Criteria to Stop Mass Drug Administration for Lymphatic Filariasis Have Been Achieved Throughout Plateau and Nasarawa States, Nigeria

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Abstract.   Nigeria has the largest population at risk for lymphatic filariasis (LF) in Africa. This study used a transmission assessment survey (TAS) to determine whether mass drug administration (MDA) for LF could stop in 21 districts, divided into four evaluation units (EUs), of Plateau and Nasarawa States, Nigeria, after 8–12 years of annual albendazole–ivermectin treatment. A total of 7,131 first- and second-year primary school children (approximately 6–7 years old) were tested for LF antigen by immunochromatographic test (ICT) from May to June 2012. The target sample size of 1,692 was exceeded in each EU (range = 1,767–1,795). A total of 25 (0.4%) individuals were ICT positive, with the number of positives in each EU (range = 3–11) less than the TAS cutoff of 20, meaning that LF transmission had been reduced below sustainable levels. As a result, 3.5 million annual albendazole–ivermectin treatments were halted in 2013. Combined with the previous halt of MDA for LF in other parts of Plateau and Nasarawa, these are the first Nigerian states to stop LF MDA statewide. Posttreatment surveillance is ongoing to determine if LF transmission has been interrupted.

Lymphatic filariasis (LF) is a debilitating mosquito-transmitted parasitic disease caused in Africa by *Wuchereria bancrofti*. Adult worms dwell in the human lymphatic system causing dysfunction that can lead to lymphedema, hydrocele, elephantiasis, and adenolymphangitis. Coadministration of albendazole (GlaxoSmithKline) with ivermectin (Mectizan®; Merck) or diethylcarbamazine (DEC; Eisai) reduces the number of microfilariae (mf) in circulation, thereby preventing transmission to mosquitoes. Annual mass drug administration (MDA) at sufficient population coverage ($\geq$ 65%) is predicted to interrupt LF transmission in 4–6 years.[1]

Nigeria has the most individuals at risk for LF in Africa and second largest globally behind India, with approximately 120 million of Nigeria's estimated 174 million inhabitants in need of MDA.[2] The Nigerian Federal Ministry of Health (FMOH), with assistance from The Carter Center, established an LF elimination program in Plateau and Nasarawa States in 1997 as an extension of ongoing ivermectin-based MDA for onchocerciasis elimination.[3] Baseline LF mapping in 1998–2000 revealed mean antigen prevalence of 23% (range = 4–62%) in adults across the 30 districts—local government areas (LGAs)—of Plateau and Nasarawa.[4] Annual albendazole–ivermectin MDA started in 2000 in two LGAs, with full geographic coverage of all 30 LGAs achieved in 2003. Each LGA was an implementation unit (IU). After at least five rounds of MDA at > 83% reported coverage, a "C-survey" recommended by the World Health Organization (WHO) Pacific regional program to eliminate LF (PacELF) was conducted in all 30 LGAs in 2007–2008 to determine whether MDA could be stopped.[5] The C-survey is a community-based cluster survey to measure antigen prevalence in individuals older than 2 years.[6] Ten of the 30 LGAs met the criterion for stopping LF MDA (antigen prevalence < 2% at the 95% confidence limit).

