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Ivermectin Non-Compliance In Some Onchocerciasis Endemic Areas
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ABSTRACT

Although ivermectin is still active in the reduction of microfilaria. A better understanding of drug compliance is essential to support elimination objectives. This study assesses the compliance of the Ivermectin Mass Drug Administration (MDA), six communities that received annual treatment for 10 to 16 years were selected. A total of 339 participants, were recruited according to ivermectin history by Convenience sampling method for population-based compliance surveys using questionnaires from males and females ≥ 5 years of age who have resided at the sample sites for ≥ 10 years or since birth. Skin snipping was performed on a total of 210 consenting participants to obtain microfilaria, positive samples and the corresponding identification numbers of the participants were recorded. The odds ratios for the association of different variables with ivermectin compliance were analyzed using Epi-Info™. The study showed a total compliance of 64.6 % (95% CI: 0.773 – 1.284) of participants in the last Ivermectin distribution. Out of 120/339 (35.4%) who did not take (swallow) the drug during the last distribution, there were reasons for not taking ivermectin during the last MDA. The microfilaria prevalence was 6.2%. The microfilaria prevalence among the participants was 6.2%, however, no significant association between the microfilaria prevalence among the MDA compliant and non-compliant participants was observed (OR =0.600; 95% CI: 0.054 – 13.479%). The majority of respondents (51.7%) indicated that the drug distributor did not come. A nationwide survey of people's responses to MDA is conducted to adopt alternative or complementary strategies for the distribution of ivermectin.

Keywords: Prevalence, Microfilaria, Mass Drug Distribution, Skin snip.

1.0 INTRODUCTION

Human Onchocerciasis is caused by infection with the parasitic worm *Onchocerca volvulus*. This neglected tropical disease is the second most common cause of infectious blindness worldwide, after trachoma (Walker *et al.*, 2012). It is transmitted to humans through exposure to repeated bites of infected blackflies of the genus *Simulium* that breed in fast-flowing rivers and streams, hence the disease's common name "river blindness" (WHO, 2017). It is classified by the World Health Organization (WHO) as a neglected tropical disease (NTD) and grouped among five preventive diseases via chemotherapy (Montresor and Ichimori, 2012). The disease exerts a burden of a million disability-adjusted annually lost life years and constitutes an obstacle to socio-economic development (Brattig, 2018). It is characterized by the presence of subcutaneous nodules harbouring adult parasites and presentation of dermatitis that can be

extremely severe, visual impairment and in some cases blindness (Wanji, *et al.*, 2015).

Humans are the only definitive host for *O. volvulus*, although chimpanzees have served as definitive hosts in experimental onchocerciasis (Hoerauf, 2002). Several species are obligatorily located in a capsule consisting of host tissue to form a nodule, the Onchocerca, which is also characteristic for the human parasite (Duerr *et al.*, 2001). *O. volvulus* like all nematodes, has a five-stage life cycle involving four moults. Infection begins with the bite of an infected *Simulium* vector. Infective larvae (L3 stage) are deposited into the skin of a new host, where 6–12 months is required for two moults and development of mature adult females (L5 stage) capable of producing new L1-stage larvae, called microfilariae (Hoerauf, 2002).

Onchocerciasis is the second most common cause of infectious blindness worldwide, after trachoma (Walker et al., 2012). The vast majority of infections occur in 31 sub-Saharan African countries (WHO, 2017) (99% of cases), with the remainder in some foci in Central and South America, and in Yemen (WHO, 2017).

Current estimates suggest that Out of some 120 million people worldwide who are at risk of onchocerciasis, 26 million people are infected with the *O. volvulus* and have dermal microfilariae in 31 sub-Saharan African countries (WHO, 2017).

Nigeria ranks among those countries with the highest burden of the disease in the world (WHO, 2017). accounting for about a third of the global prevalence with the estimate of about 8 million Nigerians infected with *O. volvulus*, Nigeria has about 50 million persons in 40,000 communities at risk with over 6.5 million suffer from severe itching or dermatitis and 500,000 are blind (Griswold et al., 2018).

