A RANDOMIZED COMMUNITY TRIAL ON SAFETY AND EFFICACY OF CO-ADMINISTRATION OF ALBENDAZOLE AND IVERMECTIN ON LYMPHATIC FILARIASIS AND ITS SECONDARY EFFECTS ON GEOHELMINTHS IN ZANZIBAR.

BY

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UNIVERSITY OF DAR-ES- SALAAM
2000.

CERTIFICATION:

The undersigned certify that they have read and hereby recommend for acceptance by the university of Dar-Es-salaam dissertation entitled: *a randomised community trial on safety and efficacy of co-administration of albendazole and ivermectin on lymphatic filariasis and its secondary effects on geohelminthes in Zanzibar*, in partial fulfilment of the requirements for the degree of Master of Science (Tropical Disease Control).

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DECLARATION AND COPYRIGHT

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DEDICATION

To my beloved wife **Nunuu**

And

Children

Nassor, Firdaous and Jabir.

ABSTRACT:

From November 1999 to February 2000 a community survey was carried out in the south district – Zanzibar and a total of **2839** individuals were screened. The purpose of this survey was (apart from detecting the magnitude and intensity of bancroftian filariasis and geohelminth infections) to determine safety and efficacy of co-administration of albendazole and Ivermectin on lymphatic filariasis and its secondary benefits on geohelminth and related factors in a sampled population in Unguja Island Zanzibar.

A sample of 418 participants positive for bancroftian filariasis and or with clinical filarial disease were recruited. Pre and post treatment levels of microfilaria were determined by night blood sample collection and geohelminth infection was determined indirectly by egg counts. Out of these 418, 259 (62%) were found to have at least one specie of geohelminth infection. These were physically examined and were randomly assigned to the two treatment arms (ivermectin -albendazole or ivermectin placebo) and followed for 96 hours to monitor for any drug related side effects. Those who developed side effects were managed accordingly.

Results showed that the overall prevalence of bancroftian filariasis and geohelminth was 13.7% and 44.7% respectively. The overall reduction on percentage and intensity of bancroftian filariasis and geohelminth infections were found to be higher in ivermectin-albendazole treatment arm (100% and 78.4% respectively) compared to ivermectin –placebo regime (reduced lymphatic and geohelminth by 97.8% and

45.83 % respectively). Similar levels of reductions were noted on infections with different geohelminth species.

Side effects were reported from six hours after drug administration reaching peak at 24 hours and declined from 72 hours. Headache and changes in respiratory rates were the major side effects associated with ivermectin –albendazole arm while high fever and dizziness were associated with ivermectin –placebo treatment regime.

In conclusion, at short-term observation, the ivermectin –albendazole combination was noted to be more efficacious and safe in treatment of both parasites than ivermectin placebo regime.

It is recommended that a long term evaluation on sustainability of these reduced parasites levels are conducted at three and six months respectively.

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LIST OF ABBREVIATIONS.

CTD: Control of Tropical Diseases.

DMO: District Medical Officer.

FCU: Filaria Control Unit.

Fig. Figure.

Mff: Microfilaraemia.

MOH: Ministry of Health.

PHCC: Primary Health Care Centre

PHCU: Primary Health Care Unit.

Ref: Refer.

WHO: World Health Organisation

1.0 INTRODUCTION AND LITERATURE REVIEW

Lymphatic filariasis is a sequel from infection with 3 species of filaria worms namely *Wuchereria bancrofti, Brugia malayi* and *Brugia timori.* Lymphatic filariasis is a disease of major social and economical burden in Tropic and sub-tropical countries of the world affecting a minimum of 120 million people in 73 countries world-wide. About 107 million of these are infected with *Wuchererian bancrofti* and *13* million with *Brugia malayi* or *Brugia timori* world-wide. Another 76 million have parasites in their blood and cause internal damage to their lymphatic and renal systems (Ottesen et. al, 1997). In 1990, the estimated burden of disease was 850,000 Disability Adjusted Life Years-DALYS. (WHO[a], 1998).

Infection with *Wuchererian bancrofti* parasite leads to a variety of clinical manifestations, including lymphoedema and elephantiasis of the leg, genital disease (including hydrocele, chylocele and elephantiasis of the scrotum and penis) and recurrent acute secondary bacterial infections (Ottesen et. al, 1997).

In tropical and sub-tropical areas of the world where the disease is well established the prevalence of the infection is continuing to increase. This is primarily due to the rapid and unplanned growth of cities, which creates numerous breeding sites for the vectors that transmits the disease. Thus lymphatic filariasis is a significant cause of acute and chronic illness in both urban and rural areas, affecting people of all ages and both sexes, particularly the poor and vulnerable (WHO[b], 1997).

Bancroftian filariasis is one of the lymphatic filariasis commonly affecting different parts of Tanzania (Minjas & Kihamia 1991). About 10 million people are estimated to live in endemic areas in Tanzania (Minjas and Kihamia, 1991). The disease distribution in the country can be grouped into three major foci and two minor foci.

