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

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4 **1 TITLE**

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6 **2 Inter-facility transfers for emergency obstetric and neonatal care in rural Madagascar:**
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8 **3 A cost-effectiveness analysis**

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9
10

11 **27 ABSTRACT**
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15 **28** *Context:* There is a substantial lack of inter-facility referral systems for emergency obstetric
16
17 **29** and neonatal care in rural areas of sub-Saharan Africa. Data on the costs and cost-
18
19 **30** effectiveness of such systems that reduce preventable maternal and neonatal deaths are
20
21 **31** scarce.
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25 **32** *Setting:* We aimed to determine the cost-effectiveness of an NGO-run inter-facility referral
26
27 **33** system for emergency obstetric and neonatal care in rural southern Madagascar by analyzing
28
29 **34** the characteristics of cases referred through the intervention as well as its costs.
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33 **35** *Design:* We used secondary NGO data, drawn from an NGO's monitoring and financial
34
35 **36** administration database, including medical and financial records.
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37
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39 **37** *Outcome measures:* We performed a descriptive and a cost-effectiveness analysis, including a
40
41 **38** one-way deterministic sensitivity analysis.
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43

44 **39** *Results:* 1,172 cases were referred over a period of 4 years, with an estimated referral cost of
45
46 **40** 336 USD and an incremental cost-effectiveness ratio (ICER) of 70 USD per additional life
47
48 **41** year saved (undiscounted, discounted 137 USD). The sensitivity analysis showed that the
49
50 **42** intervention was cost-effective for all scenarios with the lowest ICER at 99 USD and the
51
52 **43** highest ICER at 205 USD per additional life year saved. When extrapolated to the population
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54 **44** living in the study area, the investment costs of the program were 0.13 USD per person and
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56 **45** annual running costs 0.06 USD per person.
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3 46 *Conclusions:* In our study, the inter-facility referral system was a very cost-effective
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5 47 intervention. Our findings may inform policies, decision making, and implementation
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7 48 strategies for emergency obstetric and neonatal care referral systems in similar resource-
8
9 49 constrained settings.

13 50 **ARTICLE SUMMARY**

16 51 **Strengths and limitations of this study**

- 19 52 • Strength: Large study sample from a widely understudied population in remote Southern
20
21 53 Madagascar
- 23 54 • Limitation: Programmatic data and reliance of expert panel process for defining survival
24
25 55 rates
- 27 56 • Limitation: No long-term follow up data of patients available due to cross-sectional
28
29 57 nature of the study.
- 31 58 • Strength: Robust CEA methodology, including detailed and comprehensive costing data

36 59 **KEYWORDS**

38 60 Sub-Saharan Africa, maternal health, Emergency obstetric and neonatal care, cost-
39
40 61 effectiveness analysis

44 62 **FUNDING STATEMENT**

46 63 This research received no specific grant from any funding agency in the public, commercial
47
48 64 or not-for-profit sectors.

52 65 **CONFLICT OF INTERESTS**

54 66 The authors declare no conflicts of interest.

58 67 **DATA SHARING**

59
60 68 The original data are available from the corresponding author upon reasonable request.

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69 **WORD COUNT**

70 3,344

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71 **BACKGROUND**

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

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

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

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

93 We aimed to describe case and service characteristics as well as analyse the costs and cost-
94 effectiveness of an EmOC inter-facility referral system established by a non-governmental

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3 95 organization (NGO) in rural Madagascar. Our findings may inform policies, decision making
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5 96 and implementation strategies for EmOC referral systems in resource-constrained settings.
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12 98 **METHODS**

13 14 15 99 **Study design**

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17
18 100 This is a retrospective study using secondary data, routinely collected as part of an NGO
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20 101 intervention. A data-sharing agreement with the NGO was in place.
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24 102 **Study area and context**

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26
27 103 The study took place in Atsimo-Andrefana, Androy, and Anosy, rural regions in the South of
28
29 104 Madagascar. Poverty rates in the study region are high with over 80% of the population living
30
31 105 of less than 1.90\$ per day (15). Nationally, neonatal, and maternal mortality ratios remain
32
33 106 high with a maternal mortality ratio 335 per 100,000 and a neonatal mortality ratio of 20 per
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35 107 1,000 live births, respectively (16).
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40 108 The Malagasy health system is organized in 3 tiers of care. While some public emergency
41
42 109 referral services exist at the district and national level, they fall short of covering a significant
43
44 110 amount of the population, especially in rural areas of the country.
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48 111 **Intervention**

49 50 51 112 **Setting**

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55 113 To improve access to EmOC, the German-Malagasy NGO Doctors for Madagascar
56
57 114 established an inter-facility referral system for obstetric and neonatal care in Atsimo-
58
59 115 Andrefana (Ampanihy, Betsioky-sud, and Benenitra districts), Androy (Bekily district), and
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1
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3 116 Anosy region (Fort-Dauphin district). The intervention covered a catchment population of
4
5 117 around 1 million people (17). The intervention was rolled out sequentially, starting in
6
7 118 Atsimo-Andrefana and Androy in 2016 and in Anosy in 2018. A 4-wheel drive ambulance
8
9 119 was stationed at each of 3 secondary referral hospitals: Hopitaly Zoara Fotadrevo, Hopitaly
10
11 120 SALFA Manambaro, and Hopitaly SALFA Ejeda, which served 18, 23, and 13 participating
12
13 121 primary health centres, respectively.
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18 122 Participating primary health centres (locally known as Centers de Santé de Base (CSB); n =
19
20 123 54) could call the ambulance 24h per day without charge. If referral was deemed necessary
21
22 124 by a trained medical dispatcher, the ambulance was sent to the CSB to transfer the patient to a
23
24 125 higher-level care facility. The referral was free for patients and participating health centres,
25
26 126 all costs were covered by the NGO.
27
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30 127 Vehicles and equipment

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34 128 All ambulances were Toyota 4-wheel drive vehicles, equipped with a stretcher, oxygen,
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36 129 emergency medical equipment, and drugs. Supplementary File 1 summarizes the medical
37
38 130 equipment and drugs, which were available on board an ambulance vehicle.
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42 131 To improve pre-transport emergency care, the NGO equipped participating CSBs with
43
44 132 emergency kits containing alcohol, compresses, cotton swabs, isotonic glucose solution,
45
46 133 isotonic saline, intravenous catheters, IV lines, scissors, sterile and non-sterile gloves, and
47
48 134 urinary catheters. These kits were checked and refilled by NGO staff after each referral.
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52 135 Emergency medical teams

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3 136 All calls from CSBs requesting a referral were processed by a medical emergency dispatcher,
4
5 137 usually a medical doctor trained in EmOC and familiar with the local setting. If the dispatcher
6
7 138 deemed a referral to be necessary, a vehicle was sent to retrieve the patient from the CSB.
9

10
11 139 The medical team aboard each vehicle always consisted of a trained midwife and a driver
12
13 140 who had received basic life support training. If necessary, a medical doctor accompanied
14
15 141 critical referrals. This decision was made on a case-by-case basis by the dispatcher.
17
18

19 142 Performance-based bonus payments

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23 143 The referring healthcare worker received a cash bonus of 2.5 USD for each case referred
24
25 144 through the intervention, paid at the end of the month.
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27

28 145 Participants

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32 146 All women who presented at one of the participating CSBs during the intervention period
33
34 147 with an acute complication during pregnancy, childbirth, or postpartum and whose
35
36 148 emergency referral was deemed necessary by the medical dispatcher were eligible to
37
38 149 participate. Similarly, all neonates born or treated at participating CSBs within the neonatal
39
40 150 period of 28 days and whose emergency referral was deemed necessary by the medical
41
42 151 dispatcher were eligible to participate.
43
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47 152 All obstetric and neonatal patients using the ambulance referral system between January 5th,
48
49 153 2016, and September 30th, 2020, were included in the descriptive analysis.
50
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53 154 Mothers and neonates presenting at CSBs not participating in the intervention were not
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55 155 eligible for ambulance referral.
56
57

58 156 Patients could refuse referral services at any point in time.
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3 **157 Data collection and data entry**
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7 **158 Medical records**
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10 **159** The data source for patient and referral characteristics were case data sheets filled by the
11
12 **160** ambulance staff. These data sheets included details on patient characteristics (e.g., gestational
13
14 **161** age) and the referral indication.
15

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17
18 **162** All data were digitized into summary Excel tables by NGO personnel. Healthcare staff, who
19
20 **163** were not otherwise involved in this study, replaced patient identifying information with
21
22 **164** numerical pseudonyms before forwarding the Excel sheets to the research team for analysis.
23
24 **165** Codes linking pseudonyms and identifying information were not accessible to the research
25
26 **166** team.
27

