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Prevalence and severity of *Plasmodium* species among HIV infected and HIV noninfected children below 5 years in Kisumu, Kenya. *Prospective cohort study*.

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Abstract
Globally, about 3 billion individuals are at peril of contracting malaria disease annually. This disease load is intensified by the fact that about 2-3 million children are infected with HIV in sub-Saharan Africa. Malaria and HIV coinfection is rampant in the region and account for significant morbidity and mortality. Among the malaria causing parasites species, *Plasmodium falciparum* causes more severe form of malaria disease. This study determined prevalence of malaria disease by age, gender, residence; severity by species and its determinants among HIV infected and HIV non-infected children less than 5 years in Kisumu County. All the data analysis was conducted in Stata version 14. A total of 132 study participants were recruited with equal distribution of sero-status, HIV+ (n=66) and HIV- (n=66). The mean (SD) age of HIV -infected children was 3.01(0.95) years (range 1.5 – 5.0 years) while the SD age for the HIV non-infected children was 2.59 (1.21) years (range: 0.3 -5.0 years). Out of the 66 non-HIV infected children, 21.21 % (95%CI=0.13- 0.33) had *P. falciparum* and 6.06% (0.02 - 0.15) had *P. malariae*. Among the HIV infected children, 4.55% (95%CI=0.01 -0.13) had *P. falciparum* while 1.52 % (95%CI= 0.00 - 0.10) had *P. ovale.* The prevalence was highest in children 4 to 5 years old with 37.50 (95%CI=0.17 - 0.64) among HIV non-infected. Severity of disease was classified based on Lambaréné´ Organ Dysfunction Score (coma, prostration, or deep breathing), LODS >0 (2.27% (95%CI=0.01-0.07). The study concluded that LODS is a clinical predictor of severity of disease (malaria) and its assessment should be implemented by the primary healthcare provider. Similarly increased uptake of Cotrimoxazole prophylaxis coupled with methodical clinical check-ups contributed to the reduction in malaria infection in HIV infected children.

Keywords: Species, Malaria, HIV, Severe, Prevalence, relapse, LODS.

Background
Malaria is one of the most serious and complex health problems globally, and the state is crueler in Sub Saharan Africa. Over 80% of the cases of malaria worldwide occur in Africa, and especially in children(1). Both Malaria and HIV are widespread, but their distribution greatly overlaps in Sub Saharan Africa (2). Malaria is caused by infection with one or more of 5 species within the genus *Plasmodium; Plasmodium falciparum (P. falciparum), Plasmodium malariae (P. malariae), Plasmodium vivax (P. vivax), Plasmodium ovale (P. ovale),* and newly *Plasmodium knowlesi (or P. knowlesi)* (3), even though highest diseases and deaths are caused by *Plasmodium falciparum*(4). The existence of variation and inversion by other species especially in children and in HIV prevalent regions should not be wished away(5). The disease severity and the outcome depend on the species of the *Plasmodium*, similarity both (severity and outcome) is also affected by age, phenotype, immune defense, general health and nutritional status as well as existence of any chemoprophylaxis previously used. Most malaria disease in non-immune people are relatively severe but infections with P. *falciparum* may be deadly. However fatality less frequent with infection by *P. vivax* or *P. knowlesi* (6).
At the same time, the highest disease load of about 22.5 million persons living with HIV is found in low and middle income nations(7), where 2.25 million cases of clinical malaria

occur yearly (8). More than 70% of AIDS deaths and 90% of malaria-related deaths occur in SSA. Malaria and HIV interact bifacially with each other and the disease burden of the two disease are well documented in the region (9). Simultaneous coinfection could be about 30% where even tolerable interaction between the two in a populations could probably signifies the morbidity and mortality associated with these diseases in low and middle income countries(10). HIV infection reduces T-cell production and antibody responses which is important process for an effective antimalarial response. These therefore illustrates the attenuation of age-specific acquired malaria protection (11) (12) and more cases or severity of malaria infections observed in HIV-positive adults. It is also important to note that prophylactic treatment Cotrimoxazole (CTX) routinely given to HIV positive persons is presumed to provide somewhat protection from malaria infection by inhibiting the in vivo survival of some *Plasmodium* species (12).