Major foci include:

(a) Coastal belt: Includes areas of Tanga, Korogwe, and Pangani.

(b) Islands located in Indian Ocean – In Mafia and Zanzibar.

(c) The shores of Lake Victoria. – the south and south-eastern parts of the lake

The minor foci are:

(a) The North end of Lake Nyasa; and

(b) The central lowland areas in Morogoro region (Minjas & Kihamia, 1991).

The commonest type of microfilaraemia found in Zanzibar is *W. bancrofti* though *Streptocerca perstants* had been documented (Mansfield- Aders, 1927). Studies at the beginning of the twentieth century on the microfilaraemia rates in hospitalised patients irrespective of the cause of admission revealed high microfilaria prevalence. Mansfield – Aders (1927) found that *Culex quiqefaciatus*, *Anopheles costalis* and *Anopheles funestus* to be the main vectors. Studies in Pemba (McCarthy, 1930) recorded mff. rates as high as 30% in adults and 15% in children. Kilama et. al (1976) in Unguja and Pemba noted microfilaraemia (mff) rates as: Konde-11.8%, Jambiani-12%, Chake -Chake-16.2%, Makunduchi-39%, Kengeja-15.1%, and Zanzibar town 15%. Another study done by Maxwell et. al (between 1987-1991) in Unguja showed mff. to range from very low to

very high rates as follows: Pwani Mchangani-0.3%, Konde-3%, Jambiani12%, Mwoga - 32% (in 1991), Makunduchi -49% (1987), Kengeja-13% (1989), Kizimkazi-26% (1988), Zanzibar town -8% (1991), and Makunduchi-12% (1989). However, Pedersen et. al (1999) in Pemba found the overall microfilaria prevalence to be 9.7%.

Geohelminth infections (global situation):

Geohelminth are intestinal nematodes whose development takes place outside the body i.e. in the soil (Gilles, 1996).

The distribution of geohelminth is world-wide especially in tropical and sub-tropical countries. About 2 billion people world-wide are at risk of being infected while 25% of the world population (i.e. more than 1 billion people) are infected (WHO[c], 1998). These include 400 million school-aged children (infected with *Ascaris lumbricoides, Trichuris trichiura, Ancylostoma duodenale, and Necator americanus)* while 44 million pregnant women are infected with hookworm (WHO[c], 1998). Also, *A. lumbricoides* has been estimated to cause morbidity to 250 million with annual mortality of 60,000 people while *T. trichiura* has been associated with morbidity of 46 million with annual mortality of 10,000. Hookworm infections was associated with morbidity of 151 million and annual mortality of 65,000 people (WHO[c], 1998).

Furthermore geohelminth infections reduce work capacity and impede concentration. In children geohelminth infections reduce cognitive development and increases absenteeism from school. Infections also increase maternal and foetal morbidity and mortality (WHO[c] 1998, Haas HM 1996).

Geohelminth situation in Zanzibar:

In Tanzania the socio-economic status of most of its citizens is low thus contributing towards the escalation of geohelminth infection. Rural-urban migration together with the high fertility rates contributes towards overpopulation and overcrowded towns. Thus resulting in shortages of social facilities and services like safe water and sanitary facilities, hence high levels of intestinal parasitosis.

Zanzibar, an Island in the Indian Ocean does experience high levels of geohelminths infections. Albonico et. al (1997) recorded the prevalence of 87.4%, while Marti et. al (1996) recorded prevalence of 98.9% in school children in Zanzibar.

Co-existence of lymphatic filariasis and geohelminths in Tanzania do occur but not yet documented, however the geographic areas which are endemic for lymphatic filariasis do overlap with areas endemic for geohelminth. Examples include:

(a) The endemic Lake zones (Minjas and Kihamia, 1991) are also endemic for hookworm with the prevalence being up to 41% (Kilama, 1990).

(b) The coastal areas, which are endemic for lymphatic filariasis, are also endemic for geohelminth. In Tanga hookworm prevalence was up to 81.5% (Kilama, 1990).

(c) The islands of Zanzibar with lymphatic filariasis prevalence of up to 40% have also been recorded to have high prevalence of intestinal helminthes infections (Marti et. al 1996, Albonico et. al, 1998.).

Many control attempts on Bancroftian filariasis had been conducted in various parts of the world with various degrees of success. However, the disease has remained a major public health problem in Southern and South East Asia, Africa and in a number of Caribbean and Pacific Islands (Ottesen et. al, 1997).

Earlier attempts to control lymphatic filariasis in Tanzania were either in form of large-scale control trials or smaller research oriented trials (Ministry of Health, 1997). These attempts were successful on reduction of both microfilaraemia levels and mosquito infectivity rates. Control attempts on lymphatic filariasis in Tanzania have been conducted using either mass chemotherapy with di-ethyl carbamazine (DEC) integrated with either vector control and /or environmental management by using expanded polystyrene beads, temephus and *Bacillus sphaericus* (Jordan 1958, Kolstrup et. al 1981, Maxwell et. al 1990). Most of these were done in few regions or zones. Unfortunately the re-infection rates remain high even after the termination of the control programs. Hence the microfilaraemic rates remain similar to those of the pre-treatment levels (Maxwell et. al-1999,Pedersen et. al, 1999). Thus with limited control tool namely with vector control and individual treatment with DEC, a drug which requires a long treatment regime and of noted adverse side effects which might persist between two to four days or even several weeks following therapy, then the need to have a new drug with shorter treatment duration but efficacious is highly needed (Buck, 1991).