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30 **167** We collected the original data in French and translated it into English. Data were cleaned by
31
32 **168** 3 independent researchers with regular check-ups to assure consistency in data cleaning. Data
33
34 **169** were additionally cross-checked and screened for double entries, out-of-range values, and
35
36 **170** overall consistency. In case multiple referral indications were given, an expert panel of 3
37
38 **171** Malagasy physicians determined the main referral indication, which were grouped following
39
40 **172** the approach by Abegunde et al. (18). All data were stored in a password-protected database
41
42 **173** to which only the research team had access.
43
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48 **174 Financial records**
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51 **175** The data source for the costs of the intervention were NGO financial records from 2016 to
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53 **176** 2019. A researcher extracted data from the original records and categorized them into
54
55 **177** investment and running costs and corresponding sub-categories (medical equipment,
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3 178 administration, transport, communication, consumables, pre-transport care, performance-
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5 179 based bonus payments, and training activities).
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8 180 Investment costs were annualized based on lifetime estimates or records of items based on
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10 181 expert estimates from NGO staff active in the study region.
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12
13 182 We included all costs associated with the initial establishment of the referral systems, e.g.,
14
15 183 acquisition of equipment and ambulances, as well as running costs for the 3 project sites in
16
17 184 the cost-effectiveness analysis (CEA). Costs for treatments at CSBs and referral hospitals
18
19 185 were not included, as those were not supported through the program. Data were collected in
20
21 186 Malagasy Ariary or Japanese Yen (1 invoice) and converted to United States dollars for
22
23 187 analysis (Exchange rate: 1 USD = 3,867.09 Malagasy Ariary (as of September 22nd, 2020)
24
25 188 and 1 USD = 105.671 Japanese Yen (as of September 30th, 2020).
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31 32 33 190 **Data analysis**

34 35 36 191 Descriptive statistics

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40 192 We performed a descriptive analysis, including frequency distributions, for medical records
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42 193 using Stata Version 16.

43 44 45 194 Cost-effectiveness analysis

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49 195 We used a cost-effectiveness analysis to quantify the costs per life year saved, as well as the
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51 196 incremental cost-effectiveness ratio of the intervention. As this was not a randomised control
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53 197 trial, we did not develop a health economic analysis plan. We also assessed the sensitivity of
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55 198 the analysis to variation of parameters. We adhere to the CHEERS guideline for economic
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57 199 evaluations of healthcare interventions in structuring this manuscript (19).
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3 200 The main outcomes of the model were incremental cost-effectiveness ratios (ICER) per life
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5 201 year saved through the intervention overall, and separately by cohort, where one cohort was
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7 202 defined as all cases referred due to the same referral indication. To calculate the costs for
8
9 203 each cohort, we multiplied the average costs per referral with the number of patients per
10
11 204 cohort. For each cohort, we calculated the following incremental cost-effectiveness ratio
12
13 205 (ICER): $(\text{Costs of ambulance referral system} - \text{Costs of no referral system}) / ((\text{Life years saved}$
14
15 206 $\text{neonates referred} + \text{Life years saved mothers referred}) - (\text{Life years saved neonates not}$
16
17 207 $\text{referred} + \text{Life years saved mothers not referred}))$. To obtain the overall ICER of the
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19 208 intervention, we added the ICERs for individual cohorts, weighted by the frequency of their
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21 209 occurrence.
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27 211 Study population and model

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29 212 This economic evaluation followed a cost-effectiveness analysis, with a healthcare provider's
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31 213 perspective. For each medical condition that constituted a referral indication, we developed 1
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33 214 decision analytical model (if the condition affected only mother or neonate, $n = 8$ models) or 2
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35 215 (if the condition affected both mother and neonate, $n = 9$ models) intervention cohorts, as
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37 216 well as the corresponding number of control cohorts ($n = 17$ models). The starting age for
38
39 217 mothers in the models was 24 years and 0 years for neonates. Individuals from the
40
41 218 intervention cohorts were referred to secondary hospitals, while individuals from comparison
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43 219 cohorts were not referred and received only primary care. For all models, a time horizon of
44
45 220 100 years was chosen to anticipate lifetime.
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51 221 Supplementary files 2 and 3 outline the non-reversible patient journey for referred and non-
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53 222 referred mothers and referred and non-referred neonates, respectively.
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3 225 We applied these exclusion criteria for the CEA: date of referral not during the study period;
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5 226 referral indication unknown or unrelated to emergency obstetric and neonatal care; referral
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7 227 indications with less than 10 cases.
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12 229 For all cohorts, all-cause mortality was calculated on an annual basis, whereas the first 2
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14 230 stages for the comparison groups and the first 3 stages for the intervention groups were
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16 231 treated as one time stamp.
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21 233 Pathway probabilities

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24 234 Medical records were used to determine the number of mothers and neonates treated at
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26 235 participating CSBs for each referral indication.
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29 236

30
31 237 Given that there was no previously published data for this context, survival rates for both
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33 238 referred and non-referred mothers and neonates were estimated through a two-stage expert
34
35 239 panel process. 3 Malagasy physicians, otherwise not involved in this study formed the expert
36
37 240 panel. They were chosen as a convenience sample, as they were familiar with the NGO's
38
39 241 intervention and had long-term experience in maternal health in the intervention area.
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42 242

43
44 243 The research team reviewed existing literature from low- and middle-income countries on
45
46 244 maternal survival rates for all referral indications. Both Google Scholar and PubMed were
47
48 245 searched to identify relevant studies. From these, we extracted data on survival rates for
49
50 246 individual referral indications at primary and secondary facilities as well as information on
51
52 247 study design, context, strengths, and limitations. We presented these data to the expert panel.
53
54
55 248 The panel then defined survival rates for each referral indication. Results of this expert panel
56
57
58 249 process are summarized in Table 1 and 2 below. For each condition, the expert panel defined
59
60

250 a maximum and minimum survival rate for mothers and neonates at both primary and
 251 secondary facilities, as well as an average survival rate agreed upon by all experts. This rate
 252 formed the baseline estimate for our CEA models.

253

254 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 (IUID) (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]	

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

258

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]

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

264
 265 Life years

266 Health outcomes were estimated based on local life expectancy tables (56). Costs and life-
 267 years saved were discounted at a 3% discount rate. This rate reflects the average annual
 268 growth of the Malagasy economy during the study period⁵⁶ and aligns with the approach for
 269 discounting in economic evaluation suggested by Haacker et al. (58).

270
 271 Sensitivity analysis

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

276

277 **Ethics approval and consent to participate**

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2
3 278 Ethical clearance for the study was obtained from the Heidelberg University Hospital Ethics
4
5 279 Committee, registration number: S-713/2020. Informed consent was waived by the ethics
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7
8 280 committee.
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281 RESULTS

282 Referral characteristics

283 In total, 1,172 patients (48 neonates and 1,124 women, respectively) were referred through
284 the intervention. Most referrals took place in Atsimo-Andrefana region (54%), followed by
285 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
289 their first week of life. 80% of calls were made for direct obstetric causes above all for
290 obstructed/prolonged labour (40%, 445/1,124) (Table 3). For neonates, the most common
291 referral indications were respiratory distress (29%, 14/48) or infection (21%, 10/48) (Table
292 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

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

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297 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.

298 Complications during the neonatal period, which triggered the referral of neonates (n= 48)

299 from participating CSBs to secondary referral hospitals.

300

301 Not all calls resulted in a completed referral. In 97 cases the ambulance was dispatched but

302 the referral was not completed. Most commonly (65%, 63/97) the complication had been

303 resolved at the CSB either with (25%, 24/97) or without (40%, 39/97) support from the

304 ambulance staff. In 8 cases (8.2%) the woman or neonate had passed away before the

305 ambulance reached the CSB and in 4 cases (4.1%) the patient or patient's relatives refused

306 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 (IUID) (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

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

332 Sensitivity analysis

333 The sensitivity analysis showed the intervention to remain cost-effective for most scenarios
334 tested. However in the following cases either the survival rate estimates at the participating
335 CSB exceeded the baseline estimate at the referral hospital or the worst case estimate at the
336 hospital was lower than the baseline estimate at the CSB, rendering the scenario not cost
337 effective: Mothers survival for eclampsia, neonates survival for ineffective labour, neonate

