Am. J. Trop. Med. Hyg., 67(3), 2002, pp. 266–272

LYMPHATIC FILARIASIS ELIMINATION AND SCHISTOSOMIASIS CONTROL IN COMBINATION WITH ONCHOCERCIASIS CONTROL IN NIGERIA

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Abstract. This paper describes a pilot initiative to incorporate lymphatic filariasis (LF) elimination and urinary schistosomiasis (SH) control into a mature onchocerciasis control program based on community-directed ivermectin treatment in central Nigeria. In the same districts having onchocerciasis we found LF (as determined by blood antigen testing in adult males) in 90% of 149 villages with a mean prevalence of 22.4% (range 0–67%). Similarly, SH, as determined by dipstick reagent testing for blood in urine from school children, was found in 91% of 176 villages with a mean prevalence in school age children of 24.4% (range 0–87%). Health education and treatment interventions for SH resulted in 52,480 cumulative praziquantel treatments, and 159,555 combined onchocerciasis and LF treatments (with ivermectin and albendazole) as of the end of 2000. Treatments for onchocerciasis and LF were separated by at least 1 week from treatments for SH. There was no negative impact on the coverage of the onchocerciasis program by the addition of LF and SH activities.

INTRODUCTION

The control or elimination of three major helminthic infections of humans has been the subject of renewed interest and investment in the last decade. Onchocerciasis, an important cause of visual impairment in developing countries, is caused by *Onchocerca volvulus*, a parasitic filarial worm transmitted by *Simulium* species. Adult worms are often found in palpable subcutaneous nodules, and the microfilaria they release cause inflammation in the eyes as well as intense itching and disfiguring dermatitis.[1] Annual treatment with ivermectin (Mectizan®, donated by Merck & Co., Whitehouse Station, New Jersey) kills the microfilaria and prevents the severe manifestations of human onchocerciasis. Lymphatic filariasis (LF) in Africa is caused by *Wuchereria bancrofti*, another filarial worm that is transmitted (in Africa) in rural and urban areas by *Anopheline* and *Culex species (sp)* mosquitoes, respectively. The adult worms live in the lymphatic vessels and cause dysfunction often leading to poor lymphatic drainage. Clinical consequences include swelling of limbs and genital organs (lymphedema hydrocele and elephantiasis), and painful recurrent attacks of acute adenolymphangitis.[2] Microfilaria, which circulate nocturnally in blood, can be almost completely suppressed by annual single dose combination therapy, with either Mectizan (also donated by Merck & Co. for LF in Africa) and albendazole (donated by GlaxoSmithKline, Philadelphia, Pennsylvania), or DEC and albendazole.[3–5]Annual mass treatment with the combination of Mectizan and albendazole prevents mosquitoes from being infected and, when given for 4–6 years can interrupt transmission of *W. bancrofti* (which has no animal reservoir). Schistosomiasis is acquired from contact with fresh water. Cercariae, released from infected snails, penetrate the skin and develop into adult worms that reside in venules of the intestines (*Schistosoma mansoni*) or bladder (*Schistosoma hematobium*). Female worms lay thousands of eggs that exit the body in feces or urine to hatch in fresh water and infect snails, continuing the life cycle. The presence and passage of these eggs in tissues leads to inflammation and organ damage.[6] School-aged children (5–14 years old) are the most heavily infected and also tend to be the main disseminators of this infection through their urination and defecation in or near fresh water. Mass drug distribution of praziquantel (40 mg/kg) every 1–3 years can significantly reduce schistosomiasis morbidity.[7] Praziquantel, which is not being donated by pharmaceutical companies to control programs in large amounts as are Mectizan and albendazole, costs at best about US $0.08 per 600 mg tablet.