Furthermore, most of the currently used antihelminthic drugs are not effective against some geohelminth species which affect our population (Albonico et. al 1994 and Norhayati et. al 1997). These mildly reduce the infection load resulting into high re-infection patterns.

Recent research advances on the control of lymphatic filariasis on areas of severity, disease impact, new diagnostic and monitoring tools together with new treatment tools and control strategies has increased the chances for global elimination of lymphatic filariasis as a public health problem. Factors favouring its elimination include inefficient transmission (i.e. several hundred infective bites are required to produce a fertile adult worm); in case of *W. bancrofti* the absence of non-human reservoir and that there is no multiplication of the parasite in the mosquito vector (WHO[d], 1997).

The emergence of the new strategy on control using Albendazole and Ivermectin in combination is considered to be more efficacious on parasite clearance. Studies on efficacy and safety of Albendazole and Ivermectin on lymphatic filariasis in communities in Africa have been recommended (WHO[e], 1998) so as to build up on studies done in Asia (by Kumaraswami et. al 1988, Eberhard et. al 1992). Furthermore, Adenusi (1997) and Lyagoubi et. al (1992) noted effects (efficacy) of Ivermectin on geohelminths (strongyloidiosis).

However, most of these studies were done in a clinical set-up and had different findings on efficacy and safety. The microfilaria clearance rates for bancroftian filariasis with

ivermectin or DEC had been claimed to be 90% for one full year after treatment. Similarly the effects of co-administration (DEC plus Ivermectin) was noted to reduce mff. counts by 99% for one full year (WHO[d], 1997). However studies done by Ismail et. al (1998) on single dose clinical trial in 50 asymptommatic microfilaraemic males showed that at 15 months post-treatment:

- Ivermectin and Albendazole – 9 out of 13 were amicrofilaraemic (69%).
- Albendazole -1 out of 12 was amicrofilaraemic (8%).
- Albendazole and DEC-3 out 11 were amicrofilaraemic (27%).
- DEC and Ivermectin – 3 out of 10 were amicrofilaraemic (30%.)

He also noted that all four regimens had been well tolerated with an additional benefits of being potent broad-spectrum antihelminth. Another similar study done by Youssef et. al (1997) on two single doses of Ivermectin revealed that mff. clearance rate in the first three months were 31%, and the side effects noted were fever, headache, weakness, nausea and epigastric pain, with no adverse physical or laboratory findings. Also Sabry et. al (1991) noted that Ivermectin alone causes mff. reduction (abrupt) to 1.5% of the pre-treatment levels 12 hours after drug administration and to 0.06 % on day 14 with reappearance rate of 1.8% after one month and 9.2% after three months. The noted side effects included headache, body aches, which appeared as early as 4 hours after drug administration.

Effects of Ivermectin on intestinal nematodes were noted by Taticheff et. al (1994) where the efficacy on *S. stercoralis* was 100%, *A. lumbricoides* was reduced from 74.5%

(ova) pre-treatments levels to 3.5% and 48.9% in post –treatment samples of 15 days and 3 months respectively. Similarly, Datry et. al (1994) in a clinical trial to cure strongyloidosis found that parasitological cure was obtained in 83% of those treated with Ivermectin compared to 38% of those treated with albendazole alone.

This study was therefore designed to establish the efficacy and safety of co-administration of ivermectin and albendazole on lymphatic filariasis in a local environment in Zanzibar Island. In addition, since geohelminth are also endemic in this area, the secondary benefits of these drug combinations were also evaluated.

1.1 STATEMENT OF RESEARCH PROBLEM

Lymphatic filariasis (Bancroftian) and geohelminthic infections are of both medical and public health importances in Tanzania. It has been estimated that over 10 million people live in lymphatic endemic foci (Minjas & Kihamia, 1991) and are at risk. Also lymphatic filariasis contributes to morbidity and permanent disability to more than 2 million people (Michael et. al, 1996).

Currently, patient treatment for those individuals infected with *Wuchereria bancrofti* is through DEC. Also *B. sphaericus has* been used in limited areas for vector control (Ministry of Health report -Zanzibar ,1994). However DEC is accompanied by a lot of adverse effects and long treatment duration hence its use in mass treatment is normally accompanied with low compliance. Therefore a need to have a safer drug with less

adverse effects and shorter treatment regime but high microfilaria clearance rate is required. WHO Global Lymphatic Filariasis Elimination Programme (WHO[d], 1997) recommended a community-wide (mass) treatment using either one drug regimen or two drug regimen as a strategy towards the elimination of lymphatic filariasis. Thus an effective drug with effects on both microfilaria and geohelminth would be of assistance in the elimination of both diseases and thus alleviate the disease burden.

