Impacts of Ivermectin Mass Drug Administration for Onchocerciasis on Mosquito Populations of Ogun State, Nigeria.

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Research

Keywords: Ivermectin, endectocide, mosquito, vector control, Nigeria

Posted Date: December 23rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-133331/v1

Version of Record: A version of this preprint was published at Parasites & Vectors on April 20th, 2021. See the published version at https://doi.org/10.1186/s13071-021-04716-3.

Abstract

Background: This study investigated the impacts of single-dose mass drug administration (MDA) with ivermectin for onchocerciasis and lymphatic filariasis on mosquito populations in Ogun State, Nigeria.

Methods: Mosquito samples were collected indoor and outdoor in two communities before and after MDA. The communities were pair-matched with two other control communities where concurrent mosquito collection was also carried out. The mosquitoes were identified by morphological features and parity status was determined by microscopy. The density and age structure of the mosquitoes were determined and compared between intervention and control communities. Environmental and climatic data of study locations were obtained from online databases. MDA treatment coverage survey was conducted in the treated communities.

Results: Before MDA, the density of indoor *Anopheles* mosquitoes was 7.20 in the control communities. This was significantly lower ($p = 0.049$) in the intervention communities where the density was 1.43. The density of the indoor *Anopheles* population reduced significantly 2-3 days after MDA to 1.02 ($p = 0.039$) in the intervention communities. Parity rate also reduced significantly from 95.35 to 44.26 ($p < 0.001$). The density of indoor *Anopheles* rebounded to 1.45 two weeks after MDA while parity rate remained significantly lower ($p = 0.001$) than before MDA. The density of indoor *Culex* increased 2-3 days after MDA from 0.07 to 0.10 ($p = 0.527$) and to 0.25 ($p = 0.012$) 13-14 days after MDA in the intervention communities. In Amini where MDA coverage was 65.9%, the indoor density of *Anopheles* reduced significantly from 0.90 to 0.33 ($p = 0.005$) 2-3 days after MDA while in Kugba-Ajagbe where MDA coverage was 41.0%, the reduction from 1.97 to 1.70 was not statistically significant ($p = 0.446$). Exposure to MDA across sampling intervals in the intervention communities showed a significant effect on the density ($p < 0.001$) and parity rate ($p = 0.003$) of indoor *Anopheles* in the generalized linear model examining multiple factors.

Conclusion: Ivermectin MDA showed a promising potential to impact on malaria transmission and *Anopheles* abundance at high MDA coverage.

Introduction

Mosquitoes alone account for 17% of the estimated global burden of infectious diseases and every year, malaria which is transmitted by the *Anopheles* mosquito, causes the deaths of more than 400,000 people and incapacitates another 200 million for days [1]. In Nigeria, malaria accounts for about 11% maternal mortality, 25% infant mortality, 30% under-5 mortality, 60% outpatient visits, and 30% hospital admissions [2]. To avert the deaths and morbidity caused by malaria and other mosquito-borne diseases, vector control has been adopted as the mainstay of control strategies. Current methods involve the deployment of insecticides to eliminate biting or resting mosquito, by mounting long-lasting insecticidal nets (LLINs) where the mosquito may land when trying to reach the person sleeping under the net and spraying walls inside the house where blood-fed mosquitoes will often rest [3]. However, mosquitoes are still able to escape these strategies because they bite when people are not under LLINs or because they rest or feed outside the sprayed house.

Interests in the development of interventions that are capable of targeting mosquitoes which have can escape the current strategies for vector control are emerging. The adoption of ivermectin, used in the treatment of filarial worm infections, has been proposed to address limitations of the current malaria control tools such as residual transmission [4]. Ivermectin is a systemic endectocide, which when administered to humans or animals, is also toxic to mosquitoes that feed on the treated vertebrate host. This provides an opportunity to eliminate mosquitoes that may escape or survive existing vector control interventions since all female mosquitoes must obtain blood meals for the development of their eggs [3].

Studies have reported the ability of ivermectin to reduce the life span and vectorial capacity of *Anopheles* sp. that feed on treated humans [5, 4]. Although it is shown that *Anopheles* mosquitoes captured from villages after ivermectin MDA have reduced lifespan when monitored in the laboratory, this does not adequately represent the mass effect on mosquito populations under real-life settings. There is a need to evaluate how the effect of ivermectin on mosquito lifespan impacts on the density or abundance of the mosquito population in a locality.

Besides, generating local evidence of the mosquitocidal potentials of ivermectin mass drug administration will assist in effective targeting and optimized delivery of the drug in the context of vector control in endemic areas. Findings suggest the extent of the mosquitocidal effect of ivermectin may vary within the anopheline group [4]. Hence, it is important to understand how the local vector population of a geographical area, which constitutes a unique diversity of primary and secondary vector species, is affected during ivermectin mass administration. In this study, we investigated the impacts of the annual round of ivermectin MDA, used for the control of onchocerciasis and lymphatic filariasis (LF), on local mosquito vector populations in the communities of Odeda local government area (LGA) in Ogun State, Nigeria.

Methods

Study area

This study was carried out in Odeda Local Government Area (LGA) of Ogun State, Nigeria between August and September 2018. Odeda LGA is endemic for onchocerciasis and LF, where community-directed treatment with ivermectin (CDTI) is being implemented annually through mass drug administration (MDA) with single-dose administration of 150–200 µg/kg ivermectin (Mectizan®, Merck & Co Inc.). Treatment coverage was between 66–80% in the LGA between 2013 and 2017 (SMoH, 2020). Four communities - Kugba-Ajagbe (7.36102^{o}N, 3.59830^{o}E) and Amini (7.23509^{o}N, 3.74935^{o}E) as intervention communities and Olofin (7.41974^{o}N, 3.64086^{o}E) and Gbagba (7.44530^{o}N, 3.63307^{o}E) as control communities – were selected for the study. The

intervention communities have been receiving ivermectin MDA rounds consistently from 2013 to 2017, whereas the control communities have no records of ivermectin treatment (Fig. 1).

