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Full Length Research Paper

Success of lymphatic filariasis control in Benin: Effects of Ivermectin and Albendazole on microfilaraemia

Aurore Ogouyèmi Hounto^{1*}, Moudachirou Ibikounle², Yolande Sissinto Savi de Tove¹,
Aboudou Dare³, Wilfrid Batcho⁴, Achille Kabore³ and Dorothée Kinde Gazard¹

¹Unité d'Enseignement et de Recherche en Parasitologie de la Faculté des Sciences de la Santé de Cotonou/ Université d'Abomey-Calavi, 01BP526, Benin.

²Département de parasitologie de la faculté des sciences techniques/ Université d'Abomey-Calavi, 01BP526, Benin.

³RTI International, District of Columbia, 3040 Cornwallis Road, Research Triangle Park, NC 27709, WA, United States.

⁴Programme National de Lutte contre les maladies Transmissibles/ Ministère de la Santé, Côte d'Ivoire.

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Lymphatic filariasis (LF) is a parasitic disease that is endemic throughout sub-Saharan Africa, infecting approximately 40 million people. The aim of this study was to determine effect of Ivermectin and Albendazole on microfilaraemia in 10 communes that have completed 5 rounds of MDA in Benin. The study was both retrospective and prospective. The retrospective part consisted of collecting the information in the registers of the National Communicable Diseases Control Program (NCDPCP) in order to determine the geographical and therapeutic coverage during the period of MDA. The prospective part, which consisted in the realization of a nocturnal microfilaraemia, took place with the participants of 5 years and more. Data were analysed using EpiInfo (USD, Inc., Stone Mountain, GA) version 6. Differences in proportions were calculated by Chi-square, with significance level at 0.05. The average geographical and therapeutic coverage was in line with WHO recommendations in several communes. A total of 3121 people were clinically examined and sampled. Chronic manifestations were found in approximately 1% of the total population while only one person had a positive thick drop of *W. bancrofti*. Since microfilaraemia is <1% in the study communes, the standard recommended by the WHO for the success of MDA, our results confirm the effectiveness of Ivermectin and Albendazole on microfilaraemia and can therefore contribute to the control of LF in Benin.

Key words: Lymphatic filariasis and mass drug administration, microfilarémia, Benin.

INTRODUCTION

Lymphatic Filariasis (LF) is a Neglected Tropical Disease (NTD) primarily prevalent in poor populations in 73 countries (World Health Organization [WHO], 2013a). About 120 million people in 83 countries in the tropical

and subtropical regions of the world are infected, with an estimated 1.34 billion people at risk (WHO, 2010). In Africa, it is caused by *Wuchereria bancrofti* and transmitted by *Anopheles* and *Culex* mosquitoes (WHO,

*Corresponding author. E-mail: aurorefel@yahoo.fr. Tel: 0022997684645.

2010, 2013b). The main clinical manifestations being lymphedema, hydrocele, and elephantiasis (Addis et al., 1995). LF has been identified as the second leading causes of permanent and long term disability in the world (WHO, 1995, 2010). The disease is rarely fatal, but clinical manifestations carry grave personal and sociocultural consequences for those affected and their immediate family members.

The fact that humans are the only reservoir host for LF, together with the availability of simple, safe, and inexpensive drugs for treatment and effective diagnostic tools, led to the recognition that LF might be eradicable (Ottesen et al., 1997). Accordingly, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) was launched in 2000, aiming to eliminate LF as a public health problem by 2020 (WHO, 1997). The recommended strategy is to treat entire at-risk populations annually through mass drug administration (MDA) with a single dose of Ivermectin and Albendazole (IVM + ALB) in sub-Saharan Africa for a minimum of 5 years (Ottesen et al., 1997; WHO, 2013c). Indeed, following five annual rounds of MDA, the density of circulating microfilaria in infected individuals may be reduced and LF transmission disrupted.