Geohelminthic infection is also a neglected disease (despite its high prevalence) in some communities unless accompanied by serious results like worm expulsion or intestinal obstruction.

Filaria research activities in Zanzibar had been confined greatly on areas of detecting the magnitude and control of a single nematode without evaluating the impact the antifilarial drug had on other nematodes such as geohelminth. Similar attention need to be directed on peoples understanding on causes and ways of preventing filaria infections.

This study intended to address two issues of (i) safety and (ii) efficacy. Knowledge on the safety indices on single drug administration i.e. albendazole alone or ivermectin alone have been done through many safety trials (Zheng et. al 1992, Sabry et. al 1991) which have proven to be safe when used in human subjects. However knowledge on safety of co-administration of albendazole and ivermectin is an area which is not yet fully explored. Thus the rationale question is a safety/ efficacy trial on the co-

administration of albendazole and ivermectin necessary? Despite the fact that the co-administration was anticipated to have synergistic mechanism from the microfilaricidal effects of the individual drugs, i.e. albendazole and ivermectin, however there is a need to understand whether co- administration can result in any serious adverse effects? Therefore, before allowing a wide scale distribution and administration of albendazole and ivermectin there was a need for local safety data when these two drugs are co-administered.

1.2.0 OBJECTIVES:

1.2.1 Broad objective:

To determine the safety and efficacy of co- administration of Albendazole and Ivermectin on lymphatic filariasis and its secondary benefits on geohelminths and related factors in a sampled population in Unguja Island, Zanzibar.

1.2.2. Specific objectives:

1. To determine the prevalence and intensity of microfilaraemia (pre -and post treatment)
2. To determine the percentage reduction in microfilaraemia after treatment with albendazole and ivermectin by age and sex specific category.
3. To determine the prevalence of co-infection of lymphatic filariasis with geohelminths in Zanzibar.
4. To determine the proportions of the studied population infected with geohelminths and the type of species.

5. To determine the percentage reduction of geohelminths after treatment by age and sex.
6. To determine the proportion of common side effects to those receiving therapy and their types.

1.3. Rationale of the study

Lymphatic filariasis is the second leading cause of permanent and long term disability with deforming, mutilating disease of the limbs and genitals resulting not only in physical crippling but also in psychosocial consequence. Needless to say are the effects of direct economic costs of managing the acute and chronic manifestation of lymphatic filariasis which are aggravated by the enormous indirect losses that follows from the diminished productivity and incapacitation and which constitutes a severe drain on local and national economies (WHO[f] 1999, Gasarasi et. al 1996, and Ramaiah et. al 1998).

Most of the studies to determine the efficacy of co-administration of albendazole and Ivermectin were done outside East Africa with small samples, Kumaraswami et. al in India 1988, Sabry et. al in Egypt, 1991). Thus this study intends to assess the safety and efficacy of co-administration of Albendazole and Ivermectin in a community where the co-existence of lymphatic filariasis and geohelminthes occur. Thus targeting in minimising the nematode worm load in such communities.

Similarly , there have been no efficacy studies on these drug combinations in East Africa to date which might clarify the differences observed in other studies before allowing large scale drug distribution. There is therefore a need to carry out studies which will address the efficacy issues using local data so as to give evidence on the scope at which the drugs can be used on a wider scale after knowing the microfilaria clearance potential and safety in the country.

Tanzania has been earmarked as one of the countries where lymphatic filariasis elimination using co-administration strategy of Albendazole and Ivermectin would be done. Therefore, the study aimed at enabling (through the information gathered from this study) the control programs for both lymphatic filariasis and helminths to have a new tool that might be of help in working in unison towards the disease control and hence their elimination. Furthermore, in 1997 the Ministry of Health Zanzibar with technical support from WHO/CTD developed plans of actions for integrated control of filariasis, Intestinal helminthes, Malaria and schistosomiasis. The study would assist in strengthening the integration of different programs towards nematode infection control and their consequent elimination.

2.0 METHODOLOGY:

2.1 DESCRIPTION OF THE STUDY SITE:

Zanzibar comprises of two sister Islands of Unguja and Pemba. Unguja Island is made up of six districts namely North A, North B, Central, South, West, and Urban districts. Basing on the 1988 population census the island of Unguja was estimated to have a population of 375,539, of which 191,600 were males while 195,828 were females (Bureau of statistics 1988) with an annual growth rate of 3.0%. In 1999 the Unguja Island was projected to have a population of 499,466.87. The Unguja Island has one Referral hospital, one maternity hospital, two cottages Hospitals (Primary Health Care Centre, PHCC), 70 Primary Health Care Units (PHCU) 9 of which are second line dispensaries and one mental hospital. About 95% of health care units are within a 5 km distance to the population serving about 5000 to 10,000.Within the district the lowest governmental level is the shehia.