Nigerians suffer a disproportionate share of the disease burden from these three parasitic diseases. Nigeria ranks second (after Democratic Republic of Congo) for estimated numbers of persons infected with *O. volvulus* (an estimated 3.3 million),[8] but a highly successful effort led by the Federal Ministry of Health (FMOH), with assistance from the African Program for Onchocerciasis Control (APOC), nongovernment organizations (NGOs) and other partners,[9] has grown to provide over 15 million Mectizan treatments per year to the estimated 20 million Nigerians at risk.[10] For lymphatic filariasis (LF), Nigeria is thought to have the greatest numbers of persons at risk for infection in Africa and globally is ranked third behind India and Indonesia in human suffering from this parasite. One recent review estimated that 22% of Nigerians (over 25 million) are infected with LF.[11] The geographic distribution of the disease appears to show a gradient increasing from north to south in the country, coincident with increasing tropical climate.[12–15] For schistosomiasis, an estimated 20 million Nigerians need to be treated every 1–3 years with praziquantel.[16] The distribution of urinary schistosomiasis (*Schistosomiasis haematobium*[SH]) in Nigeria was explored in a FMOH survey, conducted in 1990–91,[17] that showed that infection was most prevalent in the north-central and southeast areas of the country. The main goal of the 1997–2001 Nigeria National Plan of Action on schistosomiasis control is to reduce the prevalence of the disease by 50% within 5 years, but few treatments had been given because of the expense of praziquantel.

This paper reports on a collaborative effort by the Ministries of Health of Plateau and Nasarawa States, the FMOH and The Carter Center to incorporate health education and treatment for LF elimination and SH control into ongoing onchocerciasis activities. A pilot project was established within an ongoing onchocerciasis program in central Nigeria to 1) ascertain if mass treatment programs for LF and SH were necessary, and, if so 2) implement health education and

treatment interventions with Mectizan, albendazole, and praziquantel for all three diseases, without adversely affecting operations of the onchocerciasis program. Plateau and Nasarawa States were chosen as the site of the project because of their longstanding Mectizan programs for onchocerciasis[18,19] that have provided over 4.7 million cumulative Mectizan treatments since 1992. In 1999, with the assistance of The Carter Center and the African Programme for Onchocerciasis Control (APOC), this onchocerciasis program trained more than 1,500 distributors, and treated 437,157 persons in 709 villages in Nasarawa State and 234,963 persons in 573 villages of Plateau State. Plateau and Nasarawa States also were considered because data from the state health services led us to believe that LF and SH occurred in the same villages where onchocerciasis activities were being implemented.

METHODS

Area of the Study. Plateau State (capital city, Jos) and Nasarawa State (capital city, Lafia) are located in central Nigeria. Plateau State was divided into Plateau and Nasarawa States in October 1997. The region has a mean elevation of 1,200 meters and so is cooler than surrounding states. Most of the estimated 3.6 million inhabitants are Hausa speaking and live in rural areas in agricultural villages. The Ministry of Health provides medical services through rural hospitals and clinics in central locations in each of the 30 administrative districts (called local government areas [LGAs]). Twelve of these LGAs are currently receiving mass ivermectin therapy for onchocerciasis based on a broad assessment survey carried out in 1992 with the aid of The River Blindness Foundation, and further assessment studies in 1997–8 in national Rapid Epidemiological Mapping of Onchocerciasis (REMO) exercises carried out under the auspices of APOC.[20] The project to integrate LF and SH activities was launched in two pilot LGAs, Akwanga LGA in Nasarawa and Pankshin LGA in Plateau (Figure 1); both are onchocerciasis endemic and have been served by the Mectizan distribution program since 1992.

Disease distribution. In 1992 the Plateau State Program established onchocerciasis village prevalence based on sample surveys conducted throughout most rural villages in the state. Mobile teams visited villages and requested 30 male volunteers for palpation examinations to detect onchocercal nodules. Data for villages with hyperendemic onchocerciasis (nodule prevalence $\geq$ 40%) from these early surveys, and their village Global Positioning System (GPS) coordinate data (obtained in 1992 with a four channel Sony IPS-360, Sony Inc.; New York, NY) were available for Pankshin and Akwanga LGAs. They were displayed in a Geographic Information System (GIS) (Atlas GIS, Strategic Mapping, Inc.; San Jose, Calif. U.S.A.) and overlaid with LGA boundaries digitized from available paper maps obtained from the Plateau and Nasarawa State Ministries of Health, using a small digitizing table (SummaSketch®, Summagraphics Inc.; Semour, Conn.).

