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TITLE

Inter-facility transfers for emergency obstetric and neonatal care in rural Madagascar: A cost-effectiveness analysis

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ABSTRACT

Context: There is a substantial lack of inter-facility referral systems for emergency obstetric and neonatal care in rural areas of sub-Saharan Africa. Data on the costs and cost-effectiveness of such systems that reduce preventable maternal and neonatal deaths are scarce.

Setting: We aimed to determine the cost-effectiveness of an NGO-run inter-facility referral system for emergency obstetric and neonatal care in rural southern Madagascar by analyzing the characteristics of cases referred through the intervention as well as its costs.

Design: We used secondary NGO data, drawn from an NGO's monitoring and financial administration database, including medical and financial records.

Outcome measures: We performed a descriptive and a cost-effectiveness analysis, including a one-way deterministic sensitivity analysis.

Results: 1,172 cases were referred over a period of 4 years, with an estimated referral cost of 336 USD and an incremental cost-effectiveness ratio (ICER) of 70 USD per additional life year saved (undiscounted, discounted 137 USD). The sensitivity analysis showed that the intervention was cost-effective for all scenarios with the lowest ICER at 99 USD and the highest ICER at 205 USD per additional life year saved. When extrapolated to the population living in the study area, the investment costs of the program were 0.13 USD per person and annual running costs 0.06 USD per person.

Conclusions: In our study, the inter-facility referral system was a very cost-effective intervention. Our findings may inform policies, decision making, and implementation strategies for emergency obstetric and neonatal care referral systems in similar resource-constrained settings.

ARTICLE SUMMARY

Strengths and limitations of this study

- Strength: Large study sample from a widely understudied population in remote Southern Madagascar
- Limitation: Programmatic data and reliance of expert panel process for defining survival rates
- Limitation: No long-term follow up data of patients available due to cross-sectional nature of the study.
- Strength: Robust CEA methodology, including detailed and comprehensive costing data

KEYWORDS

Sub-Saharan Africa, maternal health, Emergency obstetric and neonatal care, cost-effectiveness analysis

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

DATA SHARING

The original data are available from the corresponding author upon reasonable request.

WORD COUNT

3,344

BACKGROUND

Reducing the global maternal mortality ratio to less than 70 per 100,000 live births by 2030 is a key target of the Sustainable Development Goals (1). Haemorrhage, sepsis, unsafe abortion, and other complications of delivery account for more than 50% of maternal deaths in sub-Saharan Africa (SSA) (2). Most neonatal deaths in SSA are attributable to either intrapartum complications or complications linked to preterm delivery (3). Many of these fatalities are preventable through access to timely and high-quality emergency obstetric care (EmOC).

However, mothers and neonates in SSA often experience significant delays in accessing EmOC services, i.e., when deciding to seek, reaching, and receiving adequate care (4). Access to and availability of adequate means of transportation, including ambulance referral services to EmOC centres, reduces these delays (5,6), which, in turn, reduces maternal and neonatal mortality (7,8).

The implementation of ambulance referral systems for EmOC services in SSA have been described for several, mostly rural contexts, including in Uganda (9,10), Burundi (11), and Ethiopia (12). They mostly differed in the type of referral service provided (i.e., from home to health facility versus inter-facility referral) and the level of medical support provided to patients during referrals. Only a minority of these programs have been evaluated through a cost-effectiveness analysis (9, 12).

Africa’s health financing gap is estimated at 66 billion USD annually and the financing need for maternal and child health services is particularly acute (13,14). Thus, reliable data on costs and cost-effectiveness of ambulance programs are essential for designing and prioritizing maternal health interventions in SSA.

We aimed to describe case and service characteristics as well as analyse the costs and cost-effectiveness of an EmOC inter-facility referral system established by a non-governmental organization (NGO) in rural Madagascar. Our findings may inform policies, decision making and implementation strategies for EmOC referral systems in resource-constrained settings.

METHODS

Study design

This is a retrospective study using secondary data, routinely collected as part of an NGO intervention. A data-sharing agreement with the NGO was in place.

Study area and context

The study took place in Atsimo-Andrefana, Androy, and Anosy, rural regions in the South of Madagascar. Poverty rates in the study region are high with over 80% of the population living of less than 1.90$ per day (15). Nationally, neonatal, and maternal mortality ratios remain high with a maternal mortality ratio 335 per 100,000 and a neonatal mortality ratio of 20 per 1,000 live births, respectively (16).

The Malagasy health system is organized in 3 tiers of care. While some public emergency referral services exist at the district and national level, they fall short of covering a significant amount of the population, especially in rural areas of the country.

Intervention

Setting

To improve access to EmOC, the German-Malagasy NGO Doctors for Madagascar established an inter-facility referral system for obstetric and neonatal care in Atsimo-Andrefana (Ampanihy, Betioky-sud, and Benenitra districts), Androy (Bekily district), and

Anosy region (Fort-Dauphin district). The intervention covered a catchment population of around 1 million people (17). The intervention was rolled out sequentially, starting in Atsimo-Andrefana and Androy in 2016 and in Anosy in 2018. A 4-wheel drive ambulance was stationed at each of 3 secondary referral hospitals: Hopitaly Zoara Fotadrevo, Hopitaly SALFA Manambaro, and Hopitaly SALFA Ejeda, which served 18, 23, and 13 participating primary health centres, respectively.

Participating primary health centres (locally known as Centers de Santé de Base (CSB); n = 54) could call the ambulance 24h per day without charge. If referral was deemed necessary by a trained medical dispatcher, the ambulance was sent to the CSB to transfer the patient to a higher-level care facility. The referral was free for patients and participating health centres, all costs were covered by the NGO.

Vehicles and equipment

All ambulances were Toyota 4-wheel drive vehicles, equipped with a stretcher, oxygen, emergency medical equipment, and drugs. Supplementary File 1 summarizes the medical equipment and drugs, which were available on board an ambulance vehicle.

To improve pre-transport emergency care, the NGO equipped participating CSBs with emergency kits containing alcohol, compresses, cotton swabs, isotonic glucose solution, isotonic saline, intravenous catheters, IV lines, scissors, sterile and non-sterile gloves, and urinary catheters. These kits were checked and refilled by NGO staff after each referral.

Emergency medical teams

All calls from CSBs requesting a referral were processed by a medical emergency dispatcher, usually a medical doctor trained in EmOC and familiar with the local setting. If the dispatcher deemed a referral to be necessary, a vehicle was sent to retrieve the patient from the CSB.

The medical team aboard each vehicle always consisted of a trained midwife and a driver who had received basic life support training. If necessary, a medical doctor accompanied critical referrals. This decision was made on a case-by-case basis by the dispatcher.

Performance-based bonus payments

The referring healthcare worker received a cash bonus of 2.5 USD for each case referred through the intervention, paid at the end of the month.

Participants

All women who presented at one of the participating CSBs during the intervention period with an acute complication during pregnancy, childbirth, or postpartum and whose emergency referral was deemed necessary by the medical dispatcher were eligible to participate. Similarly, all neonates born or treated at participating CSBs within the neonatal period of 28 days and whose emergency referral was deemed necessary by the medical dispatcher were eligible to participate.

All obstetric and neonatal patients using the ambulance referral system between January 5th, 2016, and September 30th, 2020, were included in the descriptive analysis.

Mothers and neonates presenting at CSBs not participating in the intervention were not eligible for ambulance referral.

Patients could refuse referral services at any point in time.

Data collection and data entry

Medical records

The data source for patient and referral characteristics were case data sheets filled by the ambulance staff. These data sheets included details on patient characteristics (e.g., gestational age) and the referral indication.

All data were digitized into summary Excel tables by NGO personnel. Healthcare staff, who were not otherwise involved in this study, replaced patient identifying information with numerical pseudonyms before forwarding the Excel sheets to the research team for analysis. Codes linking pseudonyms and identifying information were not accessible to the research team.

We collected the original data in French and translated it into English. Data were cleaned by 3 independent researchers with regular check-ups to assure consistency in data cleaning. Data were additionally cross-checked and screened for double entries, out-of-range values, and overall consistency. In case multiple referral indications were given, an expert panel of 3 Malagasy physicians determined the main referral indication, which were grouped following the approach by Abegunde et al. (18). All data were stored in a password-protected database to which only the research team had access.

Financial records

The data source for the costs of the intervention were NGO financial records from 2016 to 2019. A researcher extracted data from the original records and categorized them into investment and running costs and corresponding sub-categories (medical equipment, administration, transport, communication, consumables, pre-transport care, performance-based bonus payments, and training activities).

Investment costs were annualized based on lifetime estimates or records of items based on expert estimates from NGO staff active in the study region.

We included all costs associated with the initial establishment of the referral systems, e.g., acquisition of equipment and ambulances, as well as running costs for the 3 project sites in the cost-effectiveness analysis (CEA). Costs for treatments at CSBs and referral hospitals were not included, as those were not supported through the program. Data were collected in Malagasy Ariary or Japanese Yen (1 invoice) and converted to United States dollars for analysis (Exchange rate: 1 USD = 3,867.09 Malagasy Ariary (as of September 22nd, 2020) and 1 USD = 105.671 Japanese Yen (as of September 30th, 2020).

Data analysis

Descriptive statistics

We performed a descriptive analysis, including frequency distributions, for medical records using Stata Version 16.

Cost-effectiveness analysis

We used a cost-effectiveness analysis to quantify the costs per life year saved, as well as the incremental cost-effectiveness ratio of the intervention. As this was not a randomised control trial, we did not develop a health economic analysis plan. We also assessed the sensitivity of the analysis to variation of parameters. We adhere to the CHEERS guideline for economic evaluations of healthcare interventions in structuring this manuscript (19).

The main outcomes of the model were incremental cost-effectiveness ratios (ICER) per life year saved through the intervention overall, and separately by cohort, where one cohort was defined as all cases referred due to the same referral indication. To calculate the costs for each cohort, we multiplied the average costs per referral with the number of patients per cohort. For each cohort, we calculated the following incremental cost-effectiveness ratio (ICER): (Costs of ambulance referral system-Costs of no referral system) / ((Life years saved neonates referred + Life years saved mothers referred) – (Life years saved neonates not referred + Life years saved mothers not referred)). To obtain the overall ICER of the intervention, we added the ICERs for individual cohorts, weighted by the frequency of their occurrence.