The West African country of Benin was among the first countries to conduct a national baseline LF prevalence survey in 2001 in order to estimate the burden of the disease. It resulted that 48 communes were endemic of FL. Shortly, following these results, Benin launched its national programme for LF elimination and began, in 2001, implementing MDA within three communes. MDA then scaled up progressively to 23 communes in 2005. They stopped MDA in 2009 and are engaging in post intervention surveillance since 2013. Currently, 25 other communes are under MDA and ten of them have already completed the World Health Organization (WHO) recommended minimum of five annual effective rounds of MDA.

The key challenge now is to determine whether this MDA has been sufficient to interrupt transmission in these communes. Following WHO guidelines (WHO, 2013c), MDA can safely be stopped after monitoring effectiveness of MDA by assessing microfilariaemia in nocturnal calibrated thick blood. Indeed, the success of MDA depends on interrupting parasite transmission by reducing the level of microfilariae circulating in the blood. The current benchmark for success as defined by WHO is <1% microfilaria prevalence in a community with five continued rounds of MDA (WHO, 2013c). The aim of this study was to monitor nocturnal microfilaraemia to ensure successful MDA for LF elimination in the 10 communes.

MATERIALS AND METHODS

The study was conducted in ten endemic communes located in five departments in south, center and north Benin (Figure 1). Table 1 shows the different communes with the departments, the villages involved in each commune, size of the population of these villages

and baseline microfilaremia before MDA. These villages were randomly selected after census of all the endemic villages that met the following criteria: (i) To house a population of at least 500 inhabitants; (ii) Have completed at least five (5) round of MDA. One village was selected in each commune. The study was undertaken from March to August 2016 with a retrospective and prospective component. The retrospective component involved review of data registers by National Communicable Diseases Control Program (NCDCP) of, Ministry of Health of Benin. The data concerned the total number of villages and populations treated, the number of tablets received, the number of tablets used, the number of tablets remaining to establish the geographic and treatment coverage rates achieved in the study sites during the 5 years of MDA. The prospective component concerned the realization of nocturnal microfilaraemia with two phases: The preparation phase and the survey phase. The preparation phase consisted of the drawing up the questionnaire, the training of the health workers involved in the study, and the meeting of local authorities. The training was focused on the objectives of the study, how to obtain the informed consent, how to complete the questionnaire, how to recognize the clinical signs of bancroftosis, and how to perform and read the thick drops. The survey phase consisted of participant recruitments, clinical examination and blood sampling for the thick drops realization.

The sample size was at least 300 participants (either male or female) aged ≥ 5 years per commune, WHO guideline based (WHO, 2013c). On arrival on the site, the study team settles in the place indicated welcome the participants and explain the study to them, and then obtaining their informed consent. The participants were then recruited progressively as they arrive until they reach the size of 300. After obtaining informed consent, visual observations of clinical manifestations of lymphatic filariasis and questionnaire administration were conducted. A structured questionnaire was administered to obtain information on the subjects' demographic data (age and sex). Trained medical personnel recruited for this study examined all the persons and chronic cases of hydrocele and elephantiasis were recorded.

Blood sampling was done from 11:00 p.m. to 03:00 a.m. using Sasa and Simonsen recommendations about nocturnal periodicity of *W. bancrofti* (Sasa, 1976; Simonsen et al., 1997). Finger prick blood samples were taken from the study participants by qualified and/or trained lab technicians for the preparation of the thick drop (WHO, 2013c). Blood samples were collected in absolute aseptic conditions using sterile and single use materials. Standard procedures were used for the processing and analysis of the blood samples (WHO, 1991). The slides were dried, stored in a slides box and transported to the laboratory of the commune health centers, and then stained with Giemsa. Microscopic examination of slides was done independently by bright field microscopy (magnification $\times 100$), by two experienced laboratory technicians. *W. bancrofti* microfilariae were identified based on the specific morphological features (Cheesbrough, 2005), counted and the results expressed as microfilariae per ml of blood (mf/ml). When any discrepancy was found, the preparation was re-examined by another lab technician. Microfilaria number was counted in each positive slide and recorded. Quality control was done on 10% of the negative slides and on all positive slides in the parasitology laboratory of Centre National Hospitalier et Universitaire de Cotonou. Subjects with a positive microfilariae thick drop were treated with Ivermectin and Albendazole. Those with chronic manifestations have been cared of by national programme for the elimination of LF.

