PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Inter-facility transfers for emergency obstetric and neonatal care in rural Madagascar: A cost-effectiveness analysis
AUTHORS	Franke, Mara; Nordmann, Kim; Frühauf, Anna; Ranaivoson, Rinja; Rebaliha, Mahery; Rapanjato, Zavaniarivo; Bärnighausen, Till; Müller, Nadine; Knauss, Samuel; Emmrich, Julius

VERSION 1 – REVIEW

REVIEWER	Patricia Janssen University of British Columbia, School of Population and Public Health
REVIEW RETURNED	15-Dec-2023

GENERAL COMMENTS	This is a well written article that addresses an under-researched area. It will serve as a model for other jurisdictions considering similar analyses. My comments relate to the level of detail. The abstract was clear and well written but would be strengthened by adding more information about the nature of the outcomes – i.e. give a couple of examples of the kinds of cases that were analyzed. In the methods section, could the authors define what level of care a secondary referral hospital offers? Also it would be useful to give more details in the definition of investment and running costs – these are included in supplementary materials but deserve a short overview in the main document for clarity. How were the lifetime estimates of costs of investments estimated? Why were the NGO staff experts in estimating lifetime costs? A time horizon of 100 years was chosen; what is the life expectancy for women in this population? In the methods, the paragraph starting on line 229 refers to stages; these need to be defined at this point rather than later in the supplemental files. In the discussion it would be interesting if possible to comment on potential policy changes likely to come from this work. What is the public willing or able to pay for the ICER's demonstrated – are the authors able to comment on this?

REVIEWER	Taylor Burkholder USC Keck School of Medicine
REVIEW RETURNED	13-Feb-2024

GENERAL COMMENTS	This manuscript provides a much-needed addition of cost-effectiveness data of an inter-facility referral system for emergency obstetric care in Madagascar. The authors thoroughly report their methods and findings according to the CHEERS checklist. Assumptions for the model are clearly stated, and the level of costing adds detail compared to other similar studies of EmOC referral systems in other sub-Saharan countries. Sensitivity analysis is presented to provide additional insights given the assumptions

	made for this CEA. The most important limitation of the study is its reliance on expert panel consensus to define survival benefits of the intervention compared to a theoretical non-intervention group, in the absence of true effectiveness data. The authors acknowledge this limitation, but further description of the potential effect of this method on the results is warranted. Additionally, if this method has previously been validated, this could be discussed in more detail. The costing approach uses comprehensive data from the NGO providing this service, however, there is reference to efforts from facilities that would be needed to make transfers. The authors have not discussed at which rate a physician would join the transport team (when deemed appropriate by the dispatcher), if that physician was part of the sending hospital team, and if so, what the costs are for taking a physician out of the facility for the duration of transport and return. Are there other costs to the health system outside of those paid by the NGO that are relevant? The conclusion that this EmOC referral system is very cost effective seems accurate, although the authors could consider defining which threshold for cost-effectiveness is being used to categorize this system as such. Or if thresholds are not being used due to their inherent limitations, perhaps the authors could place this intervention in context by comparing to other interventions in Madagascar.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

1. This is a well-written article that addresses an under-researched area. It will serve as a model for other jurisdictions considering similar analyses. We thank the reviewer for this positive feedback on our research.

2. My comments relate to the level of detail. The abstract was clear and well written but would be strengthened by adding more information about the nature of the outcomes – i.e. give a couple of examples of the kinds of cases that were analyzed. We agree with the reviewer that the abstract lacked clarity. We have revised lines 39 to 43 in the abstract accordingly:

"Results: 1,172 cases were referred over a period of 4 years. The most common referral reasons were obstructed labour, ineffective labour, and eclampsia. In total, 48 neonates were referred through the referral system over the study period. Estimated costs per referral were 336 USD and the incremental cost-effectiveness ratio (ICER) was 70 USD per additional life year saved (undiscounted, discounted 137 USD)."

