

## ASSESSMENT OF THE EPIDEMIOLOGY OF ONCHOCERCA VOLVULUS AFTER TREATMENT WITH IVERMECTIN IN THE FEDERAL CAPITAL TERRITORY, ABUJA, NIGERIA

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### ABSTRACT

**Study area:** The study was conducted in the University of Abuja teaching hospital Gwagwalada, Abuja, from February 2009-June 2010. **Methodology:** five (5) Skin snips were randomly collected from various parts of the body of volunteered onchocercal patients visiting the hospital and incubated inside normal saline to recover microfilaria. Nodules were screened by palpation and the diameter measured before and after treatment. Treatment of *Onchocerca volvulus* (Semi-annual treatment) with ivermectin was carried out for two consecutive years. **Results:** The effect of Ivermectin on the 250 onchocercal cases was quite revealing; 210 (84.2%) out of 250 subjects screened negative (had no microfilaria "mf" in their skin of) after treatment while 37 (15.8%) subjects still had positive 'mf' in their skin after treatment ( $t = 46.89P < 0.05$ ). The mean reduction in 'mf' load in the skin during the first and second treatment regime was significant ( $P < 0.05$ ). A decrease in 'mf' load from 100% positive cases to 40.24% and 3.27% during the first and second treatment regime shows that ivermectin was effective against *O. volvulus*. The ivermectin efficacy rate of 59.37% and 77.30% was recorded in the first and second treatments respectively. The effect of ivermectin was also observed on the size of the Nodules and the number of moribund worms. about 94.4% of dead or moribund worms was recovered after treatment compared to 58.4% before treatment; nodules of patients after receiving up to two times ivermectin treatment appeared smaller in size (1.92cm) compared to their initial size (3.55cm) when treatment had not commenced. More than 80% of the female worms recovered from untreated subjects were inseminated/with fertilized oocytes while most worms recovered after treatment were un-inseminated/with unfertilized oocytes. Onchocercal skin changes and other skin manifestation before and after treatment are both highlighted.

**Key words:** Skin snip, Nodules, *Onchocerca volvulus*, *Microfilaria*, Ivermectin.

### 1. INTRODUCTION

**Onchocerciasis** is a vector-borne filarial disease known as "river blindness," "Roble's disease," "craw-craw," or "sowda". It is the world's second leading cause of blindness, with trachoma being number one. Estimate shows that; 37 million people are infected at present with onchocerciasis, more than 250,000 blind and 500,000 have some degree of visual impairment (T.D.R. 2005). The disease abounds in fertile riverine areas that frequently remain abandoned for fear of being bitten by the fly and contacting infection. The disease has wide distribution in tropical Africa, Central and Southern America (Boussinesq *et al.*, 2001).

Adult worms live in subcutaneous tissues in nodules in human body and produce large numbers of microfilarial larvae, which migrate from the nodules to the sub-epidermal layer of the skin where they are picked up by the vector. Transmission is by ingestion of L<sub>3</sub> infective larvae of the parasite by the black fly (vector) of the genus *Simulium* (Crosskey, 1956; Blanks *et al.*, 1998; Cupp *et al.*, 1992). The two strains of the disease are transmitted by different siblings' species of *S. damnosum* complex that are associated with the savannah and forest habitats (Duke, 1967; Anon, 1985; Cheke *et al.*, 1992; Matur *et al.*, 2005).

The effect of *O. volvulus* on the host are unquantifiable; the greater effect could be as a result of the host body reaction resulting in the formation of nodules which encapsulates the adult worms in fibrous tissues over a long period of time. The major diagnostic features and pathologic effects of the disease are intense pruritus, skin lesions (including subcutaneous nodules, papular dermatitis, and a disfiguring depigmentation often known as Lizard, Elephant, wrinkled or Leopard skin) and ocular damage. The scratching sensation prevents sleep and decrease productivity (Anon, 1978). The disease is the cause of low productivity and poor socio-economic achievements in infected communities (WHO, 1976).

According to Gibson and Conor (1978), local irritation of the vesicle layer of the tunica virginals might occur if the scrotal skin is so heavily infected with microfilaria of *O. volvulus* in the parietal layer of the tunica virginals. They also observed that deposition of immune complexes of *O. volvulus* in lymph nodes may trigger inflammation leading to irreversible changes in the nodes and other organs.

