Am. J. Trop. Med. Hyg., 70(5), 2004, pp. 556–561

A LONGITUDINAL STUDY OF IMPACT OF REPEATED MASS IVERMECTIN TREATMENT ON CLINICAL MANIFESTATIONS OF ONCHOCERCIASIS IN IMO STATE, NIGERIA

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Abstract. We conducted a cohort study on impact of effects of eight years of annual ivermectin mass treatment administered in eight villages in Imo State, Nigeria. Physical and visual acuity examinations carried out in 462 persons in 1995, prior to the launching of mass drug administration with ivermectin, were compared with re-examinations of 411 (89%) of these same individuals in 2002. We found that gross visual impairment decreased from 16% to 1%, nodule prevalence decreased from 59% to 18%, and papular dermatitis was reduced from 15% to 2%. No change was seen in leopard skin rates (14%). The only incident lesions were three subjects from a single community having the appearance of new nodules (e.g., nodules not identified in the 1995 examinations). Differences in community coverage did not appear to influence the benefit from treatment of individual residents.

INTRODUCTION

Onchocerciasis, a vector-borne filarial disease that produces intense pruritus, skin lesions (including subcutaneous nodules, papular dermatitis, and a disfiguring depigmentation often known as leopard skin), and ocular damage, is ranked among the leading causes of visual impairment and blindness in Nigeria.[1–8] In clinical and controlled trials, periodic treatment with oral ivermectin, an microfilaricidal medication, has been shown to prevent or improve the severe manifestations of human onchocerciasis by reducing the numbers of *Onchocerca volvulus* microfilaria (mf) in the eyes and skin of the human hosts.[7–10] The generous donation of ivermectin (Mectizan® by Merck & Co., Rahway, NJ) provides an opportunity for preventing onchocerciasis-related morbidity on a vast scale in Nigeria, and more than 18.3 million treatments were provided in 2002 by the Ministry of Health (Jiya J, Federal Ministry of Health, unpublished data) through mass drug administration (MDA) programs, in partnership with the residents of the endemic communities, nongovernmental organizations, and the African Program for Onchocerciasis Control (APOC).[11,12] Monitoring the impact of this important initiative on disease manifestations is of obvious importance if these programs are to be sustained. The principal objective of this cohort study was to determine if there had been a reduction in prevalence of four onchocerciasis morbidity indicators among residents of eight communities in Imo State, Nigeria where ivermectin had been offered annually since 1995.

MATERIALS AND METHODS

Study area. Imo State in southeastern Nigeria is at approximately 5°29′N, 7°01′E. The economy is primarily rural agricultural production of palm oil, plantain, yams, cassava, palm kannel, and rice. The Ibo ethnic group predominates. Onchocerciasis, lymphatic filariasis, mansonellosis, and loaiasis are known to occur in southeastern Nigeria.[13–15] Ivermectin MDA programs for onchocerciasis were deemed necessary in Imo State based on results from national onchocerciasis assessment surveys (Rapid Epidemiologic Mapping of Onchocerciasis) that showed mesoendemic/hyperendemic prevalence of the forest strain of onchocerciasis (estimated nodule rates >20% in adults) throughout much of the southeastern Nigeria.[3,16] Ivermectin distribution began in Imo State in September 1995 as a combined effort of the State Ministry of Health, the Lions Clubs, and the River Blindness Foundation. In 1996, The Carter Center's Global 2000 Program assumed the River Blindness Foundation partner role. In 1998, Imo State began receiving APOC support.

Participant examinations. The Ministry of Health of Imo State reviewed and approved the study and human subject activities, and three of the authors (ECE, EO, and JO) were involved in both the 1995 and 2002 surveys. Prior to the launching of the MDA campaign in 1995, baseline data from random sample of 50–100 adults who were residents for at least five years were collected from each of eight sentinel villages with mesoendemic/hyperendemic onchocerciasis (1995 population: Ndiawa = 1,563, Uhiowerre = 1,111, Umungwa = 1,257, Umuoriaku = 884, Ubakuru = 396, Ikpem = 588, Amano = 520, and Umuawuchi = 522). After verbal individual consent was obtained, participants were examined for mf in the skin (1995 only), subcutaneous nodules, papular dermatitis, and leopard skin, and had their visual acuity tested. The examinations were conducted as follows.

