


Risk factors for Burkitt lymphoma in East African children and minors: A case-control study in malaria-endemic regions in Uganda, Tanzania and Kenya

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Endemic Burkitt lymphoma (eBL) is the most common childhood cancer in sub-Saharan African countries, however, few epidemiologic studies have been undertaken and none attempted enrolling cases from multiple countries. We therefore conducted a population-based case-control study of eBL in children aged 0–15 years old in six regions in Northern Uganda, Northern Tanzania and Western Kenya, enrolling 862 suspected cases and 2,934 population controls (response rates 98.5–100%), and processing ~40,000 vials of samples using standardized protocols. Risk factor questionnaires were administered, and malaria period prevalence was measured using rapid diagnostic tests (RDTs). A total of 80.9% of the recruited cases were diagnosed as eBL; 61.4% confirmed by histology. Associations with eBL risk were computed using logistic regression models adjusted for relevant confounders. Associations common in at least two countries were emphasized. eBL risk was decreased with higher maternal income and paternal education and elevated with history of inpatient malaria treatment >12 months before enrollment. Reporting malaria-attributed fever up to 6 months before enrollment and malaria-RDT positivity at enrollment were associated with decreased eBL risk. Conversely, reporting exposure to mass malaria suppression programs (e.g., indoor residual insecticide) was associated with elevated risk. HIV seropositivity was associated with elevated eBL risk, but the relative impact was small. The study shows that it is feasible to conduct networked, multisite population-based studies of eBL in Africa. eBL was inversely associated with socioeconomic status, positively associated with inpatient malaria treatment 12 months ago and with living in areas targeted for malaria suppression, which support a role of malaria in eBL.

Key words: Burkitt lymphoma, non-Hodgkin lymphoma, epidemiology, Epstein-Barr virus, *Plasmodium falciparum* malaria, HIV/AIDS

Abbreviations: CI: confidence interval; EA: enumeration area; eBL: endemic Burkitt lymphoma; EBV: Epstein-Barr virus; EMBLEM: Epidemiology of Burkitt Lymphoma in East African Children and Minors; HIV: human immunodeficiency virus; IRS: indoor residual spraying; OR: odds ratio; *Pf. Plasmodium falciparum*; pfPR: *Plasmodium falciparum* prevalence; RDTs: rapid diagnostic tests

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What's new?

Endemic Burkitt lymphoma (eBL) is the most common childhood cancer in sub-Saharan Africa, but there have been few epidemiologic studies. In this multi-country analysis, the authors used harmonized protocols to investigate infectious, environmental, and other risk factors for eBL. Socioeconomic status and recent malarial fever were associated with reduced eBL risk, while HIV infection, previous malaria, and living in areas targeted for malaria suppression increased eBL risk. These results provide new baseline data regarding eBL epidemiology, indicating that malaria may play a role. They also confirm the feasibility of multi-site, population-based enrolment for crucial future eBL studies.

Introduction

Endemic Burkitt lymphoma (eBL) is a life-threatening B-cell lymphoma that occurs relatively commonly ($\sim 50/10^6$)¹ in children in some countries in equatorial Africa and sporadically elsewhere ($\sim 1/10^6$).² Deleterious chromosomal translocations that place coding regions of *c-MYC* under regulatory control of immunoglobulin enhancer elements³ are considered primary genetic events both in endemic and in sporadic BL.⁴ Epstein-Barr virus (EBV) and *Plasmodium falciparum* (Pf) malaria are considered cofactors that either increase genetic instability in B cells or increase the systemic load of abnormal B cells, thereby increasing the incidence and skewing of the geographical distribution of BL cases.⁵ Few epidemiologic studies of eBL have been conducted, highlighting rural residence,⁶ frequent malaria attacks, lack of access to mosquito bed nets,^{7,8} having three or more siblings, sharing a bed with siblings, living in a non-monogamous family and having a deceased parent⁹ as risk factors for eBL. These risk factors share low-socioeconomic status as a common characteristic in eBL children.⁹ The mechanism of socioeconomic status for modulating eBL risk is by modulating the intensity of malaria exposure to the children¹⁰ and/or the age of EBV infection.¹¹ However, these studies have suffered some limitations, notably, their small sample sizes, not enrolling representative cases or controls, not measuring malaria infection at the time of enrollment, and largely failing to collect biospecimens suitable for use with current proteomic assays or obtaining permission for genetic studies. None recruited from multiple, networked sites, thus, the feasibility of this approach to study to conduct better powered studies eBL in Africa is unknown.

Therefore, we enrolled suspected eBL cases and population-based controls in six rural malaria-endemic areas in Northern Uganda, Northeastern Tanzania and Western Kenya (Fig. 1) in the Epidemiology of Burkitt Lymphoma in East African Children and Minors (EMBLEM) study during 2010–2016.^{12,13}

Methods**Study area, design and population**

Suspected eBL cases aged 0–15 years old were recruited at six local district or regional hospitals serving a population living in defined geographic areas illustrated in Figure 1. The ecosystem in the geographic area was characterized by lakes, rivers and swamps, and supports perennial but variable holoendemic malaria transmission

for >6 months in the year,¹⁴ except in parts of Kenya where malaria is seasonal and lasts for shorter durations.¹⁴ The selected geographic areas have historically had notable BL endemicity.^{12,15} We considered several choices of controls, including health-facility, school or neighborhood controls. Health-facility controls were rejected because they were markedly younger than eBL cases (2.2 years vs. 7.0 years) and were significantly more likely to have malaria symptoms when they were encountered at the health facilities.¹⁶ School-based controls were rejected because nonschool going children, who represent a significant proportion of children at risk of eBL, would be excluded from this sampling frame.¹⁶ Neighborhood controls were considered but rejected because of logistical challenges required to maintain consistent quality of work (a control can only be enrolled after a case has been encountered) across multiple sites in different countries and concerns about low response rates.¹⁶ Therefore, we enrolled population-based controls of a similar age distribution as the cases sampled from 300 random villages (100 villages per country) selected from national census roster according to urban/rural status and proximity to water, as previously described.^{12,13} The key assumption of this approach was that children residing in the same area as the cases would be exposed to similar exposures when broadly matched for age, geography and sex.¹⁶ Before sampling, villages in the census roster were categorized as “rural” based on having a census enumeration area (EA) population count of children below 15 years being less than the EA mean population count, otherwise as “urban.”^{12,13} Villages were further classified as near water (swamp, river or lake) based on the EA boundary being within 500 m of surface water, otherwise as far from water based on geographical information maps.

To ensure that cases and controls had been exposed to malaria, eligibility was restricted to children aged 0–15 years old who were usual residents (≥ 4 months prior to enrollment) of the study area. Because our study was conducted in rural areas, where in- and out-migration is relatively low, we did not encounter children who were recent immigrants into the study area. Children who were usual residents of another village in the study area as defined in Figure 1 were considered eligible. Cases were defined histologically or cytologically, and when this was not possible, according to clinical features, imaging and laboratory results compatible with a diagnosis of eBL. To increase ascertainment and encourage referral of suspected cases to the six participating hospitals, carefully designed, culturally appropriate health education messages