Study population and model

This economic evaluation followed a cost-effectiveness analysis, with a healthcare provider's perspective. For each medical condition that constituted a referral indication, we developed 1 decision analytical model (if the condition affected only mother or neonate, n= 8 models) or 2 (if the condition affected both mother and neonate, n = 9 models) intervention cohorts, as well as the corresponding number of control cohorts (n = 17 models). The starting age for mothers in the models was 24 years and 0 years for neonates. Individuals from the intervention cohorts were referred to secondary hospitals, while individuals from comparison cohorts were not referred and received only primary care. For all models, a time horizon of 100 years was chosen to anticipate lifetime.

Supplementary files 2 and 3 outline the non-reversible patient journey for referred and non-referred mothers and referred and non-referred neonates, respectively.

We applied these exclusion criteria for the CEA: date of referral not during the study period; referral indication unknown or unrelated to emergency obstetric and neonatal care; referral indications with less than 10 cases.

For all cohorts, all-cause mortality was calculated on an annual basis, whereas the first 2 stages for the comparison groups and the first 3 stages for the intervention groups were treated as one time stamp.

Pathway probabilities

Medical records were used to determine the number of mothers and neonates treated at participating CSBs for each referral indication.

Given that there was no previously published data for this context, survival rates for both referred and non-referred mothers and neonates were estimated through a two-stage expert panel process. 3 Malagasy physicians, otherwise not involved in this study formed the expert panel. They were chosen as a convenience sample, as they were familiar with the NGO's intervention and had long-term experience in maternal health in the intervention area.

The research team reviewed existing literature from low- and middle-income countries on maternal survival rates for all referral indications. Both Google Scholar and PubMed were searched to identify relevant studies. From these, we extracted data on survival rates for individual referral indications at primary and secondary facilities as well as information on study design, context, strengths, and limitations. We presented these data to the expert panel. The panel then defined survival rates for each referral indication. Results of this expert panel process are summarized in Table 1 and 2 below. For each condition, the expert panel defined a maximum and minimum survival rate for mothers and neonates at both primary and secondary facilities, as well as an average survival rate agreed upon by all experts. This rate formed the baseline estimate for our CEA models.

Table 1: Survival estimates mothers

Referral indications mothers (n)	**Survival rates when referred to secondary care**			**Survival rates when not-referred (primary care only)**			**References**
	Min	Max	Baseline	Min	Max	Baseline	
Obstructed labour (251)	95%	99%	98%	80%	99%	90%	[20; 21; 22]
Ineffective labour (137)	98%	99%	99%	85%	99%	95%	[23; 24; 25]
Extrauterine gravidity (50)	99%	95%	99%	1%	0%	0%	[26; 27; 28]
Post-partum haemorrhage (46)	70%	90%	80%	20%	80%	30%	[29]
Intrauterine foetal death (IUFD) (45)	90%	99%	95%	85%	95%	93%	[30]
Eclampsia	65%	96%	75%	30%	90%	50%	[31; 32; 33]

(39)							
Placenta previa (34)	85%	98%	87%	50%	95%	70%	[34; 35; 36; 37]
Abortion (30)	90%	99%	95%	85%	95%	90%	[38]
Risk of premature delivery (26)	99%	99%	99%	99%	98%	99%	[29]
Placenta retention (25)	99%	99%	99%	50%	99%	91%	[39; 40]
Delivery (22)	98%	99%	98.5%	95%	99%	96.5%	[29]
Infection postpartum (19)	90%	98%	95%	70%	95%	80%	[41; 42]
Risk of uterus rupture (17)	90%	95%	92.5%	5%	40%	35%	[43; 44; 45; 46]
Fetal distress (12)	98%	99%	98.5%	70%	99%	96.5%	[47; 48; 49]
Malaria (12)	98%	99%	99%	95%	98%	97.5%	[50]

Table 1. Minimum, maximum, and baseline survival estimates for referred and non-referred mothers grouped by referral indication. Survival estimates were obtained by expert panel consensus.

259 Table 2: Survival estimates neonates

260

Referral indications neonates (n)	Survival rates when referred to secondary care			Survival rates when not-referred (primary care only)			References
	Min	Max	Baseline	Min	Max	Baseline	
Obstructed labour (251)	60%	90%	70%	25%	80%	35%	[20; 21; 22]
Ineffective labour (137)	45%	95%	55%	30%	88%	35%	[23; 24; 25]
Eclampsia (39)	30%	80%	50%	15%	50%	25%	[31; 32; 33]
Placenta previa (34)	50%	95%	60%	20%	90%	30%	[34; 35; 36; 37]
Risk of premature delivery (26)	15%	98%	70%	15%	97%	25%	[51; 52]
Delivery (22)	85%	98%	92%	75%	95%	85%	[29]
Risk of uterus rupture (17)	20%	93%	90%	3%	40%	10%	[43; 44; 45; 46]
Fetal distress (12)	70%	99%	95%	30%	98%	55%	[47; 48; 49]

Respiratory distress (12)	5%	90%	20%	1%	50%	5%	[53;54]
Malaria (12)	90%	98%	95%	90%	94%	91%	[43]
Neonatal infection (10)	5%	85%	70%	5%	80%	50%	[51; 55]

Table 2. Minimum, maximum and baseline survival estimates for referred and non-referred neonates grouped by referral indication. Survival estimates were obtained by expert panel consensus.

Life years

Health outcomes were estimated based on local life expectancy tables (56). Costs and life-years saved were discounted at a 3% discount rate. This rate reflects the average annual growth of the Malagasy economy during the study period[56] and aligns with the approach for discounting in economic evaluation suggested by Haacker et al. (58).

Sensitivity analysis

Given that no probabilistic data was available in the literature, we performed a one-way deterministic sensitivity analysis for the survival rates for referred and non-referred mothers and neonates to assess the impact of individual model parameters and assumptions on the model outputs.

Ethics approval and consent to participate

278 Ethical clearance for the study was obtained from the Heidelberg University Hospital Ethics
279 Committee, registration number: S-713/2020. Informed consent was waived by the ethics
280 committee.

281 **RESULTS**

282 **Referral characteristics**

283 In total, 1,172 patients (48 neonates and 1,124 women, respectively) were referred through the intervention. Most referrals took place in Atsimo-Andrefana region (54%), followed by Anosy (45%) and Androy regions (1%). The average distance per referral were 52.8 km.

286

287 **Demographic and clinical characteristics**

288 Mean age of women was 23.6 years (n=1,118; IQR=12). Most neonates (78%, 36/46) were in their first week of life. 80% of calls were made for direct obstetric causes above all for obstructed/prolonged labour (40%, 445/1,124) (Table 3). For neonates, the most common referral indications were respiratory distress (29%, 14/48) or infection (21%, 10/48) (Table 4).

293 Table 3: Referral reasons mothers

Obstetric complication	**Women (n=1,124)**	**(%)**
Direct causes	906	80.6
Abortion and its complications, including intra-uterine foetal death	89	7.9
Ectopic pregnancy	52	4.6
Embolism	1	0.1
Hypertensive disorders	61	5.4
Prepartum/postpartum haemorrhage	114	10.1
Obstetric trauma	18	1.6
Obstructed/prolonged labour	445	39.6
Other direct causes	141	12.5
Indirect causes	123	10.9
Anaemia	7	0.6
Malaria	12	1.1
Tuberculosis	1	0.1
Other indirect causes	88	7.9
Other cases*	37	3.3
No obstetric complication specified	58	5.2

*Such as: no medical staff present at CSB, insufficient equipment for delivery at CSB

Complications during pregnancy, childbirth, and postpartum, which triggered the referral of mothers (n =1,124) from participating CSBs to secondary referral hospitals. CSB, Centre de Santé de Base (public primary care facility).

Table 4: Referral reasons neonates

Complication	Neonates (n=48)	%
Abdominal bloating	3	6.3
Birth defect	9	18.8
Dehydration	4	8.3
Hypothermia	1	2.1
Icterus	1	2.1
Unspecified infection*	10	20.8
Premature birth	4	8.3
Respiratory distress	14	29.2
Syphilis	1	2.1
Other (=vomiting)	1	2.1

*Unspecified infection included neonates showing signs of infection such as fever, altered cardiorespiratory status or marmorated skin.

Complications during the neonatal period, which triggered the referral of neonates (n= 48) from participating CSBs to secondary referral hospitals.

Not all calls resulted in a completed referral. In 97 cases the ambulance was dispatched but the referral was not completed. Most commonly (65%, 63/97) the complication had been resolved at the CSB either with (25%, 24/97) or without (40%, 39/97) support from the ambulance staff. In 8 cases (8.2%) the woman or neonate had passed away before the ambulance reached the CSB and in 4 cases (4.1%) the patient or patient's relatives refused the referral.

307 **Costs**

308 The total intervention costs over the study period were 394,197 USD.

309 Supplementary File 4 and 5 show the detailed distribution of cost of operating 1 vehicle over
310 the intervention time frame (January 2016-September 2020).

311 The average cost per referral was 367 USD (n=1075).

312 If the costs of the project were shared among all people living in the project area, initial
313 investment costs would be 0.13 USD per person and annual running costs 0.06 USD per
314 person.

315 Around 20% of the population in the study region are women of reproductive age. Assuming
316 that each of these women could be a potential beneficiary of the project, the costs per
317 potential beneficiary amount to 0.57 USD per person in investment and 0.26 USD in annual
318 running costs.

319 **Cost-effectiveness analysis**

320 Incremental life-years saved through the program were 37,882 (rounded to the full year)
321 undiscounted and 4,872 when discounted at 3%.

322 The overall ICER of the ambulance system was 70 USD per additional life year saved
323 undiscounted and 137 USD per additional life year saved when discounted at 3%.

