JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Spatial clustering of onchocerciasis in Bioko Island, Equatorial Guinea

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Abstract
Introduction: Onchocerciasis is a chronic neglected tropical disease caused by the filarial nematode *Onchocerca volvulus*, which is endemic in Equatorial Guinea. The aim was to estimate the current spatial distribution of onchocerciasis, and its related factors, in Bioko Island after several years of mass drug administration and vector control activities, by using GIS technics.
Methodology: The survey was carried out within the framework of a wider research project entitled "Strengthening the National Programme for Control of Onchocerciasis and other Filariasis in Equatorial Guinea". A structured questionnaire was designed to cover basic socio-demographic information and risk factors for onchocerciasis and the coordinates of household. the hydrographic network data to calculate the positive onchocerciasis rate was used. Poisson generalized linear model was used to explore the association between onchocerciasis and the following covariates: distance to the river, preventive practices, water source and household´s main source of income. Two different cluster analysis methods were used: Getis-Ord Gi statistic and SaTScan™ purely spatial statistic estimator.
Results: The risk of onchocerciasis was higher for those who drank water from external sources (RR 25.3) than for those who drank home tap water (RR 8.0). The clusters with z-score higher were located at the east of the island. For 5 km and 1 km distances, one significant cluster in the east was detected (RR 5.91 and RR 7.15).
Conclusion: No environmental factors related with onchocerciasis were found, including proximity to rivers. This could be partially explained by the fact that the vector was eliminated in 2005.

Key words: *Onchocerciasis;* Africa; environmental factors; cluster analysis.

J Infect Dev Ctries 2018; 12(11):1019-1025. doi:10.3855/jidc.10159

(Received 09 January 2018 – Accepted 05 September 2018)

Introduction

Onchocerciasis or "river blindness" is a chronic parasitic neglected tropical disease caused by the filarial nematode *Onchocerca volvulus* (*O. volvulus*). It is transmitted to humans through exposure to repeated bites of infected blackflies of the genus *Similium* [1]. Several simulid species have been incriminated in the transmission of *O. volvulus*. The complex *S. damnosum* and, to a lesser extent, the *S. naevei* complex are the most frequently found in Africa and the Arabian Peninsula [1]. *Onchocerciasis´* most important morbidity is due to cutaneous and ophthalmologic manifestations, with different clinical grades [2]. The presence of one or another clinical manifestation varies depending on the most prevalent parasite strain circulating in the area: blindness tends to occur more frequently in the West African areas of savannah while onchocerciasis cutaneous disease (OCD) prevails in African forest areas [3].

Currently, more than 99% of people infected by onchocerciasis live in 31 African countries and about 118.1 million people are at risk of contracting the disease in Africa [4]. People who live in rural areas near fast-flowing rivers and streams where there are *Simulium* blackflies are most at risk of acquiring onchocerciasis [5]. Other risk factors that influence the dynamics of onchocerciasis transmission are related to altitude, temperature and vegetation, which influence the competition of vectors, their behavior and their abundance in a given area. It has been described the seasonal variation in the activity of the vector, being in the rainy season when there is a greater increase in the number of *S. damnosum* [6,7]

On a global level, sustainable mass drug administration of ivermectin is currently the primary control strategy for onchocerciasis. WHO onchocerciasis control programs in Africa include the Onchocerciasis Control Program (OCP) which started in 1974, and was originally focused in vector control; and the African Program for Onchocerciasis Control (APOC), launched in 1995 in order to assist countries outside the original OCP area in West Africa, establishing sustainable national programs for ivermectin distribution [8]. As a result of the success due to sustained onchocerciasis control activities, APOC paradigm has recently changed from control to a strategy of onchocerciasis elimination 'where feasible' [9]. The new elimination goal requires the assessment of areas with lower infection prevalence [10].

In Equatorial Guinea, onchocerciasisis an endemic disease both in mainland and insular zones [11]. In 1987, OCP activities begun in the country, but it were only in 1998 when ivermectin distribution activities were started as part of the proposed APOC mandate [12]. Since then, ivermectin population coverages have ranged yearly between 50% and 75% [13]. Additionally, in 2005 aerial larviciding campaign was successful in eliminating *S. yahense* from Bioko Island, with no evidence of vector reappearance in the following years [14].

