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Km 58 Mbarara Fort-Portal Road, Box 324, **RC No: 144926.** sppj@spparenet.us ; Tel: +256782101486

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Retrospective evaluation of malaria parasites distribution among febrile patients attending clinics in Bushenyi, Uganda

Joram GO and *Agwu E

School of Allied Health Sciences, Kampala International University, Western Campus, Box 71, Ishaka, Bushenyi district, Uganda.

Correspondence: *E-mail: agwu@spparenet.org Tel: **256782101486 & +256703129679**

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Abstract

Background: Febrile illness due to malaria remains a public health challenge in resource-poor countries despite concerted control efforts.

Objectives: To establish a baseline database of *P. falciparum* distribution among febrile patients treated with chloroquine, fansidar, and quinine in Bushenyi.

Methods: Standard parasitology and statistics (α=0.01) methods were adopted in the analysis of data collected from 35,000 files of febrile patients who attended clinics in Bushenyi district, Uganda in the year 2005 after the first-line malaria treatment changed from chloroquine to artemisinin-based combination.

Results: There was 78.2% (27,384 of 35000) malaria prevalence among the studied 35000 febrile patients' files, while the percentage distribution of *P. falciparum* among 27,384 malaria patients included; 42.8% males and 57.1% females in Kitagata Hospital; 45.1% males and 54.9% females in Comboni Hospital and 39.8% males and 60.3% females in Ishaka Adventist Hospital. Females aged 41-50 and 21-30 in Ishaka Adventist Hospital had an overall prevalence of 69.5% and 68.7%, followed by 68.4% and 64.8% from participants aged 41-50 and 21-30 in Kitagata Hospital. The highest *P. falciparum* prevalence among males less than 10 years old was 54.2% in Comboni and 52.4% in Kitagata. Overall malaria prevalence between January-December 2005 was highest (72.6%) in Ishaka; 34.4% in Kitagata and 22.3% in Comboni hospitals respectively. Malaria prevalence was significantly ($p<0.01$) dependent on age, sex, and season.

Conclusion: In this retrospective study, *P. falciparum* pre-dominated (78.2%) malaria patients were treated with chloroquine, fansidar, and quinine. This may serve as a database for prospective evaluation

of malaria prevalence in the same location. Socio-demographic and poor socio-economic status significantly ($p<0.01$) influenced malaria spread in Bushenyi. The cause of *P. falciparum* malaria persistence among the studied population despite treatment warrants further investigation.

Keywords: Plasmodium falciparum, malaria patients, anti-malaria, Bushenyi,

Introduction

Febrile illnesses remain a significant public health challenge in developing and resource-poor countries despite the use of multi-disciplinary research approaches in its management, prevention, and control. Febrile illness due to malaria is among the most controversial vis-à-vis management, prevention, and control due to poor facilities and multidrug resistance which has made eradication a mirage in developing countries. Malaria is a vector-borne disease caused by the protozoa parasite of the genus *Plasmodium.* Out of four species of man (P*lasmodium falciparum, Plasmodium vivax, Plasmodium ovale,* and *Plasmodium malariae*), *Plasmodium falciparum* is the most common and most dangerous because it is associated with a severe form of malaria (1).

Malaria is common in all parts of Africa except in very high altitudes. Young children and pregnant women are mostly at the highest risk for malaria morbidity and mortality. The mortality rate is highest during the second year of life and by school age, a considerable degree of immunity has been gained and attack tends to be mild. About one million people in Africa die from malaria each year and most of these are children under 5 years old (2).

According to Steketee *et al.*, (3), three principal ways in which malaria contributes to death in young children include an overwhelming acute infection (which frequently presents as seizures or coma); repeated malaria infections (which contributes to the development of severe anemia), and low birth weight (the major risk factor for death in the first month of life).

Besides, repeated malaria infections make young children more susceptible to other common childhood illnesses, such as diarrhea and respiratory infections, and thus contribute indirectly to mortality (4). About 2% of children who recover from cerebral malaria suffer from learning impairments and disabilities due to brain damage, including epilepsy and plasticity (5).

Bushenyi district receives stable rainfall and is wet due to bimodal equatorial rain in March-June and October-November and Malaria seasonality mirrors this rainfall pattern (6). Research efforts to debunk the mysteries of malaria may still be a mirage because malaria is still highly endemic in most regions of Africa. Thus, in the last decades, malaria control and treatment have been complicated by the emergence of resistance to anti-malarial drugs. Half of the world's population is at risk of malaria and about 247 million cases led to nearly 881 000 deaths in 2006 (7).