Study design

The cross-sectional study involved the collection of mosquito samples from each community at three (3) different sampling intervals. The sampling intervals are illustrated in Fig. 2.

In each community, 15 houses were enumerated for the collection of indoor-resting mosquitoes using systematic selection, beginning with the village head's resident as the reference house. Where consent could not be obtained, the next consenting household was selected. Three outdoor locations, where inhabitants commonly gather in the evenings were also selected in each community for outdoor mosquito selection [6]. Sampling intervals were spaced to allow sufficient time for recoil in the mosquito populations and minimize the effect of the mosquito collection on the population density. MDA with ivermectin was carried out by the Ogun State neglected tropical diseases programme.

Collection, identification and dissection of mosquitoes

Mosquitoes were collected indoors between 05.00 and 09.00 hours in the morning, using the pyrethrum spray catch (PSC) method as recommended [7]. Commercial aerosol Raid® (containing 0.250% allethrin, 0.150% tetramethrin, 0.015% deltamethrin and 99.585% inert ingredients) was sprayed in each room by two collectors, who returned after 10 minutes to retrieve the knocked down mosquitoes. Outdoor collection of mosquitoes was carried out using the CDC Miniature Light Traps (Model 512; John W. Hock Company, FL, USA). During each mosquito collection visit, one light trap was set up in each outdoor location at 22.00 hour and retrieved at 06.00 hours in the morning. Mosquitoes were collected from the rooms and traps into labelled Petri dishes and the mosquito samples were transported to the laboratory at the Department of Pure and Applied Zoology. The mosquito samples were identified using morphological keys [8]. The mosquitoes were dissected for age grouping (parity status) based on the ovarian tracheoles [9, 6].

Entomological parameters

Mosquito population characteristics were measured in terms of density (abundance) and parity rate (age structure). Density was calculated as shown below:

$$\text{Mosquito density} = \frac{\text{Number of female mosquitoes collected}}{\text{Number of rooms and traps x Number of nights}}$$

Parity rate was also calculated as shown below:

$$\text{Parity rate} = \frac{\text{Number of parous female mosquitoes}}{\text{Total number of female mosquitoes collected}}$$

Determination of ivermectin MDA coverage

MDA coverage was determined 3–4 weeks after MDA in the intervention communities using the coverage survey builder (CSB) protocol and a questionnaire developed by the WHO [10]. The number of households surveyed was calculated with the CSB, estimated at 15 households per community. The questionnaire was administered, and respondents were shown a sample of the drug package to facilitate recall during the interviews. Interviews were conducted by translating the questionnaire into the local language. Every member of the selected household was interviewed, regardless of their age or eligibility for MDA. Where a household member was absent or too young to respond personally, the household head or an available adult member of the household responded on their behalf.

Remote-sensing climatic and environmental data

Rainfall and vegetation index data were collected as possible confounders on mosquito populations during the study. Using geographic coordinates of the communities obtained with a portable GPS receiver (eTrex®10, Garmin™ International, Olathe, KS, USA), precipitation and normalized difference vegetation index (NDVI) data were obtained from open-access satellite imagery databases: EarthExplorer [11], Precipitation Estimation from Remotely Sensed Information using Artificial Neural Networks (PERSIANN) [12]. For each mosquito collection visit, available data for 14 days up to the collection date were retrieved since mosquito development lasts for about 5–14 days.

Data analyses

Secondary data from remote sensing resources were processed using the HDF-EOS to GeoTIFF (HEG) Conversion Tool (Raytheon Company, Riverdale, MD, USA) and ArcGIS 10.3 (ESRI Incorporation, Redlands, CA, USA) to extract numerical values for the relevant climatic and environmental variables. These data, together with primary data from mosquito collection and coverage survey, were inputted into Microsoft Office Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics (IBM Corporation, Somers, NY) for statistical analyses. Data were subjected to descriptive statistics to present frequency, total, mean and percentage tables. Independent student t-test, analysis of variance (ANOVA), and chi-square goodness-of-fit test were used to compare mosquito abundance between sampling intervals within a community and between study areas. Pearson chi-square test was used to compare mosquito parity rates between the sampling intervals, and to compare MDA coverage between communities. Ivermectin exposure was graded into (1) Early Post-MDA (2) Late Post-MDA (3) Pre-MDA Zero Exposure, based on the relative degree to which MDA was expected to impact on the mosquito populations at the different sampling intervals. A generalized linear model was applied to determine the effects of MDA alone as well as the

effects of MDA alongside other factors on the density and parity rate of the mosquitoes in the intervention communities. In all the instances of statistical analyses, p-value < 0.05 was used to determine statistical significance.

Results

Comparison of mosquito density between sampling intervals

Figure 3 illustrates the indoor density of mosquito populations at the sampling intervals in the intervention and control communities. Before the MDA, the indoor density of *Anopheles* sp. was significantly (p = 0.049) higher in the control communities (7.20) than in the intervention communities (1.43). The difference between the indoor density of *Culex* sp. in the control (0.10) and intervention communities (0.07) before MDA was not statistically significant (p = 0.669).

The indoor density of *Anopheles* sp. reduced to 1.02 in the intervention communities 2–3 days after MDA and was significantly lower than the density before MDA (p = 0.039). In the control communities, the indoor density of *Anopheles* sp. also reduced significantly (p < 0.001) to 5.14 within the same period. At 13–14 days after MDA, the indoor density of *Anopheles* sp. was 1.45 in the intervention communities and not significantly (p = 0.939) different from the density before MDA. The indoor density of *Anopheles* sp. reduced further to 5.47 (p < 0.001) in the control communities within the same period.

In the intervention communities, the indoor density of *Culex* sp. increased to 0.10 (p = 0.527) 2–3 days after MDA and 0.25 (p = 0.012) 13–14 days after MDA. In the control communities, the indoor density of *Culex* sp. reduced to 0.04 (p = 0.257) 2–3 days after MDA and was 0.11 (p = 0.849) 13–14 days after MDA.