Despite the achievements in onchocerciasis control in Bioko Island, there is no spatial information on the current situation of onchocerciasis. Thus, the aim of this study were estimated the current spatial distribution of onchocerciasis, and its related factors, in Bioko Island after several years of mass drug administration and vector control activities, by using Geographical Information System (GIS) technics.

Methodology

Study area

This study was carried out in Bioko Island, Equatorial Guinea, from mid-January to mid-February 2014. The Island of Bioko is a part of the Republic of Equatorial Guinea, which also includes the mainland and the island of Annobon. It is located in the Bay of Guinea in Central Africa, about 40 km southwest of the Cameroon coast. The surface area of Bioko Island is of approximately 2,017 km^2, and is about 72 km in length. Malabo is the largest city on the island and the capital city of Equatorial Guinea. Four different districts can be found in the Island. According to the 2011 census, the population was 260,000, most of the inhabitants living in the northern part of the island [15]. The island is mostly covered by tropical rainforest. Its interior is covered with dense forests on the steep slopes of volcanoes and calderas. The highest peak reaches 3,011 m above sea level. The island has a humid tropical environment. Mean daily maximum and minimum temperatures range between 29-32°C and 19-22°C, respectively.

Study design and sample size

The survey was carried out within the framework of a wider research project entitled "Strengthening the National Programme for Control of onchocerciasis and other Filariasis in Equatorial Guinea". This project aimed at improving and updating the current epidemiological data on these infectious diseases in this country.

Sample size was calculated according to previous estimates of onchocerciasis prevalence in the area, based on MF skin snip assessments (0-10% in 2013 epidemiological evaluation). The sample size was computed using Epi-Info version 3.4.1 free software considering the following parameters: 95% CI, 80% power and 3% standard error. A multistage sampling technique was carried out. Firstly, twenty sub-districts were randomly selected. Secondary, sampling units were randomly selected houses in each of the selected sub-districts the main caregivers in every household were identified for the interview. In absence of the caregiver, the head of the household answered the questionnaire. Only those houses, whose caretaker or head of household had lived in Bioko Island for at least 5 years prior to the survey, were included in the study. Exclusion criteria included: immigrants from other countries, and not usual habitation in the household. Each interview was made by house-to-house visit.

Data collection

A structured questionnaire was designed to cover basic socio-demographic information and risk factors for onchocerciasis. It was pre-tested on close communities not included in the study to check cultural acceptability and validity. When needed, the participants were interviewed in their local languages by trained data collectors (health extension workers) who speak the local languages.

The coordinates (longitude and latitude) of every selected household were recorded on-site using DakotaTM 10 Garmin single handheld GPS receivers, and processed with Google Earth Pro.

The hydrographic network to analyze the environmental conditions in the study area was used; the data in shape file format were obtained from the interactive Atlas of the Republic of Equatorial Guinea [16].

To assess the distance to the river, a 1, 1.5 and 2 kilometer-buffer around each river were created and we added the household distance.

Onchcocerciasis positivity was assessed by detecting the presence of IgG4 antibodies to Ov16 antigen using ELISA assay as diagnostic test. Positive onchocerciasis rate per house-hold based on the total number of individuals in each household and the number of positive individuals were estimated.

Statistical analysis

Data were aggregated by household level to describe the characteristics of the distribution of positive onchocerciasis rate. As the prevalence of onchocerciasis positive rate across households was non-normal, a generalized linear model (GLM), Poisson distribution modeling was used, in order to explore the association between onchocerciasis positive cases at household level and the following covariates: distance to the river, preventive practices, water source and household´s main source of income. The water source was split up in the following categories: water tap within the household, water tap outside the household, fountain, river and others. The source of income was split up into the following categories: agriculture, hunting and fishing, employee, own-business, and others. Participation in preventive practices referred to the intake of ivermectine during past mass drug administration campaigns.