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3 338 survival for neonatal infection, neonates survival for respiratory distress and neonates
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5 339 survival for risk of premature delivery tested.
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3 **341 DISCUSSION**
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6 **342** The aim of this study was to evaluate the characteristics, costs, and cost-effectiveness of an
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8 **343** NGO-run inter-facility referral system for EmOC in rural Madagascar.
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12 **344** This study revealed three main findings: First, the most common referral indication for
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14 **345** mothers was obstructed/prolonged labour and unspecified infection or respiratory distress for
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16 **346** neonates. Second, the largest drivers of costs for the intervention were initial investment costs
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18 **347** for the vehicles and running costs including staff wages. Consequently, ambulance lifespan is
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20 **348** a particularly important determinant of the intervention's cost-effectiveness. Lastly, the CEA
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22 **349** demonstrated the intervention to be very cost-effective, with an ICER of 137 USD per
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24 **350** additional life year saved (discounted at 3%). The intervention was particularly cost-effective
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26 **351** for the following conditions: extrauterine gravidity, risk of uterus rupture, and post-partum
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28 **352** haemorrhage. The sensitivity analysis conducted showed the intervention to remain cost-
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30 **353** effective in most scenarios tested.
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36 **354** In accordance with our findings, other systems for EmOC referral in SSA have found direct
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38 **355** obstetric complications, especially abortion and obstructed labour to be the main referral
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40 **356** indications for mothers to secondary health facilities in resource-constrained settings (11, 59).
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44 **357** Compared with other ambulance referral systems in Uganda (9), Burundi (11) and Ethiopia
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46 **358** (12), costs for our intervention were high. This finding is however not surprising considering
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48 **359** that referrals in other interventions were not accompanied by trained medical personnel
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50 **360** receiving salaries. Neither ambulance carried medical equipment and neither publication
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52 **361** included overhead costs such as administrative costs in their cost-effectiveness analysis. In
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54 **362** addition, our intervention covered a large rural area in the remote south of Madagascar; there
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56 **363** were no paved roads and conditions deteriorated during the rainy season when parts of the
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58 **364** intervention became inaccessible. This increased costs for vehicle maintenance and fuel.
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3 365 These differences in the design of the interventions as well as their contexts of
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5 366 implementation likely explain the higher ICER of 137 USD per additional life year saved
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7 367 (discounted) when compared to ICERs of 16 USD (9) and 25 USD per additional life year
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9 368 saved (12) in Uganda and Ethiopia, respectively. Further, these studies only included referrals
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11 369 in their analysis which were deemed “undoubtedly effective” (9,12), i.e., cases in which the
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13 370 referral was likely to have a large impact on life-years saved. Our model on the other hand
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15 371 included all cases in the calculation of the overall ICER.

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20 372 Consequently, costs per referral were higher for our setting than in other studies. Tayler-
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22 373 Smith et al. reported costs of 61 USD per referral, with 1,478 ambulance referrals per year
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24 374 (11), compared to 1,075 completed referrals over 4 years, with an average cost per referral of
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26 375 367 USD in our setting.

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30 376 Regarding the per capita costs, our intervention compares preferably, with investment costs
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32 377 of 0.13 USD per person and annual running costs 0.06 USD per person, when extrapolated to
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34 378 the entire population serviced. This is much lower than what has been reported in other rural
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36 379 settings, for example in Burundi (€ 0.43/capita/year) (11), suggesting that the intervention
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38 380 described here served a much larger population at comparable costs and suggesting that the
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40 381 intervention could be sustainable, even in a setting where most of the population lives in
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42 382 extreme poverty (60).

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47 383 Our study has three main strengths: First, we used secondary NGO data as the basis for all
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49 384 analyses. This reduced the potential for erroneous data as there was no need to rely on
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51 385 estimations. Further, our data provide insights into a particularly vulnerable and resource-
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53 386 constrained setting for which data is otherwise hard to obtain. Second, we included all costs
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55 387 for the running of the ambulance system in the cost-effectiveness analysis, including
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57 388 overhead costs such as administrative costs, rendering more realistic cost estimates than other
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3 389 studies. Third, we obtained survival estimates using a multi-step expert consensus process,
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5 390 when these data were not available from the literature.
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8 391 Our study has several limitations. First, we were constrained by the availability of
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10 392 programmatic data and had to rely on expert opinions to estimate equipment lifespans as well
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12 393 as survival rates for the economic model. For the latter, to mitigate potential bias we
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14 394 established an expert panel consensus process to estimate survival rates. Second, data were
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16 395 not available on mothers' post-delivery complications or their previous patient history to
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18 396 allow for more nuanced calculations for life years saved and our model only accounted for
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20 397 mothers and neonates, for whom referral was successful. However, we do not expect either
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22 398 factor to have a large impact on the model's cost-effectiveness and are confident that the
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24 399 approach of constructing separate models per cohort can robustly identify the most cost-
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26 400 effective applications of inter-facility EmOC referrals. Last, we did not assess whether the
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28 401 intervention met the referral needs of the population in the study area.
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34 402 **CONCLUSION**

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38 403 Our study is the first to report the cost-effectiveness of an EmOC inter-facility referral system
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40 404 in Madagascar. We find the intervention to have been very cost-effective, especially for cases
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42 405 requiring surgical care. Our findings highlight the need for a comprehensive approach to
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44 406 providing rural EmOC services and may provide guidance on public health resource
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46 407 allocation in Madagascar.
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3 **409 AUTHOR CONTRIBUTIONS**
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5 410 MAF, AF, KN, NM, SK, and JVE developed the study design in collaboration with TB.
6

7 411 MAF, AF, RMR, MR, ZR and KN were responsible for data collection and study
8

9 412 administration. MAF, AF, KN, NM, RMR, ZR, SK, and JVE contributed to the analysis.
10

11 413 MAF, AF, and KN prepared the first draft of the manuscript. All authors contributed to
12

13 414 writing the manuscript. All authors read and approved the final manuscript.
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20

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22

23 418 collecting the data that support the findings of this study.
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28 **420 PATIENT AND PUBLIC INVOLVEMENT STATEMENT**
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30 421 This study did not involve patients in the research process. However, we did involve three
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32 422 independent Malagasy clinicians in the research process as key informants for the expert
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34 423 panel process to define survival probabilities for the different patient pathways. This greatly
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36 424 enhanced the applicability and relevance of our research for the context of Southern
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38 425 Madagascar.
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3 **596 SUPPLEMENTARY FILE LEGENDS**
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6 **597** Supplementary file 2. Non-reversible patient journey for referred and non-referred mothers.

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9 **598** For referred mothers, the model included 4 stages: 1) presentation at a participating CSB

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11 **599** because of an emergency during pregnancy or childbirth, 2) referral to secondary referral

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13 **600** hospital, 3) likelihood of survival at referral hospital, 4) all-cause mortality. The model

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15 **601** included 3 stages for non-referred mothers: 1) presentation at a CSB because of an

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17 **602** emergency during pregnancy or childbirth, 2) likelihood of survival at CSB, 3) all-cause

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19 **603** mortality. CSB, Centre de Santé de Base (public primary care facility).
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23 **604**

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25 **605** Supplementary file 3. Non-reversible patient journey for referred and non-referred neonates.

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27 **606** For referred neonates the model included 4 stages: 1) presentation at a CSB because of an

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29 **607** emergency peripartum or in the neonatal period, 2) referral to secondary referral hospital, 3)

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31 **608** likelihood of survival at referral hospital, 4) all-cause mortality. For non-referred neonates,

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33 **609** the model included 3 stages: 1) presentation at a CSB because of an emergency peripartum or

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35 **610** in the neonatal period, 2) likelihood of survival at CSB, 3) all-cause mortality. CSB, Centre