In 1999, rapid village SH and LF assessments were conducted by mobile teams throughout the two LGAs, using a similar 30 subject per village sample technique employed in

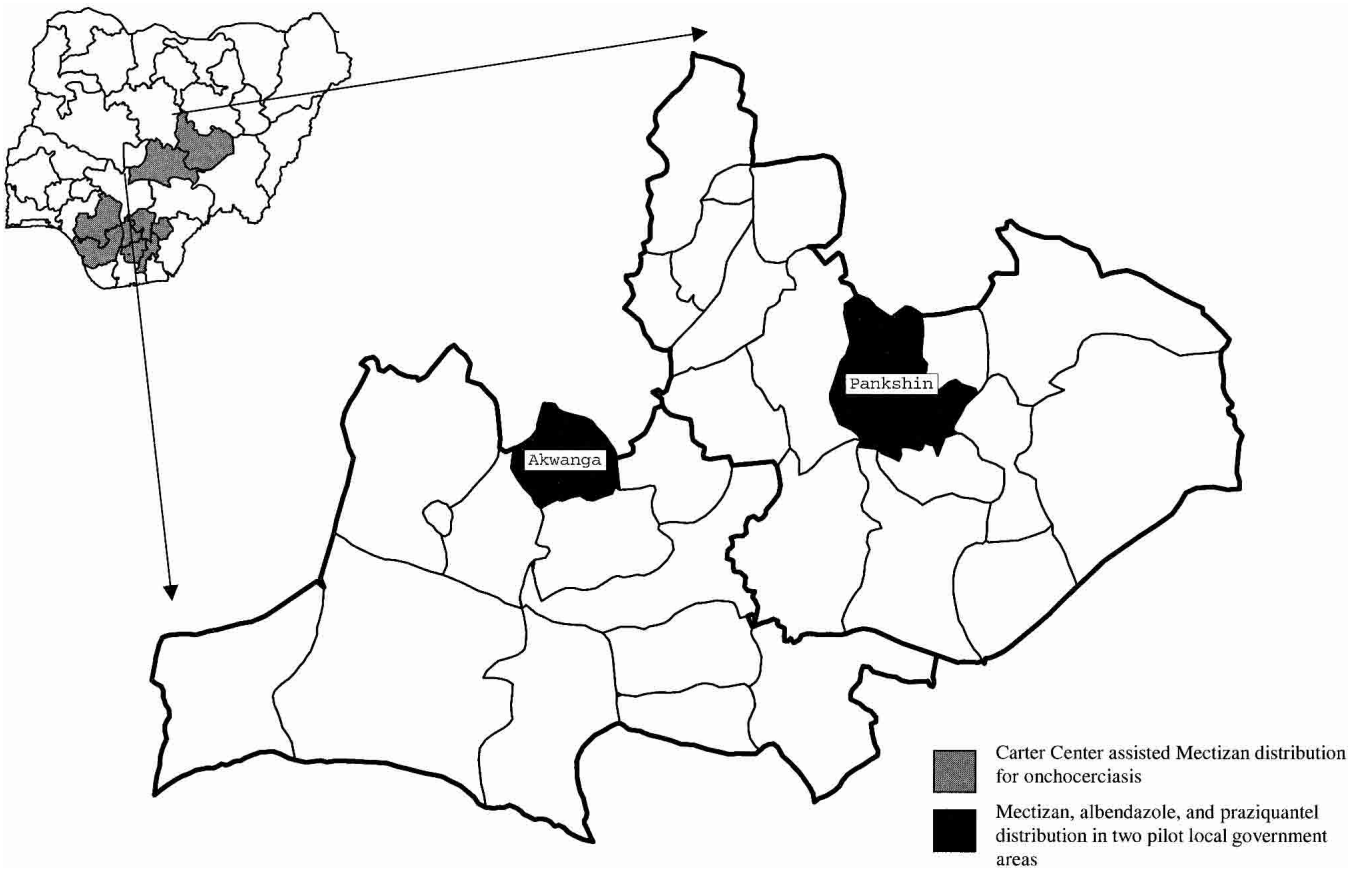

FIGURE 1. Nigeria: Carter Center River Blindness Assisted States, and Location of the Lymphatic Filariasis and Urinary Schistosomiasis Project

