Am. J. Trop. Med. Hyg., 87(2), 2012, pp. 272–280
doi:10.4269/ajtmh.2012.11-0718

Evidence for Stopping Mass Drug Administration for Lymphatic Filariasis in Some, But Not All Local Government Areas of Plateau and Nasarawa States, Nigeria

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Abstract. An average of six annual rounds of ivermectin and albendazole were distributed in Plateau and Nasarawa States, Nigeria, to eliminate lymphatic filariasis. From 2007 to 2008, population-based surveys were implemented in all 30 local government areas (LGAs) of the two states to determine the prevalence of *Wuchereria bancrofti* antigenemia to assess which LGA mass drug administration (MDA) could be halted. In total, 36,681 persons from 7,819 households were examined for filarial antigen as determined by immunochromatographic card tests. Overall antigen prevalence was 3.05% (exact upper 95% confidence interval [CI] = 3.41%) with an upper 95% CI range by LGA of 0.50–19.3%. Among 3,233 children 6–7 years of age, overall antigen prevalence was 1.71% (exact upper 95% CI = 2.19%), too high to recommend generally halting MDA in the two-state area. However, based on criteria of < 2% antigenemia among persons > 2 years of age, stopping MDA was recommended for 10 LGAs.

INTRODUCTION

Lymphatic filariasis (LF), a parasitic, neglected tropical disease, is targeted for elimination as a public health problem by the year 2020 through a dual strategy of 1) mass drug administration (MDA) to interrupt transmission of the infection and 2) morbidity control to alleviate disability of persons affected by chronic LF manifestations (lymphedema, elephantiasis, and hydrocele).[1] As of 2010, 10 years from the World Health Assembly's 2020 elimination target, only 19 out of 34 filariasis-endemic countries in the World Health Organization (WHO) African Region had initiated MDA.[2] Nigeria, estimated to have the highest population at risk for LF in sub-Saharan Africa at 80 million, is only just scaling up its national MDA program.[3] However, a pilot LF elimination program, executed in partnership with Nigeria Federal and State Ministries of Health and The Carter Center in the two central states of Plateau and Nasarawa, has operated since 1999.[4,5] *Anopheles gambiae* s.l. and *Anopheles funestus* are the vectors of *Wuchereria bancrofti* in these two states.[6] Baseline LF mapping using rapid blood antigen detection tests showed mean local government area (LGA) prevalence of 23% (range 4–62%) among persons 15 years of age and older in 70 randomly selected sites in the two states.[7,8] Since 2000, health education plus MDA using 150 μg/kg of ivermectin (Mectizan®; donated by Merck & Co., Inc., Whitehouse Station, NJ) and 400 mg of albendazole (donated by GlaxoSmithKline, Brentford, Middlesex, UK) have been implemented annually according to WHO guidelines to eliminate LF transmission, using each LGA as an independent MDA implementation unit. A phased LGA scale-up to implementing MDA was adopted in the two states as capacity of the program increased and by 2003 all 30 LGAs within the states were under MDA interventions.[7] Reported treatment coverage for each round was ≥ 85%, with over 3.1 million persons being treated annually of the treatment eligible population of 3.7 million. A population-based coverage survey in 2003 estimated coverage of 72.2% of the eligible population (95% confidence interval [CI] = 65.5–79.0%) for the overall two-state area.[7]

Encouraged by the fact that eight of 10 sentinel villages (used for serial monitoring of program impact) had achieved the < 1% nocturnal microfilaremia (mf) prevalence goal,[7] we elected to conduct population-based cluster surveys in 2007–2008 to evaluate impact of MDA beyond sentinel areas. We aimed to determine antigen prevalence in various age groups for each LGA implementation unit to decide where MDA could be stopped, and where MDA needed to continue. These results are reported here.

In planning these 2007–2008 surveys, we studied both the WHO Geneva 2005 guidelines for determining when MDA could be stopped, and the corresponding WHO Pacific regional program to eliminate LF (PacELF) stop MDA guidelines developed in 2004. The 2005 WHO guidelines involved a multi-stage process that focused first on antigen in children 2–4 years of age.[9] Following the fifth round of MDA, assuming sentinel villages had mf < 1%, a 30-cluster lot quality assurance (LQA) survey of 300 children 2–4 years of age was recommended, followed by a larger survey of 3,000 older (school entry level) children. All children tested needed to be antigen negative before programs could stop MDA[9]; this complex, multi-stage strategy was logistically and financially impossible to implement across 30 LGA implementation units. The PacELF guidelines for stopping MDA were simpler, yet maintained the epidemiological rigor. These were based on population-based antigen prevalence surveys encompassing all age groups, conducted after five annual rounds, in the so-called "C-survey." If the antigenemia was < 1% (upper CI antigenemia was < 2%), MDA could then be stopped; a transmission assessment among children was recommended after stopping as part of a post MDA surveillance strategy.[10,11]

We considered the "PacELF criterion" of < 2% antigenemia (upper 95% CI) in the total population as the best approach for two reasons: 1) it was less costly to execute in each LGA implementation unit and 2) because LF becomes more prevalent with age, the PacELF criterion would be a more conservative assessment compared with one that focused only on antigenemia in young children. A prevalence of < 2% antigenemia in the total population has been shown to

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correspond to mf prevalence of < 0.5% that is likely below the capabilities of the poorly efficient *Anopheles* vector to continue LF transmission.[12]

In 2011, new WHO guidelines superseded the ones we considered in 2007. The new guidelines call for transmission assessment surveys (TAS) that consist of LQA surveys of antigenemia among children in "a programmatically feasible evaluation unit (EU)."[13] The formation of EUs is to be flexible, based on epidemiological and programmatic similarities of implementation units. The threshold for stopping MDA is a 95% upper CI antigenemia of < 2% in children 6–7 years of age. Accordingly, in this report we attempt to analyze our 2007–2008 data to also conform to the 2011 antigen guidelines for the 6- to 7-year-old age group, and compare those findings with antigenemia in the total population.