324 The ambulance intervention proved particularly cost-effective for cases of extrauterine
325 gravidity, risk of uterus rupture, and post-partum haemorrhages with ICERs of less than 30
326 (discounted at 3%). The program proved least effective for cases of malaria in pregnancy and
327 post-partum infection. Table 5 below lists the costs per life year saved as well as the ICER
328 per diagnosis.

329 Table 5: Results of CEA

Referral indication (n)	Cost per life year saved discounted/undiscounted (USD)	ICER discounted/undiscounted
Obstructed labour (251)	11.2/5.9	62.9/30.1
Ineffective labour (137)	11.7/6.2	115.1/54.7
Extrauterine gravidity (50)	14.4/8.0	14.4/8.0
Post-partum haemorrhage (46)	17.1/9.5	26.4/14.6
Intrauterine foetal death (IUFD) (45)	15.0/8.3	710.9/394.0
Eclampsia (39)	14.8/7.8	40.1/20.7
Placenta previa (34)	12.3/6.5	57.8/28.3
Abortion (30)	15.0/8.3	284.3/157.6
Risk of premature delivery (26)	11.0/5.8	72.9/32.7

Placenta retention (25)	14.3/7.9	171.3/94.9
Delivery (22)	10.4/5.4	288.5/138.9
Infection postpartum (19)	59.9/33.2	379.1/210.1
Risk of uterus rupture (17)	10.9/5.7	15.6/8.0
Fetal distress (12)	10.3/5.3	76./34.5
Malaria (12)	10.3/5.3	447.8/217.8
Respiratory distress neonate (12)	170.2/75.8	227.0/101.0
Neonatal infection (10)	48.6/21.7	107.2/75.6

Table 5: Costs per life-year saved (in USD) and ICER per diagnosis, undiscounted and discounted at 3%.

Sensitivity analysis

The sensitivity analysis showed the intervention to remain cost-effective for most scenarios tested. However in the following cases either the survival rate estimates at the participating CSB exceeded the baseline estimate at the referral hospital or the worst case estimate at the hospital was lower than the baseline estimate at the CSB, rendering the scenario not cost effective: Mothers survival for eclampsia, neonates survival for ineffective labour, neonate survival for neonatal infection, neonates survival for respiratory distress and neonates survival for risk of premature delivery tested.

DISCUSSION

The aim of this study was to evaluate the characteristics, costs, and cost-effectiveness of an NGO-run inter-facility referral system for EmOC in rural Madagascar.

This study revealed three main findings: First, the most common referral indication for mothers was obstructed/prolonged labour and unspecified infection or respiratory distress for neonates. Second, the largest drivers of costs for the intervention were initial investment costs for the vehicles and running costs including staff wages. Consequently, ambulance lifespan is a particularly important determinator of the intervention's cost-effectiveness. Lastly, the CEA demonstrated the intervention to be very cost-effective, with an ICER of 137 USD per additional life year saved (discounted at 3%). The intervention was particularly cost-effective for the following conditions: extrauterine gravidity, risk of uterus rupture, and post-partum haemorrhage. The sensitivity analysis conducted showed the intervention to remain cost-effective in most scenarios tested.

In accordance with our findings, other systems for EmOC referral in SSA have found direct obstetric complications, especially abortion and obstructed labour to be the main referral indications for mothers to secondary health facilities in resource-constrained settings (11, 59).

Compared with other ambulance referral systems in Uganda (9), Burundi (11) and Ethiopia (12), costs for our intervention were high. This finding is however not surprising considering that referrals in other interventions were not accompanied by trained medical personnel receiving salaries. Neither ambulance carried medical equipment and neither publication included overhead costs such as administrative costs in their cost-effectiveness analysis. In addition, our intervention covered a large rural area in the remote south of Madagascar; there were no paved roads and conditions deteriorated during the rainy season when parts of the intervention became inaccessible. This increased costs for vehicle maintenance and fuel.

These differences in the design of the interventions as well as their contexts of implementation likely explain the higher ICER of 137 USD per additional life year saved (discounted) when compared to ICERs of 16 USD (9) and 25 USD per additional life year saved (12) in Uganda and Ethiopia, respectively. Further, these studies only included referrals in their analysis which were deemed “undoubtedly effective” (9,12), i.e., cases in which the referral was likely to have a large impact on life-years saved. Our model on the other hand included all cases in the calculation of the overall ICER.

Consequently, costs per referral were higher for our setting than in other studies. Tayler-Smith et al. reported costs of 61 USD per referral, with 1,478 ambulance referrals per year (11), compared to 1,075 completed referrals over 4 years, with an average cost per referral of 367 USD in our setting.

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 much lower than what has been reported in other rural settings, for example in Burundi (€ 0.43/capita/year) (11), suggesting that the intervention described here served a much 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 (60).

Our study has three main strengths: First, we used secondary NGO data as the basis for all analyses. This reduced the potential for erroneous data as there was no need to rely on estimations. Further, our data provide insights into a particularly vulnerable and resource-constrained setting for which data is otherwise hard to obtain. Second, we included all costs for the running of the ambulance system in the cost-effectiveness analysis, including overhead costs such as administrative costs, rendering more realistic cost estimates than other studies. Third, we obtained survival estimates using a multi-step expert consensus process, when these data were not available from the literature.

Our study has several limitations. First, we were constrained by the availability of programmatic data and had to rely on expert opinions to estimate equipment lifespans as well as survival rates for the economic model. For the latter, to mitigate potential bias we established an expert panel consensus process to estimate survival rates. Second, data were not available on mothers' post-delivery complications or their previous patient history to allow for more nuanced calculations for life years saved and our model only accounted for mothers and neonates, for whom referral was successful. However, we do not expect either factor to have a large impact on the model's cost-effectiveness and are confident that the approach of constructing separate models per cohort can robustly identify the most cost-effective applications of inter-facility EmOC referrals. Last, we did not assess whether the intervention met the referral needs of the population in the study area.

CONCLUSION

Our study is the first to report the cost-effectiveness of an EmOC inter-facility referral system in Madagascar. We find the intervention to have been very cost-effective, especially for cases requiring surgical care. Our findings highlight the need for a comprehensive approach to providing rural EmOC services and may provide guidance on public health resource allocation in Madagascar.

AUTHOR CONTRIBUTIONS

MAF, AF, KN, NM, SK, and JVE developed the study design in collaboration with TB. MAF, AF, RMR, MR, ZR and KN were responsible for data collection and study administration. MAF, AF, KN, NM, RMR, ZR, SK, and JVE contributed to the analysis. MAF, AF, and KN prepared the first draft of the manuscript. All authors contributed to writing the manuscript. All authors read and approved the final manuscript.

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PATIENT AND PUBLIC INVOLVEMENT STATEMENT

This study did not involve patients in the research process. However, we did involve three independent Malagasy clinicians in the research process as key informants for the expert panel process to define survival probabilities for the different patient pathways. This greatly enhanced the applicability and relevance of our research for the context of Southern Madagascar.

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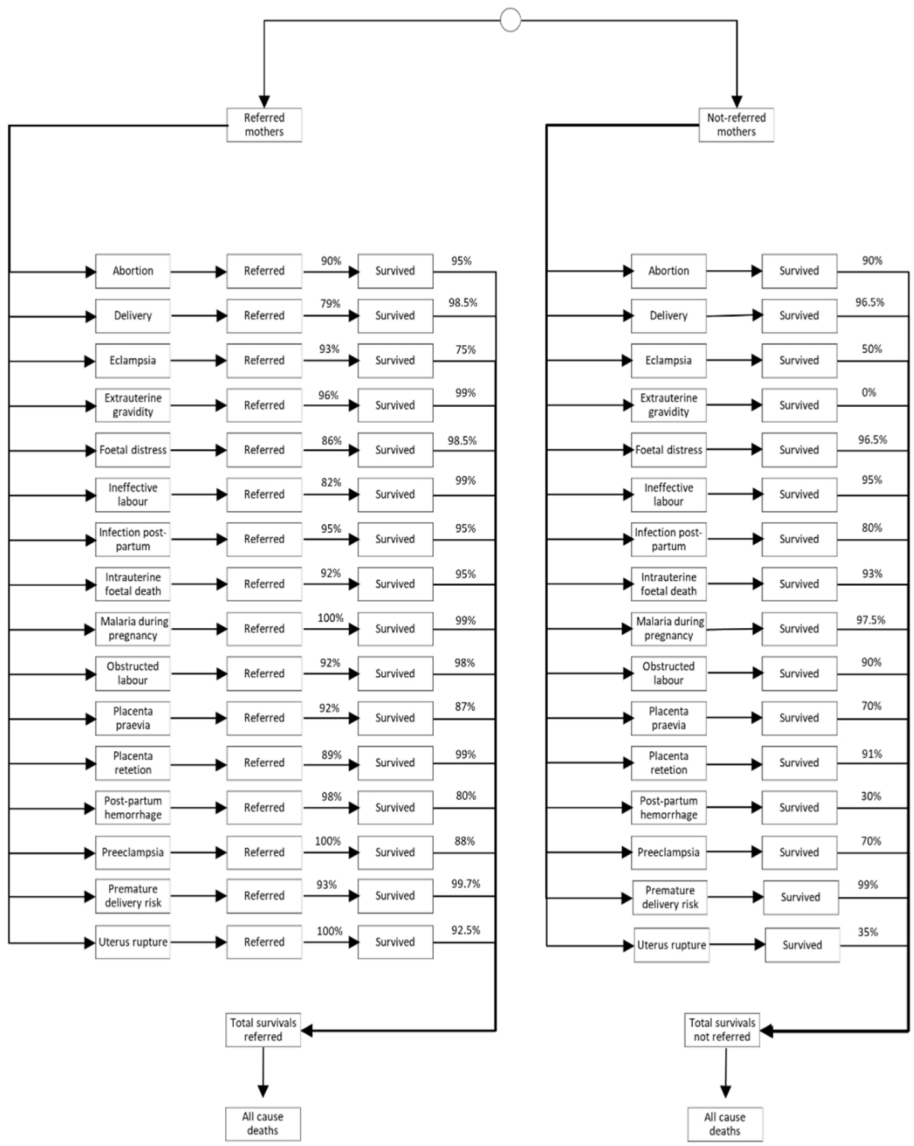
596 **SUPPLEMENTARY FILE LEGENDS**

597 Supplementary file 2. Non-reversible patient journey for referred and non-referred mothers.
598 For referred mothers, the model included 4 stages: 1) presentation at a participating CSB
599 because of an emergency during pregnancy or childbirth, 2) referral to secondary referral
600 hospital, 3) likelihood of survival at referral hospital, 4) all-cause mortality. The model
601 included 3 stages for non-referred mothers: 1) presentation at a CSB because of an
602 emergency during pregnancy or childbirth, 2) likelihood of survival at CSB, 3) all-cause
603 mortality. CSB, Centre de Santé de Base (public primary care facility).
604
605 Supplementary file 3. Non-reversible patient journey for referred and non-referred neonates.
606 For referred neonates the model included 4 stages: 1) presentation at a CSB because of an
607 emergency peripartum or in the neonatal period, 2) referral to secondary referral hospital, 3)
608 likelihood of survival at referral hospital, 4) all-cause mortality. For non-referred neonates,
609 the model included 3 stages: 1) presentation at a CSB because of an emergency peripartum or
610 in the neonatal period, 2) likelihood of survival at CSB, 3) all-cause mortality. CSB, Centre
611 de Santé de Base (public primary care facility).