3. In the methods section, could the authors define what level of care a secondary referral hospital offers? We have added the following description to lines 123-124 of the methods section:

"Secondary referral hospitals offer inpatient care surgical care, obstetric care, including emergency C-sections, and basic neonatal care."

4. Also it would be useful to give more details in the definition of investment and running costs – these are included in supplementary materials but deserve a short overview in the main document for clarity. We agree with the reviewer that the definitions lacked clarity and have added the following clarification to lines 184 to 187 of the methods section:

"Costs were classified as investment costs, if they were one-time costs paid for the initial set-up of the intervention (e.g. costs for the ambulance vehicles). Conversely, costs were defined as running costs if they were recurring costs necessary to continue programmatic activities (e.g. fuel costs)."

5. How were the lifetime estimates of costs of investments estimated? Why were the NGO staff experts in estimating lifetime costs? For the estimation of lifetimes of investments, we drew on the

insights of NGO staff members who possessed extensive experience with past projects in the study region. These staff members participated in an expert panel process where they collectively evaluated the typical lifetimes of various items based on their historical involvement in similar programmatic activities. The utilization of an expert panel ensured that the estimates were informed by real-world experiences and regional nuances. We then incorporated the average of these estimates into our final model.

6. A time horizon of 100 years was chosen; what is the life expectancy for women in this population? The average life expectancy for women in Madagascar is 67 years according to the most recent World Bank data [1]. As this low average life expectancy is in part caused by the high under-5 mortality rate in Madagascar (currently 66/1,000 live births) [2], we chose the time horizon of 100 years to account for individuals that may live significantly longer than the average life expectancy and were included in the model as neonates.

7. In the methods, the paragraph starting on line 229 refers to stages; these need to be defined at this point rather than later in the supplemental files. We agree with the editor that this paragraph lacked clarity. We have therefore added the following definition of the model's stages to lines 230 to 237 of the methods section:

"For the intervention cohort, the patient journey consisted of the following stages: i) initial presentation at the health centre with a certain pathology, ii) likelihood of referral to a higher level of care, iii) likelihood of survival upon reaching the referral hospital, and iv) follow-up period after the referral for which all-cause mortality was applied. For the control group, the patient journey differed in that it lacked the stage of referral. It consisted of the following stages: i) initial presentation at the health centre with a certain pathology, ii) likelihood of survival with a given pathology at the primary care level."

8. In the discussion it would be interesting if possible to comment on potential policy changes likely to come from this work. What is the public willing or able to pay for the ICER's demonstrated – are the authors able to comment on this? We would like to draw the reviewer's attention to lines 402 to 411 in our manuscript (see below), which we have expanded to describe the potential policy changes imaginable through our work. Given that maternal and child health is a key priority of the Malagasy health system development plan [3] and that the referral system analysed in our study has a notably lower ICER than interventions already integrated into national health policies in Madagascar, it would seem that the intervention could feasibly be adapted into national healthcare policies.

"Regarding the per capita costs, our intervention compares preferably, with investment costs of 0.13 USD per person and annual running costs 0.06 USD per person, when extrapolated to the entire population serviced. This is lower than what has been reported in other rural settings, for example in Burundi (€ 0.43/capita/year) [4], suggesting that the intervention described here served a larger population at comparable costs and suggesting that the intervention could be sustainable, even in a setting where most of the population lives in extreme poverty [5]. The fact that the referral system has such low per capita costs and a lower ICER than components already incorporated into the national malaria control program in Madagascar [6], suggests that the referral system described herein could be feasibly adapted into the national care system in Madagascar."

Reviewer #2

1. This manuscript provides a much-needed addition of cost-effectiveness data of an inter-facility referral system for emergency obstetric care in Madagascar. The authors thoroughly report their methods and findings according to the CHEERS checklist. Assumptions for the model are clearly stated, and the level of costing adds detail compared to other similar studies of EmOC referral systems in other sub-Saharan countries. Sensitivity analysis is presented to provide additional insights given the assumptions made for this CEA. We thank the reviewer for this positive feedback on our work, we appreciate it greatly.