METHODS

In Nigeria, the LGA is the equivalent of a district with population of ~100,000 persons. We conducted three different rounds of LGA-level population-based antigen prevalence surveys that provided prevalence estimates for all 30 LGAs. The three rounds of surveys, each of the same cluster random sampling design, were conducted between October 2007 and November 2008. In the first survey round (October 2007, in LGAs that had completed at least five annual rounds of MDA), we performed LF antigen assessment integrated with the mapping of trachoma and urinary schistosomiasis in eight LGAs.[14] In the second survey round (March to April 2008), the assessment of LF antigen was conducted with the simultaneous mapping of trachoma in six LGAs.[15] Finally, (October to November 2008) the remaining 16 LGAs were assessed solely for LF antigenemia. The LGAs were considered for stopping MDA where the one-sided upper 95% CI of antigen prevalence was < 2% among the population 3 years of age and older (PacELF criterion). Additionally, we re-evaluated a sample of adults in non-sentinel, baseline mapping sites[7] for antigen, and mf in LGAs meeting the < 2% total population antigen criterion.

Sampling. We estimated that for each LGA 20 clusters of at least 13 households per cluster would provide a minimum sample size of 1,179 that would allow a precision of ±0.85% with an estimated LF antigen prevalence in the population aged 3 years and above of 1% and design effect of two. We assumed an average household size of six based on previous household surveys conducted in Plateau and Nasarawa States, where proportion of total population 3 years of age and older was 83%, and non-response rate was 12%. Clusters were selected by taking a systematic, random sample of 20 census enumeration areas (EA) from the list of all EAs in each LGA. The EA were ~300–500 people in size; typically smaller than a village, but in some rural areas the EA were the entire village. The Nigerian Bureau of Census provided maps of the selected EA. After walking the boundaries of the EA, the survey teams divided the map into segments of approximately equal size (at least 13 households) and allowed the village chief to randomly select one segment by lottery. Because the number of segments in each EA varied, we weighted differentially all data according to selection probabilities. All households in selected segments were surveyed and all household residents 3 years of age and older were examined. A follow-up visit was made to households with missing residents on the day of the survey, but empty households were not replaced.

LF circulating antigen assessment. All residents of selected households were enumerated. Consenting and available residents 3 years of age and older were asked to provide a finger prick, 100 μL sample of blood to assess the presence of *W. bancrofti* circulating filarial antigen (CFA) using the Filariasis NOW immunochromatographic card test (ICT) (Inverness Medical, Princeton, NJ). All tests were read at 10 minutes and results were recorded on standardized forms.[16]

Re-assessment of baseline mapping sites. Where LGA-level estimates of antigenemia were < 2%, we re-assessed antigen prevalence in communities where a convenience sample of 50–100 adults had been examined with ICT for LF baseline mapping in 1999 and 2000.[7] In each of these baseline sites, households were systematically sampled from a listing of all households within the community starting from a random house on the list. All consenting residents > 2 years of age in selected households were examined with ICT. However, to align with the mapping methodology used at baseline, only antigen prevalence among adults 15 years of age and older was used for comparison to baseline prevalence. All ICT-positive persons were tested for mf by blood slide: 60 μL of blood were obtained by fingerstick and used to prepare a thick blood film. The slides were air dried and returned to the laboratory at Carter Center headquarters in Jos for Giemsa staining and qualitative examination for *W. bancrofti* mf by trained microscopists. Slides were read qualitatively ("positive" or "negative") and quantitatively (counting any microfilaria). All slides were reviewed twice, each by two separate microscopists as a quality control measure.

Quality control and data management. Before each round of surveys, laboratory technicians and data recorders were trained to trace an EA and sketch houses within the boundaries, use EA maps for orientation in the village, segment maps, randomly select segments, and record findings on standardized forms. Laboratory technicians had further training in how to conduct the ICT appropriately and time reading the results precisely at 10 minutes. For additional training and supervision, the teams practiced the survey techniques in two non-selected sites before commencing the assessment.

Data were double-entered, compared, and corrected. Data were analyzed using SAS version 9.1 (SAS Institute Inc., Cary, NC). Because of the sampling design, we weighted the data based on the selection probabilities that adjusted for population differences between clusters, segments, and LGA. Additionally, in the analysis we adjusted for correlation within the data caused by clustering. Cluster survey results were reported as LGA, state, and combined overall (two-state) prevalences in all ages, in children 6–7 years of age, and (because of low LGA level sample sizes for 6–7 year olds) children 3–9 years of age.

Ethical considerations. The State Ministry of Health for both Plateau and Nasarawa approved the surveys as an evaluation of the ongoing LF elimination program. Additionally, this study was approved by the Emory University Institutional Review Board (IRB) under protocol 609-97. Informed verbal consent and assent was received according to the principles of the Declaration of Helsinki. All persons identified ICT positive by detection of CFA were offered ivermectin and albendazole and instructed to continue taking these drugs when offered during mass distribution.

Table 1
Demographic distribution of residents in selected households

	Registered population						Examined population					
	Female		Male		Total		Female		Male		Total	
Age group	Count	% Total	Count	% Total	Count	% Total	Count	% Total	Count	% Total	Count	% Total
3–9*	6,886	13.4	6,915	13.4	13,801	26.8	5,241	14.3	5,264	14.3	10,505	28.6
10–19	6125	11.9	6,170	12.0	12,295	23.9	4,457	12.2	4,276	11.7	8,733	23.8
20–29	5405	10.5	4,010	7.8	9,415	18.3	3,975	10.8	2,584	7.1	6,559	17.9
30–39	3578	7.0	2,924	5.7	6,502	12.6	2,623	7.2	1,755	4.8	4,378	11.9
40–49	2113	4.1	2,094	4.1	4,207	8.2	1,558	4.3	1,198	3.3	2,756	7.5
50–59	1178	2.3	1,163	2.3	2,341	4.6	887	2.4	665	1.9	1,552	4.3
60–69	815	1.6	843	1.6	1,658	3.2	678	1.9	570	1.6	1,248	3.4
70+	498	0.9	721	1.4	1,219	2.4	420	1.1	530	1.5	950	2.6
Total	26,598	51.7	24,840	48.3	51,438	100	19,905	54.1	16,886	45.9	36,681	100

*3,502 children were ineligible for examination because of age younger than 3 years.

