EFFECT OF DEMOGRAPHIC AND SOCIO-ECONOMIC FACTORS ON OCCURRENCE AND CO-OCCURRENCE OF *PLASMODIUM FALCIPARUM* MALARIA AND ENDEMIC BURKITT'S LYMPHOMA AMONG CHILDREN IN WESTERN KENYA

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The Strategic JOURNAL of Business & Change MANAGEMENT
ISSN: 2312-9492 www.strategicjournals.com
Vol. 7, Iss. 4, pp 975 - 984 November 12, 2020. www.strategicjournals.com, ©Strategic Journals

EFFECT OF DEMOGRAPHIC AND SOCIO- ECONOMIC FACTORS ON OCCURRENCE AND CO-OCCURRENCE OF *PLASMODIUM FALCIPARUM* MALARIA AND ENDEMIC BURKITT'S LYMPHOMA AMONG CHILDREN IN WESTERN KENYA

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Accepted: November 11, 2020

ABSTRACT

Endemic Burkitt's lymphoma (eBL) is the most common cancer that affects children in Africa. Co-infection of re-current Plasmodium falciparum (P.falciparum) Malaria with Epstein- Barr virus (EBV) is among risk factors of developing eBL. The study compared methods used to diagnose Plasmodium falciparum malaria, EBV, eBL and effect of socio-economic factors on occurrence and co-occurrence of Plasmodium falciparum malaria and eBL among children in Vihiga and Kisumu sub-Counties. From each sub-County, the study assessed thirty homesteads using a questionnaire to collect data on socio-economic factors and ten health centers for the case-control study. Results obtained showed that methods used to diagnose Plasmodium falciparum malaria, EBV and eBL in Vihiga and Kisumu East sub-Counties were inadequate. Rapid diagnostic test and microscopy were the main laboratory methods used to diagnose P. falciparum in the study regions but were not available in all health centers used. EBV and eBL were mainly tested at KEMRI due to lack of facilities in the sub-Counties. P. falciparum malaria infection occurred more in children below five years old probably because of their low body immunity. Endemic Burkitt's lymphoma was more in children aged five to nine years old more likely because of early age co-infection of EBV and re-current Plasmodium falciparum malaria. The diseases were more prevalent in male than female children in both Vihiga and Kisumu East sub-Counties. Age had a statistically significant impact on co-occurrence of Plasmodium falciparum malaria and eBL where p-value = 0.004 for Vihiga sub-County and p-value = 0.048 for Kisumu East sub-County. Locations that had low occurrence of Plasmodium falciparum malaria also had low occurrence of eBL because the two diseases are correlated. Socio-economic factors influenced mosquito bites and they impacted only on occurrence of Plasmodium falciparum malaria in Vihiga sub-County. Chi—square, bar graphs and binary logistic regression were used to compare data variables where $p \leq 0.05$ results were considered statistically significant. To prevent development of eBL, malaria prevention and control programmes should be intensified and evaluated more regularly in the regions and in Kenya as recommended by Moormann in 2011.

Keywords: *Diagnosis, Re-current falciparum malaria, Epstien-Barr virus, Activation of B cell lymphocytes, endemic Burkitt's lymphoma, Demographic and socio-economic factors*

CITATION: Muzame, A. B., Ngeiywa, M., Makwali, J., Odada, P. S., & Mulama, D. (2020). Effect of demographic and socio-economic factors on occurrence and co-occurrence of Plasmodium Falciparum Malaria and Endemic Burkitt's Lymphoma among children in Western Kenya. *The Strategic Journal of Business & Change Management,* 7 (4), 975 – 984.

INTRODUCTION

Malaria is the main killer disease in global South Africa (AMREF). Endemic Burkitt's lymphoma (eBL) is a type of cancer that affect the B cell lymphocytes and it is mainly found among children in equatorial Africa and New Guinea which are poor countries (Burkitt, 1958, Ferry, 2006, World Health Organization (WHO), 2009 and Israel *et al.,* 2010). The name Burkitt's lymphoma (BL) was derived from a surgeon Dennis Burkitt who was working in Uganda (Kampala) where he observed children with swollen abdomen and swollen faces (Burkitt's, 1958, Ferry, 2006 and WHO., 2009). In 1961, Epstein an experimental pathologist and Dr. Burkitt discovered that there was a virus which was associated with eBL which they named Epstein -Barr virus. *Plasmodium falciparum* and Epstein-Barr virus (EBV) are infectious agents associated with eBL (Asito *et al*, 2010 and Mutalima *et al*., 2008). B cell lymphocytes which Epstein-Barr virus (EBV) infects play a very vital role in the production of antibodies during an infection (Chemtai, 2007).

