

Quantifying the acute care costs of neonatal bacterial sepsis and meningitis in Mozambique and South Africa

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ABSTRACT

Background

Sepsis and meningitis are amongst the leading causes of neonatal deaths in Sub-Saharan Africa (SSA). Neonatal sepsis caused around 400000 deaths globally in 2015, half occurring in Africa. Despite this, there are few published data on the acute costs of neonatal sepsis or meningitis, particularly in low- and middle-income countries, and none in SSA.

Methods

We collected data on neonates admitted to two hospitals between April 16, 2020 and April 1, 2021. In South Africa cases were microbiologically confirmed either by culture or PCR. In Mozambique clinically suspected and microbiologically confirmed cases were included. Data were collected on healthcare resource use and length-of-stay. A caregivers questionnaire gathered data on expenditure and caregiving. We used unit costs of healthcare resources in local currencies to estimate average healthcare provider cost per patient and average costs per household. Results were converted to 2019 international dollars (I\$).

Results

We enrolled 11 neonates in Mozambique, 18 neonates in South Africa. Mean length-of-stay was 10 days (median=9; IQR=4-14) and 16 days (median=15; IQR=13-18). In Mozambique we estimated mean household costs of I\$49.62 (median=10.19, IQR=5.10-95.12) and hospitalisation costs of I\$307.58 (median=275.12; IQR=149.43-386.12). In South Africa these costs were I\$52.31 (median=30.82; IQR=19.25-73.08) and I\$684.06 (median=653.62; IQR=543.33-827.53), respectively. On average, parents in Mozambique spent an extra 52 hours (median=38.5; IQR=19-86) on caregiving, and in South Africa an extra 76 (median=3.5; IQR=0-120).

Conclusion

We found substantial costs associated with acute neonatal bacterial (all-cause) sepsis and meningitis in SSA. Our estimates will inform cost-effectiveness analyses of interventions to prevent invasive bacterial infections in neonates.

Key words: sepsis, meningitis, neonate, costs, health economics

LIST OF ABBREVIATIONS

CI	Confidence Interval
GBS	Group B Streptococcus
IQR	Inter Quartile Range
I\$	International Dollar
LMIC	Low- and Middle-Income Country
SSA	Sub-Saharan Africa (United Nations region)
USD	United States Dollar

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KEY FINDINGS BOX

1. WHAT WAS KNOWN AND WHAT IS NEW?

Globally, the few published studies on acute healthcare costs of neonatal sepsis and/or meningitis are from high-income countries, and mainly from the United States. There are no studies from sub-Saharan Africa despite the high disease burden in this region. Our study provides estimates of health care and household costs associated with acute neonatal sepsis and meningitis hospitalisations in Mozambique and South Africa.

2. WHAT DID WE DO AND WHAT DID WE FIND?

Using hospital records and discharge questionnaires of 29 neonates hospitalized in Mozambique and South Africa, we estimated mean costs to households and healthcare providers to be I\$49.62 (median=10.19, IQR=5.10-95.12) and I\$307.58 (median=275.12; IQR=149.43-386.12), and I\$52.31 (median=30.82; IQR=19.25-73.08) and I\$684.06 (median=653.62; IQR=543.33-827.53), respectively in 2019 I\$.

3. WHAT TO DO NOW IN PROGRAMMES?

Neonatal complications including infections are an important cost to health systems and families, and are an important consideration for inclusion in financial protection schemes. Interventions to prevent neonatal sepsis and meningitis could reduce the costs to healthcare providers and households, as well as improving health outcomes.

4. WHAT NEXT IN RESEARCH?

Our results could be used in future research on the cost-effectiveness of interventions to prevent neonatal bacterial infections. Further costing studies with larger study populations, across a range of hospital settings and countries, and using similar tools to ours would make findings more generalisable and give insights into cost drivers and contextual differences.

BACKGROUND

Although child mortality has halved in the last two decades, deaths in the neonatal period accounted for a larger proportion, ~47% (2.4 million) of all under-5 deaths in 2019 [1]. The highest neonatal mortality rate is in the Sub-Saharan Africa region (United Nations; SSA), with sepsis and meningitis amongst the leading causes of neonatal deaths [2]. Neonatal sepsis, due to pathogens including Group B Streptococcus (GBS), led to about 400000 deaths globally in 2015, half of which occurred in the African region [3].