RESULTS

Population-based cluster surveys. A total of 36,681 persons (66.5%) of 51,143 registered persons of eligible age for the study were examined from 7,819 selected households in 590 communities within the two states. Ten communities were not accessible by the survey teams because of environmental restraints or insecurity in areas of civil conflict. These clusters were not replaced with other accessible communities. The demographics of the combined sample are listed in Table 1; the response rate in children 3–14 years of age was 75.1% and did not differ by gender. The response rate in adult men 15 years of age and older was 62.6%, which differed from the 73.9% response in adult women ($P < 0.001$). Adult men were more likely than women to be absent from the household at the time of the survey. However, the examined population distribution did not differ from those registered and the age distribution of the registered population reflected that found in a 2003 national health survey.[17]

The MDA background information is presented in Table 2 for the surveyed area by state with LGAs ordered according to the number of MDA rounds distributed. The number of MDA treatment rounds administered before the antigen survey ranged from five to eight rounds with a median of six rounds. Four LGAs in the Plateau state and one LGA in Nasarawa had received only five rounds at the time of the survey. Note that 12 LGAs had also received (from 1992 to 1999) an additional 8–9 years of annual ivermectin MDA monotherapy for onchocerciasis.

The prevalence of antigenemia among all ages (3 years of age and above) is listed in Table 3 by state with LGA numbered in order of ascending antigen prevalence. On average, 1,220 persons were tested in each LGA with a range by LGA of 947–1,755 persons. The overall prevalence in the two-state area was 3.05% (upper 95% CI = 3.41%). Antigen prevalence was 3.48% for Plateau State (upper 95% CI = 3.96%; range by LGA 0.19–14.8%) and 2.22% for Nasarawa (upper 95% CI = 2.69; range by LGA 0.42–4.72%). Ten of the 30 LGAs met the PacELF < 2% upper 95% CI criterion for stopping MDA and included: Jos North, Jos South, Jos East, Langtang South, Bassa, and Bokkos in Plateau State; Keffi, Kokona, Karu, and Keana in Nasarawa State. The geographical distribution of the upper 95% CI antigen prevalence among all ages by LGA administrative boundaries is displayed in Figure 1.

The age- and sex-specific antigen prevalence is shown in Figure 2; among the study population, antigen prevalence ranged by a 10-year age group from 1.56% (upper 95% CI = 1.88%) among children < 10 years of age to 6.25% (upper 95% CI = 7.78%) among adults 50–59 years of age. Antigen prevalence was 4.66% (upper 95% CI = 5.24%) among adults 20 years of age and older (N = 17,443). Among children and adolescents < 20 years of age (N = 19,238), antigen prevalence was 1.62%, (upper 95% CI = 1.88%). In these two states, adults 20 years of age and older were nearly three times more

Table 2
Number of combined albendazole and ivermectin MDA rounds by LGA at the time of 2007–2008 population-based antigen surveys

LGA	Population estimate	Year MDA launched	MDA rounds before survey
Pankshin*	170,208	2000	8
Jos East*	39,278	2001	7
Bokkos*	154,320	2001	7
Bassa*	181,393	2001	7
Kanke*	101,441	2002	7
Jos South	219,269	2002	6
Barkin Ladi	97,576	2002	6
Quaanpan	152,568	2002	6
Riyom	55,806	2002	6
Mangu	234,539	2002	6
Langtang N.	168,010	2002	6
Wase	182,289	2002	6
Kanam	101,299	2002	6
Jos North	428,593	2003	5
Langtang S.	66,069	2003	5
Shendam	188,131	2003	5
Mikang	66,349	2003	5
Plateau State subtotal	2,607,138		Mean 6.1
Akwanga*	188,500	2000	8
Kokona*	82,579	2001	7
Karu*	229,966	2001	7
Nas. Eggon*	167,928	2001	7
Toto*	138,125	2001	7
Wamba*	90,875	2001	7
Keffi	80,570	2002	6
Keana	68,993	2002	6
Lafia*	471,715	2002	6
Nasarawa	193,449	2002	6
Obi	111,020	2002	6
Doma	94,113	2002	6
Awe	102,440	2003	5
Nasarawa State subtotal	2,020,273		Mean 6.5
Total two-state area	4,627,411		Mean 6.3

*Ivermectin MDA for Onchocerciasis 1992–1999.
LGA = local government area; MDA = mass drug administration.

TABLE 3
Population-based prevalence of *Wuchereria bancrofti* antigenemia in Plateau and Nasarawa States by LGA

LGA	Prevalence of antigenemia (ages 3 years and above)	
	Examined	% ICT positive
1. Jos North	1,056	0.19 (0.50)*
2. Jos South	1,140	0.56 (0.99)*
3. Langtang South	1,235	0.62 (0.99)*
4. Jos East†	1,377	0.76 (1.12)*
5. Bokkos†	1,755	1.09 (1.73)*
6. Bassa†	1,331	1.11 (1.79)*
7. Barkin Ladi	947	1.74 (2.98)
8. Quaanpan	1,379	2.73 (3.44)
9. Riyom	1,249	2.74 (3.73)
10. Mangu	1,450	3.19 (4.23)
11. Langtang North	1,480	2.91 (5.05)
12. Pankshin†	1,338	3.87 (6.00)
13. Wase	1,018	5.69 (8.13)
14. Shendam	1,231	5.70 (7.40)
15. Kanke†	1,306	14.1 (18.5)
16. Mikang	1,086	14.7 (18.3)
17. Kanam	1,088	14.8 (19.3)
Plateau State	21,466	3.48 (3.96)
18. Keffi	1,485	0.42 (0.75)*
19. Kokona†	1,178	0.72 (1.40)*
20. Karu†	1,267	1.20 (1.83)*
21. Keana	1,207	1.29 (1.85)*
22. Nasarawa Eggon†	1,144	1.62 (2.54)
23. Toto†	1,080	1.84 (4.10)
24. Wamba†	1,224	1.96 (2.84)
25. Awe	1,085	2.07 (3.98)
26. Lafia†	1,013	2.43 (4.28)
27. Nasarawa	1,051	2.84 (4.45)
28. Obi	1,224	3.03 (4.19)
29. Akwanga†	1,189	3.19 (4.50)
30. Doma	1,068	4.72 (6.51)
Nasarawa State	15,215	2.22 (2.69)
TOTAL two-state area	36,681	3.05 (3.41)