the 1992 onchocerciasis survey. LF rapid assessments were performed using a rapid diagnostic test (immunochromatographic card test [ICT]: Binax; North South Wales, Australia)[21] for filarial antigen on finger-puncture capillary blood drawn from samples of 30 randomly selected adult males from each of 149 villages in the two pilot LGAs. SH prevalence was determined by using heme reagent dipsticks (Bayer; Leverkusen, Germany) to test urine from randomly selected samples of 30 children (aged 5–14 years) drawn from school visits in each of 176 villages. The rapid assessment procedure was approved by the Emory University Institutional Review Board and the Plateau and Nasarawa State Ministries of Health. Coordinates of surveyed villages were recorded using hand held Global Positioning System (GPS) units (GPS 12CX, Garmin Inc.; Olathe, Kansas, U.S.A.). SH and LF survey results for the pilot LGAs were superimposed on the 1992 hyperendemic onchocerciasis community survey results in the GIS.

Targeting villages for treatment. All rural communities in the two LGAs were already receiving annual treatment with Mectizan for onchocerciasis (150 ug/kg dose estimated by height). All communities having one or more males in the assessment sample with a positive antigen test for LF by ICT were now offered a single oral dose of albendazole (400 mg/dose) together with the Mectizan (i.e., these communities were simultaneously treated for onchocerciasis and lymphatic filariasis). Single dose praziquantel treatment at 40 mg/kg (dose determined by weight using scales) was provided to all school-aged children in communities where dipstick samples showed hematuria prevalence of $\geq$ 20%, and to eligible adults (not pregnant by history; not chronically ill) as well when the prevalence in children was $\geq$ 50%.[6] For communities with prevalence under 20%, only those children positive in the sampling process were treated. Praziquantel was given at least 1 week before or after the combined Mectizan and albendazole treatment, because the safety of simultaneous treatment with all three drugs has not yet been established. A 1-week interval was chosen arbitrarily because that interval would clearly provide sufficient time for drugs to be cleared (and so avoid any drug-drug interactions). Most tablets were delivered by community-directed distributors (CDDs) selected and trained under the community-directed treatment guidelines developed by APOC and the World Health Organization's (WHO's) Tropical Disease Research (TDR) Programme.[22]

Health education in preparation for LF and SH treatment programs. Before community interventions for LF and SH were launched, we conducted a Knowledge-Attitudes-Practices (KAP) survey in six villages (three villages per pilot LGA) as a foundation for preparing health education materials. Information was gathered using semistructured interviews, focus group discussions, and other standard techniques. Based on the KAP results, we prepared health education materials for SH and LF. Health education materials (posters, pamphlets, flip charts, and calendars) were introduced during group community mobilization sessions carried out for CDDs and community members by teams composed of ministry of health workers and Carter Center personnel. Feedback from villagers and health workers on these materials was reviewed after the initial launching periods, and materials were revised before large quantities were printed for use in the LGA wide efforts.

Impact of treatment. The impact of praziquantel treatment on hematuria was measured in two villages in Pankshin LGA that had been offered full community treatment due to baseline hematuria prevalence assessments (Mungkohot village with a prevalence of 83.3% and Timjim village, 50%). Prior to the third round of treatment in 2001, all school children in the villages were asked to provide a urine sample for testing. Differences in pre- and posttreatment observations were tested using Chi square. Entomologic assessment (based on dissection of *Anopheline* mosquitoes captured in sentinel areas) of the impact of combined treatment on LF transmission is being carried out in the two pilot LGAs and will be the subject of another report. There have been no impact assessments in the long-standing onchocerciasis program.

RESULTS

Disease overlap: results of rapid assessment activities. The 1992 survey for onchocerciasis identified 56 hyperendemic villages (mean nodule rate 49.3% among 2,040 persons examined) in Pankshin and Akwanga LGAs. In 1999, LF assessment activities were carried out in 149 villages; 22.4% of 4,451 male villagers tested positive for LF antigenemia by the ICT rapid card test. Only 10.1% of villages examined were negative for LF in ICT testing of samples of 30 males. For SH, assessment of 176 villages in the two LGAs showed a mean dipstick hematuria prevalence among 5,214 school-aged children of 20.6% (range 0–87%), and 91.4% of villages had at least one child with hematuria in the sample of thirty. Fifty-four percent of villages tested had prevalences $\geq$ 20% and required mass treatment of school children, including twenty-two villages (12.5%) with $\geq$ 50% hematuria prevalence in school children that required community-wide mass treatment.