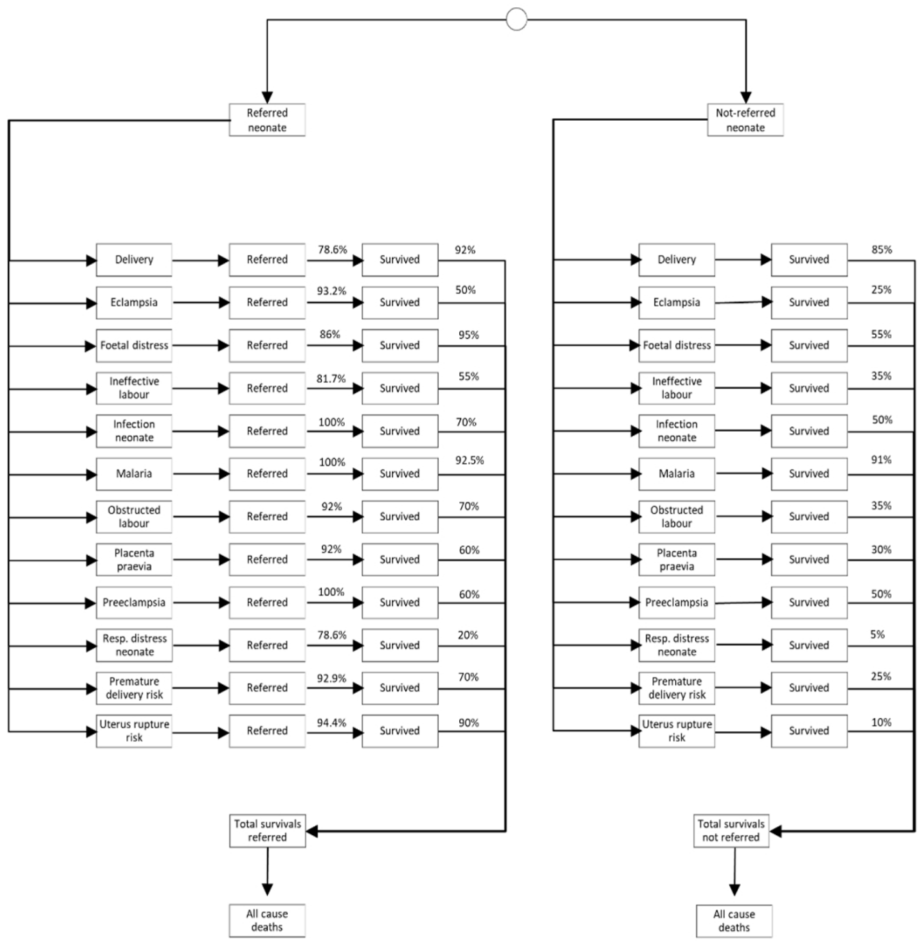
Supplementary File 1: Ambulance furnishings

Medical equipment	**Drugs**
• Alcohol • Betadine • Blood sugar testing strips • Cord clamps • Echography gel • Intravenous catheters • Non-sterile compresses • Non-sterile gloves • IV lines • Plasters • Pregnancy test • Sterile compresses • Sterile gloves • Ultrasound machine • Urinary catheters and bags	• Analgesics ◦ Paracetamol • Antibiotics ◦ Ampicillin ◦ Amoxicillin • Antihypertensive agents ◦ Magnesium Sulphate ◦ Nicardipine • Infusion solutions ◦ Isotonic Glucose solution ◦ Isotonic saline ◦ Lactated Ringer's ◦ Natrium Chloride • Uterotonic agents ◦ Misoprostol ◦ Oxytocin • Other ◦ Calcium gluconate ◦ Diazepam ◦ Paracetamol ◦ Salbutamol ◦ Tranexamic acid ◦ Vitamin K

Medical equipment and drugs available aboard ambulance vehicles.



453x560mm (87 x 87 DPI)



464x468mm (87 x 87 DPI)

Supplementary File 2: Investment costs

Item	Cost per unit (USD)	Quantity
Ambulance		
Port charges, forwarding agent	3,620	1
Shipment from Japan to Madagascar including insurance	3,020*	1
Vehicle	38,254	1
Subtotal	45,487	
Equipment ambulance		
Carpet	38	1
Fire extinguisher	26	1
Luggage rack	282	1
Mattress cover	54	1
Phone for ambulance	45	1

Item	Cost per unit (USD)	Quantity
Steering wheel cover	74	1
Tarpaulin	74	1
Subtotal	593	
Administration		
IT equipment, furniture)	528	1
Mobile phone	45	1
Subtotal	573	
Total	**45,487**	

Initial ambulance investment costs for 1 ambulance vehicle. Prices are expressed in USD with an exchange rate of 1 USD = 3,867.09 Malagasy Ariary (MGA) and 1 USD = 105.671 Japanese Yen (JPY) (costs marked *).

Supplementary File 3: Running costs

Item	**Cost per unit (USD)**	**Quantity**	**Annual costs (USD)**
Transport			
Fuel	Average: 0.98 USD/l (0.91/l – 1.03/l)	Average 147l /months (96l-205l)	1,729
Insurance	44	1	44
Licensing in Madagascar	194	1	194
Maintenance	1,707	Yearly average	1,707
Repair	467	Yearly average	467
Subtotal			4,141
Car equipment			
Air chamber for tire	72	4	288
Cleaning equipment (shovel, broom, brush, scraper)	13	1	13
Tires	142	4	568
Subtotal			869

Item	Cost per unit (USD)	Quantity	Annual costs (USD)
Consumables			
Cleaning materials	1	12	12
Drugs on board ambulance	49	12	588
Medical equipment on board ambulance	36	12	432
Oxygen bottle	43	1	43
Subtotal			1,075
Pre-transport care			
Drugs and consumables	78	6	468

Item	Cost per unit (USD)	Quantity	Annual costs (USD)
Staff wages			
Drivers	Average: 116/months (range 103-129)	12	1,392
Local coordinator	413/month	12	4,956
Midwives	155/month	12	1,860
Subtotal			8,208
Communication			
Free phone number for ambulance calls	9/month**	12	108
Phone credits driver	5/month	12	60
Phone credits coordination	8/month	12	96
SIM card for GPS tracking of vehicles	10/month	12	120
Subtotal			384

Item	Cost per unit (USD)	Quantity	Annual costs (USD)
Performance-based bonuses			
Medical director of participating CSBs	55	12	660
Item	**Cost per unit (USD)**	**Quantity**	**Annual costs (USD)**
Midwife of participating CSBs	70	12	840
Additional renumeration during ambulance services (staff on extra duty for at least 4 hours)	4	Average: 20 times/months	960
Subtotal			2,460
Training activities			
Yearly training for drivers	297*	1	297
Administration			
Consumables	128	12	1,536
Electricity	15	12	180
Rent	155	12	1,860
Subtotal			3,576

Total annual running costs	**21,478**

Annual running costs for 1 ambulance vehicle. Prices are expressed in USD with an exchange rate of 1 USD = 3,867.09 Malagasy Ariary (MGA) and 1 USD = 0.840618 Euros (costs marked *).

** on average, depending on the number of calls received

CHEERS 2022 Checklist

	Item	Guidance for Reporting	Reported in section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Page 1
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	Pages 2-3
INTRODUCTION			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	Pages 4-5
METHODS			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Page 9
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Page 7
Setting and location	6	Provide relevant contextual information that may influence findings.	Pages 5-6
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Pages 5-7
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Page 10
Time horizon	9	State the time horizon for the study and why appropriate.	Page 7
Discount rate	10	Report the discount rate(s) and reason chosen.	Page 15
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Pages 9-10
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Page 15
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Pages 10-15
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Pages 8-9
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Page 8-9
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Pages 10-15
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Pages 11, 15
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups.	Page 15
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	Pages 11, 15
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	Pages 11-12
RESULTS			
Study parameters	22	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	Pages 12-15, 18-20, Suppl.
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Pages 20-23
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Pages 23-24
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Pages 11-12
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	P. 25-27
OTHER RELEVANT INFORMATION			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Page 3
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Page 3

Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S; CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. BMJ. 2022;376:e067975.

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Inter-facility transfers for emergency obstetric and neonatal care in rural Madagascar: A cost-effectiveness analysis

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TITLE

Inter-facility transfers for emergency obstetric and neonatal care in rural Madagascar: A cost-effectiveness analysis

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ABSTRACT

Context: There is a substantial lack of inter-facility referral systems for emergency obstetric and neonatal care in rural areas of sub-Saharan Africa. Data on the costs and cost-effectiveness of such systems that reduce preventable maternal and neonatal deaths are scarce.