Whether HIV infection predisposes the child to malaria in children under 5 years is unclear, with some studies suggesting that children who are HIV infected and on antiretroviral (ARV) or CTX are less prone to malaria infection, implying that CTX may provide protection to malaria infection to the children (13). Variation with respect to child age and the local malaria transmission patterns, and presence or lack of adaptive immunity to malaria infection may have contributed to the heterogeneity observed across studies (14). In addition, studies conducted early in the HIV epidemic have lacked association and causation since they are limited by the use of a cross-sectional or hospital-based case-control design (15). This cohort study was conducted prospectively among children less than 5 years who were HIV infected and HIV non-infected living in Kisumu County to determine prevalence and severity of malaria by species in the two cohorts over a three-month follow-up for each subject. The severity of malaria infection was estimated using Lambaréné Organ Dysfunction Score (LODS) which is clinical predictor of fatal malaria in children, it combined three key variables; coma, deep breathing and prostration. The LOD score relies on easily clinically visible signs with a minimum of 0 and a maximum of 3(each variable had a maximum score of 1) score points, showing the possibility of fatality respectively(16).The study also investigated the relationship between HIV status and duration between malaria relapses among children with ≥1 episode of malaria. We hypothesized that HIV infected children would develop both first and second malaria episodes sooner than HIV-infected children.

Methodology

Research design: This was a prospective cohort study design where data was collected from Kisumu County and Lumumba Sub-County hospitals both in Kisumu County, western Kenya. Male and female subjects below 5 years were recruited then followed up for 3 months.

Study population: The study population comprised of male and female children aged below 5 years with those who were HIV infected being the exposed group and HIV non infected as unexposed group. They were recruited from the comprehensive care centre (CCC) and the outpatient departments (OPD) of Kisumu County hospital and Lumumba sub county hospital in Kisumu County.

Sample size and sampling technique: Sample size was calculated at 132. Samples were selected and data collected via a structured questionnaire and case report forms (CFR) including the LOD Score during the scheduled visits and screening days.

Data collection: The structured questionnaire consisted of 3 parts, part A, giving child level risk factors, part B, depicting the caretaker level risk factors and part C, Showing the household level risk factors. Laboratory analysis done my examining blood film on a blood slide. A drop of blood was put on glass slide then spreader used to make a 3–5 mm in diameter as well as thin film on the same slide. The smear was air dried, thin film fixed with methanol. The slide was then stained with a Romanowsky stain for 15 minutes, washed with running tap water then allowed to air dry. The blood slide was then examined under a well-maintained microscope by a competent microscopist to detect malaria presence and for speciation. Calculation of malaria parasites was then done using the WHO Malaria microscopy manual-version 2 (17), as shown below;

$$\text{Parasites / } \mu\text{L blood} = \frac{\text{Parasites counted x 8000 WBC/}\mu\text{L}}{\text{Number of WBC counted.}}$$

Inclusion criteria	Exclusion criteria
1. Male and female child less than 5 years of age seeking health services from the comprehensive care clinic or outpatient department	1. Parent or guardian unwilling or unable to participate in the study.
2.mRDT negative on the screening/recruiting day	2. mRDT positive on the screening/recruiting day
3. Willingness of the parent(s) or guardian(s) to adhere to the study protocol.	3. Unwillingness of the parent(s) or guardian(s) to adhere to the study protocol.
4. Child who was confirmed to be HIV infected and was on CTX for the exposed group.	4. A child who is on CTX, but their HIV status is unknown (HEI)
5. The child who was HIV negative and was born of HIV negative mothers as control group	5. Child who is on any known malaria prophylaxis
6. Parent or guardian willing to consent to participate in the study.	6. A child who is participating in any malaria related clinical trial
	7. Any other condition clinical condition that may result in an unfavorable outcome should the subject participate in the study

