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Research Article

Investigating the Effect of Prompt Treatment on Malaria Prevalence in Children Aged below Five Years in Zambia: A Nested Case-Control Study in a Cross-Sectional Survey

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Background. In a highly malaria endemic country like Zambia, prompt treatment of cases is known to reduce morbidity and mortality; however, it is not known whether it has a role as an effective prevention strategy because of the presence of asymptomatic chronic carriers who do not seek treatment and maintain the reservoirs of infection in the population. This study investigated the role of treatment of malaria cases as a prevention strategy in low, moderate, and high endemic settings. *Methods*. A nested case-control design was employed using datasets from a large countrywide national Malaria Indicator Survey of 2015. Self-reported malaria cases ($n = 209$) who took treatment in the two weeks preceding the survey were matched with controls ($n = 511$) who did not report malaria and did not take treatment during the same period using nearest neighbour propensity score matching for age, sex, and district. The data were analysed using conditional logistic regression in STATA version 15.1. *Results*. The malaria cases were more likely to be from rural areas ($p = 0.001$), poorest households ($p = 0.049$), and who lived in improvised housing structures ($p = 0.004$) compared with the controls. Data from low and moderate malaria endemic areas did not have sufficient cases for the analysis to proceed; however, data from high endemic areas showed borderline evidence ($p = 0.054$) that prompt treatment reduces the risk of malaria by almost half in the short-term aOR 0.057 (95% CI 0.32–1.01). *Conclusion*. We found borderline evidence which suggests that prompt treatment of malaria cases even in high endemic areas has potential to reduce the risk of malaria by almost half in the short term.

1. Introduction

Prompt treatment of malaria infections within 24 to 48 hours of onset of symptoms is not only one of the documented strategies of fighting malaria morbidity and mortality but also a key strategy in preventing further spread of infections [1, 2]. Institution of therapy with an effective antimalarial drug in an infected person will help clear the parasites and reduce the symptoms. The onset of symptoms is associated with circulating parasites in the peripheral blood which are released from synchronized schizont rapture [3]; these can be ingested by mosquito vectors during a bite and start another phase of the life cycle in the vector [4]. Prompt treatment clears the parasites from the blood and interrupts the inoculation of parasites from the host into the vector. Since mosquito vectors live only up to a number of months depending on environmental conditions and do not transmit the parasites to other mosquitos, it is possible that reduction of human reservoirs of infection will eventually lead to reduction in infectious mosquitos passing parasites to human hosts. From ingesting sporozoites in a blood meal, a female anopheles mosquito becomes infectious in about 16 days [5].

In low and nonendemic malaria settings, prompt treatment has been shown to reduce malaria incidence [2]. In one systematic review in the United States of America, diagnosis and treatment was shown to be an effective way in reducing morbidity and mortality of malaria in patients with a travel history to malaria countries [6]. Another systematic review in Kenya highlighted that effective treatment of cases is central in reducing morbidity and mortality due to malaria [7]. In Zambia, prompt and effective treatment of cases is

one of the key strategies in the fight against malaria and it is aimed that at least 80% of all malaria cases receive an effective antimalarial within 24 hours of onset of symptoms [8]. However, there is paucity of data on the effect of prompt treatment on malaria incidence or prevalence, except for coverage of the intervention during the Malaria Indicator Surveys (MIS) [9]. In 2015, at least 22% of children aged below five years who had had fever in the two weeks preceding the MIS had sought treatment, confirmed malaria, and received antimalarial treatment [10]. One study attributed a reduction of 66% of in-patient malaria cases and deaths between 2000 and 2008 to the combined effects of nationwide rolled out of insecticide treated nets (ITN), indoor residual spraying (IRS), and case management with artemisinin-based therapies (ACTs) [11] but this did not single out the contribution of prompt treatment.