*Passes Pacific regional program to eliminate lymphatic filariasis (PacELF) C-survey criteria for stopping mass drug administration (MDA).
†Ivermectin MDA for Onchocerciasis 1992–1999.
Values are weighted according to sampling probabilities and local government area (LGA) size and have been adjusted for clustering; Parentheses show exact one-sided upper 95% confidence limit.

likely to be antigen positive than children and adolescents under 20 years of age (odds ratio [OR] = 2.98, 95% CI = 2.5–3.6). A significant gender difference in antigenemia occurred by the third decade of life, and overall men were more likely to be antigen positive than women (OR = 1.66, 95% CI = 1.4–2.0).

To examine antigenemia among younger age groups according to 2005 and 2011 WHO guidelines, we limited our analysis to children ages 3–9 (N = 10,505) and 6–7 (N = 3,233) in our sample as seen in Table 4. The number of 3- to 9-year-old children examined per LGA ranged from 250 to 543 children with a median of 342 children examined per LGA. The overall prevalence of antigenemia among children 3–9 years of age in the two-state area was below the important threshold of 2% (1.56%, upper 95% CI = 1.88%). Antigen prevalence among 3- to 9-year-old children living in Plateau state was 1.47% (upper 95% CI = 1.86%; LGA range by upper 95% CI = 0.99–8.08%) and 1.73% (upper 95% CI = 2.29%; LGA range by upper 95% CI = 0.62–6.48%) among children living in Nasarawa state.

Comparing thresholds in the 3- to 9-year-old age group (Table 4, left panel) with all ages (Table 3), antigen prevalence among children 3–9 years of age was > 2% in only one LGA (Bassa) of the 10 LGAs that met the PacELF criteria of < 2% among all ages. However, no ICT-positive children were found in three LGAs (Barkin Ladi and Quaanpan in Plateau state, Toto in Nasarawa state) that failed PacELF criteria. Among the age group recommended in the recent WHO TAS[13] (children 6–7 years of age) the prevalence of antigenemia was 1.71% (upper 95% CI = 2.19%) (Table 4, right panel). Prevalence in the Plateau state was 1.77% (upper 95% CI = 2.38%) and 1.60% (upper 95% CI = 2.40%) in Nasarawa state among 6–7 years of age. Sample sizes obtained for 6–7 year olds per LGA ranged from 69 to 163 children with a median of 111 children per LGA and have little power to estimate LGA-level antigen prevalence. If current WHO TAS guidelines were used to make a decision to stop MDA, neither state would pass (Table 5). If the 10 LGAs that passed the PacELF criterion in Table 3 were combined and taken as a domain, the antigen prevalence estimate among children 6–7 years of age would also pass the WHO TAS criteria. Similarly, the domain of 20 LGAs that failed the PacELF criterion would also fail the WHO TAS criterion in the 6–7 year olds.

Re-assessment of baseline mapping sites. We assessed 16 communities for which baseline mapping data were available from 1999 to 2000 in nine out of the 10 LGAs from Table 3 where antigen prevalence was < 2.0%. At the time of implementing these baseline-site investigations (in third quarter 2008) we had not analyzed the data for Keana LGA and were not aware that the criteria had been met. Once the analysis was complete, we were out of ICT and unable to obtain antigen data from the baseline site in Keana. Antigen prevalence among 1,602 adults 15 years of age and older was 2.43% (upper 95% CI = 3.88; range by site 0.0–8.9%). In five communities (Gauta, Gidan Mudu, Laminga, Fursum, and Barkin Kogi) not one adult tested positive for filarial antigen. Compared with antigen prevalence found at baseline, the decrease in prevalence in 2008 was statistically significant (Figure 3) in all but one site (Bassa Village in Kokona LGA). Blood smears to determine mf were collected from all ICT-positive individuals in each site (N = 51) and from 100 persons in the baseline site in Keana LGA. No microfilaria positive slides were identified (data not shown).

DISCUSSION

We report herein a large population-based survey that examined over 36,000 persons for circulating filarial antigen sampled from a two-state program area that had been offered an average of six rounds of annual MDA with ivermectin and albendazole. These surveys were undertaken after most sentinel villages in the project area indicated the nocturnal mf had dropped below 1%[7]; the surveys were designed to determine if MDA at the implementation unit (LGA-level) could be stopped. We chose to apply the "PacELF criterion" of an exact upper 95% CI of < 2% antigenemia in all ages (defined as age 3 years and above) because we believed this is more conservative for making a stop MDA decision. Using this criterion we found that MDA could be stopped in only 10 of the 30 LGAs. We also found that the aggregate two-state project area (upper 95% CI = 3.41%) did not reach the stop MDA goal, nor did any individual state (Plateau upper 95% CI = 3.96%, Nasarawa upper 95% CI = 2.69%).