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37 **611** de Santé de Base (public primary care facility).
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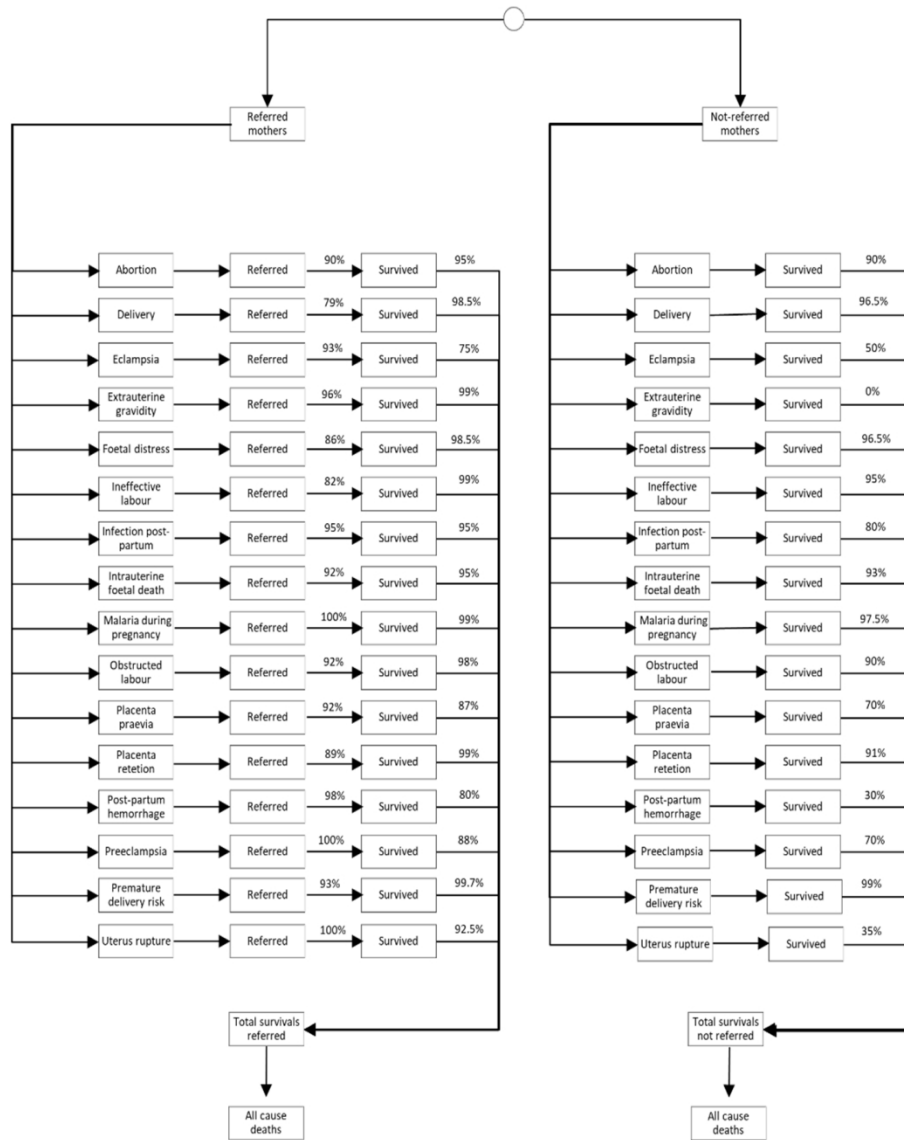
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2 Supplementary File 1: Ambulance furnishings
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5 **Medical equipment**

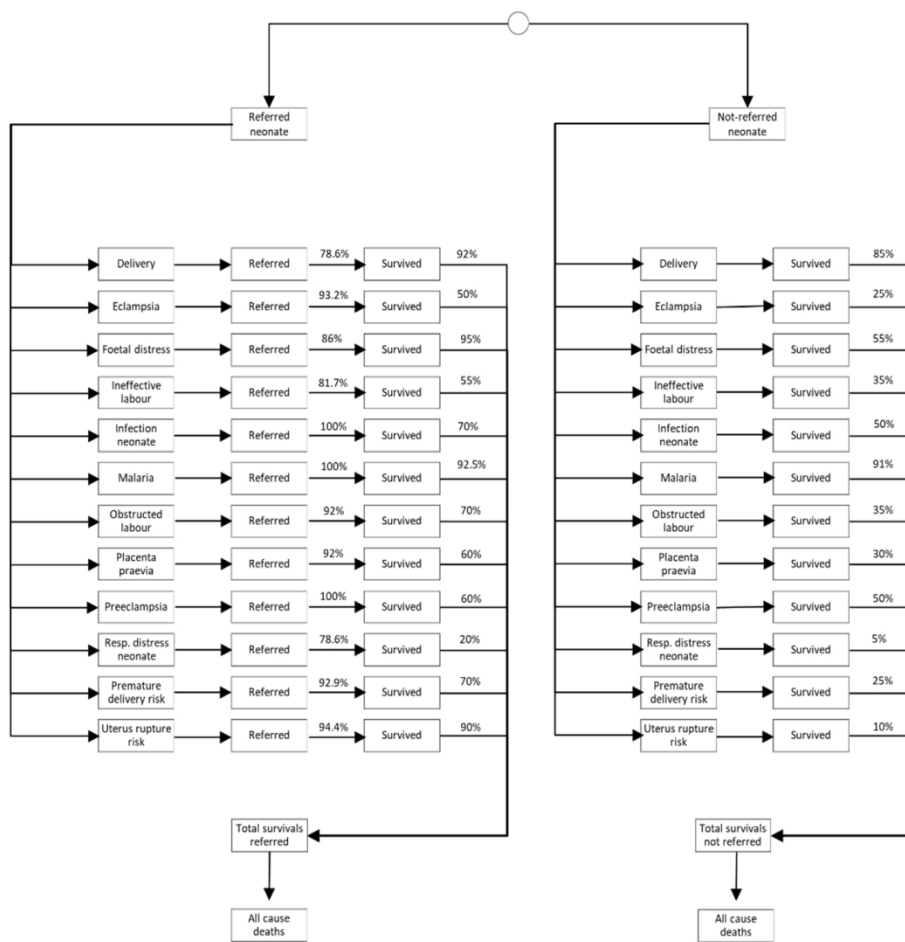
6 **Drugs**

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|---------------------------------|--------------------------------|
| 10 ● Alcohol | 10 ● Analgesics |
| 11 ● Betadine | 11 ○ Paracetamol |
| 12 ● Blood sugar testing strips | 12 ● Antibiotics |
| 13 ● Cord clamps | 13 ○ Ampicillin |
| 14 ● Echography gel | 14 ○ Amoxicillin |
| 15 ● Intravenous catheters | 15 ● Antihypertensive agents |
| 16 ● Non-sterile compresses | 16 ○ Magnesium Sulphate |
| 17 ● Non-sterile gloves | 17 ○ Nicardipine |
| 18 ● IV lines | 18 ● Infusion solutions |
| 19 ● Plasters | 19 ○ Isotonic Glucose solution |
| 20 ● Pregnancy test | 20 ○ Isotonic saline |
| 21 ● Sterile compresses | 21 ○ Lactated Ringer's |
| 22 ● Sterile gloves | 22 ○ Sodium Chloride |
| 23 ● Ultrasound machine | 23 ● Uterotonic agents |
| 24 ● Urinary catheters and bags | 24 ○ Misoprostol |
| | 25 ○ Oxytocin |
| | 26 ● Other |
| | 27 ○ Calcium gluconate |
| | 28 ○ Diazepam |
| | 29 ○ Paracetamol |
| | 30 ○ Salbutamol |
| | 31 ○ Tranexamic acid |
| | 32 ○ Vitamin K |
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52 Medical equipment and drugs available aboard ambulance vehicles.
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453x560mm (87 x 87 DPI)



464x468mm (87 x 87 DPI)

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2 Supplementary File 2: Investment costs
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6 **Item** **Cost per unit (USD)** **Quantity**
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10 **Ambulance**
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15 Port charges, forwarding agent 3,620 1
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19 Shipment from Japan to Madagascar including insurance 3,020* 1
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25 Vehicle 38,254 1
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29 Subtotal 45,487
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33 **Equipment ambulance**
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38 Carpet 38 1
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43 Fire extinguisher 26 1
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48 Luggage rack 282 1
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Item	Cost per unit (USD)	Quantity
Steering wheel cover	74	1
Tarpaulin	74	1
<u>Subtotal</u>	593	
Administration		
IT equipment, furniture)	528	1
Mobile phone	45	1
<u>Subtotal</u>	573	
<u>Total</u>	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 *).

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2 Supplementary File 3: Running costs
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Item	Cost per unit (USD)	Quantity	Annual costs (USD)
Transport			
Fuel	Average: 0.98 USD/l (0.91/l – 1.03/l)	Average 1471 /months (961-2051)	1,729
Insurance	44	1	44
Licensing in Madagascar	194	1	194
Maintenance	1,707	Yearly average	1,707
Repair	467	Yearly average	467
<u>Subtotal</u>			4,141
Car equipment			
Air chamber for tire	72	4	288
Cleaning equipment (shovel, broom, brush, scraper)	13	1	13
Tires	142	4	568
<u>Subtotal</u>			869

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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
<u>Subtotal</u>			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
<u>Subtotal</u>			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
<u>Subtotal</u>			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 remuneration 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

For peer review only

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, Staniszevska 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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BMJ Open

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

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Primary Subject Heading:	Global health
Secondary Subject Heading:	Health services research, Obstetrics and gynaecology
Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NEONATOLOGY, OBSTETRICS, ACCIDENT & EMERGENCY MEDICINE

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1
2
3
4 **1 TITLE**

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6 **2 Inter-facility transfers for emergency obstetric and neonatal care in rural Madagascar:**
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8 **3 A cost-effectiveness analysis**