As a prevention strategy, prompt treatment has been suggested to be more effective than ITN and IRS in some settings such as low burden areas elsewhere [12, 13]. One study in Haiti which did not find ITNs effective against clinical malaria suggested that drug-based interventions that target parasites might be more effective in those settings [12]. Another study in Myanmar recommended early diagnosis and effective treatment of malaria cases over ITNs as the local vectors fed outdoors, at dawn and dusk, so indoor interventions such as ITNs were not significant [13]. In Zambia, however, the primary vectors are predominantly those that feed and rest indoors; therefore, indoor interventions such as ITNs and IRS have been found to be effective in field settings [11, 14]. Some parts of Zambia such as Macha area in Southern province have low malaria burden, and the primary vector *Anopheles Arabiensis* has been shown to be highly anthropophilic (preferring human host) but has some propensity to feed outdoors and early at dusk probably to circumvent the high coverage of ITNs [15]. *A. Arabiensis* as a primary vector has been noted to generally support low malaria transmission probably due to its foraging behavior; however, *A. funestus* and *A. gambiae* which are found to be primary vectors in the northern parts of the country like Nchelenge in Luapula and Nyimba district in the Eastern province support holoendemic malaria transmission due to higher sporozoite infection rate (SIR) and entomological inoculation rate (EIR) [16, 17].

Given that some parts of Zambia such as Lusaka and Southern provinces have become low-transmission areas over time, some secondary vectors become important in the transmission. Some of the secondary vectors show exophagic and zoophilic behavior, so reliance on indoor prevention interventions such as ITS and IRS may not be effective in these areas [17]. Drug-based interventions such as prompt treatment of cases and mass drug administration become important in low-transmission settings. Even in high-transmission settings such as most parts of the country, prompt treatment of cases hypothetically reduces the reservoir of infections, thereby reducing the entomological inoculation rates as some bites will not transmit parasites from host to the vector. However, in high-burden areas, the downside to prompt treatment of symptomatic cases as a prevention strategy is that there are many asymptomatic carriers of infections in the communities that will be missed as they will not seek treatment but will continue to be infectious [18]. In such high-endemic settings, one study suggested that chronic asymptomatic cases on average take six times longer than clinical cases and therefore play a major role as reservoirs of infections [19]. If there is delayed parasite clearance or drug resistance [20], the standard three-day courses of artemisinin combination therapies (ACTs) may not have significant effects on prevalence; however, at the time of writing this paper, there was hardly any evidence of resistance to ACTs in Zambia. In other parts of Africa, there is inchoate evidence of some indigenous resistance [21, 22]; however, ACT resistance has largely been reported in South East Asia [20, 23]. It is not clear whether prompt treatment would have a significant effect on malaria prevalence in the Zambian context with a large pool of chronic asymptomatic cases as prompt treatment targets only symptomatic cases. In malaria endemic areas like Zambia, many people become chronic asymptomatic carriers of parasites because of acquired immunity due to repeated infective bites [18, 24]. This study investigated the effect of prompt treatment of cases on malaria prevalence in children aged below five years in Zambia as a whole and stratified by high-, moderate-, and low-burden malaria settings.

2. Methods

2.1. Study Settings. Zambia is a landlocked country in Southern Africa; it has forests and savanna grasslands which are traversed by rivers and streams. Malaria is endemic to the whole country; however, it is highest in the north where prevalence in 2015 was a high as 32% in some provinces, moderate in the middle part of the country where prevalence is about 14% in some provinces, and lowest in the southern province where prevalence was as low as 0.6% in 2015 [9]. Malaria transmission is highest during the rainy season from December to May and lowest during cold and dry season from June to August and beginning to rise in the hot and dry season from September to November [10].

2.2. Study Design. This study used secondary data collected during a nationwide cross-sectional survey, the Malaria Indicator Survey (MIS) [9]; however, due to insufficient numbers of children who received prompt treatment captured by the MIS 2015 in some provinces [10], a nested case-control design was adopted in order to match the cases with similar controls [25].