The decision to discontinue MDA must be taken with caution. Stopping MDA before interruption of transmission

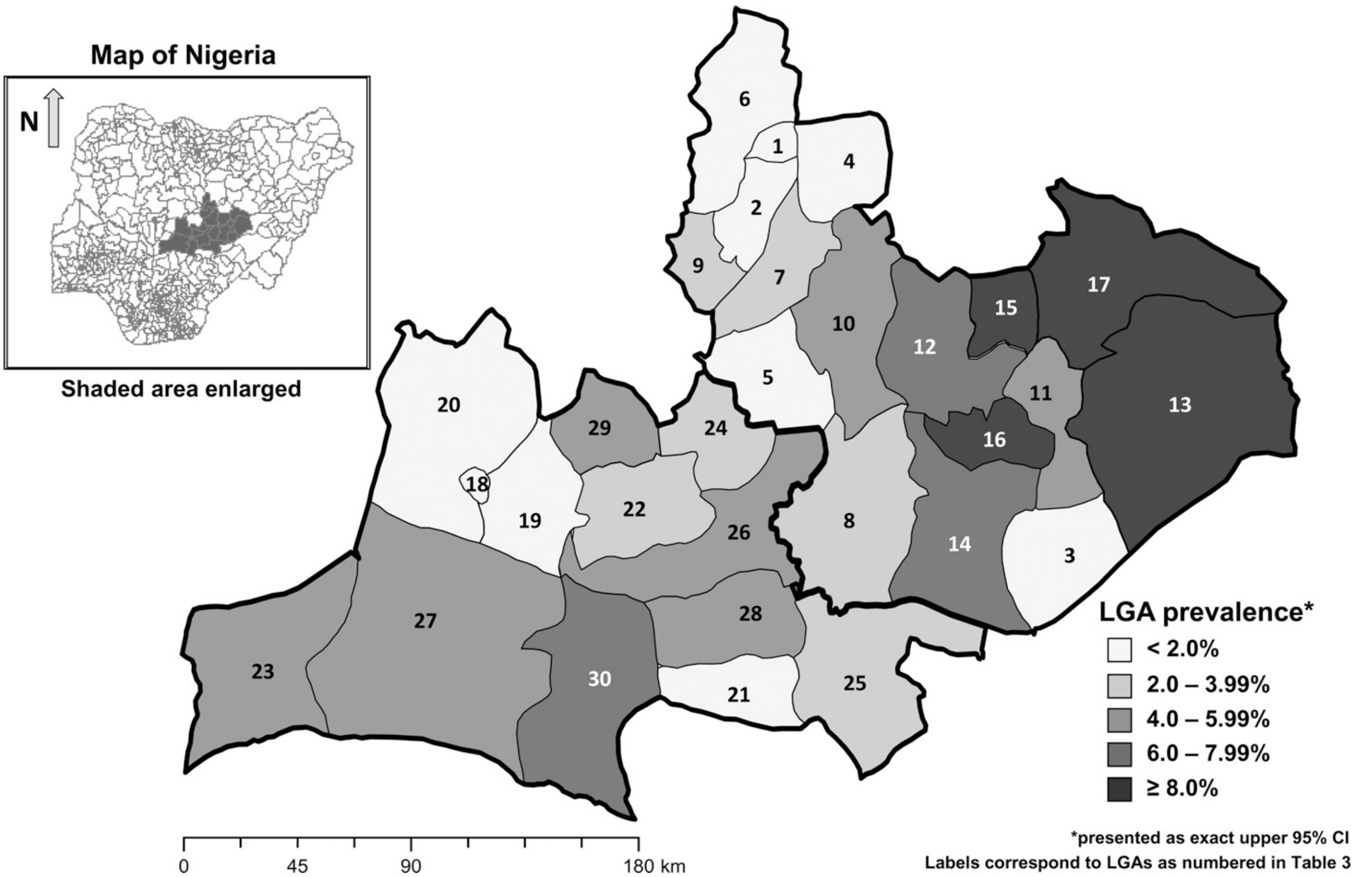

FIGURE 1. Prevalence of *Wuchereria bancrofti* antigenemia in persons > 2 years of age in Plateau and Nasarawa States, Nigeria 2008.

poses the risk of recurrence that may not be detected for years, possibly after elimination has been declared. On the other hand, continuing to distribute medications in the absence of disease absorbs crucial resources that should be directed to other endemic areas. Survey methods to determine stopping points must be pragmatic for programs to implement at reasonable costs, but such less costly approaches may not have the resolution needed to pick up residual "hotspots" of transmission that need special attention. Our study had such resolution to detect prevalence down to the original implementation unit, but our costs of the ICT tests alone (at US$4/test) were nearly US$150,000. Thus, the resolution of our expensive survey may be higher than what most programs could be resourced to accomplish. For this reason, our EU analyses at state level, or as a two-state unit, are more germane than our LGA analysis to nascent LF MDA programs in Nigeria.

The new WHO TAS guidelines call for the combining of similar implementation units into larger EU to make "stop MDA" surveys more feasible and less costly. However, as stated in the guidelines, this approach poses risk. The focal nature of LF transmission complicates the ability of an EU analysis (with lower resolution but more affordable sampling approaches) to give an epidemiological picture of "hotspots" and present a programmatically useful interpretation. Figure 1 shows the considerable spatial variability of antigen results by LGA and findings from the follow-up assessments in baseline mapping sites (Figure 4) indicate the residual antigen heterogeneity of LF at even higher resolution, the community level.

The recently recommended TAS guidelines focus on antigen prevalence among up to 1,700 children 6–7 years of age per EU.[13] Although we did not have sufficient numbers to use this age group to make decisions at the LGA level, we found at higher administrative levels likely to have been defined as our EU, that decisions to stop MDA based on antigenemia in the TAS age group were the same as decisions based on antigenemia in all ages. In other words, the aggregate two-state area and both states failed to reach the WHO TAS stop MDA goal. However, aside from organizing EU along the obvious political boundaries, we do not think that we could have identified programmatic or epidemiological reasons *a priori* to link LGAs that met our stopping criteria as an evaluation unit in the TAS. Therefore, we would have failed implementation units that have met the < 2% antigenemia criteria in the total population. This gives evidence that decisions made at large EU risk misclassifying smaller implementation units that may have achieved transmission interruption. Therefore, we recommend implementing stopping surveys and making decisions at the highest resolution (lowest level) affordable.

