

Burkitt Lymphoma Research in East Africa: Lessons from the EMBLEM Study



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Background and Etiology

Burkitt lymphoma (BL) is an aggressive non-Hodgkin B-cell lymphoma first described by Denis Burkitt in 1958 in African children. It manifests as the following subtypes.

- **Endemic** – most common childhood cancer in equatorial Africa
- **Sporadic BL** – occurs worldwide, but 10-100 times more rare than endemic BL
- **Immunodeficiency-related** – occurs in persons with HIV or transplant recipients

Subtypes share similar histologic characteristics and involve translocation/mutations of the c-myc region.

Diagnosis and treatment of BL remains sub-optimal in Africa. Previous etiologic investigations have demonstrated that endemic BL is linked to recurrent malaria infection and early EBV infection, but the role of malaria and EBV in BL etiology has not been proven. In addition, the role of genetic factors is unknown.

Methods

In 2010, the National Cancer Institute (NCI) launched a multi-year, multi-country case-control study - Epidemiology of Burkitt Lymphoma in East-African Children and Minors (EMBLEM) to:

- Determine whether malaria resistance genes are associated with decreased risk of endemic BL, to determine whether rare EBV genetic variants are associated with increased risk of endemic BL
- Conduct GWAS to identify novel gene variants associated with endemic BL
- Improve case-spotting, pathology diagnosis and treatment of BL at study sites

Study Design:

The study design is a population-based case-control study in rural East Africa, involving 2 rural lake-shore or riverine regions in Uganda, Tanzania, Kenya, where malaria transmission is high.

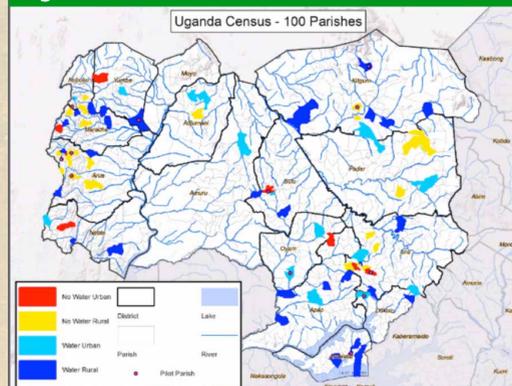


Cases are 1500 clinically stable children < 16 years with newly diagnosed, untreated BL residing in defined geographic regions.

Controls consist of the following three types:

- **Pilot population controls** – healthy children from randomly selected geographic regions
- **Health Center controls** – healthy children attending health centers serving the pilot villages
- **Matched population controls** – 3000 children frequency-matched to cases by age, gender, and residence

Uganda Control Distribution



Data collection:

Questionnaire data:

- Birth information, residence history of child, parent/family details, socio-economic status, household exposures, childhood health history, illnesses within 6 months.

Clinical and laboratory data:

- **All Participants:** CBC; malaria testing (rapid test, thin and thick smears), HIV serology, and stool parasitology.
- **Cases only:** Ultrasound results; tumor stage, tumor location, tumor histology; renal function; and chest x-ray results

Biospecimens:

- **All participants:** Venous blood (plasma, RBCs, buffy coats), saliva
- **Cases only:** H&E Slides, formalin-fixed paraffin-embedded tissue blocks, and frozen tissue

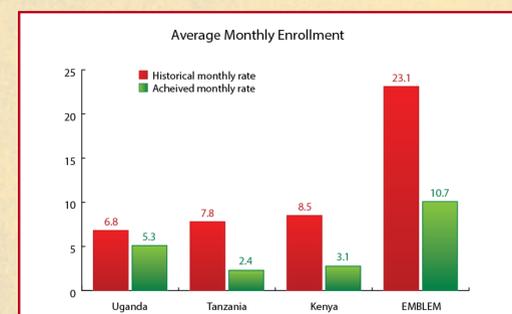
EMBLEM Sample Flow



Current Status

Case Spotting and Enrollment

	Uganda	Tanzania	Kenya	TOTAL
Spotted	343	289	180	762
Eligible	180	40	59	279
Enrolled	166	38	52	256
Ineligible	163	199	121	483



Control Enrollment in Uganda

Control Type	Selected/Targeted	Completed/Enrolled to date
Pilot Population		
Villages	12	10
Control	1,247	786
Health Centers		
Villages	12	10
Control	180-360	167
Matched		
Villages	100	To begin late 2013
Control	3,000	To begin late 2013

Biospecimen Collection

Specimen	Uganda	Tanzania	Kenya	TOTAL
Plasma samples	3,981	143	208	4,332
RBCs	2,012	73	104	2,189
Buffy coats	2,115	72	104	2,291
Saliva	3,655	111	148	3,914
Slides	68	76	55	196
Tissue blocks	73	16	38	127
Frozen tissues	5	0	0	5
TOTAL	11,909	488	657	13,054

Achievements

After establishing administrative and logistical infrastructure and obtaining ethical approval in all three countries and from two US IRBs, field work began in 2010. Besides the ongoing field data and biospecimen collection, EMBLEM has also:

- Documented historical BL experience in East Africa.
- Initiated preliminary studies of malaria biomarkers.
- Described accuracy of pathologic diagnosis of BL in East Africa.
- Completed initial studies of molecular abnormalities in BL.
- Held capacity-building workshops at Cairo, Egypt in conjunction with the November 2011 African Organization for Research and Training in Cancer (AORTIC) conference and also during a study update meeting in Mwanza, Tanzania in September 2012.
- Facilitated EMBLEM-related research projects by graduate students and residents.

Current and Future Plans

- Continue capacity building efforts
- Review and clean data for initial analyses
- Transport biospecimens to US to begin initial experiments/analyses
- Conduct key analyses:
 - Tumor genome sequencing
 - DNA extraction and genetic testing using GWAS
 - Malaria antibodies description using PCR malaria arrays
- Establish International BL Consortium

www.emblem.cancer.gov