Am. J. Trop. Med. Hyg., 99(1), 2018, pp. 116–123
doi:10.4269/ajtmh.18-0163

In Southern Nigeria *Loa loa* Blood Microfilaria Density is Very Low Even in Areas with High Prevalence of Loiasis: The Carter Center, Owerri, Nigeria;

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Abstract. Ivermectin treatment can cause central nervous system adverse events (CNS-AEs) in persons with very high-density *Loa loa* microfilaremia (≥ 30,000 mf/mL blood). Hypoendemic onchocerciasis areas where *L. loa* is endemic have been excluded from ivermectin mass drug administration programs (MDA) because of the concern for CNS AEs. The rapid assessment procedure for *L. loa* (RAPLOA) is a questionnaire survey to assess history of eye worm. If ≥ 40% of respondents report eye worm, this correlates with ≥ 2% prevalence of very high-density loiasis microfilaremia, posing an unacceptable risk of CNS-AEs after MDA. In 2016, we conducted a *L. loa* study in 110 ivermectin-naïve, suspected onchocerciasis hypoendemic villages in southern Nigeria. In previous RAPLOA surveys these villages had prevalences between 10% and 67%. We examined 10,605 residents using the LoaScope, a cell phone–based imaging device for rapidly determining the microfilaria (mf) density of *L. loa* infections. The mean *L. loa* village mf prevalence was 6.3% (range 0–29%) and the mean individual mf count among positives was 326 mf/mL. The maximum individual mf count was only 11,429 mf/mL, and among 2,748 persons sampled from the 28 villages with ≥ 40% RAPLOA, the ≥ 2% threshold of very high *Loa* mf density could be excluded with high statistical confidence ($P < 0.01$). These findings indicate that ivermectin MDA can be delivered in this area with extremely low risk of *L. loa*–related CNS-AEs. We also concluded that in Nigeria the RAPLOA survey methodology is not predictive of ≥ 2% prevalence of very high-density *L. loa* microfilaremia.

INTRODUCTION

Onchocerciasis, commonly known as river blindness, is a filarial nematode infection caused by *Onchocerca volvulus*, transmitted by certain insect vector species of the genus *Simulium*.[1] This disease is of public health importance because of its associated visual impairment, blindness, stigmatizing skin disease, and debilitating itching. Human disease results from inflammation around microfilaria (mf) released from fertilized adult female worms residing in fibrous subcutaneous "nodules." Disease is more severe in individuals who have high numbers ("intensities") of mf. The *Simulium* black fly vectors breed in rapidly flowing rivers and streams and become infected when they ingest mf during a blood meal; mf develop into third stage larvae that can infect humans when the vector takes subsequent blood meals. The World Health Organization (WHO) estimates that about 198.2

O. volvulus to maintain the transmission cycle independent of the human population, permanent elimination of transmission of onchocerciasis can be achieved, such as in four countries in the Americas and in some parts of Africa.

[6,7] In 2014 the African Program for Onchocerciasis Control called for a new goal of onchocerciasis transmission elimination for Africa. As part of that policy, an expansion of ivermectin MDA into previously untreated areas was proposed. These areas (the so-called "hypoendemic" areas) are those with sufficient *O. volvulus* transmission to maintain the adult parasite population but very little morbidity due to the near absence of high mf density infections. Untreated areas bordering ivermectin MDA programs are those most likely to be hypoendemic and therefore newly targeted for MDA.[8]

Loa loa, another filarial parasite prevalent in central Africa, is complicating the MDA expansion plan under the new onchocerciasis elimination paradigm. *Loa loa* is transmitted by deerflies (*Chrysops* species) that breed in high canopy-forested areas in Africa. Adult *L. loa* worms may migrate under the eye's conjunctiva and be recognized by the infected individual.[9–11] Adult female *L. loa* worms produce mf that (unlike in onchocerciasis) enter the blood stream; circulating *L. loa* mf can reach extremely high densities in the blood. The abrupt death of mf after the administration of a microfilaricidal agent such as ivermectin can rarely result in central nervous system adverse events (CNS-AEs) shortly after treatment that include changes in consciousness and, rarely, coma. Deaths have resulted from complications arising from prolonged coma events.[12] Only individuals with very high *L. loa* mf densities (≥ 30,000/mL of blood) are at risk of these CNS-AEs.[13–15]

