms would be affected differently, the costs would increase identically in both arms. Thus, the increased cost would effectively cancel out and the ICER would remain unchanged.

Comment  
In terms of provider training (line 4, page 6), does it include training of technicians in charge of repairing/maintaining the equipment? In many places technical maintenance is in principle available but not always efficient, which results in many machines to lie abandoned after few months. A robust comprehensive and sustainable training package of technicians should be part of provider training. Can you clarify this point?

Response  
This is an excellent point and relates to the long-term sustainability of bCPAP implementation. The provider training as modeled does not include technicians, as the equipment is not new to this setting, only the application and clinical management. Oxygen concentrators were introduced as part of the Child Lung Health Programme (CLHP), which included extensive technician training (Enarson 2008).

Comment  
Extra time for personnel was not included in the model. We are currently analysing data from a qualitative study in India about the views of healthcare providers on using CPAP in their units. One of the main constraints they unanimously describe is staffing. Even though your study is in children, not in neonates, providing care with CPAP is likely to increase workload in already very busy paediatric wards. I understand it is difficult to precisely estimate the increase in workload, but perhaps this should be acknowledge as a limitation of the study.
Response
We agree that bCPAP could increase the workload, and it is hard to quantify this effect. We do mention under Inputs and Assumptions: “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 to be minimal and prior analysts have made the same assumption.” We have also noted this uncertainty as a limitation of the study and performed the sensitivity analysis that will be uploaded separately (Figure S1). Specifically, we examined the effect of increased personnel time using data from a time and motion study conducted on pediatric pneumonia providers in rural Malawi (Bozzani et al 2016; see full citation below). Bozzani et al. estimate a provider cost of $2.20 USD per bed-day for pediatric patients with very severe pneumonia by Integrated Management of Childhood Illnesses criteria (equivalent to the WHO severe pneumonia criteria), though this did not specifically include bCPAP as a supportive therapy. We examined added personnel cost in the bCPAP treatment arm, varying this value from 0 (no increase) to $2.20 per patient bed-day. As Figure S1 depicts below, a 100% increase in personnel time for patients receiving bCPAP results in an ICER of $14.94 per DALY averted (bCPAP vs. standard of care), similar to the base case and well within the confidence bounds for our existing sensitivity analysis in Figure 4 for daily cost of bCPAP.


Reviewer: 2
Reviewer Name: Erik Jensen
Institution and Country: CHOP. USA.

Comment
Unfortunately, only figure 5 was available for review. Figure 1-4 were not present in the PDF or HTML version available online. This makes it difficult to fully review the results. Other than the missing results, I have no major concerns with the results that are present.

Response
We apologizing for this inconvenience and do not know why it happened. When we submitted our manuscript, all figures and tables were included. We will bring it to the attention of the journal.

Comment
The methods section states that treatment failure rate on low flow support in the RCT used to inform this study was used as a proxy for mortality. I suspect that would overestimate mortality as not all babies who meet "failure" criteria will necessarily die. This is likely addressed in the sensitivity analysis, but may be a limitation.

Response
We did not use the reported mortality rates from the RCT in Bangladesh (Chisti, 2015) for two reasons. The first reason is that there was crossover between groups; children who failed low-flow oxygen were reassigned to bCPAP or high-flow oxygen, and children who failed bCPAP or high-flow oxygen at any point were intubated and mechanically ventilated. The second reason is that intubation and mechanical ventilation are available in this setting in Bangladesh, but this is not a realistic rescue for children in Malawi. If we had used the lower mortality rates from the Bangladesh RCT, the bCPAP mortality rate would have been 4% and the low-flow oxygen rate would have been 14.9%. Reported case fatality rates for severe pneumonia in Malawi are available from Enarson, et al (2014) and range from 21.9-23.1%. Given this local data, the treatment failure rate from Chisti, et al, of 24% seemed consistent and appropriate. Regardless, the sensitivity analyses included bCPAP and low-flow oxygen
mortality ranges of 0.6-12% and 12-36%, respectively. We now also include this as a limitation.

Comment
The presentation of the results in Table 4 may benefit from an estimate of certainty around the ICER. While this is presented in figure 5, a numerical instead of graphical presentation in the table may help the readers.

Response
Though we appreciate the reviewer’s comment, we wanted to be clear which ICER results were from the base-case analysis (now Table 3) as compared to a sensitivity analysis (Figures 2-4, 2A). We have added additional information to Figure 2A in supplemental material including a legend, so that the information is presented in both numerical and graphical form.

Reviewer: 3
Reviewer Name: Maurizio Bonati
Institution and Country: Head, Department of Public Health, IRCCS Mario Negri Institute, Milan, Italy

Comment
The authors chose Malawi as national example using pertinent available data and resorting to the missing data to Bangladesh setting up their model. They did a good theoretical work. However, they have failed to contextualize the results, and explain also with examples clinical and economical outcomes in the Malawian practice and elsewhere.