Setting: We aimed to determine the cost-effectiveness of an NGO-run inter-facility referral system for emergency obstetric and neonatal care in rural southern Madagascar by analyzing the characteristics of cases referred through the intervention as well as its costs.

Design: We used secondary NGO data, drawn from an NGO's monitoring and financial administration database, including medical and financial records.

Outcome measures: We performed a descriptive and a cost-effectiveness analysis, including a one-way deterministic sensitivity analysis.

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 cost per referral were 336 USD and the incremental cost-effectiveness ratio (ICER) was 70 USD per additional life year saved (undiscounted, discounted 137 USD). The sensitivity analysis showed that the intervention was cost-effective for all scenarios with the lowest ICER at 99 USD and the highest ICER at 205 USD per additional life year saved. When extrapolated to the population living in the study area, the investment costs of the program were 0.13 USD per person and annual running costs 0.06 USD per person.

Conclusions: In our study, the inter-facility referral system was a very cost-effective intervention. Our findings may inform policies, decision making, and implementation strategies for emergency obstetric and neonatal care referral systems in similar resource-constrained settings.

ARTICLE SUMMARY

Strengths and limitations of this study

- Strength: Large study sample from a widely understudied population in remote Southern Madagascar
- Limitation: Programmatic data and reliance of expert panel process for defining survival rates
- Limitation: No long-term follow up data of patients available due to cross-sectional nature of the study.
- Strength: Robust CEA methodology, including detailed and comprehensive costing data

KEYWORDS

Sub-Saharan Africa, maternal health, Emergency obstetric and neonatal care, cost-effectiveness analysis

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

DATA SHARING

The original data are available from the corresponding author upon reasonable request.

WORD COUNT

3,404

BACKGROUND

Reducing the global maternal mortality ratio to less than 70 per 100,000 live births by 2030 is a key target of the Sustainable Development Goals [1]. Haemorrhage, sepsis, unsafe abortion, and other complications of delivery account for more than 50% of maternal deaths in sub-Saharan Africa (SSA) [2]. Most neonatal deaths in SSA are attributable to either intrapartum complications or complications linked to preterm delivery [3]. Many of these fatalities are preventable through access to timely and high-quality emergency obstetric care (EmOC).

However, mothers and neonates in SSA often experience significant delays in accessing EmOC services, i.e., when deciding to seek, reaching, and receiving adequate care [4]). Access to and availability of adequate means of transportation, including ambulance referral services to EmOC centres, reduces these delays [5,6], which, in turn, reduces maternal and neonatal mortality [7,8].

The implementation of ambulance referral systems for EmOC services in SSA have been described for several, mostly rural contexts, including in Uganda [9,10], Burundi [11], and Ethiopia [12]. They mostly differed in the type of referral service provided (i.e., from home to health facility versus inter-facility referral) and the level of medical support provided to patients during referrals. Only a minority of these programs have been evaluated through a cost-effectiveness analysis [9, 12].

Africa's health financing gap is estimated at 66 billion USD annually and the financing need for maternal and child health services is particularly acute [13,14]. Thus, reliable data on costs and cost-effectiveness of ambulance programs are essential for designing and prioritizing maternal health interventions in SSA.

We aimed to describe case and service characteristics as well as analyse the costs and cost-effectiveness of an EmOC inter-facility referral system established by a non-governmental organization (NGO) in rural Madagascar. Our findings may inform policies, decision making and implementation strategies for EmOC referral systems in resource-constrained settings.

METHODS

Study design

This is a retrospective study using secondary data, routinely collected as part of an NGO intervention. A data-sharing agreement with the NGO was in place.

Study area and context

The study took place in Atsimo-Andrefana, Androy, and Anosy, rural regions in the South of Madagascar. Poverty rates in the study region are high with over 80% of the population living of less than 1.90$ per day [15]. Nationally, neonatal, and maternal mortality ratios remain high with a maternal mortality ratio 335 per 100,000 and a neonatal mortality ratio of 20 per 1,000 live births, respectively [16].

The Malagasy health system is organized in 3 tiers of care. While some public emergency referral services exist at the district and national level, they fall short of covering a significant amount of the population, especially in rural areas of the country.

Intervention

Setting

To improve access to EmOC, the German-Malagasy NGO Doctors for Madagascar established an inter-facility referral system for obstetric and neonatal care in Atsimo-Andrefana (Ampanihy, Betioky-sud, and Benenitra districts), Androy (Bekily district), and

Anosy region (Fort-Dauphin district). The intervention covered a catchment population of around 1 million people (Malagasy Ministry of health, “Sectorisation”, 2020). The intervention was rolled out sequentially, starting in Atsimo-Andrefana and Androy in 2016 and in Anosy in 2018. A 4-wheel drive ambulance was stationed at each of 3 secondary referral hospitals: Hopitaly Zoara Fotadrevo, Hopitaly SALFA Manambaro, and Hopitaly SALFA Ejeda, which served 18, 23, and 13 participating primary health centres, respectively Secondary referral hospitals offer inpatient care surgical care, obstetric care, including emergency C-sections, and basic neonatal care.

Participating primary health centres (locally known as Centers de Santé de Base (CSB); n = 54) could call the ambulance 24h per day without charge. If referral was deemed necessary by a trained medical dispatcher, the ambulance was sent to the CSB to transfer the patient to a higher-level care facility. The referral was free for patients and participating health centres, all costs were covered by the NGO.

Vehicles and equipment

All ambulances were Toyota 4-wheel drive vehicles, equipped with a stretcher, oxygen, emergency medical equipment, and drugs. Supplementary File 1 summarizes the medical equipment and drugs, which were available on board an ambulance vehicle.

To improve pre-transport emergency care, the NGO equipped participating CSBs with emergency kits containing alcohol, compresses, cotton swabs, isotonic glucose solution, isotonic saline, intravenous catheters, IV lines, scissors, sterile and non-sterile gloves, and urinary catheters. These kits were checked and refilled by NGO staff after each referral.

Emergency medical teams

All calls from CSBs requesting a referral were processed by a medical emergency dispatcher, usually a medical doctor trained in EmOC and familiar with the local setting. If the dispatcher deemed a referral to be necessary, a vehicle was sent to retrieve the patient from the CSB.

The medical team aboard each vehicle always consisted of a trained midwife and a driver who had received basic life support training. If necessary, a medical doctor accompanied critical referrals. The medical doctor was an employee of the implementing NGO and accompanied approximately 5% of referrals. This decision was made on a case-by-case basis by the dispatcher.

Performance-based bonus payments

The referring healthcare worker received a cash bonus of 2.5 USD for each case referred through the intervention, paid at the end of the month.

Participants

All women who presented at one of the participating CSBs during the intervention period with an acute complication during pregnancy, childbirth, or postpartum and whose emergency referral was deemed necessary by the medical dispatcher were eligible to participate. Similarly, all neonates born or treated at participating CSBs within the neonatal period of 28 days and whose emergency referral was deemed necessary by the medical dispatcher were eligible to participate.

All obstetric and neonatal patients using the ambulance referral system between January 5th, 2016, and September 30th, 2020, were included in the descriptive analysis.

Mothers and neonates presenting at CSBs not participating in the intervention were not eligible for ambulance referral.

Patients could refuse referral services at any point in time.

Data collection and data entry

Medical records

The data source for patient and referral characteristics were case data sheets filled by the ambulance staff. These data sheets included details on patient characteristics (e.g., gestational age) and the referral indication.

All data were digitized into summary Excel tables by NGO personnel. Healthcare staff, who were not otherwise involved in this study, replaced patient identifying information with numerical pseudonyms before forwarding the Excel sheets to the research team for analysis. Codes linking pseudonyms and identifying information were not accessible to the research team.

We collected the original data in French and translated it into English. Data were cleaned by 3 independent researchers with regular check-ups to assure consistency in data cleaning. Data were additionally cross-checked and screened for double entries, out-of-range values, and overall consistency. In case multiple referral indications were given, an expert panel of 3 Malagasy physicians determined the main referral indication, which were grouped following the approach by Abegunde et al. [17]. All data were stored in a password-protected database to which only the research team had access.

Financial records

The data source for the costs of the intervention were NGO financial records from 2016 to 2019. A researcher extracted data from the original records and categorized them into investment and running costs and corresponding sub-categories (medical equipment, administration, transport, communication, consumables, pre-transport care, performance-based bonus payments, and training activities). 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).

Investment costs were annualized based on lifetime estimates or records of items based on expert estimates from NGO staff active in the study region.

We included all costs associated with the initial establishment of the referral systems, e.g., acquisition of equipment and ambulances, as well as running costs for the 3 project sites in the cost-effectiveness analysis (CEA). Costs for treatments at CSBs and referral hospitals were not included, as those were not supported through the program. Data were collected in Malagasy Ariary or Japanese Yen (1 invoice) and converted to United States dollars for analysis (Exchange rate: 1 USD = 3,867.09 Malagasy Ariary (as of September 22nd, 2020) and 1 USD = 105.671 Japanese Yen (as of September 30th, 2020).

Data analysis

Descriptive statistics

We performed a descriptive analysis, including frequency distributions, for medical records using Stata Version 16.

Cost-effectiveness analysis

We used a cost-effectiveness analysis to quantify the costs per life year saved, as well as the incremental cost-effectiveness ratio of the intervention. As this was not a randomised control trial, we did not develop a health economic analysis plan. We also assessed the sensitivity of the analysis to variation of parameters. We adhere to the CHEERS guideline for economic evaluations of healthcare interventions in structuring this manuscript [18].

The main outcomes of the model were incremental cost-effectiveness ratios (ICER) per life year saved through the intervention overall, and separately by cohort, where one cohort was defined as all cases referred due to the same referral indication. To calculate the costs for each cohort, we multiplied the average costs per referral with the number of patients per cohort. For each cohort, we calculated the following incremental cost-effectiveness ratio (ICER): (Costs of ambulance referral system-Costs of no referral system) / ((Life years saved neonates referred + Life years saved mothers referred) – (Life years saved neonates not referred + Life years saved mothers not referred)). To obtain the overall ICER of the intervention, we added the ICERs for individual cohorts, weighted by the frequency of their occurrence.