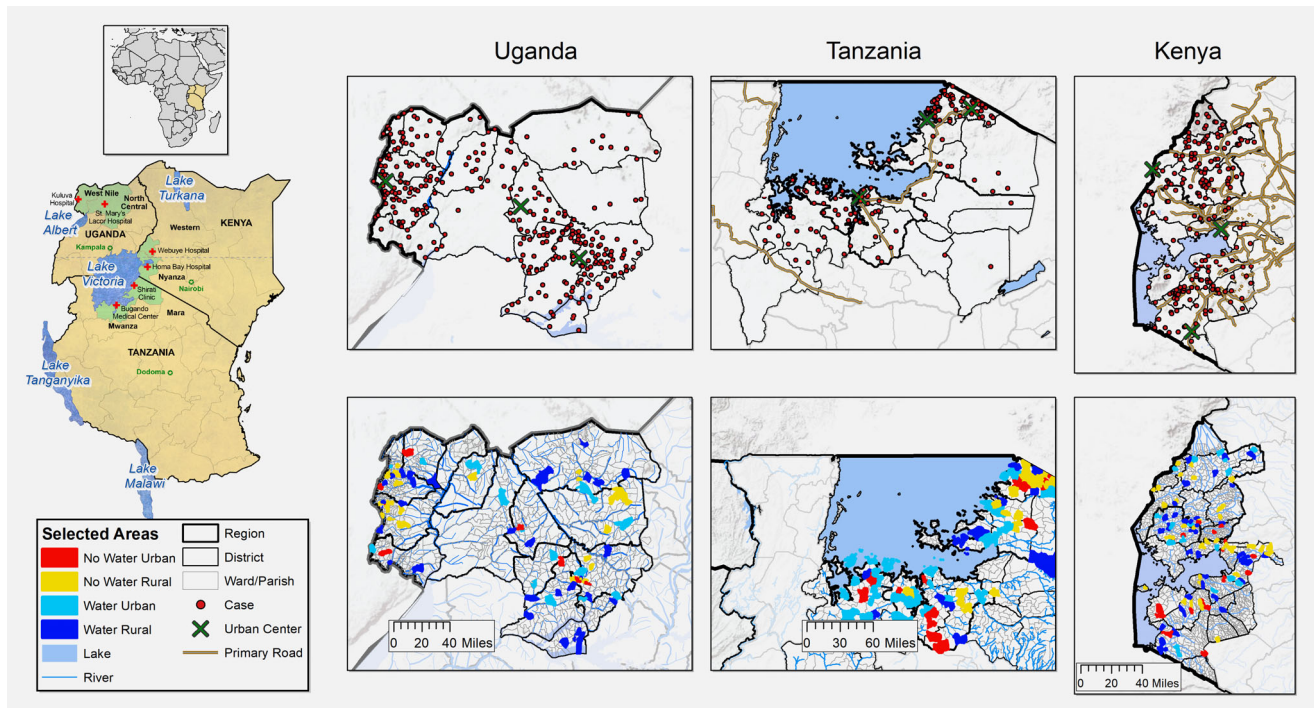


Figure 1. Map showing the EMBLEM study area marked with green shading and the participating hospitals marked with a red cross (St. Mary's Hospital, Lacor and Kuluva Hospital in Northern Uganda; Bugando Medical Center and Shirati District Hospital in Northern Tanzania; Homa Bay District and Webuye District Hospitals and Moi University Teaching and Referral Hospital in Western Kenya). Two regions were selected per country. A locator map shows East Africa within Africa. Multi-panel maps show the zoom out of the study areas for each country. The bottom row shows the relief features, including rivers and the location of 100 villages randomly sampled per country as a source of matched population controls. The sampled villages are indicated according to their stratification category, that is, proximity to water and population density (see "Methods" section). The upper row shows the geographical distribution of the cases that were enrolled in the EMBLEM study plotted within their district of origin (large urban centers are marked on the map). The primary all season roads serving the study areas are included to give a rough idea of the geographical dispersion of cases in relation to the villages where the matched population controls were sampled and the transport infrastructure in the study areas. [Color figure can be viewed at wileyonlinelibrary.com]

about eBL were developed and disseminated in the study area, stressing the availability of facilitated pathology diagnosis and treatment.¹⁷

The primary data were collected by interviewers following standardized protocols. The data study encompassed individual- and household-level risk factor questions, including age, sex, parental and household exposures, history of inpatient and outpatient malaria treatment, malaria-related and unrelated fevers and use of indoor residual spraying (IRS) in the house, insecticides and mosquito bed nets.^{12,13} The questionnaires were designed in English at the National Cancer Institute and approved by the Technical Evaluation of Questionnaires Committee of the Division of Cancer Epidemiology and Genetics. They were then translated into Swahili and three Luo languages (Acholi, Madi and Lugbara) that are widely spoken in the region. The season of case or control enrollment was classified as wet or dry, based on country-specific calendars. All subjects provided venous blood specimens (collected pretreatment in the cases) for research (10 ml) and for clinical tests (4 ml) in EDTA tubes. Clinical specimens were immediately examined by light microscopy for asexual malaria parasite forms and for malaria antigens

(HRP-2 and pan-LDH) using commercial malaria rapid diagnostic tests (malaria-RDTs).^{12,13} Malaria antigens remain detectable by RDTs for 35–42 days after treatment of symptomatic malaria.¹⁸ Human immunodeficiency virus (HIV) infection was assessed using three approved commercial RDTs (Determine HIV1/2, Stat Pack, Unigold commercial kits) following National Guidelines. Two concordant positive test results were required to give a participant a positive result and refer them to local counseling and treatment centers.

Research samples were transported in cold boxes to field laboratories within two hours of collection and centrifuged for 15 min at 1300g to separate into plasma, buffy coat and red cell fractions for storage at -80°C . About 40,000 vials of samples were processed, and half of the vials (one-half from each subject) were shipped under liquid nitrogen vapor to the Frederick National Cancer Laboratory, Frederick, MD.

Data quality

The success of the study was dependent of harmonization of procedures, taking into account prior lessons about eBL epidemiology^{16,19} and pathology.¹⁷ Research infrastructure to

support high-quality data and biological sample collection was established and nested within the local health systems.²⁰ Full-time field staff were hired to implement the study in the three countries and trained by the same instructors at Makerere University College of Health Sciences in Uganda. Compliance with standard protocols was monitored through weekly teleconference calls, periodic field visits and biennial joint investigator-staff meetings.²⁰

Questionnaires and laboratory forms were processed at the field offices using DataFax, a technology that uses character recognition software to extract data from customized, barcoded forms to generate electronic spreadsheets, to reduce data entry errors. This eliminated the need for double manual entry and reduced the number of computers and data clerks needed to process data. Computerized data were reviewed centrally and corrected before generating analysis files.

Ethical issues

The study was approved by Uganda Virus Research Institute Research and Ethics Committee, Uganda National Council for Science and Technology (H816), Tanzania National Institute for Medical Research (NIMR/HQ/R.8c/Vol. IX/1023), Moi University/Moi Teaching and Referral Hospital Institutional Research and Ethics Committee (000536) and in the US by National Cancer Institute Special Studies Institutional Review Board (10-C-N133). Written informed consent was given by guardians; children aged 7 years or older assented.

Statistical methods

Analyses were performed separately for each country, and then with the data from the three countries combined. Associations of eBL risk with questionnaire variables and period prevalence for malaria, based on malaria-RDT positivity, were based on odds ratios and 95% confidence intervals (ORs, 95% CIs) adjusted for age (0–2, 3–5, 6–8, 9–11, 12–15 years), sex and village characteristics (rural/urban or proximity to surface water; “baseline models”) and further for variables with a $p < 0.05$ when added to the baseline models (SAS Institute, Cary, NC). Six other variables about animal exposures, not included in this article but previously found to be associated with pfPR,^{12,13} were additionally included in the multivariable models.

We minimized collinearity between variables by dropping one variable of any pair with a Spearman correlation coefficient (ρ) > 0.6 (2 pairs in Uganda; 1 pair in Tanzania; and 2 pairs in Kenya), based on having a lower p -value or based on other *a priori* considerations. Stratified analyses were performed to evaluate the impact of including clinical cases and of enrolling cases from rural vs. urban villages. Our study was conducted to generate a new resource for eBL research, and the current analysis was conducted to generate baseline data to explore hypotheses; thus, we did not adjust for multiple comparisons, and a two-sided $p < 0.05$ was considered significant. To reduce dangers of overinterpretation of our results,

we place greater emphasis on findings that were consistent in at least two countries.

Results

Of 862 suspicious cases recruited, 697 (80.9%) were enrolled as eBL; 428 (61.4%) with histological confirmation. We excluded 165 suspicious cases (135 from Uganda, 12 from Tanzania and 18 from Kenya) after histological or clinical review. Of the 2,970 population-based controls approached, 2,934 (98.8%) were enrolled; 36 controls (Uganda = 17, Tanzania = 5 and Kenya = 14) refused to participate.^{12,13} Response patterns are shown in Supporting Information Figure S1.

The male:female ratio was 1.69:1 among cases and 1.13:1 among controls (Table 1). Cases and controls had statistically similar mean ages in Uganda (8.0 vs. 7.7 years) and Tanzania (6.8 years vs. 7.4 years) but they were younger in Kenya (6.6 years vs. 7.4 years; Table 1). The mean age of the cases in boys and girls was similar in the three countries; 9.5% ($n = 66$) of all the cases were younger than 3 years old (Uganda: 3.1% [$n = 10$]; Tanzania: 10.2% [$n = 13$]; and Kenya: 17.4% [$n = 43$]). The proportion of cases younger than 3 years old in histologically confirmed cases was: 5.8% ($n = 25$; Uganda: 2.0% [$n = 5$]; Tanzania: 8.3% [$n = 3$]; and Kenya: 12.5% [$n = 17$]). In all the countries, most cases lived in villages near water (64.8–86.3%). Most cases in Uganda lived in rural villages (62.7%, $n = 151$), but the proportion was slightly over one-third in Tanzania (37.7%, $n = 46$) and slightly over one-half in Kenya (59.0%, $n = 125$).

Associations of eBL with malaria-RDT and measures of mass malaria suppression

More cases were diagnosed during the wet season in Uganda (vs. dry: OR = 2.18, $p < 0.0001$) and Tanzania (OR = 1.49, $p = 0.05$), but fewer in Kenya (OR = 0.45, $p < 0.0001$; Table 2). Compared to controls, malaria-RDT positivity in blood was lower in eBL cases in Uganda (OR = 0.44, $p < 0.0001$), Tanzania (OR = 0.36, $p = 0.0001$) and Kenya (OR = 0.26, $p < 0.0001$). The markedly lower malaria-RDT positivity in eBL cases was not explained by exposure to IRS in the past 12 months (Fig. 2a) or bed net ownership/use (Fig. 2b), although eBL cases were more likely to report owning a bed net, particularly in Uganda (Fig. 2c), suggesting a small bias.