Despite this, there are few published studies on the cost of acute healthcare for sepsis and/or meningitis in neonates from low- and middle-income countries (LMICs), with data concentrated mainly in the United States [4]. Furthermore, no studies have reported the costs borne by households, including indirect costs of care, thereby leading to a potential underestimation of the true societal costs [4]. Knowledge of the economic consequences of sepsis and/or meningitis is essential for economic evaluations that inform policy-making to prevent invasive bacterial infections in neonates [5].

The study was conducted both in Mozambique (categorized as a low-income country) and South Africa (categorized as an upper-middle income country). In 2019, the gross domestic product per capita based on the purchasing power parity was I\$1336 in Mozambique and I\$13010 in South Africa [6].

Objective

This paper is part of a series on GBS worldwide. This paper addresses the lack of empirical data in LMICs, and SSA specifically, by estimating the costs to the healthcare system and households during acute episodes of bacterial sepsis and/or meningitis among neonates admitted to hospital in Mozambique and South Africa.

METHODS

Data collection

This costing study was a linked component of a larger study on the outcomes after invasive GBS disease in young infants, for which the protocol has been published previously [7]. Data were collected among young infants (0–89 days of life) admitted for clinically suspected bacterial sepsis and/or meningitis. In South Africa all cases were confirmed microbiologically either by culture or detection by polymerase chain reaction (for meningitis cases) in a normally sterile site (blood or cerebrospinal fluid). In Mozambique cases were defined based on clinical suspected sepsis and/or meningitis at admission, with only some being microbiologically confirmed. Babies born with severe congenital abnormalities or culture positive results of organisms considered contaminants or skin commensals were excluded [7]. Furthermore, babies born below 32 weeks of gestational age were excluded as they may incur additional costs related to being born prematurely.

We enrolled all participants who met the inclusion criteria and who were admitted between April 16, 2020, and April 1, 2021 at the Chris Hani Baragwanath Academic Hospital, a tertiary-academic hospital situated in Soweto, South Africa; and the Manhiça District Hospital, the referral hospital for the district of Manhiça in Mozambique. The hospitals included in this study are public ones; healthcare is normally provided free of charge to all patients in Mozambique and to patients under 6 years old in South Africa. Data collection took place during the middle of the SARS-CoV-2 pandemic, which prevented us from reaching the initial set sample size of 20 neonates per site.

Most participants were identified prospectively on admission. About 14 % (4/29) of the neonates were admitted from birth. These were already in hospital and kept in due to developing sepsis and/or meningitis shortly after birth. Neonates who died shortly after admission were not excluded from the study. Data on hospital resource use were collected from medical records, including information on length-of-stay, drug use, diagnostic tests and surgical procedures (**Supplemental Annex Tool 2**). Unit costs for resources were provided by the hospitals in each study site, except for

the cost per bed day in Mozambique, which was taken from published literature [8]. To capture the economic impact of an infant's hospitalization on households, a questionnaire was administered to the main caregiver at the time of discharge or soon after discharge, and included questions on out-of-pocket payments, medical, transportation and accommodation expenses as well as caregiving time (**Supplemental Annex Tool 1**). Both hospital and household costs only refer to costs incurred during the length of neonatal hospital admission. If an infant died in hospital, no questionnaires were administered but data were still collected from hospital records. The final version of the questionnaire was first piloted before it was administered by trained local research team members. A consent form was signed by all neonates' caregivers participating in the study.

Analysis

We estimated household costs associated with the acute episode including direct and indirect costs, namely medical, transportation and accommodation costs, as well as costs of informal caregiving. Healthcare provider costs were calculated based on the average length-of-stay, use of drugs, diagnostics, and supportive care, among others. Most unit costs were provided by the sites in local currencies for the year 2019. Wherever estimates were in another currency (i.e. USD) and/or for another fiscal year, these were converted into the local currency using the appropriate exchange rate and/or inflated using the local consumer price index [9,10]. To facilitate comparison between countries, estimates were converted into international dollars (I\$) using the purchasing power parity conversion factor for 2019 [11]. Given cost data are skewed, we report the median and interquartile range (IQR) alongside the mean costs. As a sensitivity analysis, we calculated costs for only microbiologically confirmed Mozambican cases. Data were analyzed in Stata and Excel.