Study population and model

This economic evaluation followed a cost-effectiveness analysis, with a healthcare provider's perspective. For each medical condition that constituted a referral indication, we developed 1 decision analytical model (if the condition affected only mother or neonate, n= 8 models) or 2 (if the condition affected both mother and neonate, n = 9 models) intervention cohorts, as well as the corresponding number of control cohorts (n = 17 models). The starting age for mothers in the models was 24 years and 0 years for neonates. Individuals from the intervention cohorts were referred to secondary hospitals, while individuals from comparison cohorts were not referred and received only primary care. For all models, a time horizon of 100 years was chosen to anticipate lifetime.

Supplementary files 2 and 3 outline the non-reversible patient journey for referred and non-referred mothers and referred and non-referred neonates, respectively. 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.

For all cohorts, all-cause mortality was calculated on an annual basis, whereas the first 2 stages for the comparison groups and the first 3 stages for the intervention groups were treated as one time stamp.

We applied these exclusion criteria for the CEA: date of referral not during the study period; referral indication unknown or unrelated to emergency obstetric and neonatal care; referral indications with less than 10 cases.

Pathway probabilities

Medical records were used to determine the number of mothers and neonates treated at participating CSBs for each referral indication.

Given that there was no previously published data for this context, survival rates for both referred and non-referred mothers and neonates were estimated through a two-stage expert panel process. 3 Malagasy physicians, otherwise not involved in this study formed the expert panel. They were chosen as a convenience sample, as they were familiar with the NGO's intervention and had long-term experience in maternal health in the intervention area.

The research team reviewed existing literature from low- and middle-income countries on maternal survival rates for all referral indications. Both Google Scholar and PubMed were searched to identify relevant studies. From these, we extracted data on survival rates for individual referral indications at primary and secondary facilities as well as information on study design, context, strengths, and limitations. We presented these data to the expert panel. The panel then defined survival rates for each referral indication. Results of this expert panel process are summarized in Table 1 and 2 below. For each condition, the expert panel defined a maximum and minimum survival rate for mothers and neonates at both primary and secondary facilities, as well as an average survival rate agreed upon by all experts. This rate formed the baseline estimate for our CEA models.

Table 1: Survival estimates mothers

Referral indications mothers (n)	**Survival rates when referred to secondary care**			**Survival rates when not-referred (primary care only)**			**References**
	Min	Max	Baseline	Min	Max	Baseline	
Obstructed labour (251)	95%	99%	98%	80%	99%	90%	[19, 20, 21]
Ineffective	98%	99%	99%	85%	99%	95%	[22, 23, 24]

labour (137)							
Extrauterine gravidity (50)	99%	95%	99%	1%	0%	0%	[25, 26, 27]
Post-partum haemorrhage (46)	70%	90%	80%	20%	80%	30%	[28]
Intrauterine foetal death (IUFD) (45)	90%	99%	95%	85%	95%	93%	[29]
Eclampsia (39)	65%	96%	75%	30%	90%	50%	[30, 31, 32]
Placenta previa (34)	85%	98%	87%	50%	95%	70%	[33, 34, 35, 36]
Abortion (30)	90%	99%	95%	85%	95%	90%	[37]
Risk of premature delivery (26)	99%	99%	99%	99%	98%	99%	[28]
Placenta retention (25)	99%	99%	99%	50%	99%	91%	[38, 39]
Delivery (22)	98%	99%	98.5%	95%	99%	96.5%	[28]
Infection	90%	98%	95%	70%	95%	80%	[40, 41]

postpartum (19)							
Risk of uterus rupture (17)	90%	95%	92.5%	5%	40%	35%	[42, 43, 44, 45]
Fetal distress (12)	98%	99%	98.5%	70%	99%	96.5%	[46, 47, 48]
Malaria (12)	98%	99%	99%	95%	98%	97.5%	[49]

Table 1. Minimum, maximum, and baseline survival estimates for referred and non-referred mothers grouped by referral indication. Survival estimates were obtained by expert panel consensus.

Table 2: Survival estimates neonates

Referral indications neonates (n)	**Survival rates when referred to secondary care**			**Survival rates when not-referred (primary care only)**			**References**
	Min	Max	Baseline	Min	Max	Baseline	
Obstructed labour (251)	60%	90%	70%	25%	80%	35%	[19, 20, 21]
Ineffective labour (137)	45%	95%	55%	30%	88%	35%	[22, 23, 24]

Eclampsia (39)	30%	80%	50%	15%	50%	25%	[30, 31, 32]
Placenta previa (34)	50%	95%	60%	20%	90%	30%	[33,34, 35, 36]
Risk of premature delivery (26)	15%	98%	70%	15%	97%	25%	[50, 51]
Delivery (22)	85%	98%	92%	75%	95%	85%	[28]
Risk of uterus rupture (17)	20%	93%	90%	3%	40%	10%	[42, 43, , 44, 45]
Fetal distress (12)	70%	99%	95%	30%	98%	55%	[46, 47, 48]
Respiratory distress (12)	5%	90%	20%	1%	50%	5%	[52,53]
Malaria (12)	90%	98%	95%	90%	94%	91%	[42]
Neonatal infection (10)	5%	85%	70%	5%	80%	50%	[50, 54]

Table 2. Minimum, maximum and baseline survival estimates for referred and non-referred neonates grouped by referral indication. Survival estimates were obtained by expert panel consensus.

Life years

Health outcomes were estimated based on local life expectancy tables [55]. Costs and life-years saved were discounted at a 3% discount rate. This rate reflects the average annual growth of the Malagasy economy during the study period [56] and aligns with the approach for discounting in economic evaluation suggested by Haacker et al. [57].

Sensitivity analysis

Given that no probabilistic data was available in the literature, we performed a one-way deterministic sensitivity analysis for the survival rates for referred and non-referred mothers and neonates to assess the impact of individual model parameters and assumptions on the model outputs.

Patient and public involvement statement

This study did not involve patients in the research process. However, we did involve three independent Malagasy clinicians in the research process as key informants for the expert panel process to define survival probabilities for the different patient pathways. This greatly enhanced the applicability and relevance of our research for the context of Southern Madagascar.

Ethics approval and consent to participate

Ethical clearance for the study was obtained from the Heidelberg University Hospital Ethics Committee, registration number: S-713/2020. Informed consent was waived by the ethics committee.

RESULTS

Referral characteristics

In total, 1,172 patients (48 neonates and 1,124 women, respectively) were referred through the intervention. Most referrals took place in Atsimo-Andrefana region (54%), followed by Anosy (45%) and Androy regions (1%). The average distance per referral were 52.8 km.

Demographic and clinical characteristics

Mean age of women was 23.6 years (n=1,118; IQR=12). Most neonates (78%, 36/46) were in their first week of life. 80% of calls were made for direct obstetric causes above all for obstructed/prolonged labour (40%, 445/1,124) (Table 3). For neonates, the most common referral indications were respiratory distress (29%, 14/48) or infection (21%, 10/48) (Table 4).

Table 3: Referral reasons mothers

Obstetric complication	**Women (n=1,124)**	**(%)**
Direct causes	906	80.6
Abortion and its complications, including intra-uterine foetal death	89	7.9
Ectopic pregnancy	52	4.6
Embolism	1	0.1
Hypertensive disorders	61	5.4
Prepartum/postpartum haemorrhage	114	10.1
Obstetric trauma	18	1.6
Obstructed/prolonged labour	445	39.6
Other direct causes	141	12.5
Indirect causes	123	10.9
Anaemia	7	0.6
Malaria	12	1.1
Tuberculosis	1	0.1
Other indirect causes	88	7.9
Other cases*	37	3.3
No obstetric complication specified	58	5.2

*Such as: no medical staff present at CSB, insufficient equipment for delivery at CSB

Complications during pregnancy, childbirth, and postpartum, which triggered the referral of mothers (n =1,124) from participating CSBs to secondary referral hospitals. CSB, Centre de Santé de Base (public primary care facility).

320 Table 4: Referral reasons neonates

Complication	Neonates (n=48)	%
Abdominal bloating	3	6.3
Birth defect	9	18.8
Dehydration	4	8.3
Hypothermia	1	2.1
Icterus	1	2.1
Unspecified infection*	10	20.8
Premature birth	4	8.3
Respiratory distress	14	29.2
Syphilis	1	2.1
Other (=vomiting)	1	2.1

*Unspecified infection included neonates showing signs of infection such as fever, altered cardiorespiratory status or marmorated skin.

321 Complications during the neonatal period, which triggered the referral of neonates (n= 48)
322 from participating CSBs to secondary referral hospitals.

323

324 Not all calls resulted in a completed referral. In 97 cases the ambulance was dispatched but
325 the referral was not completed. Most commonly (65%, 63/97) the complication had been
326 resolved at the CSB either with (25%, 24/97) or without (40%, 39/97) support from the
327 ambulance staff. In 8 cases (8.2%) the woman or neonate had passed away before the
328 ambulance reached the CSB and in 4 cases (4.1%) the patient or patient's relatives refused
329 the referral.

330 **Costs**

331 The total intervention costs over the study period were 394,197 USD.

332 Supplementary File 4 and 5 show the detailed distribution of cost of operating 1 vehicle over
333 the intervention time frame (January 2016-September 2020).

334 The average cost per referral was 367 USD (n=1075).

335 If the costs of the project were shared among all people living in the project area, initial
336 investment costs would be 0.13 USD per person and annual running costs 0.06 USD per
337 person.

338 Around 20% of the population in the study region are women of reproductive age. Assuming
339 that each of these women could be a potential beneficiary of the project, the costs per
340 potential beneficiary amount to 0.57 USD per person in investment and 0.26 USD in annual
341 running costs.

342 **Cost-effectiveness analysis**

343 Incremental life-years saved through the program were 37,882 (rounded to the full year)
344 undiscounted and 4,872 when discounted at 3%.

345 The overall ICER of the ambulance system was 70 USD per additional life year saved
346 undiscounted and 137 USD per additional life year saved when discounted at 3%.