In the 10 LGAs considered for stopping MDA, we visited 16 non-sentinel, 1999 baseline mapping sites to assess antigen reductions in the adult populations. High statistically significant drops in antigen rates were observed in all but one of these follow-up assessments. Among antigen-positive adults who remained in these sites, circulating mf were not observed. However, we found village-level antigen prevalence up to 9% among the adult population after five or more rounds of MDA (Figure 3, Binchi village after 7 MDAs in Bassa

TABLE 4
Prevalence of *Wuchereria bancrofti* antigenemia among children in Plateau and Nasarawa States, Central Nigeria

LGA	Children 3–9 years of age			Children 6–7 years of age		
	Examined	n ICT+	% ICT+	Examined	n ICT+	% ICT+
1. Jos North	304	0	0.0 (0.99)*	85	0	0.0 (3.53)*
2. Jos South	326	3	1.02 (1.90)	105	2	2.23 (4.70)
3. Langtang South	328	2	0.60 (1.31)	111	1	1.33 (3.42)
4. Jos East†	543	5	0.82 (1.49)	136	2	1.15 (3.01)
5. Bokkos†	477	3	1.04 (1.88)	137	3	3.42 (6.03)
6. Bassa†	407	7	1.35 (2.29)	122	1	0.96 (2.36)
7. Barkin Ladi	250	0	0.0 (1.20)*	69	0	0.0 (4.35)*
8. Quaanpan	412	3	0.39 (0.78)	119	1	0.57 (1.53)
9. Riyom	421	5	1.51 (2.66)	126	3	2.68 (4.80)
10. Mangu	412	6	1.55 (2.61)	128	1	0.96 (2.49)
11. Langtang North	356	5	1.40 (2.58)	119	2	1.68 (3.58)
12. Pankshin†	347	5	1.59 (2.78)	96	1	0.99 (2.61)
13. Wase	240	6	3.33 (6.94)	91	4	6.43 (13.0)
14. Shendam	355	13	3.34 (5.08)	116	2	1.59 (3.37)
15. Kanke†	358	9	2.42 (4.53)	120	5	4.15 (7.68)
16. Mikang	306	6	1.96 (3.17)	96	5	5.21 (9.13)
17. Kanam	297	19	5.69 (8.08)	87	7	7.59 (12.1)
Plateau State	6,139	97	1.47 (1.86)	1,863	40	1.77 (2.38)
18. Keffi	459	1	0.24 (0.62)	163	0	0.0 (1.84)*
19. Kokona†	412	3	0.55 (1.16)	121	0	0.0 (2.48)*
20. Karu†	364	2	0.45 (1.17)	128	2	1.20 (3.18)
21. Keana	350	0	0.0 (0.86)*	93	0	0.0 (3.23)*
22. Nasarawa Eggon†	303	4	1.21 (2.74)	89	2	1.98 (4.47)
23. Toto†	323	0	0.0 (0.93)*	91	0	0.0 (3.30)*
24. Wamba†	336	5	1.87 (3.74)	112	1	1.67 (4.40)
25. Awe	292	3	0.85 (2.23)	90	0	0.0 (3.33)*
26. Lafia†	264	4	1.91 (3.32)	86	2	1.81 (5.67)
27. Nasarawa	249	8	3.66 (6.48)	91	2	2.48 (5.41)
28. Obi	406	10	2.94 (4.54)	116	1	0.28 (0.74)
29. Akwanga†	309	5	1.58 (2.83)	79	3	3.94 (7.33)
30. Doma	299	8	3.20 (4.92)	111	3	3.50 (6.56)
Nasarawa State	4,366	53	1.73 (2.29)	1,370	16	1.60 (2.40)
TOTAL area	10,505	150	1.56 (1.88)	3,233	56	1.71 (2.19)

*Derived from the Poisson approximation to the binomial distribution.
†Ivermectin MDA for Onchocerciasis 1992–1999.
Values are weighted according to sampling probabilities and local government area (LGA) size and have been adjusted for clustering. Parentheses show exact upper 95% confidence limit. MDA = mass drug administration; ICT = immunochromatographic card test.

LGA). Further investigation is needed to determine whether these "antigen hot spots" resume transmission once MDA is stopped, and if such local transmission could then spread to surrounding communities. Knowing the transmission dynamics over time in areas surrounding "hot spots" may help provide evidence to help determine how much resolution is needed for a TAS.

Antigenemia in children has been the target threshold indicator for MDA treatment decisions in past and current WHO recommendations for LF elimination progams.[9,13,18] Age ranges proposed as the key indicator group, however, have varied. Focusing on 6- to 7-year-old children makes the most sense, because it is based on the principle that a lack of positives in this age group reflects an absence of transmission during the average 6-year period suggested to permanently halt reproduction in the *W. bancrofti* population. This is the point at which MDA can therefore be halted because transmission is highly unlikely to resume thereafter. We found similar prevalence between antigenemia among children 6–7 years of age and among children of a wider age range, 3–9 years of age (Table 4), yet different decisions about stopping MDA would have been made depending on which age range of children is selected. The 6–7 year age group best reflected the all-age PacELF decisions at the levels of the state and the two-state project area. Being more plentiful, however, meant that more robust data were available for children 3–9 years of

TABLE 5
Prevalence of *Wuchereria bancrofti* antigenemia among children 6–7 years of age by different domains

Domain	Examined	Total ICT+	% ICT+ (exact upper 95% CI)*	TAS[8] criteria†
Two-state area combined	3,233	56	1.71 (2.19)	Fail
Nasarawa State	1,370	16	1.60 (2.41)	Fail
Plateau State	1,863	40	1.83 (2.44)	Fail
10 LGAs < 2% antigenemia among ages 3 years and above	1,201	11	1.06 (1.69)	Pass
20 LGAs ≥ 2% antigenemia among ages 3 years and above	2,032	45	1.95 (2.57)	Fail

*Values are weighted according to sampling probabilities and local government area (LGA) size and have been adjusted for clustering.
†Less than the critical value of immunochromatographic card test (ICT)-positive children (as proxy for < 2% antigen prevalence).
TAS = transmission assessment surveys.

