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Incidence of Endemic Burkitt Lymphoma in Three Regions of Mozambique

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Abstract. Data on the burden and incidence of endemic Burkitt lymphoma (eBL) across Mozambique are scarce. We retrospectively retrieved information on eBL cases from reports of the three main hospitals of Mozambique: Maputo Central Hospital (MCH), Beira Central Hospital (BCH), and Nampula Central Hospital (NCH) between 2004 and 2014. For 2015, we prospectively collected information of new eBL cases attending these hospitals. A total of 512 eBL cases were reported between 2004 and 2015: 153 eBL cases were reported in MCH, 195 in BCH, and 164 in NCH. Mean age of cases was 6.9 years (standard deviation = 2.8); 63% (319/504) of cases were males. For 2015, the estimated incidence rate of eBL was 2.0, 1.7, and 3.9 per 10^6 person-year at risk in MCH, BCH, and NCH, respectively. Incidence was higher in NCH (northern Mozambique), where intensity of malaria transmission is higher. Data presented show that eBL is a common pediatric malignancy in Mozambique, as observed in neighboring countries.

Endemic Burkitt lymphoma (eBL) is a B-cell non-Hodgkin lymphoma genetically characterized by a chromosomal translocation t(8,14) that results in deregulation of the *c-MYC* oncogene. eBL is the main pediatric cancer in equatorial Africa accounting for about 50% of childhood cancers, and 90% of lymphomas. In high-income settings, BL is cured in more than 90% of cases. However, in limited-resource settings, this percentage is much lower, given poor access to adequate and complete treatment, late presentation, or treatment-related mortality. eBL is generally found in areas of sub-Saharan Africa and Papua New Guinea where *Plasmodium falciparum* transmission is holoendemic (reviewed in Molyneux and others[1]). Epstein–Barr virus is a necessary agent for eBL pathogenesis.[2] The ecological association between eBL and *P. falciparum* was shown in the 1970s,[1] but there is still limited evidence from studies examining this association at an individual level.[3–8] In 2012, the International Agency for Research on Cancer classified *P. falciparum* infection in holoendemic areas as "probably carcinogenic to humans."[9] A better description of eBL epidemiology is needed to enhance current understanding of the etiology of the disease. Also, baseline descriptive epidemiological data are needed to evaluate changes in incidence rates within and between countries especially with the implementation of malaria control programs.[10]

Mozambique stretches from about 2,500 km along the Indian Ocean in southern Africa, and is part of the "eBL belt." Malaria is endemic in Mozambique all year long, although transmission intensity is higher during the rainy season (November–April) and varies within the country.[11] Data on eBL in Mozambique are scarce. A recent publication reports data on pediatric cancer from years 1999–2000 (data from Maputo city) and 2009–2010 (data from the cities of Maputo and Beira).[12] Between 1999 and 2000, eBL was the most common pediatric cancer in Maputo, representing 25% of all pediatric cancers. Between 2009 and 2010, eBL was the third most common cancer in Maputo (12% of all pediatric cancers) given the increase of other cancer types (i.e., renal tumors and Kaposi sarcoma), but the number of eBL cases was higher than in the preceding period. In Beira city, between 2009 and 2010, eBL accounted for 6% of all pediatric cancers. The burden of eBL in other parts of the country is unknown. However, the high levels of malaria transmission as well as the high eBL burden in neighboring countries such as Malawi and Zambia[13,14] suggest that eBL may represent a major cause of pediatric cancer. The current report provides for the first time a description of eBL epidemiology across different regions of Mozambique.

We reviewed the records of the departments of pathology of Maputo Central Hospital (MCH), Beira Central Hospital (BCH), and Nampula Central Hospital (NCH) from January 1, 2004, to December 31, 2014, and recorded information on age, sex, clinical presentation, and diagnostic methods used for each case of eBL under 15 years of age. During 2015, we prospectively collected information from all new eBL cases under 15 years of age diagnosed in these hospitals, including information on the lifelong residential history of the children. MCH is the referral hospital for the southern region (provinces of Maputo, Gaza, and Inhambane), BCH is the referral hospital for the central region (provinces of Sofala, Manica, Tete, Zambezia), and NCH for the northern region (provinces of Nampula, Niassa, and Cabo Delgado). These hospitals include the only three pathology departments of the country.