Of a total of 271 villages in Pankshin and Akwanga LGAs, assessment data were obtained for at least one of the three diseases in 246 (91%). 1999 LF surveys carried out in 35 communities that were hyperendemic for onchocerciasis in 1992 showed that 91% (32) were coendemic for LF. For the 39 communities with data available for both hyperendemic onchocerciasis and SH, 49% (19) required praziquantel mass treatment for SH (with prevalence $\geq$ 20%). Mapping of villages' endemicity was possible for the 201 villages having latitude and longitude coordinates measured with GPS. The results showed that even when communities were not sufficiently endemic for all three conditions to require mass treatment with all three agents, villagers were at risk of acquiring all three diseases if they traveled relatively small distances of a few miles from their community (Figure 2).

KAP studies. We found that community members generally were aware of the manifestations of lymphatic filariasis (hydrocele and leg swelling) and urinary schistosomiasis (blood in urine). There were many misconceptions as to the causes, however, and none knew that these manifestations were due to parasites transmitted by mosquitoes or associated with water and snails. Some attributed hydrocele to adultery, for example. Affected persons themselves sought both traditional and modern medical remedies, and communities were anxious to see the popular onchocerciasis program expanded to address LF and SH.

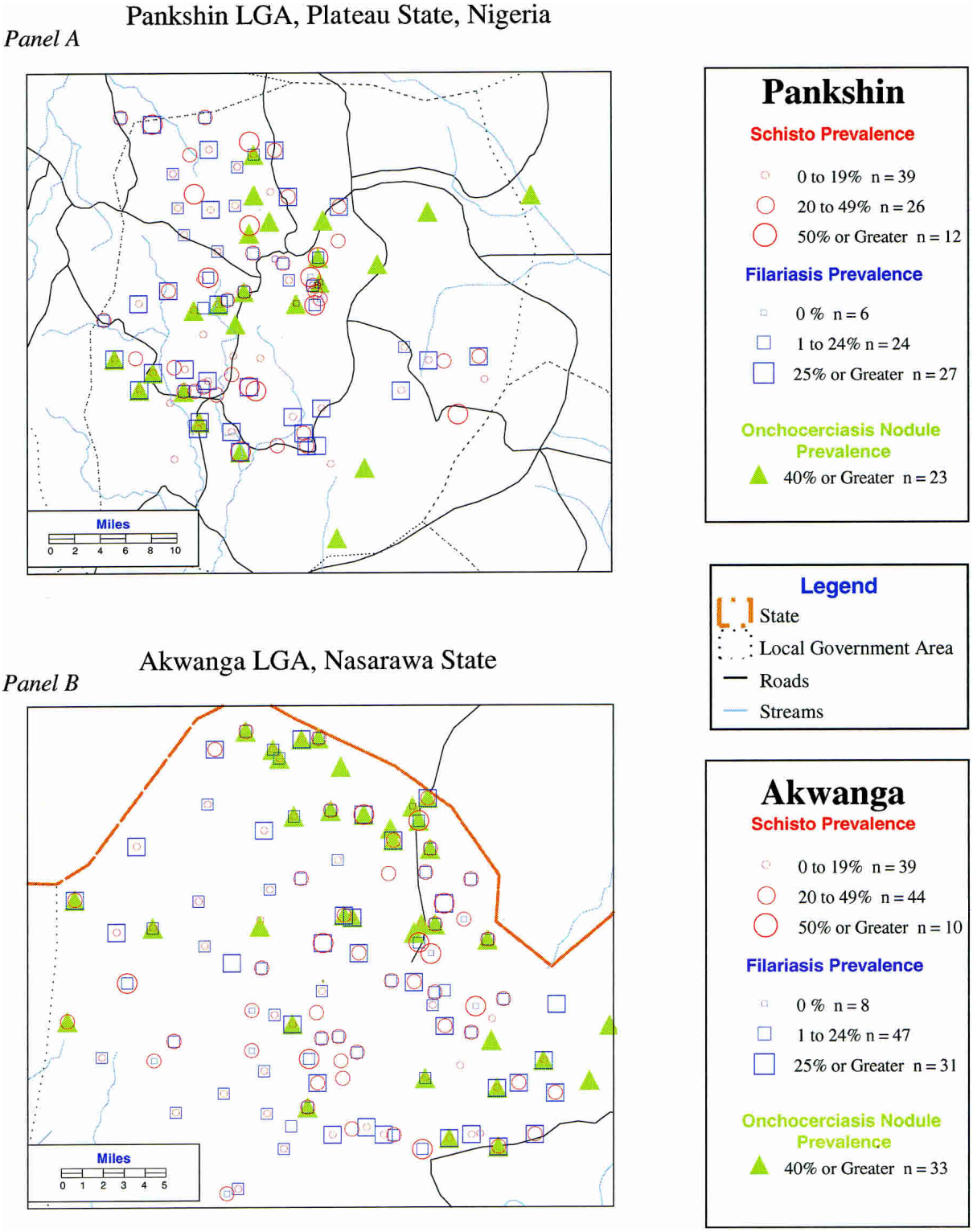

FIGURE 2. Panel A: Plots of 88 villages in Pankshin local government areas (LGA), Plateau State, for which latitude and longitude data were available, showing prevalence of urinary schistosomiasis (77 villages—red circles), lymphatic filariasis (57 villages—blue squares), and hyperendemic onchocerciasis (23 villages—green triangles). Considerable overlap of all three diseases is noted (note distance scale of 10 miles). For schistosomiasis, 49.4% of villages had prevalence (by positive urinary dipstick) of 20% or greater, and 15.6% had prevalence of 50% or higher. For lymphatic filariasis, 89.5% of villages showed evidence of infection by immunochromatographic card test (ICT) test method, with 47.4% of villages showing prevalence of 25% or greater. Panel B: Plots of 108 villages in Akwanga LGA, Nasarawa State, for which latitude and longitude data were available, showing prevalence of urinary