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Impact Assessment of Repeated Mass Ivermectin Treatment on Onchocerciasis in Abia State, Nigeria

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Abstract
The impact assessment of repeated mass ivermectin treatment on onchocerciasis in Abia state, south eastern Nigeria was carried out between June and September 2011, using skin snipping method. Abia state is made up of 17 Local Government Areas, eight of which are endemic for onchocerciasis (2 hyper-endemic and 6 meso-endemic LGAs). The study captured the two LGAs of the state that were rated as hyper-endemic by REMO assessment and had been receiving treatment since 1995. Out of 547 individuals skin snipped, only 3 (0.55%) were infected with microfilariae of *Onchocerca volvulus,* and this occurred in one community Amiyi-Obilohia. The distribution of infection showed that 0.50% of the infected were males while 0.58% were females. The overall age specific prevalence showed that infection only occurred in individuals 60 years and above, who were low compliers and were not treated during the last treatment period. A CMFL of 0.28 mf/mg obtained is an indication that ivermectin is an effective microfilaricide.
Key words: Impact assessment, Repeated, mass, ivermectin, treatment, Onchocerciasis.

1. Introduction

Ivermectin, a microfilaricide, developed by Merck & Co. Inc. and launched commercially in 1981 remains currently the most effective broad-spectrum antiparasitic agent against a wide range of nematode and arthropod parasites of plants, animals and human (Campbell, *et al.*, 1983; Ottesen and Campbell, 1994). Ivermectin has been extensively used in veterinary medicine for treating internal and external parasites (Campbell, 1985) and was later introduced for human Onchocerciasis (WHO, 1987). It is considered one of milestones of tropical disease treatment and a revolutionary breakthrough, as it has an effective microfilaricidal action that could clear effective microfilariae from the skin with minimal side effect (Aziz *et al.*, 1982; Campbell, 1991). The advent of ivermectin has revolutionized the treatment of onchocerciasis, ivermectin being the first effective drug safe enough for mass chemotherapy (Chijioke, 2009). Ivermectin has been shown to be an effective long-lasting microfilaricide which has no serious adverse effect and suitable for mass treatment (Ali, 2006).

One of the most important and striking characteristics of ivermectin is that despite its short half-life, a single dose not only eliminates skin microfilariae but also provides long lasting suppression of microfilariderma (Awadzi *et al.,*1986). Ivermectin kills 99% of microfilariae with a single treatment (APOC/WHO, 2005). Repeated treatments cause mass reduction in the number of multicellular embryonic stages of the worm (Duke *et al.,* 1991). Multiple ivermectin treatments at various intervals result in increased numbers of calcified nodules and of dead or moribund female and male adult worms. There are reduced numbers of male worms per nodule and reduced insemination of female worms (Duke *et al.,* 1992).
A pioneering study by Aziz *et al* (1982), demonstrated the extraordinary potent effect of ivermectin in causing a dramatic reduction in skin snip microfilarial counts within 48 hours of oral doses of 30-ug/kg and 50-ug/kg. Subsequent studies have confirmed and expanded these findings (Awadzi *et al*., 1986; Diallo *et al*., 1986). Ivermectin is more effective at 100 to 200-ug/kg than 50-ug/kg, and cause a massive reduction in skin microfilarial counts which reached a minimum at about 2 weeks after dosing (Chijioke, 2009). Studies in Senegal and Mali showed that after 15 to 17 years of treatment, the prevalence of infection and the intensity of transmission fell below postulated threshold values for elimination (APOC /WHO, 2010).Treatment was stopped and a follow-up data over a period of three years showed no evidence of new infection or transmission. This provided the first evidence that ivermectin treatment can eliminate onchocerciasis infection and transmission.
In Nigeria, ivermectin has drastically reduced the incidence of onchocerciasis. A study conducted in the Imo River Basin revealed that community microfilarial load (CMFL) as well as the community nodule rate were reduced from 57.3 mf/ss and 59% respectively to 18.3 mf/ss and 21% within the first 4 years of ivermectin treatment (Dozie *et al.,* 2004a). Furthermore, reports of nodule dissolution (Ukaga *et al.,* 2001, Emukah *et al.,* 2004), improvement in eye lesions/low vision (Emukah *et al.,* 2004) and onchocercal skin disease (Dozie *et al.,* 2004b), expulsion of intestinal worms (Abanobi *et al.,* 1994) and resumption of menstruation (Anosike and