We described eBL cases recorded between 2004 and 2015. We calculated overall incidence rates of eBL for years 2010–2014. We did not include previous years as estimation of population was not available before 2007, and we had incomplete information of number of eBL cases from Nampula for the years 2007–2009. For 2015, we calculated overall incidence

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TABLE 1

Number of endemic Burkitt lymphoma cases per year according to pathological records of Maputo Central Hospital, Beira Central Hospital, and Nampula Central Hospital

Year	Maputo *n* (%)	Beira *n* (%)	Nampula *n* (%)	Total *n* (%)
2004	14 (39)	18 (50)	4 (11)	36 (100)
2005	17 (27)	27 (42)	20 (31)	64 (100)
2006	30 (38)	33 (42)	15 (19)	78 (100)
2007	13 (42)	17 (55)	1 (3)*	31 (100)
2008	11 (41)	14 (52)	2 (7)*	27 (100)
2009	12 (36)	13 (39)	8 (24)*	33 (100)
2010	11 (32)	9 (26)	14 (41)	34 (100)
2011	13 (35)	9 (24)	15 (41)	37 (100)
2012	7 (17)	18 (43)	17 (60)	42 (100)
2013	10 (20)	10 (20)	31 (61)	51 (100)
2014	11 (24)	16 (36)	18 (40)	45 (100)
2015	4 (12)	11 (32)	19 (40)	34 (100)
Total	153 (30)	195 (38)	164 (32)	512 (100)

*Registers were incomplete for these years.

rate and incidence rates of eBL for 5-year age groups and sex by province of birth (cases with unknown province of birth were excluded for incidence calculation). To calculate incidence, we used the population estimates from the official projections of the National Institute of Statistics of Mozambique, which are based on data from the censuses conducted in 1997 and 2007.[15] For 2015, we also mapped the origin of eBL cases (considering province at onset of eBL) to check the geographical distribution of the disease and the real coverage of the three hospitals. Places of residence at onset of eBL were mapped and overlapped with malaria incidence in Mozambique according to data from the Malaria Atlas Project[16] using ArcGIS Desktop (ESRI, Redlands, CA, 2016). Data management and analysis were done using STATA 12.1 (StataCorp, College Station, TX). Ethical approval was obtained from the Manhiça Health Research Center Institutional Bioethics Committee (CIBS-CISM, Manhiça, Mozambique) and from the ethical committee for clinical research from Hospital Clínic/Universitat de Barcelona (CEIC, Barcelona, Spain).

Overall, 512 eBL cases were recorded between 2004 and 2015 in any of the three pathology departments of Mozambique (Table 1). There were 153 eBL cases in MCH, 195 in BCH, and 164 in NCH. The majority of cases were males (63%, 319/504; sex unknown for eight cases). Median age at eBL diagnosis was 6.9 years (standard deviation: 2.8; age unknown for one case). Facial involvement was the most common clinical presentation (86% [398/465]), followed by abdominal involvement (9% [43/465]) and other presentations (5% [24/465]), among cases with information on clinical presentation. For most of the eBL cases, diagnosis was based on fine-needle aspiration cytology (82% [404/494]). Histology (using hematoxylin–eosin stain) was conducted in 18% (88/494) of cases with information on diagnosis method. Diagnosis was confirmed by two pathologists. In two cases (0.4% [2/494]), diagnosis was based exclusively on clinical presentation. The overall estimated incidence rates of eBL in Mozambique for the years 2010, 2011, 2012, 2013, 2014, and 2015 were 2.6, 2.2, 2.7, 2.7, 2.5, and 3.0 per 10^6 person-year at risk (pyar), respectively. The 6-year average annual incidence was 2.6 per 10^6 pyar. Data from 2015 showed that estimated incidence of eBL varied in the three regions of the country, being 2.0, 1.7, and 3.9 per 10^6 pyar in the southern region, in the central region, and the northern region, respectively. In all regions, eBL incidence was higher among males than among females, and higher among the age range between 5 and 9 years than among other ages. Details on estimated incidence by province are presented in Table 2. The geographical distribution of these cases is presented in Figure 1.