A technique called the Rapid Assessment Procedure for *L. loa* (RAPLOA) was developed over a decade ago to quickly and noninvasively assess an area for the risk of *L. loa*–related

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CNS-AEs after ivermectin MDA. A sample of 80 residents aged 15 years and older are individually asked if they at some point in the past experienced a worm moving across the surface of their eye. During the interview the respondents are shown a photograph of a *L. loa* worm in the eye. A multicountry study showed a strong correlation with ≥ 40% of residents answering "yes" (e.g., a RAPLOA prevalence of ≥ 40%), a village prevalence of *L. loa* microfilaremia ≥ 20%, and the village prevalence of very high-density *L. loa* ≥ 2%.[16–20] These critical and correlated thresholds (RAPLOA ≥ 40%, *L. loa* microfilaremia prevalence ≥ 20% and very high-density *L. loa* ≥ 2%) define an area at high risk for *L. loa* CNS-AEs. The magnitude of this risk is poorly defined.[14]

High RAPLOA determinations in onchocerciasis hypoendemic areas are roadblocks to the onchocerciasis elimination agenda in *L. loa*–endemic countries such as Nigeria. Expansion of MDA into these hypoendemic areas is difficult to justify because the benefit from MDA in reducing morbidity from onchocerciasis is low compared with the risk of CNS-AEs from *L. loa* treatment. We report a survey in just such an area in Nigeria where there is presumed hypoendemic onchocerciasis and hyperendemic *L. loa.* Our purpose was to reevaluate the relationships among RAPLOA, *L. loa* microfilaremia prevalence, and most importantly, very high-density *L. loa*. We also assessed for onchocerciasis endemicity using a rapid diagnostic test for OV16 IgG4 antibodies; the results of that study will be reported elsewhere.

MATERIALS AND METHODS

Stud area. The survey was conducted in fi

TABLE 1

Village sample size, Rapid Assessment Procedure for *Loa loa* (RAPLOA) information, max and average cellScope counts, and LoaScope prevalence