Response
We agree about the importance of “application, generalization, access, and sustainability”, especially when proposing the implementation of new technologies in limited resource settings. Unfortunately, to fully explore, test and discuss all of these issues is beyond the scope of a CEA and belongs perhaps more appropriately in a manuscript based on implementation science. We view the CEA as an analytical tool that adds data – in this case favorable – to support the next steps of research and implementation, which, ideally, should be designed to measure the above factors that are critical to long-term success of an intervention.

Comment
The main suggestion is to consider that BMJ Open is not a Journal of health economics area.

Response
Thank you for taking the time to review our manuscript. One of the principle reasons we submitted to this journal and not a health economics journal is the audience BMJ Open reaches. We are confident that the results of this study will be relevant to medical providers, clinical researchers, hospital administrators, and ministers of health in a variety of settings worldwide. Medical resources are finite, and especially in resource-limited settings, decision makers must make difficult decisions regarding resource allocation. Oftentimes, interventions that require upfront investment for capacity building, new technology, or infrastructure development appear unfavorable when compared to options that are less complicated, or to the current standard of care. The power of the CEA is that it can provide evidence that such investment is not only worthwhile, but also cost-effective when one considers all costs and health benefits. CEAs provide valuable data so that decision makers can make more informed and beneficial decisions regarding resource allocation.

Comment
Tables and Figures should be reduced.

Response
We have made Table 2 (detailed costs) and Figure 5 (the multi-way sensitivity analysis) available in an online supplement.

Reviewer: 4  
Reviewer Name: Robert Heggie  
Institution and Country: Health Economics and Health Technology Assessment (HEHTA), University of Glasgow, United Kingdom

Comment  
The only thing I felt was missing was a graphical representation of the decision tree model used for analysis.

Response  
Thank you for your comment. We have included Figure 1, a simple decision tree in the manuscript and have made the full decision tree available online in the supplemental material (Figure 1A).

| REVIEWER | Erik Jensen  
| Reviewer Name: Children's Hospital of Philadelphia, USA |
| REVIEW RETURNED | 25-Apr-2017 |
| GENERAL COMMENTS | I have no further concerns. The manuscript is well done. One subtle point of clarification - on page 4, 3rd paragraph under "Inputs and assumptions," the authors quote studies on bCPAP complication rates, reporting these events as "negligent." This may be a direct quote, but negligible may be a better word choice given the implied context. |

| REVIEWER | Maurizio Bonati  
| Reviewer Name: Public Health Department, Mario Negri Research Institute, Milan, Italy |
| REVIEW RETURNED | 12-Apr-2017 |
| GENERAL COMMENTS | New version is a little improved. Aims and objectives of CEAs are questionable and legitimate. To improve the discussion and reflections concerning the potential decisions in the practice a CEA paper should address application, generalization, access, and sustainability. CEAs studies distant from real-life application, however good, risk being inductors of "further studies...", and papers. |

| REVIEWER | Robert Heggie  
| Reviewer Name: University of Glasgow, UK |
| REVIEW RETURNED | 18-Apr-2017 |
| GENERAL COMMENTS | The paper appears to have addressed the concerns which were raised, in particular my own request for a visual illustration of the decision tree model in the appendix. |
VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Erik Jensen
Institution and Country: Children's Hospital of Philadelphia, USA

Comment: I have no further concerns. The manuscript is well done. One subtle point of clarification - on page 4, 3rd paragraph under "Inputs and assumptions," the authors quote studies on bCPAP complication rates, reporting these events as "negligent." This may be a direct quote, but negligible may be a better word choice given the implied context.

Response: Thank you for pointing this out; you are correct, negligible is the better word choice and the text has appropriately been updated.

Reviewer: 3
Reviewer Name: Maurizio Bonati
Institution and Country: Public Health Department, Mario Negri Research Institute, Milan, Italy

Comment: Aims and objectives of CEAs are questionable and legitimate.

Response: It is unclear if the Reviewer is referring to CEAs in general, or this CEA. As the authors of this study, we will address the latter. This study has a clear and legitimate objective: to assess if bCPAP is a cost-effective intervention for children with severe pneumonia in Malawi by 1) quantifying the clinical benefits of bCPAP; 2) assessing the costs associated with bCPAP implementation; and 3) determining the cost-effectiveness of bCPAP for severe pediatric pneumonia in Malawi. We feel that we have achieved this objective, and that it is relevant and timely.

Comment: To improve the discussion and reflections concerning the potential decisions in the practice a CEA paper should address application, generalization, access, and sustainability. CEAs studies distant from real-life application, however good, risk being inductors of "further studies...", and papers.

Response: We share your opinion that application, generalizability, access and sustainability are critically important. However, we believe that the primary role of the CEA is to add data to support – or not support – the implementation of a health intervention. CEA is not designed to evaluate the application, generalizability, access or sustainability of the intervention; other study designs are far more suited to assess these important issues.

The manuscript text has been updated to read as follows:
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.