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9
10

11 **27 ABSTRACT**
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15 **28** *Context:* There is a substantial lack of inter-facility referral systems for emergency obstetric
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17 **29** and neonatal care in rural areas of sub-Saharan Africa. Data on the costs and cost-
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19 **30** effectiveness of such systems that reduce preventable maternal and neonatal deaths are
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21 **31** scarce.
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25 **32** *Setting:* We aimed to determine the cost-effectiveness of an NGO-run inter-facility referral
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27 **33** system for emergency obstetric and neonatal care in rural southern Madagascar by analyzing
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29 **34** the characteristics of cases referred through the intervention as well as its costs.
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33 **35** *Design:* We used secondary NGO data, drawn from an NGO's monitoring and financial
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35 **36** administration database, including medical and financial records.
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39 **37** *Outcome measures:* We performed a descriptive and a cost-effectiveness analysis, including a
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41 **38** one-way deterministic sensitivity analysis.
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44 **39** *Results:* 1,172 cases were referred over a period of 4 years. The most common referral reasons
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46 **40** were obstructed labour, ineffective labour, and eclampsia. In total, 48 neonates were referred
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48 **41** through the referral system over the study period. Estimated cost per referral were 336 USD
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50 **42** and the incremental cost-effectiveness ratio (ICER) was 70 USD per additional life year
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52 **43** saved (undiscounted, discounted 137 USD). The sensitivity analysis showed that the
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54 **44** intervention was cost-effective for all scenarios with the lowest ICER at 99 USD and the
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56 **45** highest ICER at 205 USD per additional life year saved. When extrapolated to the population
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3 46 living in the study area, the investment costs of the program were 0.13 USD per person and
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5 47 annual running costs 0.06 USD per person.
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9 48 *Conclusions:* In our study, the inter-facility referral system was a very cost-effective
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11 49 intervention. Our findings may inform policies, decision making, and implementation
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13 50 strategies for emergency obstetric and neonatal care referral systems in similar resource-
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15 51 constrained settings.
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19 52 **ARTICLE SUMMARY**

20 53 **Strengths and limitations of this study**

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24
25 54 • Strength: Large study sample from a widely understudied population in remote Southern
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27 55 Madagascar
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30 56 • Limitation: Programmatic data and reliance of expert panel process for defining survival
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32 57 rates
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34 58 • Limitation: No long-term follow up data of patients available due to cross-sectional
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36 59 nature of the study.
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39 60 • Strength: Robust CEA methodology, including detailed and comprehensive costing data
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42 61 **KEYWORDS**

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45 62 Sub-Saharan Africa, maternal health, Emergency obstetric and neonatal care, cost-
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47 63 effectiveness analysis
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50 64 **FUNDING STATEMENT**

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53 65 This research received no specific grant from any funding agency in the public, commercial
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55 66 or not-for-profit sectors.
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67 **CONFLICT OF INTERESTS**

68 The authors declare no conflicts of interest.

69 **DATA SHARING**

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

71 **WORD COUNT**

72 3,404

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73 BACKGROUND

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

80 However, mothers and neonates in SSA often experience significant delays in accessing
81 EmOC services, i.e., when deciding to seek, reaching, and receiving adequate care [4]).

82 Access to and availability of adequate means of transportation, including ambulance referral
83 services to EmOC centres, reduces these delays [5,6], which, in turn, reduces maternal and
84 neonatal mortality [7,8].

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

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

95 We aimed to describe case and service characteristics as well as analyse the costs and cost-
96 effectiveness of an EmOC inter-facility referral system established by a non-governmental

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3 97 organization (NGO) in rural Madagascar. Our findings may inform policies, decision making
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5 98 and implementation strategies for EmOC referral systems in resource-constrained settings.
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10 100 **METHODS**

11 101 **Study design**

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18 102 This is a retrospective study using secondary data, routinely collected as part of an NGO
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20 103 intervention. A data-sharing agreement with the NGO was in place.
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23 104 **Study area and context**

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27 105 The study took place in Atsimo-Andrefana, Androy, and Anosy, rural regions in the South of
28
29 106 Madagascar. Poverty rates in the study region are high with over 80% of the population living
30
31 107 of less than 1.90\$ per day [15]. Nationally, neonatal, and maternal mortality ratios remain
32
33 108 high with a maternal mortality ratio 335 per 100,000 and a neonatal mortality ratio of 20 per
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35 109 1,000 live births, respectively [16].
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40 110 The Malagasy health system is organized in 3 tiers of care. While some public emergency
41
42 111 referral services exist at the district and national level, they fall short of covering a significant
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44 112 amount of the population, especially in rural areas of the country.
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48 113 **Intervention**

49 114 **Setting**

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55 115 To improve access to EmOC, the German-Malagasy NGO Doctors for Madagascar
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57 116 established an inter-facility referral system for obstetric and neonatal care in Atsimo-
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59 117 Andrefana (Ampanihy, Betioky-sud, and Benenitra districts), Androy (Bekily district), and
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3 118 Anosy region (Fort-Dauphin district). The intervention covered a catchment population of
4
5 119 around 1 million people (Malagasy Ministry of health, “Sectorisation”, 2020). The
6
7 120 intervention was rolled out sequentially, starting in Atsimo-Andrefana and Androy in 2016
8
9 121 and in Anosy in 2018. A 4-wheel drive ambulance was stationed at each of 3 secondary
10
11 122 referral hospitals: Hopitaly Zoara Fotadrevo, Hopitaly SALFA Manambaro, and Hopitaly
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13 123 SALFA Ejeda, which served 18, 23, and 13 participating primary health centres, respectively
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15 124 Secondary referral hospitals offer inpatient care surgical care, obstetric care, including
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17 125 emergency C-sections, and basic neonatal care.
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23 126 Participating primary health centres (locally known as Centers de Santé de Base (CSB); n =
24
25 127 54) could call the ambulance 24h per day without charge. If referral was deemed necessary
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27 128 by a trained medical dispatcher, the ambulance was sent to the CSB to transfer the patient to a
28
29 129 higher-level care facility. The referral was free for patients and participating health centres,
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31 130 all costs were covered by the NGO.
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35 131 Vehicles and equipment

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39 132 All ambulances were Toyota 4-wheel drive vehicles, equipped with a stretcher, oxygen,
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41 133 emergency medical equipment, and drugs. Supplementary File 1 summarizes the medical
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43 134 equipment and drugs, which were available on board an ambulance vehicle.
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47 135 To improve pre-transport emergency care, the NGO equipped participating CSBs with
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49 136 emergency kits containing alcohol, compresses, cotton swabs, isotonic glucose solution,
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51 137 isotonic saline, intravenous catheters, IV lines, scissors, sterile and non-sterile gloves, and
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53 138 urinary catheters. These kits were checked and refilled by NGO staff after each referral.
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57 139 Emergency medical teams

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3 140 All calls from CSBs requesting a referral were processed by a medical emergency dispatcher,
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5 141 usually a medical doctor trained in EmOC and familiar with the local setting. If the dispatcher
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7 142 deemed a referral to be necessary, a vehicle was sent to retrieve the patient from the CSB.
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11 143 The medical team aboard each vehicle always consisted of a trained midwife and a driver
12
13 144 who had received basic life support training. If necessary, a medical doctor accompanied
14
15 145 critical referrals. The medical doctor was an employee of the implementing NGO and
16
17 146 accompanied approximately 5% of referrals. This decision was made on a case-by-case basis
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19 147 by the dispatcher.
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24 148 Performance-based bonus payments
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27 149 The referring healthcare worker received a cash bonus of 2.5 USD for each case referred
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29 150 through the intervention, paid at the end of the month.
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33 151 Participants
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36 152 All women who presented at one of the participating CSBs during the intervention period
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38 153 with an acute complication during pregnancy, childbirth, or postpartum and whose
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40 154 emergency referral was deemed necessary by the medical dispatcher were eligible to
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42 155 participate. Similarly, all neonates born or treated at participating CSBs within the neonatal
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44 156 period of 28 days and whose emergency referral was deemed necessary by the medical
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46 157 dispatcher were eligible to participate.
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51 158 All obstetric and neonatal patients using the ambulance referral system between January 5th,
52
53 159 2016, and September 30th, 2020, were included in the descriptive analysis.
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57 160 Mothers and neonates presenting at CSBs not participating in the intervention were not
58
59 161 eligible for ambulance referral.
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3 162 Patients could refuse referral services at any point in time.
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7 163 **Data collection and data entry**
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10 164 Medical records
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13 165 The data source for patient and referral characteristics were case data sheets filled by the
14
15 166 ambulance staff. These data sheets included details on patient characteristics (e.g., gestational
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17 167 age) and the referral indication.
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21 168 All data were digitized into summary Excel tables by NGO personnel. Healthcare staff, who
22
23 169 were not otherwise involved in this study, replaced patient identifying information with
24
25 170 numerical pseudonyms before forwarding the Excel sheets to the research team for analysis.
26
27 171 Codes linking pseudonyms and identifying information were not accessible to the research
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29 172 team.
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34 173 We collected the original data in French and translated it into English. Data were cleaned by
35
36 174 3 independent researchers with regular check-ups to assure consistency in data cleaning. Data
37
38 175 were additionally cross-checked and screened for double entries, out-of-range values, and
39
40 176 overall consistency. In case multiple referral indications were given, an expert panel of 3
41
42 177 Malagasy physicians determined the main referral indication, which were grouped following
43
44 178 the approach by Abegunde et al. [17]. All data were stored in a password-protected database
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46 179 to which only the research team had access.
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51 180 Financial records
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55 181 The data source for the costs of the intervention were NGO financial records from 2016 to
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57 182 2019. A researcher extracted data from the original records and categorized them into
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59 183 investment and running costs and corresponding sub-categories (medical equipment,
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3 184 administration, transport, communication, consumables, pre-transport care, performance-
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5 185 based bonus payments, and training activities). Costs were classified as investment costs, if
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7 186 they were one-time costs paid for the initial set-up of the intervention (e.g. costs for the
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9 187 ambulance vehicles). Conversely, costs were defined as running costs if they were recurring
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11 188 costs necessary to continue programmatic activities (e.g. fuel costs).