Data analysis

Geographic coverage is the proportion expressed as a percentage of villages implementing MDA among all the villages that need this treatment in the commune. The therapeutic coverage is the

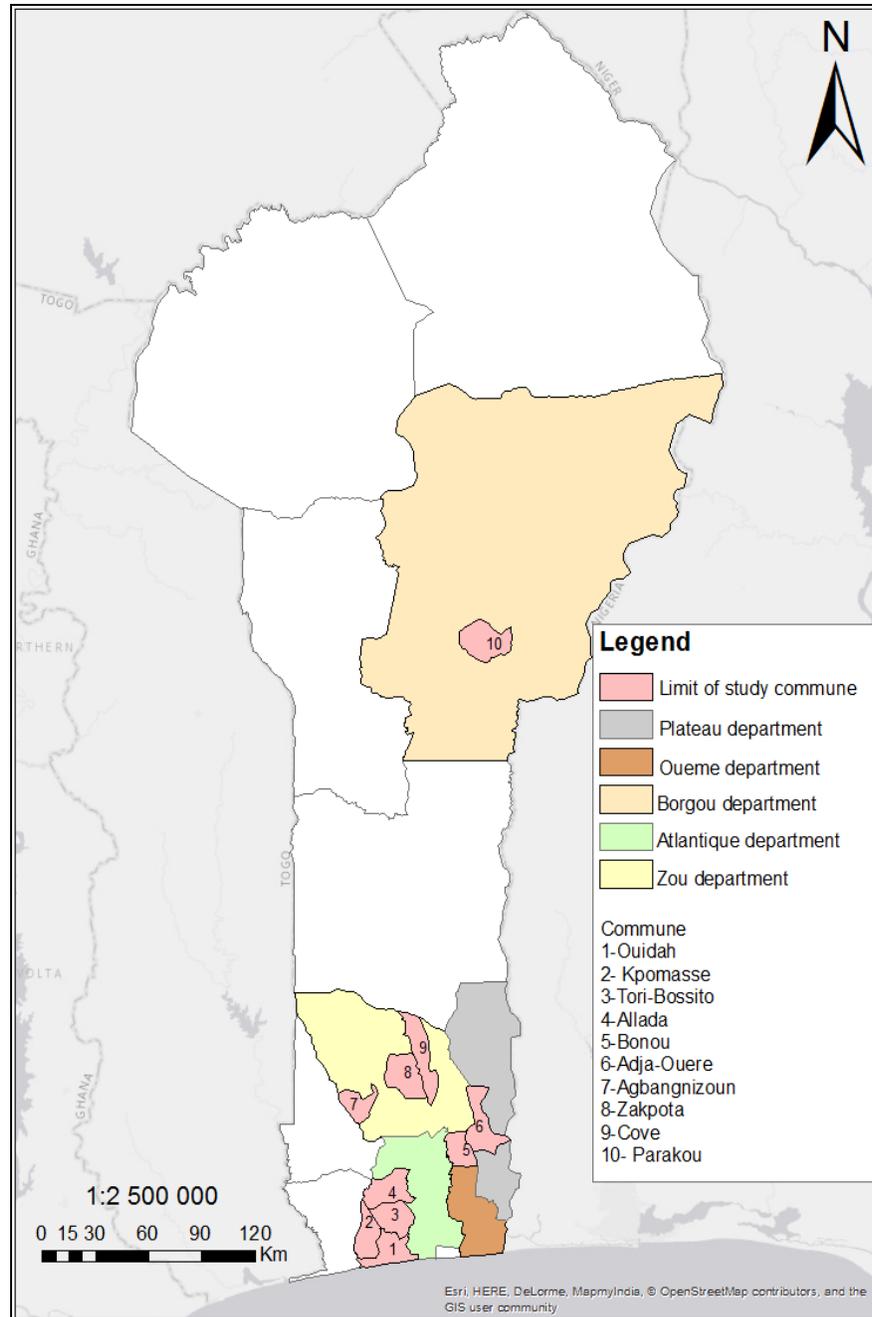


Figure 1. Map of republic of Benin showing study sites (fond topographique IGN, Benin).

proportion expressed as a percentage of the individuals who ingested the drug among the population of the commune. The microfilaria prevalence per site were calculated as the proportion of blood slides found positive for microfilariae. The microfilarial density (mfd) per site was calculated as the average number of microfilariae in slides found positive for microfilariae per milliliter of blood (presuming 60 µl per slide) (WHO, 2013c).

Data were analysed using EpiInfo (USD, Inc., Stone Mountain, GA) version 6. For qualitative variables, frequencies and proportions were determined. For quantitative ones, averages with

their standard deviations, minima and maxima were calculated. Differences in proportions were calculated by Chi-square, with significance level at 0.05.

Ethics statement

The surveys obtained the ethical approval of the National Ethic Committee for Health Research of Benin (Comite National d’Ethique pour la Recherche en Sante; Ministere de la Sante CNERS-MS)

Table 1. The different communes of the study with the departments and villages involved, the size of the population as well as the basic prevalence of microfilaraemia.

Department	Commune	Villages	Population	Baseline microfilaremia (%)
Ouémé (south)	Bonou	Dogba	1494	11
Plateau (south)	Adja ouere	Houedamé	3779	12.5
	Allada	Dovo	1539	1.2
Atlantique (south)	Tori bossito	Houngo	1068	1.2
	Ouidah	Adjarra-hounvè	2195	1.3
	kpomasse	Sègbéya 1	897	1.3
Zou (center)	Agbangnizou	Abigo	1852	1.6
	Cove	Dekpada	1141	1.2
	Zakpota	Zakékéré	2570	1.3
Borgou (north)	Parakou	Kabassira	1105	2.5