Contrary to our expectations, exposure to malaria suppression interventions was associated with elevated eBL risk. Although reporting application of IRS in the house 1 year before enrollment was not different between eBL cases and healthy controls in Uganda (vs. no IRS: OR = 1.02, $p = 0.91$), it was significantly associated with eBL risk in Tanzania (OR = 5.27, $p < 0.0001$) and Kenya (OR = 3.13, $p < 0.0001$). Consistent with this pattern, reporting use of a mosquito bed net the night before interview was associated with eBL risk in children Uganda (vs. not owning a mosquito bed net: OR = 2.90, 95% CI 2.12–3.97), Tanzania (OR = 2.19, 95% CI 1.31–3.67) and Kenya (OR = 1.90, 95% CI 1.26–2.88). Moreover, the association with eBL risk was stronger among children who reported

Table 1. Characteristics of endemic Burkitt lymphoma cases and controls the EMBLEM Study in Uganda, Tanzania and Kenya, 2010–2016

| | Uganda | | Tanzania | | Kenya | | All countries combined ¹ | |
|--|--------------|-----------------|--------------|-----------------|--------------|-----------------|-------------------------------------|-----------------|
| | Cases, n (%) | Controls, n (%) | Cases, n (%) | Controls, n (%) | Cases, n (%) | Controls, n (%) | Cases, n (%) | Controls, n (%) |
| Demographics | | | | | | | | |
| Age, years | | | | | | | | |
| 0–2 | 10 (3.1) | 56 (4.9) | 13 (10.2) | 45 (5.5) | 43 (17.4) | 92 (9.5) | 66 (9.5) | 193 (6.6) |
| 3–5 years | 78 (24.2) | 262 (22.8) | 45 (35.2) | 198 (24.2) | 63 (25.5) | 242 (25.1) | 186 (26.7) | 702 (23.9) |
| 6–8 years | 101 (31.4) | 376 (32.7) | 25 (19.5) | 281 (34.3) | 67 (27.1) | 261 (27.1) | 193 (27.7) | 918 (31.3) |
| 9–11 years | 78 (24.2) | 286 (24.9) | 26 (20.3) | 181 (22.1) | 44 (17.8) | 203 (21.0) | 148 (21.2) | 670 (22.8) |
| 12–15 years | 55 (17.1) | 170 (14.8) | 19 (14.8) | 114 (13.9) | 30 (12.2) | 167 (17.3) | 104 (14.9) | 451 (15.4) |
| Mean age, (standard deviation) | 8.0 (3.4) | 7.7 (3.3) | 6.8 (3.8) | 7.4 (3.3) | 6.6 (3.8) | 7.4 (3.7) | 7.3 (3.7) | 7.5 (3.5) |
| Sex | | | | | | | | |
| Female | 120 (38.0) | 541 (47.0) | 56 (44.1) | 387 (47.3) | 80 (32.5) | 448 (46.4) | 256 (37.2) | 1,376 (46.9) |
| Male | 196 (62.0) | 609 (53.0) | 71 (55.9) | 432 (52.8) | 166 (67.5) | 517 (53.6) | 433 (62.8) | 1,558 (53.1) |
| Missing/unknown | 6 | | 1 | | 1 | | 8 | |
| Male:female ratio | 1.6 | 1.1 | 1.3 | 1.1 | 2.1 | 1.2 | 1.7 | 1.1 |
| Design variables | | | | | | | | |
| Proximity to water ² | | | | | | | | |
| Far | 33 (13.7) | 486 (42.3) | 43 (35.3) | 411 (50.2) | 55 (26.1) | 500 (51.8) | 131 (22.8) | 1,397 (47.6) |
| Near | 208 (86.3) | 664 (57.7) | 79 (64.8) | 408 (49.8) | 156 (73.9) | 465 (48.2) | 443 (77.2) | 1,537 (52.4) |
| Missing/unknown | 81 | | 6 | | 36 | | 123 | |
| Population density of children 0–15 years ³ | | | | | | | | |
| Low | 151 (62.7) | 753 (65.5) | 46 (37.7) | 418 (51.0) | 125 (59.0) | 652 (67.6) | 322 (56.0) | 1,823 (62.1) |
| High | 90 (37.3) | 397 (34.5) | 76 (62.3) | 401 (49.0) | 87 (41.0) | 313 (32.4) | 253 (44.0) | 1,111 (37.9) |
| Missing/unknown | 81 | | 6 | | 35 | | 122 | |
| Year of study enrollment | | | | | | | | |
| 2010–2012 | 109 (33.9) | 68 (5.9) | 20 (15.6) | | 21 (8.5) | | 150 (21.5) | 68 (2.3) |
| 2013–2015 | 177 (55.0) | 1,082 (94.1) | 96 (75.0) | 178 (21.7) | 206 (83.4) | 369 (38.2) | 479 (68.7) | 1,629 (55.5) |
| 2016 | 36 (11.2) | | 12 (9.4) | 641 (78.3) | 20 (8.1) | 596 (61.8) | 68 (9.8) | 1,237 (42.2) |

¹This column shows the observed characteristics based on data from all the three study countries combined; the percentages are for columns.

²Villages were classified as “near water” if any part of their boundary was within 500 m of surface water; otherwise they were classified as “far from water.”

³Villages were classified as “high-population density”, a surrogate for urban areas, if the population count of children aged 0–15 years was greater than or equal to the average population count for census enumeration areas in the regions studied for each country; otherwise as “low-population density” (see Methods).

owning but not using their mosquito bed net the previous night (*vs.* not owning: 22-fold in Uganda, eightfold in Tanzania and sevenfold in Kenya; Table 2). Despite regular use of insecticide being relatively rare, reported by only 1.6–4.8% of the controls, eBL risk was associated with reporting regular use of insecticide sprays in Uganda (*vs.* nonuse: OR = 5.62, $p < 0.0001$) and Tanzania (OR = 2.31, $p = 0.02$), but not in Kenya (OR = 1.26, $p = 0.63$).

Associations of eBL with fevers, inpatient or outpatient malaria treatment and HIV

A history of fevers may provide clues about exposure and immunity to malaria as well as to other pathogens and the state of health in the children. When considering any fever experienced up to 12 months before enrollment, no difference was observed between eBL cases and controls in Uganda (*vs.*

no fever: OR = 0.82, $p = 0.40$), but eBL cases were less likely than controls to report these fevers in this period in Tanzania (OR = 0.49, $p = 0.06$) and Kenya (OR = 0.22, $p < 0.0001$). Considering fevers attributed to malaria in the period up to 6 months before enrollment eBL cases were less likely than controls to report these fevers in Uganda (*vs.* none: OR = 0.56, $p \leq 0.001$) and Kenya (OR = 0.47, $p < 0.0001$) but not in Tanzania (OR = 0.90, $p = 0.64$, Table 2). Inpatient malaria treatment is necessary in children who lack immunity to malaria and becomes less necessary in older children who have acquired immunity.²¹ Inpatient malaria treatment >12 months before enrollment or not receiving such treatment was reported more frequently by cases than controls in Uganda (*vs.* ≤ 12 months before enrollment: OR = 2.55 and OR = 2.04, respectively, $p = 0.01$) while not receiving treatment was more frequently reported by cases in Tanzania (OR = 1.94, 95% CI

Table 2. Associations between endemic Burkitt lymphoma and patient characteristics in Uganda, Tanzania and Kenya, 2010–2016

| Characteristics | Uganda | | | Tanzania | | | Kenya | | |
|---|--------------|-----------------|--------------------------|--------------|-----------------|--------------------------|--------------|-----------------|--------------------------|
| | Cases, n (%) | Controls, n (%) | OR ¹ (95% CI) | Cases, n (%) | Controls, n (%) | OR ¹ (95% CI) | Cases, n (%) | Controls, n (%) | OR ¹ (95% CI) |
| Season ² | | | | | | | | | |
| Dry | 138 (42.9) | 731 (63.6) | Ref | 47 (36.7) | 395 (48.2) | Ref | 108 (43.7) | 267 (27.7) | Ref |
| Wet | 184 (57.1) | 419 (36.4) | 2.18 (1.63, 2.92) | 81 (63.3) | 424 (51.8) | 1.49 (1.00, 2.23) | 139 (56.3) | 698 (72.3) | 0.45 (0.33, 0.62) |
| <i>p</i> -value | | | <0.0001 | | | 0.050 | | | <0.0001 |
| Measures of malaria | | | | | | | | | |
| Indoor residual insecticide sprayed in house | | | | | | | | | |
| No | 191 (61.0) | 752 (65.7) | Ref | 38 (30.7) | 551 (68.2) | Ref | 190 (81.9) | 880 (92.5) | Ref |
| Yes | 122 (39.0) | 393 (34.3) | 1.02 (0.75, 1.38) | 86 (69.4) | 257 (31.8) | 5.27 (3.43, 8.09) | 42 (18.1) | 71 (7.5) | 3.13 (1.97, 4.96) |
| Missing/unknown | 9 | 5 | | 4 | 11 | | 15 | 14 | |
| <i>p</i> -value | | | 0.906 | | | <0.0001 | | | <0.0001 |
| Mosquito net ownership and use the night before | | | | | | | | | |
| No | 125 (39.8) | 767 (67.1) | Ref | 21 (16.7) | 289 (35.4) | Ref | 44 (18.9) | 322 (33.8) | Ref |
| Yes, but not used | 35 (11.2) | 11 (1.0) | 22.5 (9.94, 51.0) | 17 (13.5) | 30 (3.7) | 8.29 (3.81, 18.1) | 38 (16.3) | 43 (4.5) | 7.09 (3.91, 12.8) |
| Yes, and used | 154 (49.0) | 366 (32.0) | 2.90 (2.12, 3.97) | 88 (69.8) | 497 (60.9) | 2.19 (1.31, 3.67) | 151 (64.8) | 589 (61.7) | 1.90 (1.26, 2.88) |
| Missing/unknown | 8 | 6 | | 2 | 3 | | 14 | 11 | |
| <i>p</i> -value | | | <0.0001 | | | <0.0001 | | | <0.0001 |
| Regularly uses mosquito insecticide sprays | | | | | | | | | |
| No | 298 (95.2) | 1,126 (98.4) | Ref | 114 (89.8) | 775 (95.2) | Ref | 226 (97.0) | 924 (97.5) | Ref |
| Yes | 15 (4.8) | 18 (1.6) | 5.62 (2.62, 12.0) | 13 (10.2) | 39 (4.8) | 2.31 (1.15, 4.62) | 7 (3.0) | 24 (2.5) | 1.26 (0.49, 3.26) |
| Missing/unknown | 9 | 6 | | 1 | 5 | | 14 | 17 | |
| <i>p</i> -value | | | <0.0001 | | | 0.019 | | | 0.628 |
| Malaria rapid diagnostic test | | | | | | | | | |
| Negative | 204 (65.4) | 561 (49.0) | Ref | 95 (80.5) | 473 (58.7) | Ref | 192 (84.2) | 542 (57.0) | Ref |
| Positive | 108 (34.6) | 583 (51.0) | 0.44 (0.32, 0.60) | 23 (19.5) | 333 (41.3) | 0.36 (0.22, 0.59) | 36 (15.8) | 409 (43.0) | 0.26 (0.17, 0.39) |
| Missing/unknown | 10 | 6 | | 10 | 13 | | 19 | 14 | |
| <i>p</i> -value | | | <0.0001 | | | 0.0001 | | | <0.0001 |
| History of fevers, malaria treatment and hospital admission | | | | | | | | | |
| Has fever at enrollment | | | | | | | | | |
| No | 136 (43.5) | 1,122 (97.9) | Ref | 41 (32.3) | 767 (94.0) | Ref | 70 (31.1) | 836 (87.5) | Ref |
| Yes | 177 (56.6) | 24 (2.1) | 49.7 (30.4, 81.2) | 86 (67.7) | 49 (6.0) | 32.1 (19.6, 52.7) | 155 (68.9) | 120 (12.6) | 16.5 (11.1, 24.4) |
| Missing/unknown | 9 | 4 | | 1 | 3 | | 22 | 9 | |
| <i>p</i> -value | | | <0.0001 | | | <0.0001 | | | <0.0001 |