Abanobi, 1995) are documented. The present study is designed to assess the impact of ivermectin on onchocerciasis in Abia state, Nigeria, where ivermectin has been offered annually for over 14 years.

2. Materials and Methods

2.1. Study Area: Abia state located in south eastern Nigeria, lies between latitude $4^{o}\,45^{1}$ and $6^{o}\,15^{1}$ North and longitude $6^{o}\,30^{1}$ and $8^{o}\,9^{1}$ East. It is bordered on the North and Northeast by Ebonyi and Enugu states respectively and on the east by cross River and Akwa Ibom states. Its southern border is shared with River State while its western border is shared with Imo and Anambra States.

Ivermectin MDA programmes for onchocerciasis were deemed necessary in the state based on the result from the national onchocerciasis assessment surveys (Rapid Epidemiology Mapping of Onchocerciasis) that showed meso-endemic/hyper-endemic prevalence of the forest stain of onchocerciasis (estimated nodule rates >20% in adults) throughout much of the south eastern Nigeria (Emukah et al., 2004). Ivermectin distribution started in the state in 1991 with Mbala-Isuochi chosen as pilot area. By 1994/1995, the control spread to other LGAs of the state (Onuoha, 2004).These LGAs are currently the CDTI sites in the state. Currently, the project has completed fourteen years in 2011 and has 564 communities at risk of the disease (WHO/APOC, 2009).

2.2. Research Ethics: Ethical review and clearance of the research protocol, research instruments and informed consent procedures were obtained from the Ethical Review Committee of the Department of Animal and Environmental Biology, Imo State University, Owerri. Permission was sought from the State Ministry of Health and community leaders. Community meetings were held in all sampled communities to explain the research objectives and procedures, and the right of individuals to decide whether to participate in the examination or not. Before each examination, each individual who voluntarily came to the examination point and agree to participate signed or put a thumb print if not literate, on the examination form to indicate consent. For children, one of the parents or a responsible guardian signed the examination form. All subjects who voluntarily presented themselves at the screening center for the survey were asked for identification data (name, age, sex, occupation and number of years resident).

2.3. Sample Collection Process: The samples were collected from the two hyper-endemic LGAs of Abia State (Umunneochi and Isuikwuato LGAs). The sample population was determined according to Krejcie and Morgan (1970) and samples collected from eight communities selected by a stratified simple random sampling (4 communities from each LGA). After obtaining individuals verbal consent, participants were examined for microfilariae in the skin, subcutaneous nodules and leopard skin, and had their visual acuity tested. The examinations were conducted as follows:

- **Microfilariae in skin**: Parasitological examination was carried out by two techniques namely skin snipping and microscopy (Ukaga and Nwoke, 2007) on 547 individuals. Prior to the skin snipping, the area of the skin (left and right iliac crest) were carefully swabbed with cotton wool soaked in 70% alcohol and allowed to dry. A sterilized needle on a syringe was pushed into the skin where two bloodless skin snips were taken. A sterile scalpel was used for cutting. No two individuals used the same needle or scalpel to prevent transmission of blood viruses. The skin biopsies were placed in microtitre plates containing 3 drops of 40% normal saline and incubated for 24 hours at room temperature. The emerging microfilariae from each anatomical site were observed directly on the microtitre plates using inverted microscope and recorded in the individual clinical and parasitological form. The preservation of any specimen that could not be examined after 24 hours was carried out by the addition of 10% formalin into each microtitre well.
- **Palpation for the Presence of Mobile Nodules:** Participants were examined in a private area for characteristic subcutaneous onchocercal nodules by partially disrobing and then undergoing palpation around the lower ribs, back, waist, iliac crest, sacrum, lips and legs (Albiez *et al.*, 1988). The locations of the nodules were noted on the individual's patient record form.
- **Physical Examination of Skin for Papular Dermatitis and Leopard skin:** While examining for the mobile nodules, popular dermatitis and leopard skin were also sought around the lower ribs, back, waist, iliac crest, sacrum and hips, as well as on the head, legs and arms. Acute and chronic popular dermatitis could not be distinguished (Murdoch *et al.*, 2002). Notations of locations of popular dermatitis and leopard skin when found were made on the anatomic diagram in the individual patient record.