In Fig. 4, the outdoor densities of mosquito populations at the sampling intervals are shown. Before the MDA, the difference in the outdoor density of *Anopheles* sp. between the control (5.92) and intervention communities (0.58) was not statistically significant (p = 0.172). The difference between the outdoor density of *Culex* sp. in the control (0.58) and intervention communities (2.83) was also not statistically significant (p = 0.172).

The outdoor density of *Anopheles* sp. increased to 0.90 in the intervention communities 2–3 days after MDA. The 54.29% increase was not significantly different from the density before MDA (p = 0.394). In the control communities, the outdoor density of *Anopheles* sp. reduced significantly (p = 0.001) to 2.75 within the same period. At 13–14 days after MDA, the outdoor density of *Anopheles* sp. was 0.20 in the intervention communities and not significantly (p = 0.160) different from the density before MDA. The outdoor density of *Anopheles* sp. reduced further to 0.88 (p < 0.001) in the control communities within the same period.

In the intervention communities, the outdoor density of *Culex* sp. increased to 3.90 (p = 0.173) 2–3 days after MDA and was 1.10 (p = 0.005) 13–14 days after MDA. In the control communities, the outdoor density of *Culex* sp. increased to 3.25 (p < 0.001) 2–3 days after MDA and was 2.25 (p = 0.001) 13–14 days after MDA.

Comparison of mosquito parity rate between sampling intervals

Figure 5 illustrates the parity rate of the indoor *Anopheles* and *Culex* populations of the intervention and control communities. In the intervention communities, the parity rate of indoor *Anopheles* populations decreased significantly (p < 0.001) from 95.35% before MDA to 44.26% 2–3 days after MDA. This increased to 75.86% 13–14 days after MDA, but remaining significantly (p = 0.001) lower than the parity rate before MDA. The parity rate of indoor *Anopheles* populations in the control communities was 89.92% before MDA, 89.31% 2–3 days after MDA (p = 0.910) and 92.68% 13–14 days after MDA (p = 0.303), showing no statistically significant changes after MDA.

The parity rate of indoor *Culex* populations in the intervention communities was 100.00% before MDA, 100.00% 2–3 days after MDA and 93.33% 13–14 days after MDA (p = 0.789). In the control communities, the parity rate of indoor *Culex* populations was 80.00% before MDA, 100.00% 2–3 days after MDA (p = 0.714) and 100.00% 13–14 days after MDA (p = 0.500).

In Fig. 6, the parity rate of outdoor *Anopheles* populations in the intervention communities was 85.71% before MDA, 66.67% (p = 0.392) 2–3 days after MDA and 0.00% (p = 0.083) 13–14 days after MDA. The parity rate of outdoor *Anopheles* populations in the control communities was 61.97% before MDA, increased to 77.27% (p = 0.288) 2–3 days after MDA and further increased to 100.00% (p = 0.044) 13–14 days after MDA.

The parity rate of outdoor *Culex* populations in the intervention communities was 70.59% before MDA, 97.44% (p = 0.004) 2–3 days after MDA, and 90.91% (p = 0.170) 13–14 days after MDA. In the control communities, the parity rate of outdoor *Culex* populations was 71.43% before MDA, 76.92% (p = 0.556) 2–3 days after MDA and 88.89% (p = 0.307) 13–14 days after MDA.

MDA coverage and changes in mosquito populations in the intervention communities

The coverage evaluation survey showed that MDA coverage was significantly (p = 0.024) higher in Amini than Kugba-Ajagbe (Table 1). In Amini, MDA coverage was 65.9% and the indoor density of *Anopheles* sp. reduced significantly (p = 0.005) 2–3 days after MDA from 0.90 to 0.33. The parity rate of indoor *Anopheles* sp. in Amini also reduced significantly (p = 0.002) 2–3 days after MDA from 92.59–40.00%. In Kugba-Ajagbe, MDA coverage was 41.0% and reduction in the indoor density of *Anopheles* sp. 2–3 days after MDA from 1.97 to 1.70 was not statistically significant (p = 0.446). However, the parity rate of indoor *Anopheles* sp. was reduced significantly (p < 0.001) from 96.61–45.10% 2–3 days after MDA, and this remained significantly (p < 0.001) lower 13–14 days after MDA (67.24%) than before MDA.

Table 1
Ivermectin MDA coverage and mosquito population changes in the intervention communities

		Kugba-Ajagbe	*Amini*	p-value
N^{o} of Eligible Persons Surveyed				
Female		32	23	
Male		29	18	
Total		61	41	
N^{o}. of Persons Treated (%)				
Female		17 (68.0)	14 (51.9)	
Male		8 (32.0)	13 (48.1)	
Total coverage		25 (41.0)	27 (65.9)	**0.024***
Anopheles **sp.**				
Indoor density	14 – 13 days before MDA	1.97	0.90	
	2–3 days before MDA	1.70 (p = 0.446)	0.33 (p = 0.005)†	
	13–14 days before MDA	1.93 (p = 0.926)	0.97 (p = 0.789)	
Outdoor density	14 – 13 days before MDA	1.00	0.17	
	2–3 days before MDA	0.83 (p = 0.763)	1.00 (0.068)	
	13–14 days before MDA	0.33 (p = 0.157)	0.00	
Indoor parity rate	14 – 13 days before MDA	96.61	92.59	
	2–3 days before MDA	45.10 (p < 0.001)†	40.00 (p = 0.002)†	
	13–14 days before MDA	67.24 (p < 0.001)†	93.10 (p = 0.667)	
Outdoor parity rate	14 – 13 days before MDA	83.33	100.00	
	2–3 days before MDA	80.00 (p = 0.727)	50.00 (p = 0.600)	
	13–14 days before MDA	0.00 (p = 0.107)	-	
Culex **sp.**				
Indoor density	14 – 13 days before MDA	0.13	0.00	
	2–3 days before MDA	0.07 (p = 0.414)	0.13	
	13–14 days before MDA	0.23 (p = 0.366)	0.27	
Outdoor density	14 – 13 days before MDA	1.50	4.17	
	2–3 days before MDA	5.33 (p < 0.001)†	1.75 (p = 0.036)†	
	13–14 days before MDA	1.50 (p = 1.000)	0.50 (p = 0.001)†	
Indoor parity rate	14 – 13 days before MDA	100.00	-	
	2–3 days before MDA	100.00	100.00	
	13–14 days before MDA	100.00	87.50	
Outdoor parity rate	14 – 13 days before MDA	88.89	64.00	
	2–3 days before MDA	96.88 (p = 0.395)	100.00 (p = 0.073)	
	13–14 days before MDA	88.89 (p = 0.765)	100.00 (p = 0.436)	