True elephantiasis (enlargement of the scrotum) is sometimes caused by these worms that can cause inflammatory dermatitis that might be accompanied by intense irritation, raised papules in the skin and subsequently alteration in the pigmentation of the skin. The term sauda (black disease) is used to describe a severe allergic response usually affecting only one limb with darkening of the skin. The lymph nodes, draining the limbs becomes swollen and painful. (Kläger *et al.*, 1996).

Among the social and economic problems caused by onchocerciasis, Abandonment of fertile lands near river valleys (Buck, 1974), incapacitation of a large segment of the adult working population preventing them from reaching their maximum productivity because of high blinding rates are of paramount importance (WHO, 1995). Infection with *O. volvulus* can last for 11 years or more and encapsulated worms do not get demised.

Ignorance about the natural history of the disease may be a factor in onchocerciasis epidemic. Imperator and Snow (1971) reported that in the Senegal River basin, people do not associate the sign and symptoms with the disease processes, rather they consider them as aspects of normal anatomy and or part of the ageing process. They could dismiss the signs with some superstitious explanations such as curse within particular families. This is one major cause of divorce, relegation and stigmatization within spouses (WHO, 1996).

In clinical and controlled trials, periodic treatment with oral ivermectin a microfilaricidal drug has been shown to reduce the severe manifestations of human onchocerciasis by reducing the number of *Onchocerca volvulus* microfilaria (mf) in the eyes and skin of the human hosts (Akpala *et al.*, 1993; Alley *et al.*, 2001; Duke *et al.*, 1991). High prevalence of onchocerciasis has been observed in the FCT. Reports shows onchocerciasis rates of 61.7% (Crosskey, 1956 and 1960) 79.5% (Braide (1981) and 83% (Mabogunje *et al.*, 1977) from skin snips. Adult worms within the sub epidermal nodules are said to be responsible for the continued production of millions of (L1) microfilariae for up to 10 to 15 years; this supply guarantees the continued supply of microfilaria in the skin.

Ivermectin (Mectizan<sup>®</sup>; produced by Merck and Rahway company) is an efficacious microfilaricidal drug that has been used extensively in Africa (Nigeria inclusive) and Latin America for treatment of human onchocerciasis. Where onchocerciasis is endemic, a treatment regimen of two times per year was recommended by the Onchocerciasis control Program (OCP). Mass treatment with ivermectin is given every six months, with the aim of reaching at least 85% elimination of morbidity and interruption of transmission where possible. Monitoring the impact of this important initiative on disease manifestations is of obvious importance for sustainable development and health care delivery.

The aim of the study is to evaluate the effect of repeated ivermectin treatment on the prevalence of onchocerciasis and density of onchocerciasis “mf” after two years of distribution and to determine the epidemiology of onchocerciasis and level of psychological stigmatization.

## 2. MATERIALS AND METHODS

### 2.1 Description of the study area:

Gwagwalada is the second largest Area Council in the Federal Capital Territory (FCT), Abuja. It lies on longitude 8° 57' N and latitude 9° 11' E of the equator. Rain fall is seasonal, characterized by heavy thunder storm and torrential down pour. Vegetation is guinea savanna type with patches of riparian vegetation. The major occupation of the local indigenes is subsistence farming (Mabogunje *et al.*, 1977). The University teaching hospital (UATH) is one of the oldest hospitals in the FCT.

#### 2.1.1 Methodology

Positive onchocercal cases numbering two hundred and fifty (250) Samples were selected, diagnosed (using clinical and parasitological techniques of onchocerciasis) and treated with ivermectin for a period of 18 months (February 2009 to June 2010), to determine the effect of treatment with Ivermectin on “mf” in the skin. Structured questionnaires were administered to all the 250 positive cases and informations such as; occupation, personal hygiene, social activities, nature and structure of the skin (before and after treatment), level/accuracy of sight, reaction to insect bites reaction to ivermetin drugs, number of times ivermectin have been taken and if at all they have once attended any clinical test due to strange skin reaction on their bodies were obtained.

#### 2.1.2 Participant examinations:

The staff of UATH laboratory unit reviewed the activities of selected subjects. Prior to the distribution of the drug in 2009, baseline data from the 250 selected subjects was obtained through oral interview. After individual consent was obtained, the participants were examined for presence of “mf” in the skin, subcutaneous nodules, papular dermatitis, leopard skin, and visual acuity tested. Examinations were conducted as follows.