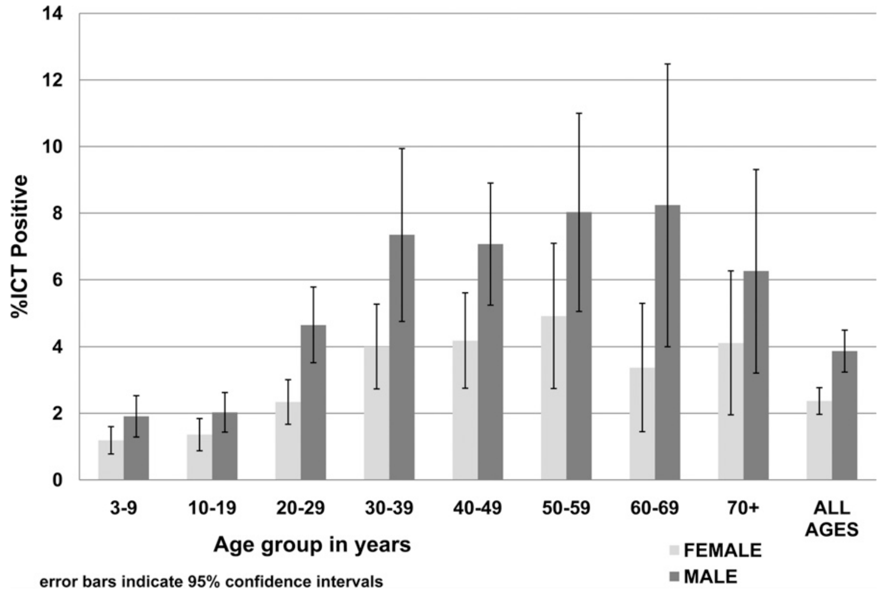

FIGURE 2. Age and gender-specific prevalence of *Wuchereria bancrofti* antigenemia in Plateau and Nasarawa States, Nigeria 2008 (N = 36,681).

age and thus the differences in decisions may have been only a matter of sample size.

This survey included over 10,000 children 3–9 years of age. We analyzed antigenemia for this age group and for a subset of 6- to 7-year-old children in our sample. The LGA-level estimates could not be made using 6- to 7-year-old children because of a small sample size at that level. Antigenemia among children 3–9 years of age was > 2% in only one LGA of the 10 LGAs that met our PacELF criteria of < 2% among all ages. Three other LGAs (that did not pass the PacELF criteria) achieved < 2% in the 3–9 year age groups. Basing the stop MDA decision on data from 3- to 9-year-old children also gave different results compared with data from all-ages when estimating prevalence at higher administrative levels (e.g., above LGA level). The two-state area prevalence of antigenemia among children ages 3–9 years of age would "pass" a < 2% stop MDA goal. Analyzed by state, Plateau State would have also "passed" (upper CI 1.86%), whereas Nasarawa "failed" (upper CI = 2.29%). It is concerning that Plateau State would pass using a criterion in 3–9 year olds because it had some of the highest LGA-level antigen prevalence among all age groups (up to 14.8%, Table 3).

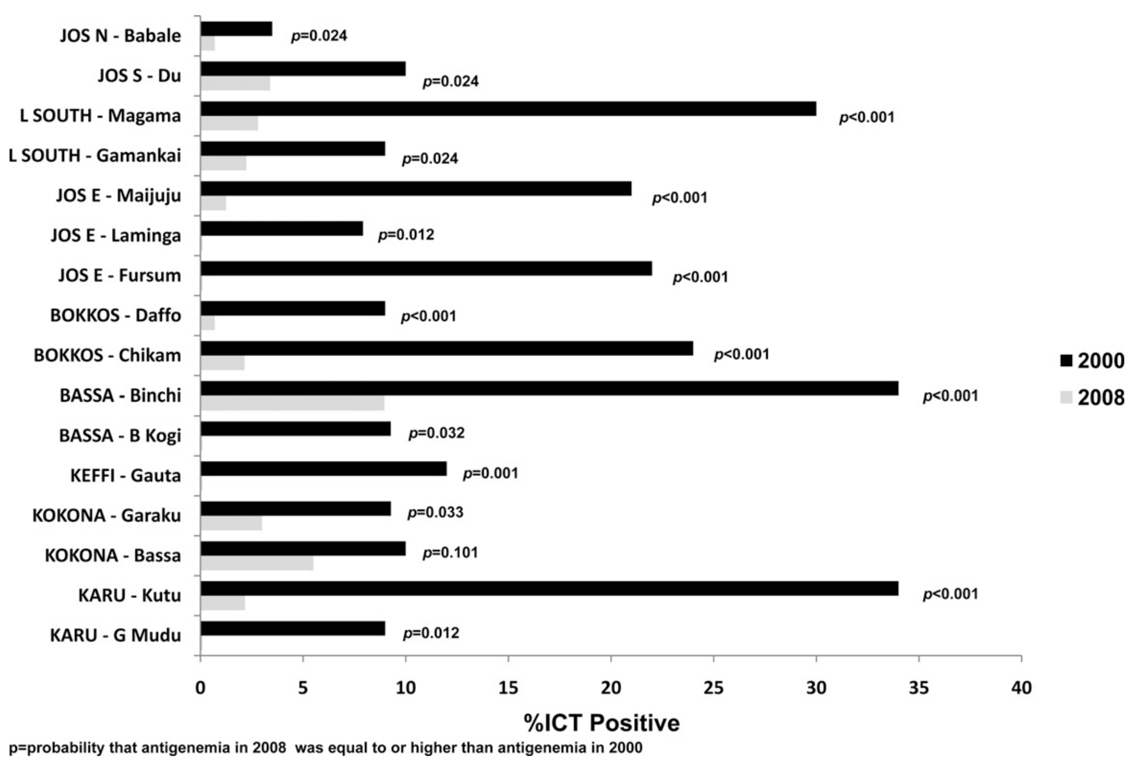

FIGURE 3. Antigen prevalence among adults > 14 years of age living in baseline mapping villages in 2000 and 2008.

