

Epidemiological Status of *Mycobacterium ulcerans* Infections in Togo, 2010 - 2015

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Abstract Buruli ulcer is a mycobacterial disease caused by *Mycobacterium ulcerans*. The infection affects skin through the production of an exotoxin that causes necrosis of hypodermic fat. Children are the main target of the infection. In Togo, some data are available. This article is a report of the epidemiological situation in the five regions of Togo between 2010 and 2015. Three hundred and fifty-three (353) cases were reported. The Maritime Region, especially Zio District, is the location where most of the cases were recorded. It appears that in-depth studies must be carried out to understand the factors of the elevated numbers of Buruli ulcer cases in the Maritime Region.

Keywords: Buruli ulcer, epidemiology, epidemiological status, Togo, Sub-Saharan Africa

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1. Introduction

Buruli ulcer is an infection caused by *Mycobacterium ulcerans*. The infection affects the skin and sometimes bone, and can lead to permanent disfigurement and long-term disability. Children are the population most affected by the infection, and limbs are the most affected parts of the body [1]. The mode of transmission of *M. ulcerans* is not well known, but sources of water may be involved in the spread [2].

The early stage of the infection is characterized by a painless area of swelling (nodule), a large painless area of induration (plaque), or a diffuse painless swelling of the legs, arms or face (edema). The bacteria produce mycolactone, a toxin with local immunosuppressive properties that enable the disease to progress without pain and fever. Nodule plaque or edema results in ulcerations with undermined borders within 4 weeks without treatment or, sometimes, during antibiotics treatment; this corresponds to the paradoxical reaction, an intense immunological reaction that develops against the persisting mycobacterial antigens. All the stages of the disease are still painless, unless there is a bacterial secondary infection occurring during the ulceration stage, which make the disease painful. Arms and legs are the body parts most commonly affected by Buruli ulcer. Occasionally, bone is affected causing irreversible chronic functional disability [3].

The first detailed description of Buruli ulcer dates back to 1940s and was published by Mac Callum P et al. (1948) in Australia [4]. A hundred of cases were reported in Congo in 1959 and later, forty cases were reported in the Buruli infested region in Uganda in 1961 [5]. Progressively, other cases have been reported in other regions of Africa [6,7,8], in Asia and Pacific [9,10,11], and in Americas [12,13,14] with an increasingly prevalence causing concern.

In Togo, since the first cases reported by Meyers et al. in 1996 [15] through 2006, some 2 000 cases were clinically suspected, but not laboratory confirmed. They are usually registered and treated in the country's hospitals. Bretzel et al. (2011), through a study on the laboratory confirmation of Buruli Ulcer in Togo, described the situation in the country between 2007 and 2010. This study proposes to present the epidemiological situation of the disease in Togo from 2010, the year of the development of a national database dedicated to Buruli cases, to 2015, to review whether the quality of BU control has remained constant since 2010.

2. Methods

This a time-series study covering all records of patients received at the National Reference Center of Buruli ulcer (Tsevie Regional Hospital, Maritime Region), and at the Buruli ulcer Care Unit of Sotouboua (Central Region). Clinic and epidemiological information of diagnosed

patients from January 2010 to December 2015 were accessible from the national Buruli ulcer database.

Access to the data was authorized by the board of the National Program against Buruli Ulcer, Leprosis and Pian (Reference: 159/2015/MS/ DGS/ DSSP/ PNLUB-LP of November 20, 2015). The Bioethics Committee for Health Research (CBRS) approved the study project (N ° 21 / 2017 / CBRS of October 8, 2017). Personal identifying information was removed from all data collected and analyzed. The variables of interest were: age, gender, education level, place of residence, and types of lesions and their location.

Among suspected cases, only those confirmed by microscopy (Ziehl-Neelsen acid fast staining technique) or molecular biology (polymerase chain reaction, IS2404 PCR) at the National Reference Laboratory, Lomé, Togo were included in this study. Diagnosed patients received appropriate mycobacterial treatment, but the

implementation of preventive measures to limit functional disabilities as proposed by the WHO seems to not be well integrated in the routine activities.

Data were analyzed with Epi Info 3.5.1 (Centers for Disease Control, Atlanta, Georgia, United States). Frequencies were compared using the Chi-squared test or the Fisher exact test if expected frequencies were less than 5 at 95% level of confidence.

3. Results

From 2010 to 2015, 353 of the 362 suspect cases received in the two Buruli ulcer care units were confirmed by clinical presentation, microscopy or PCR. 165 cases were confirmed by microscopy representing 46.75% of confirmation. 271 cases were confirmed by PCR, which represents 76.77% of confirmation.