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14 189 Investment costs were annualized based on lifetime estimates or records of items based on
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16 190 expert estimates from NGO staff active in the study region.

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20 191 We included all costs associated with the initial establishment of the referral systems, e.g.,
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22 192 acquisition of equipment and ambulances, as well as running costs for the 3 project sites in
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24 193 the cost-effectiveness analysis (CEA). Costs for treatments at CSBs and referral hospitals
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26 194 were not included, as those were not supported through the program. Data were collected in
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28 195 Malagasy Ariary or Japanese Yen (1 invoice) and converted to United States dollars for
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30 196 analysis (Exchange rate: 1 USD = 3,867.09 Malagasy Ariary (as of September 22nd, 2020)
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32 197 and 1 USD = 105.671 Japanese Yen (as of September 30th, 2020).

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38 39 40 199 **Data analysis**

41 42 43 200 Descriptive statistics

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47 201 We performed a descriptive analysis, including frequency distributions, for medical records
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49 202 using Stata Version 16.

50 51 52 203 Cost-effectiveness analysis

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56 204 We used a cost-effectiveness analysis to quantify the costs per life year saved, as well as the
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58 205 incremental cost-effectiveness ratio of the intervention. As this was not a randomised control
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3 206 trial, we did not develop a health economic analysis plan. We also assessed the sensitivity of
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5 207 the analysis to variation of parameters. We adhere to the CHEERS guideline for economic
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7 208 evaluations of healthcare interventions in structuring this manuscript [18].
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11 209 The main outcomes of the model were incremental cost-effectiveness ratios (ICER) per life
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13 210 year saved through the intervention overall, and separately by cohort, where one cohort was
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15 211 defined as all cases referred due to the same referral indication. To calculate the costs for
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17 212 each cohort, we multiplied the average costs per referral with the number of patients per
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19 213 cohort. For each cohort, we calculated the following incremental cost-effectiveness ratio
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21 214 (ICER): $(\text{Costs of ambulance referral system} - \text{Costs of no referral system}) / ((\text{Life years saved}$
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23 215 $\text{neonates referred} + \text{Life years saved mothers referred}) - (\text{Life years saved neonates not}$
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25 216 $\text{referred} + \text{Life years saved mothers not referred}))$. To obtain the overall ICER of the
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27 217 intervention, we added the ICERs for individual cohorts, weighted by the frequency of their
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29 218 occurrence.
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35 36 220 Study population and model

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38 221 This economic evaluation followed a cost-effectiveness analysis, with a healthcare provider's
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40 222 perspective. For each medical condition that constituted a referral indication, we developed 1
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42 223 decision analytical model (if the condition affected only mother or neonate, $n = 8$ models) or 2
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44 224 (if the condition affected both mother and neonate, $n = 9$ models) intervention cohorts, as
45
46 225 well as the corresponding number of control cohorts ($n = 17$ models). The starting age for
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48 226 mothers in the models was 24 years and 0 years for neonates. Individuals from the
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50 227 intervention cohorts were referred to secondary hospitals, while individuals from comparison
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52 228 cohorts were not referred and received only primary care. For all models, a time horizon of
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54 229 100 years was chosen to anticipate lifetime.
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3 230 Supplementary files 2 and 3 outline the non-reversible patient journey for referred and non-
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5 231 referred mothers and referred and non-referred neonates, respectively. For the intervention
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7 232 cohort, the patient journey consisted of the following stages: i) initial presentation at the
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9 233 health centre with a certain pathology, ii) likelihood of referral to a higher level of care, iii)
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11 234 likelihood of survival upon reaching the referral hospital, and iv) follow-up period after the
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13 235 referral for which all-cause mortality was applied. For the control group, the patient journey
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15 236 differed in that it lacked the stage of referral. It consisted of the following stages: i) initial
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17 237 presentation at the health centre with a certain pathology, ii) likelihood of survival with a
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19 238 given pathology at the primary care level.
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24 239 For all cohorts, all-cause mortality was calculated on an annual basis, whereas the first 2
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26 240 stages for the comparison groups and the first 3 stages for the intervention groups were
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28 241 treated as one time stamp.
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35 244 We applied these exclusion criteria for the CEA: date of referral not during the study period;
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37 245 referral indication unknown or unrelated to emergency obstetric and neonatal care; referral
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39 246 indications with less than 10 cases.
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47 249 Pathway probabilities

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49 250 Medical records were used to determine the number of mothers and neonates treated at
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51 251 participating CSBs for each referral indication.
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56 253 Given that there was no previously published data for this context, survival rates for both
57
58 254 referred and non-referred mothers and neonates were estimated through a two-stage expert
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60

255 panel process. 3 Malagasy physicians, otherwise not involved in this study formed the expert
 256 panel. They were chosen as a convenience sample, as they were familiar with the NGO's
 257 intervention and had long-term experience in maternal health in the intervention area.

258

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

269

270 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	99%	95%	99%	1%	0%	0%	[25, 26, 27]
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gravidity (50)

Post-partum	70%	90%	80%	20%	80%	30%	[28]
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haemorrhage

(46)

Intrauterine	90%	99%	95%	85%	95%	93%	[29]
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foetal death

(IUD) (45)

Eclampsia	65%	96%	75%	30%	90%	50%	[30, 31, 32]
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(39)

Placenta	85%	98%	87%	50%	95%	70%	[33, 34, 35,
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previa (34)

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Abortion (30)	90%	99%	95%	85%	95%	90%	[37]
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Risk of	99%	99%	99%	99%	98%	99%	[28]
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premature

delivery (26)

Placenta	99%	99%	99%	50%	99%	91%	[38, 39]
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retention (25)

Delivery (22)	98%	99%	98.5%	95%	99%	96.5%	[28]
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Infection	90%	98%	95%	70%	95%	80%	[40, 41]
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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]

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

274
 275 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]

277 Table 2. Minimum, maximum and baseline survival estimates for referred and non-referred
 278 neonates grouped by referral indication. Survival estimates were obtained by expert panel
 279 consensus.
 280
 281 Life years

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3 282 Health outcomes were estimated based on local life expectancy tables [55]. Costs and life-
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5 283 years saved were discounted at a 3% discount rate. This rate reflects the average annual
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8 284 growth of the Malagasy economy during the study period [56] and aligns with the approach
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10 285 for discounting in economic evaluation suggested by Haacker et al. [57].
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14 287 Sensitivity analysis

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17 288 Given that no probabilistic data was available in the literature, we performed a one-way
18
19 289 deterministic sensitivity analysis for the survival rates for referred and non-referred mothers
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21 290 and neonates to assess the impact of individual model parameters and assumptions on the
22
23 291 model outputs.
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28 293 **Patient and public involvement statement**

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31 294 This study did not involve patients in the research process. However, we did involve three
32
33 295 independent Malagasy clinicians in the research process as key informants for the expert
34
35 296 panel process to define survival probabilities for the different patient pathways. This greatly
36
37 297 enhanced the applicability and relevance of our research for the context of Southern
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39 298 Madagascar.
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44 300 **Ethics approval and consent to participate**

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47 301 Ethical clearance for the study was obtained from the Heidelberg University Hospital Ethics
48
49 302 Committee, registration number: S-713/2020. Informed consent was waived by the ethics
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51 303 committee.
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304 RESULTS

305 Referral characteristics

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

309

310 Demographic and clinical characteristics

311 Mean age of women was 23.6 years (n=1,118; IQR=12). Most neonates (78%, 36/46) were in
312 their first week of life. 80% of calls were made for direct obstetric causes above all for
313 obstructed/prolonged labour (40%, 445/1,124) (Table 3). For neonates, the most common
314 referral indications were respiratory distress (29%, 14/48) or infection (21%, 10/48) (Table
315 4).

316 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

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3 317 Complications during pregnancy, childbirth, and postpartum, which triggered the referral of
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5 318 mothers (n =1,124) from participating CSBs to secondary referral hospitals. CSB, Centre de
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7 319 Santé de Base (public primary care facility).
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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.