*Difference between total MDA coverage is statistically significant

†Density or parity rate is statistically significantly higher or lower than before MDA

Data for rainfall and vegetation index

In all the communities, average rainfall progressively increased from the period before MDA to the period after MDA (Table 2). In Kugba-Ajagbe, Amini and Gbagba, rainfall increased significantly (p = 0.028, p = 0.040, p = 0.033) from 0.2760, 0.8827, and 0.7887 before MDA to 2.2273, 3.9467, and 4.7653 (2–3 days after MDA). Rainfall was also significantly (p = 0.018, p = 0.012, p = 0.018) higher 13–14 days after MDA than before MDA in Kugba-Ajagbe, Olofin and Gbaba. Normalized Difference Vegetation Index (NDVI) increased progressively in Kugba-Ajagbe (0.2535 to 0.5298 to 0.5862) and Gbagba (0.2535 to 0.5756 to 0.6360) from before MDA to 13–14 days after MDA. However, in Amini, NDVI initially increased from 0.1872 to 0.4779 and then decreased to 0.4156 while in Olofin, NDVI initially decreased from 0.2269 to 0.1118 and then increased to 0.5318.

Table 2
Data for rainfall and vegetation index across the sampling intervals

	14 – 13 days before MDA	2–3 days after MDA	13–14 days after MDA
Rainfall (mm)			
Kugba-Ajagbe	0.2760	2.2273 (0.028*)	4.5480 (0.018*)
Amini	0.8827	3.9467 (0.040*)	4.7820 (0.071)
Olofin	0.2539	1.4413 (0.093)	5.3407 (0.012*)
Gbagba	0.7887	4.7653 (0.033*)	5.2660 (0.018*)
Vegetation Index			
Kugba-Ajagbe	0.2535	0.5298 (< 0.001*)	0.5862 (< 0.001*)
Amini	0.1872	0.4779 (< 0.001*)	0.4156 (< 0.001*)
Olofin	0.2269	0.1118 (< 0.001*)	0.5318 (< 0.001*)
Gbagba	0.2535	0.5756 (< 0.001*)	0.6360 (< 0.001*)

*Rainfall or vegetation index is statistically significantly lower or higher than before MDA

Effects of ivermectin MDA, rainfall and vegetation index on mosquito density and parity rate in the intervention and control communities

In Table 3, the generalized linear model showed that ivermectin MDA alone had a significant effect on the parity rate of indoor (p < 0.001) and outdoor (p < 0.001) *Anopheles* populations in the intervention communities but no significant effects on density. Ivermectin MDA alone also showed a significant effect on the density of indoor (p = 0.005) and outdoor (p = 0.041) *Culex* populations in the intervention communities but no significant effects on parity rate.

Table 3
Effect of ivermectin MDA alone on mosquito density and parity rate in the intervention communities

		***Anopheles* sp.**		***Culex* sp.**	
			p-value		**p-value**
Density	Indoor	*Intercept*	*0.170*	*Intercept*	*< 0.001*
		Exposure to MDA	0.663	Exposure to MDA	**0.005***
	Outdoor	*Intercept*	*0.249*	*Intercept*	*< 0.001*
		Exposure to MDA	0.826	Exposure to MDA	**0.041***
Parity rate	Indoor	*Intercept*	*< 0.001*	*Intercept*	*< 0.001*
		Exposure to MDA	**< 0.001***	Exposure to MDA	0.517
	Outdoor	*Intercept*	*< 0.001*	*Intercept*	*< 0.001*
		Exposure to MDA	**< 0.001***	Exposure to MDA	0.104

*Statistically significant effect on mosquito density or parity rate

In Table 4, the generalized linear model showed that ivermectin MDA had a significant effect on the density (p < 0.001) and parity rate (p = 0.003) of indoor *Anopheles* populations in the intervention communities. Rainfall also showed a significant effect (p < 0.001) on the density of indoor *Anopheles* populations in the intervention communities whereas vegetation index showed a significant effect (p = 0.031) on the density of outdoor *Anopheles* population in the intervention communities.

Table 4
Generalized linear model showing effects of MDA, rainfall and vegetation index in the intervention communities

		Indoor				Outdoor			
		B	S.E	C.I	p-value	B	S.E	C.I	p-value
Anopheles **sp.**									
Density	*Intercept*	*0.134*	*0.5810*	*-1.004–1.273*	*0.319*	*-6.375*	*2.8019*	*-11.86 – (-0.883)*	*0.029*
	Exposure to MDA†				**< 0.001***				0.094
	Rainfall	-0.868	0.2240	-1.307 – (-0.429)	**< 0.001***	0.838	0.4699	-0.084–1.759	0.075
	Vegetation index	2.971	2.1644	-1.271–7.213	0.170	24.235	11.213	2.258–46.211	**0.031***
Parity Rate	*Intercept*	*5.011*	*0.3920*	*4.242–5.779*	*< 0.001*	*5.985*	*2.0793*	*1.910–10.060*	*0.048*
	Exposure to MDA†				**0.003***				0.457
	Rainfall	-0.127	0.1510	-0.423–0.169	0.399	-0.333	0.3487	-1.017–0.350	0.339
	Vegetation index	-1.732	1.4594	-4.593–1.128	0.235	-5.799	8.3210	-22.108–10.510	0.486
Culex **sp.**									
Density	*Intercept*	*-1.801*	*0.5176*	*-2.816 – (-0.787)*	*0.216*	*0.487*	*1.1259*	*-1.720–2.694*	*0.996*
	Exposure to MDA†				0.099				0.650
	Rainfall	-0.025	0.2189	-0.454–0.404	0.910	0.302	0.4486	-1.181–0.577	0.501
	Vegetation index	-0.817	1.7724	-4.290–2.657	0.645	3.857	4.3361	-4.641–12.356	0.374
Parity Rate	*Intercept*	*4.313*	*0.1723*	*3.976–4.651*	*< 0.001*	*4.406*	*0.5203*	*3.387–5.426*	*< 0.001*
	Exposure to MDA†				0.434				0.442
	Rainfall	0.034	0.0729	-0.109–0.176	0.644	-0.093	0.1990	-0.483–0.297	0.639
	Vegetation index	1.115	0.5900	-0.042–2.271	0.059	-1.045	1.9234	-4.814–2.725	0.587

