Factors influencing severity of recurrent malaria in a conflict-affected State of south Sudan

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Abstract

Background South Sudan has borne the brunt of years of chronic warfare and remains endemic of malaria, with increasing mortality and morbidity. Limited data still exists on factors influencing the severity of recurrent malaria, especially in emergency context as South Sudan. This study therefore aimed to investigate factors influencing recurrence of severe malaria in selected primary healthcare centres in South Sudan. This would assist and guide in malaria prevention, treatment, and eradication efforts.

Methods We conducted a retrospective study of routinely collected clinic data collected for individuals aged 1 year and above who received a diagnosis of severe malaria at 3 primary healthcare centres (PHCC); Malual Bab PHCC, Matangai PHCC and Malek PHCC between September 15, 2019 to December 15, 2019 in South Sudan. Patient characteristics were analyzed using simple descriptive statistics. Inferential statistics were also conducted to identify the associated factors influencing recurrence of severe malaria. All analyses were conducted using R Version 3.6.2.

Results A total of 289 recurrent malaria cases were included in this study. More than half of the participants were female. Overall, the prevalence of severe recurrent malaria was 66.1% (191) while 74.4% (215) did not complete malaria treatment. Among those who did not complete malaria treatment, 76.7% (165) had severe recurrent malaria, while among those who completed malaria treatment 35.1% (26) had severe recurrent malaria ($p<0.001$). There is a significant association between marital status (OR= 0.33, 95% CI: 0.19-0.56, $p<0.001$), employment status (OR=0.35, 95% CI: 0.14-0.87, $p=0.024$), the use of preventive measures (OR=3.82, 95% CI: 1.81-8.43, $p<0.001$) and nutrition status (OR=0.22, 95% CI: 0.13-0.37, $p<0.001$). When adjusted for employment, marital status, nutritional and prevention measures in turns using Mantel-Haenszel test of association, this effect remained statistically significant.

Conclusion Our study showed that there is a high prevalence of severe recurrent malaria in South Sudan and that significant relationship exists between severe recurrent malaria and antimalarial treatment dosage completion influenced by certain personal and social factors. Findings from our study would be useful for effective response to control and prevent malaria in endemic areas of South Sudan.

Introduction

According to the World Health Organization (WHO) - World Malaria report, there has been a substantial achievement in the reduction of the global burden of malaria since 2010 (1). However, a critical analysis of the reported data in recent years strongly indicates a stall in the progress between 2015 and 2019. Globally, in 2017, 219 million malaria cases were reported, compared with 214 million and 239 million cases reported in 2015 and in 2010 respectively. The falloff in the malaria burden reduction progress between 2015 to 2019 is caused by the thwart effect from the eighteen highest malaria burden countries inclusive of South Sudan. For example, Ghana and Nigeria, one of the eight highest malaria burden countries reported the highest absolute increases in cases of malaria in 2018 compared to 2017, while other highest burden countries reported a similar burden estimate from 2016 to 2018 except for Uganda

and India. Though the exact burden of malaria in these countries still remains partially elusive not excluding South Sudan (2, 3). This is because most of the malaria-related deaths turn out majorly in the community, and not in the government owned healthcare facilities (4), where death registration is usually processed in the civil registration and vital statistics (CRVS) system (5). No doubt, in the past decade, there was an abated population at risk of malaria infection in the five regions of WHO (1,3,6,7,8); and few countries with previous high malaria estimates are now on track towards malaria elimination reporting a slump in trend for malaria cases. China, known to have in the past, reported an approximated 30 million malaria cases in a year, now reports zero cases since 2017 (9).