In this work, we provided a description of the epidemiology of eBL across Mozambique during 12 years, from where information on eBL was limited.[12] Distribution by sex, age, and anatomical location of eBL in Mozambique are in line with the published literature.[3,4,17,18] Incidence of eBL between 2010 and 2014 ranged between 2.2 in 2011 to 3.0 per 10^6 pyar in 2015. The higher incidence observed in 2015 can be potentially explained by the active detection of cases. eBL incidence reported here is similar to crude incidence estimated in Kenya between 1999 and 2004 (i.e., 2.15 per 10^6 pyar).[18] Reported crude incidence rate in Uganda is lower (1.8 per 10^6 pyar),[19] whereas in Tanzania is higher (i.e., 4.2 per 10^6 pyar).[17] Information on population-based incidence of eBL in other African countries is scarce but several reports indicate that eBL is the most common childhood cancer in several African settings.[14] For 2015, we showed for the first time the estimated

TABLE 2

Incidence rate of endemic Burkitt lymphoma per 10^6 person-year at risk by province of birth and by age group and sex for the year 2015

		Age group*											
		1–4			5–9			10–14			All		
Region of birth	Province of birth†	All	Male	Female	All	Male	Female	All	Male	Female	All	Male	Female
South	Maputo	0.0	0.0	0.0	0.0	0.0	0.0	4.7	9.6	0.0	1.5	3.1	0.0
	Gaza	0.0	0.0	0.0	4.7	9.4	0.0	0.0	0.0	0.0	1.6	3.1	0.0
	Inhambane	0.0	10.5	0.0	4.4	0.0	8.6	0.0	0.0	0.0	1.5	3.0	2.9
Central	Sofala	0.0	0.0	0.0	3.2	6.5	0.0	0.0	0.0	0.0	1.1	2.1	0.0
	Manica	3.5	0.0	7.0	6.6	6.6	6.5	0.0	0.0	0.0	3.2	2.1	4.2
	Tete‡	–	–	–	–	–	–	–	–	–	–	–	–
	Zambezia§	2.9	2.9	2.9	2.7	0.0	0.0	1.6	3.2	0.0	2.2	1.8	0.9
North	Nampula¶	7.5	9.0	3.0	8.3	8.3	8.2	3.2	3.2	3.2	5.9	6.4	4.6
	Niassa	0.0	0.0	0.0	4.0	0.0	8.0	0.0	0.0	0.0	1.3	0.0	2.6
	Cabo Delgado	0.0	0.0	0.0	3.6	7.2	0.0	0.0	0.0	0.0	1.2	2.4	0.0

*All eBL cases were ≥ 1 year.

†Five eBL cases had no information on province or region of birth and therefore could not be included in incidences calculated by province. They were included in the overall incidence calculation reported in the text.

‡No eBL cases were diagnosed from Tete.

§Two eBL cases had no information on sex and were not included in incidence calculation stratified by sex, but they were included in the overall incidence calculation for Zambezia.

¶One eBL case from Nampula had no information on age and was not included in incidence calculation; one eBL case had no information on sex and was not included in incidence calculation stratified by sex, but it was included in the overall incidence calculation for Nampula.