The purpose of this study, conducted from May to June 2012, was to determine whether MDA for LF could be stopped in the 20 LGAs that did not meet stop-MDA criterion in 2007–2008. A 21st LGA, Jos South, was also included. Jos South met the criterion in 2007–2008 but continued MDA due to high antigen prevalence observed in a pre-survey spot-check site. The 2012 survey followed the 2011 WHO transmission assessment survey (TAS) protocol, which permits the aggregation of multiple, noncontiguous IUs into a TAS evaluation unit (EU) if the IUs share similar epidemiologic features and have completed at least five effective rounds of MDA.[1] The 21 LGAs were grouped into four EUs (Figure 1) based on 2007–2008 LGA-specific antigen prevalence[5]: two EUs, one per state, that were likely to pass TAS, "Plateau EU1" (mean LGA-specific 2007–2008 antigen prevalence = 2.5%; range = 0.6–3.9%) and "Nasarawa EU1" (mean = 2.0%; range = 1.6–2.4%); and two EUs less likely to pass TAS, "Plateau EU2" (mean = 11.0%; range = 5.7–14.8%), and "Nasarawa EU2" (mean = 3.5%; range = 2.8–4.7%). Formation of EUs on epidemiological, rather than strictly geographical, basis minimized the risk that a high-burden area could cause an entire EU to fail and require continued MDA. The population size in each EU was less than 2 million in accordance with TAS guidelines, and the estimated target population (6- to 7-year-old children) was greater than 50,000. The corresponding target sample size was 1,692 per EU, with a critical cutoff value of 20 antigen-positive children. TAS sample sizes and critical cutoff values are powered so that an EU has at least a 75% chance of passing if the true antigen prevalence is 1.0% and no more than about a 5% chance of passing (incorrectly) if the true antigen prevalence is $\geq$ 2.0%—the level below which *Anopheles*-transmitted *W. bancrofti* is believed to be unsustainable.[1]

A school-based TAS was implemented due to high enrollment rates (> 75%) in the survey area. Within each EU, 45 schools were selected by interval (systematic) selection following a random start from an ordered list of Ministry of Education-registered schools. Approximately 45 first- and second-year primary school children (approximately 6–7 years old) were randomly selected from each school (maximum 55 children from any one school). Finger prick blood

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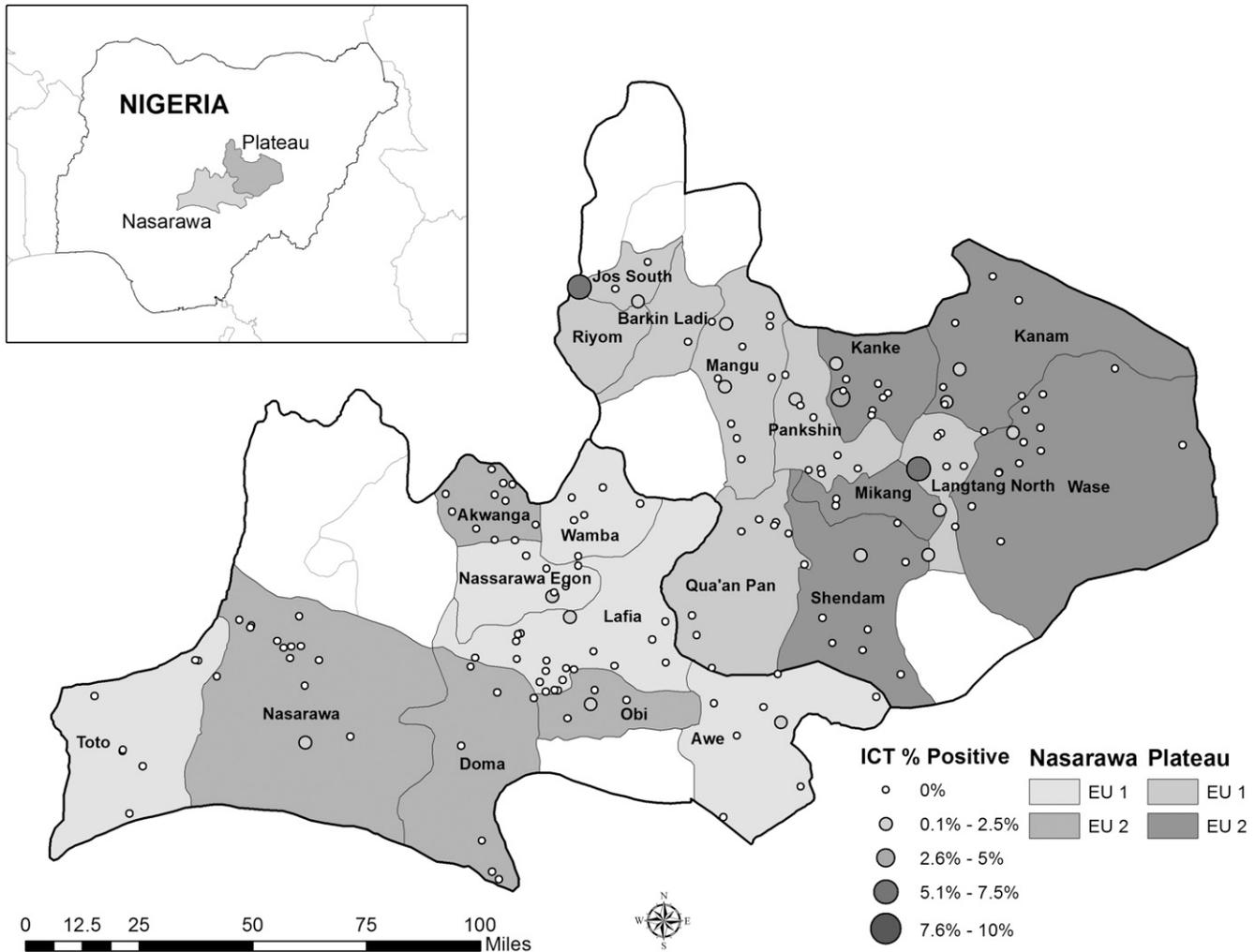
FIGURE 1. Lymphatic filariasis antigen prevalence by cluster in a school-based transmission assessment survey (TAS), Plateau and Nasarawa States, Nigeria, 2012. Divisions show local government area (LGA) boundaries and colored areas show evaluation units (EUs) established for TAS. Formation of EUs was based on likelihood of passing TAS based on previous antigen levels, with EU1 in each state being more likely to pass, and EU2 being less likely to pass (see Methods). The 9 LGAs not included in the study were previously found to meet criteria for stopping MDA.