The reduction in the malaria burden to a scale-up of combinations of control strategies which comprise of: insecticide treated nets (ITNs) or long-lasting insecticide-treated nets (LLINs), intermittent preventive therapy for pregnant women for prevention, and indoor residual spraying, better diagnostics for case ascertainment, and effective treatments using artemisinin-based combination therapies (ACTs) (10, 11). ITNs was not generally singled out by the majority of directly observed studies as the sole or major driver of the decline as suggested recently [12]. The proportion of children under 5 years of age and sleeping under ITNs in sub-Saharan Africa, has increased to an estimated 68% (95% CI: 61–72%) in 2015 from <2% in the year 2000, although the estimates vary widely between countries (8). Despite these gains, recent studies highlighted the fact that the distribution, ownership, and actual use of ITNs is still inefficient and potentially undermines its effectiveness (12). Investments in health systems and improved availability of ACTs and rapid diagnostic tests (RDTs) have also played a role in the gain (13), including South Sudan. A study in South Sudan however identified compliance to effective malaria prevention and treatment measures as a major challenge (14). Other approaches are under investigation, and some have shown promise, but have not yet been widely deployed, these include seasonal malaria chemoprevention (SMC) (15) and mass drug administration (MDA) (16). During this research, no published and unpublished literature has stated the wide scale implementation of the two latter approaches in South Sudan.

With this regard, it is of huge concern that despite the progress being made in the global fight against malaria, the population living in malaria endemic areas often experience more than one malaria attack in a single season. The distribution and determinants of the recurrent malaria attacks have been reported to depend on the local epidemiological environment. According to past studies conducted, children may suffer repeated Plasmodium falciparum attacks every 4 to 6 weeks over many years, in the hyper-endemic areas of Africa (17,18,19). In low-transmission settings in Africa, it was estimated that on average a person might have 1–3 episodes of malaria infection in a year (20). Also, a severe malaria study finding showed that mortality increased with repeated convulsion (21). With severe recurrent malaria, the chance of repeated convulsion is higher and thus increases in mortality.

It is important to note that several studies have been conducted on risk factors of malaria and/or severe malaria, however, most of the previous studies examined the risk factors of malaria or severe malaria with little or no attention given to the factors of severity of recurrent severe malaria. Some studies examined malaria and severe malaria in relation to use of malaria preventive and control measures

(14,22,23,24,25). One of the studies examined the social determinants of malaria but it did not evaluate the relationship between social determinants and recurrent severe malaria (26). Hence, limited data thus still exists on factors influencing the recurrence of malaria and the severity of its recurrence especially in emergency context as South Sudan, affected by various conflicts and humanitarian situations, which limit the health systems and research optimization (7). South Sudan, a fragile and conflict-affected country, is believed to be among the farthest from achieving the Millennium Development Goals (MDGs) on health. Estimations show that more than half of the world's poorest people are residing in countries with the most fragile governing system (27,28,29). It is beneficial to know and understand factors responsible for recurrence of malaria if the goal of controlling the endemic nature of malaria in South Sudan is to be achieved. No doubt, this will contribute to the Global Malaria Programme GMP efforts to control and eliminate malaria.

This study therefore aimed at identifying factors associated with severe recurrent malaria in the capital town of Lakes State in South Sudan. This would assist and guide the malaria control programme efforts in the country.

Methods

Study design and location

South Sudan consists of 10 states and 79 counties with a population of 11,062,000 people in 2019. The Lakes State includes Rumbek Centre, Wulu, Rumbek North, Rumbek East, Cueibet, Yirol West, Yirol East, and Aweiral counties. Rumbek Centre county is the capital and politico-economic centre of the state; it is also known as the highest populated county in the state of about 232,752 people in 2017. The county has about six government-owned primary healthcare centres and 13 primary healthcare units, which are supported by few international non-governmental organizations (INGOs) and governed by the county health department, an epitome of the state ministry of health at the county level.