Data management and analysis: Data cleaning and validation was performed in order to achieve a clean dataset that was exported from excel into a Stata version 14 for analysis (18). Exploratory data analyses were done at the initial stage to uncover the structure of data and identify possible outliers or unusual values. The threshold for statistical significance was $P < 0.05$ with corresponding 95% CI.

Ethical considerations: Ethical approval (ERC.1B/VOL.1/368) was obtained from Ethical Review Committee of JOOTRH and JKUAT. Written informed consent for participation in the study was obtained from the Subject's parents or guardians or legally acquired

representative (LAR). The study protocol was also explained clearly to the subjects in English or Kiswahili or local language (Dholuo) before signing the consent form.

Results

Socio demographic characteristics of the children and caretaker

A total of 132 study participants was recruited with equal distribution of sero-status, HIV+ (n=66) and HIV- (n=66). The average (SD) age of HIV -infected children was found to be 3.01(±0.95) years (range: 1.5 – 5.0 years) while the SD age for the HIV non infected children was found to be 2.59(±1.21) years (range: 0.3 -5.0 years). Out of 66 HIV infected children, 7 (10.61%) children less than two years old, 38(57.58%) 2 – 3.9 years old and 21(31.82%) 4 – 5 years old. Out of the 66 non-HIV infected children, 17(25.79%) were of age less than 2 years, 33(50.00%) were of age group 2 – 3.9 years and 16(24.24%) of age group 4 - 5 years. Majority 34(51.52%) of HIV -infected were male while 32(48.48%) were female. Half of the non-HIV infected children were male (Table 1).

The distribution of the children in terms of area of residence revealed that majority 49(74.24%) of the HIV infected children were staying in rural setups while majority 60(90.91%) of the HIV non infected children were staying in urban setups. Among the caretakers of the HIV infected children, 49(74.24%) were married, 12(18.18%) were single, 4(6.06%) were divorcee and 1(1.52%) was widowed. Among caretakers of the HIV non infected children recruited, 59(89.39%) were married, 6 (9.09%) were single and 1 (1.52%) was divorced. Majority 24(36.36%) of the caretakers of HIV -infected children had primary level of education, 22(33.33%) had secondary level of education, 12(18.18%) had tertiary and above as the level of education and 8(12.12%) had no level of education. Similarly, 1(1.52%) among the caretakers of the HIV non-infected children did not have any level of education, 10(15.15%) had primary level of education, 12(18.18%) had secondary level of education and 43(65.15%) tertiary level of education.

Majority 42(63.64%) of caretakers of the HIV infected children were self-employed, 12(18.18%) were formally employed and 12(18.18%) were unemployed. Among the caretakers of HIV non infected children, 27(40.91%) were unemployed, 29(43.94%) were self-employed and 10(15.15%) were formally employed. Majority 63(95.45%) of the HIV infected children were taken care of by their parents. Similarly, majority 65(98.48%) of the non-HIV infected children were taken care of by their parents. Distribution of the house occupants showed that household with a greater number of people was between 4-6 people. Among them 44 (66.67) were HIV infected arm while 36(54.55) was from the HIV non infected arm (Table 1).

Table 1: Socio demographic characteristics of the children and caretakers.