schistosomiasis (93 villages—red circles), lymphatic filariasis (83 villages—blue squares), and hyperendemic onchocerciasis (34 villages—green triangles). Again, considerable overlap of all three diseases is noted (note distance scale of 5 miles). For schistosomiasis, 60.2% of villages had prevalence by positive urinary dipstick of 20% or greater, and 12.9% had prevalence >50% or higher. For lymphatic filariasis, 95.2% of villages shown had evidence of infection by ICT test method, with 36.1% of villages showing prevalence of 25% or greater.

Implementation of Interventions. By the end of 2000, 53,480 persons had been treated with praziquantel, in 105 villages of the two LGAs, including 8,650 persons treated in 1999 (Figure 3). This represented 84.8% of the combined annual treatment objective for the two years. Health education and combined Mectizan/albendazole treatment for lymphatic filariasis began in March 2000. A total of 159,555 persons (over 90% of the eligible population of the two LGAs) were treated for LF (and onchocerciasis) by the end of December 2000, representing 99.7% of the annual treatment objective (160,000 for those two diseases). No serious adverse reactions occurred. As was suspected from the KAP studies, communities, traditional leadership, and state and local ministry of health officials remain extremely positive about the expanded program. The integration of new treatment activities did not reduce the numbers of persons treated in the two LGAs by the onchocerciasis program (Figure 3). In 2001, the LF program was extended into an additional ten (onchocerciasis coendemic) LGAs and provided an additional 675,395 combined Mectizan and albendazole treatments in 914 villages; the SH effort in 2001 expanded into two new LGAs, providing a total of 84,313 additional praziquantel treatments in 124 villages.

Impact of two rounds of praziquantel treatment on hematuria. For the village of Mungkohot (where pretreatment hematuria prevalence in school children was 83.3%), 226 children were examined with urine dipsticks prior to the third round of praziquantel treatment offered in 2001 (Figure 4); seven children were urine heme test positive (3%), a reduction of 96% (Chi-square 155, $P < .0001$). Similarly, for the village of Timjim (baseline 50% hematuria prevalence in 1999), 12 of 240 school children (5%) were positive, a reduction of 90% (Chi-square 60, $P < .0001$).