347 The ambulance intervention proved particularly cost-effective for cases of extrauterine
348 gravidity, risk of uterus rupture, and post-partum haemorrhages with ICERs of less than 30
349 (discounted at 3%). The program proved least effective for cases of malaria in pregnancy and
350 post-partum infection. Table 5 below lists the costs per life year saved as well as the ICER
351 per diagnosis.

Table 5: Results of CEA

Referral indication (n)	Cost per life year saved discounted/undiscounted (USD)	ICER discounted/undiscounted
Obstructed labour (251)	11.2/5.9	62.9/30.1
Ineffective labour (137)	11.7/6.2	115.1/54.7
Extrauterine gravidity (50)	14.4/8.0	14.4/8.0
Post-partum haemorrhage (46)	17.1/9.5	26.4/14.6
Intrauterine foetal death (IUFD) (45)	15.0/8.3	710.9/394.0
Eclampsia (39)	14.8/7.8	40.1/20.7
Placenta previa (34)	12.3/6.5	57.8/28.3
Abortion (30)	15.0/8.3	284.3/157.6
Risk of premature delivery (26)	11.0/5.8	72.9/32.7

Placenta retention (25)	14.3/7.9	171.3/94.9
Delivery (22)	10.4/5.4	288.5/138.9
Infection postpartum (19)	59.9/33.2	379.1/210.1
Risk of uterus rupture (17)	10.9/5.7	15.6/8.0
Fetal distress (12)	10.3/5.3	76./34.5
Malaria (12)	10.3/5.3	447.8/217.8
Respiratory distress neonate (12)	170.2/75.8	227.0/101.0
Neonatal infection (10)	48.6/21.7	107.2/75.6

Table 5: Costs per life-year saved (in USD) and ICER per diagnosis, undiscounted and discounted at 3%.

Sensitivity analysis

The sensitivity analysis showed the intervention to remain cost-effective for most scenarios tested. However in the following cases either the survival rate estimates at the participating CSB exceeded the baseline estimate at the referral hospital or the worst case estimate at the hospital was lower than the baseline estimate at the CSB, rendering the scenario not cost effective: Mothers survival for eclampsia, neonates survival for ineffective labour, neonate survival for neonatal infection, neonates survival for respiratory distress and neonates survival for risk of premature delivery tested.

DISCUSSION

The aim of this study was to evaluate the characteristics, costs, and cost-effectiveness of an NGO-run inter-facility referral system for EmOC in rural Madagascar.

This study revealed three main findings: First, the most common referral indication for mothers was obstructed/prolonged labour and unspecified infection or respiratory distress for neonates. Second, the largest drivers of costs for the intervention were initial investment costs for the vehicles and running costs including staff wages. Consequently, ambulance lifespan is a particularly important determinator of the intervention's cost-effectiveness. Lastly, the CEA demonstrated the intervention to be very cost-effective, with an ICER of 137 USD per additional life year saved (discounted at 3%). The intervention was particularly cost-effective for the following conditions: extrauterine gravidity, risk of uterus rupture, and post-partum haemorrhage. The sensitivity analysis conducted showed the intervention to remain cost-effective in most scenarios tested. 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 [58], 177 USD per DALY averted for a drone-supported community treatment programm for TB [59], and 531.2 USD per DALY averted [60] for the Indoor-residual spraying activities of the national tuberculosis control programm, showing our intervention to have a much lower ICER.

In accordance with our findings, other systems for EmOC referral in SSA have found direct obstetric complications, especially abortion and obstructed labour to be the main referral indications for mothers to secondary health facilities in resource-constrained settings [11, 12].

Compared with other ambulance referral systems in Uganda [9], Burundi [11] and Ethiopia [12], costs for our intervention were high. This finding is however not surprising considering that referrals in other interventions were not accompanied by trained medical personnel receiving salaries. Neither ambulance carried medical equipment and neither publication included overhead costs such as administrative costs in their cost-effectiveness analysis. In addition, our intervention covered a large rural area in the remote south of Madagascar; there were no paved roads and conditions deteriorated during the rainy season when parts of the intervention became inaccessible. This increased costs for vehicle maintenance and fuel. These differences in the design of the interventions as well as their contexts of implementation likely explain the higher ICER of 137 USD per additional life year saved (discounted) when compared to ICERs of 16 USD [9] and 25 USD per additional life year saved [12] in Uganda and Ethiopia, respectively. Further, these studies only included referrals in their analysis which were deemed “undoubtedly effective” [9,12], i.e., cases in which the referral was likely to have a large impact on life-years saved. Our model on the other hand included all cases in the calculation of the overall ICER.

Consequently, costs per referral were higher for our setting than in other studies. Tayler-Smith et al. reported costs of 61 USD per referral, with 1,478 ambulance referrals per year [11], compared to 1,075 completed referrals over 4 years, with an average cost per referral of 367 USD in our setting.

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) [11], 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 [61]. 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 [60], suggests that the referral system described herein could be feasibly adapted into the national care system in Madagascar.

Our study has three main strengths: First, we used secondary NGO data as the basis for all analyses. This reduced the potential for erroneous data as there was no need to rely on estimations. Further, our data provide insights into a particularly vulnerable and resource-constrained setting for which data is otherwise hard to obtain. Second, we included all costs for the running of the ambulance system in the cost-effectiveness analysis, including overhead costs such as administrative costs, rendering more realistic cost estimates than other studies. Third, we obtained survival estimates using a multi-step expert consensus process, when these data were not available from the literature.

Our study has several limitations. First, we were constrained by the availability of programmatic data and had to rely on expert opinions to estimate equipment lifespans as well as survival rates for the economic model. For the latter, to mitigate potential bias we established an expert panel consensus process to estimate survival rates. 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 [62]. 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. Second, data were not available on mothers' post-delivery complications or their previous patient history to allow for more nuanced calculations for life years saved and our model only accounted for mothers and neonates, for whom referral was successful. However, we do not expect either factor to have a large impact on the model's cost-effectiveness and are confident that the approach of constructing separate models per cohort can robustly identify the most cost-effective applications of inter-facility EmOC referrals. Last, we did not assess whether the intervention met the referral needs of the population in the study area.

CONCLUSION

Our study is the first to report the cost-effectiveness of an EmOC inter-facility referral system in Madagascar. We find the intervention to have been very cost-effective, especially for cases requiring surgical care. Our findings highlight the need for a comprehensive approach to providing rural EmOC services and may provide guidance on public health resource allocation in Madagascar.

AUTHOR CONTRIBUTIONS

MAF, AF, KN, NM, SK, and JVE developed the study design in collaboration with TB. MAF, AF, RMR, MR, ZR and KN were responsible for data collection and study administration. MAF, AF, KN, NM, RMR, ZR, SK, and JVE contributed to the analysis. MAF, AF, and KN prepared the first draft of the manuscript. All authors contributed to writing the manuscript. All authors read and approved the final manuscript.

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638 **SUPPLEMENTARY FILE LEGENDS**

639 Supplementary file 2. Non-reversible patient journey for referred and non-referred mothers.
640 For referred mothers, the model included 4 stages: 1) presentation at a participating CSB
641 because of an emergency during pregnancy or childbirth, 2) referral to secondary referral
642 hospital, 3) likelihood of survival at referral hospital, 4) all-cause mortality. The model
643 included 3 stages for non-referred mothers: 1) presentation at a CSB because of an
644 emergency during pregnancy or childbirth, 2) likelihood of survival at CSB, 3) all-cause
645 mortality. CSB, Centre de Santé de Base (public primary care facility).

646

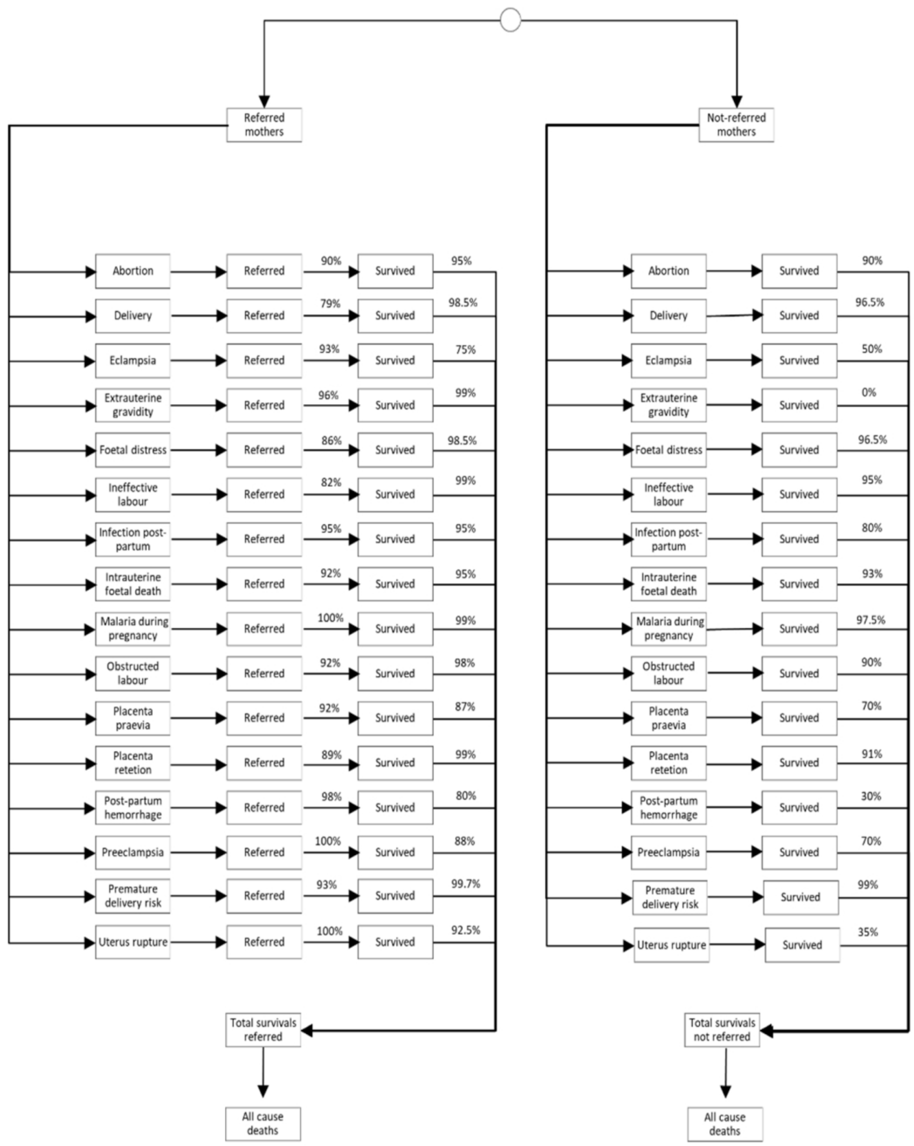
647 Supplementary file 3. Non-reversible patient journey for referred and non-referred neonates.
648 For referred neonates the model included 4 stages: 1) presentation at a CSB because of an
649 emergency peripartum or in the neonatal period, 2) referral to secondary referral hospital, 3)
650 likelihood of survival at referral hospital, 4) all-cause mortality. For non-referred neonates,
651 the model included 3 stages: 1) presentation at a CSB because of an emergency peripartum or
652 in the neonatal period, 2) likelihood of survival at CSB, 3) all-cause mortality. CSB, Centre
653 de Santé de Base (public primary care facility).