Microfilariae in skin. The skin was cleansed over the left and right iliac crests with alcohol, and superficial skin biopsies (skin snips) weighing 1–2 mg were taken with a corneoscleral punch (Walser type with a 2.0-mm bite). Between sampling of each patient, the instruments were washed sequentially with chlorhexidine, bleach, distilled water, and alcohol, and then air-dried. The skin specimens were transferred to a microtiter plate containing normal saline, incubated for 24 hours at room temperature, removed, and the fluid in each original well was fixed by adding two drops of 40% formosaline. The wells were later examined for mf with an inverted microscope at 40×. The results were expressed as positive (mf present) or negative (mf absent); mf prevalence was expressed as number of persons positive divided by the total number of persons examined. Due to concerns about human immunodeficiency virus and other blood-borne infections, skin snips were not repeated in 2002.

Palpation for the presence of nodules. Participants were examined in a private area for characteristic subcutaneous onchocercal nodules by partially disrobing and then undergoing palpation around the lower ribs and back, waist, iliac crest, sacrum, hips, and legs.[17] The locations of the nodules were noted on a human anatomic diagram on the individual's patient record form.

Physical examination of skin for papular rashes and leopard skin. At the same time as the examination for nodules, papular dermatitis and leopard skin were sought around the lower ribs, back, waist, iliac crest, sacrum, and hips, as well as on the head, legs, and arms. We did not attempt to distinguish between acute and chronic papular dermatitis.[6,10] Notations of locations of papular dermatitis and leopard skin, when found, were made on the anatomic diagram in the individual patient record.

Visual acuity screening. The participant stood at a measured distance of six meters from the examiner (ECM, EO, or JO) and was asked to tell how many fingers were being shown to them by the examiner (alternating between one, two, or three fingers).[18] The patient was allowed to use both eyes. Visual impairment was defined as three failures to properly identify the correct number of fingers shown by the examiner.

Re-evaluation of the cohort in 2002. Data forms containing personal identifiers (name and village of residence) and results of the 1995 evaluations, which were kept in locked drawers at the Imo/Abia Project office in the Owerri City, were retrieved. The project team then went to the eight villages on several occasions over a three-month period (February–April 2002) and sought all those who had been examined in 1995. Those who were found had the study explained to them and were asked to give their verbal permission for re-examination. Those who agreed were re-evaluated in the manner described earlier (with the exception of skin snipping). The repeat physical examinations of the cohort were guided by the old data forms collected in the first surveys, and in particular by the original 1995 location notations of nodules, papular dermatitis, and leopard skin on anatomic drawings in the patient's file. Visual acuity was examined using the same three-finger counting at six meters technique by the same examiners who had examined them in 1995. New (incident) findings were defined as any nodule, rash, leopard skin, or visual acuity loss that had not been identified in 1995 examinations. Results of the examinations were recorded on forms similar to those used in the 1995 surveys.

Treatment coverage. We determined the total numbers of persons treated in each village each year during the period 1995–2002 by reviewing the village treatment registries and annual summary treatment statistics kept by the local and state ministry of health offices. Treatment coverage was defined as number of persons treated divided by the total population denominator determined each year during the treatment exercise. When these denominator data were missing, the previous year's denominator was used. Interval treatment coverage was defined as the sum of all treatments provided over the eight years divided by the sum of the population denominators. In addition, a short questionnaire was administered to cohort participants that asked about their regularity of taking annual ivermectin treatment and their personal observations on the effect ivermectin had had on their health over the eight-year period. Questions on perceived impact of treatment were open-ended while those on regularity of ivermectin treatments required structured (categorical) responses.