Clusters analysis

Two different cluster analysis methods were used. Firstly, we carried out a Hot Spot analysis using the Getis-Ord Gi statistic. This method identifies those clusters of points with values higher in magnitude than expected by random chance. Then, SaTScan™ purely spatial statistic estimator developed by Kulldorff [17] based on the assumption of a Poisson distribution to detect spatial clusters was used. This method consists of creating a circular window which scans the entire study area. In this study, the spatial window to a maximum radius of the average distance between cases was restricted. The radius of the centroid varies continuously in size from 0 to the specified upper limit. An infinite number of overlapping windows of different size and shape are thus generated, which together cover the entire study area. Each circle is a possible candidate cluster. The null hypothesis that the risk is constant in space is tested against the alternative hypothesis: the risk is different in at least one circle (or window). For each circle, the number of observed cases inside and outside the window is counted along with the number of expected cases, estimated according to the model. On this basis, the likelihood within each circle is then calculated. The circle having the maximum likelihood and containing more cases than expected is denominated the most likely cluster.

$$\left(\frac{c}{E[c]}\right)^{c}\left(\frac{C-c}{C-E[c]}\right)^{C-c} I()$$

Where: C is the total number of cases, c is the observed number of cases within the window, and E[c] is the covariate-adjusted expected number of cases within the window under the null-hypothesis. I() is an indicator function, which is equal to 1 in cases where the window has more cases than those expected under the null hypothesis, and 0 otherwise.

Table 1. Description of households participating in the study, Bioko Island, January 2014.

Variables		**N total (%)**	**Positive households (%)**	**Negative households n (%)**	**p- value**
Source of income	Agriculture, fishing, hunting	45 (34.6)	32 (21.3)	13 (43.3)	0.578
	Employee	33 (25.4)	26 (17.3)	7 (23.3)	
	Own business	25 (19.2)	19 (12.6)	6 (20)	
	Others	27 (20.8)	23 (15.3)	4 (13.3)	
Water source	Water tap within the household	25 (19.3)	24 (45.2)	1 (1.2)	0.105
	Water tap outside the household	26 (20.1)	8 (15)	26 (30.9)	
	Fountain	51 (39.5)	12 (22.6)	39 (46.4)	
	Rivers	11 (8.5)	4 (7.5)	7 (8.3)	
	Others	16 (12.4)	5 (9.4)	11 (13)	
Previous intake of ivermectin	Yes	38 (27.1)	10 (30.3)	28 (26.1)	0.482
	No	91 (65)	22 (66.6)	69 (64.4)	
	UK/UA	11 (7.8)	1 (3)	10 (9.3)	

*UK/UA: Unknown/Unanswered.

The increase in observed cases above the number expected was assessed using Monte Carlo test simulations (999 replications) with a 95% confidence interval.

ArcGIS 10.1 and SaTScan 9 were used to do the spatial analysis and to produce the maps.

Ethics Statement

The study protocol was approved by the Ethical Committee of Health Institute Carlos III in Madrid, Spain. Permission was obtained from the Equatoguinean Ministry of Health and the National Programme for Control of Onchocerciasis and other Filariasis.

Written informed consent was obtained from all participants prior to study inclusion. Participants were informed about the objective of the study. Anonymity was assured and it was emphasized that participation was voluntary. A written statement was also included on the introductory part of the questionnaires in which further information concerning the purpose of the study and the confidentiality of the research information was given. Data were analysed in anonymous form.

Results

A total of 150 households were analysed throughout the study area. Five house-holds were excluded from the analysis for not having collected coordinates.

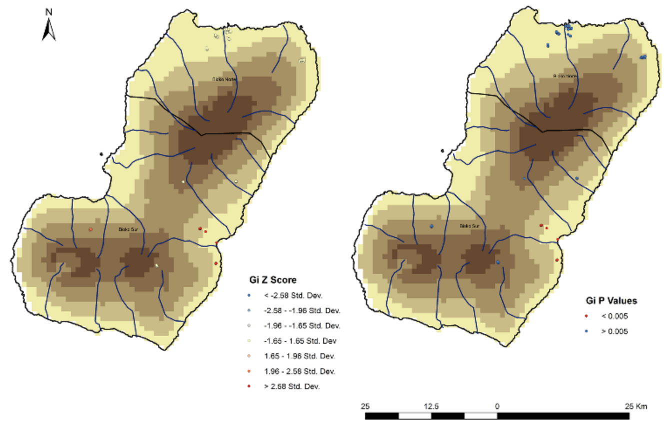
From the analysed households, 33 presented at least one positive case for onchocerciasis: 26 had only one positive case for onchocerciasis (17.2%), and 4.7% of households had two or more positive cases.

In most positive households, the source of income was related to outdoor activities (agriculture, hunting or fishing) (32/150, 21.3%), but this association was not significant (p = 0, 578) (Table 1).