352 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 (IUID) (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

353 Table 5: Costs per life-year saved (in USD) and ICER per diagnosis, undiscounted and

354 discounted at 3%.

355 Sensitivity analysis

356 The sensitivity analysis showed the intervention to remain cost-effective for most scenarios

357 tested. However in the following cases either the survival rate estimates at the participating

358 CSB exceeded the baseline estimate at the referral hospital or the worst case estimate at the

359 hospital was lower than the baseline estimate at the CSB, rendering the scenario not cost

360 effective: Mothers survival for eclampsia, neonates survival for ineffective labour, neonate

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3 361 survival for neonatal infection, neonates survival for respiratory distress and neonates
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5 362 survival for risk of premature delivery tested.
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364 DISCUSSION

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

367 This study revealed three main findings: First, the most common referral indication for
368 mothers was obstructed/prolonged labour and unspecified infection or respiratory distress for
369 neonates. Second, the largest drivers of costs for the intervention were initial investment costs
370 for the vehicles and running costs including staff wages. Consequently, ambulance lifespan is
371 a particularly important determinant of the intervention's cost-effectiveness. Lastly, the CEA
372 demonstrated the intervention to be very cost-effective, with an ICER of 137 USD per
373 additional life year saved (discounted at 3%). The intervention was particularly cost-effective
374 for the following conditions: extrauterine gravidity, risk of uterus rupture, and post-partum
375 haemorrhage. The sensitivity analysis conducted showed the intervention to remain cost-
376 effective in most scenarios tested. While there are no other studies evaluating similar
377 interventions in Madagascar, our intervention shows itself to be more cost-effective than
378 other CEAs conducted in Madagascar, which reported ICERs of 1023 USD per QALY
379 gained for an intervention expanding access to antibiotics for plague care and prevention
380 [58], 177 USD per DALY averted for a drone-supported community treatment programm for
381 TB [59], and 531.2 USD per DALY averted [60] for the Indoor-residual spraying activities of
382 the national tuberculosis control programm, showing our intervention to have a much lower
383 ICER.

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

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3 387 Compared with other ambulance referral systems in Uganda [9], Burundi [11] and Ethiopia
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5 388 [12], costs for our intervention were high. This finding is however not surprising considering
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7 389 that referrals in other interventions were not accompanied by trained medical personnel
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9 390 receiving salaries. Neither ambulance carried medical equipment and neither publication
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11 391 included overhead costs such as administrative costs in their cost-effectiveness analysis. In
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13 392 addition, our intervention covered a large rural area in the remote south of Madagascar; there
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15 393 were no paved roads and conditions deteriorated during the rainy season when parts of the
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17 394 intervention became inaccessible. This increased costs for vehicle maintenance and fuel.
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19 395 These differences in the design of the interventions as well as their contexts of
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21 396 implementation likely explain the higher ICER of 137 USD per additional life year saved
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23 397 (discounted) when compared to ICERs of 16 USD [9] and 25 USD per additional life year
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25 398 saved [12] in Uganda and Ethiopia, respectively. Further, these studies only included referrals
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27 399 in their analysis which were deemed “undoubtedly effective” [9,12], i.e., cases in which the
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29 400 referral was likely to have a large impact on life-years saved. Our model on the other hand
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31 401 included all cases in the calculation of the overall ICER.
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34 402 Consequently, costs per referral were higher for our setting than in other studies. Tayler-
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36 403 Smith et al. reported costs of 61 USD per referral, with 1,478 ambulance referrals per year
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38 404 [11], compared to 1,075 completed referrals over 4 years, with an average cost per referral of
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40 405 367 USD in our setting.
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43 406 Regarding the per capita costs, our intervention compares preferably, with investment costs
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45 407 of 0.13 USD per person and annual running costs 0.06 USD per person, when extrapolated to
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47 408 the entire population serviced. This is lower than what has been reported in other rural
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49 409 settings, for example in Burundi (€ 0.43/capita/year) [11], suggesting that the intervention
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51 410 described here served a larger population at comparable costs and suggesting that the
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3 411 intervention could be sustainable, even in a setting where most of the population lives in
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5 412 extreme poverty [61]. The fact that the referral system has such low per capita costs and a
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8 413 lower ICER than components already incorporated into the national malaria control program
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10 414 in Madagascar [60], suggests that the referral system described herein could be feasibly
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12 415 adapted into the national care system in Madagascar.

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15 416 Our study has three main strengths: First, we used secondary NGO data as the basis for all
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17 417 analyses. This reduced the potential for erroneous data as there was no need to rely on
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19 418 estimations. Further, our data provide insights into a particularly vulnerable and resource-
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21 419 constrained setting for which data is otherwise hard to obtain. Second, we included all costs
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23 420 for the running of the ambulance system in the cost-effectiveness analysis, including
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25 421 overhead costs such as administrative costs, rendering more realistic cost estimates than other
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27 422 studies. Third, we obtained survival estimates using a multi-step expert consensus process,
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29 423 when these data were not available from the literature.

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32 424 Our study has several limitations. First, we were constrained by the availability of
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34 425 programmatic data and had to rely on expert opinions to estimate equipment lifespans as well
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36 426 as survival rates for the economic model. For the latter, to mitigate potential bias we
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38 427 established an expert panel consensus process to estimate survival rates. This may have led to
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40 428 an over- or underestimation of survival rates for the different conditions included in the
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42 429 model, as expert opinion builds on subjective experience, not representative data. Despite
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44 430 these limitations of expert opinion, however, they are commonly used in cost-effectiveness
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46 431 analyses in the absence of stronger data to estimate model parameters, as was the case in our
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48 432 setting [62]. Additionally, we drew on the available literature from similar settings in sub-
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50 433 Saharan Africa to put the estimates obtained from the expert panel process into context and
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52 434 verify for any outliers or implausible values. Second, data were not available on mothers'
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54 435 post-delivery complications or their previous patient history to allow for more nuanced

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3 436 calculations for life years saved and our model only accounted for mothers and neonates, for
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5 437 whom referral was successful. However, we do not expect either factor to have a large impact
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7 438 on the model's cost-effectiveness and are confident that the approach of constructing separate
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9 439 models per cohort can robustly identify the most cost-effective applications of inter-facility
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11 440 EmOC referrals. Last, we did not assess whether the intervention met the referral needs of the
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13 441 population in the study area.
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18 442 **CONCLUSION**

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21 443 Our study is the first to report the cost-effectiveness of an EmOC inter-facility referral system
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23 444 in Madagascar. We find the intervention to have been very cost-effective, especially for cases
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25 445 requiring surgical care. Our findings highlight the need for a comprehensive approach to
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27 446 providing rural EmOC services and may provide guidance on public health resource
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29 447 allocation in Madagascar.
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3 **449 AUTHOR CONTRIBUTIONS**
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5 450 MAF, AF, KN, NM, SK, and JVE developed the study design in collaboration with TB.
6

7 451 MAF, AF, RMR, MR, ZR and KN were responsible for data collection and study
8

9 452 administration. MAF, AF, KN, NM, RMR, ZR, SK, and JVE contributed to the analysis.
10

11 453 MAF, AF, and KN prepared the first draft of the manuscript. All authors contributed to
12

13 454 writing the manuscript. All authors read and approved the final manuscript.
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23 458 collecting the data that support the findings of this study.
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3 **638 SUPPLEMENTARY FILE LEGENDS**
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6 **639** Supplementary file 2. Non-reversible patient journey for referred and non-referred mothers.

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9 **640** For referred mothers, the model included 4 stages: 1) presentation at a participating CSB

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11 **641** because of an emergency during pregnancy or childbirth, 2) referral to secondary referral

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13 **642** hospital, 3) likelihood of survival at referral hospital, 4) all-cause mortality. The model

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15 **643** included 3 stages for non-referred mothers: 1) presentation at a CSB because of an

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17 **644** emergency during pregnancy or childbirth, 2) likelihood of survival at CSB, 3) all-cause

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19 **645** mortality. CSB, Centre de Santé de Base (public primary care facility).
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23 **646**

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25 **647** Supplementary file 3. Non-reversible patient journey for referred and non-referred neonates.