Diagnosis of eBL and EBV requires expensive equipment which most developing countries such as Kenya cannot afford to buy for their public health centers (Biko *et al*, 2009 and Israel *et al*, 2010). Despite modern health techniques that are currently in use, endemic Burkitt's lymphoma still remains the main pediatric cancer that kills African children (Mutalima *et al., 2008* Isreal *et al., 2010*). The main cause of this type of cancer remains unknown although it is linked to co-infection of Epstein-Barr virus and re-current *P. falciparum* malaria (Chene *et al*., 2009). Endemic Burkitt's lymphoma is common among children of five to nine years old while malaria is more prevalent among children who are below five years old (Moormam *et al*, 2005 and WHO, 2011). Re-current *Plasmodium falciparum* malaria re-activates and proliferate the rather dormant EBV within DNA of B cells causing endemic Burkitt's lymphoma (Chene *et al.,* 2007 and Moorman *et al.*, 2011). Endemic Burkitt's lymphoma is more prevalent in *Plasmodium falciparum* malaria holoendemic areas (Ferry, 2006, Rainey *et al.*, 2007 b, Moormann *et al.,* 2007, and Israel *et al.*, 2010).

A lot of research has been done by scientists including members of EMBLEM but real cause of eBL is not fully known (EMBLEM, 2012). Factors associated with endemic Burkitt lymphoma include; *Plasmodium falciparum* malaria, Epstein-Barr virus, (Arora *et al*, 2005 and Moormann *et al.,* 2005), socio-demographic factors, malnutrition (Israel *et al.,* 2010) deficiency of: iron, vitamin A, and selenium (Mutalima *et al.*, 2008), social-cultural status, position of a child in a family since it is associated with last or second last born and immune-suppressed people such as HIV/AIDS victims (Chene *et al.,* 2009 and WHO, 2009).

Generally there seem to be no accurate data on eBL prevalence in Sub-Sahara Africa which may be due to misdiagnosis although childhood cancer mortality is estimated at 0.14 per 1000 children per year in this region with Burkitt's lymphoma (BL) accounts for 50% (World Health Organization, 2009 and Israel *et al*., 2010). Research carried out in; Kenya, Uganda, Tanzania, Nigeria, Malawi, Ghana, Senegal, South Africa and Morocco showed that one to seven children out of 100,000 children have eBL per year (WHO, 2009). In Kenya it has been reported that cases of eBL are 0.6 cases per 100,000 children per year with Nyanza province having 2.15 cases per 100,000 children per year (Moormann *et al., 2005* & Israel *et al.*, 2010). The children who had re-current *Plasmodium falciparum* malaria were also found to be having endemic Burkitt's lymphoma where polymerase chain reaction based on merozoites surface protein-2 was used to test average number of distinct genotypes (malaria biomarkers) per positive blood sample (Emmanuel *et al*., 2011). When there is re-current *Plasmodium falciparum* malaria infection, B lymphoid cells turn cancerous and results in tumors developing in lymph nodes causing African endemic Burkitt's lymphoma (Khamsi, 2007 & Chene *et al.,* 2009). This can lead to death if jaws are badly affected and the child is unable to eat (Ferry, 2006 and WHO, 2009). Research carried out in Blantyre in Malawi in 2005-2006 in the Pediatric Oncology Unit showed that, endemic Burkitt's lymphoma is related to Epstein-Barr virus and re-current *Plasmodium falciparum* malaria but association with human immunodeficiency virus (HIV) is not yet known

The Strategic Journal of Business & Change Management. **ISSN** 2312-9492 (Online) 2414-8970 (Print). www.strategicjournals.com

(Asito *et al*, 2010, Mutalima *et al.,* 2008 and Israel *et al.,* 2010). Research was conducted using interviews where 148 children were diagnosed with endemic Burkitt's lymphoma (children aged 15 years) and 104 controls used (Mutalima *et al*., 2008).Malaria re-infection may not re-activate EBV if one gets malaria before getting EBV infection because he or she will have acquired some immunity to malaria (Khamsi, 2007). Another research released by Piriou *et al* in 2012 early February showed that in Western Kenya, EBV infected infants and children at an early age of 6-28 months with repeated malaria infection developed endemic Burkitt's lymphoma (Moormann *et al*, 2005 and Rainey *et al*., 2007 a). In Nandi sub-County which is a less malaria holoendemic zone as compared to Kisumu sub-county there was less malaria and less endemic Burkitt's lymphoma prevalence (Moormann *et al.,* 2005 & Piriou *et al.,* 2012).