Statistical analysis. The cohort was defined as those persons with dual observations (e.g., who were examined both in 1995 and in 2002). Cohort data were analyzed in Microsoft Excel® (Microsoft, Redmond, WA) by calculating the village cohort and total cohort prevalence of the four morbidity indicators attributable to onchocerciasis (nodule, rash, leopard skin, or visual acuity loss). Percent change was calculated as the number of persons with the condition in 1995 minus the number with the condition in 2002 divided by the number of persons with the condition in 1995. The 1995 and 2002 prevalence figures for each of the morbidity indicators were compared statistically as independent observations using a simple chi-square test (Epi-Info6; Centers for Disease Control and Prevention, Atlanta GA). Extrapolation of results to the overall state-wide impact of ivermectin MDA on visual acuity was performed by applying the cohort rates of visual loss before and after the eight-year period to the estimated number of adults residing in all hyperendemic/mesoendemic onchocerciasis villages in the Imo State. Impact of the MDA program on visual impairment was calculated as the estimated number of persons with visual impairment for 1995 minus the number estimated for 2002.

RESULTS

Original versus cohort baseline data. We found the records of physical and visual examinations for 462 persons who had been examined in the eight sentinel villages in 1995. The mean age was 47 years, and 66% were female. The mean microfilaria prevalence was 61.6% (village range = 27.1–84.5%) (Table 1). The village of Amano had the highest initial mf skin snip prevalence and nodule rate. Four hundred eleven (89%) of the original participants were identified and re-examined in 2002. No one we identified refused to participate in the 2002 cohort phase of the study. The mean cohort age (2002) was 53 years (range = 21–79) and females comprised 69%. Of the 51 persons in the original 462 who could not be found, 5 were reported to be dead and 46 persons to have permanently relocated or were traveling during the three months of the study (February–April 2002). Table 1 shows the 1995 results of the original entire sample of 462 persons compared with the original 1995 results of the 411 in the cohort. The prevalence of nodules, leopard skin, skin rash, and visual impairment was similar in the original survey compared with the cohort.

Cohort impact study. In 1995, 242 (59%) persons in the cohort had nodules (village range = 21–93%), 56 (14%) had leopard skin (range = 10–19%), 62 (15%) had a papular skin rash (range = 0–35%), and 66 (16%, range 0–27%) were classified as visually impaired based on the inability to accurately count fingers at a distance of six meters. Upon re-examination of the cohort in 2002, we observed dramatic decreases in all parameters except leopard skin, which remained unchanged at 14% (Table 2). Nodule prevalence among cohort participants was 18% (a reduction of 69% [village reduction range = 0–86%] from 1995), papular dermatitis was 1.7% (a reduction of 95% [range = 60–100%]), and visual impairment was 1% (a 94% decrease [range = 67–100%]).

TABLE 1

Baseline 1995 prevalence of selected indicators in sentinel villages of Imo State, Nigeria: Original 1995 sample compared with 2002 baseline cohort study data

	1995 Prevalence total sample						1995 Prevalence cohort sample				
Village	Original sample size	Skin snip %	Nodule %	Leopard skin %	Papular rash %	Visual impairment %	2002 sample size	Nodule %	Leopard skin %	Papular rash %	Visual impairment %
Ndiawa	50	80.2	34	12	16	16	48	31	13	17	17
Uhiowerre	50	45.6	56	10	10	10	49	55	10	10	10
Umungwa	50	66.7	38	16	0	0	46	41	17	0	0
Umuoriaku	50	77.3	20	18	18	18	48	21	19	19	19
Ubakuru	50	27.1	42	10	0	0	45	47	11	0	0
Ikpem	67	69.1	90	9	4	19	56	89	11	5	23
Amano	92	84.5	82	11	23	20	71	93	14	28	25
Umuawuchi	53	69.1	64	13	34	25	48	71	15	35	27
Total	462	61.6	57	12	14	14	411	59	14	15	16

The mean decrease in prevalence of nodules, papular dermatitis, and visual impairment (Figure 1) were all highly statistically significant ($\chi^2 > 50$, $P < 0.0001$).

Development of new lesions attributable to onchocerciasis was rare. Only three subjects (all from the village of Amano) developed new nodules. There were three cases of new papular skin rashes among the cohort (one in Ndiawa village and 2 in Umuoriaku). No new diagnoses of impaired vision were made (the four persons who failed the six-meter, three-finger test in 2002 had also failed it in 1995), and no new leopard skin patients or lesions were observed.