### 2.1.3 Microfilaria from skin:

An average of 5 bloodless skin snips was taken using the corneoscleral punch (Walser type with 2.0 mm bite) from the left and right iliac crests, buttocks and shoulders and head of each participant and incubated in 0.5ml micro titer tube containing 0.2ml normal saline for 24 hrs. Before microscopic examination and enumeration of microfilariae, the fluid in each well was removed and fixed in two drops of 40% formal-saline. 1 drop of the fixed solution was transferred unto a microscopic slide and viewed under 10x and 40x objective power (Chesbrough, 1978). The microfilarial load (mfl) being the most sensitive parasitologic indicator, was computed. The prevalence and density of microfilariae is currently the best indicator for measuring the impact of mass drug administration (MDA) in any endemic area of onchocerciasis (Chesbrough, 1978). The percentage microfilariae prevalence (mf %) was calculated as the proportion of skin snips slides found positive for microfilariae i.e.

**Number of individuals whose slides are positive for microfilariae/total number of individuals examined for microfilariae X 100**

The microfilariae density (mfd) per skin snip was the average number of microfilariae found on a slide. This is calculated as follows:

**Total count of microfilariae on slide found positive/total no. of slide found positive X 16.7.**

**Palpation for the presence of nodules:** Participants were examined 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 (Kläger, 1988).

### 2.1.4 Physical examination of skin for papular rashes and leopard skin:

This was done at the same time as the examination of nodules was carried out. Popular 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 (Anonymous *et al.*, 1990).

### 2.1.5 Visual acuity screening:

The participant stood at a measured distance of six meters from the examiner and was asked to tell how many fingers were being shown to them by the examiner (alternating between one, two, or three fingers) (Walsh *et al.*, 1981). 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.

### 2.1.6 Drug administration:

The microfilaria load in the skin was determined before the drugs was administered and also at the end of the treatment. The drug was administered as a single dose twice every year. The treatment coverage was 100% since all the selected cases were treated.

## 2.2 Statistical analysis:

The cohort was defined as those persons with dual observations (e.g., who were examined both in 2009 and in 2010). Cohort data were analyzed in by calculating the total prevalence of the four morbidity indicators attributed to onchocerciasis (nodule, rash, leopard skin, or visual acuity loss). Percentage change in total microfilaria load was calculated as the number of persons with the disease condition at initial diagnosis (before treatment) minus the number of person with the disease condition at final diagnosis (after treatment) divided by the total number of persons sampled and expressed as a percentage. The data was analyzed using student t-test and chi-square statistics to test for goodness of fit at 95% confidence limit, for the effect of ivermectin on *O. volvulus* and also to determine level of stigmatization of the disease.

## 3. RESULTS

A total of 1215 skin snips were collected from 250 onchocercal patients. Of this number, an average of 751.36 skin snips was screened positive with “mf” while 463.64 were negative. This represents 61.83% and 38.17% respectively (table 1). It was observed that the age brackets of 6-10 and <46 years had “mf” in their skins. The percentage prevalence rate of microfilaria recorded from the age bracket of 11-15 and 16-20 years was 7.84 and 7.77 % respectively. The age bracket of 11-15 years recorded the highest number of positive skin snips of 95.24 while the age bracket of 1-5 years had no account of “mf” in their skin. Only 9 subjects out of 250 were seen with onchocercal nodules (Table 1).

The mean percentage numbers of skin snips positive before treatment and after the first and second treatment regimens were 61.83%, 40.24% and 3.27% respectively. The percentage ivermectin efficacy (“mf” in skin of onchocercal patients) for the first and second treatment regimens was 59.37% and 77.30%. It was observed that the age bracket of 6-10 years recorded the highest ivermectin percentage efficacy rate (85.95% and 99.10% in the first

and second treatment regimen respectively). Of the 250 positive cases that had ivermectin treatment, 37 (15.8%) still screened positive with “mf” in their skin while a total of 210 (84.2%) subjects screened negative (Table 2).

Information obtained from onchocercal patients showed evidence of both clinical and pathological symptoms. It was observed that 28% had itching of the skin, 16% with eye irritation and 32.4% had skin de-pigmentation. Also recorded are visual impairment (22.2%) and social stigmatizations (36.4%) (Table 3).

The status of worm populations varied significantly, with important differences noted among age groups. Not fewer than six (6) nodules representing 66.7% from 9 positive cases had moribund worms after treatment. Worthy of noting is that nodules from treated samples were smaller in size than those observed before treatment (Table 4).