(Continues)

Table 2. Associations between endemic Burkitt lymphoma and patient characteristics in Uganda, Tanzania and Kenya, 2010–2016 (Continued)

| | Uganda | | | Tanzania | | | Kenya | | |
|--|--------------|-----------------|-------------------|--------------|-----------------|-------------------|--------------|-----------------|-------------------|
| | Cases, n (%) | Controls, n (%) | OR* (95% CI) | Cases, n (%) | Controls, n (%) | OR* (95% CI) | Cases, n (%) | Controls, n (%) | OR* (95% CI) |
| ≥1 fever up to 12 months before enrollment | | | | | | | | | |
| No | 31 (22.8) | 254 (22.6) | Ref | 11 (26.8) | 115 (15.0) | Ref | 54 (76.1) | 320 (38.2) | Ref |
| Yes | 105 (77.2) | 868 (77.4) | 0.82 (0.51, 1.31) | 30 (73.2) | 652 (85.0) | 0.49 (0.23, 1.03) | 17 (23.9) | 517 (61.8) | 0.22 (0.12, 0.40) |
| Missing/unknown | 186 | 28 | | 87 | 52 | | 176 | 128 | |
| <i>p</i> -value | | | 0.401 | | | 0.059 | | | <0.0001 |
| ≥1 fever due to malaria up to 6 months before enrollment | | | | | | | | | |
| No | 113 (36.2) | 313 (27.3) | Ref | 42 (33.6) | 250 (30.7) | Ref | 108 (48.7) | 288 (30.1) | Ref |
| Yes | 199 (63.8) | 832 (72.7) | 0.56 (0.41, 0.76) | 83 (66.4) | 565 (69.3) | 0.90 (0.60, 1.37) | 114 (51.4) | 668 (69.9) | 0.47 (0.34, 0.65) |
| Missing/Unknown | 10 | 5 | | 3 | 4 | | 25 | 9 | |
| <i>p</i> -value | | | 0.0002 | | | 0.636 | | | <0.0001 |
| ≥1 fever not due to malaria up to 6 months before enrollment | | | | | | | | | |
| No | 181 (59.5) | 1,062 (92.9) | Ref | 44 (34.9) | 599 (73.6) | Ref | 100 (44.6) | 772 (81.1) | Ref |
| Yes | 123 (40.5) | 81 (7.1) | 8.40 (5.79, 12.2) | 82 (65.1) | 215 (26.4) | 5.17 (3.42, 7.82) | 124 (55.4) | 180 (18.9) | 5.17 (3.67, 7.28) |
| Missing/unknown | 18 | 7 | | 2 | 5 | | 23 | 13 | |
| <i>p</i> -value | | | <0.0001 | | | <0.0001 | | | <0.0001 |
| ≥1 hospital admission | | | | | | | | | |
| No | 112 (35.7) | 626 (54.7) | Ref | 31 (24.4) | 516 (63.2) | Ref | 71 (30.3) | 697 (73.2) | Ref |
| Yes | 202 (64.3) | 519 (45.3) | 2.01 (1.49, 2.70) | 96 (75.6) | 300 (36.8) | 5.45 (3.50, 8.51) | 163 (69.7) | 255 (26.8) | 6.67 (4.70, 9.47) |
| Missing/unknown | 8 | 5 | | 1 | 3 | | 13 | 13 | |
| <i>p</i> -value | | | <0.0001 | | | <0.0001 | | | <0.0001 |
| Inpatient malaria treatment | | | | | | | | | |
| Yes, past 12 months | 24 (7.6) | 150 (13.1) | Ref | 10 (7.9) | 106 (13.0) | Ref | 35 (15.0) | 95 (10.0) | Ref |
| Yes, >12 months | 82 (26.1) | 269 (23.5) | 2.55 (1.39, 4.67) | 13 (10.2) | 136 (16.7) | 1.15 (0.47, 2.82) | 12 (5.1) | 117 (12.3) | 0.24 (0.11, 0.50) |
| Never | 208 (66.2) | 725 (63.4) | 2.04 (1.17, 3.57) | 104 (81.9) | 574 (70.3) | 1.94 (0.94, 3.99) | 187 (79.9) | 743 (77.8) | 0.55 (0.35, 0.86) |
| Missing/unknown/unknown | 8 | 6 | | 1 | 3 | | 13 | 10 | |
| <i>p</i> -value | | | 0.010 | | | 0.066 | | | 0.001 |
| Outpatient malaria treatment | | | | | | | | | |
| Yes, past 12 months | 153 (48.9) | 532 (46.5) | Ref | 62 (48.8) | 255 (31.3) | Ref | 106 (45.3) | 539 (56.4) | Ref |
| Yes, >12 months | 73 (23.3) | 90 (7.9) | 3.69 (2.44, 5.56) | 14 (11.0) | 69 (8.5) | 0.87 (0.45, 1.68) | 23 (9.8) | 64 (6.7) | 1.86 (1.05, 3.28) |
| Never | 87 (27.8) | 523 (45.7) | 0.88 (0.63, 1.24) | 51 (40.2) | 492 (60.3) | 0.44 (0.29, 0.67) | 105 (44.9) | 352 (36.9) | 1.49 (1.06, 2.09) |
| Missing/unknown | 9 | 5 | | 1 | 3 | | 13 | 10 | |
| <i>p</i> -value | | | <0.0001 | | | 0.0004 | | | 0.021 |

(Continues)

Table 2. Associations between endemic Burkitt lymphoma and patient characteristics in Uganda, Tanzania and Kenya, 2010–2016 (Continued)