Resistance to the anti-malarial drug, poor diagnostic facilities, and difficult geographical factors complicated malaria management in the Bushenyi district and necessitated a change in first-line antimalarial drug from chloroquine and sulfadoxine-pyrimethamine to artemether-lumefantrine or amodiaquine and artesunate with other regional government (8). There is no sentinel malaria survey in this region and to establish a good prospective study, there is a need to analyze the huge data generated by different health centers on yearly basis. Even before the old Bushenyi was divided into smaller districts for more effective administration, the endemicity of malaria was never in doubt. Therefore the need to establish a baseline database after the first-line malaria treatment changed from Chloroquine to artemisinin-based combination, cannot be over-emphasized.

The report of Ogah et al (9), is a pilot three months retrospective study conducted few months after Kampala International University Teaching Hospital was established was 29.8%. It is not clear if this result of the new Bushenyi may be extrapolated to represent the former Bushenyi now made of five districts namely Shema, Mitooma, Buhweju, Kyamuhunga, and Bushenyi. So for insight into the pattern of malaria distribution in the entire district, we also needed to analyze data generated before the old Bushenyi was divided. This study was designed to retrospectively determine the pattern (gender, age, and season) of malaria prevalence among febrile malaria patients treated with chloroquine, fansidar, and quinine in the Bushenyi district of Uganda with the ultimate goal of using the lesson to be learned from the outcome to design a better future prospective diagnosis, effective intervention, and a data which has policy implications.

Materials And Method

Bushenyi lies between 0^0N and $0^0$46'S of the equator and $29^0$41''E and $30^0$30' east of Greenwich. It has a population of 738,355, (51.7% are females and 48.3% are males); an altitude of 2400-3660 feet above sea level and a mean annual maximum temperature is 22.5-30^0C. Ishaka Adventist Hospital has 200 beds, Comboni Hospital has 90 beds and the hospital has about 120 beds. Ishaka Adventist Hospital is a missionary hospital (with subsidized services), located at the relatively highly populated center of Ishaka Town and is close to Ishaka Trading Center [which attracts people from nearby districts of Kasese, Mbarara, and Rukungiri for business] and the western campus of Kampala International University. Comboni Hospital is also a missionary hospital (with subsidized services) located in the hard-to-reach Kyamuhunga sub-region of Bushenyi District whereas Kitagata is a government-owned hospital found in the kitagata sub-county in Bushenyi district. The ethical review board of Kampala International University and Bushenyi District health division approved this survey. The management of the three hospitals which participated also consented for patient data to be used in this study.

This is a retrospective cross-sectional hospital-based one year survey of malaria prevalence among 35,000 febrile patients who received malaria treatment from three main hospitals in Bushenyi district (Ishaka Adventist hospital; Comboni hospital and Kitagata hospital) in the year 2005 before Bushenyi was divided into Shema, Mitooma, Kyamuhunga, Buhweju, and Bushenyi respectively. The 3 hospitals were selected because they collectively attend to over 60% of febrile patients in Bushenyi district; diagnosed malaria patients are given bed-rest to enable nursing officers to administer and monitor malaria drugs, have side laboratories where malaria tests are done for febrile and other tropical illnesses and have consistent clinical and laboratory malaria data for the year 2005. All attempts to include more recent data from the 3 hospitals were not possible because of poor information storage and retrieval methods, occasioned by the change in hospital policies in which patients are now allowed to go home with their files and because we water a database before Bushenyi was split into 5 districts.

Patient's data included hospital records indicating a presumptive clinical diagnosis of malaria during the first visit (up to seven days after admission) at the three participating hospitals and also, a laboratory record of the same patient microscopically diagnosed with malaria. Besides, the patient's data included must also contain the type of antimalarial drugs prescribed by the attending physician and treatment sheets indicating prescribed drugs were administered. Patients' data whose malaria was detected after seven days of hospital admission and laboratory data not confirmed by hospital records or hospital records not confirmed by laboratory data were excluded. Also excluded were patients' data which had no treatment sheet to have shown that the drug was administered.

The 3 selected hospitals detected and reported *Plasmodium* species using Giemsa-stained thick blood film and the species of *Plasmodium* were identified by the centers using Giemsa-stained thin blood film. The reliability of the clinical and laboratory data was hinged on the experiences of the Medical superintendents who made the clinical diagnosis and also on the experiences of the malaria microscopists who analyzed the blood samples. Data on anti-malaria usage by patients as recorded on the patient's files by the attending physicians were retrieved and analyzed. Data generated were analyzed using Statistical Package for the Social Sciences (SPSS) version 11. Pearson Chi-square test (α=0.01) was used to test the strength of association between malaria prevalence and age, sex, months, and hospital regions surveyed.