Study design

We conducted a retrospective study of routine clinic data collected for individuals aged 1 year and above who received a diagnosis of recurrent malaria at only 3 primary healthcare centres (PHCC); Malual Bab PHCC, Matangai PHCC and Malek PHCC between September 15, 2019 to December 15, 2019 in Rumbek Centre County, Lakes state, South Sudan. All cases of malaria included in this analysis were diagnosed recurrent malaria using the antigen Plasmodium lactate dehydrogenase-rapid diagnostic test (RDT) for malaria and self-report on previous consultation visitation by the patients or their carer; which were all confirmed from the out-patient department (OPD) register. Recurrent malaria was defined as a subsequent malaria case that occurred after 7 days to 43 days of the first dose of the anti-malaria treatment. This was based on the recent study on the clinical efficacy of clearing falciparum parasites within 5 days of artemisinin-based combination therapy (ACT) (30). Patients were only categorized into under 5 and 5 years old or above to avoid likely own-age bias. Those that had fever (>38∘C) and vomiting (> 1-day duration) with any of the following symptoms; convulsions, abnormal sleep, inability to drink,

coma, severe anaemia, jaundice, coloured urine, bleeding, dyspnoea and shock, were categorized as having severe recurrent malaria (31). Other client level data was extracted from the malaria registers and client records as applicable into Microsoft Excel templates.

Data Analysis

Bivariate analysis was conducted to determine associations between the main exposure variable (incomplete malaria treatment) and other independent variables with the primary outcome (severe recurrent malaria), using Chi-square test (of Fisher's exact test in cases of small subgroup sample sizes). Crude odds ratios (OR) with 95% confidence intervals (CI) were estimated using binary logistic regression to quantify the association between severe recurrent malaria and other independent variables including the main exposure variable. The Mantel-Haenszel method was used to test the association between incomplete malaria treatment and severe recurrent malaria, stratifying for each of these potential confounding variables in turn. Crude odds ratio obtained from association between main exposure and primary outcome was compared with Mantel-Haenszel odds ratio for confounders' identification. Homogeneity test was carried out to compare stratum-specific odds ratios to identify effect modifiers.

Multivariable logistic regression models were used to estimate the causal effect of incomplete malaria treatment on severe recurrent malaria while controlling for potential confounding and calculated 95% confidence intervals for these estimates. We considered p-values less than 0.05 as statistically significant and all analyses were conducted using R Version 3.6.2.

Results

A total of 289 participants were included in this study. As summarized in table 1, 64.2% (185) of the participants were females, 38.1% (110) were under 5 years of age, 26.0% (75) were married, 47.8% (138) ate once or twice daily and 88.9% (257) had environmental measures and/or insecticide treated nets as malaria prevention measures. Overall, the prevalence of severe recurrent malaria was 66.1% (191) while 74.4% (215) did not complete their anti-malaria treatment. Among those who did not complete anti-malaria treatment, 76.7% (165) had severe recurrent malaria, while among those who completed anti-malaria treatment, 35.1% (26) had severe recurrent malaria ($p<0.001$).

Among those who were married, 46.7% (35) had severe recurrent malaria compared with 81.7% (156) of those who were single. Married participants were less likely to have severe recurrent malaria compared with those who were single (OR= 0.33, 95% CI: 0.19-0.56, $p<0.001$). Similarly, 42.9% (9) of employed participants had severe recurrent malaria compared with 67.9% (182) of unemployed participants. Employed participants were therefore less likely to have recurrent malaria compared with those who were unemployed (OR=0.35, 95% CI: 0.14-0.87, $p=0.024$). Furthermore, 51.0% (77) of participants who ate at least twice daily had severe recurrent malaria compared with 82.6% (114) of those who ate a maximum of one meal daily. This association was significant as those who ate at least twice daily were 0.2 times as likely to have severe malaria compared to those who ate a maximum of one meal daily (OR=0.22, 95% CI: 0.13-0.37, $p<0.001$). Conversely, 69.6% (179) of participants who had at least one malaria preventive

measure developed malaria compared with 37.5% (12) of those who had no prevention. Therefore, those with at least one preventive measure were 3.8 times more likely to have severe recurrent malaria compared with those who had no prevention measure (OR=3.82, 95% CI: 1.81-8.43, p<0.001).