under the authorisation reference 008/CNERS-MS. With the approval of the CNERS-MS, written consent was obtained from the chief of each village and traditional authorities. The objectives and schedules of the study were first explained to community leaders and to all eligible individuals in local languages. Writing agreements were obtained from those who agree to participate, under the discretion of community leaders. Approval of parents or legal guardians was taken for minor participants.

RESULTS

Average geographical coverage rates during the 5 years of MDA exceeded 95% for most municipalities except the communes of Adja-ouèrè which has an average rate of 91.5%. 100% of geographical coverage was achieved by five communes throughout the duration of the MDA (Figure 2). The average rate of therapeutic coverage for each commune during the MDA period was greater than 80% in all commune. Kpomasse had the highest average rate while Agbangnizoun had the lowest rate (Figure 3).

A total of 3121 inhabitants with 48.2% of males were enrolled from the 10 communes with their age distribution ranging from 6 to 78 years. The mean age was 25.85 ±0.59 years. Subjects under the age of 50 years were the most represented (87% versus 13% for those over 50 years of age). Thirty one out of 3121 were found to be having either elephantiasis or hydrocele thus showing the disease endemicity rate of 1%. Of the 31 clinical cases, 16 (50%) were having elephantiasis and 15 (50%) having hydrocele. Of the 16 elephantiasis cases, Only two were female and most of the clinical cases were in the age group greater than 50 years $p < 0.001$) (Table 2). Only one person was found microfilaraemic giving an overall prevalence of 0.03% with 0.33% in the commune of Parakou which registered the only positive case against zero percentage for the nine other communes. The one person who was microfilaria positive was a 50-year-old female, with a microfilarial density of 869 mf/ml without

clinical manifestations. She is a trader with frequent travel to the Federal Republic of Nigeria.