In Taraba state, despite the regime of annual Mass Drug Administration (MDA) of Ivermectin, persistence transmission was reported in some foci among the human population with the prevalence of 37.4% with *O. volvulus* (Danladi et al., 2018). Reports indicated that the annual treatment regimen had achieved a high degree of onchocerciasis control in some areas (Higazi et al., 2013). The burden of disease has been reduced significantly through the annual treatment of large programmes of community-directed treatment with ivermectin (CDTI). (Cruz-Ortiz et al., 2012). Several field studies have achieved significant reductions in the transmission of infection (Winnen et al., 2002). In a multi-site study evaluating five CDTI projects in Nigeria and Cameroon, where at least eight annual IVM distributions had taken place, it was demonstrated that over one-quarter of age-

eligible people in study communities were low compilers and thus serve as a reservoir for continued transmission of onchocerciasis (Wanji et al., 2015). One of the key parameters essential for the success of elimination programmes built on preventive chemotherapy (PCT), is the sustained high-level compliance amongst the population at risk (Senyonjo et al., 2016)

In this study, participants' oral declarations were used as a proxy to determine the relationship between adherences to ivermectin treatment. Ivermectin (Mectizan®) is a broad spectrum drug used to control many animal and human diseases. Initial clinical trials in the 1980s showed a remarkable efficacy of this drug against *O. volvulus*, the causative agent of river blindness (Nana-djeunga et al., 2012).

This study determined the current situation of onchocerciasis in the study area by Quantitative survey and qualitative assessment by two-stage cluster sampling method using Structured questionnaire to evaluate factors associated with dependent variables (Ivermectin non-compliance, programmatic challenges and MDA coverage) determined by independent variables (demographic factors, time lived in the village, travel and ivermectin uptake history).

2.0 MATERIALS AND METHODS

2.1 Study Area

Eight (8) selected communities in the 4 Local Government Areas (LGAs) Gashaka: 7° 49' N 11° 21' E, Ardo-kola: 8° 30' N 11° 25' E, Yorro 9° 10' N 11° 40' E and Lau: 9° 6' N 11° 40' E. of Taraba State; six were onchocerciasis endemic while two were non-onchocerciasis endemic communities (Figure 1) were investigated. Taraba state shares an international border with Northern Cameroon which are innervated with rivers with tributaries of streams traversing the communities and draining into River Benue, where the fast-flowing streams create numerous breeding sites for the blackflies (Akogun, 1999).

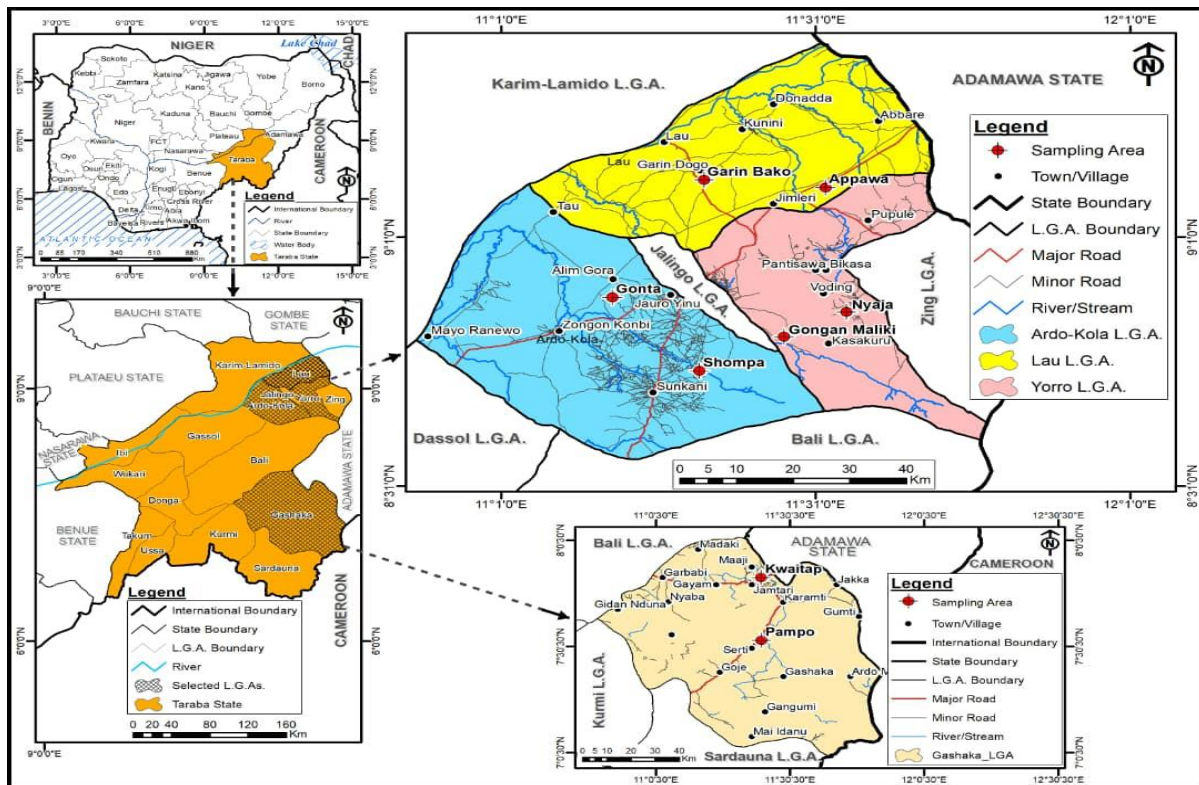


Figure 1. Map of study site in Taraba state, Nigeria

Prepared by Map Gallery, Geography Department, Ahmadu Bello University Zaria, Nigeria (2020).