S.E = standard error; C.I = 95% confidence interval

*Statistically significant effect on mosquito density or parity rate; †Categorical variable

Discussion

Before the MDA with ivermectin, the density of the indoor and outdoor populations of *Anopheles* mosquitoes was lower by more than five times in the intervention communities than in the control communities. This difference was statistically significant between the indoor populations. In contrast, there was no statistically significant difference in the density of *Culex* between the two study areas. A similar observation was reported in a longitudinal study carried out in north-eastern Tanzania, where a decline in the density of *Anopheles* was observed while the abundance of *Culex* mosquitoes remained unaffected [13,14]. Derua *et al.* [15] attributed this observation in Tanzania to the use of ivermectin for the control of onchocerciasis and LF in the area for more than 10 years. In our study, the intervention communities had received ivermectin MDA for at least five years while there has been no MDA in the control communities within the same period. Although we did not conduct a longitudinal investigation, the baseline densities observed in our study suggest that the lower density of *Anopheles* in the intervention communities may also be attributable to the long-term use of ivermectin for onchocerciasis and LF control in the communities.

A reduction in the daily survival rate is recognised as a primary effect of ivermectin MDA on malaria vectors in insectary-based studies [16]. In our field-based evaluation, this translated to a reduction in the abundance of malaria vectors after MDA. In the intervention communities, the indoor density of *Anopheles* mosquitoes reduced 2-3 days after ivermectin MDA, and a rebound had become noticeable after two weeks. These changes in the malaria vector abundance followed a consistently similar pattern in the two intervention communities. In contrast, the abundance of *Culex* sp. increased significantly in the intervention communities 2-3 days after ivermectin MDA. Studies have shown that unlike the *Anopheles* sp., the other mosquito vectors are not readily susceptible to the concentrations of ivermectin found in human blood after MDA with the currently recommended dosage of the drug [17,15]. This indicates that factors other than the MDA likely account for the observed reduction in the indoor density of *Culex* sp. in one of the intervention communities.

The short-lived reduction in the indoor density of *Anopheles* sp. in the two intervention communities is similar to observations from previous studies on the life span or survival rate of *Anopheles* mosquitoes captured from villages treated with ivermectin. In a study carried out in Senegal, Liberia and Burkina Faso, reduction in the daily survival rate of *An. gambiae* was only observable within the first week after MDA [16]. Also, a clinical trial in Burkina Faso showed that mortality increased for up to 7 days in *An. gambiae* which were fed with blood from individuals treated with a single dose of ivermectin [5]. It

is generally believed that the recommended dose of ivermectin for onchocerciasis and LF control programmes will not have long-lasting lethal effects on malaria vectors [18,17].

On the other hand, disruption in the age structure of *Anopheles* mosquitoes can last up to three weeks after ivermectin MDA [19,16]. In our study, the proportion of parous (older) female *Anopheles* of the indoor population also remained significantly reduced by more than 20% in the intervention communities two weeks after ivermectin MDA. This significant shift to a younger population of female *Anopheles* sp. has important implication for malaria transmission because the older or parous female mosquitoes are commonly the infectious vectors [17]. It has been indicated that the impact on the mosquito population age structure may be the main mechanism by which ivermectin MDA affects malaria transmission [4]. Ivermectin-treated blood meal kills most of the infectious mosquitoes leaving behind a population predominated by young nulliparous mosquitoes, which require some time to become infectious [17].

Importantly, the reduction in the indoor density of *Anopheles* mosquitoes by 29.07% in the intervention communities 2-3 days after MDA was statistically significant. However, our models suggest that ivermectin MDA did not show a clear effect on the indoor density of the *Anopheles* mosquitoes. Using the relative exposure to ivermectin during the three sampling intervals, the model indicated that ivermectin exposure alone showed no significant effect on the indoor density of *Anopheles* sp. but showed a significant effect when other factors are considered. On the other hand, ivermectin exposure showed a clear effect on the parity rate of the indoor *Anopheles* mosquitoes in the intervention communities in our generalized linear models. Hence, although ivermectin MDA may not have a long-lasting impact on the density of *Anopheles* sp., it reduced the proportion of parous older mosquitoes which are critical for the transmission of malaria in the localities.

Our finding suggests that ivermectin MDA will have more profound effects of on the density and parity rate of the *Anopheles* populations at higher MDA coverage. In Amini, where the coverage of ivermectin MDA was significantly higher, the density and parity rate of the indoor *Anopheles* population reduced by 63% and 57% respectively 2-3 days after MDA. These reductions in the density and parity rate were higher and statistically significant compared to Kugba-Ajagbe where the MDA coverage was lower. Therefore, higher MDA coverage in the intervention communities has the potential to enhance the mosquitocidal effects of ivermectin than the current observations. However, it is interesting that although ivermectin MDA coverage was lower in Kugba-Ajagbe, the age structure (parity rate) of indoor *Anopheles* mosquitoes was disrupted for a longer period of time compared to Amini where the coverage was higher. Also, the indoor density of *Anopheles* in Kugba-Ajagbe did not rebound fully two weeks after MDA unlike in Amini. A study in Burkina Faso suggests that ivermectin accumulates in adipose tissues in female individuals as a slow-release mechanism and accounts for higher plasma concentrations as well as lethal effects that are stronger and more prolonged in the *Anopheles* mosquitoes that feed on female individuals [5]. In our study, more female individuals constituted the persons treated with ivermectin in Kugba-Ajagbe than Amini. Hence, this may also account for the more prolonged disruption of the density and age structure of the indoor *Anopheles* population in Kugba-Ajagbe despite the lower MDA coverage.