2. The most important limitation of the study is its reliance on expert panel consensus to define survival benefits of the intervention compared to a theoretical non-intervention group, in the absence

of true effectiveness data. The authors acknowledge this limitation, but further description of the potential effect of this method on the results is warranted. Additionally, if this method has previously been validated, this could be discussed in more detail. We agree with the reviewer that this major limitation of our paper merits deeper discussion. We have therefore added the additional details to lines 430-437. of the manuscript:

“This may have led to an over- or underestimation of survival rates for the different conditions included in the model, as expert opinion builds on subjective experience, not representative data. Despite these limitations of expert opinion, however, they are commonly used in cost-effectiveness analyses in the absence of stronger data to estimate model parameters, as was the case in our setting [7]. Additionally, we drew on the available literature from similar settings in sub-Saharan Africa to put the estimates obtained from the expert panel process into context and verify for any outliers or implausible values.”

3. The costing approach uses comprehensive data from the NGO providing this service, however, there is reference to efforts from facilities that would be needed to make transfers. The authors have not discussed at which rate a physician would join the transport team (when deemed appropriate by the dispatcher), if that physician was part of the sending hospital team, and if so, what the costs are for taking a physician out of the facility for the duration of transport and return. We thank the reviewer for highlighting this lack of clarity in our description. The doctors that accompanied the referral were employed by the NGO, meaning that no costs occurred to the facilities in case the referrals were accompanied by the medical doctor. The costs of the doctor’s salaries are included in the costing analysis.

To improve the clarity of our paper, we have amended lines 144-145 as follows:

“The medical doctor was an employee of the implementing NGO and accompanied approximately 5% of referrals.”

4. Are there other costs to the health system outside of those paid by the NGO that are relevant? While there are other costs to the health system outside the inter-facility transfer system, such as the salaries of facility-based healthcare providers, these costs are likely consistent regardless of the presence of the referral system. We focused our analysis on costs directly associated with the referral system and are confident that our analysis adequately captured and accounted for any additional costs incurred by the referral system.

5. The conclusion that this EmOC referral system is very cost effective seems accurate, although the authors could consider defining which threshold for cost-effectiveness is being used to categorize this system as such. Or if thresholds are not being used due to their inherent limitations, perhaps the authors could place this intervention in context by comparing to other interventions in Madagascar. We thank the reviewer for posing this important question. Given the limitations of the cost-effectiveness thresholds, we did not opt to compare our intervention to a pre-defined threshold. As there are no cost-effectiveness analyses for similar interventions in Madagascar, we would like to highlight lines 391 to 397 in our manuscript, which put the intervention in context with other, similar interventions from Sub-Saharan Africa. Additionally, we have now added the following section in lines 372 to 379, comparing the ICER of our intervention with those of other interventions in Madagascar:

“While there are no other studies evaluating similar interventions in Madagascar, our intervention shows itself to be more cost-effective than other CEAs conducted in Madagascar, which reported ICERs of 1023 USD per QALY gained for an intervention expanding access to antibiotics for plague care and prevention [8], 177 USD per DALY averted for a drone-supported community treatment programm for TB [5], and 531.2 USD per DALY averted [6] for the Indoor-residual spraying activities of the national tuberculosis control programm, showing our intervention to have a much lower ICER.”

We would equally like to draw the reviewer’s attention to our reply to question 8 of reviewer 1.

VERSION 2 – REVIEW

REVIEWER	Taylor Burkholder USC Keck School of Medicine
REVIEW RETURNED	17-Mar-2024

GENERAL COMMENTS	Thank you for this thoughtful revision to an important cost-effectiveness evaluation of inter-facility referrals for emergency obstetric care in Madagascar. The authors have satisfactorily responded to comments from the first review and added helpful clarity to several aspects of program design and research methods. They have also added detail to their discussion of the limitation related to expert panel consensus to estimate the survival benefit and its potential impact on study findings.