Factors associated with onchocerciasis prevalence at household level

The results obtained from Poisson regression model (Table 2) suggest that the risk of onchocerciasis is higher for those who drink water from external sources than for those who drink home tap water. Relative risks were: 25.3, 15.0 and 8.0 for drinking water from a river, an outdoor tap source, and a fountain, respectively. All these associations were statistically significant ($p < 0.05$). The rest of analyzed variables were not significantly associated with the risk of onchocerciasis.

Figure 1. Clusters distribution of positive onchocerciasis households using Getis-Ord_Gi, Bioko Island, Equatorial Guinea, 2014.



Clusters analysis

The Figure 1 shows the spatial clusters distribution using the Getis-Ord Gi. The higher z score values, in red color, correspond to the houses aggregated with higher prevalence rates. These clusters were located at the east of the island. On the other hand, the clusters with the lowest z score values (colored in blue),

Figure 2. Spatial cluster distribution of positive onchocerciasis households using Scan statistic, Bioko Island, Equatorial Guinea, January 2014.

Table 2. Factors associated with onchocerciasis prevalence at household level, January 2014, Bioko Island, Equatorial Guinea.

Water source	RR	(IC 95%)	P value
External tap water	15.0	(2.96 - 274)	0.009
Fountain	8.0	(1.61 - 145)	0.044
Rivers	25.3	(4.50 - 473)	0.003

representing aggregations of houses with low rates of serological prevalence, were detected in the north area, around Malabo city. The right figure shows the statistical significance of these values.

Different distances to detect clusters using Scan statistic (1 and 5 kilometers) were used. For 5 km, one significant cluster located in the East of the island (Figure 2) was detected, this cluster included 13 houses and 11 positive cases. The expected cases were 2.36. The Relative Risk (RR) was 5.91 and the likelihood ratio 9.26 (p value < 0.005). When 1 km distance was used, detected one significant clusters in the same area but smaller (Figure 2). This cluster included 9 houses and 7 positive cases. The expected case was 1.14 and the RR was 7.15. The likelihood ratio was 7.28 (p value < 0.005).

Discussion

Only a few articles in the literature have simultaneously examined household and environmental risk factors associated to onchocerciasis in Sub-Saharan Africa. To our knowledge, this is the first time that this association is addressed in Equatorial Guinea.

Using spatial statistics and GIS, the spatial distribution of the positive rate for onchocerciasis in 150 households in Bioko Island was investigated. Onchocerciasis positivity was assessed by detecting the presence of IgG4 antibodies to Ov16 antigen using ELISA assay as diagnostic test. This test has demonstrated to be a useful indicator of exposure and a validated tool to monitor progress towards elimination.

Higher prevalence of onchocerciasis in those households located in rural areas, especially on the East (Riaba district) was found. In contrast, lower prevalence was found in urban areas of Malabo district.

In this study, no identify significant spatial clusters of onchocerciasis in relation to proximity to rivers. The relation between onchocerciasis rates and the distance to a river and/or forest (as potential breeding sites) has been well documented in the literature [5,18,19]. Furthermore, an increase in the number of *S. damnosum* during the period of heavy rainfall tends to occur in many endemic areas [7]. This increase may be due to the stimulus of increased oxygen content of the water during the rainy season, which causes flies to emerge from pupae [7].

This is also observed in Bioko Island, where the rainfall is highly seasonal, with a dry season which lasts from December to April, and many of the rivers and the streams dry up soon after the end of the rainy season. Vector biting densities also follow the two seasons in this area, with low monthly biting rates (MBR) in the dry seasons, and rising a peak in the rainy season [19].

The current study was performed during the dry season (January 2014) in order to facilitate the field work. The lack of association between onchocerciasis risk and proximity to rivers in our study could be explained by the fact that successful onchocerciasis control activities have been performed in Bioko Island for the last 20 years, and that larviciding campaigns were successful in eliminating *S. yahense* from Bioko Island in 2005 [14].