2.3. Sample Size Calculation. In the primary survey the MIS 2015, the sample size was calculated using the assumption of malaria prevalence of 14.9%, from the preceding survey, the MIS 2012, 95% confidence level, 80% power, design effect of 2, and adjusted for 20% nonresponse rate. Altogether, the survey sampled 3720 households, and all children below the age of five years were included in the screening for malaria using microscopy. This nested case-control study included all children below the age of five years whose guardians

reported that the children had fever in the two weeks preceding the survey, sought treatment within 24–48 hours, were tested by finger prick and confirmed malaria, and took standard antimalarial treatment according to national guidelines.

For the unstratified data of the whole country with the estimated prevalence of 19.4% in 2015, 95% confidence level, power 80%, delta 50%, and case to control ratio of 3, the sample size for cases was estimated to be 184 cases and 552 controls. In the low-endemic zone where prevalence was estimated at 1.3%, the sample size was 2,515 for cases and 7,545 for controls. In the moderately endemic zone where prevalence was estimated at 14.1%, the sample size was estimated to be 246 cases and 738 controls, whilst in the high-endemic zone, the estimated prevalence was 132 cases and 396 controls.

2.4. Data Collection. Data for the primary MIS were collected during the peak transmission season between April and May of 2015. Respondents' demographics and socioeconomic data were collected using a questionnaires loaded on smartphones. Blood samples were collected in the field using rapid diagnostic tests (RDTs), and thick film blood slides were prepared in the field for malaria examination at the central laboratory in Lusaka using light microscopy. Each slide was read independently by three experienced laboratory technologists, and the outcome was reached by consensus for every slide among the three [9].

The nested case-control study extracted data on all children who had fever in the last 2 weeks, had a malaria test by finger prick, and received antimalarial treatment in the 2 weeks before the survey. For the controls, three nearest neighbours for each case were assigned using the propensity score matching in STATA version 15.1 [26] for age, sex, and district of residence. The controls did not have fever, were not tested test, and did not take antimalarial drugs in the 2 weeks preceding the survey.

2.5. Variable Selection. The outcome variable was children aged below the age of five years who were diagnosed with malaria by microscopy at the time of the survey. The exposure variable (cases) was children aged below five years who had fever, got tested for malaria by finder prick, were diagnosed as malaria by either microscopy or rapid diagnostic tests (RDTs), and received treatment in the two weeks preceding the survey. Malaria treatment was in line with national guidelines which comprise of artemisinin combination therapy regimens as first-line treatment, and the current combinations include artemether/lumefantrine combination tab and dihydroartemisinin/piperaquine combination. For the controls, three nearest neighbours for each case were assigned using the propensity score matching for age, sex, and district of residence. The controls did not have fever, were not tested, nor did they take antimalarial drugs in the two weeks preceding the survey. Confounding variables adjusted for were basic sociodemographic variables such as age, sex, and area of residence whether urban or rural and wealth status. Further confounding variables known to affect malaria such as type of housing, ITN use, whether the house sprayed with IRS, altitude, rainfall, and temperature were included. For the age group, the children were categorized into two groups; one below one completed year and older children aged below five years down to one completed year. For wealth status, in the primary survey, household wealth status was assessed and categorized in five ascending groups based on ownership of household assets. In this nested case-control study, the poorest quintile (lowest group) was compared to the combined group of the upper four quintiles.

2.6. Data Analysis. Basic characteristics of the participants were summarized using descriptive statistics such as Student's t test and chi square. Bivariable and multivariable conditional logistic regression was performed on the whole country dataset and later stratified by malaria epidemiological zones, namely, high-, moderate-, and low-prevalence areas. STATA software version 15 was used for the analysis [26]. The level of significance was set at 0.05.

2.7. Ethical Considerations. This study utilized secondary data, so no physical participants were involved; however, permission was obtained from the Ministry of Health to use the secondary data and ethical clearance of the protocol was granted by ERES Converge Institutional Review Board (IRB) (Ref 2018-Aug-005) and the National Health Research Authority of Zambia.