METHODOLOGY

Fever, headache, vomiting, loss of appetite, anemia, splenomegaly, feeling chilly and joint pains were used as clinical signs of the suspect malaria infection**.** Laboratory methods used blood from malaria suspected patients used to diagnose *Plasmodium falciparum* malaria were microscopy where field and rapid diagnostic test to test for *P. falciparum* antibodies in suspected malaria patients.

Clinical diagnosis of Epstein-Barr virus (EBV) was; fever, sore throat, swollen lymph nodes, swollen spleen and swollen liver where the disease is referred to as infectious mononucleosis. Epstein-Barr virus was diagnosed in the laboratory using saliva or blood of the suspected patients where EBV antigens were added to blood or saliva to test for EBV antibodies. Levels of antibodies lg M and antibodies lg G in blood of EBV infected people were elevated when EBV was re-activated causing infectious. Clinical diagnosis of endemic Burkitt's lymphoma (eBL) caused; swelling in; breast, liver, abdomen, jaws, kidney, ovaries, in lymph nodes and it also spread to the bone marrow or central nervous system. Abdominal pain, vomiting, nausea, palpable mass, acute appendicitis, weight loss, fever, renal failure and intestinal obstruction when abdomen and kidney are affected were also clinical presentation of eBL.

Source: Burkitt, (1958) Swollen Jaw Caused by Endemic Burkitt's Lymphoma

The diagnostic predictors in eBL diagnosis included biomarkers such as EBV viral loads, phenotype and function of specific EBV-T-cell immunity and EBV serological profiles. Laboratory diagnosis of eBL involved staging using laboratory, imaging and clinical examination test. Diagnosis of endemic Burkitt's lymphoma was done basing on histology, cytology and genetic (showing translocation in chromosomes causing C-myc mutation and immunophenotypic feature) where neoplastic cells were checked and presence of EBV done using human blood and saliva. It involved needle surgical, surgical biopsy and fine needles aspiration (FNA) to extract tissues from eBL infected body tissues done by pathologists for cytology to give a definitive diagnosis of eBL. FNA is cheap, safe and quick to perform than surgical biopsy. Tissues obtained from eBL body parts were aired or fixed with 95 % alcohol for cytologic examination.

Immunohistochemistry was used to measure B cell surface and cytoplasmic markers while translation mutation on chromosomes was done using cytogenetic markers mutation. Wright's stained air dried smears showed eBL cells of medium-size, round with several small basophilic scanty cytoplasm, round to ova nuclei with multiple small nucleoli per nuclear with clear numerous vacuoles in their cytoplasm. The cytoplasm appeared deep blue with giemsa stain, with multiple vacuole and cytoplasm which retracted with formalin fixation and rate of mitosis was very high (Burkitt, 1958 and Moormann *et al.,* 2007). Information on demographic and socio-economic was collected using a structured questionnaire were participants

were requested to sign the consent form before the research commenced.

RESULTS

Results obtained showed that clinical observation was used in both sub- counties to diagnose *P. falciparum* malaria, endemic Burkitt's lymphoma and Epstein - Barr virus. Laboratory diagnosis for *P. falciparum* malaria in Vihiga sub-county was done by rapid diagnostic test and microscopy. In Kisumu East sub-county beside RDT and microscopy, Aga Khan Hospital in Kisumu East sub-county also used ELISAs test to diagnose *P. falciparum* malaria and diagnosed eBL by histology. Endemic Burkitt's lymphoma was also diagnosed by histology at KEMRI laboratory found in Kisumu sub-county. Laboratory tests done on endemic Burkitt's lymphoma and polymerase chain reactions in the study regions were mainly done at KEMRI, Kisian, Kisumu County. Vihiga sub-county lacked facilities to diagnose eBL and EBV in the laboratories but it was done in some health institutions in Kisumu East sub-county with assistance of medical laboratory expertise from KEMRI, Kisian in Kisumu City. Polymerase chain reactions in Kisumu East sub-county were done at KEMRI which is found in Kisian, Kisumu County close to health centers used in Kisumu East sub-county.