| | Uganda | | | Tanzania | | | Kenya | | |
|--|--------------|-----------------|--------------------------|--------------|-----------------|--------------------------|--------------|-----------------|--------------------------|
| | Cases, n (%) | Controls, n (%) | OR ¹ (95% CI) | Cases, n (%) | Controls, n (%) | OR ¹ (95% CI) | Cases, n (%) | Controls, n (%) | OR ¹ (95% CI) |
| HIV status | | | | | | | | | |
| Negative | 302 (98.1) | 1,135 (99.4) | Ref | 114 (96.6) | 775 (99.9) | Ref | 203 (93.1) | 936 (98.4) | Ref |
| Positive | 6 (2.0) | 7 (0.6) | 5.49 (1.52, 19.9) | 4 (3.4) | 1 (0.1) | 25.6 (2.76, 236) | 15 (6.9) | 15 (1.6) | 4.32 (1.90, 9.86) |
| Missing/unknown | 14 | 8 | | 10 | 43 | | 29 | 14 | |
| <i>p</i> -value | | | 0.009 | | | 0.004 | | | 0.001 |
| Parental characteristics | | | | | | | | | |
| Mother's education | | | | | | | | | |
| Up to standard 4 | 200 (63.7) | 581 (50.8) | Ref | 1 (32.3) | 201 (24.6) | Ref | 36 (15.7) | 182 (19.0) | Ref |
| Standard 5–7 | 100 (31.9) | 446 (39.0) | 0.70 (0.51, 0.95) | 82 (64.6) | 570 (69.9) | 0.74 (0.48, 1.13) | 105 (45.7) | 455 (47.6) | 1.36 (0.84, 2.21) |
| >Senior secondary school | 14 (4.5) | 117 (10.2) | 0.51 (0.28, 0.96) | 4 (3.2) | 45 (5.5) | 0.43 (0.14, 1.29) | 89 (38.7) | 319 (33.4) | 1.58 (0.96, 2.61) |
| Missing/unknown | 8 | 6 | | 1 | 3 | | 17 | 9 | |
| <i>p</i> -value | | | 0.019 | | | 0.193 | | | 0.201 |
| <i>p</i> -trend | | | 0.005 | | | 0.070 | | | 0.079 |
| Father's education | | | | | | | | | |
| Up to standard 4 | 85 (27.5) | 212 (18.7) | Ref | 35 (27.8) | 111 (13.7) | Ref | 27 (11.8) | 151 (16.1) | Ref |
| Standard 5–7 | 148 (47.9) | 547 (48.3) | 0.73 (0.51, 1.05) | 76 (60.3) | 619 (76.1) | 0.37 (0.23, 0.60) | 86 (37.6) | 371 (39.6) | 1.80 (1.02, 3.15) |
| >Senior secondary school | 76 (24.6) | 373 (33.0) | 0.59 (0.39, 0.89) | 15 (11.9) | 83 (10.2) | 0.55 (0.28, 1.11) | 116 (50.7) | 416 (44.4) | 1.93 (1.11, 3.36) |
| Missing/unknown | 13 | 18 | | 2 | 6 | | 18 | 27 | |
| <i>p</i> -value | | | 0.040 | | | <0.001 | | | 0.063 |
| <i>p</i> -trend | | | 0.013 | | | 0.011 | | | 0.040 |
| Mother's occupation | | | | | | | | | |
| Trader/Sales | 11 (3.5) | 94 (8.2) | Ref | 13 (10.2) | 62 (7.6) | Ref | 45 (19.4) | 254 (26.5) | Ref |
| Peasant farmer | 286 (90.8) | 1,009 (88.1) | 1.30 (0.65, 2.61) | 103 (81.1) | 724 (88.7) | 0.64 (0.34, 1.23) | 145 (62.5) | 570 (59.6) | 1.39 (0.94, 2.07) |
| Manual laborer | 18 (5.7) | 43 (3.8) | 3.28 (1.28, 8.42) | 11 (8.7) | 30 (3.7) | 1.65 (0.64, 4.21) | 42 (18.1) | 133 (13.9) | 1.48 (0.87, 2.52) |
| Missing/unknown | 7 | 4 | | 1 | 3 | | 15 | 8 | |
| <i>p</i> -value | | | 0.021 | | | 0.026 | | | 0.207 |
| Father's occupation | | | | | | | | | |
| Trader/Sales | 40 (12.7) | 173 (15.1) | Ref | 22 (17.3) | 100 (12.3) | Ref | 54 (23.4) | 243 (25.4) | Ref |
| Peasant farmer | 243 (77.4) | 831 (72.7) | 0.83 (0.54, 1.27) | 97 (76.4) | 669 (82.1) | 0.60 (0.36, 1.02) | 111 (48.1) | 422 (44.1) | 1.11 (0.75, 1.65) |
| Manual laborer | 31 (9.9) | 139 (12.2) | 1.00 (0.56, 1.79) | 8 (6.3) | 46 (5.6) | 0.75 (0.30, 1.84) | 66 (28.6) | 291 (30.4) | 0.92 (0.60, 1.42) |
| Missing/unknown | 8 | 7 | | 1 | 4 | | 16 | 9 | |
| <i>p</i> -value | | | 0.535 | | | 0.161 | | | 0.602 |
| Mother's income, US dollars ³ | | | | | | | | | |
| ≤7.5 | 213 (66.2) | 565 (49.1) | Ref | 81 (63.3) | 279 (34.1) | Ref | 88 (35.6) | 244 (25.3) | Ref |

(Continues)

Table 2. Associations between endemic Burkitt lymphoma and patient characteristics in Uganda, Tanzania and Kenya, 2010–2016 (Continued)

| | Uganda | | Tanzania | | Kenya | |
|---|--------------|-----------------|--------------------------|--------------|-----------------|--------------------------|
| | Cases, n (%) | Controls, n (%) | OR ^a (95% CI) | Cases, n (%) | Controls, n (%) | OR ^a (95% CI) |
| 7.6 to ≤15.0 | 76 (23.6) | 247 (21.5) | 1.05 (0.74, 1.48) | 30 (23.4) | 260 (31.8) | 0.43 (0.27, 0.69) |
| >15.0 | 33 (10.3) | 338 (29.4) | 0.33 (0.20, 0.52) | 17 (13.3) | 280 (34.2) | 0.23 (0.13, 0.41) |
| <i>p</i> -value | | | <0.0001 | | | <0.0001 |
| <i>p</i> -trend | | | <0.0001 | | | <0.0001 |
| Home characteristics | | | | | | |
| Distance of home from main road | | | | | | |
| Far from the main road | 239 (75.9) | 812 (70.9) | Ref | 73 (57.5) | 642 (78.8) | Ref |
| Near the main road | 53 (16.8) | 281 (24.5) | 0.86 (0.58, 1.28) | 40 (31.5) | 114 (14.0) | 3.37 (2.13, 5.33) |
| In town or city | 23 (7.3) | 53 (4.6) | 1.83 (1.02, 3.28) | 14 (11.0) | 59 (7.2) | 2.30 (1.17, 4.50) |
| Missing/unknown | 7 | 4 | | 1 | 4 | 15 |
| <i>p</i> -value | | | 0.078 | | | <0.0001 |
| Number of rooms in house | | | | | | |
| 1–2 rooms | 273 (86.9) | 987 (86.1) | Ref | 47 (37.0) | 481 (59.0) | Ref |
| ≥3 rooms | 41 (13.1) | 159 (13.9) | 1.43 (0.94, 2.17) | 80 (63.0) | 335 (41.1) | 2.43 (1.62, 3.63) |
| Missing/unknown | 8 | 4 | | 1 | 3 | 16 |
| <i>p</i> -value | | | 0.094 | | | <0.0001 |
| Number of children and adult resident | | | | | | |
| 2–4 people | 173 (55.1) | 703 (61.3) | Ref | 28 (22.1) | 302 (37.0) | Ref |
| 5–7 people | 115 (36.6) | 385 (33.6) | 1.45 (1.06, 1.96) | 56 (44.1) | 334 (40.9) | 1.96 (1.18, 3.24) |
| ≥8 people | 26 (8.3) | 58 (5.1) | 2.19 (1.21, 3.97) | 43 (33.9) | 180 (22.1) | 2.81 (1.62, 4.86) |
| Missing/unknown | 8 | 4 | | 1 | 3 | 16 |
| <i>p</i> -value | | | 0.006 | | | 0.001 |
| <i>p</i> -trend | | | 0.002 | | | 0.0002 |
| Number of people sleeping in the same room as child | | | | | | |
| 0–2 people | 49 (15.6) | 202 (17.6) | Ref | 28 (22.1) | 269 (33.0) | Ref |
| 3 people | 99 (31.5) | 275 (24.0) | 1.55 (0.99, 2.42) | 46 (36.2) | 288 (35.3) | 1.41 (0.84, 2.37) |
| ≥4 people | 166 (52.9) | 669 (58.4) | 1.07 (0.71, 1.63) | 53 (41.7) | 259 (31.7) | 1.88 (1.13, 3.13) |
| Missing/unknown | 8 | 4 | | 1 | 3 | 16 |
| <i>p</i> -value | | | 0.058 | | | 0.049 |
| <i>p</i> -trend | | | 0.691 | | | 0.014 |
| Connected to electricity grid | | | | | | |
| No | 306 (97.1) | 1,092 (95.4) | Ref | 122 (96.1) | 745 (91.3) | Ref |
| Yes | 9 (2.9) | 53 (4.6) | 0.75 (0.26, 2.17) | 5 (3.9) | 71 (8.7) | 0.44 (0.17, 1.13) |
| | | | | | | 202 (86.7) |
| | | | | | | 835 (87.6) |
| | | | | | | 118 (12.4) |
| | | | | | | 1.22 (0.77, 1.93) |

(Continues)

Table 2. Associations between endemic Burkitt lymphoma and patient characteristics in Uganda, Tanzania and Kenya, 2010–2016 (Continued)

| | Uganda | | Tanzania | | Kenya | |
|-----------------------------|--------------|-----------------|--------------|-----------------|--------------|-----------------|
| | Cases, n (%) | Controls, n (%) | Cases, n (%) | Controls, n (%) | Cases, n (%) | Controls, n (%) |
| Missing/unknown | 7 | 5 | 1 | 3 | 14 | 12 |
| <i>p</i> -value | 0.598 | | 0.087 | | 0.397 | |
| Source of drinking water | | | | | | |
| Unprotected spring/well | 244 (77.5) | 882 (77.0) | 59 (46.5) | 453 (55.5) | 130 (55.6) | 572 (59.9) |
| Protected spring/well | 61 (19.4) | 202 (17.6) | 42 (33.1) | 218 (26.7) | 46 (19.7) | 171 (17.9) |
| Public tap/piped household | 10 (3.2) | 61 (5.3) | 26 (20.5) | 145 (17.8) | 58 (24.8) | 212 (22.2) |
| Missing/unknown | 7 | 5 | 1 | 3 | 13 | 10 |
| <i>p</i> -value | 0.073 | | 0.254 | | 0.029 | |
| Distance to water source, m | | | | | | |
| <500 | 38 (12.1) | 383 (33.5) | 52 (40.9) | 136 (16.7) | 149 (64.5) | 356 (37.2) |
| 500–999 | 63 (20.0) | 126 (11.0) | 22 (17.3) | 159 (19.5) | 33 (14.3) | 230 (24.0) |
| 1,000–4,999 | 122 (38.7) | 511 (44.6) | 32 (25.2) | 440 (53.9) | 38 (16.5) | 268 (28.0) |
| ≥5,000 | 92 (29.2) | 125 (10.9) | 21 (16.5) | 81 (9.9) | 11 (4.8) | 104 (10.9) |
| Missing/unknown | 7 | 5 | 1 | 3 | 16 | 7 |
| <i>p</i> -value | <0.0001 | | <0.0001 | | <0.0001 | |
| <i>p</i> -trend | <0.0001 | | <0.0001 | | <0.0001 | |

Note: *p* values are for heterogeneity.