Supplementary File 1: Ambulance furnishings

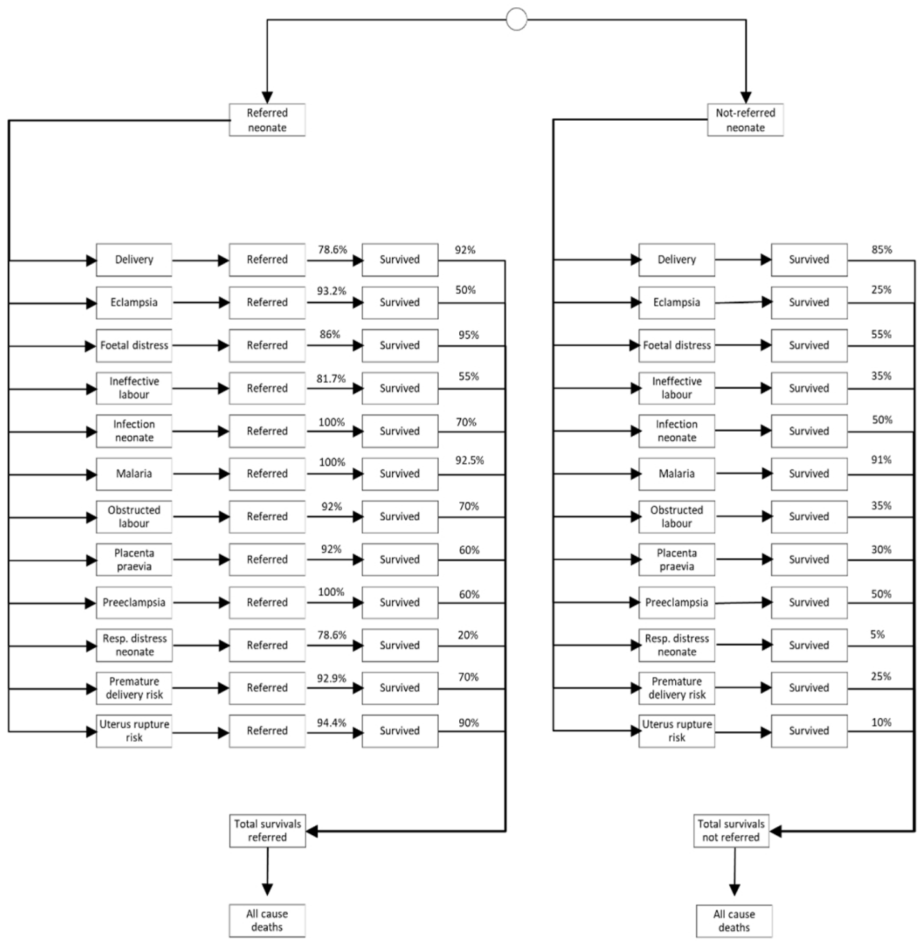
Medical equipment	**Drugs**

• Alcohol
• Betadine
• Blood sugar testing strips
• Cord clamps
• Echography gel
• Intravenous catheters
• Non-sterile compresses
• Non-sterile gloves
• IV lines
• Plasters
• Pregnancy test
• Sterile compresses
• Sterile gloves
• Ultrasound machine
• Urinary catheters and bags
	• Analgesics
	  ○ Paracetamol
	• Antibiotics
	  ○ Ampicillin
	  ○ Amoxicillin
	• Antihypertensive agents
	  ○ Magnesium Sulphate
	  ○ Nicardipine
	• Infusion solutions
	  ○ Isotonic Glucose solution
	  ○ Isotonic saline
	  ○ Lactated Ringer's
	  ○ Natrium Chloride
	• Uterotonic agents
	  ○ Misoprostol
	  ○ Oxytocin
	• Other
	  ○ Calcium gluconate
	  ○ Diazepam
	  ○ Paracetamol
	  ○ Salbutamol
	  ○ Tranexamic acid
	  ○ Vitamin K

Medical equipment and drugs available aboard ambulance vehicles.



453x560mm (87 x 87 DPI)



464x468mm (87 x 87 DPI)

Supplementary File 2: Investment costs

Item	Cost per unit (USD)	Quantity
Ambulance		
Port charges, forwarding agent	3,620	1
Shipment from Japan to Madagascar including insurance	3,020*	1
Vehicle	38,254	1
Subtotal	45,487	
Equipment ambulance		
Carpet	38	1
Fire extinguisher	26	1
Luggage rack	282	1
Mattress cover	54	1
Phone for ambulance	45	1

Item	Cost per unit (USD)	Quantity
Steering wheel cover	74	1
Tarpaulin	74	1
Subtotal	593	
Administration		
IT equipment, furniture)	528	1
Mobile phone	45	1
Subtotal	573	
Total	**45,487**	

Initial ambulance investment costs for 1 ambulance vehicle. Prices are expressed in USD with an exchange rate of 1 USD = 3,867.09 Malagasy Ariary (MGA) and 1 USD = 105.671 Japanese Yen (JPY) (costs marked *).

Supplementary File 3: Running costs

Item	Cost per unit (USD)	Quantity	Annual costs (USD)
Transport			
Fuel	Average: 0.98 USD/l (0.91/l – 1.03/l)	Average 147l /months (96l-205l)	1,729
Insurance	44	1	44
Licensing in Madagascar	194	1	194
Maintenance	1,707	Yearly average	1,707
Repair	467	Yearly average	467
Subtotal			4,141
Car equipment			
Air chamber for tire	72	4	288
Cleaning equipment (shovel, broom, brush, scraper)	13	1	13
Tires	142	4	568
Subtotal			869

Item	Cost per unit (USD)	Quantity	Annual costs (USD)
Consumables			
Cleaning materials	1	12	12
Drugs on board ambulance	49	12	588
Medical equipment on board ambulance	36	12	432
Oxygen bottle	43	1	43
Subtotal			1,075
Pre-transport care			
Drugs and consumables	78	6	468

Item	Cost per unit (USD)	Quantity	Annual costs (USD)
Staff wages			
Drivers	Average: 116/months (range 103-129)	12	1,392
Local coordinator	413/month	12	4,956
Midwives	155/month	12	1,860
Subtotal			8,208
Communication			
Free phone number for ambulance calls	9/month**	12	108
Phone credits driver	5/month	12	60
Phone credits coordination	8/month	12	96
SIM card for GPS tracking of vehicles	10/month	12	120
Subtotal			384

Item	Cost per unit (USD)	Quantity	Annual costs (USD)
Performance-based bonuses			
Medical director of participating CSBs	55	12	660
Item	**Cost per unit (USD)**	**Quantity**	**Annual costs (USD)**
Midwife of participating CSBs	70	12	840
Additional renumeration during ambulance services (staff on extra duty for at least 4 hours)	4	Average: 20 times/months	960
Subtotal			2,460
Training activities			
Yearly training for drivers	297*	1	297
Administration			
Consumables	128	12	1,536
Electricity	15	12	180
Rent	155	12	1,860
Subtotal			3,576

Total annual running costs	**21,478**

Annual running costs for 1 ambulance vehicle. Prices are expressed in USD with an exchange rate of 1 USD = 3,867.09 Malagasy Ariary (MGA) and 1 USD = 0.840618 Euros (costs marked *).

** on average, depending on the number of calls received

CHEERS 2022 Checklist

	Item	Guidance for Reporting	Reported in section
TITLE			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	Page 1
ABSTRACT			
Abstract	2	Provide a structured summary that highlights context, key methods, results and alternative analyses.	Pages 2-3
INTRODUCTION			
Background and objectives	3	Give the context for the study, the study question and its practical relevance for decision making in policy or practice.	Pages 4-5
METHODS			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Page 9
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Page 7
Setting and location	6	Provide relevant contextual information that may influence findings.	Pages 5-6
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Pages 5-7
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Page 10
Time horizon	9	State the time horizon for the study and why appropriate.	Page 7
Discount rate	10	Report the discount rate(s) and reason chosen.	Page 15
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Pages 9-10
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Page 15
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Pages 10-15
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Pages 8-9
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Page 8-9
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Pages 10-15
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Pages 11, 15
Characterizing heterogeneity	18	Describe any methods used for estimating how the results of the study vary for sub-groups.	Page 15
Characterizing distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	
Characterizing uncertainty	20	Describe methods to characterize any sources of uncertainty in the analysis.	Pages 11, 15
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study.	Pages 11-12
RESULTS			
Study parameters	22	Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.	Pages 12-15, 18-20, Suppl.
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Pages 20-23
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Pages 23-24
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Pages 11-12
DISCUSSION			
Study findings, limitations, generalizability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.	P. 25-27
OTHER RELEVANT INFORMATION			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Page 3
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Page 3

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