RESULTS

Study population

Overall, 29 neonates (18 from South Africa and 11 from Mozambique) were enrolled in the study population, which is summarized in **Table 1** (the sensitivity analysis for Mozambique is summarized in **Supplementary Table A1**.) The mean gestational age at birth was 38 weeks (median=38; IQR=37-39). The mean age on admission was 5 days (median=2; IQR=1-7) in Mozambique and 11 days (median=9; IQR=6-13) in South Africa. Among the study participants, 93% (27/29) had sepsis, while 7% (2/29) were diagnosed with meningitis. Ninety percent (26/29) of neonates were discharged alive; two were transferred to another hospital in Maputo, Mozambique (outcome unknown), and one South African neonate admitted at 4 days old died after 19 days in hospital following diagnosis with sepsis (*E. coli*).

Cost estimates

Hospitalization and household costs for the two countries are described in **Table 2**. For Mozambique, results of the sensitivity analysis including only microbiologically confirmed cases are provided in **Supplementary Table A2**.

Hospitalization costs

The mean length-of-stay of 16 days (median=15; IQR=13-18) in South Africa was substantially longer than in Mozambique, which was 10 days (median=9; IQR=4-14) and 11 days (median=10; IQR=7-14) when including only microbiologically confirmed cases. The mean hospitalization cost per neonate of I\$684.06 (median=653.62; IQR=543.33-827.53) in South Africa, was also higher than the cost of I\$307.58 (median=275.12; IQR=149.43-386.12) in Mozambique. However, for microbiologically confirmed cases this increased to I\$413.41 (median=386.12; IQR=221.48-514.39), primarily due to higher laboratory costs.

Household direct costs

Most households incurred no direct healthcare expenses related to their child's acute infection. The mean healthcare expenditure per patient was I\$40.04 in Mozambique and I\$10.03 in South Africa, but median costs were zero in both countries.

In both countries, food and accommodation at the hospital are provided to caregivers without charge, so the main direct costs were transportation expenses. On average, households spent I\$9.58 in Mozambique and I\$41.64 in South Africa on transportation. Therefore, the overall direct household costs were I\$49.62 (median=10.19; IQR=5.10-95.12) and I\$52.31 (median=30.08; IQR=19.25-73.08) in Mozambique and South Africa respectively.

Household costs of informal care (indirect costs)

In 97% of cases the caregiver accompanying the child to the hospital was the mother, and otherwise the father. Caregivers' age ranged from 15 to 36 years old. In Mozambique, caregivers reported spending 52 hours (median=38.5; IQR=19-86) on extra care. In South Africa, hours of informal care varied significantly between caregivers with a mean of 76 hours (median=3.5; IQR=0-120). Amongst caregivers, 79% did not earn an income, but all reported that none of the extra time spent caring for their child would have been normally spent in paid work.

DISCUSSION

The mean healthcare provider costs of treating neonatal sepsis and meningitis were substantially higher in South Africa than Mozambique: I\$684.06 (median=653.62; IQR=543.33-827.53) versus I\$307.58 (median=275.12; IQR=149.43-386.12), although this difference was smaller when including only microbiologically confirmed cases in Mozambique. Higher costs in South Africa can be partly explained by inter-country differences in resource unit costs, and by the shorter length-of-stay and more limited standard of care provided in Mozambique. However, the direct costs from the household perspective were more similar between the two countries. These were estimated to be I\$49.62 (median=10.19; IQR=5.10-19.25) in Mozambique and I\$52.31 (median=30.82; IQR=19.25-

73.08) in South Africa. Such expenses were not considered catastrophic except for two households, one in each country, for whom these costs represented over 40% of their monthly income [12]. Although, the cost of informal caregiving could not be calculated for most caregivers as they did not earn an income, all caregivers reported that the extra hours that they spent with their child would not have been spent in paid work. This suggests zero financial opportunity cost for caring for the child, but also may reflect the poor communities from which these children come.