2.2 Ethical clearance and Participants Consent

Ethical clearance was obtained from Ahmadu Bello University Zaria, Committee for Human Subject Research (ABUCUHSR/Zoology/2020/006). Verbal informed consent from the participants was obtained.

2.3 Population-based treatment compliance survey

A total of three hundred and thirty nine (339) participants were interviewed using a structured questionnaire by Convenience sampling method (Senyonjo *et al.*, 2016). Questionnaire were administered to the participants that resident in the community for at last ten years or from birth, records of key demographic information, if they received and swallowed ivermectin or the reason for not taking the drug, historical ivermectin compliance and information on side effects were documented.

2.4 Collection of Skin Snips

Immediately after the collection of treatment compliance of ivermectin data from the

participants. Skin snipping was performed on a total of 211 consenting participants to obtain microfilaria. The superficial skin biopsies were taken from the skin around the iliac crest as previously described by Wanji *et al.* (2015). This was done by partially undressed participants following Rapid Epidemiological Assessment (REA) guidelines (Noma *et al.*, 2014). From each participant, skin biopsies from the upper iliac crest were taken using a sharp sterile sclera punch as described by Cheesbrough (2012). Each snip from individual participants was immediately placed into the 1.5ml microcentrifuge tubes with approximately 100 μ l physiological saline in a 1.5ml and incubated for 12–24 hours (Thiele *et al.*, 2016). The emerging microfilaria were examined microscopically at 40–400 \times magnification, the positive samples and the corresponding identity numbers of the participants were recorded.

2.5 Data analysis

All survey questionnaires were entered into a pre-designed Epi-Data 3.0 database. Descriptive statistics were employed to present simple frequencies of the dependent variables (ivermectin compliance) and its distribution by

sex, age, education, occupation, years lived in the village, history of taking the drug, the perceived risk from onchocerciasis and self-reported side effects experienced in the past (Senyonjo *et al.*, 2016). Adjusted odds ratios for the association of various variables with ivermectin compliance were analyzed using Epi-Info™.

3.0 RESULTS

3.1 Study Participants

The median age of the survey participants was 29 years old (mean 31 years), with 57.6% of them being male. Most do not go to school (41.7% 95% CI: 30.6–46.2%). The primary occupation of

the respondents was farming (70.7%; 95% CI: 38.1–61.4%). Most had lived in the village all of their life (85.9%) and less than a quarter (17.7%) travelled outside the village for periods of two weeks or more (Table 4.1).

There was compliance among male participants, which showed a significant association between gender and compliance of MDA of IVM (OR = 1.803; 95% CI: 1.124 – 2.906). Those that travelled out of the community for a long time showed evidence of compliance (OR = 2.120; 95% CI: 1.087 – 4.452) (Table 4.1). In terms of educational status, those that attended secondary stated they took ivermectin in the last distribution (OR = 1.803; 95% CI: 1.124 – 2.906) (Table 4.1).

Table 1. Mass Drug Administration compliance among the Participants by Demographic factors

Factors	n	Odd ratio	95%CI	Significance
Age(years)				
<10	24	0.382	0.165 – 0.883	NS
11 -20	71	0.592	0.346 – 1.014	NS
21 - 30	88	0.751	0.452 – 1.248	NS
31 - 40	780	1.496	0.855 – 2.619	NS
41 - 50	36	1.552	0.690 – 3.358	NS
>50	40	0.788	0.395 – 1.563	NS
Total	339	0.337	0.277 – 0.410	NS
Sex				
Male	195	1.743	1.102 – 2.757	SIG
Female	144	0.574	0.363– 0.708	NS
Total	339	1.000	0.721 – 1.378	NS
Education status				
Do not go to school	153	0.840	0.533 – 1.324	NS
Primary	116	0.745	0.464 – 1.195	NS
Secondary	65	2.227	1.156 – 4.292	SIG
Tertiary	06	0.973	0.176 – 5.396	NS
Total	339	1.000	0.769 – 1.299	NS
Occupation				
Farming	245	1.014	0.612 – 1.684	NS
Trading	07	2.970	0.354 – 25.001	NS
Student	68	1.113	0.627 – 1.974	NS
Others	19	1.000	0.770 – 1.299	NS
Total	339	1.211	0.762 – 1.312	NS
Number of years in this Village				
Born here	294	1.441	0.756 – 2.747	NS
>20 years	21	2.156	0.708 – 6.564	NS
10 – 20 years	07	0.357	0.078 – 1.622	NS
<10 years	17	0.320	0.118 – 0.865	NS
Total	339	1.000	0.770 – 1.299	NS
Travelled out of the village for long time				
Yes	57	2.298	1.139 – 4.635	SIG
No	282	0.432	0.216 – 0.878	NS
Total	339	1.000	0.757 – 1.378	NS