Any significant association between onchocerciasis risk and altitude in this study were not found. Altitude has been found to be positively correlated with onchocerciasis prevalence in various foci of Cameroon, Venezuela, and Guatemala up to an altitude of 1,500 meters above sea level, and negatively correlated above that altitude, with most of the proportional increase taking place at altitudes up to 500 m. This association may also depend on the type of river and its geomorphological substrate, determining vector breeding suitability [6]. Previous studies suggest that the majority of breeding sites in Bioko Island are located below 1000 meters of altitude, being the highest concentration below 500 meters, where the temperatures are also more suitable for vector reproduction [19]. Bioko Island altitude is above sea level, except in the mountainous areas, whose maximum height is the Pico Basile (3,011 meters). The potential elimination of the vector in the Island and its limited altitude might partially explain the lack of association in our analysis.

Other relevant factors influencing onchocerciasis transmission in endemic countries include temperature and humidity [6,20]. Bearing in mind the cross-sectional nature of this study and the absence of previous environmental data to compare, no considered these factors in the analysis.

Regarding household risk factors, it was found that the risk of onchocerciasis was higher for those who drink water from external sources, in comparison to those people who drink tap water at home or from other sources. The rest of analyzed variables, including source of income/occupation and previous participation in ivermectin preventive activities do not appear to be associated with the risk of onchocerciasis.

The observed association between onchocerciasis positivity and source of household water still needs to be clarified. One hypothesis could be related to the fact that biting activity manifested itself in a bimodal pattern with an early morning peak (10:00 AM to noon) and a late afternoon peak (4:00 PM to 6:00 PM) [7]. The cause of biting activity peaks is still poorly understood, but could be coherent with the range in which most individuals (house-keepers and workers) perform their daily routines outdoors, as previously described in some studies conducted in the Lower Cross River Basin in Nigeria [7]. In contrast, occupation/source of income, which is also closely related to outdoor human activity, was not significantly associated with an increasing risk of onchocerciasis in our study.

The cluster analysis for 5 km and 1 Km distance revealed one significant cluster in the East of the island, located in Riaba district. This hotspot include some of the most neglected and rural communities in Bioko and corresponds to an area where a positive case for active onchocerciasis has recently been identified by molecular identification (PCR) [20].

It needs to be highlighted that our results are expected to be strongly influenced by the fact that huge advances have been achieved in onchocerciasis control in the last twenty years in the study area, which is currently considered as hypoendemic. Additionally, in 2005 the larviciding campaign was successful in eliminating *S. yahense* from Bioko Island, with no evidence of vector reappearance in the following years [14]. No additional entomological assessments have been performed since 2008.

The geographic isolation of the Bioko focus from vector re-invasion is likely to have played a major role to approach vector elimination in this area and might also be influencing our results. Nevertheless, even though the risk is low, still remains the danger that a different vector cytoform of the *S. damnosum complex* could migrate from the mainland (or neighboring countries with higher onchocerciasis prevalence, such as Cameroon) to the island and become established. If this situation eventually happens and there are still enough parasite reservoirs due to human migration between both areas, the reemergence of the disease might occur.

However, this situation would be expected to be easily controlled, given that *S. yahense* is one of the most efficient vectors of West Africa and any other vector is expected to be less efficient in the transmission [14]. Hence, entomological and spatial analysis surveillance is highly desirable in this area.

The present study was conducted in Bioko Island, thus, the findings may not be generalizable to the whole country.

Some households were included in the spatial analysis although no additional data were recorded from them. Additionally, the small sample size and the cross-sectional nature of this data do not allow us to examine causality in the relationship between onchocerciasis prevalence and several risk factors.

Moreover, it was not possible to evaluate variables such as humidity, vegetation and temperatures in the analysis. Finally, entomological data would have also been desirable to better explain the relation between onchocerciasis prevalence and some environmental factors.

Finally, it must be noted that the ELISA test to detect IgG4 antibodies against Ov16 is not a real estimator of onchocerciasis prevalence as it does not distinguish between past and acute infections.

Conclusions

In this study, no environmental factors related with onchocerciasis were found, including proximity to rivers. This could be partially explained by the fact that the vector was eliminated in 2005.

Only one significant cluster was identified in the east of Bioko Island, which correspond to Riaba district, one of the most rural and neglected districts in the Island. The results are coherent with the fact that onchocerciasis transmission could have been interrupted in Bioko Island after two decades of control activities. The spatial methods can help policy makers to plan and undertake new national and regional initiatives to streamline recommendations. They can be especially useful to monitor progress towards onchocerciasis elimination in Equatorial Guinea.

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Conflict of interests: No conflict of interests is declared.