Results:

There was a 27,384 (78.2%) prevalence of malaria among the studied 35,000 case files of patients treated for malaria in the participating hospitals. Precisely, 3974 case files were from Kitagata Hospital; 6,097 case files were from Ishaka Adventist Hospital while 17313 case files were from Comboni Hospital respectively. From (Table 1), the most frequently used antimalarial agent across the surveyed district was quinine followed by fansidar, and lastly Chloroquine. In Kitagata Hospital, the use of fansidar (54.4%) was higher than quinine (45.6%). In Comboni Hospital, the use of Chloroquine (56.5%) was higher than quinine (43.5%) while in Ishaka Adventist Hospital; the use of fansidar (57.2%) was higher than quinine (42.8%). The relative Malaria prevalence was therefore significantly ($p<0.01$) dependent on the type of antimalarial drug available for administration and use by diagnosed patients.

In addition to the observed 78.2% relative malaria prevalence in this study, Table (2) depicts the average percentage distribution of *P. falciparum* among the studied population of known malaria patients to include: 42.8% male and 57.1% female in Kitagata Hospital (KH); 45.1% male and 54.9% female in Comboni hospital (CH) and 39.8% male and 60.3% female in Ishaka Adventist Hospital (IAH). Again females were generally more susceptible to malaria than males with females from age groups 41-50 years in Ishaka Adventist Hospital having the highest overall malaria prevalence of 69.9%. This was followed by 68.7% malaria prevalence in females aged between 21-30 years from Ishaka Adventist Hospital; 68.4% malaria prevalence in females aged 41-50 years from Kitagata hospital; 64.8% malaria prevalence in females aged between 21-30 years from Kitagata Hospital. The highest malaria prevalence in males was 54.2% in Comboni hospital and 52.4% in Kitagata Hospital from the age group of < 10 years (Table 1). Malaria prevalence was significantly ($p<0.01$) dependent on age and sex.

Finally, the data in (Table 3) shows that malaria distribution is fairly constant between April and December and with an average distribution of 21.9%. This is drastically reduced 12.6% between January and March probably reflecting a sharp decline in rainfall seen during this period every year. However dividing the year into 4 quarters of 3 months in each quarter, it was found that malaria prevalence during January-December 2005 was consistently highest in Ishaka; followed by Kitagata and then Comboni Hospitals. The highest overall malaria prevalence (72.6%) in Ishaka Adventist hospital was during October-December. This was followed by 68.1% reported in April-June; 60.1% reported in July-September and 43.4% reported in January-March all from Ishaka Adventist Hospital (Table 2). In Kitagata Hospital, the highest malaria prevalence (34.4%) was reported in January-March followed by 22.5% in July-September; 21.0% in April-June, and 16.7% in October-December. In Comboni the highest malaria prevalence (22.3%) was reported in January-March followed by 17.4% in July-September; 10.9% in April-June and 10.7% in October-December). Malaria prevalence was

significantly ($p<0.01$) dependent on months.

Discussion

Febrile illness has remained a public health challenge, especially in resource-poor countries despite the improved understanding of its epidemiology, management, and control. The incidences and public health importance of febrile illnesses are unknown in many African regions because of poor diagnostic facilities and polymicrobial involvement (11-12). Among the known agents of febrile illnesses such as malaria, typhoid, West Nile virus, and HIV, malaria has remained one of the most common public health challenge in Uganda and other geographically related sub-Saharan African countries due to multi-drug resistance, poor diagnostic, and prevention/control facilities (2, 12, 13, and 14). The widening divide between the malaria epidemic in developing countries and simple prevention and control measures warrants more studies to provide the necessary data needed to design effective result-oriented interventions

Therefore in this study, a 78.2% relative retrospective prevalence of *Plasmodium falciparum* among the studied population of 35,000 malaria patients treated with quinine, chloroquine, and sulfadoxine-pyrimethamine (Fansidar) in Bushenyi (Table 1) could indicate an endemicity of malaria parasites in this region is the result of prospective survey support this observation. Escalation of antimalarial drug resistance remains a challenge to malaria control efforts in developing countries (15) and Artemisinin-based combination treatments (ACTs) remain the recognized effective antimalarial available in many African countries. To prevent the development of artemisinin resistance, the short-acting artemisinin component is "protected" by a longer-acting partner drug of known high efficacy (16). The spread of *P. falciparum* was significantly ($p<0.01$) dependent on the type of antimalarial drug administered (Table 1).

From this investigation, it can only be said that 78.2% of malaria parasites were able to survive and/or multiply despite the administration and absorption of malaria drugs given in doses equal to or higher than those usually recommended but within the tolerance of the subject (17).