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27 **648** For referred neonates the model included 4 stages: 1) presentation at a CSB because of an

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29 **649** emergency peripartum or in the neonatal period, 2) referral to secondary referral hospital, 3)

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31 **650** likelihood of survival at referral hospital, 4) all-cause mortality. For non-referred neonates,

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33 **651** the model included 3 stages: 1) presentation at a CSB because of an emergency peripartum or

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35 **652** in the neonatal period, 2) likelihood of survival at CSB, 3) all-cause mortality. CSB, Centre

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37 **653** de Santé de Base (public primary care facility).
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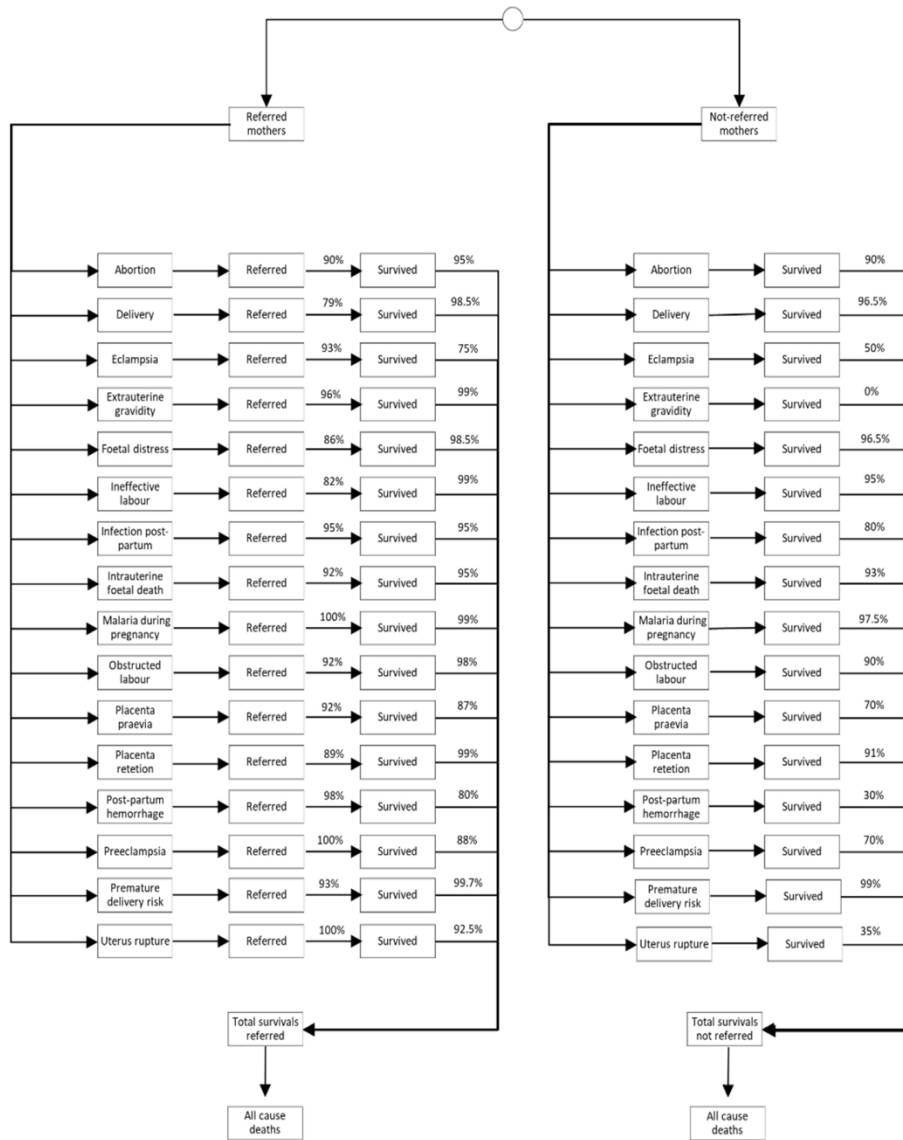
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2 Supplementary File 1: Ambulance furnishings
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5 **Medical equipment**

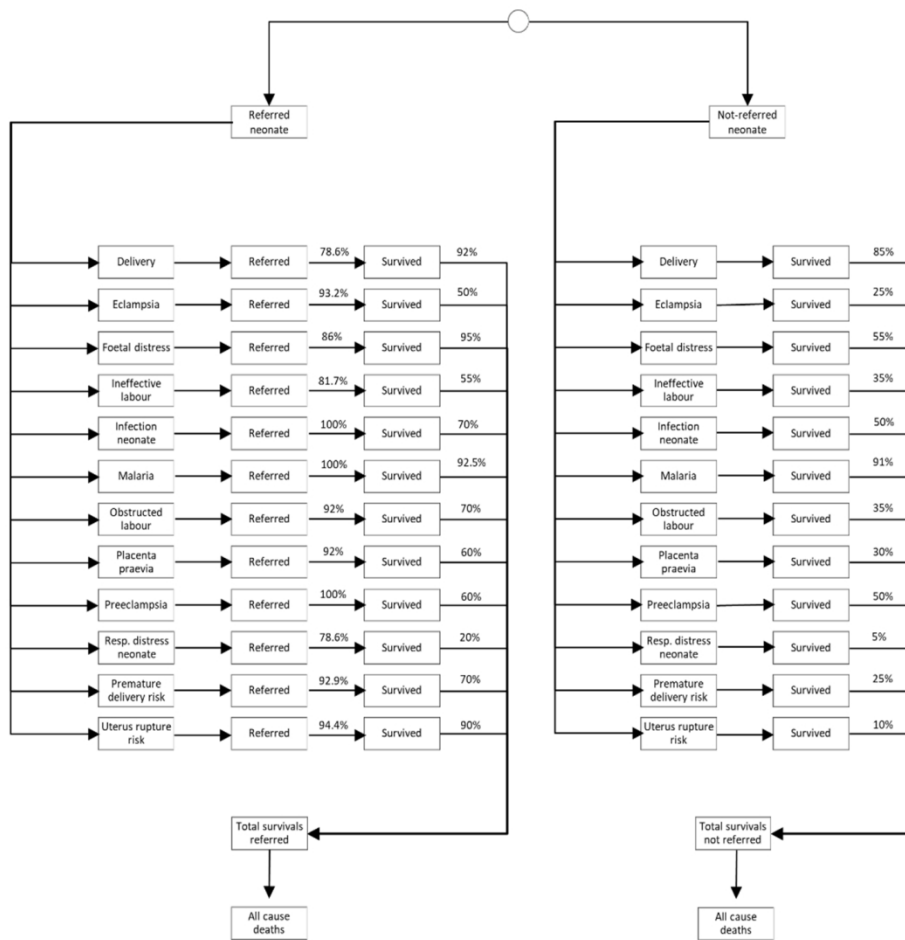
6 **Drugs**

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|---------------------------------|--------------------------------|
| 10 ● Alcohol | 10 ● Analgesics |
| 11 ● Betadine | 11 ○ Paracetamol |
| 12 ● Blood sugar testing strips | 12 ● Antibiotics |
| 13 ● Cord clamps | 13 ○ Ampicillin |
| 14 ● Echography gel | 14 ○ Amoxicillin |
| 15 ● Intravenous catheters | 15 ● Antihypertensive agents |
| 16 ● Non-sterile compresses | 16 ○ Magnesium Sulphate |
| 17 ● Non-sterile gloves | 17 ○ Nicardipine |
| 18 ● IV lines | 18 ● Infusion solutions |
| 19 ● Plasters | 19 ○ Isotonic Glucose solution |
| 20 ● Pregnancy test | 20 ○ Isotonic saline |
| 21 ● Sterile compresses | 21 ○ Lactated Ringer's |
| 22 ● Sterile gloves | 22 ○ Sodium Chloride |
| 23 ● Ultrasound machine | 23 ● Uterotonic agents |
| 24 ● Urinary catheters and bags | 24 ○ Misoprostol |
| | 25 ○ Oxytocin |
| | 26 ● Other |
| | 27 ○ Calcium gluconate |
| | 28 ○ Diazepam |
| | 29 ○ Paracetamol |
| | 30 ○ Salbutamol |
| | 31 ○ Tranexamic acid |
| | 32 ○ Vitamin K |
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52 Medical equipment and drugs available aboard ambulance vehicles.
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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
<u>Subtotal</u>	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
<u>Subtotal</u>	593	
Administration		
IT equipment, furniture)	528	1
Mobile phone	45	1
<u>Subtotal</u>	573	
<u>Total</u>	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 1471 /months (961-2051)	1,729
Insurance	44	1	44
Licensing in Madagascar	194	1	194
Maintenance	1,707	Yearly average	1,707
Repair	467	Yearly average	467
<u>Subtotal</u>			4,141
Car equipment			
Air chamber for tire	72	4	288
Cleaning equipment (shovel, broom, brush, scraper)	13	1	13
Tires	142	4	568
<u>Subtotal</u>			869

Item	Cost per unit (USD)	Quantity	Annual costs (USD)
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Consumables			
<hr/>			
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
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<u>Subtotal</u>			1,075
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Pre-transport care			
<hr/>			
Drugs and consumables	78	6	468
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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
<u>Subtotal</u>			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
<u>Subtotal</u>			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 remuneration during ambulance services (staff on extra duty for at least 4 hours)	4	Average: 20 times/months	960
<u>Subtotal</u>			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
<u>Subtotal</u>			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

For peer review only

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, Staniszezwska 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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