- **Visual Acuity Screening:** The participants stood at a measured distance of six meters from the examiner and were asked to tell how many fingers were shown to them by the examiner alternating between one, two or three fingers (Emukah *et al.,* 2004). The patients were allowed to use both eyes. Visual impairment was considered as three failures to properly identify the correct number of fingers shown by the examiner.

2.4. Statistical Analysis: The data obtained from skin snipping were analyzed using Epi-info version 6 soft ware [CDC, Atlanta]. Percentages were used to determine the different levels of prevalence while the chi-square (X^2) test was used to determine the level of significance of the onchocercal symptoms among the community members.

3.0. Results

A total of 547 individuals were examined for the microfilariae of O*nchocercal volvulus.* Only 3 (0.55%) were infected. All infected individuals came from one community-Amiyi-Obilohia. The infected individuals were low compliers who had not taken the drug for more than three times since the treated started in 1995 and were not treated during the last treatment period (Table 1). The result also revealed that 1(0.50%) of the infected were males while 2(0.58%) were females (Table 1). The overall sex-specific prevalence showed that out of 62 individuals skin snipped from Amiyi-Obilohia (the only community where infection was observed) only 3(4.84%) of the total population sampled were infected. The gender prevalence in that community showed that 1(6.26%) of the infected were males while 2(4.35%) were females (Table 2). The overall aged-specific prevalence of infection in the sampled communities revealed that infection only occurred in individuals 60 years and above (Table 3). A moderate skin microfilarial count of 55 was obtained with community microfilarial load (CMFL) of 0.28mf/mg (Table 4).

Table 5 showed the onchocercal symptoms observed during the period of investigation. Out of 547 individuals examined, 142 (26.0%) showed symptoms: 50 (9.1%) had mobile nodules, 49 (9.0%) had ocular infections, 24 (4.4%) had itching, 18 (3.3%) had leopard skin and 1(0.2%) had lizard skin. The communities most infected with symptoms were Amakpoke with infection rate of 44.3%, followed by Amiyi-Obilohia with infection rate of 41.9%. The least infected community was Obiagu-Uturu with infection rate of 1.1%. Since the calculated X^2_{cal} = 50.56 > the critical value X^2_{tab} = 49.8%, we conclude that at 0.05 level of significance, the identified symptoms among community members are significantly different.

Table 1: Overall Prevalence of infected individuals with *Onchocerciasis* in the sampled Communities.

Community	Number Examined	Number and Percentage infected	Number and percentage uninfected
Umuobiala	63	0	63 (100)
Amiyi Obilohia	62	3(4.84)	59 (95.16)
Obiagu-Uturu	36	0	36 (100)
Amiyiuhu	98	0	98 (100)
Mbala-Isuochi	104	0	104 (100)
Amuda-Isuochi	42	0	42 (100)
Amakpoke	70	0	70 (100)
Lokpanta	72	0	72 (100)
Total	547	3(0.55)	544 (99.45)