It may be better to include adults when monitoring transmission because antigenemia is more prevalent among adults in endemic areas.[19,20] Reproductively viable (mf positive) infections have been found in adults in communities where no antigen-positive children could be identified.[21] However, using adults in stop MDA assessments has the disadvantage of potentially failing an area if CFA is caused by persistent antigen from non-viable worms. Antigen-positive, mf-negative adults in an ongoing MDA setting may or may not be interpreted to mean the presence of reproductively viable worms, because the absence of mf could reflect the impact of successful chemotherapy.[22] The LF elimination programs will have no knowledge of whether antigen-positive adults will produce mf until a year or two after MDA has ceased. Therefore, using the all-age antigen criteria gives us more confidence in making stop MDA decisions in Plateau and Nasarawa than decisions based on children alone. However, stopping MDA based on antigen levels in either age group must be accompanied by implementation of a surveillance strategy to monitor antigenemia for several years after MDA.

The data suggest that 10 LGAs interrupted LF transmission. Three of these (Jos North, Jos South, and Keffi) are urban areas, and may not have the anopheline vector abundance needed to maintain transmission in the face of MDA, and was, perhaps, easily broken. There is little evidence that *Culex* species, a better urban breeding mosquito, plays an important role in the transmission of LF in Nigeria.[6] For the other seven LGAs, the explanation for their MDA success is less obvious. Mathematical modeling has predicted that where LF prevalence at baseline is highest, longer and better MDA coverage is required, and may require the addition of vector control measures.[23] Our baseline mapping data did not indicate that these 10 LGAs were spatially clustered, but these LGA did have a fewer number of highly endemic baseline sites than the other 20 LGAs. Three baseline mapping villages (Magama in Langtang South, Kutu in Karu, and Binchi in Bassa; Figure 3) in the successful LGAs had 1999 antigen levels above 30% (the upper tercile of antigen prevalence among the 30 LGAs)[7], whereas 15 out of the other 20 unsuccessful LGAs had one or more baseline sites with antigen levels above 30% (data not shown). Our original 1999 mapping data showed upper antigen terciles clustered in a central band shared by the two states, a pattern that is considerably different from the 2008 map reported here, where antigen rates are highest in eastern Plateau.[7] Within the current data there seems to be no relation of antigen prevalence at the LGA level to the number of MDA rounds distributed in each LGA and the coverage achieved. Further investigation of the data is warranted to determine whether spatial and non-spatial predictors could explain individual LGA survey outcome, the altered spatial distribution of antigenemia, and suggest new ways to target more tailored interventions.

Our findings assume that all persons ICT positive were true positive and all ICT-negative persons were true negative. During the household surveys we were unable to quality control our ICT results to determine whether there were any incorrect readings, or false positive/false negative tests. We did not perform repeat ICT testing in positive persons, nor did we use other confirmatory diagnostic tests in ICT positives. Several false ICT positives occurred among children in stop MDA surveys in Togo that were implemented around the same time as our surveys.[24] Those results conflict with historical performance of the filarial antigen-based diagnostics in adults.[19] In contrast to the methodology of our population-based surveys, in the follow-up assessments in baseline sites, all adults who were ICT positive were checked for mf; no mf positives were found. The ICT positive, mf negative findings are not uncommon,[19] especially during the MDA phase of an LF elimination program.[7,25] However, a single 60 μL blood slide is less sensitive for detecting mf than are 1 mL blood filtration techniques, and true mf positives therefore may not have been identified. False negatives (mf positive, ICT negative) are unlikely given the reported high sensitivity of the ICT.[16]

An additional MDA round was given in all LGAs in 2009 as partners contemplated what to do with the results of this survey. In 2010 and early 2011, the Nigeria National Malaria Program and partners (including The Carter Center) distributed long-lasting insecticidal nets (LLIN) throughout Plateau and Nasarawa States, with the aim of providing two LLIN per household. The LLIN will likely have benefits of suppressing transmission in unidentified foci in LGAs where MDA has stopped, preventing resurgence of transmission as suggested by Burkot and others[26]; accordingly, the Federal Ministry of Health gave permission for stopping MDA in five LGAs. In LGAs where onchocerciasis (river blindness) is coendemic, MDA continues until onchocerciasis stop MDA surveys can be completed. Unfortunately, WHO guidelines for stopping onchocerciasis (ivermectin monotherapy) MDA in Africa are less well accepted than those for LF.[3] In terms of the 20 LGAs where antigen prevalence did not meet the PacELF criteria for stopping, continued MDA together with LLIN will likely act synergistically to hasten LF transmission interruption there. We plan to implement another survey following current TAS guidelines in 2012 in these LGAs, possibly at a combined EU level rather than LGA level, due to financial constraints. LF post-treatment surveillance is needed in all LGAs where MDA is halted, in accord with WHO guidelines.

Despite the scale of these surveys, in LGAs where we judged transmission was interrupted, it is impossible to rule out ongoing LF transmission. Focality of antigenemia remains; we often found the distribution of antigen-positive individuals in some LGAs was focused only within a few communities (data not shown). As mentioned earlier, antigen focality was also evident among the reassessed of baseline mapping sites. This "zero-inflated" distribution should be explored and may be useful in modeling LF elimination to determine whether transmission from a few focal communities in a majority of infection-free communities could spread in the post MDA environment, and jeopardize the program's achievements. Finally, Plateau and Nasarawa States are surrounded by other states recently found in mapping exercises to have LF transmission. It is the hope of the program that the distribution and use of LLIN for malaria might prevent resurgence from potential imported infections from these surrounding endemic states where MDA is just starting.

Received November 17, 2011. Accepted for publication March 8, 2012.

Acknowledgments: We thank the contribution of the Nasarawa and Plateau States Ministry of Health, the Nigeria Federal Ministry of Health, medical technicians, students and community volunteers for coordinating logistics and performing field work. We thank Fidelis Maigida and Solomon E. Adelamo for supervising data entry and the data entry staff at The Carter Center Office in Jos. We acknowledge Huiqing Zhu, MS candidate from the Georgia Institute of Technology Department of Statistics, for reviewing the statistical analysis of this data set. Finally, we thank the participants of the survey and the village leaders of the selected communities.

Financial support: The survey described in this work was funded by generous grants to The Carter Center by GlaxoSmithKline and by The Bill & Melinda Gates Foundation. The funders had no role in study design; collection, analysis, and interpretation of data; writing of the paper; and decision to submit it for publication.

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