*Table 1: Percentage Prevalence rate of skin snips positive with Onchocerca volvulus mf and number of positive Nodules determined by REA method (Feb. 2009 - June 2010)*

Age	No of +ve subjects sampled for skin snip	Skin snip			Nodules No. with Nodules
		No of skin snips collected	No. of +ve skin snips with MF (%)	No. of -ve skin snips	
1-5	20	100	0.00(0.00)	100	0
6-10	29	140	66.67(5.49)	73.33	0
11-15	25	125	95.24(7.84)	29.76	0
16-20	22	100	94.34(7.77)	5.66	2
21-25	20	100	85.83(7.06)	14.17	0
26-30	29	140	72.92(6.00)	67.08	0
31-35	25	125	76.09(6.26)	48.91	0
36-40	23	115	87.50(7.20)	27.5	1
41-45	27	135	86.21(7.09)	48.79	2
<46	27	135	86.46(7.12)	48.34	4
Total	N=250	1, 215 (4.8=mean skin snip/person)	751.36 (61.83%) Mean Skin Snip +ve= 82.67	463.64 (38.17) Mean skin snip -ve= 46.56	9

*Table 2: Effect of Semiannual treatment with Ivermectin on Onchocerca volvulus mf (February 2009-June, 2010)*

Age	Feb. 2009-Oct. 2009		Nov. 2009 – July 2010		Total No.	
	Mean No. of +ve skin snip after treatment	Percentage efficacy of ivermectin on mf	Mean No. of +ve skin snip after treatment	Percentage efficacy of ivermectin on mf	Subjects +ve after treatment	Subjects -ve after treatment
1-5	0.0	0.00	0.00	0.00	0	20
6-10	57.3	85.95	0.60	99.10	1	28
11-15	60.2	63.21	3.10	96.75	6	19
16-20	48.3	51.2	3.2	96.61	5	17
21-25	52.1	60.70	1.10	98.72	2	18
26-30	59.3	81.32	2.2	96.98	2	27
31-35	44.8	58.88	1.20	99.74	4	21
36-40	59.1	67.54	2.40	97.26	3	20
41-45	57.2	66.35	10.60	87.70	9	18
<46	50.6	58.52	15.30	82.65	5	22
Total	488.9 (40.24) Mean mf =48.9	59.37	39.7 (3.27) Mean mf =4.0	77.30	37 (15.8)	210 (84.2)

Table 3: Responses from onchocercal patients on Onchocercal Morbidity Indicators

Category	Onchocercal morbidity indicators				
	Itching skin	Itching eyes	Skin de-pigmentation	Visual impairment	Social stigma
Untreated	30	17	60	38	60
Treated	40	23	21	17	31
Total	70(28.0%)	40(16.0%)	81(32.4%)	55(22.0%)	91(36.4%)

Table 4: Effect of Semi-annual Treatment with Ivermectin on the Size of *Onchocerca volvulus* Nodules

Years	Size of nodules Before treatment	Size of nodules (after Treatment)	Nodules with dead/moribund worms
16-20	<3cm	>3cm	1
36-40	<3.5cm	>2cm	1
41-45	<3.78cm	>1.5cm	1
<46	<3.90cm	>1.2cm	3
Average	<3.55cm	>1.93cm	6 (66.7%)

#### 4. DISCUSSION

High prevalence (61.83%) of positive skin snips recorded from 1215 skin snips is an indication that onchocerciasis is endemic in the Federal Capital Territory, Abuja. This report agrees with Crosskey, (1956; 1960), Braide (1981) and Mabogunje *et al.* (1977) who first reported that FCT is endemic with high prevalence rates of 61.7%, 79.5% and 83.0% respectively. Their report depicts gradual increase in the disease prevalence since 1956 to 1977 before OCP intervention started.

The age groups of 11-20 years recorded the highest percentage prevalence rate of the disease (7.77-7.88 microfilaria per skin snip). This might not be unconnected to their level of exposure to *Simulium* bite.