Treatment coverage. The interval ivermectin treatment coverage (Table 3) over the eight-year period was 65%, but annual village coverages ranged widely from 24% to 86%. Amano, Ikpem, Uhiuwere, and Umuawuchi had the poorest coverage (<65% for at least half of their eight treatment rounds). The best coverage was in Ubakuru and Umuoriaku (which surpassed 65% coverage in seven of the eight treatment rounds). Figure 2 shows villages in order of interval ivermectin treatment coverage (highest to lowest) and also displays percentage reduction in the four morbidity indicators. There was no suggestion that villages having the highest coverage had a greater impact on morbidity indicators. In individual questionnaires given to the cohort, 87.6% claimed to have taken uninterrupted annual treatment over the entire interval, whereas only 51 subjects (12.4%) had irregular or interrupted treatments, ranging from two to seven years without receiving treatment.

Perceptions of benefit. Although we did not perform a formal knowledge, attitudes, and practices study among the cohort, the participants appeared to have a good understanding of onchocerciasis morbidity and ivermectin action.[19] All cohort participants were positive in their responses to our questionnaire about the ivermectin program and its benefits to their health. All were willing to continue to take the medicine. One subject told us that ivermectin had allowed him to now "read his Bible." Another said, "I could not see far but thanks to ivermectin I need no help again" and "Ivermectin has been good for our sight." Skin improvement also was recognized. For example we heard, "After taking ivermectin my troublesome skin disease is gone," and "My whitened skin is now becoming dark again." All those with leopard skin commented that their skin had improved (darkened) over the time interval.

Projection of cohort finding to statewide impact. Imo State reported 4,607,425 ivermectin treatment encounters since 1996, and in 2002, 574,462 treatments were provided in MDA programs operating in 1,940 villages with mesoendemic/hyperendemic onchocerciasis. The estimated total population of the 1,940 mass treatment villages was 914,754 persons (based on community distributor registration tallies). The adult Nigerian population (age range = 18–79 years) was estimated to be 48% of this population (439,082) based on the last Nigerian census projections.[20] Extrapolating the visual impairment results of the cohort study to this figure, we estimated that 70,253 persons had visual impairment in Imo State in 1995 ($0.16 \times 439{,}082$) compared with 4,391 persons ($0.01 \times 439{,}082$) in 2002. This crude analysis suggested that 65,862 persons benefited from better visual acuity as a result of the ivermectin distribution program.

TABLE 2

Onchocerciasis: Prevalence of selected morbidity indicators in the Imo State, Nigeria cohort, baseline 1995 compared to 2002 re-examinations

		Nodule rate		Leopard skin		Papular rash		Visually impaired	
Village	No.	1995	2002	1995	2002	1995	2002	1995	2002
Ndiawa	48	31%	25%	13%	13%	17%	2%	17%	2%
Uhiowerre	49	55%	6%	10%	10%	10%	4%	10%	0%
Umungwa	46	41%	13%	17%	17%	0%	0%	0%	0%
Umuoriaku	48	21%	21%	19%	19%	19%	8%	19%	6%
Ubakuru	45	47%	16%	11%	11%	0%	0%	0%	0%
Ikpem	56	89%	13%	11%	11%	5%	0%	23%	0%
Amano	71	93%	20%	14%	14%	28%	0%	25%	0%
Umuawuchi	48	71%	31%	15%	15%	35%	0%	27%	0%
Total	411	59%	18%	14%	14%	15%	2%	16%	1%

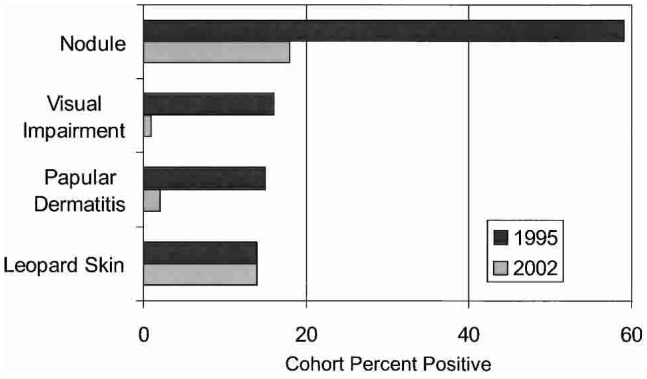

FIGURE 1. Impact of eight years of mass ivermectin treatment for onchocerciasis on the prevalence of nodules, papular dermatitis, leopard skin, and poor visual acuity in a cohort of 411 persons in Imo Sate, Nigeria.