Bivariate analysis summarily revealed an association between malaria treatment completion and severe recurrent malaria (table 2). Participants with incomplete malaria treatment were more likely to have recurrent malaria compared with those who completed malaria treatment (OR=6.09, 95% CI: 3.47-10.93, p<0.001). When adjusted for employment, marital status, feeding habit and prevention measures in turns using Mantel-Haenszel test of association, this effect remained statistically significant at (OR=5.73, 95% CI:3.22-10.22, p<0.001), (OR=6.44, 95% CI:3.54-11.75, p<0.001), (OR=9.03, 95% CI:4.52-18.00, p<0.001) and (OR=5.52, 95% CI:3.07-9.90, p<0.001) respectively. In multivariable analysis (table 3), adjusted for employment, marital status, nutritional and preventive measures, those with incomplete malaria treatment were more than 10 times as likely to have severe recurrent malaria compared with those with complete malaria treatment (aOR=10.62, 95% CI: 4.95-24.54, p<0.001).

Discussion

This study aimed to investigate and identify factors that influence recurrence of malaria in a severe form in selected primary healthcare centres in South Sudan. The finding of the study hence would contribute to the understanding of factors limiting the achievement of the malaria control and elimination programme objectives in South Sudan. The finding of this study showed that a good proportion of the population had access to insecticide treated net and other environmental preventive measures. This suggested the population in the study area might have benefitted from the investment made towards improving access to proven preventive measures for malaria, especially the treated mosquito nets. Previous studies have shown that access to an effective utilization of treated mosquito net significantly prevents the occurrence of both uncomplicated malaria (8,,22,23), and complicated malaria (14).

The finding of this study also showed prevalence of severe recurrent malaria among the participants to be higher in the five years old and above population when compared to the under-five years old population. This is in consistency with previous studies; however, more sub-classifications of age were applied in those studies (14,23,32). Further investigation on this may be suggested, in line with the WHO request for continuous monitoring of drug efficacy (33,34), as the possibility of gradual emergence of drug resistance malaria infection may not be ruled out, and this may undermine the malaria control efforts. According to WHO, in areas of moderate or intense malaria transmission, partial immunity is developed over years of exposure especially among adults; and while it never provides complete protection, it does reduce the risk that malaria infection will cause severe diseases (33,34). Notwithstanding, It is important to conduct further investigation to detect if the prevalence of severe recurrent malaria among adult participants was as a result of waned immunity (being an area of malaria endemicity), or a factor of drug resistance or otherwise.

One major finding this study revealed was that among those who did not complete their treatment, 76.7% had severe recurrent malaria, unlike 35.1% seen among those who completed their treatment. While there is dearth of data on recurrence of severe malaria, previous study has shown 24.1% recurrence of malaria at least one episode within 180 days of treatment completion and were attributed to treatment failure (35). Other studies showed 0-13.5% malaria recurrence following treatment with standard regimen (36,37,38). The finding of this study further revealed that 'completion or not' of prescribed standard malaria treatment regimen by patient was a significant factor to the severity of malaria recurrence among the population. The finding showed significant association irrespective of the employment, marital, nutritional, or preventive measure access status of the participants. Previous malaria studies have shown non-completion of treatment to be a predisposing factor of severe recurrent malaria (14,39). The government through the ministry of health and various partners have been investing enormous resources in the prevention and control of malaria including increasing access to treatment. Further studies to investigate the types of anti-malaria treatment given, whether treatment is completed or not by the patient, and factors influencing adherence to anti-malaria treatment in post-conflict settings like the South Sudan's population is highly recommended. Meanwhile, it is necessary for clinicians and health stakeholders to create methods and/or strategies that will ensure patients take and complete medications accordingly as prescribed, on time, including patient follow-up.

Our study also revealed that severity of recurrent malaria had a significant relationship with marital status. Married participants were less likely to have severe recurrent malaria when compared with those who were single. The finding might have resulted from the fact that married persons could lend more care and protection to one another at home including preventive and prevention of health care such as providing reminders on medication, providing support in the proper utilization of treated mosquito nets among others, unlike single persons. Most of the previous studies that examined the social determinants of malaria did not evaluate the relationship between severe malaria or recurrent severe malaria and marital status. However, similar to the finding reported in this study for the factor of marital status, previous studies found significant relationship between age, gender, and occurrence of severe malaria (26).