	HIV non infected children(n=66) (%)	HIV infected children (n=66) (%)
Age (in years)		
Minimum	0.3	1.5
Maximum	5.0	5.0
Mean (SD)	2.59(1.21)	3.01(0.95)
Age group (in years)		
<2years	17(25.76)	7(10.61)
2 - 3.9 years	33(50.00)	38(57.58)
4-5 years	16(24.24)	21(31.82)
Gender		
Male	33(50.00)	34(51.52)
Female	33(50.00)	32(48.48)
Area of residence		
Rural area	6(9.09)	17(25.76)
Urban area	60(90.91)	49(74.24)
Care giver marital status		
Married	59(89.39)	49(74.24)
Single	6(9.09)	12(18.18)
Divorced	1(1.52)	4(6.06)
Widow	0(0.00)	1(1.52)
Care giver Level of education		
Never	1(1.52)	8(12.12)
Primary	10(15.15)	24(36.36)
Secondary	12(18.18)	22(33.33)
Tertiary+	43(65.15)	12(18.18)
Care giver Employment status		
Not employed	27(40.91)	12(18.18)
Self-employed	29(43.94)	42(63.64)
Employed	10(15.15)	12(18.18)
Child's caretaker		
House help	1(1.52)	2(3.03)
Mother/Father	65(98.48)	63(95.45)
Relative	0(0.00)	1(1.52)
Number of people in the household		
1 - 3	27(40.91)	15(22.73)
4 - 6	36(54.55)	44(66.67)
7+	3(4.55)	7(10.61

Prevalence of malaria Species by HIV status

Out of the 66 HIV non infected children, 21.21 % (95%CI=0.13- 0.33) had *P. falciparum* while only 6.06% (0.02 - 0.15) had *P. malariae*. Among the HIV infected children, 4.55% (95%CI=0.01 -0.13) had *P. falciparum* while only 1.52 % (95%CI= 0.00 - 0.10) had *P. ovale* as shown in Table 2 below.

Table 2: Proportions of malaria species by HIV status.

	Non-HIV infected children (N=66)			HIV infected children (N=66)		
Species	**n**	**Proportion (%)**	**95% CI**	**n**	**Proportion (%)**	**95% CI**
P. falciparum	14	21.21	0.13- 0.33	3	4.55	0.01 -0.13
P. malariae	4	6.06	0.02 - 0.15	0	0.00	--
P. ovale	0	0.00	-	1	1.52	0.00 - 0.10

Prevalence of malaria by age gender, and area of residence.

Prevalence of malaria disease varied with age group, gender and area of residence. Among the non-HIV infected, the prevalence was highest in children aged 4 to 5 years 37.50(95%CI=0.17 - 0.64) followed by those aged 2 to 3.9 years old 21.21% (95%CI= 0.10 - 0.39) and 29.41% (95%CI=0.12 - 0.55) among children <2 years. For the HIV infected children, prevalence of malaria increased with an increase in age from 0% among children of < 2 years old to 2.63 % (95%CI=0.01 - 0.17) among children aged 2 to 3.9 years and 14.29% (95%CI= 0.04 - 0.37) among children aged 4 to 5 years.

Prevalence of malaria by gender revealed that among the HIV non infected children, there was a higher prevalence of 36.36% (95%CI=0.22 - 0.54) among male children than 18.18% (95%CI=0.08 - 0.36) among female children. However, for the HIV infected children, malaria prevalence was lower at 5.88% (95%CI= 0.01 - 0.22) among male children as compared to 6.25% (95%CI= 0.01 - 0.23) among female children.

There was higher malaria prevalence of 66.67% (95%CI=0.23 - 0.93) among HIV non infected children leaving in rural areas as compared to 23.33% (95%CI=0.14 - 0.36) among non-HIV infected children in urban areas. On the other hand, there was higher prevalence of malaria (6.12% (95%CI= 0.02 - 0.18)) among the HIV -infected children living in urban areas compared to 5.88% (95%CI= 0.01 - 0.34) for children that living in rural setups (Table 3).

Table 3: Prevalence of malaria by Age Gender, and Area of residence.