DISCUSSION

After an eight-year period of annual mass drug administration with ivermectin, we found remarkable improvements in the prevalence of three of four morbidity impact indicators for onchocerciasis. There was a 69% reduction in onchocercal nodule rates, a 95% reduction of papular dermatitis, and a 94% reduction in gross visual impairment. The cohort allowed us to uniquely study incident lesions. These were remarkably low and limited to new nodules (0.7% of the cohort) and new papular dermatitis (0.7% of the cohort). There were no new cases of visual impairment or leopard skin. These results suggest that the MDA program both reduced transmission (and so the incidence of new nodules) and mf prevalence and density (resulting in fewer new cases of papular and depigmenting skin lesions, and visual impairment).

There have been several reports documenting improvement of anterior segment eye disease, visual acuity, and skin disease after ivermectin treatment of onchocerciasis.[7–10,21–23] However, our findings of community level impact are most similar to a recent report by Kennedy and others, working in Central African Republic, who demonstrated in two cross-sectional surveys conducted before and after five years of annual ivermectin treatment an 18% decrease in nodules, a 28% reduction in the prevalence of visual impairment (using the Snellen illiterate E chart), and a 46% reduction in functional blindness.[24] Our visual impact results are not directly comparable to this study since we defined visual impairment as the inability to correctly count fingers at a distance of six meters.[25] Counting fingers is a crude measure of visual acuity that can be easily explained, rapidly carried out, and reproducibly performed in illiterate populations.[18,25–27] The recommended criteria of the World Health Organization for functional blindness is the inability to count fingers at a distance of three meters; since our study used twice that distance, we presented our findings as visual impairment rather than functional blindness.[1]

A weakness of our study was that we did not perform ocular examinations to classify or diagnose the clinical cause for the visual impairment. As a result, we made certain assumptions about our visual acuity data. First, we assumed that most of the eye disease was due to onchocerciasis in these hyperendemic and mesoendemic villages, although other common blinding conditions in southeast Nigeria, such as cataract and glaucoma, could have been the cause.[14] Since these would not have been affected by ivermectin treatment, we believed this assumption was justified. Improvement in vision detected in 2002 suggested that the visual loss registered in 1995 was attributable to onchocerciasis and responsive to ivermectin. However, a fault in these assumptions is that it is generally believed that advanced onchocercal eye lesions (such as sclerosing keratitis and ocular nerve atrophy) are static and will not improve with ivermectin treatment. Indeed, we expected visual acuity to behave in a manner similar to leopard skin, another supposedly static lesion that indeed did not regress over time in the cohort. Thus, our visual acuity findings are quite intriguing. Interestingly, in the study of Kennedy and others where ocular examinations were conducted, the researchers found a dramatic improvement in community vision between the surveys without a similarly dramatic regression of onchocercal ocular lesions.[24]

Another intriguing finding was the disappearance of 69% of cohort nodules whose anatomic locations had been precisely documented in 1995. This loss could not be explained by nodulectomy (which is not commonly performed in Nigeria and because there were no scars or history of nodulectomy to suggest surgical removal). Our study provides clinical support of the study of Ukaga and others, who reported the results of a questionnaire survey in southeast Nigeria among 324 adults who previously had onchocercal nodules and found that 21% of those surveyed claimed their nodules were gradually disappearing with repeated doses of ivermectin.[28] If we assume there was involution of two-thirds of the nodules over the eight-year period, we might also question the current estimates for the life span of adult *O. volvulus* worms as being 10–15 years.[1] Rapid nodule involution could suggest that the