Table 2: Overall sex-specific prevalence of *Onchocerciasis* in the communities

Communities Sampled	Number Examined	Number (%) Infected	Male		Female	
			No (%) Examined	No (%) Infected	No (%) Examined	No (%) Infected
Umuobiala	63	–	19	–	44	–
Amiyi-Obilohia	62	3(4.84)	16	1(6.25)	46	2(4.35)
Obiagu-Uturu	36	–	15	–	21	–
Amiyiuhu	98	–	37	–	61	–
Mbala-Isuochi	104	–	43	–	61	–
Amuda-Isuochi	42	–	16	–	26	–
Amakpoke	70	–	34	–	36	–
Lokpanta	72	–	21	–	51	–
Total sampled	547	3(0.55)	201	1(0.50)	346	2(0.58%)

Table 3: Overall age-specific prevalence of *Onchocerciasis* in the sampled communities

Age Range(years)	Number Sampled	Number infected	% infected
5 – 9	79	0	0
10 – 19	62	0	0
20 – 29	37	0	0
30 – 39	37	0	0
40 – 49	49	0	0
50 – 59	77	0	0
≥ 60	206	3	1.46
Total	547	3	0.55

Table 4: Community Microfilarial Load of Positive Individuals in the Sampled Communities

Community	Number of people sampled	Total Num. of mf counted	Total weight of skin	CMFL (mf/mg)
Umuobiala	63	0	87.50	0
Amiyi Obilohia	62	55	196.26	0.28
Obiagu-Uturu	36	0	125.00	0
Amiyiuhu	98	0	207.50	0
Mbala-Isuochi	104	0	253.00	0
Amuda-Isuochi	42	0	269.5	0
Amakpoke	70	0	218.00	0
Lokpanta	72	0	182.50	0
Total	547	55	1,539.26	0.28

Table 5: Prevalence of Onchocercal symptoms among community members

			Number (%) of onchocercal symptoms				
Community	*No. examined*	*No. of infected*	*Itching*	*Nodules*	*impaired vision*	*Leopard Skin*	*Elephant skin*
Umuobiala	63	12(19.0)	2(3.2)	4(6.3)	3(4.8)	3(4.8)	0(0)
Amiyi Obilohia	62	26(41.9)	6(9.7)	9(14.5)	9(14.5)	2(3.2)	0(0)
Obiagu-Uturu	36	4(11.1)	0(0)	0(0)	2(5.6)	1(2.8)	0(0)
Amiyiuhu	98	21(21.4)	4(4.1)	8(8.2)	6(6.1)	2(2.0)	1(1.0)
Mbala-Isuochi	104	28(26.9)	5(4.8)	10(9.6)	8(7.7)	3(4.8)	0(0)
Amuda-Isuochi	42	09(21.4)	2(4.8)	2(4.8)	4(9.5)	1(2.4)	0(0)
Amakpoke	70	31(44.3)	3(4.3)	14(20.0)	14(20)	0(0)	0(0)
Lokpanta	72	12(16.7)	2(2.8)	3(4.2)	3(4.2)	4(5.6)	0(0)
Total	547	142(26.0	24(4.4)	50(9.1)	49(9.0)	18(3.3)	1(0.2)

Applying the test statistic, $\chi^2_{cal} = 50.56$, where $\chi^2_{tab} = 49.8$

4.0. Discussion

After 14 years or more of annual mass drug administration with ivermectin, it was observed that there was remarkable reduction in the prevalence and intensity of onchocerciasis in the sampled communities. The study revealed a CMFL of 0.28mf/mg. This result agrees with the findings of Chijioke *et al* (1998) that after 3 annual ivermectin dosing rounds at Achi in Enugu state, CMFL was reduced from 2.56mf/mg to 0.43mf/mg. Alley *et al* (1994) also observed that a 93% reduction in microfilarial load was maintained one year after 5 successive annual ivermectin treatments. This result could be attributed to the mass treatment of endemic communities with ivermectin which had gone through 14 cycles of treatment and even more in some areas like Mbala-Isuochi, before the commencement of this study. This confirms the findings of some researchers that ivermectin has a prolong effect on skin microfilariae (Boatin *et al.,* 1998; Dozie, 2002). It was not surprising that most