The severity of malaria recurrence was also more likely among those who are not employed when compared with those gainfully employed. The possibility of reduced positive emotional state of mind might have affected the health seeking behaviour of the unemployed population. Furthermore, the finding of the study showed significant association between participants who ate at most once or twice daily had severe recurrent malaria compared with those who ate a minimum of thrice meal daily. This can be argued that participants with access to more or adequate meals should have better health status to prevent and /or respond to illness. This does not contradict the fact that there could be a possibility that those who had access to more meals might not have had access to a balanced or quality diet, hence limited benefit to their body health systems; and therefore could have reduced the protective effect against the severity of recurrent malaria in our study (adjOR=9.03, 95% CI: 4.52-18.00, $p<0.001$) . This study should have but could not further investigate the type and quality of meal the participants had; hence, it will be beneficial to the government of South Sudan if further studies can explore the type and

effect of meal quality on the recurrence of severe malaria. The findings of various studies conducted suggested poor feeding as a result of poverty to be a factor influencing malaria occurrence (40,41,42). Available evidence alluded to the fact that where malaria thrives most, human societies have prospered least, and this suggests that malaria and poverty are closely linked (43,44). Programmes which focus on sustainable empowerment of families and communities economically may contribute to reducing the incidence of recurrent severe malaria and should be more advocated in the area and other areas with similar epidemiological patterns for severe malaria.

The findings of this study conversely showed that participants who had at least one malaria preventive measure developed severe malaria compared with those who had no prevention. Those with at least one preventive measure were more 3.8 times as likely to have severe recurrent malaria compared with those who had no prevention measure. Factors responsible for this finding should be investigated. There is a likelihood of poor compliance to effective utilization of these preventive measures. Furthermore, the chance of false protection might have existed among the population, hence increasing their exposure to having recurrent severe malaria. It will be useful to investigate further the type and quantity of preventive measures the population had access to and how effectively they comply with the use of these measures. The findings from previous studies showed that attitude and inadequate knowledge of the effective use of malaria preventive and control measures affect compliance and the outcome (14,22,23,24,25). Among available preventive measures, WHO recommends protection for all people at risk of malaria with effective malaria vector control – insecticide-treated mosquito nets and indoor residual spraying which are effective in a wide range of circumstances (33).

Study limitation

Findings of our study must be considered in view of its limitations. Firstly, the use of patient-provided clinical data may have exposed the study to recall bias. However, considering that data was collected without specific attention drawn to our research question, we believe this bias to be minimal. Further, our retrospective use of the data implied that the spectrum of covariates that could be controlled in this study were limited. Within the available data, we made the best use of the available data to determine our final estimates. Lastly, we acknowledge that the use of antigen Plasmodium lactate dehydrogenase- RDT instead of the gold-standard microscopy blood film malaria test may have resulted in a number of false positive recurrent malaria cases in the study as past studies has proven that these RDTs can still detect antigen Plasmodium lactate dehydrogenase in the blood plasma as positive 28 (18–35) days after an antimalarial treatment. Although, this depends on the age and type of anti-malaria treatment received (45).

Conclusion

This study indicated high prevalence of severe recurrent malaria in South Sudan, with significant relationship to certain characteristics of individuals within the population such as marital status, employment status, the use of preventive measures and feeding habit. There was significant association

between the severity of malaria recurrence and non-completion of prescribed malaria treatment regimen. Further studies on factors influencing anti-malaria treatment adherence, prevalence of anti-malaria drug resistance to malaria and compliance to preventive measures is recommended.