TABLE 3
Treatment coverage of selected villages in Imo State, Nigeria, 1995–2002

Village	Treatment percentage coverage/year								
	1995	1996	1997	1998	1999	2000	2001	2002	Total
Ndiawa	66%	64%	59%	40%	60%	80%	80%	68%	65%
Uhiowerre	57%	68%	68%	69%	48%	60%	60%	39%	59%
Umungwa	70%	61%	72%	56%	58%	67%	70%	70%	66%
Umuoriaku	83%	84%	83%	45%	78%	78%	81%	70%	75%
Ubakuru	69%	69%	72%	74%	83%	65%	40%	89%	70%
Ikpem	41%	70%	50%	56%	58%	69%	83%	71%	59%
Amano	58%	27%	60%	56%	60%	68%	79%	68%	60%
Umuawuchi	29%	69%	68%	58%	43%	68%	39%	69%	56%
Total	62%	65%	68%	56%	62%	70%	66%	68%	65%

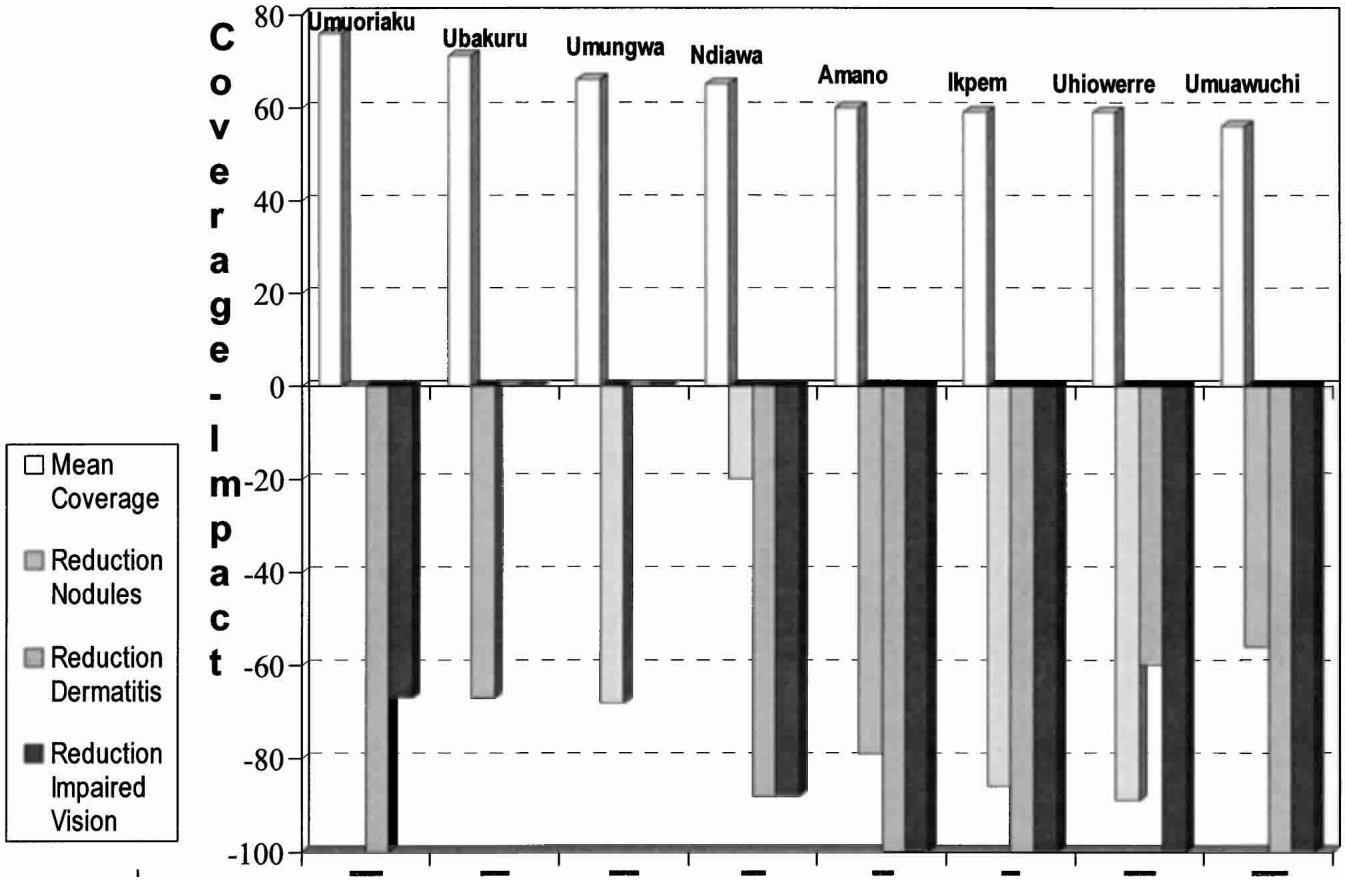

FIGURE 2. Mean total ivermectin population coverage compared with the impact on prevalence of selected morbidity indicators by community.

life span of adult worms is shorter, or that repetitive ivermectin dosing reduces the life span (through accelerated aging and death) of the adult *O. volvulus* worms. This observation could have important implications for the required duration of ivermectin therapy.

We found no new nodules among the cohort in seven of the eight sentinel villages, which suggested that transmission had been reduced or interrupted by the MDA program. Only in the village of Amano, one of the four villages having treatment coverage <65%, were new nodules discovered (a 4.2% interval nodule incidence among cohort participants in that village). Amano also had the highest nodule (82%) and microfiladermia (85%) rates in 1995 at the initiation of the program, suggesting that the force of onchocerciasis transmission was greatest in this village. Low community treatment coverage and high transmission potential in Amano could explain why it was the only village where we observed new nodules in the cohort. We did not observe a relationship between community coverage and community morbidity reduction. This is probably because morbidity (therapeutic) impact is related to individual compliance, rather than community coverage, and questionnaire data from the cohort suggested high cohort compliance with therapy.