¹Associations are minimally adjusted for age, sex, proximity to water and population density of children 0–15 years.

²The months of April–June and September–December were classified as wet season months, while the months of January–March and July–August were classified as dry season months.

³Income was categorized based on the international poverty line of \$1.90 per a day to calculate the average 30-day monthly income. Total household income or father's income were not analyzed because the results for these were considered unreliable.

Abbreviation: CI, confidence interval.

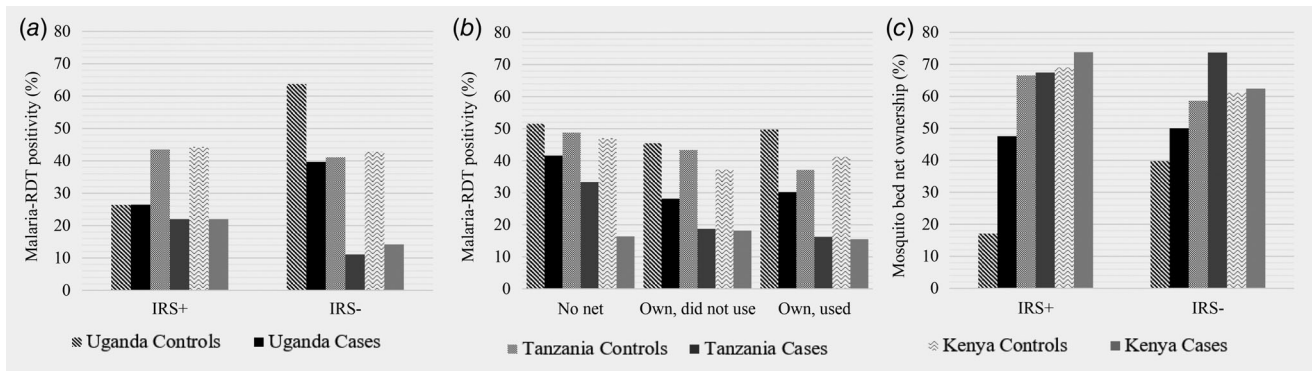


Figure 2. Figure shows malaria-RDT positivity among cases and controls by indoor residual spraying (IRS) use (IRS+) or not (IRS-) in the past year (Panel A) and by mosquito bed net ownership (Panel B) and mosquito bed net ownership by IRS use in the past year (Panel C). The results are ordered as controls first followed by cases for Uganda, Tanzania and Kenya.

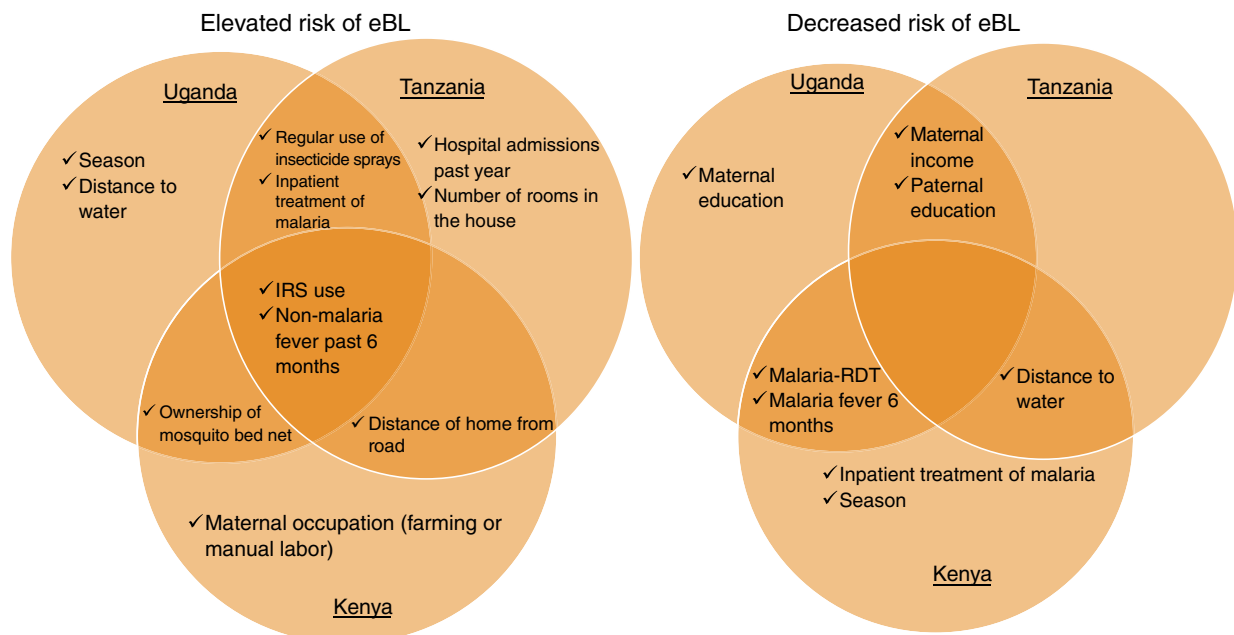


Figure 3. Venn diagram showing the characteristics associated with elevated or decreased risk of eBL in Uganda, Tanzania, and Kenya, highlighting findings common in the three or two countries. [Color figure can be viewed at wileyonlinelibrary.com]

0.94–3.99; $p = 0.07$). However, the findings were heterogeneous in Kenya with cases being less likely to report inpatient malaria treatment >12 months before enrollment or never receiving such treatment ever (OR = 0.24 and OR = 0.55, respectively, $p = 0.001$).

In contrast to inpatient malaria treatment, outpatient malaria treatment is given to people with immunity to malaria when they experience breakthrough infections and it is a surrogate of intensity of exposure. Compared to controls, cases frequently reported malaria outpatient treatment >12 months before enrollment in Uganda (vs. ≤12 months: OR = 3.69)

and Kenya (OR = 1.86). A history of no outpatient malaria treatment was associated with decreased eBL risk in Tanzania (OR = 0.44, $p = 0.004$; Table 2).

In all the three countries, fevers not attributed to malaria experienced up to 6 months before enrollment were associated with eBL risk in Uganda (OR = 8.40, $p < 0.0001$), Tanzania (OR = 5.17, $p < 0.0001$) and Kenya (OR = 5.17, $p < 0.0001$). This association was stronger for fever reported at enrollment (OR = 49.7, $p < 0.0001$, OR = 32.1, $p < 0.0001$ and OR = 16.5, $p < 0.0001$, for Uganda, Tanzania and Kenya, respectively, Table 2).

Table 3. Multivariate associations with endemic Burkitt lymphoma the EMBLEM study, 2010–2016

| | Uganda | Tanzania | Kenya | All countries combined ¹ |
|---|---------------------------|---------------------------|---------------------------|-------------------------------------|
| Characteristics | aOR ² (95% CI) | aOR ² (95% CI) | aOR ² (95% CI) | aOR ² (95% CI) |
| Season³ | | | | |
| Dry | Ref | Ref | Ref | Ref |
| Wet | 2.54 (1.67, 3.86) | 1.51 (0.79, 2.86) | 0.28 (0.18, 0.45) | 1.28 (0.99, 1.66) |
| <i>p</i> -value | <0.0001 | 0.211 | <0.0001 | 0.058 |
| Measure of malaria | | | | |
| Indoor residual insecticide sprayed in house | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 1.71 (1.07, 2.73) | 3.93 (2.03, 7.62) | 6.78 (3.51, 13.10) | 2.32 (1.75, 3.09) |
| <i>p</i> -value | 0.026 | <0.0001 | <0.0001 | <0.0001 |
| Mosquito net ownership and use the night before | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes, but not used | 39.7 (13.3, 118) | 4.09 (1.25, 13.35) | 5.74 (2.48, 13.3) | 9.23 (5.59, 15.24) |
| Yes, and used | 4.12 (2.64, 6.42) | 1.32 (0.60, 2.90) | 1.47 (0.86, 2.53) | 2.36 (1.76, 3.18) |
| <i>p</i> -value | <0.0001 | 0.058 | 0.0002 | <0.0001 |
| Regularly uses mosquito insecticide sprays | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 5.62 (1.85, 17.01) | 3.47 (1.16, 10.37) | Ref | 2.97 (1.65, 5.32) |
| <i>p</i> -value | 0.002 | 0.026 | Ref | 0.0003 |
| Malaria rapid diagnostic test | | | | |
| Negative | Ref | Ref | Ref | Ref |
| Positive | 0.43 (0.28, 0.68) | 0.56 (0.27, 1.16) | 0.33 (0.20, 0.55) | 0.46 (0.35, 0.60) |
| <i>p</i> -value | 0.0003 | 0.120 | <0.0001 | <0.0001 |
| History of fevers, and malaria treatment | | | | |
| ≥1 fever due to malaria up to 6 months before enrollment | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 0.48 (0.29, 0.77) | Ref | 0.59 (0.35, 0.98) | 0.63 (0.47, 0.84) |
| <i>p</i> -value | 0.003 | Ref | 0.042 | 0.001 |
| ≥1 fever not due to malaria up to 6 months before enrollment | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 8.82 (5.37, 14.49) | 3.88 (2.05, 7.36) | 6.98 (4.39, 11.09) | 5.66 (4.31, 7.42) |
| <i>p</i> -value | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| ≥1 hospital admission | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | Ref | 21.29 (9.61, 47.17) | Ref | 9.35 (6.85, 12.77) |
| <i>p</i> -value | Ref | <0.0001 | Ref | <0.0001 |
| Inpatient malaria treatment | | | | |
| Yes, past 12 months | Ref | Ref | Ref | Ref |
| Yes, >12 months | 3.97 (1.66, 9.51) | 2.89 (0.80, 10.41) | 0.18 (0.07, 0.48) | 0.99 (0.62, 1.57) |
| Never | 3.41 (1.52, 7.67) | 26.43 (7.73, 90.36) | 0.48 (0.25, 0.91) | 5.59 (3.61, 8.66) |
| <i>p</i> -value | 0.007 | <0.0001 | 0.003 | <0.0001 |
| Outpatient malaria treatment | | | | |
| Yes, past 12 months | Ref | Ref | Ref | Ref |
| Yes, >12 months | 2.17 (1.17, 4.03) | 0.45 (0.14, 1.48) | 1.61 (0.70, 3.72) | 2.23 (1.50, 3.31) |
| Never | 0.59 (0.35, 0.99) | 0.54 (0.27, 1.07) | 1.48 (0.87, 2.53) | 0.96 (0.71, 1.29) |
| <i>p</i> -value | 0.0001 | 0.154 | 0.277 | <0.0001 |