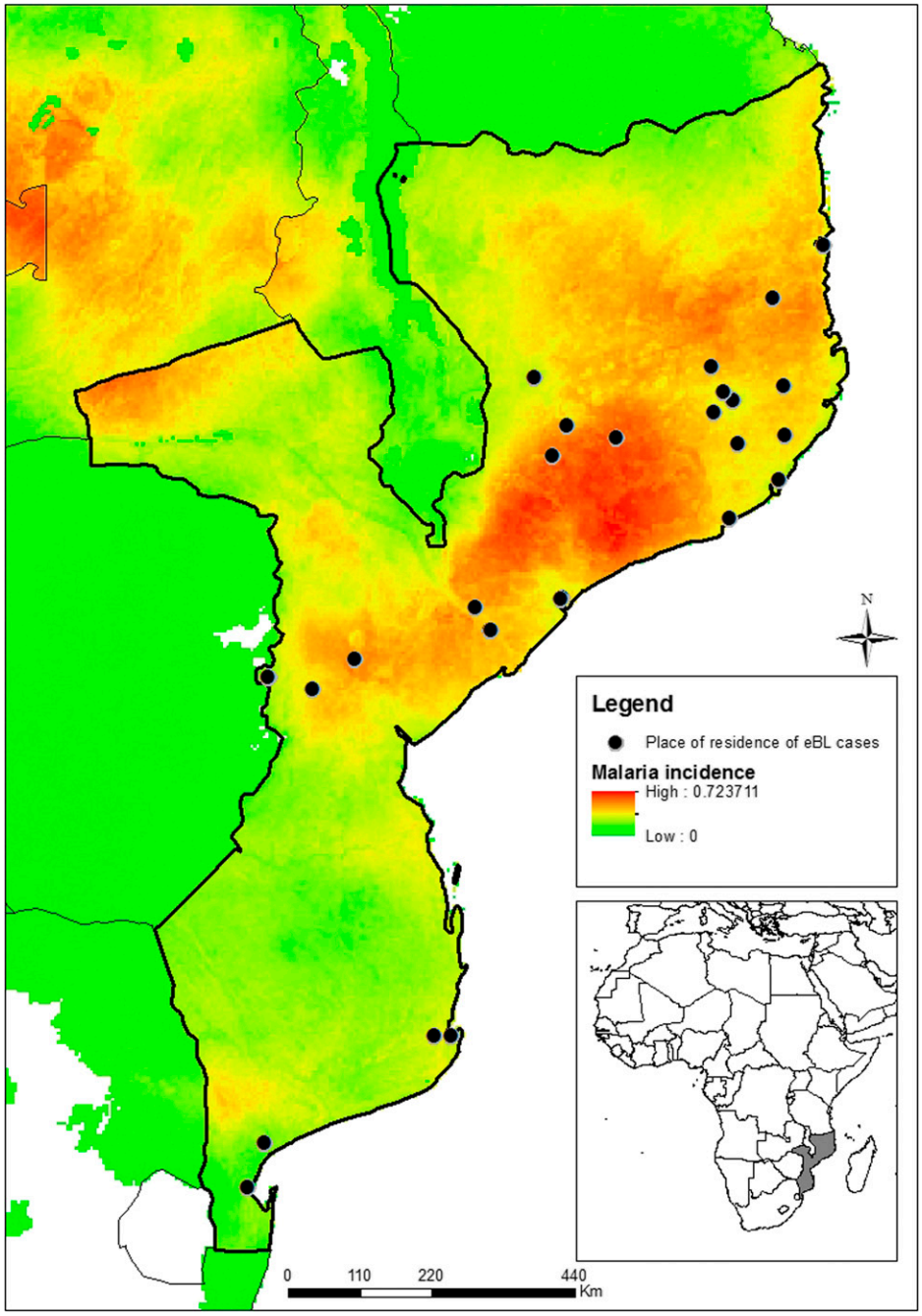

FIGURE 1. Place of residence of each endemic Burkitt lymphoma (eBL) case at onset of eBL during 2015 and malaria incidence in Mozambique based on the Malaria Atlas Project (http://www.map.ox.ac.uk/).

incidence rates of eBL for different regions of the country. Incidence rate of eBL was higher in NCH, in the northern region of Mozambique, where the intensity of malaria transmission is higher.[16]

There are important limitations that might have underestimated the incidence of eBL. First, Mozambique has large borders with Malawi, Zambia, and Zimbabwe, which might prompt patients with residences at long distances from national referral hospitals to go to closer health facilities in foreign countries. For example, there were no cases recorded during 2015 from Tete, the province that borders with Malawi, Zambia, and Zimbabwe, that is more distant to the central region referral hospital (i.e., BCH). In a study conducted in Malawi in 2005–2006, 31 of 664 children recruited with cancer, including 20 eBL cases, were from Mozambique.[4] Second, attendance to hospital in Mozambique is low,[20] and therefore we can assume that not all eBL cases reach one of the three referral hospitals. This might be specially the case in rural and poorest areas, where eBL incidence is expected to be higher. On the other hand, diagnosis of eBL in Mozambique was mainly based on cytology, with no further tests on immunocytochemistry or genetics. This might have led to misclassification of some eBL cases. Despite these limitations, the data presented here show

that eBL is a common pediatric malignancy in Mozambique, as observed in neighboring countries. Given the climatic and geographic diversity and the variation in levels of malaria transmission in Mozambique, studies on eBL involving different regions of the country would help in identifying additional cases, risk factors, and eventually implementing measures for the control of this disease.

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