Table 1. Distribution of Buruli ulcer cases reported in Togo by district, by year, 2010 - 2015

Districts	Years						Total	Percentage (%)
	2010	2011	2012	2013	2014	2015		
Distribution of buruli ulcer cases by district								
SAVANNAH REGION								
Tone	1	1	0	0	0	0	2	0.56
KARA REGION								
Kozah	0	0	0	0	1	0	1	0.28
CENTRAL REGION								
Anié	0	0	1	0	0	0	1	
Blitta	0	0	0	0	1	0	1	4.25
Sotouboua	7	2	0	2	1	0	12	
Tchaoudjo	1	0	0	0	0	0	1	
PLATEAUX REGION								
Amou	0	1	0	0	0	0	1	
Haho	1	0	0	1	0	0	2	1.13
Ogou	0	1	0	0	0	0	1	
MARITIME REGION								
Avé	1	0	1	0	0	1	3	
Bas-Mono	0	0	1	1	0	0	2	
Golfe	0	1	2	1	0	0	4	
Lacs	0	1	1	0	0	1	3	94.05
Vo	2	0	2	3	1	0	8	
Yoto	27	29	21	18	18	23	136	
Zio	23	18	22	13	45	55	176	
LOME TOWNSHIP REGION								
D5	0	0	0	0	0	1	1	0.28
TOTAL	63	54	51	39	67	79	353	100.00

Significant differences were observed in the number of cases between 2013 and 2014 ($p = 0.0032$) and between 2013 and 2015 ($p = 0.0001$). The Maritime Region reports the highest number of cases.

Table 2. Distribution of Buruli ulcer cases reported in Togo, by age group and gender, types of lesions, by WHO categories and sites of lesions, 2010 - 2015

Distribution according age group and gender			
Age median = 12 (1 - 95) years			
Age (years)	Number (Percentage)		p value
	Male	Female	
1-14	116 (33)	97 (27)	N/A
15-29	35 (10)	28 (8)	N/A
≥30	24 (7)	53 (15)	N/A
TOTAL	175 (50)	178 (50)	
TOTAL	353(100)		
Distribution according types of lesions			
Types of lesions	Number	Percentage (%)	p value
Ulceration	169	48	p < 0.0001
Nodule	81	23	
Blotch	62	18	
Oedema	27	8	
Mixte types	14	4	
TOTAL	353	100	
Distribution of Buruli ulcer cases in Togo by WHO lesions categories			
Categories	Number	Percentage (%)	p value
Catégorie I	126	37	N/A
Catégorie II	124	36	
Catégorie III	95	2	
TOTAL	345	100	
Distribution of Buruli ulcer cases in Togo by lesion sites			
Lesion sites	Number	Percentage (%)	p value
Lower right limb	90	25	p < 0.0001
Upper right limb	78	22	
Upper left limb	69	20	
Lower left limb	67	19	
Buttock	13	4	
Trunk	11	3	
Abdomen	9	3	
Back	7	2	
Head	5	1	
Multiples sites	4	1	
TOTAL	353	100	

Ulcerations are the most frequent lesions seen in cases ($p < 0.0001$) while category III is the least frequent distribution. The limbs are the sites most affected ($p = 0.0001$).

4. Discussions

Buruli ulcer remains a disease of public health concern in Africa and particularly in Togo, as shown by the data and the increasing trend in the number of cases within the

last two years. In 2013, fewer cases were recognized because of fewer public health staff available to perform surveillance. The increase could be associated with the management training for detection of Buruli cases who were attended by nurses, and may have led to increased cases notifications. This could also be associated with regular surveys for the National Program associated with the Non-Governmental Association in the rural areas, specifically for physical therapy. Moreover, this increasing trend could be explained by better knowledge, identification, care, and proper reporting of the disease by

the health workers. Togo's neighboring countries, such as Benin, Ghana, and Cote d'Ivoire, are also confronted with this issue [6,8,16].

Buruli ulcer is unevenly distributed throughout the country. The south of the country, especially the Maritime Health Region, is the most affected. This could be explained by the presence of many streams and lagoons of the region, and confirms the findings of Christinet et al. 2012 in Cameroon [17]. Furthermore, Walsh et al. 2008 found that man-induced environmental changes such as deforestation, irrigation systems, and increasing wetland areas contribute to the spread of the disease [18]. This applies to the Yoto and Zio districts where populations are involved in important rice production activities. It is also important to emphasize that even though the other health regions in Togo present fewer cases, they should also be investigated since practitioners may not be familiar with the disease.