The southern district, located at the south end of the Unguja Island partially surrounded by the Indian Ocean, is comprised of 18 shehias. These include: Makunduchi (with four closely stationed shehias viz. Kajengwa- Makunduchi, Kijini- Makunduchi, Mzuri-Makunduchi, Nganani-Makunduchi), Bwejuu, Jambiani –Kibigija, Kibuteni, Jambiani Kikadini, kitogani, Kizimkazi-Dimbani, Kizimkazi – Mkunguni, Mtende, Muungoni, Muyuni A, Muyuni B, Muyuni C, Paje and Pete with a total population of 31,703 (Projection of 1988 census- Bureau of statistics.) The district has nine Primary Health Care Units, two of which are second line dispensaries with one cottage hospital i.e.

primary health care centre. Major occupation include subsistence farming (where seaweed farming is a major occupation for women along the coastal areas), governmental employment, small-scale business and fishing. Parasitic infections such as malaria, geohelminth infections, lymphatic filariasis and anaemia, cut wounds, diarrhoea are the common illnesses attended at PHCC/PHCU (MOH-1997).

2.2: TRIAL POPULATION

All individuals aged two years and above of either sex (who were either microfilaraemic or with clinical active disease) not sick, not pregnant and with no history of allergy to any drug were eligible to participate in the study. The two years old children were included as recommended by the Zanzibar Research Council basing on past experiences of observing infected children within these age categories (2-5years).

2.3: STUDY DESIGN

The study was a randomised doubled blind parallel group trial comparing effects of Ivermectin plus placebo and Ivermectin plus albendazole on bancroftian filariasis and their benefits on geohelminth. The study was conducted between November 1999 to February 2000. Pre -and post treatment levels of microfilaria were determined by night blood sample collection and geohelminth infection was determined indirectly by egg count. Side effects and their types were determined by follow up of recruited individuals and close monitoring and observations for development of adverse signs and symptoms.

2.4: SAMPLE SIZE CALCULATIONS:

It was estimated that coverage of 80% or more of the eligible population with chemotherapy was effective in interrupting transmission and reduction /control of transmission when the microfilaria prevalence was maintained at levels of ≤ 5% (WHO[f], 1999). Although experience from China have suggested that recrudescence of transmission might occur unless the prevalence of mff. has been brought to less than 1% (WHO[f], 1999). However, achieving and sustaining the prevalence rates to values less than 5% requires multiple community exposures to mass chemotherapy before achieving this level. In this study microfilaria reduction to prevalence level equal to 5% was then targeted as baseline i.e. a drug with a potentiality of reducing the current prevalence of 39% to 5% i.e.34/39=87% after the first exposure.

The minimum sample size required was obtained by using the formula:

a) **For efficacy determination:**

$$n = \frac{Z^2 \times P \times (1-P)}{d^2}$$

Where:

Z = 1.96 corresponding to 95% confidence level.

P= estimated prevalence reduction by the drug combination. Efficacy of not less than 87% ± 5% i.e. with maximal potential of 92%

d= margin of error set at 5%.

Substituting the values:

$$n = \frac{1.96^2 \times 0.92 \times 0.08}{0.05^2}$$

$$n = \frac{3.8416 \times 0.0736}{2.5 \times 10^{-3}}$$

$\therefore n = 113.096 \cong 113.$

Considering non-response rate of 10% then 113+11.3=124 participants were required.

As the study involves two arms then the sample size required was 124×2=248 participants.

b) <u>For safety determination</u>:

The sample size needed should be able to detect a harmful effect occurring in at least 5% of the subjects ± 4%.

$$n = \frac{Z^2 \times p \times (1-p)}{d^2}$$

<u>Where:</u>

n= the required sample size. ,

p= Proportion of individuals which would be able to detect a minimum of 5% (±4%) prevalence of adverse effects due to drug administration.

d= margin of error set at 4%.

$$n = \frac{1.96^2 \times 0.09 \times 0.91}{0.04^2}$$

$$n = \frac{3.8416 \times 0.0819}{1.6 \times 10^{-03}}$$

$= 196.6$ participants.$\cong 197$

As there were two treatment arms then the required study sample needed was 197×2 which was equal to **394 people**. As the sample size required for efficacy determination was less than that required for safety determination , the sample size of 394 people was taken for the whole study.

2.5 SAMPLING PROCEDURES/TECHNIQUES

The list of all shehias in the district was obtained from the district commissioner's office and were arranged alphabetically and were given a serial number. The Makunduchi four closely placed shehias where people intermingle profundously were considered as one. Using random number tables two shehias Mtende and Makunduchi were selected. Community sensitisation was done and all individuals residing in these shehias were invited to participate in the study.

The minimum required sample size was exceeded by extra participants, as it was unethical not to include them as they did actively participate throughout the course of the trial.

2.5.1: Definition of terms:

1. Microfilaraemia: presence of filaria larva in the blood circulation.
2. Endemic: constant presence of a disease or an infectious agent in a given locality or geographical area.
3. Geohelminth: soil transmitted helminths the infective stages are reached only after a period of embryonation in the soil e.g. *A. lumbricoides*, *T. trichiura,* Hookworms.
4. Clinical active (filaria) disease: was defined as history of recurrent fevers associated with local pains, local warmth and local Lymphadenopathy and may or may not be accompanied by oedema of the genitalia or limbs.