	HIV-non infected children		HIV infected children	
Factors	Proportion (%)	95% CI	Proportion (%)	95% Conf.
Age group				
>2	29.41	0.12 - 0.55	0.00	-
2-3.9	21.21	0.10 - 0.39	2.63	0.01 - 0.17
4.5	37.50	0.17 - 0.64	14.29	0.04 - 0.37
Gender				
Male	36.36	0.22 - 0.54	5.88	0.01 - 0.22
Female	18.18	0.08 - 0.36	6.25	0.01 - 0.23
Area of residence				
Rural	66.67	0.23 - 0.93	5.88	0.01 - 0.34
Urban	23.33	0.14 - 0.36	6.12	0.02 - 0.18

Severity of malaria (indicated by LODS, coma or prostration or deep breathing)

There were three severe symptoms of malaria identified in this study namely Coma, Prostration and Respiratory distress. The proportion for HIV non infected children with coma was found to be 2.27% (95%CI=0.01-0.07) which was the same as the proportion for those who had prostration. There was no LODs reported among HIV infected children. (Table 4)

Table 4: Severity of malaria by LODS (coma, prostration, or deep breathing).

	Non-HIV infected children (N=66)		HIV infected children (N=66)	
LODs	**Proportion (%)**	**95% CI**	**Proportion (%)**	**95% CI**
Coma	2.27	0.01-0.07	0.00	-
Prostration	2.27	0.01-0.07	0.00	-
Respiratory distress	0.00	-	0.00	-

During the study period, there was no case of recrudescence or relapse of malaria infection reported among the study subjects.

Discussion

Prevalence of malaria: This study has demonstrated a higher prevalence of malaria in the HIV non infected children than the HIV infected counterparts. This finding is contradicting a study done in Nigeria by Amodu *et al* (19) which concluded that malaria is common in HIV-infected children and that almost half of the sick HIV-infected children had severe of malaria. This significantly lowered prevalence of the disease among HIV-infected children compared with the non-HIV infected children was related to the low mean serum level of glucose in HIV-infected children since glucose is needed for parasite growth and survival(8) (20). The reduced prevalence among this cohort may also imply that ART which majority of the subject were on had some impact on malaria. Each study subject was followed up for a period of three months but the whole

study ran for one year, thus covering all the seasons in a year. It therefore confirms the holoendemic nature of malaria in this region, hence malaria prevalence in this region is independent of the on seasons. Generally, in regions bordering Lake Victoria, malaria disease is endemic (21).

Prevalence of *plasmodium* species: In addition to *P. falciparum*, which is the predominating species in this region, (19), this study also found *P. ovale* and *P. malariae* in study populations, where 21.21 % (95%CI=0.13- 0.33) had *P. falciparum* and 6.06% (0.02 - 0.15) had *P. malariae.* Among the HIV infected children infected with malaria, 4.55% (95%CI=0.01 -0.13) had *P. falciparum* while 1.52 % (95%CI= 0.00 - 0.10) had *P. ovale.* This study agrees with one done by Keiser *et al* that determined the impact of irrigation and as well as dams on the burden of malaria disease globally and regionally. The study reported ≥40% *P. falciparum* parasite rate burden in the overall population (22). Another study done by Patel *et al.* concluded that multiple factors could contribute to severe malaria including co-infections with HIV, bacteria, and nutritional deficiencies (23), even though the study did not consider these variants, the study partly disagrees with this finding. We did not diagnose any form of *P. vivax* amongst the study subjects though it is mostly prevalent outside Africa since most of the population possess the Duffy-negative phenotype, which protect red blood cell invasion by the parasite (24).

Prevalence of malaria by age: This study also revealed variation in prevalence of malaria across the age categories of the children. However, there was high prevalence in children of 4 to 5 years old among the HIV non infected children. Lin *et al*,.2010 in young Papua New Guinean children determined patterns of infection and malaria disease with *P. vivax* and *P. falciparum* concluded that exact nature of the processes underlying the observed difference in immune acquisition remain to be elucidated but differences in the interaction of parasite with the human red cell are likely to play key role (25). *P. falciparum* can escape spleen clearance through sequestration of infected RBC into microvasculature via binding of variant surface antigens (VSA) to a variety of host receptors.