The number of skin snip screened positive (with “mf”) showed a spontaneous decrease at the first and second treatment regimen with ivermectin drug. According to OCP, a treatment regimen of two times per year is recommended to treat onchocerciasis and that it has up to 85% rate of eliminating morbidity and interrupting transmission where possible. The decrease in number of positive skin snip from 61.83% when subjects were first screened positive to 40.24% and 3.27% after the first and second treatment regimen is an indication that ivermectin is effective (59.37% and 77.30%) against *Onchocerca volvulus*. The effect was statistical significant ( $P < 0.05$ ). This report concurs with that of clinical studies reported by Duke *et al.*, (1991) that treatments at varied intervals could significantly affect the vigor and health of adult female worms. Also, from elsewhere in Guatemala and Ecuador, reports shows that Six-month use of ivermectin at the community level for 3–4 years had significant impacted on the transmission of *O. volvulus* vertebrate infective stage larvae ( $L_3$ s). That few if any  $L_3$ s were available to produce new infections. It was also pointed out that unlike vector control, wide-spread treatment with ivermectin has an immediate dampening effect on transmission of new infections (Cupp *et al.*, 1992; Trpis *et al.*, 1990). Consequently, with long term treatment of at least six-month, the input of  $L_3$ s that might successfully develop to adult males and continue the insemination process in pre-existing infections or develop to young females that are highly fecund is severely restricted (Chavasse *et al.*, 1995).

The result depicts a deteriorating condition of *O. volvulus* “mf” in the skin as of 2009, indicating that recurrent treatment of onchocerciasis using ivermectin had profound effect on survival and development of parasite. It was observed that not more than 33.3% (3) of the female worms in treated samples were still viable and likely to

continue with microfilariae production. A number considered to be less than the 6 (66.7%) nodules with moribund/dead worms after the treatment. This change is probably due to a variety of inter-related factors associated with long-term exposure to ivermectin given at six-month intervals. Gardon *et al.* (2002) in a similar study evaluating dosage levels and timing of ivermectin treatment gave essentially similar result. Furthermore, in evaluating the reproductive status of surviving female worms, a process which lends itself better to histologic methodology, more than 80% of adult worms in each country were uninseminated, indicating that the counterpart male populations were considerably diminished and unable to maintain gene flow. This follows the trend reported earlier by Duke and others (Duke *et al.*, 1991), in which insemination rates were decreased by  $\geq 25\%$  following 4 to six-months of treatment.

Repetitive mating is a key factor in the maintenance of *O. volvulus* populations and it has been estimated that for continued production of microfilariae, insemination must take place at roughly three-month intervals (Schulz-Key and Karam, 1986; Schulz-Key, 1990). To maintain sufficient gene flow, Plaisier *et al.*, (1991) suggested that the probability of mating should be equal to the ratio of male: female worms, with a value of 1.0 (100% insemination) occurring when there are more male than female worms.

The high rate of dead adult worms likely occurred because transmission of L<sub>3</sub>s had been greatly reduced or interrupted in the treated group. The report concurs with Cupp *et al.* (1992), Guevara *et al.* (2003) and Rodriguez-Perez *et al.* (2004) who reported that the worm populations at this point are undergoing senescence. According to Guderian *et al.* (1997), high percentage of dead female worms in treated samples is most likely a reflection of the broad coverage and extensive use of ivermectin on a recurrent basis. Kläger *et al.* (1996) also reported that as few as four to six-month treatments could caused significant increases in the proportions of moribund and dead females and of live, un-inseminated females when compared with corresponding controls. This observation was confirmed in Sierra Leone (Kläger *et al.*, 1996) where treatments repeated at six-month intervals significantly decreased the proportion of living and gravid female worms and reduced the overall reproduction by approximately 90%.

The significantly smaller sizes of nodules recovered from treated samples is not likely to be unconnected with the number of dead worms. This observation agrees with Darge *et al.* (1994) who observed a mean reduction in nodule size of 27% when suramin was used as a macrofilaricide, with the proportion of dead female worms increasing from 17% at the end of therapy to 48% six months later and 61% at one year.

Other forms of papular dermatitis can be due to causes other than onchocerciasis, such as infectious agents (scabies, pediculosis, larval migrants, dermatophytes), insect (including *Simulium*) bites, and contact allergens. Since ivermectin is also effective against scabies, pediculosis, and larval migrants. The decrease in papular dermatitis noted in this study might have been attributable to a beneficial side effect of mass ivermectin administration (Del *et al.*, 2002). One mother commented: "My child used to be very sickly but after taking ivermectin and passing out bags of worms he became healthy."

Since its launching, the FCT onchocerciasis program has delivered more than 1.5 million ivermectin treatments to an estimated 500 thousand people at risk. Projection of the results from this study to the overall population at risk suggests more than 2,500 of these persons (2.3%) 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.

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