3.2 Compliance in the Last Round of MDA

Mass drug administration of Ivermectin compliance varies by communities/LGAs (Figure 4.1). Overall, 68.2% (95% CI: 0.655 – 1.086%) of participants (all ages), stated they had taken (swallowed) ivermectin during the last distribution (Table 4.2). There was evidence of compliance in Kwaitap community, Gashaka LGA (OR =6.695; 95% CI: 2.341 – 19.142). (Table 2).

Table 2. Mass Drug Administration compliance among the Participants by communities

LGA	Community	n	No. of compliance (%)	Odd ratio	95%CI
Gashaka	Kwaitap-Pampo	69	47(92.2)	6.695	2.341 – 19.142
Yorro	Nyaja	67	36(53.7)	0.451	0.295 – 0.783
	Gogan Malaki	74	51(68.9)	1.043	0.593 – 1.828
Ardokola	Kasakure	28	20(71.4)	1.181	0.502 – 2.779
Lau	Appawa	61	47(77.0)	1.718	0.897 – 3.289
	Garin bako	40	18(45.0)	0.326	0.166 – 0.639
	Total	339	219(64.6)	1.000	0.773 - 1.294

3.3 Microfilaria prevalence

The microfilaria prevalence among the participants was 6.2% (Table3), however there was statistically no significant association between the microfilaria prevalence among the MDA compliant and non-compliant participants (OR =0.600; 95% CI: 0.054 – 13.479%) (Table 3).

Table 3. Mass Drug Administration compliance among the Participants by microfilaria prevalence

LGAs	Community	n	No. positive			Odd ratio	95%CI
			Total (%)	Complied	Non-complied		
Gashaka	Kwaitap-Pampo	69	7(10.1)	5	2	1.250	0.118 – 13.241
	Nyaja	67	3(4.5)	2	1	0.875	0.054 – 13.479
Yorro	Gogan malaki	74	3(4.1)	2	1	0.875	0.054 – 13.479
Total		210	13(6.2)	9	4	0.600	0.169 – 2.135

3.4 Reasons for Non-Compliance

Out of the 120/339 (35.4%) participants that did not take (swallow) the drug during the last distribution, gave reasons for not taking ivermectin during last mass drug administration. The majority of respondents (51.7%) indicated that the drug distributor did not come (Fig. 2).

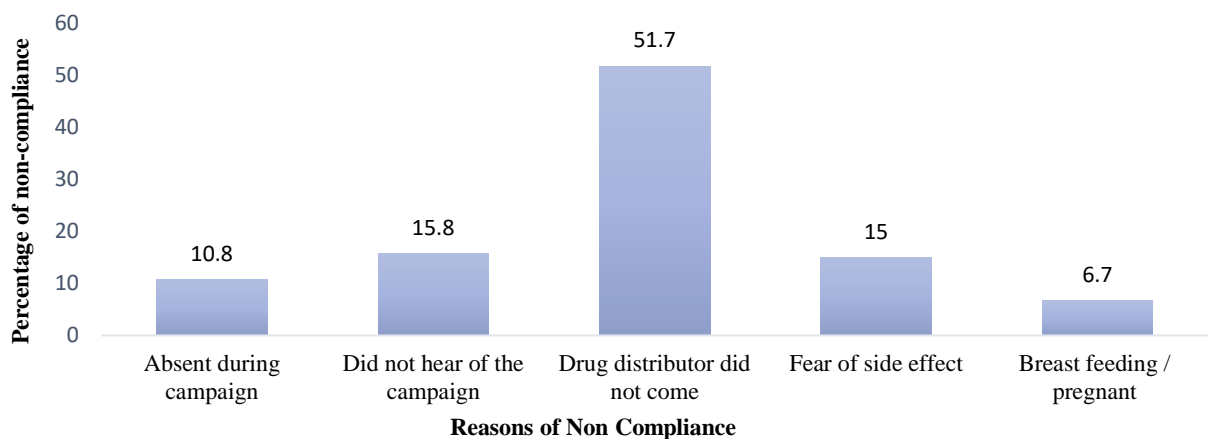


Fig. 2. Main Reasons for non-compliance in the last round

4.0 DISCUSSION

Ivermectin has been routinely distributed in endemic areas in Taraba state over 15 years ago (FMoH, 2017). However, to date, there is no evidence of interruption of transmission. There is still some uncertainty over the relative contribution of various programmatic, epidemiological and ecological factors in sustaining transmission (Turner *et al.*, 2013).