Prevalence of malaria by residence: According to this study, the increased prevalence of malaria among the subjects living in rural residential areas than in urban areas could be explained by the fact that individuals living in rural areas minimal access to several amenities such as; proper formal settlements, near water bodies which are breeding sites for mosquitoes, education opportunities, accessibility to health facilities and so forth. In addition, most of the individuals living in rural areas live in poor housing conditions. Furthermore, study done by Legesse *et al*.,2019 to determine prevalence of malaria and associated risk factors among febrile children less than 5 years in Gamo-Gofa Ethiopian concluded that proximity of residence to stagnant water and the use of ITNs are the most dominant risk factors for malaria infection (26). This agrees with study done in Kenya by Sultan *et al.*,2017 which determined prevalence and the possible determinants of malaria parasites in children (27). Our study also agrees with Gaston *et al,*.2020 in Malawi who showed prevalence and factors associated with malaria in children less than 5 years of age, it proved that risk of contracting malaria disease reduced in children from mothers with higher education (28). This might be linked to socio-economic status, as educated individuals are likely to have better standard of living and comprehend health-related issues. Furthermore, it agrees with this study that the individuals with higher levels of education are likely to be employed or in business and therefore can easily access healthcare services or afford the use of other preventive measures such as indoor residual spray (IRS) among others. Our results are by and large consistent with the fact that the risk of contracting malaria disease is strongly associated with closeness to the breeding areas (29).

Lambaréné´ Organ Dysfunction Score (LODS): Study done by Helbok *et al* demonstrated that LODS is a good predictor of death among children admitted to the hospital with malaria diagnosed by simple clinical evaluation(16). This study on the hand has revealed that LODS is a good predictor of severe malaria and that most of the progression of disease from moderate to severe and fatal disease is mostly but not entirely restricted to *P. falciparum* species only. According to this study, LODS comprised of; Respiratory distress (acidotic breathing). The most important and common signs of severe malaria is the Kussmaul's breathing associated with increased inspiratory and expiratory chest excursion (30). Moreover, patients with acidosis may also illustrate deep labored breathing. However, in children it is important to note sustained nasal flaring and recession of the bony structures of the lower chest wall on inspiration. Study done by Patel *et al*,.2020 to determine predictors of outcome in childhood *Plasmodium falciparum* found that prostration resulting in the inability to sit unsupported or to be able to breastfeed in children less than 6 months. This can progress to a coma or lead to a seizure.

Limitations. we did not include hematological assays or blood culture to determine if the LODS above were associated with any bacterial infection or MUAC to determine the nutritional status of the children.

Conclusion

This study concluded that increased access to CTX prophylaxis and ART coupled with methodical clinical visits to health facility contributed to reduction in malaria infection in HIV infected children (31). Even though *P. falciparum* still predominate among the other common malaria species in Kisumu, the overall parasitic burden is on reducing trend in view of the escalated preventive measures. The increased accessibility to treatment facilities, will go a long way to curb the disease burden of malaria in children less than 5 years. The LODS is a simple clinical predictor tool for severe or fatal malaria in children. This score provides accurate and rapid identification of children in need of either referral or augmented attention. Assessment for a child for LODS (coma, deep breathing, and prostration) clinically should be noted by specialized health provider at the primary healthcare level.

Authors' contributions: JO developed the concept and designed the study protocol, data collection, entry, checking/cleaning and analyses as well as drafted the

manuscript. SK concept reviewed the manuscript and approved final manuscript. DK Supported the drafting of the manuscript.BO and EY were involved in the conception and design of the protocol and coordination as well as edited, reviewed and approved final manuscript. HA supported data collection, entry, checking and analyses and interpretation as well as drafted the manuscript.

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