3. Results

A total of 209 cases of children under the age of five who had self-reported fever tested and treated for malaria in the two weeks preceding the 2015 MIS were found and extracted from the dataset; these were matched one to three with 511 nearest neighbour controls for age, sex, and district. Of the cases, 62 (30%) were slide positive for malaria, while 133 (26%) of the controls were positive at the time of the survey; this difference between the cases and controls was not statistically significant (p value 0.998). Table 1 summarizes the numbers of cases and controls per province. A total of 122 cases came from the high-burden epidemiological zones followed by the moderate zone with 78 and least of all only seven cases from the two provinces of low malaria epidemiological zone.

The mean age of the cases was 3.3 (standard deviation = 1.1), while for the controls, it was 3.4 years with a standard deviation of 1.1 years; there was no statistically significant difference between the mean age of the cases and controls ($p = 0.555$). The sex distribution between cases and controls was also not statistically different ($p = 0.972$); about 55% of the cases were female while 54% of the controls were female. However, preliminary observations indicate that cases with malaria were more likely to come from rural areas and the poorest wealth quintile households and less likely to reside in a standard house. It is also worth noting that coverage in terms of interventions, namely, IRS and ITNs, was not statistically significant between the cases and

Table 1: Number of malaria cases and controls per epidemiological zone.

2015 malaria epidemiological zone	Province	Cases (%)	Controls (%)	Total (%)
Low (prev. < 5%)	Lusaka	3 (1.5)	9 (1.8)	12 (1.7)
	Southern	4 (1.9)	14 (2.7)	18 (2.5)
Moderate (prev. 5–15%)	Central	6 (2.9)	15 (2.9)	21 (2.9)
	Copper belt	22 (10.6)	57 (11.2)	79 (11.0)
	Eastern	25 (12.1)	58 (11.4)	83 (11.6)
	Western	25 (12.1)	60 (11.7)	85 (11.8)
High (prev. > 15%)	Luapula	70 (33.8)	172 (33.7)	242 (33.7)
	Muchinga	20 (9.7)	50 (9.8)	70 (9.8)
	Northern	19 (9.2)	49 (9.6)	68 (9.5)
	Northwestern	13 (6.3)	27 (5.3)	40 (5.8)
Total	Missing	2 (1.0)	—	2 (<0.01)
		209 (100)	511 (100)	720 (100)

controls. Table 2 summarizes the basic characteristics of the cases and controls.

Unstratified data from the whole country in the 10 provinces indicated that prompt treatment of malaria cases was not significantly associated with malaria prevalence as the adjusted odds ratio aOR was 1.07 (95% CI 0.07–1.63) compared with the control group, neither was sex nor age. Importantly, aOR of residing in urban areas was 0.11 (95% CI 0.04–0.34) and that of living in a standard house was 0.33 (95% CI 0.11–0.97) among cases which were significantly associated with reduced odds of malaria prevalence. Interventions such as IRS and ITN were not associated with reduced odds of malaria prevalence. Table 3 summarizes adjusted and unadjusted odds ratio exposure variables on malaria prevalence.

In line with the objective of this study, the model was tested in each of the malaria epidemiological zones in order to address effect modification of prompt treatment of malaria in the three different settings. In the low malaria epidemiological zone, seven children were reported to have had fever, got tested, and received malaria treatment in the preceding two weeks to the survey. However, when they were tested at the time of the survey, all were negative for malaria; so the model could not run because of homogeneity in the outcome variable.

In the moderate malaria epidemiological zone, there were 78 cases of self-reported malaria in the preceding two weeks to the survey who reported having received antimalarial drugs out of which 24 were positive at the time of the survey. This sample size of 78 was not adequate compared with the estimated sample size in this zone of 246 cases; therefore, further analysis was not done to avoid committing type II error.

In the high malaria epidemiological zone, there were 122 cases out of which 38 tested positive at the time the survey; this was adequate as 132 cases were estimated as the sample size for this zone. The cases were matched with 299 controls out of which 106 tested positive at the time of the survey. Table 4 summarizes the effect sizes of exposure variables on malaria prevalence. In high malaria epidemiological zone in Zambia, prompt treatment of malaria as a prevention strategy showed reduced odds of malaria prevalence compared with the control aOR = 0.57 (95% CI 0.32–1.01); however, this effect was only borderline ($p = 0.054$). Urban residence, however, was found to be significant, whilst all other exposure variables were not significant.