Results showed that age of children used in case - control study had a statistically significant impact on co-occurrence of endemic Burkitt's lymphoma and *Plasmodium falciparum* malaria prevalence in Kisumu East sub-county (p-value 0.048) and in Vihiga sub-county (p-value = 0.004) as shown in Table 1. *P. falciparum* malaria was more prevalent among children below five years old in both sub-counties. EBL was more in children below nine years in Kisumu East sub-county and all children who had eBL in Vihiga sub-County were between five to nine years old. Both *P. falciparum* malaria and eBL were more prevalent among male children than female children in the study sub-counties (Table 1).

Table 1: Impact of Age and Gender on Occurrence and Co-occurrence of *P. falciparum* Malaria and Endemic Burkitt's Lymphoma in Kisumu East and Vihiga Sub-counties in Case-Control Study Using *Chi*-square

Sub-county		**Kisumu East**		**Vihiga**	
		P. falciparum	**eBL**	***P. falciparum***	**eBL**
N (Number of children)		**30**	**30**	**30**	**4**
Age	1. ≤ 5years old	22 (73.3%)	13 (43.3%)	22 (73.3%)	0 (0%)
	2. 5-9 years old	7 (23.3%)	13 (43.3)	6 (20%)	4 (100%)
	3.10-14 years old	1 (3.3%)	4 (13.3%)	2 (6.7%)	0 (0%)
Chi-value for co-occurrence of *P. falciparum* and eBL in age groups		P-value 0.048*		P-value 0.004*	
Sex	1. Male	23 (76.7%)	18 (60%)	23 (76.7%)	3 (75%)
	2. Female	7 (23.3%)	12 (40%)	7 (23.3%)	1 (25%)
Chi-value for co-occurrence of *P. falciparum* and eBL in male and female children		P-value 0.165		P-value 0.941	

Key: * Significant at p-value ≤ 0.05 Dependent Variables : *P. falciparum* malaria and eBL Independent variables : Age and Sex

Results obtained from research done showed that in Kisumu East sub-county, locations had a statistically insignificant impact on co-occurrence of endemic Burkitt's lymphoma and *Plasmodium falciparum* malaria (p-value = 0.242) as shown in figure 1. In Kisumu East sub-county Miwani and Kondele locations recorded low *P. falciparum* malaria prevalence and low eBL prevalence.