communities sampled recorded zero microfilariae, as the study in Senegal and Mali claimed that elimination can be achieved in most foci after 13 to 17 years of annual treatment (APOC/WHO, 2010). Onchocerciasis is considered an important public health problem when prevalence of microfilariae in the skin exceeds 40% of the total population of a community, or when the community microfilarial load (CMFL: a measure of the intensity of the infection in the community) exceeds 5mf/s (Diawara *et al*., 2009). A CMFL of 0.28mf/mg is a good move towards accomplishing APOC objective of eliminating onchocerciasis.

The overall sex-related incidence of infection showed a similar pattern in males and females. The result showed that 0.50% of the males and 0.58% of the female are infected. This agrees with the findings of some authors like Edungbola (1991), Nwoke *et al* (1994) and Dozie *et al* (2006), that sex-differential with respect to infection may be the same in the rainforest zone irrespective of the degree of endemicity. The overall age-specific prevalence of onchocerciasis in the studied areas also showed that infection occurred only in ages 60 years and above. The absence of microfilariae in children 5 to 12 years of age is a confirmation that transmission can totally be interrupted in the studied areas as the incidence of infection in the 5 year old who were receiving Mectizan for the first time was zero. This finding is similar with the finding of Boatin *et al* (1998) that transmission was totally interrupted in the hypo-endemic Rio Geba Basin, as the prevalence was reduced by almost 100% and the incidence of infection in the 5 year old who were receiving Mectizan for the first time was zero.

There have been several reports documenting improvement of some *onchocercal* symptoms after ivermectin treatment on onchocerciasis (Cousens *et al*., 1997; Chippaux *et al.*, 1999). The most common *onchocercal* symptoms identified in this study were nodules (9.1%), impaired vision (9.0%), and itching (4.4%). The nodule rate of 9.1% shows a decrease from the >20% nodule rate specified for definite CDTI areas (Gemade *et al*., 1998; Noma *et al*., 2002). This is an indication that annual treatment with ivermectin is effective. The claim by a respondent that his nodules disappeared after several annual ivermectin treatments provides credence to the findings of some researchers that onchocercal nodules were gradually disappearing with repeated doses of ivermectin (Ukaga *et al*., 2001; Emukah *et al*., 2004). The presence of *onchocercal* nodules and the absence of microfilariae in the skin of most individuals examined is indicative that ivermectin may have caused the calcification of the nodules, as well as some attrition in adult worm numbers and the viability of the survivors after multiply doses of ivermectin (Schulz-Key, 1990; Duck *et al*., 1990), thus giving credence to the susceptibility of the disease to repeated ivermectin treatment. The chi-square analysis on prevalence of the symptoms among the community members shows that prevalence is not the same among the different communities ($P< 0.05$). The major reason for this could be attributed to different rates of compliance among the community members.

The impaired vision of 9.0% observed in this study was determined by inability to count fingers correctly at distance of six meters (Emukah *et al., 2004*). This is however a crude measure of visual acuity that can be easily explained, rapidly carried out, and reproducibly performed on illiterate population (Onabolu, 1989; Emukah *et al*., 2004s). The recommended criterion of the World Health Organization for functional blindness is the inability to count fingers at a distance of three meters; since twice that distance was used in this study, visual impairment was presented rather than functional blindness (WHO, 1995). A weakness to this method of study is that ocular examination to classify or diagnose the clinical cause for the visual impairment was not carried out. This is an assumption which was not ascertained since the other blinding conditions like glaucoma, cataract etc, could be the cause. In conclusion, the present study revealed the absence of microfilarial in children 5 to 12 years of age and a reduction in the community microfilarial load to a less critical level (0.28mf/mg), after 14 years of annual ivermectin treatment. This is a good move towards accomplishing APOC objectives of eliminating onchocerciasis as disease of public health. It is suggested therefore, that the current control efforts with annual dose of ivermectin be sustained.

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