Declarations

Ethical approval and Consent to participate

Ethical approval for the study to be conducted and published was granted by the Health Research Ethics Committee of the State Ministry of Health (SMoH) of Lakes State (formerly Western Lakes State), South Sudan (Reference Number: MOH/WLS/14/09/2019). The research was carried out in accordance with the principles of the Helsinki declaration. Written informed consent was obtained from all study participants, which was a supplementary to the questionnaire with full confidentiality of participants' personal details like name, address, phone number, etc.

Consent for publication

Not applicable

Availability of data and materials

On reasonable request from the corresponding author as datasets used in this study are readily available.

Declaration of interests

We declare no competing interests.

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Authors' contribution

IOI conceptualized this study, coordinated the research study, collected and organised data management, planned the methodology, analyzed the data and led the report writing. GOA was involved in the conceptualization of the study, collected and organized data management and participated in report writing. IOI-Iyamu participated in data analysis and report writing. ABS was involved in report writing. YAA was involved in the conclusive report writing. JGO was involved in the study conceptualization, report writing and supervised the study implementation.

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Tables

Table 1 – Distribution of study sample characteristics and the risk of severe malaria

Variable	Severe recurrent malaria		Crude Odds Ratio	P-value
	No (%)	Yes (%)	(95% CI)	
Malaria treatment				
Complete treatment	48 (49.0)	26 (13.6)	Ref	
Incomplete treatment	50 (51.0)	165 (86.4)	6.09 (3.47, 10.93)	<0.001*
Age				
Less than 5 years	32 (32.7)	78 (40.8)	Ref	
5 years and above	66 (67.3)	113 (59.2)	0.7 (0.42, 1.17)	0.176
Sex				
Female	58 (59.8)	127 (66.5)	Ref	
Male	39 (40.2)	64 (33.5)	0.75 (0.45, 1.25)	0.263
Marital status				
Single	58 (59.2)	156 (81.7)	Ref	
Married	40 (40.8)	35 (18.3)	0.33 (0.19, 0.56)	<0.001*
Employment status				
Unemployed	86 (87.8)	182 (95.3)	Ref	
Employed	12 (12.2)	9 (4.7)	0.35 (0.14, 0.87)	0.024*
Rapid diagnostic test				
Negative	13 (13.3)	40 (20.9)	Ref	
Positive	85 (86.7)	151 (79.1)	0.58 (0.28, 1.11)	0.113
Feeding habit				
Once/twice daily	24 (24.5)	114 (59.7)	Ref	
At least thrice daily	74 (75.5)	77 (40.3)	0.22 (0.13, 0.37)	<0.001*
Preventive measures				
None	20 (20.4)	12 (6.3)	Ref	
Environmental sanitation and/or ITN	78 (79.6)	179 (93.7)	3.82 (1.81, 8.43)	<0.001*
				N=289

*- Significant: p<0.05

Table 2 – Adjusted estimates of the odds ratio for the association between incomplete malaria treatment and severe recurrent malaria estimated using the Mantel-Haenszel method (n=289)

Variable	Odds Ratio (95% CI)	P-value
Crude Association	6.09 (3.47, 10.93)	<0.001*
Association Adjusted For:		
Employment status	5.73 (3.22, 10.22)	<0.001*
Marital status	6.44 (3.54, 11.75)	<0.001*
Feeding habit status	9.03 (4.52, 18.00)	<0.001*
Preventive measures	5.52 (3.07, 9.90)	<0.001*

Table 3 – Adjusted estimate of the odds ratio for the association between incomplete malaria treatment and Severe recurrent malaria using multivariable Logistic regression models (n=289)

Model	Variables	Odds Ratio (95% CI)	P-value
1	Malaria treatment	6.09 (3.47, 10.93)	<0.001*
2	Malaria treatment + employment status	5.76 (3.25, 10.41)	<0.001*
3	Malaria treatment + employment status + marital status	6.45 (3.56, 11.98)	<0.001*
4	Malaria treatment + employment status + marital status + nutritional status	12.84 (6.04, 29.64)	<0.001*
Final	Malaria treatment + employment status + marital status + nutritional status + preventive measures	10.62 (4.95, 24.54)	<0.001*

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