samples (100 μL) were collected by certified laboratory scientists from all assenting children to determine the presence of circulating filarial antigen using the BinaxNOW Filariasis immunochromatographic test (ICT) (Alere Inc., Scarborough, ME). Results were read at 10 minutes, recorded on paper forms, and communicated to each child confidentially. ICT-positive children were offered albendazole–ivermectin according to FMOH guidelines. Participation in the surveys was voluntary. Individual oral assent was obtained from selected students and written informed consent obtained from each school head or his/her representative. The survey was

conducted as a non-research public health evaluation under an Emory University Institutional Review Board-approved protocol (153-2001).

A total of 7,131 children were tested in 173 schools across four EUs, of whom 25 (0.4%) were ICT positive (Table 1). In each EU, the target sample size of 1,692 was exceeded (range = 1,767–1,795). The number of ICT-positive individuals in each EU (range = 3–11) was less than the cutoff of 20, meaning that each EU "passed" TAS. In Nasarawa State, no single LGA or school had more than one positive individual. In Plateau, only Riyom (4/85 = 4.7%) in EU-1, and Kanam

TABLE 1
Summary of TAS results in 21 LGAs of Plateau and Nasarawa States, Nigeria, 2012

State	EU	Number of LGAs	Number of schools sampled	Target sample size	Number of children tested	Number ICT positive (%)	TAS critical cutoff	TAS result (pass/fail)
Plateau	1	7	43	1,692	1,767	8 (0.5)	20	Pass
	2	5	45	1,692	1,776	11 (0.6)	20	Pass
Nasarawa	1	5	43	1,692	1,793	3 (0.2)	20	Pass
	2	4	42	1,692	1,795	3 (0.2)	20	Pass
Total		**21**	**173**	**6,768**	**7,131**	**25 (0.4)**		

(4/537 = 0.7%) and Mikang (5/249 = 2.0%) in EU-2 had more than two positive samples, with focal clustering (more than one positive per school) observed in only one school in Riyom and Mikang. Antigenemia was significantly more prevalent among males (20/3,710 = 0.54%) than females (5/3,421 = 0.15%; $\chi^2 = 7.87$, $P = 0.005$).