4. Discussion

Despite the limitation of the study design in eliciting cause-effect, borderline strength evidence that suggests that prompt treatment of malaria cases may reduce the risk of malaria prevalence by about half in the high malaria endemic zone at least in the short term. This study brought out an aspect that is seldom studied in Zambia, and there was paucity of data on the effect of prompt treatment of malaria as a prevention strategy in high malaria endemic settings.

About a third of both the cases who had reported having had fever tested and received treatment, and the controls were positive for malaria with no statistically significant difference; nonetheless, children who had reported having malaria and received treatment in the two weeks preceding the MIS 2015 were more likely to be from rural areas, poorest quintile households, and substandard housing structures. This is consistent with other studies that studied malaria determinants in Zambia [27, 28]. Antimalarial drugs such as artemisinin combination therapies (ACTs) are known to clear parasiteamia within few days of commencement of effective treatment; one study in Cote d'Ivoire found a median parasite clearance of 30 hrs [29]. Another study recommended a day-three blood slide as a good predictor of treatment success [30]. In the ACTs that are currently used in Zambia, the artemisinin component acts quickly whilst the other components such as Lumifantrine or Piperaquine have a longer acting time with terminal elimination half-life of four to five days and 14 days, respectively [31, 32]. So the testing of children for malaria within two weeks after treatment is probably reasonable as clearance of the primary infection would have occurred.

This study found that, in the high malaria endemic zone, the effect size of prompt treatment on malaria prevalence in the short term was reducing the risk by almost half, statistically though it was a borderline effect. Due to a combination of low- and moderate malaria endemic provinces with high-endemic provinces, the effect of prompt treatment on malaria was masked as the overall effect size from

Table 2: Basic characteristics of the cases and controls.

No.	Variable	Cases	Controls	Total	p values
1	Age—mean (std. dev.)	3.30 (1.10)	3.35 (1.08)	3.34 (1.09)	0.555
2	Sex—female (%)	114 (54.6)	278 (54.4)	392 (54.4)	0.972
3	Residence—rural (%)	184 (88.0)	397 (77.7)	581 (80.1)	0.001
4	Wealth—poorest 5th (%)	62 (29.7)	116 (22.7)	178 (24.7)	0.049
5	Standard house—yes (%)	11 (5.3)	64 (12.5)	75 (10.4)	0.004
6	IRS—yes (%)	51 (24.4)	114 (29.0)	251 (27.6)	0.214
7	ITN slept—yes (%)	73 (35.0)	178 (35.0)	251 (35.0)	0.981
8	Malaria treated past 2 weeks—yes (%)	209 (100.0)	—	209 (29.0)	<0.001
	Total (%)	209 (29.0)	511 (71.0)	720 (100)	

Table 3: Effect size measures of variables on prevalence using data from the whole country.

Variable	Unadjusted odds ratio				Adjusted odds ratio			
	OR	95% CI		p value	aOR	95% CI		p value
Malaria treated (yes)	1.44	0.97	2.13	0.067	1.07	0.70	1.64	0.752
Sex (female)	0.31	0.05	2.05	0.228	0.21	0.03	5.63	0.506
Age group (<12 months)	<0.001	—	—	—	<0.001	—	—	0.990
Residence (urban)	0.09	0.03	0.26	<0.001	0.11	0.03	0.32	<0.001
Altitude location (metres)	1.00	1.00	1.00	0.845	1.00	1.00	1	0.575
Standard house (yes)	0.2	0.07	0.56	0.002	0.33	0.11	0.99	0.047
IRS (yes)	0.58	0.35	0.97	0.037	0.65	0.36	1.17	0.150
ITN slept (yes)	0.88	0.57	1.36	0.579	0.98	0.61	1.56	0.928
Rainfall (mm)	1.00	1.00	1.01	0.087	1.01	0.99	1.01	0.961
Temperature (°C)					0.5	0.17	1.53	0.227
Wealth (poorest quintile)	1.73	1.11	2.72	0.016	1.43	0.91	2.45	0.116

Table 4: Effect sizes of variables on prevalence using data from the high malaria endemic zone.