DISCUSSION

Our results confirm the feasibility and logic of using mass anthelmintic chemotherapy and health education for a combined assault on three important parasitic diseases in Nigeria. The Onchocerciasis Control Program (OCP) and the African Program for Onchocerciasis Control (APOC) are mature programs in Africa that represent a major public-private initiative to help ministries of health provide millions of tablets of donated Mectizan for onchocerciasis. The new initiative to eliminate lymphatic filariasis could expand rapidly in Africa by exploiting the existing APOC and OCP infrastructures. Similar logic applies to praziquantel treatment and health education for control of schistosomiasis in Africa. Integration of LF and SH initiatives within the established onchocerciasis programs could in turn strengthen the latter's sustainability by capitalizing on cost savings and broadening the program benefits and popularity. Importantly, our results show no suggestion of a detrimental impact of integration on Mectizan coverage for onchocerciasis, compared with previous years' treatments with Mectizan alone, despite the need for an additional round of treatment for schistosomiasis. In fact, the enthusiasm expressed for the expansion of the popular Plateau/Nasarawa State programs during KAP surveys and launching ceremonies suggests that integration with LF and SH could increase Mectizan consumption for onchocerciasis, rather than decrease it.

The rapid assessment approach for LF used here is not one that is currently recommended by WHO, according to which ICT testing should be carried out in 100 individuals (males and females) in at most one village per LGA. Any positive result would lead to a decision to treat all villages in the LGA with combined Mectizan and albendazole. Assessments completed in 2000 throughout Plateau and Nasarawa (data not shown) based on these new WHO guidelines indicated that combined treatment with Mectizan and albendazole will be needed in all 30 LGAs of the two states. To interrupt LF transmission in these two states, we project that the program will need to treat 3.6 million persons per year. This is five to six times the number served under the current Mectizan distribution program for onchocerciasis in the two states. Current interventions for LF in 12 onchocerciasis endemic LGAs will be extended to include the 18 nononchocerciasis endemic LGAs of the two states in 2002–3.

Schistosomiasis control could benefit from the momentum surrounding onchocerciasis control and LF elimination in Africa, but expansion of the SH program beyond this pilot study will be challenging for a number of reasons. First, the tedious and expensive process of village by village urine dipstick assessments of school-aged children makes the village stratifi-

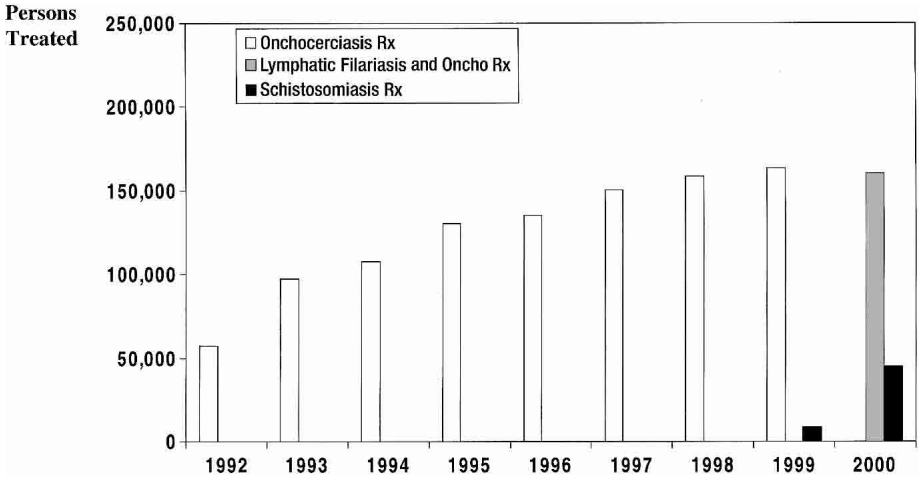

FIGURE 3. Onchocerciasis, Schistosomiasis, and Lymphatic Filariasis Treatments in Pankshin LGA (Plateau State) and Akwanga LGA (Nasarawa State), Nigeria, 1992–2000