Table I: Distribution of antimalarial drugs in the treatment of 27,384 known malaria patients in 3 selected hospitals of Bushenyi District

N=35,000, p<0.01

		Number (%) people who received treatment		
Hospitals	No (%) prevalence	Chloroquine	Fansidar	Quinine
Kitagata	3974 (11.3)	*Not used*	2162 (54.4%)	1812(45.6%)
Comboni	17313 (49.5)	9782 (56.5%)	*Not used*	7531 (43.5%)
Ishaka	6097 (17.4)	*Not used*	3487 (57.2%)	2610 (42.8)
Total		**27,378 (78.2), p**<0.01		

Table 2: Age and Sex distribution of 27,384 positive malaria cases among febrile patients attending the three selected hospitals in Bushenyi District

	(Kitagata Hospital)			(Comboni Hospital)			(Ishaka Adventist Hospital)		
	No (%) positive			No (%) positive			No (%) positive		
(Age yrs)	(No Exam)	Male	Female	(No Exam)	Male	Female	(No Exam)	Male	Female
<10	2051	1075 (**52.4**)	976 (47.6)	6983	3791 (**54.2**)	3195(45.8)	3036	1543(**50.8**)	1493(49.2)
11-20	562	248 (44.1)	314 (55.9)	2665	1210 (45.4)	1455 (54.6)	920	395 (42.8)	526 (57.2)
21-30	457	162 (35.4)	295(**64.6**)	2462	1007 (40.9)	1455(59.1)	815	255 (31.3)	560 (**68.7**)
31-40	404	162 (40.1)	242 (59.9)	2457	1060 (43.1)	1397 (56.9)	509	198 (38.9)	311 (**61.1**)
41-50	285	90 (31.6)	195 (**68.4**)	1503	576(38.3)	927 (**61.7**)	370	113 (30.5)	257 (**69.5**)
51-60	170	79 (46.5)	91 (53.5)	736	317 (43.0)	419 (**57.0**)	265	93 (35.9)	172 (64.9)
>60	45	22 (49.9)	23 (50.1)	507	258 (**50.8**)	249 (49.2)	182	88 (48.4)	94 (**51.6**)
Average % prevalence		42.8%	57.1%		45.1%	54.9%		39.8%	60.3%

Age yrs = Age in years; No Exam = Number examined; % = percentage (X^2=881.9 & p<0.01), Total number is 35,000

Table 3: Monthly Distribution of 27,384 Positive Malaria Cases In 3 Hospitals of Bushenyi District

n=35,000; p<0.01

		Number (%) distribution of malaria cases		
Months	No (%) prevail	Kitagata	Comboni	Ishaka
January-March	4416 (12.6)	1516 (34.4)	985(22.3)	1915(43.4)
April-June	7483 (21.4)	1570(21.0)	813 (10.9)	5100(68.1)
July-September	7459 (21.3)	1677(22.5)	1297(17.4)	4485(60.1)
Oct-December	8026 (22.9)	1344(16.7)	858 (10.7)	5824(72.6)

Discussion

The in-depth perspective laboratory-based study is now highly needed to ascertain whether the observed 78.2% prevalence of *P. falciparum* was due to treatment failure caused by resistance to used antimalarial drugs (chloroquine, sulfadoxine-pyrimethamine, and quinine) or treatment failure simply due to insufficient blood concentrations of the drug, incorrect dosing, problems of patient compliance, poor drug quality, interactions with other drugs, inter-individual variation in pharmacokinetics including poor absorption, rapid elimination (due to diarrhea or vomiting), insufficient biotransformation of pro-drugs because of human genetic characteristics (17) and by misdiagnosis (10). Data made available by the participating hospitals clearly showed that poor patient's compliance may have played little or no part in causing the observed 78.2% relative prevalence of *P. falciparum* because participants were in-patients whose intravenous malaria drugs were administered by a nurse and oral drugs were taken under the supervision of a nurse.

Again all drugs administered were supplied by Uganda National dug authority and proper prescriptions made by attending clinicians ruling out incorrect dosing and poor drug quality as a factor for the observed 78.2% relative prevalence of *P. falciparum* among the studied population. Furthermore, some of the case files of malaria patients excluded from this study did not contain details of administered antimalarial drugs. To account for this population of excluded but important data, a prospective study is recommended whereby antimalarial drugs are assayed from the body fluids of patients to establish the types of drug taken, its concentration in the tissues, and their possible interaction with other drugs and individual variations in pharmacokinetics. A thorough prospective examination of Giemsa-stained thick and thin films by experienced microscopists in the side laboratories of all participating hospitals may confirm the accuracy of the 78.2% relative retrospective prevalence of *P. falciparum* in this survey. The recrudescent concept, where the parasites are not completely cleared from the bloodstream, may also help to explain the observed 78.2% prevalence of *P. falciparum* among the studied population.