DISCUSSION

To evaluate MDA, WHO recommends a 100% geographic coverage rate and 65% therapeutic coverage for a significant effect on microfilarial density and transmission (WHO, 2013c). Having completed the five consecutive MDA rounds by the ten communes of the study, it was necessary to assess the rates of geographic coverage and therapeutic coverage to see if they are in line with WHO suggestions. The average rate of 100% geographical coverage in five communes suggests that these communes have a good geographical coverage rate during the five years of MDA, which is not the case with other communes whose average rate is less than 100%. This decline in performance could be explained by the difficulties in mobilizing financial and human resources during certain years of MDA. The geographic coverage rates obtained in our study are close to those obtained at the national level in Benin in 2014, which was 98.2% (WHO, 2015). On the other hand, they are better than the rate obtained in Nigeria during the same year which was 64.7% (WHO, 2015). This low rate in Nigeria could be explained by armed conflict in some endemic Nigeria states where difficult access to some areas prevents a successful MDA campaign. Therapeutic coverage rates, on the other hand, are almost all in line with WHO recommendations. These good results can be explained by the effectiveness of the awareness campaigns and treatment strategy under community directive actively involving the community in the distribution of medicines. Also the fact that very few side effects are observed after taking the drugs would promote adherence to the treatment. Indeed, even minor side effects can negatively affect treatment coverage

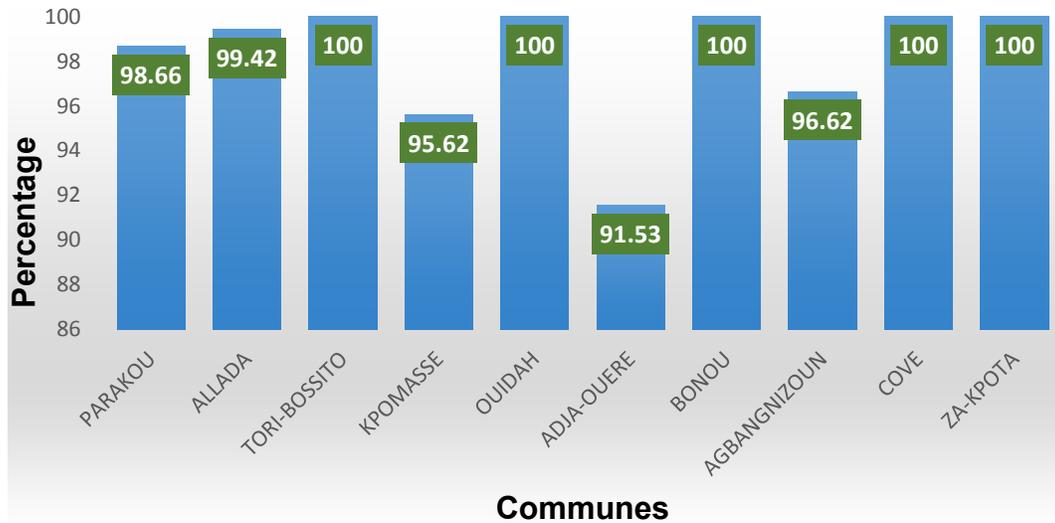


Figure 2. Average geographical coverage for the distribution of Albendazole / Ivermectin from 2011 to 2015 for each of the 10 communes.