Ivermectin did not show an effect on the outdoor populations of malaria vectors in our study. Unlike the indoor *Anopheles* populations, the outdoor density of *Anopheles* mosquitoes in the intervention communities increased 2-3 days after ivermectin MDA. Although the parity rate of the outdoor *Anopheles* population decreased progressively after MDA, our models showed no effects of ivermectin MDA on both the density and parity rate of outdoor *Anopheles* populations. More so, variations in the density and parity rate of the outdoor *Anopheles* populations in the two intervention communities did not show corresponding patterns as observed for the indoor populations.

Conclusions

The abundance of *Anopheles* mosquitoes was significantly lower in the intervention communities where annual ivermectin MDA round has been ongoing for a long period of time. The density of malaria vectors was reduced in the two intervention communities after ivermectin MDA for onchocerciasis and LF. Although the density of *Anopheles* mosquito may rebound quickly after single-dose ivermectin MDA, disruption of the age structure and its implication on malaria transmission will likely last for a longer period of time. Overall, a high MDA coverage targeting a high proportion of female inhabitants in a community will maximize the benefits of ivermectin as a control tool for malaria vectors.

Abbreviations

MDA: Mass Administration of Medicine; LF: Lymphatic Filariasis; LLIN: Long-lasting Insecticidal Net; IRS: Indoor Residual Spraying; LGA: Local Government Area; WHO: World Health Organization; DDT: Dichlorodiphenyltrichloroethane; CDD: Community-directed Distributor.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Review Committee of the Department of Planning, Research and Statistics of the Ogun State Ministry of Health, Abeokuta (Registration number: HPRS/381/276). Permission was also obtained from the Department of Primary Health Care of Odeda LGA and the primary healthcare facilities for each of the selected communities. Communities assented to the study through verbal consents from the village heads and community leaders. The research purpose and protocol were explained in the local language in a meeting with the community leaders. Houses and households were enrolled for the study after consents were obtained from the head of the household.

Consent for publication

Not applicable.

Availability of data and materials

The datasets for climatic and environmental variables generated and analysed during the current study are publicly available in the remote sensing data repositories cited. The primary datasets generated and analysed are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The study was funded by the Association of African Universities (https://www.aau.org/) through the 2017 Small Grants for Graduate Theses and Dissertations (№: PC/06). The funders had no role in the study design, data collection and analysis, interpretation of data, decision to publish or writing of the manuscript.

Authors' contributions

OOO and UFE conceived the study and participated in fund seeking for the research. OOO, ASO, TSA, AAO, SOS and UFE designed the study. OOO, CUE, AAB, SAA and SNA participated in the acquisition, curating, and analysis of data. OOO, HOM, AAO, SOS and UFE interpreted the data for the study. TSA, AAO, SOS, and UFE supervised the study. OOO, CUE, AAB, SAA, HOM, SNO, ASO, and UFE contributed to the drafting and revising of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We are thankful to the staffs of the Ogun State Ministry of Health's NTD unit as well as Odeda LGA's NTD unit and Primary Healthcare Directorate for the support to access the communities and for providing the population data, MDA records, and other relevant data for the study. We appreciate the communities' heads, members, CDDs and staff of the frontline primary healthcare facilities for their cooperation throughout the study.

Footnotes

*statistical significance where $p < 0.05$.

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Figures

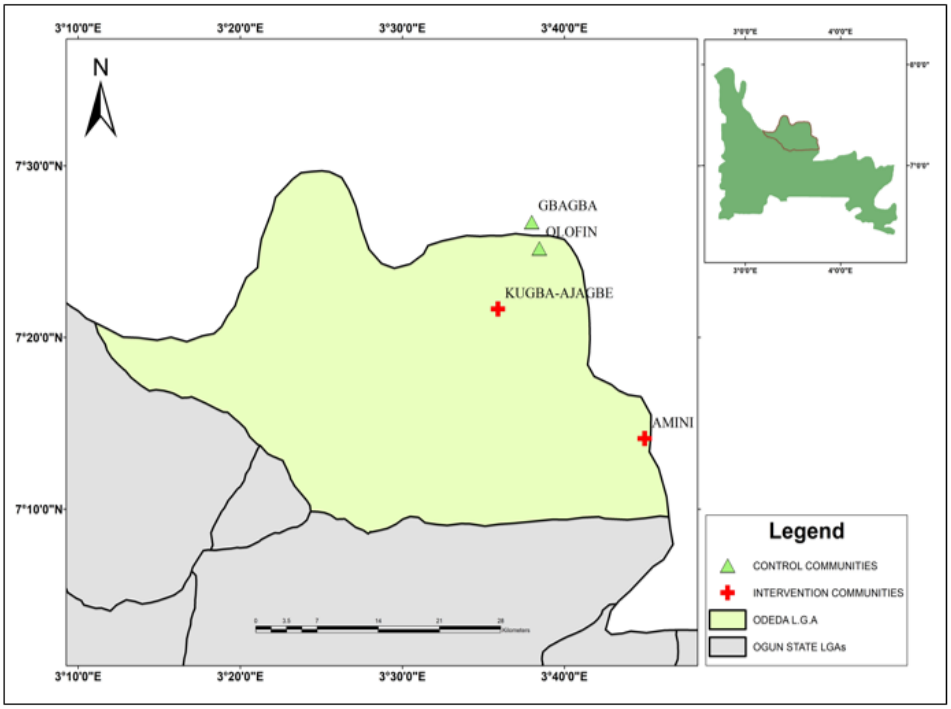

Figure 1

Map of the study area showing the Ogun State communities where the study was conducted. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