Our observed overall 78.2% *P. falciparum* relative prevalence in this study, is in line with 70– 80% reported from Asia, other African countries, the Amazon region, and the Americas (1, 18-19). Besides, molecular elucidation of high failure rates of post-Fansidar treatment over the last 10 years has been well documented even in East Africa (20, 21-22). The observed 78.2% relative prevalence of *P. falciparum* may therefore point to the fact that malaria prevention and control in endemic areas like Bushenyi Uganda by direct chemotherapy and other allied protocols such as the use of dichlorodiphenyltrichloroethane (DDT) and environmental sanitation to break malaria parasite reproductive cycle need urgent re-evaluation to confirm the effective outcome. Strategies that will make mosquito's refractile to malaria parasite transmission are also an option that should be explored to achieve a malaria-free society.

The 54.2% *Plasmodium falciparum* distribution observed among the males under ten years of age in Comboni hospital is lower than 70% reported from a similar age group of HIV/AIDS patients in Nigeria (12). Table (2) also shows a 69.5% distribution of malaria parasites among the age group 41-50 years of age as different from the expected high distribution among children (23). The Spread of *P. falciparum* was significantly ($p<0.01$) dependent on the age and sex of the studied population (Table 1). It is not clear why malaria distribution among adults (41-50years) was higher than in those less than 10 years of age (Table 2). Underlying medical condition such as HIV/AIDS, geographical factors such as the location of residents near stagnant lakes and ponds surrounded by a banana plantation, sleeping without mosquito nets, the problem of re-infection, and occupational risk may have contributed to enhancing the proliferation of *P. falciparum* in the population who results were analyzed (24, 10, 12). Health status of a population, drug resistance, man-vector contact, malnutrition, mosquito longevity, and density may also account for malaria endemicity in a region (25)

It is very interesting to note that the distribution of malaria showed monthly or seasonal variation (Table 3) and the spread of *P. falciparum* was also significantly ($p<0.01$) dependent on the month and season of the year. Table (3) depicts a relatively stable and high malaria distribution between April and December which may be explained by the observed uniform distribution of rain between April and December each year. In Bushenyi, the malaria burden may be high between April and December, because of the availability of breeding sites for mosquito vectors commonly seen in water-logged areas, cesspools, swamps, and even around banana plantations found close to residential areas.

Despite the availability of insecticide-treated mosquito nets frequently seen in most homes, this retrospective study could not be used to confirm if these nets are properly utilized, and even when the intention to use these nets are established, the common practice of staying outdoors in social and

cultural gatherings and finally going to bed late (26) may ultimately explain the endemicity of malaria in Bushenyi district. This is because nobody goes to a nightclub and social functions while under a treated mosquito net neither does anyone watch television programs in the sitting room while under the mosquito net, thus highlighting some of the limitations of mosquito nets in the prevention of malaria in an endemic resource-limited setting.

Unfortunately, mosquito skin repellants which might have helped reduce the incidence of outdoor exposure to mosquito among the patients is not readily available in these localities and the few available ones are simply unaffordable. Bushenyi district, therefore, needs multidisciplinary studies that will combine behavioral science results with biomedical investigations and this is likely to produce results for use in the design of inclusive and effective result-oriented interventions which may help in rolling back malaria to the barest minimum.

Meanwhile, Ishaka Adventist Hospital had the highest overall malaria distribution followed by Kitagata Hospital and Comboni Hospital (Table 2). If development is measured by available social amenities, Ishaka town is then more developed than Kitagata which in turn is more developed than Comboni. The trend of decreasing malaria distribution between Ishaka, Kitagata, and Comboni further supports the notion that urbanization is a major factor that increases the rate of spread of mosquito and malaria in a community (12). From the observations of this study (Table 2), the lack of gross inadequacy of malaria control initiatives is obvious (27) emphasizing the need to strengthen local capacities in research to promote the regular assessment of malaria situations.

In conclusion, we report a 78.2% relative prevalence of *P. falciparum* among the malaria patients in the study population. This observation of relative malaria prevalence in retrospect warrants a prospective survey to establish and confirm disease trends in the study region. Malaria prevalence also was dependent on the season or months of the year in which the investigation was conducted. Socio-demographic (age and sex) and poor socio-economic status significantly ($p<0.01$) influenced malaria spread in the Bushenyi District. A prospective laboratory-based study is needed to confirm the course of treatment failure in this region.

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