2.5.2 DATA COLLECTION

The researcher requested for ethical clearance and approval from the Ministry of health Research council where some recommendations were made and adhered to. Recommendations were to change the inclusion criteria so as to include those individuals aged two years and above and also to include those with clinical active disease.

An introductory letter was forwarded to the District Commissioners office where a general briefing on the study was planned and done to the local leaders (shehas) and was chaired by the District Commissioner. All necessary details on the nature and the would be benefits of the study were clearly outlined.

The research team was then allowed to conduct the research in the randomly identified shehias. This was followed by community sensitisation meetings where all vital information concerning the study were made clear to the public and verbal consent for screening was sought.

2.5.2.1 PILOT STUDY:

Training on the questionnaire was done to the four research assistants prior to pre – testing. Pre-testing was done in one of the villages in the south district. The pre-test helped to modify and correct the questionnaire.

2.5.3. COMMUNITY SCREENING:

Verbal consent was obtained from each individual at the time of screening. Parents and guardians of those children aged under ten years of age gave consent on their behalf. Age was the only restriction at the screening level. Individuals totalling to **2839** were screened for both lymphatic filariasis and geohelminth. The aim was to identify participants who met the inclusion criteria (microfilaraemic and those with active clinical filaria disease). Available information were recorded in the register book where identification numbers corresponding to the numbers for parasitological investigations were allocated. Also recorded were name, sex, age, body weight, area of residence, local leader's name, clinical status and parasitological indices for lymphatic filariasis and geohelminths.

2.5.4. CLINICAL EXAMINATION:

All recruited individuals were examined by both, the principal investigator and one research assistant; the District Medical Officer (DMO); where general body examination inclusive of the limbs and genitalia was done. Female genital examination was done by a qualified registered public health nurse with midwifery background. This minimised the cultural sensitivity associated with the procedure.

2.6. PARASITOLOGICAL INVESTIGATIONS

2.6.1 BLOOD SURVEY

Verbally consented individuals aged two years and above were gathered at a locally selected neutral area (outside the clinic or political groups) and informed on the procedures concerning the blood specimen collection. Blood sample collection was done between 10 .00 p.m. in the evening to 3.00 am in the morning. Individuals index finger was disinfected (using methylated spirit) and pricking was done using a sterile lancent pricker. The blood was then collected using a 200 micro-litres micropippete and was later on transferred to a microtube (Eppendorf) containing 0.5mls. of 3% glacial acetic acid labelled with an individual's registered number. Another blood drop was smeared on the glass slide (from the same pricked finger) and labelled using the same registration number for subsequent parasitological examination. The same procedures were repeated two weeks after treatment where blood samples were collected between 10.00pm and 12.00pm.

2.6.2 BLOOD EXAMINATION

Collected blood samples were transferred to the Filaria Control Unit laboratory and examination done by the principle investigator with the assistance of the qualified technicians. Each blood sample was carefully examined in a counting chamber under low magnification (10×10) of a binocular microscope. The counting chambers were carefully designed so as to contain micro-chambers thus ensuring that no area was left unexamined. Samples, which revealed microfilaria, were re-examined and careful microfilaria count was done and recorded per 200microlitres of blood. Blood smears were dried and stained with 5% giemsa and were later on examined under low power objective (10×10) of the binocular microscope. The same procedure was repeated after treatment.

2.6.3 STOOL EXAMINATION

Individuals who had undergone blood examination were given labelled plastic containers and were requested to place fresh stool in the containers (early in the morning) so that samples will have to be ready for transportation by 7.30am at shehas place.

Collected specimens were transported to the Schisto-helminth Control Program research laboratory (located 80kms. from the study site). Individuals who failed to produce specimens on the said day and time were requested to bring their stool samples on the subsequent day. An average of 100 stool samples were examined per day by the principle investigator with the assistance of a qualified and experienced research

laboratory technicians using WHO-Kato Katz technique. Species identification basing on egg characteristics was done. Eggs were counted per gram of faeces and counts were corrected by multiplying the number of eggs obtained with a correction factor of 24 to establish the intensity of infections (Helm. Tec. Kato Katz -manufacturers guides). The intensity of infection was later on classified into light, moderate and heavy intensity infection as per WHO[c] (1987) geohelminth intensity classification as shown in Table A in the appendix B. The same procedure was repeated two weeks after treatment.

2.7 PATIENT TREATMENT

2.7.1: Recruitment

Individuals who were either found to be microfilaraemic or with active clinical disease were then recruited (willingly) for the study and written informed consent obtained. Out of 390 who were microfilaraemic positive only 267 gave their consent and 151 of those with clinical active filaria disease also gave their consent. These 418 were included in both studies but there were dropouts later on.