The study showed that compliance for the last round of ivermectin distribution was low 68.2% (95% CI: 0.655 – 1.086%). Poor compliance and particularly high levels of systematic non-compliance have been highlighted in some earlier research in Ghana (Turner *et al.*, 2013) and Cameroon (Senyonjo *et al.*, 2016) as likely contributors to the potential non-interruption of transmission in this area. It is conceivable that individuals who are non-compliant to treatment may not be present during parasitological assessments, biasing results and potentially leading to erroneous decisions concerning the cessation of treatment (Turner *et al.*, 2013). This scenario may depict potential danger as such an individual may serve as a reservoir of the parasite and eventual reemergence of Onchocerciasis after the MDA had ended.

Men in this study showed relative compliance (OR = 1.803; 95%CI: 1.124 – 2.906) compared to the female participants. Female systematic non-compliers (OR=0.553; 95%CI 0.344 – 0.890) might be as the result of complaint of women on the side effects and some myths concerning the drug such as sterility and the rashes associated with taking of the drug. A similar study also

observed the same reasons provided by the female non-compliers included fear of sterility and issues related to irregular menstruation, which they thought maybe a result of taking ivermectin (Senyonjo *et al.*, 2016).

The socio-demographic characteristics associated with drug uptake were educational qualifications which showed significant odd of compliance, as those participants that completed secondary education indicated relative compliance to taken of the drug (OR = 1.803; 95%CI: 1.124 – 2.906). This is not surprising, since they understood the efficacy of the drug and danger of non-compliance, this as well implies to the community members that have the history of travelling outside the community for a long time (OR= 2.120; 95% CI: 1.087 – 4.452). Compliance among the participants by communities grossly varies, Kwaitap in Gashaka LGA significantly complied with drug administration (OR=6.695; 95%CI: 2.341 – 19.142) which is a clear variance with other communities in Yorro and Lau LGAs. This may be attributed to perception and knowledge of the programme, Community Drug Distributors (CDDs) may be a major factor in both coverage and compliers. The drug compliance could have been influenced by many factors amongst which is proximity to the drug collection Centre, prompt management of side effects experienced from taking the drug, level of awareness (Idowu *et al.*, 2013). Other characteristics, including occupation, age, or the number of years in the village showed either weak or no association with ivermectin compliance.

However, studies have shown low compliance to treatment amongst populations largely due to

distrust of the drug, side effects and absence Drug Distributors. In this study majority of the participants (43.1%) stated that “Drug Distributor did not come”, this report showed that lack of education and promotion activities, taking the census, recording of side effects, treating minor side effects and referring major ones to more competent health facilities by CDD (Njim and Aminde, 2017) may be a major setback in attempt to achieve the elimination goal.

The microfilaria prevalence of 6.2% (13/211), as well as no association between microfilaria prevalence and MDA compliance (OR= 0.600; 95%CI: 0.169 – 2.135) in the study area is an indication of continual transmission despite MDA. This may be attributed to factors such as inconsistencies in the drug distribution as reported in Cameroon (Elhassan *et al.*, 2016); sub-optimal response of the parasite to Ivermectin (Boussinesq and Prichard, 2012) and some underlying factors which may require further investigation.

5.0 CONCLUSION AND RECOMMENDATIONS

The overall level of compliance in the study area is significantly low (68.2% (95% CI: 0.655 – 1.086%). The main reason for non-compliance

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reported among the participants was the absence of Drug Distributor (43.1%). The microfilaria prevalence is 6.2% (13/211). There is no association between microfilaria prevalence and MDA compliance (OR= 0.600; 95%CI: 0.169 – 2.135). This might be the major factor attributed to the continue transmission of the infection in the study area.

To solve the major problem of non-compliance in the study area, consideration should be given to the delivery of MDA through the better use of the kinship system, this may help to improve compliance amongst the communities. Further study is required to address the issues of CDDs’ absence and their relationship to poor administration drug compliance.

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