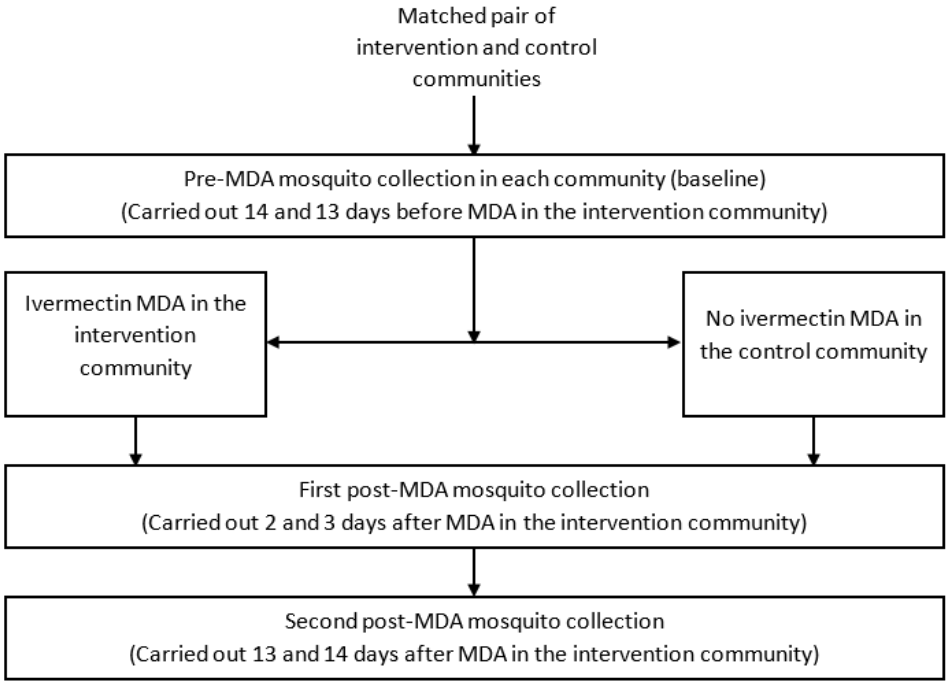

Figure 2

An illustration of the study design for mosquito collection.

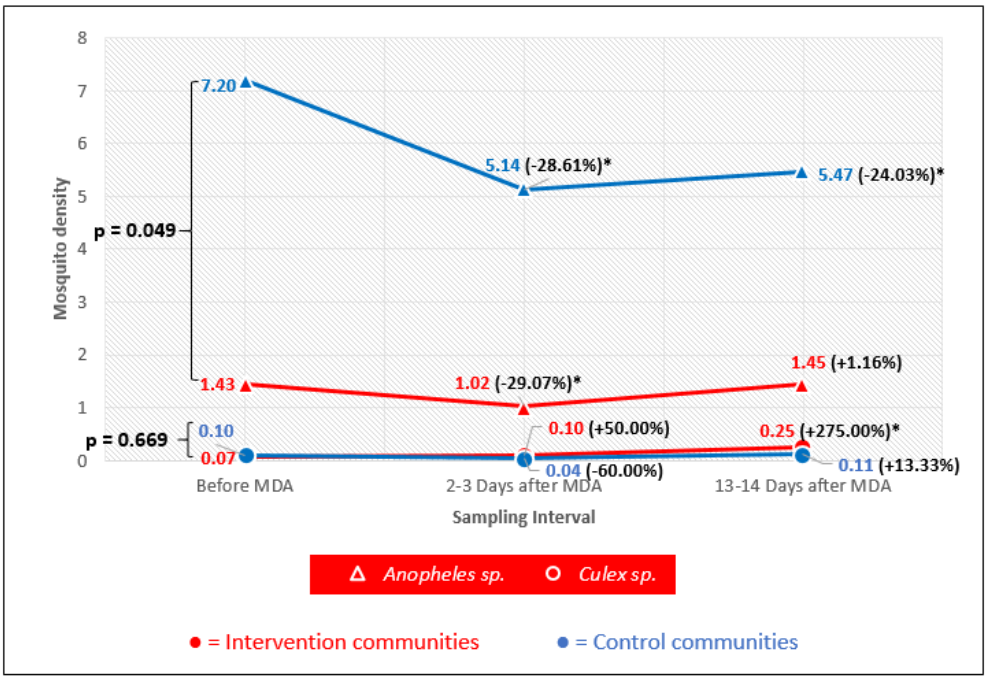

Figure 3

Indoor density of Anopheles and Culex in the intervention and control communities across sampling intervals. *Statistically significantly lower or higher density than before MDA.