(Continues)

Table 3. Multivariate associations with endemic Burkitt lymphoma the EMBLEM study, 2010–2016 (Continued)

| | Uganda | Tanzania | Kenya | All countries combined ¹ |
|---|-------------------|--------------------|-------------------|-------------------------------------|
| Parental characteristics | | | | |
| Mother's education | | | | |
| Up to standard 4 | Ref | | | Ref |
| Standard 5–7 | 0.81 (0.52, 1.26) | | | 0.81 (0.60, 1.08) |
| ≥Senior secondary school | 0.46 (0.19, 1.12) | | | 0.77 (0.50, 1.20) |
| <i>p</i> -value | 0.197 | | | 0.319 |
| <i>p</i> -trend | 0.082 | | | 0.227 |
| Father's education | | | | |
| Up to standard 4 | Ref | Ref | Ref | Ref |
| Standard 5–7 | 0.75 (0.44, 1.26) | 0.25 (0.11, 0.55) | 1.13 (0.54, 2.37) | 0.71 (0.51, 1.00) |
| ≥Senior secondary school | 0.53 (0.28, 0.99) | 0.19 (0.05, 0.68) | 1.03 (0.49, 2.17) | 0.70 (0.47, 1.04) |
| <i>p</i> -value | 0.136 | 0.002 | 0.908 | 0.116 |
| <i>p</i> -trend | 0.033 | 0.002 | 0.943 | 0.068 |
| Mother's occupation | | | | |
| Trader/Sales | Ref | Ref | Ref | Ref |
| Peasant farmer | 0.64 (0.23, 1.75) | 0.47 (0.17, 1.34) | 2.80 (1.53, 5.11) | 1.31 (0.86, 1.97) |
| Manual laborer | 0.79 (0.19, 3.21) | 0.75 (0.18, 3.02) | 2.36 (1.07, 5.22) | 1.54 (0.89, 2.69) |
| <i>p</i> -value | 0.668 | 0.334 | 0.004 | 0.272 |
| Mother's income, US dollars ⁴ | | | | |
| ≤7.5 | Ref | Ref | Ref | Ref |
| 7.6 to ≤15.0 | 0.97 (0.60, 1.58) | 0.68 (0.31, 1.46) | 0.78 (0.42, 1.43) | 0.88 (0.65, 1.20) |
| >15.0 | 0.27 (0.14, 0.52) | 0.20 (0.08, 0.47) | 0.70 (0.40, 1.24) | 0.46 (0.33, 0.64) |
| <i>p</i> -value | 0.0004 | 0.001 | 0.468 | <0.0001 |
| <i>p</i> -trend | 0.0003 | 0.001 | 0.249 | <0.0001 |
| Home characteristics | | | | |
| Distance of home from main road | | | | |
| Far from the main road | | Ref | Ref | Ref |
| Near the main road | | 4.33 (2.00, 9.37) | 1.88 (1.15, 3.07) | 1.66 (1.23, 2.24) |
| In town or city | | 9.17 (2.84, 29.63) | 1.94 (0.97, 3.90) | 2.92 (1.83, 4.67) |
| <i>p</i> -value | | <0.0001 | 0.026 | <0.0001 |
| Number of rooms in house | | | | |
| 1–2 room | | Ref | Ref | Ref |
| ≥3 rooms | | 1.33 (0.67, 2.65) | 1.46 (0.91, 2.33) | 1.19 (0.88, 1.62) |
| <i>p</i> -value | | 0.419 | 0.117 | 0.256 |
| Number of children and adult resident | | | | |
| 2–4 people | Ref | Ref | | Ref |
| 5–7 people | 1.51 (0.99, 2.31) | 1.12 (0.49, 2.58) | | 1.23 (0.92, 1.66) |
| ≥8 people | 1.47 (0.62, 3.49) | 1.35 (0.56, 3.29) | | 1.21 (0.81, 1.80) |
| <i>p</i> -value | 0.144 | 0.788 | | 0.365 |
| <i>p</i> -trend | 0.08 | 0.497 | | 0.428 |
| Number of people sleeping in the same room as child | | | | |
| 0–2 people | | | Ref | Ref |
| 3 people | | | 1.27 (0.75, 2.16) | 1.42 (1.02, 1.97) |
| ≥4 people | | | 1.10 (0.63, 1.93) | 1.31 (0.94, 1.84) |
| <i>p</i> -value | | | 0.673 | 0.109 |
| <i>p</i> -trend | | | 0.649 | 0.177 |
| Source of drinking water | | | | |
| Unprotected spring/well | | | Ref | Ref |
| Protected spring/well | | | 1.44 (0.82, 2.53) | 1.53 (1.11, 2.10) |

(Continues)

Table 3. Multivariate associations with endemic Burkitt lymphoma the EMBLEM study, 2010–2016 (Continued)

| | Uganda | Tanzania | Kenya | All countries combined ¹ |
|-----------------------------|---------------------|-------------------|-------------------|-------------------------------------|
| Public tap/piped household | | | 0.97 (0.53, 1.76) | 1.08 (0.72, 1.63) |
| <i>p</i> -value | | | 0.395 | 0.032 |
| Distance to water source, m | | | | |
| <500 | Ref | Ref | Ref | Ref |
| 500–999 | 5.58 (2.81, 11.08) | 0.32 (0.13, 0.78) | 0.57 (0.32, 1.02) | 1.30 (0.91, 1.86) |
| 1,000–4,999 | 3.48 (1.99, 6.10) | 0.10 (0.05, 0.24) | 0.38 (0.21, 0.70) | 0.84 (0.61, 1.14) |
| ≥5,000 | 14.75 (7.34, 29.66) | 0.46 (0.17, 1.28) | 0.19 (0.07, 0.50) | 2.39 (1.60, 3.57) |
| <i>p</i> -value | <0.0001 | <0.0001 | 0.0004 | <0.0001 |
| <i>p</i> -trend | <0.0001 | <0.0001 | <0.0001 | 0.034 |

Note: *p* values are for heterogeneity.

¹This column shows the observed associations based on data from all the three study countries combined, adjusted for each country.

²In addition to the adjustment for age, sex, proximity to water and population density of children 0–15 years, the associations are mutually adjusted for all variables included in the multivariate model. In addition, the multivariate models were adjusted for keeping animals inside the house or nearby (chicken, pigs, goat, cows, birds, dogs).

³The months of April–June and September–December were classified as wet season months, while the months of January–March and July–August were classified as dry season months.

⁴Income was categorized based on the international poverty line of \$1.90 per a day to calculate the average 30-day monthly income. Total household income or father's income were not analyzed because the results for these were considered unreliable.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

These nonmalaria fevers were not explained by HIV infection, which was rare (25 cases, 3.6%; 23 controls, 0.78%; Table 2); it was less common in Uganda (2.0%) than in Tanzania (3.4%) and Kenya (6.9%). HIV infection was associated with eBL risk in Uganda (OR = 5.49, *p* = 0.01), Tanzania (OR = 25.6, *p* = 0.004) and Kenya (OR = 4.32, *p* = 0.001).

Associations of eBL with parental and household characteristics

In all three countries, higher maternal income (Uganda: *p*-trend <0.0001; Tanzania: *p*-trend <0.0001; and Kenya: *p*-trend = 0.004) and higher maternal and paternal education in Uganda and Tanzania were associated with decreased eBL risk (Table 2). Consistently, reporting lower status maternal occupations, like farming or manual labor, was associated with elevated eBL risk in Uganda (*vs.* sales: OR = 3.28) and Tanzania (OR = 1.65) but not in Kenya (OR = 1.48, *p* = 0.21). Although living in a house connected to electricity is an indicator of higher socioeconomic status, this was not associated with eBL risk.

Location of one's house, house size and crowding within the house may be an indicator of socioeconomic status. Living in a house near a road (*vs.* far: OR = 3.37 and 2.15 in Tanzania and Kenya, respectively) or living in house in a town (OR = 1.83, 2.30 and 3.30 in Uganda, Tanzania and Kenya, respectively) were associated with elevated eBL risk. Living in a house with 3 + rooms (*vs.* 1–2 rooms: OR = 1.43, 2.43 and 1.46 for Uganda, Tanzania and Kenya, respectively) or with 5–7 people (range OR = 1.45–1.96) or ≥8 people (range OR = 1.57–2.81, Table 2). Compared to children who obtained drinking water from an unprotected spring or well, eBL was associated with those whose drinking water was obtained from a protected spring or in Uganda (OR = 1.58, *p* = 0.07) or from piped-in/public tap in Kenya (OR = 1.63, *p* = 0.03). No difference in the sources of

drinking water was observed between cases and controls in Tanzania (*p* = 0.25). Distance of the home to the source of drinking water may be associated with greater exposure to environmental risk factors. Consistently, higher eBL risk in Uganda but lower eBL risk in Tanzania and Kenya were associated with increasing distance from home to the source of drinking water (all *p* < 0.0001, Table 2).