These results indicate that LF transmission in these EUs was below sustainable levels and that stopping MDA was warranted according to WHO guidelines. A final round of 3.5 million albendazole–ivermectin MDA was provided in September 2012 in the 21 LGAs. In total, they received a median of 10 years (range = 8–12 years) of MDA. Although the Global Program to Eliminate LF assumes that 4–6 years of MDA at effective coverage is sufficient to interrupt transmission,[1] the Plateau–Nasarawa experience is consistent with models predicting 10 or more years of albendazole–ivermectin MDA are required in areas with baseline prevalence > 15%.[7] Reported treatment coverage, however, was not verified in all LGAs by coverage surveys, and actual consumption of medicines may have differed from reported coverage. Besides MDA, long-lasting insecticidal nets helped reduce LF transmission in this area.[8] Continued efforts to further increase net ownership and use in Nigeria through universal net coverage should help prevent LF recrudescence following the halt of MDA in Plateau and Nasarawa.

WHO guidelines recommend approximately 5 years of posttreatment surveillance (PTS) following MDA stoppage.[1] Ongoing transmission in neighboring states and potential residual foci identified here highlight the importance of PTS to detect importation or recrudescence. A major challenge for interpreting PTS data, however, is the continued distribution of ivermectin for onchocerciasis in 12 of the 30 LGAs of Plateau and Nasarawa.[9] Though not recommended as an MDA strategy for LF elimination, ivermectin monotherapy exerts microfilaricidal activity against *W. bancrofti*,[10] and continued ivermectin MDA for onchocerciasis may sufficiently suppress microfilaremia among remaining infected persons to prevent recrudescence. This raises the question of whether repeated TAS in areas with ongoing ivermectin MDA for onchocerciasis can be considered as true PTS for LF. If elimination of LF transmission becomes the goal (as opposed to elimination as a public health problem), then delayed PTS until the halt of ivermectin MDA would appear to be necessary, in line with WHO guidelines for onchocerciasis elimination.[11]

This study has several limitations: 1) follow-up mf testing was not conducted for antigen-positive individuals. However, as antigen levels persist following mf clearance, the true transmission potential among the sample population is likely lower than antigen prevalence estimates. 2) Five selected schools were not visited due to ethnic conflicts. Such events occur periodically in central Nigeria, meaning that affected areas may not have received MDA and that pockets of transmission may persist. Such areas should be specifically monitored during PTS. 3) The sampling of primary school children may underestimate community-wide LF burden as prevalence is lower in children compared with other age groups.[5,12] Therefore, the absence of infection in children does not preclude sustained transmission among older groups. 4) Children older than 7 were occasionally included, as TAS guidelines recommend enrolling participants by class rather than by age to increase survey efficiency.[1] Inclusion of older children would likely lead to an overestimate of antigen prevalence among the TAS target population of 6-to 7-year olds, providing greater certainty that stop-MDA thresholds have been achieved. 5) Finally, selection of a similar number of children per school differed from the recommended TAS procedure of selecting children with probability proportional to school size. Although our method was chosen to maximize efficiency and minimize confusion for survey teams, it did not yield equal selection probabilities for individuals, which is assumed in TAS sample sizes and cutoff calculations. Our result therefore may not be uniformly representative of the EU, though this would not alter the "pass" result of these EUs, given the low frequency of antigen positives. Conversely, by including approximately 50% more clusters (target 45 schools per EU) than the *Survey Sample Builder*[13] recommendations (30 schools), our results are likely to be more representative of the survey area compared with a conventional TAS, and more conservative in the pass/fail decisions.

In conclusion, this study determined that 21 LGAs in Plateau and Nasarawa have met WHO criteria for stopping LF MDA. Taken together with previous surveys,[5] Plateau and Nasarawa can stop MDA statewide—the first states in Nigeria to achieve this milestone. PTS, coordinated with the onchocerciasis program, is needed to determine if these areas have completely interrupted LF transmission.

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