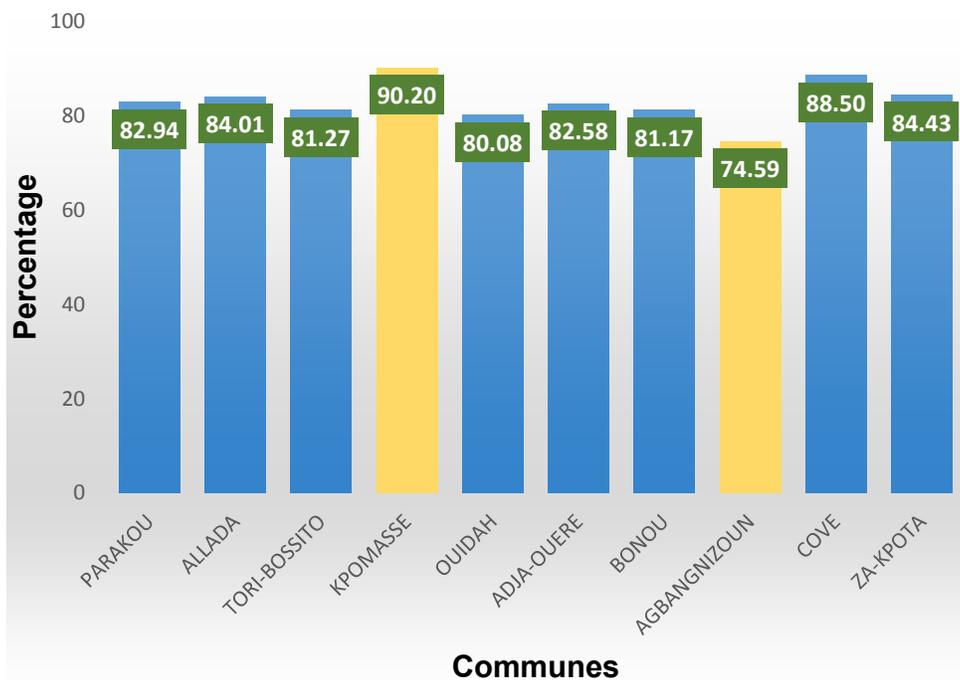


Figure 3. Average rate of therapeutic coverage for the distribution of Albendazole / Ivermectin from 2011 to 2015 for each of the 10 communes.

(Bockarie et al., 2009; Taylor et al., 2010a; Coulibaly et al., 2015; Gyapong et al., 2005). It should be noted that the communes of Agbangnizoun having registered the low average rate had in 2012 a therapeutic coverage of 54.3%. This low coverage could be caused by the period chosen for the campaign of MDA and the insufficient number of community drug distributors (CDD). This period coincided with the rural work where the population,

mostly farmers, was not at home during the community distributing passages. The insufficient number of CDD also made it impossible to return to homes where absences had been observed. Our results diverge from those of Sodahlon et al (2013), who reported a therapeutic coverage that remained above 80% throughout the duration of MDA in all districts endemic to Togo. The same think was observed in Ghana, which had

Table 2. Distribution of chronic manifestations by age.

Age range	Chronic manifestations effective (%)	P value
<50	12/2713 (0.4)	0<001
≥50	19 /408 (4.6)	

also achieved a therapeutic coverage consistently above 70% during all cycles of MDA (WHO, 2012). For WHO, therapeutic coverage is the best indicator for evaluating the implementation of MDA (Ottesen et al., 1997; WHO, 2013c). Indeed this indicator gives information on the number of people who actually ingested Ivermectin and Albendazole, so it can be said that a microfilaricidal effect is expected in such a population. Thus, with high coverage levels of 80 to 90%, a few rounds of mass treatment already give a high probability of elimination. When the coverage is low (40%–50%), many rounds of mass treatment will be necessary to achieve a high probability of elimination.

The large number of subjects included in our study could be explained by the adherence of the village chiefs with the involvement of the community workers who reside in the communes and speak various local languages.