Consented individuals were interviewed using the Swahili version of the questionnaire, which was designed to collect information on the social demographic features of the respondent, and general clinical examination was done to respondents. There was a separate form for safety information and post treatment parasitological information was recorded in the register book.

2.7.2: RANDOMIZATION PROCEDURES

Since the tested drugs were received unrandomised, drug randomisation had to be done locally basing on patient weight as shown on Table B in the appendix B. This procedure was done by an experienced clinical officer and drugs were coded.

Treatment was provided outside health facilities but were arranged so as to be able to accommodate emergencies, follow up observation and primary management whenever necessary.

Participants were advised not to have taken meals before and two hours post drug administration. All participants took drugs on site.

Participant's allocation to treatment arms was done by tossing a coin. A block system of 6-8 was used. This was done so as to minimise any biases or leakage of information that might influence the outcome. Drug codes were broken when post –treatment parasitological examination was completed.

2.7.3 PATIENT FOLLOW UP

Patient follow up was done smoothly as planned after 6 hours post-drug administration. Further monitoring of side effects (signs and symptoms) was done after 24 hrs, 48 hrs, 72 hrs and 96 hrs and respondents were informed to report on any adverse effects a week post drug administration.

Treatment to patients basing on observed signs or symptoms was rendered. No individual was hospitalised during follow up.

Patients with other clinical ailment were advised and referred to their respective clinics for further expertise management after receiving baseline therapeutic management (i.e. first line management).

2.7.4 ETHICAL CONSIDERATION

Microfilaraemic individuals who were treated and found to be positive at the end of the study were informed and will be followed by the Filaria Control Unit (FCU) for further management. Similarly individuals who remained positive with geohelminth infection will be treated on follow-up. Those individuals with advanced clinical chronic disease e.g. hydrocele were advised to see the DMO who would assist them for further surgical management.

Furthermore individuals who were identified to have been infected with malaria were also treated while pregnant microfilaria positive individuals were advised to seek help at the Filaria Control Unit after delivery.

2.8. DATA ANALYSIS

Data entry was done using a computer. EPI-Info and SPSS (statistical package for social scientists) software programs were used for data analysis. Indices that summarise the

prevalence, intensity and percentage reduction on microfilaria and geohelminth were calculated. The chi-square test was used for testing the differences between proportions (or percentages).

Multivariate analysis of variance was used for the repeated continuos measures to compare the safety levels of the two regimes. The statistical significance was reached when p-value was less than 0.05.

2.9. STUDY LIMITATIONS

1. Participants might have received antihelminth drugs just few days prior to the trial but may have not wanted to reveal it.
2. Some participants did not comply fully with the study requirements as they did drop out in the middle of the study follow up especially during the post treatment parasitological sample collection (for both stool and blood).
3. Reported (subjective) symptoms might have resulted from participants bias so as to seek extra attention or care from the research team. However, this was reduced through indirect verbal cross-examination coupled with physical examination when necessary.

3.0 RESULTS

3.1 Screening (baseline):

A total of two thousand eight hundred and thirty-nine (2839) individuals were screened from the four shehias (areas/villages) for bancroftian filariasis and geohelminth infections. Of these 1635 (57.6%) were females while 1204 (42.4%) were males. The age structure and distribution of the screened population by area of residence (shehia) is shown in Table 1. Those aged between 11 and 20 years of age constituted 28.3% of all the screened population.

Table 1: Distribution of the screened population by age, sex and area of residence (shehia).

Characteristic	Females (n=1635) n (%)	Males (n=1204) n (%)	Total (n=2839) n (%)
Age (years):			
1-10	388(51.1)	372 (48.9)	760 (26.7)
11-20	430 (53.5)	374 (46.5)	804 (28.3)
21-30	209 (71.8)	82(28.2)	291 (10.2)
31-40	250 (74.0)	88(26.0)	338 (11.9)
≥41	358 (55.4)	288(44.6)	646 (22.8)
Total	1635(57.6)	1204(42.4)	2839
Area of residence:			
Kijini	502 (61.0)	321 (39.0)	823 (29.0)
Kajengwa	448 (55.4)	360 (44.6)	808 (28 .0)
Mtende	369 (54.3)	311 (45.7)	680(24.0)
Mzuri	316 (59.8)	212 (40.2)	528 (19.0)