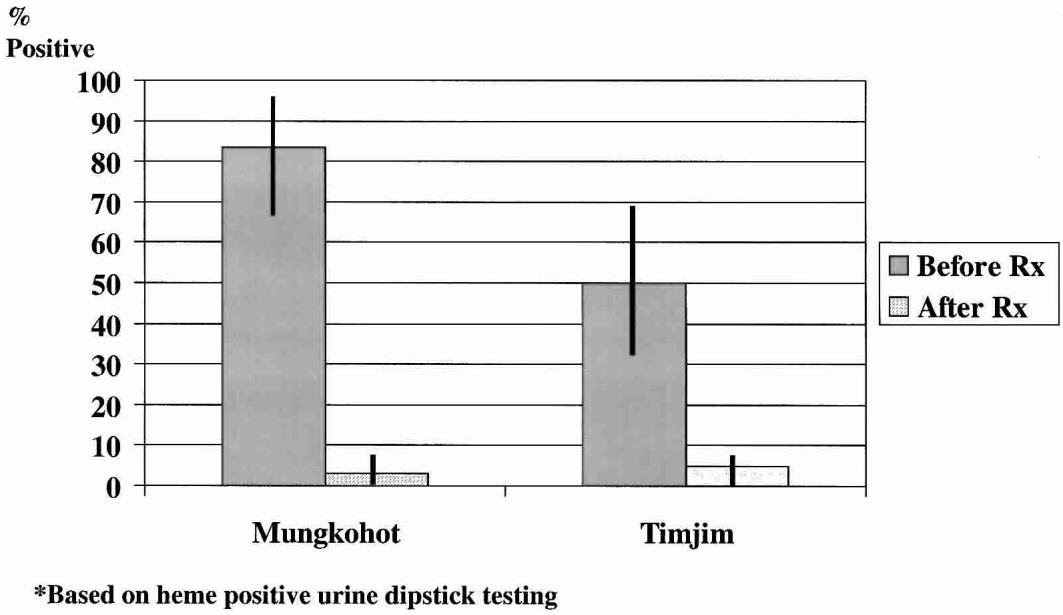

FIGURE 4. Impact on Schistosomiasis haematobium prevalence in school aged children: Hematuria* (blood in urine) before (1999) and after two annual rounds of praziquantel treatment in two villages in Nigeria. (Bars show 95% Confidence Intervals)

cation process comparatively difficult. Second, to promote smoother integration of SH into the integrated program, praziquantel dosage should be calculated by height (as is done with Mectizan), rather than weight.[23] This is also important as scales are not generally available, or malfunction quickly under harsh conditions. Third, studies are needed to document the safety of simultaneous combination therapy with praziquantel, Mectizan, and albendazole so that a separate annual praziquantel round of village treatment activity can be avoided. Lastly, praziquantel is not yet being widely donated, as are Mectizan and albendazole, and drug costs are considerable (an average 2.6 tablets per treatment, costing about US$0.21). If we extrapolate our experience in these two LGAs to all 30 LGAs of the two states' populations, one million persons would require treatment at a cost of US$210,000 per year for praziquantel alone.

In addition to the impact on onchocerciasis, lymphatic filariasis, and urinary schistosomiasis, the three drugs distributed by this pilot project cure or reduce the infection intensity of 11 other helminthic diseases of humans. The ancillary impact associated with reduction of intestinal parasites in school-aged children, in particular, has likely been a major health benefit. Ongoing operational research is critical to effectively measure the impact of this effort, and to adapt and refine the delivery interventions. Combined with the health education and community empowerment stemming from expanding community directed treatment, the integrated concept demonstrated here represents an important opportunity that should be seized by governments and donors alike, as it may ultimately be as important to the public health of Africa as childhood immunization.[24]

Acknowledgments: We would like to thank the following individuals for their help: J. C. Anisoke, B. Bagnall, R. Barwick, D. Bauer, D. Blaney, D. Colley, I. Dhillon, M. Iwamoto, J. Jiya, C. MacKenzie, L. Rakers, J. Roberts, S. Sullivan, C. Withers, and P. Wuichet.

Financial support: LF and schistosomiasis activities in this project were carried out with support from GlaxoSmithKline. The Carter Center works in close partnership with Lions Club's SightFirst Program in its onchocerciasis activities, with additional support for the onchocerciasis activities was provided by the African Program for Onchocerciasis Control. Mectizan® was donated by Merck & Co, and albendazole by GlaxoSmithKline. 150,000 tablets of praziquantel used in the projected were donated to The Carter Center by Bayer (Germany), Medochemie (Cyprus), and Shin Poong (South Korea) (50,000 tablets each).

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