In addition, according to Johnson et al. 2005 in Benin, Buruli ulcer reporting through routine data from health facilities shows that in the same district, the number of cases may vary considerably from one village to another. These variations from the continuous control of Buruli ulcer reveal that the relevant geographical unit for the analysis of the disease must be a smaller entity instead of a national, regional, or even district one [19]. However, the number of cases we found might have been underestimated because of the hospital-based nature of our study. In fact, all strata of the population in Togo may not have an equal geographical and financial access to healthcare facilities.

Buruli ulcer equally affects men and women and, in our case, children under 15 are mostly the victims as Joose et al. (1994), Kanga et al. (2001), and the WHO (2017) confirmed. They also report that, in Africa, about 48% of the affected population are children under 15, whereas in Australia and Japan, they represent only 10% and 19% of the cases respectively [3,6,8].

As children under 15 are the most affected, the average age is 12 years. This average age is close to those described in Benin (12 years) by Vincent et al. (2014), in Cameroon and Nigeria (15.5 years) by Porten et al. (2009) and Ukwaja et al. (2016) respectively [20,21,22]. On the other hand, it is lower than that described in Ghana (25 years) by Amofah et al. (2002) and in the Democratic Republic of Congo (27 years) by Mavinga Phanzu et al. (2013) [23,24].

According to the types of lesions, no osteomyelitis, a severe form associated with complications, was noticed. Most of the cases were ulcerative forms (47.03%), which are often very painful and constitute the causes of consultation in care centers. Our data confirm those of Amofah et al. (2002) and Johnson et al. (2005) in Ghana and Benin, who found 48 and 58% respectively.

The ulcerative forms were found to have the greatest proportion (48%), however, we found it is still lower than those reported by Ukwaja et al. (2016) in Nigeria, who found a proportion of 90% and Mavinga Phanzu et al. (2013) in the Democratic Republic of Congo (83%).

According to Lagarrigue, Portaels, Meyers and Aguiar (2000), HIV infection seems to be the predominant factor favoring the occurrence of osteomyelitis [25]. Since our target population is on average 18 years old, rural, with a

low HIV prevalence (Togo- 2.5%, rural- 1.5%), these factors could explain the absence of osteomyelitis. However, our study did not involve HIV testing.

In this study, the categorization of lesions according to WHO categories yielded 37% for Category I (single small lesion), 36% for Category II (non-ulcerative and ulcerative plaque and oedematous form) and 27% for Category III (disseminated and mixed forms such as osteitis, osteomyelitis, joint involvement). Some practitioners did not classify eight of the lesions in those categories (345/353). These results are very similar to the WHO Global Data in Africa where 32% of the cases are Category I, 35% are Category II and 33% are Category III [3]. These results are also comparable with those of Beissner and al (2013) who identified 45.7% of category I lesions, 34.1% category II lesions and 20.2% of category III lesions. These results show that the control program of BU in Togo is performing well because of the lower numbers of the Category III. Furthermore, this number has decreased by 12% up to 2010.

Buruli ulcer disease leads to large ulcerations and causes disabilities in approximately 25% of the patients. Available data on treatment outcome of BUD patients suggest that recurrences are rare; however, paradoxical reactions and functional limitations frequently occur. In 2013, Beissner and al, [26] found 84.5% patients healed without complications, and 3.9% had secondary lesions. Among the Togolese patients from 2010 to 2015, disability, functional limitations, scarification, and relapses were fully reduced; only twelve patients had functional limitations and one patient had arm amputation.

In our study, Buruli ulcer mainly affects the limbs (86% of cases), and the same finding was made by Beissner et al. (2015), Bretzel et al. (2011) [27]. According to Eddyani & Portaels (2007), these findings argue in favor of the thermosensitivity of *Mycobacterium ulcerans* to develop within the ulcerous cutaneous lesions in the area of the limbs [28].

As in many studies, our results show that the lower limbs are the most affected (44.2%). This confirms the WHO report that lesions frequently affect the lower limbs in 55% of cases. According to Debacker et al., 2004, this can be attributed to the fact that limbs are mostly in contact with soil, watercourses, plants and insects [29].

Only a few studies, such as the one conducted by Stoffel, Barthelmé, & Chagué (2005), showed that Buruli ulcer independently affects the whole integument and that ulcers due to other causes have a demonstrated tropism for the lower limbs [30].

5. Conclusion

Buruli ulcer remains a real public health problem in Togo with regard to the annual increase in cases reported in hospitals and the proximity of border countries in which it is observed with a high prevalence. These results show that the control program of BU in Togo is performing since 2010. As Togo contains several wetlands areas and lagoons considered to be hazardous zones according to the studies in the field, further research is required to better document the Buruli ulcer prevalence found in Togo.

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