Table 3 shows the results from the multivariable models and Figure 3 shows the associations that were significant in at least one country; we emphasize associations observed in at least two countries. Higher maternal income was associated with decreased eBL risk in Uganda (*p* = 0.0004) and Tanzania (*p* = 0.001), whereas living in a house near the road or in a town or city were associated with elevated eBL risk in Tanzania (*p* < 0.0001) and Kenya (*p* = 0.03). Despite consistent evidence in our study that exposure to IRS was associated with reduced low-grade malaria prevalence whereas the use of mosquito bed nets or regular use of insecticide sprays were not,^{12,13} all these variables were associated with elevated eBL risk. Specifically, reporting IRS in the house in the past year was associated with eBL risk in all the three countries (Uganda: OR = 1.71, *p* = 0.026; Tanzania: OR = 3.93, *p* < 0.0001; and Kenya: OR = 6.78, *p* < 0.0001), as was regular use of insecticide sprays was associated with eBL risk in Uganda (OR = 5.62, *p* = 0.002) and Tanzania (OR = 3.47, *p* = 0.026). Interestingly, the association with eBL was stronger in children who owned but did not use their mosquito bed net the night before interview in Uganda (OR = 39.7, *p* = 0.0001) and Kenya (OR = 5.74, *p* = 0.002).

The associations of elevated eBL risk with reporting a history of inpatient malaria treatment >12 months before enrollment remained significant in Uganda (*p* = 0.007) and Tanzania (*p* = 0.001), consistent with being exposed to malaria at an

early age. The inverse associations between eBL and malaria-RDT positivity remained significant in Uganda ($p = 0.0003$) and Kenya ($p < 0.0001$) as did the associations with fever attributed to malaria up to 6 months before enrollment with eBL remained significant in Uganda ($p = 0.003$) and Kenya ($p = 0.042$). However, a history of fever not attributed to malaria in the period up to 6 months before enrollment was associated with eBL in all the three countries (Uganda: OR = 8.82, $p < 0.0001$; Tanzania OR = 3.88, $p < 0.0001$; Kenya OR = 6.98, $p < 0.0001$).

These results remained unchanged when we changed the analytic approach and used a combined data set (Supporting Information Tables S1 and S2) or when we stratified analyses by diagnosis or rural/urban status of the case/control villages.

Discussion

Our EMBLEM study demonstrated the feasibility of conducting a networked, multisite population-based case-control study of eBL in Uganda, Tanzania and Kenya. The novel aspects of EMBLEM include implementing harmonized protocols to collect data and biospecimens, collecting local- and regional-area factors to adjust for macrogeographic and microgeographic factors, and conducting the study in rural areas where children are exposed from birth to intense malaria.^{12,13} Our study revealed significant associations both with elevated and decreased eBL risk, but it also exposed tremendous heterogeneity in many of the associations based on observation of significance in one, two or all the three countries (Fig. 3). The heterogeneity of associations may indicate false positive associations; thus, we emphasize associations found in at least two countries. Or it might indicate weakness in questionnaire-based methodology to accurately measure underlying malaria and/or EBV exposures for eBL, hence there is a need to use other techniques to accurately quantify these biologic exposures.

Focusing on the findings that were consistent in at least two countries, our observation that eBL risk is elevated with low-maternal income and paternal education is not surprising. There is evidence that lower socioeconomic status is associated with higher malaria intensity,^{12,13} providing a mechanistic link with the elevated eBL risk.¹⁵ Maternal income could be the reason for the long-term declines in trends in eBL incidence observed in Northern Tanzania during 2000–2009.²² These declines in eBL incidence coincided, paradoxically, with increasing drug and insecticide resistance which led to worse malaria morbidity trends and it predated the introduction of mass malaria suppression programs in 2005.²³ However, because the BL trends are concomitant with long-term increases in maternal income globally and in Tanzania,^{24,25} we speculate that they may be causally related.

We found a heterogenous pattern in the relationship between eBL and some variables used as surrogates of malaria exposure and immunity. For example, inpatient malaria treatment >12 months before enrollment or absence of that history were associated with a twofold higher risk of eBL among children

in Uganda and Tanzania. This is consistent with the high and persistent malaria transmission experienced for more than 7 months in the year in those countries¹⁴ and the notion that inpatient malaria treatment is required in younger children before they acquire immunity,^{26,27} and such treatment is rarely required in older children because of acquired immunity which enables children to tolerate heavy exposure to malaria.^{12,13} However, the association with this variable was opposite in Kenya, where 0.18–0.48-lower risk of eBL was observed. This may reflect slower acquisition of immunity in Kenya where malaria is seasonal and less persistent,¹³ associated with, such that any exposure is more likely to result in symptomatic infections that require treatment. In this setting, the same variable may be compatible with lighter malaria exposure. Definitive research using serological assays may help clarify these heterogenous patterns. Our findings with respect to HIV confirm the association between eBL and HIV and that it is not a major population factor for eBL in this region.^{8,28}

Mass malaria suppression programs have been widely implemented in the study region. Unexpectedly, we found that exposure to mass malaria suppression, notably, use of mosquito bed nets, insecticide sprays and IRS, was associated with elevated eBL risk. This was surprising because IRS was associated with decreased pfPR,^{12,13} whereas use of mosquito bed nets or regular use of insecticide sprays were not.^{12,13} The consistent association of these variables with eBL, on the one hand, and lack of consistent association with pfPR, on the other hand, suggests that the associations with eBL risk are not mediated by alteration of malaria intensity.^{12,13}

We suggest that these apparently paradoxical patterns reflect the preferential targeting for malaria suppression areas with both high malaria intensity and eBL incidence.¹⁵ We speculate that the continuing elevated eBL risk in these areas reflected in our data is due to progression of early pre-eBL lesions triggered by malaria prior to implementation of IRS. Because IRS successfully suppressed malaria in areas where it was applied,^{12,13} our results suggest that the early pre-eBL lesions continue to progress to eBL for up to 20 months, i.e., during the time when the IRS effects, which last 4–6 months per cycle and assuming 3–4 consecutive IRS cycles, are effectively suppressing malaria.²⁹ The early pre-eBL lesions are genetically unstable B cells³⁰ triggered by the historical malaria,³ which irreversible secondary mutations³¹ and undergo oligoclonal expansion stimulated by recurrent malaria⁵ and through Darwinian selection³² progress to eBL despite the absence of intense malaria pressure. The period of heightened risk of 1–2 years approximates the estimated latency period for eBL.^{33,34}

Because we previously observed heterogenous malaria patterns in IRS areas in Uganda,¹² it is possible that heightened eBL risk in IRS areas is driven by pockets of high malaria intensity that persist at levels compatible with eBL development. This hypothesis may be refuted or confirmed by careful geographic analysis of case activity in IRS areas.

The markedly reduced frequencies of malaria-RDT positivity and of reported malaria fevers up to 6 months before enrollment in eBL cases are paradoxical, considering the malaria model for eBL etiology.³⁵ Because cases are more likely to have contact with health facilities and be treated or receive mosquito bed nets, this could explain the lower their malaria risk. However, stratified analysis by IRS and mosquito bed nets and revealed similar patterns. An alternative explanation is that cases received malaria treatment before hospital admission. This was favored by authors of two reports that found lower malaria parasitemia in their eBL cases than controls in a case-control study in Kenya³⁶ and a prospective study in Uganda.³⁷ However, this explanation does not apply to our study because the primary malaria results are based on the presence of malaria antigens in blood, which remain detectable for 4–6 weeks after malaria treatment.¹⁸ Furthermore, we collected data about malaria morbidity up to 6 months before enrollment and found it to be lower in eBL cases than controls. These results indicate that immunity acquired by eBL cases early in life before eBL onset^{26,27} is not only critical to protecting these young children from severe malaria,³⁸ but continues to protect them from the risk of malaria after disease onset.

Our results highlight nonmalaria-related fevers as a common problem associated with eBL. These fevers are often referred to as “B” symptoms, fever of undetermined origin in patients with neoplasia.³⁹ Determining the causal factors could inform clinical management of eBL cases or lead to discovery of infections that may play role in the late stages of progression to eBL.

Our results have some limitations. We relied on questionnaire data, which are subject to multiple errors, including recall bias, inaccurate responses and variability in their distributions in different geographic, social and political contexts. Despite its population-based design, the study is susceptible to differential case ascertainment within and between region, and the incompleteness in obtaining pathology diagnosis was a concern.¹⁷ The impact of geographic and diagnostic distortions is minimal, based qualitatively similar results from analyses stratified by rural/urban status and histological diagnosis. We performed multiple comparisons, thus some of the associations should be considered for hypothesis-generation. The strengths of our study are collecting data under a uniform

protocol in three countries, and performing analyses following a common approach are strengths of our study.

To conclude, we show the feasibility of conducting population-based studies of eBL in multiple countries using uniform protocols. We observed elevated risk of eBL with nonmalaria-related fevers up to before 6 months of enrollment, with exposure to mass malaria suppression, and HIV status; and decreased risk with indicators of higher socioeconomic status, current malaria antigenemia and malaria history within 6 months of admission. The other associations identified likely reflect biological and ecological relationships, including effects mediated by malaria, HIV or unknown infections.

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