The presence of chronic lesions in this study even in a very small proportion confirms the existence of LF in the study communes but also confirms the ineffectiveness of the drugs used on the chronic manifestations constituted. The same finding was made by Hafiz et al (2015) in Bangladesh who found chronic manifestations in 4.4% of subjects despite a decade of MDA. This justifies the second Global Programme to Eliminate Lymphatic Filariasis (GPELF) strategy, which consists in surgical management of these chronic lesions. This low proportion of lesions observed in our study could be due to a low endemicity in the communes of the study, because before MDA, microfilaraemia prevalences in the endemic communes varied between 1.2 and 12.5% [unpublished data]. It should also be noted that the prevalence may be underestimated because sometimes people with this complication were ashamed and preferred to hide. Coulibaly et al. (2015) in their study had a higher prevalence of hydrocele this study (2.8%). The fact that these manifestations are objectified especially in subjects over 50 years confirms that LF is a parasite of accumulation with chronic manifestations that appear late after the first acute manifestations badly treated. The same observation was made by Coulibaly et al. (2015) who obtained the most chronic manifestations in subjects over 45 years.

The very low prevalence of microfilaraemia obtained after five rounds of MDA suggest that chemotherapy has a positive and remarkable effect on the reduction of microfilaraemia and consequently on the reduction of the transmission thus contributing to the elimination of LF.

The microfilariae prevalence and density are the best indicators of epidemiology, management and control of LF (WHO, 2005). This efficacy of chemotherapy is confirmed by Stolk et al. (2005) who showed that a single dose of Ivermectin reduced microfilaraemia by 96%. Our results being in line with WHO guidelines that link the success of MDA to the reduction of microfilariae prevalence below 1%, Transmission Assessment Survey (TAS) should be implemented shortly in 10 communes to determine whether MDA can be stopped and confirm that interventions have reduced the infection levels below a critical threshold. Thus, in addition to the 23 communes already under MDA post surveillance, 10 other are in the process to stop the treatment and moving on to the surveillance phase, which will bring to 33 the number of communes under surveillance on the 48 endemic communes.

The efficacy of MDA in the elimination of LF has also been demonstrated in several countries. Thus Ramzy et al. (2006) in Egypt found zero prevalence after five rounds. Other authors also reported zero prevalence but after more than 5 rounds (Richards et al., 2011; King et al., 2012; Coulibaly et al., 2015). In Togo Sodahlon et al. (2013) had reached zero microfilariae prevalence after nine round because of proximity to endemic areas in Burkina Faso, a proximity that could be the cause of reinfestations, thus requiring more MDA. However, after six rounds of MDA, Simonsen et al. (2013) reported a significant decrease in microfilarial prevalence in Tanzania, 2.7% compared with 24.5% before MDA. Despite this decrease, the rate obtained remains high, >1%. In view of all the foregoing, the number of treatment rounds necessary to achieve elimination depended to a large extent on coverage, drug efficacy, and endemicity level in the country and in the neighbouring regions. This leads to consider a regional or sub-regional approach for MDA campaigns, that is, the implementation of MDA simultaneously in border countries with a rigorous surveillance system to prevent frequent travellers from escaping mass treatment with a higher risk of reinfestation. Which may explain the only case of microfilaria found in our study, especially as neighbouring Nigerian country is highly endemic (Anosike et al., 2005; Mbah and Njoku, 2002; Udoidung et al., 2008; Okon et al., 2010; Iboh et al., 2012). The microfilarial density obtained in this patient could justify the absence of clinical manifestations given the correlation that exists between the importance of the microfilarial density and the clinical manifestations. Indeed, in the absence of a MDA, densities can be high as is the case in Ghana with a dmf of 5010 mf/ml in an endemic zone awaiting MDA (Aboagye-Antwi et al., 2015).

Conclusion

In this study, MDA data showed geographic and therapeutic coverage almost in line with WHO recommendations

for LF elimination. The microfilarial prevalence less than 1% in the study communes after 5 rounds of MDA confirms the efficacy of Ivermectin and Albendazole on the reduction of microfilaraemia and therefore on transmission in Benin. This efficacy increases from 23 to 33 the number of communes under surveillance. MDA thus proves to be an adequate strategy for the elimination of LF in Benin.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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