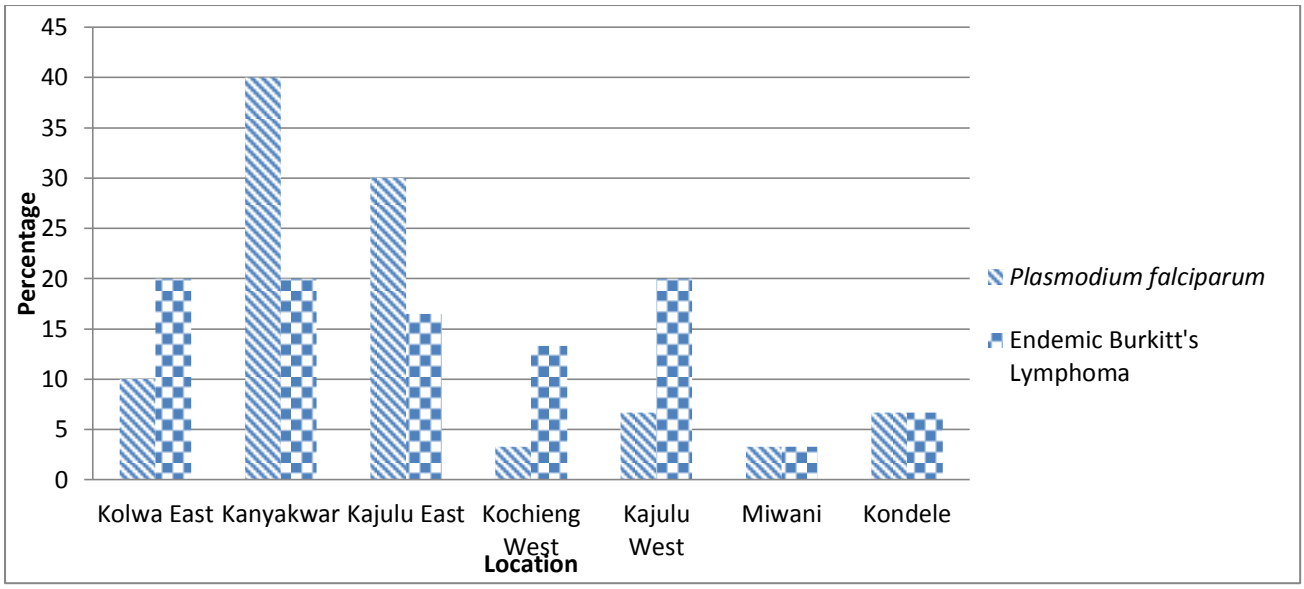

Figure 1: Percentages for Impact of Location on Occurrence of *P. falciparum* Malaria and Endemic Burkitt's Lymphoma in Kisumu East Sub- county

In Vihiga sub-county locations had a statistically insignificant impact on co-occurrence of endemic Burkitt's lymphoma and *Plasmodium falciparum* malaria (p-value = 0.917). Lugaga and Wamuluma locations in Vihiga sub-county had high prevalence of eBL and also had high prevalence of *Plasmodium falciparum* malaria (Bar graph).

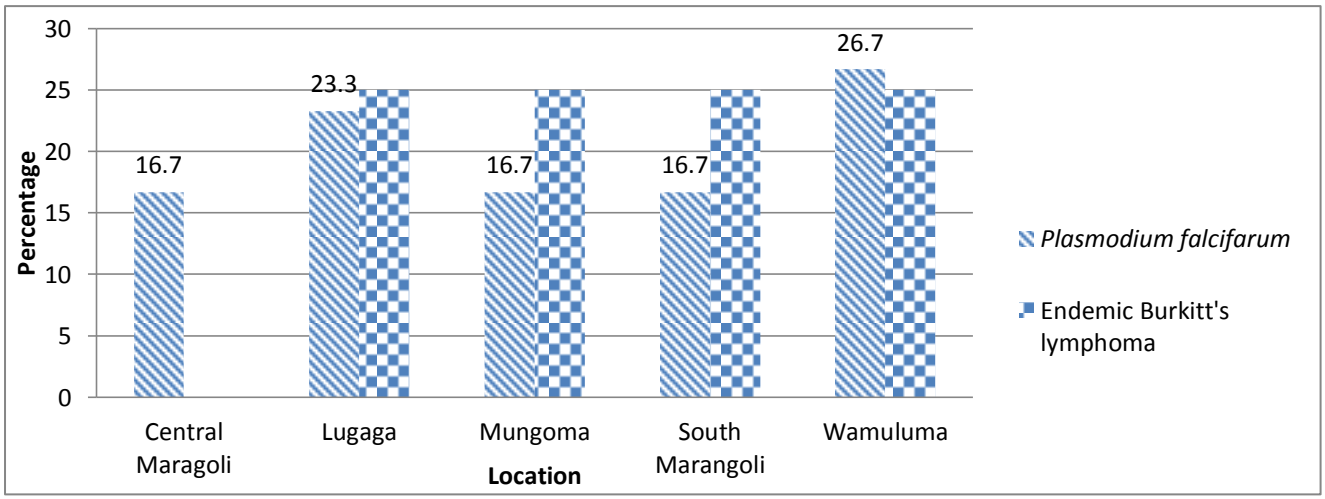

Figure 2: Percentages for Impact of Locations on Occurrence of *P.falciparum* Malaria and Endemic Burkitt's Lymphoma in Vihiga Sub-County

Results from study showed that economic status, household size, source of water, distance from source of water and vegetation at source of water (p-value 0.004, 0.041, 0.004, 0.005, and 0.030 respectively) impacted on occurrence of *P. falciparum* malaria in Vihiga sub-county as shown in Table 2. These individual socio-economic factors were found to be important determinants of malaria practices and knowledge which influenced participants to seek treatment early enough and reduce mosquito bites. Overall socio-economic factors which influenced malaria transmission had a statistically significant impact on occurrence of *P. falciparum* malaria in Vihiga sub-county where p – value = 0.025 while overall socio-economic factors had no impact on eBL (p-value = 0.118).