Papular dermatitides can be due to causes other than onchocerciasis, including other infectious agents (scabies, pediculosis, larva migrans, dermatophytes), insect (including *Simulium*) bites, and contact allergens. Since ivermectin is also effective against scabies, pediculosis, and larva migrans, the decrease in papular dermatitis noted in this study might have been attributable to a beneficial side effect of mass ivermectin administration.[29] Included among these additional benefits were also the prompt loss of *Ascaris* and *Trichuris* intestinal worms. One mother commented: "My child used to be very sickly but after taking ivermectin and passing out bags of worms he became healthy." In our experience, the numerous ancillary benefits from the MDA program resulted in its popularity in the community. We did not observe a trend of decreased coverage over the eight-year period, so willingness to take ivermectin seemed to have remained steady even through perceived morbidity from onchocerciasis (and the benefit of repetitive ivermectin treatment) was apparently less obvious.[30,31]

Since its launching, the Imo State onchocerciasis program has delivered more than 4.5 million ivermectin treatments to an estimated one million people at risk. Projection of the results from this study to the overall population at risk suggests that more than 65,500 of these persons (6%) have had a substantial improvement in their vision as a result of this program. If we considered the numbers of cases of impaired vision prevented, and the impact of treatment on skin disease and intestinal parasitic infection, the calculation of benefit from the MDA program would be even greater.

Received August 26, 2003. Accepted for publication December 14, 2003.

Acknowledgments: We acknowledge the assistance of Rosalyn Ajigbeda, B. C Anyanwu, Edem Bassey, Brian Duke, George Garlong, Donald Hopkins, Kenneth Ihedioha, Rita Ike, Josephine Obiezu,

Kevin Okonkwo, Stella Okorie, Oluwasesan Onofowokan, Davis Onyewuchi, Lindsay Rakers, Lucky Umesi, and Craig Withers.

Financial support: The Imo State Onchocerciasis Program and the study received support from The Carter Center, Lions Clubs International (SightFirst Program), the River Blindness Foundation, and the African Program for Onchocerciasis Control. Ivermectin (Mectizan®) was donated by Merck & Co.

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