Variable	Unadjusted odds ratio				Adjusted odds ratio			
	OR	95% CI		p value	aOR	95% CI		p value
Malaria treated (yes)	0.91	0.55	1.50	0.704	0.57	0.32	1.01	0.054
Sex (female)	1.00	—	—	—	1.00	—	—	—
Age group (<12 months)	1.00	—	—	—	1.00	—	—	—
Residence (urban)	0.06	0.01	0.26	<0.001	0.06	0.01	0.26	<0.001
Altitude location (metres)	0.99	0.99	1.00	0.600	1.00	1.00	1.00	0.337
Standard house (yes)	0.20	0.04	0.73	0.015	0.29	0.07	1.18	0.084
IRS (yes)	0.71	0.36	1.39	0.316	0.8	0.36	1.76	0.576
ITN slept (yes)	1.07	0.62	1.87	0.796	0.97	0.54	1.77	0.933
Rainfall (mm)	1.00	0.99	1.01	0.840	1.00	0.98	1.02	0.861
Temperature (°C)	0.90	0.41	1.99	0.792	0.74	0.19	2.90	0.666
Wealth (poorest 5th)	1.63	0.94	2.83	0.081	1.3	0.70	2.41	0.409

unstratified data for the whole country was statistically not significant. Stratifying the country into malaria epidemiological zones did not yield adequate malaria cases for the low and moderate epidemiological zones as the primary survey, the MIS, did not capture enough cases who were treated for malaria in the two weeks preceding the survey. Further analysis in these two zones was not done because of the high likelihood of committing type II error [33, 34]. In theory, in the low malaria epidemiological zone, the effect of prompt treatment as a prevention strategy on malaria is likely to be more compared with the high malaria endemic zone as the reservoirs of infections would be fewer leading to a lower entomological inoculation rate (EIR).

The effect of prompt treatment on prevalence was expected to be reduced in the moderate malaria endemic zone as more people have partial immunity and likely to be chronic carriers who are asymptomatic and not likely to seek treatment [35]. The least effect of prompt treatment was expected in the high malaria epidemiological zone because of more repeated infective bites; more people are expected to build partial immunity and become chronic carriers and therefore the effect of treating those with symptoms only is

likely to be diluted by the many reservoirs of infections [18, 19]. It is therefore promising that evidence even if borderline was found in the "least likely" of the malaria epidemiological zones, more research with larger number of cases may be able to confirm higher effects in the low and moderate epidemiological malaria zones.

5. Conclusion

The risk of malaria was found to be more in rural areas, amongst the poorest households and those who live in substandard housing structures.

This study found borderline evidence which suggests that, even in high malaria endemic areas, prompt treatment of malaria cases has potential to reduce risk of malaria by almost half in the short term. Whilst it was not conclusive, this is promising because this effect was demonstrated in the least likely of areas in the highly malaria endemic zones where high presence of chronic asymptomatic carriers dilutes the effect of prompt treatment of cases as a prevention strategy.

Data Availability

The primary data used in this analysis are available upon request to the National Malaria Elimination Program (website: https://www.nmec.org.zm/).

Additional Points

Limitations. The key limitation to this study as a nested-case control in a cross-sectional survey was that it could not analyze and interpret results from low and moderate malaria epidemiological zones because only few children in those zones met the criteria for inclusion as cases. *Recommendations.* This study does not make any policy recommendations on the use of prompt treatment of malaria cases as a strategy for prevention because of the borderline evidence that was found. However, it is promising because this evidence was found in the "least likely" zone which was the only one with sufficient numbers of cases. The author recommends more research on the effects of prompt treatment as a prevention strategy for malaria in Zambia, for example, an open prospective cohort study will be able to recruit sufficient numbers of both cases and controls over time in both the low and moderate epidemiological zones as opposed to a cross-sectional survey design used in our primary data source.

Conflicts of Interest

The author declares no conflicts of interest.

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