The lack of existing literature on this topic prevents any comparison with other studies in SSA. However, based on a few other LMIC studies, the hospitalization costs found in our study appear broadly consistent with previously reported cost of treating sepsis (2017 I\$642) and meningitis (2017 I\$198-8078) [4].

While our study is one of the first to report costs associated with bacterial sepsis and meningitis in SSA, it has some limitations. First, our analysis was only descriptive since the small sample size prevented us from investigating the determinants of costs and differences between countries. Second, we collected data from only one hospital in each country, which together with the sample size limits the generalizability of our findings. Third, in Mozambique our results include suspected, as well as microbiologically confirmed cases of sepsis, which may underestimate the true costs. Lastly, this study does not include the healthcare costs associated with the longer-term impact of the disease such as neurodevelopment deficit. Furthermore, this study does not include preterm infants because it would require a larger sample size and controlling for potential cofounders, which is beyond the scope of this study.

Despite these limitations, our multi-country study addresses an important gap in the literature that can inform policymaking. We found substantial costs associated with acute neonatal bacterial sepsis and meningitis in two countries in SSA, and our estimates will be useful to inform cost-effectiveness analyses of interventions to prevent invasive bacterial infections in neonates.

DECLARATIONS

Authors' contributions

MJ, JEL, SP, ZD and QB conceptualized the study and developed the methodology. CT helped devise the data collection instrument. CA, SLe, HM, SLA, JB, and AB collected the data. CA conducted the analysis with input from SP, QB and ZD. The manuscript was drafted by CA and SP. All authors reviewed and helped to revise the manuscript and agreed the final version.

Ethics and consent to participate

The overarching protocol for this multi-country observational study was granted ethical approval at the London School of Hygiene & Tropical Medicine (approval number 16246). Institutional review boards in each of the operating countries granted ethics approval (Mozambique approval numbers 98/CNBS/2019; South Africa approval number M190241), as well as the institutional review board of the World Health Organization (approval number ERC.0003169).

Availability of data and material

Data sharing agreements were jointly developed and signed by all collaborating partners. Data collection instruments used in this study are available in Supplemental Web Annex.

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Table 1: Descriptive statistics of neonatal inpatients with bacterial sepsis and/or meningitis recruited between April 16, 2020 and April 1, 2021.

	Mozambique	South Africa	Total
	N (%)	N (%)	N (%)
Total	11	18	29
Sex			
Male	4 (36%)	12 (67%)	16 (55%)
Female	7 (64%)	6 (33%)	13 (45%)
Age in days			
0-6 days	7 (64%)	6 (33%)	13 (45%)
7-14 days	4 (36%)	8 (44%)	12 (41%)
15-28 days	0 (0%)	4 (22%)	4 (14%)
Place of delivery			
Home	1 (9%)	0 (0%)	1 (3%)
Hospital	10 (91%)	18 (100%)	28 (97%)
Gestational age (weeks)			
32-34 weeks	0 (0%)	2 (11%)	2 (7%)
35-37 weeks	4 (36%)	6 (33%)	10 (35%)
>37 weeks	4 (36%)	10 (56%)	14 (48%)
Unknown	3 (27%)	0 (0%)	3 (10%)
Admitted at birth			
Yes	4 (36%)	0 (0%)	4 (14%)
No	7 (64%)	18 (100%)	25 (86%)
Birthweight (grams)			
<1500	1 (9%)	0 (0%)	1 (3%)
1500-2500	4 (36%)	5 (28%)	9 (31%)