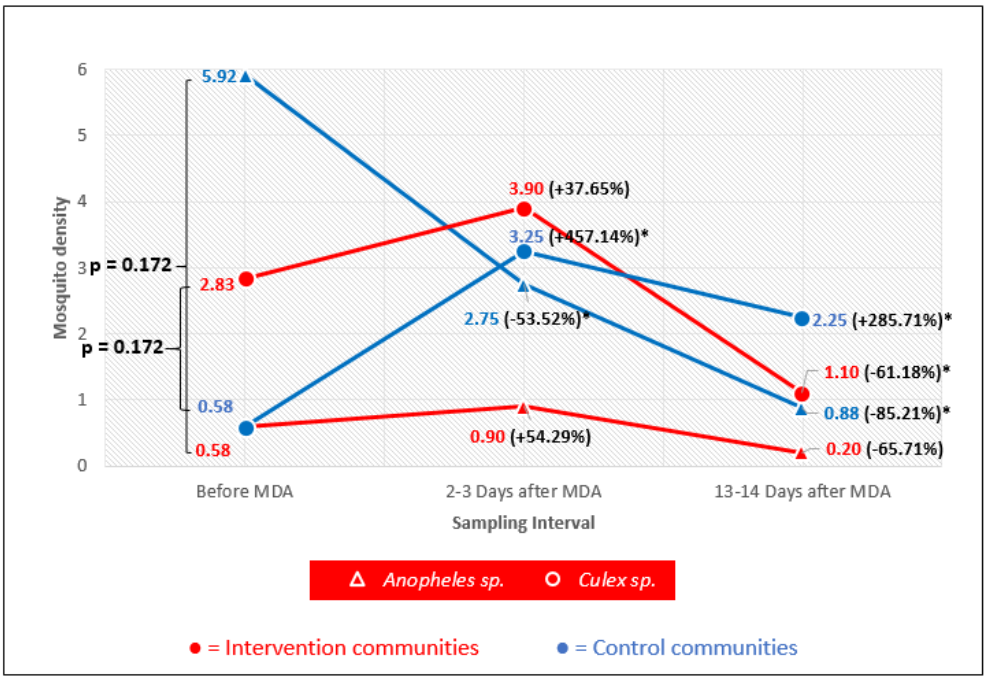

Figure 4

Outdoor density of Anopheles and Culex in the intervention and control communities across sampling intervals. *Statistically significantly lower or higher density than before MDA.

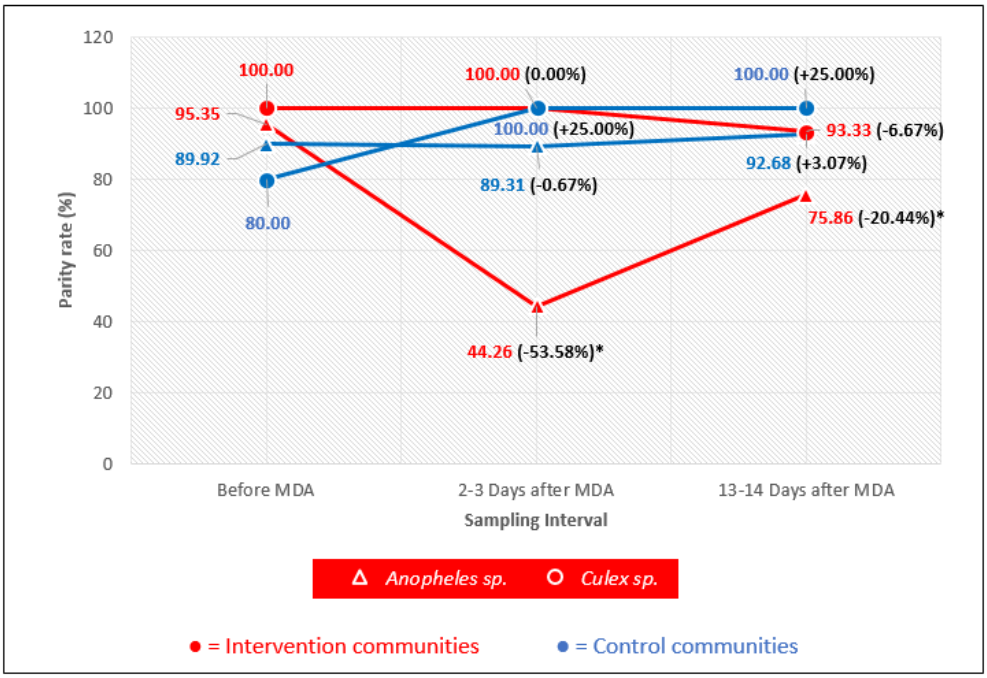

Figure 5

Parity rate of indoor Anopheles and Culex in the intervention and control communities. *Statistically significantly lower or higher parity rate than before MDA.

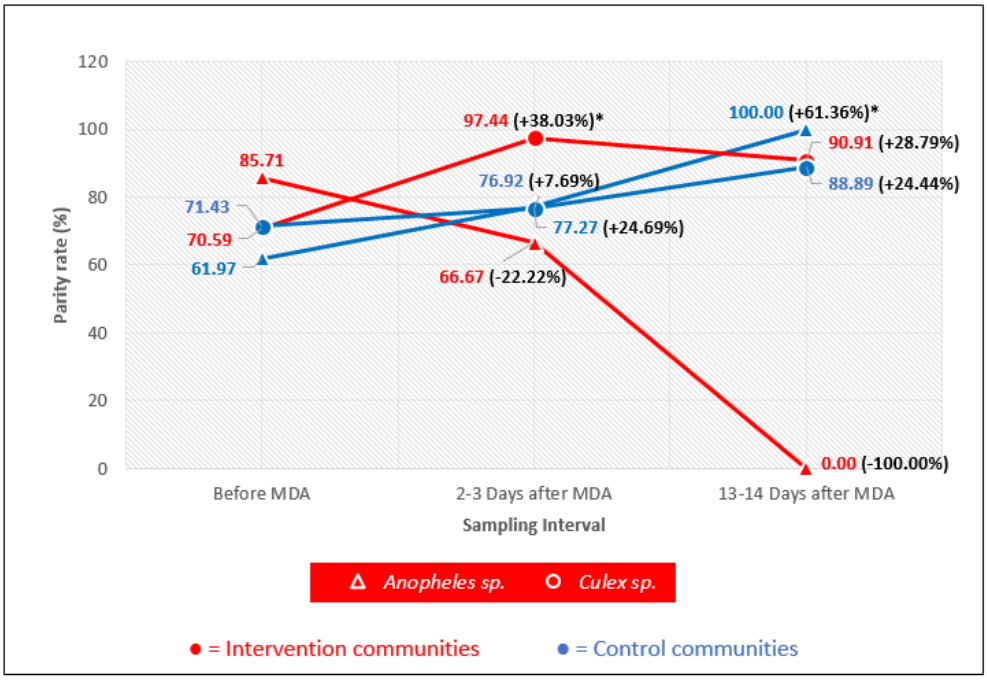

Figure 6

Parity rate of outdoor Anopheles and Culex in the intervention and control communities. *Statistically significantly lower or higher parity rate than before MDA.

Supplementary Files

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- Graphicalabstract.jpg