State	LGA	Village	Number surveyed	Max of RAPLOA (%)	Source of max RAPLOA value	Year of RAPLOA survey	Max of LoaScope mf/mL	Average LoaScope mf/mL among positives	Prevalence of LoaScope positives (%)
Abia	Osisioma	Amapu Ife	96	15	FMOH	2015	439	207	7
		Umuakpara	99	14	FMOH	2015	592	229	9
		Umule	101	19	FMOH	2015	282	179	7
		Umumba	77	23	FMOH	2015	526	209	6
	Ugwunagbo	Owerri Aba	100	14	FMOH	2015	1,049	602	2
		Umule Osoamadi	100	11	FMOH	2015	92	92	1
		Umuode	100	13	TCC	2013	461	370	4
		Umuodo	87	24	FMOH	2015	921	271	8
Anambra	Anambra east	Agbudu Nando	98	65	TCC	2012	921	264	14
		Nneyi Umueri	98	67	TCC	2012	877	263	26
		Ogwari Nsugbe	100	62	TCC	2012	680	237	21
		Otuocha	100	49	TCC	2012	263	197	2
		Ubaru Ugwuoji	104	55	TCC	2012	1,259	313	19
	Anambra west	Mmiata Anam	101	46	TCC	2012	1,254	292	11
		Nzam Assa	99	56	TCC	2012	197	121	5
		Umuenwelum	100	47	TCC	2012	856	179	11
		Umueze Anam	100	59	TCC	2012	461	197	18
		Umuoba Abegbu	101	47	TCC	2012	1,930	301	15
	Ogbaru	Atani	100	20	FMOH	2015	486	166	18
		Isiolu Ugalo	97	61	TCC	2012	307	143	10
		Odekpe	102	14	FMOH	2015	2,632	297	15
		Ohita	99	13	FMOH	2015	614	298	6
		Okpoko	99	18	FMOH	2015	1,290	208	22
		Onyili/Ibelenta	101	67	TCC	2012	128	59	12
		Umudashi/Esielle	100	65	TCC	2012	329	128	10
		Umuezegbo	100	50	TCC	2012	1,100	182	20
		Umunankwo	100	26	FMOH	2015	1,290	184	21
		Umuokoloigbo	101	49	TCC	2012	351	120	13
	Onitsha north	American Quarters	100	16	FMOH	2015	61	61	1
	Onitsha south	Fegge	100	21	FMOH	2015	154	137	3
Delta	Ethiope east	Ekrejeta	69	28	TCC	2013	1,791	591	6
		Eku (Emure)	99	43	TCC	2012	2,610	569	7
		Igun	100	48	TCC	2012	563	216	9
		Okpara Inland	100	11	TCC	2013	11,429	4,047	3
		Okurekpo	99	35	TCC	2012	1,177	405	6
		Orhoakpo	100	25	TCC	2012	461	217	3
		Oria Abraka	100	29	TCC	2013	921	368	3
		Otorho Abraka	100	29	TCC	2013	307	165	5
		Samagidi	100	34	TCC	2012	31	31	1
		Urhuovie Igun	99	13	FMOH	2015	522	522	1
	Isoko north	Ofagbe	100	40	TCC	2012	338	338	1
		Okpe Isoko	100	60	TCC	2012	184	107	5
		Otor-Igho/Emevor	100	13	TCC	2013	7,568	1,281	8
		Owhelogbo	100	20	TCC	2012	338	148	5
		Ozoro	100	40	TCC	2012	706	231	9
	Isoko south	Emede	101	15	TCC	2012	329	142	6
		Emore	99	20	TCC	2012	746	172	7
		Irri	100	21	TCC	2012	998	363	5
		Olomoro	100	21	TCC	2012	526	287	4
		Uzere	100	29	TCC	2012	307	149	4
	Patani	Abari	97	36	TCC	2012	0	0	0
		Bolu Angiama	97	16	TCC	2013	465	465	1
		Bulu Aperebiri	100	39	TCC	2012	154	92	2
		Odorubu	100	35	TCC	2012	369	138	4
		Patani II	100	34	TCC	2012	0	0	0
		Uduophri	100	35	TCC	2012	0	0	0
	Ugheli north	Odovie	100	13	TCC	2013	44	44	1
		Oghara Agharha	101	20	TCC	2013	397	229	2
		Onidjor Uwheru	100	25	TCC	2013	92	51	3
		Orogun	97	21	TCC	2013	0	0	0
		Otovwodo	102	18	TCC	2013	0	0	0
Ebonyi	Abakaliki	Abofia (Unagbo Oke)	100	33	TCC	2012	439	126	5
		Amachi Unuhu	100	25	FMOH	2015	491	321	2
		Amagu Onicha	100	28	TCC	2012	526	396	5
		Ametta Amachi	100	25	FMOH	2015	483	228	5
		Azugwu	98	21	FMOH	2015	768	257	8
		Azuiyiokwu	100	28	FMOH	2015	230	99	4
		Egwudinagu	100	39	FMOH	2015	0	0	0

(continued)

Procedures. In each village, we aimed to test 50 adults (more than 18 years of age) and 50 children (≥ 5 and < 10 years of age). We excluded anyone who was ill or who might not tolerate fi

No participants were detected with high-density *L. loa* microfilaremia. The highest count in the study (11,429 mf/mL) was in a resident of the low risk RAPLOA village of Okpara Inland (RAPLOA 11%) of Ethiope East LGA in Delta State. The second (7,875 mf/mL) and third highest (7,568 mf/mL) mf densities were in residents of villages with RAPLOAs of 33% and 13%, respectively.

The 2% prevalence of very high-density microfilaremia did not occur in the overall sample ($P < 0.01$) and the subsample of 2,748 persons resident in ≥ 40% RAPLOA villages (

3. World Health Organization, 2017. Summary of global update on preventive chemotherapy implementation in 2016: crossing the billion. *Wkly Epidemiol Rec 92:* 589–593.
4. Herricks JR et al., 2017. The global burden of disease study 2013: what does it mean for the NTDs? *PLoS Negl Trop Dis 11:* e0005424.
5. Mectizan Donation Program, 2017. Available at: https://www.mectizan.org/achievements. Accessed December 21, 2017.
6. Katabarwa M, Richards F, 2014. Twice-yearly ivermectin for onchocerciasis: the time is now. *Lancet Infect Dis 14:* 373–374.
7. Diawara L et al., 2009. Feasibility of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: first evidence from studies in Mali and Senegal. *PLoS Negl Trop Dis 3:* e497.
8. Kelly-Hope LA, Unnasch TR, Stanton MC, Molyneux DH, 2015. Hypo-endemic onchocerciasis hotspots: defining areas of