2501-3000	1 (9%)	7 (39%)	8 (28%)
> 3000	5 (45%)	6 (33%)	11 (38%)
Syndrome			
Meningitis	0 (0%)	2 (11%)	2 (7%)
Sepsis	11 (100%)	16 (89%)	27 (93%)
Bacteria detected			
Group B Streptococcus	1 (3%)	8 (44%)	9 (31%)
<i>Escherichia coli</i>	0 (0%)	6 (33%)	6 (21%)
<i>Staphylococcus aureus</i>	0 (0%)	4 (22%)	4 (14%)
Gram negative rod	5 (45%)	0 (0%)	5 (17%)
Not microbiologically tested	5 (45%)	0 (0%)	5 (17%)
Length of stay (days)			
0-7 days	5 (45%)	0 (0%)	5 (17%)
8-14 days	4 (36%)	6 (33%)	10 (34%)
>15 days	2 (18%)	12 (67%)	14 (48%)
Discharge status			
Discharged alive	9 (82%)	17 (94%)	26 (90%)
Referred to another hospital	2 (18%)	0 (0%)	2 (7%)
Died	0 (0%)	1 (6%)	1 (3%)

Legend: Percentage may not sum up to 100% due to rounding

Table 2: Descriptive analysis of cost data for neonatal sepsis and/or meningitis inpatients (International Dollars 2019)

Hospitalisation costs						
	Mozambique (N=11)			South Africa (N=18)		
	Mean	Median	IQR	Mean	Median	IQR
Hospital stay (routine ward or intensive care bed)	136.31	123.81	75.66-171.95	379.41	349.62	308.83-419.55
Supportive care						
Oral feeding	9.26	0.00	0.00-0.00	Included in the hospital daily rate		
NG feeding	/			Included in the hospital daily rate		
IV fluid	/			Included in the hospital daily rate		
Parenteral feeding	/			Included in the hospital daily rate		
Nasal cannula oxygen	/			Included in the hospital daily rate		
Phototherapy	/			Included in the hospital daily rate		
Hypothermia		Data not available				
Antimicrobial therapy						
Antibiotics (first line)	43.68	0.00	0.00-78.77	25.29	14.19	7.02-45.28
Antibiotics (second line)	3.78	0.00	0.00-0.00	14.04	2.93	0.00-17.26
Antibiotics (third line)	/			0.89	0.00	0.00-0.00
Antifungals	/			0.64	0.00	0.00-0.00
Anticonvulsants	/			2.27	0.00	0.00-0.00
Other drugs*	0.46	0.46	0.00-0.00	2.45	0.00	0.00-5.02
Laboratory test						
Blood culture	22.75	0.00	0.00-41.71	19.20	16.08	16.08-24.12
Lumbar puncture	44.07	0.00	0.00-121.19	27.65	23.70	23-70-23.70
CSF culture	35.53	0.00	0.00-97.72	17.26	14.79	14.79-14.79
Urine culture	6.05	0.00	0.00-0.00	9.99	8.99	8.99-8.99

Full blood count test	2.72	0.00	0.00-0.00	18.32	18.32	9.16-27.48
Blood biochemistry	/			81.00	36.45	36.45-100.24
Serum bilirubin test	/			5.46	0.00	0.00-5.79
Blood glucose test	2.96	0.00	0.00-0.00	12.25	4.79	0.00-4.79
Diagnostic assesment						
Hearing assessment	/			Included in the hospital daily rate		
Electrocardiogram	/			Included in the hospital daily rate		
Diagnostic imaging						
X-ray	/			4.18	0.00	0.00-7.52
Ultrasound scan	/			13.03	0.00	0.00-19.55
Echocardiogram	/			50.13	0.00	0.00-0.00
TOTAL	307.58	275.12	149.43-386.12	684.35	653.92	543.64-827.83
Household expenses						
	Mozambique (N=7)**			South Africa (N=18)		
	Mean	Median	IQR	Mean	Median	IQR
Healthcare	40.04	0.00	0.00-67.94	10.03	0.00	0.00-0.00
Transportation	9.58	7.64	4.25-12.74	42.28	30.83	19.25-70.38
Food and accommodation	0.00	0.00	0.00-0.00	0.00	0.00	0.00-0.00
TOTAL	49.62	10.19	5.10-95.12	52.31	30.82	19.25-73.08

* based on one estimate; ** less than 11 due to missing values in the cost of transportation

Legend: IQR=interquartile range; "/"=does not apply/service not provided to the neonate