In Kisumu East sub-county ventilation that releases insecticide sprays and allowed mosquitoes access to inside houses p-value = 0.047 and distance from

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source of domesticated water that influenced exposure to mosquito bites p-value = 0.033 had a statistically significant impact on occurrence of *P. falciparum* malaria. Economic status p-value = 0.031, residence p-value = 0.018, ventilation p-value = 0.034 and distance from source of domestic water p-value = 0.049 had an impact on occurrence of eBL in Kisumu East sub-county. Overall Socio-economic factors had no impact on occurrence of eBL and *P. falciparum* malaria in Kisumu East sub-county (p-value= 0.349 and p-value = 0.349 respectively) as shown in Table 2.

Table 2: Binary Logistic Regression Results Showing Impact of Socio-economic Factors on Occurrence of *P. falciparum* malaria and eBL in Vihiga and Kisumu East sub-Counties

Sub-County	Vihiga		Kisumu East	
	P. falciparum	eBL	*P. falciparum*	eBL
Socio-economic factors	P-value		P- value	
Education	0.203	0.397	0.219	0.189
Economic status	0.004*	0.919	0.242	0.031*
Residence	0.642	0.340	0.332	0.018*
Land size	0.346	0.122	0.718	0.282
Household size	0.041*	0.423	0.176	0.387
House type	0.768	0.543	0.486	0.369
Doors/windows	0.613	0.263	0.047*	0.034*
Plants in compound	0.383	0.853	0.085	2.652
Domestic Water source	0.004*	0.063	0.603	1..311
Distance from water source	0.005*	0.190	0.033*	0.049*
Vegetation at water source	0.030*	0.389	0.493	0.122
Constant	0.467	0.149	0.277	0.149
Overall	0.025*	0.118	0.081	0.349

Key: * Statistically Significant at $p \leq 0.05$.

Dependent variables: eBL and *P. falciparum* malaria, Independent variables: socio-economic factors.

DISCUSSION AND CONCLUSION

Kisumu East sub-county is a malaria endemic zone with malaria transmission throughout the year while Vihiga sub-county is a highland malaria epidemic zone with seasonal malaria transmission. This explains why there were more eBL cases and *Plasmodium falciparum* malaria infected children in Kisumu East sub-county as opposed to Vihiga sub-county. Children in malaria Lake endemic zones are more prone to malaria attacks as compared to those in highland epidemic malaria zones. *P. falciparum* malaria was more prevalent among children below five years old in both sub-counties probably because of low body immunity among these children. EBL was more in children below nine years in Kisumu East sub-county and all children who had eBL in Vihiga sub-county were between five to nine years old. EBL cases in this age group could have been due to co-infection of repeated malaria infection and early age infection of EBV which increased risks of developing eBL in these children.

P. falciparum malaria led to re-activation and proliferate of EBV latently infected B cells and may have also suppressed EBV- specific cell immunity causing eBL. This resulted in infectious mononucleosis and it explains why elevated EBV antibodies were seen among eBL patients. Both *P. falciparum* malaria and eBL were more prevalent among male children than female children in the study sub-counties due to difference in genetic make-up among different sex. *P. falciparum* had been treated in some patients who had eBL and that is why it was detected in some eBL patients but not others. Records in health institutions used showed eBL patients had re-current *P. falciparum* and infectious mononucleosis before developing eBL.

Overall socio-economic strategies used which determined malaria transmission impacted only on *Plasmodium falciparum* malaria in Vihiga sub-county. Economic status (income or poverty) in the study areas was related to malaria transmission since it had a bearing on type of house, education, size of land and disease treatment and management which impacted on occurrence of *Plasmodium falciparum* malaria infection in Vihiga sub-county. High income made people to be in a position to go for better medical attention, spray their houses regularly with insecticides and buy enough mosquito bed nets for the family members which poor people could not afford in Vihiga sub-county. Houses without ceiling board and with many windows and doors for ventilation allowed mosquitoes to gain entry into the house impacting on occurrence of *Plasmodium falciparum* malaria infection in Kisumu East sub-county.

Methods used to diagnose *Plasmodium falciparum* malaria, endemic Burkitt's lymphoma and Epstein-Barr virus in Vihiga and Kisumu East sub-counties were inadequate. There are chances of misdiagnoses of diseases due to lack of laboratory facilities to confirm the suspected diseases which include; malaria, eBL and EBV. Both endemic Burkitt's lymphoma and falciparum malaria were more common among male children than female children. Falciparum malaria was more among children below five years while Ebl was more common among children between 4-9 years old. Overall socio-economic factors used in the study had an impact on only occurrence of *P. falciparum* malaria in Vihiga sub-county. *P. falciparum* malaria occurrence in Kisumu East sub-county and eBL occurrence in both study sub-counties were not affected by overall socio-economic factors used. Malaria control strategies used in both Vihiga and Kisumu East sub-counties were not well implemented in reducing occurrence of *P. falciparum* malaria and eBL. Locations that had low prevalence of *Plasmodium falciparum* malaria also had low prevalence if eBL since the two diseases are correlated.

Malaria projects and programmes should be emphasized, monitored and evaluated regularly for people to have a positive attitude and more knowledge towards malaria control in the two study regions and other parts of Kenya. Parents should be educated on importance of taking their children for routine medical check-up. The government should consider educating people on net treatment campaign because many bed nets in use were torn and not re-treated with insecticides and more insecticide treated bed nets should be taken to malaria endemic zones such as Kisumu County. When there is a co-infection between *P. falciparum* malaria re- infection and Epstein-Barr virus risks of developing endemic Burkitt's lymphoma tended to increase among children in the study area. Free malaria treatment should be given in public health centers where most poor people get their treatment and the government should have more health personnel in order to reach the remote areas and give malaria treatment which may reduce endemic Burkitt's lymphoma prevalence.

Abbreviations and Acronyms

MREF – The African Medical and Research Foundation
CDC- Centre of Disease Control and prevention
CIDRI- α- Cystein-rich inter-domain region alpha
DEET - Diethyl-meta-toluamide.
DEPA- Dimosia Epichirisi Paroxis Aeriou.
DFID – Department for International Development
DNA-Deoxyribose Nucleic Acid
DOMC - Division of Malaria Control.
EBL/eBL- endemic Burkitt's Lymphoma.
EBV - Epstein - Barr Virus.
ELISAs -Enzyme-Linked Immunosorbent - Assay
EMBLEM - Epidemiology of Burkitt's Lymphoma in East-African Children and Minors
HIV- Human Immunodeficiency Virus
KEMRI – Kenya Medical Research Institute
LLINS- Long-Lasting Insecticide Nets
ITNS - Insecticide-Treated Nets.
IRS - Indoor Residual Spraying.
JOORTH -Jaramogi Oginga Odinga Teaching and Referral Hospital
PfEMP - *Plasmodium falciparum* erythrocyte membrane protein.
PMI- President's Malaria Initiative.
SAA - Surface Active Agents.

USAID - United States Agency for International Development.
WHO - World Health Organization.

Ethical Issues

Since the study involved gathering medical reports from health institutions, interviewing patients, their guardians, their parents and general public, it was a must that an ethical approval be obtained which was done at Jaramogi Oginga Odinga Teaching and Referral Hospital, Kisumu. Sample numbers were used to conceal the identity of the respondents and patients instead of using their names and information volunteered in interview and questionnaire was kept confidential and solely for research purpose where participants signed the consent form before the study commenced. All sources of secondary data used in this study were acknowledged.

Acknowledgments

We would like to thank all those who contributed to the completion of this thesis. A great deal of appreciation to; Dr. Moses, M. Ngeiywa, Dr. Judith, A. Makwali, Dr. Sumba, P. Odada for their advice and encouragement during the study. Dr. Mulama David assisted in advising and publication of this research. We acknowledge the contribution of all lecturers in the Department of Biological Science under the leadership of the Chairman Dr. Elizabeth, W. Njenga who immensely contributed towards academic growth. We would also like to sincerely thank the staff of Jaramogi Oginga Odinga Teaching and Referral Hospital for enabling us get an ethical review letter which was used to collect research data. Appreciation to all staff members of the twenty health institutions we used to collect case and control population data and to diagnose *Plasmodium falciparum* malaria, Epstein-Barr virus and endemic Burkitt's lymphoma in Vihiga and Kisumu East sub-counties. We also thank all the thirty homesteads we used in each study sub-County to collect data on impact of socio-economic factors and impact of malaria control strategies on occurrence and co-occurrence of *Plasmodium falciparum* malaria and endemic Burkitt's lymphoma in the two sub-Counties by filling the questionnaire. Lastly, We wish to thank Abisay Mudaki, Tracy, Wancy, Clancy and Percy for moral support and encouragement they gave.

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