Baseline prevalence of parasitological indices

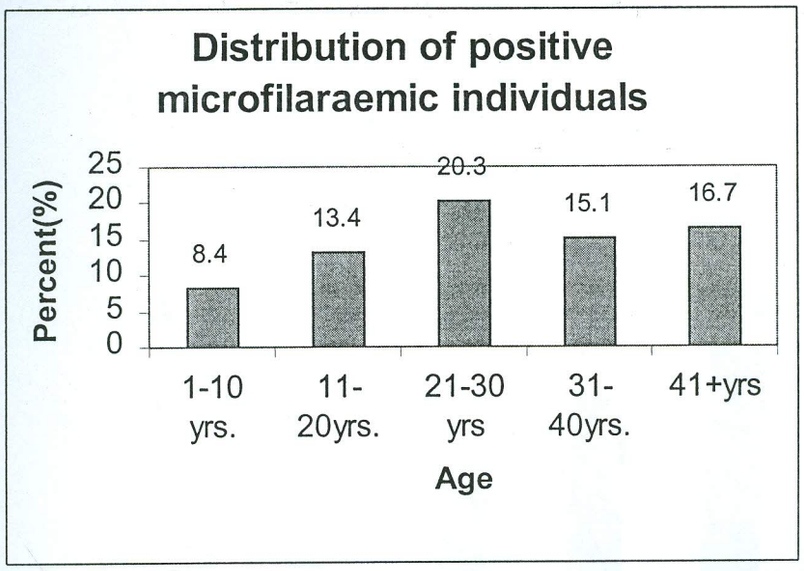
The overall prevalence of microfilaraemia was 13.7%. Prevalence was high in males (15.2%) compared to that of females (12.7%). Microfilaria prevalence was highest in males ageing between 21 and 30 years (28%) compared to females of the same age group (17.2%).However, the overall differences observed in prevalence rates between males and females was not statistically significant (χ^2 =3.58, p = 0.06). This is shown in Table 2.

Table 2: Baseline prevalence of microfilaraemia by age and sex.

Age (years).	Positive microfilaraemic individuals.		
	Females	**Males**	**Total**
	n(%)	**n(%)**	**n(%)**
1-10	29 (7.5)	35 (9.4)	64 (8.4)
11-20	56 (13.0)	52 (13.9)	108 (13.4)
21-30	36 (17.2)	23 (28.0)	59 (20.3)
31-40	36 (14.4)	15 (17.0)	51 (15.1)
≥41	50 (14.0)	58 (20.1)	108 (16.7)
Total	207 (12.7)	183 (15.2)	390

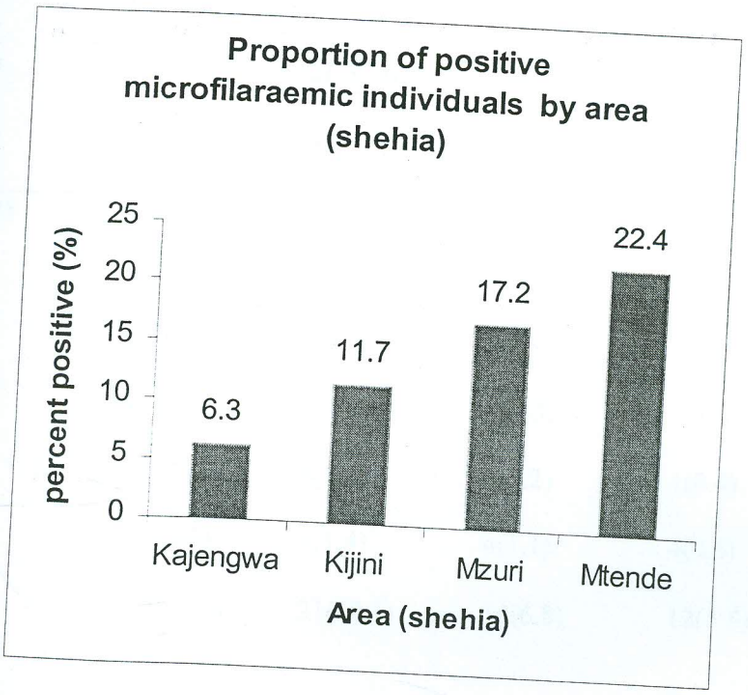
Analysis was done to determine age group differences in prevalence rates of microfilaraemia as shown in Table 2. Microfilaria prevalence was lowest in the age group 1-10 years and highest in the age group 21-30 years (20.3%). Microfilaria prevalence started to decrease (stabilise) as age increases as illustrated in figure 1.

Figure 1. Distribution of microfilaraemic individuals by age.



Further analysis was carried out to determine differences in prevalence rates on microfilaraemia by area of residence. Prevalence was low for Kajengwa (6.3%), and was highest for Mtende (22.4%) as shown in figure 2. The difference observed between the prevalence rates was statistically significant (χ^2 =80.65, p<0.0001).

Figure 2: Prevalence of microfilaria by area (shehia)



Microfilaria density

Analysis was done to quantify microfilaria infection. The highest prevalence was observed in the 1-20 mff/200µl category, which is low. There was no difference in microfilaria density with sex. Out of the 207 positive females 160 (77.3%) had low infection and this was statistically comparable with that in males, 80.3% ($\chi^2 = 1.06$, p=0.30) as shown in Table 3.

Table 3: Distribution of microfilaria density by age and sex

Age (years)	Microfilaria counts /200μl				Total
	1-20mff. n(%)	21-39mff. n(%)	40-59mff. n(%)	≥60mff n(%)	
Females					
1-10	27(7.0)	1(0.3)	1(0.3)	0	29(7.5)
11-20	42(9.8)	6(1.4)	4(0.9)	4(0.9)	56(13.0)
21-30	28(13.4)	3(1.4)	2(1.0)	3(1.4)	36(17.2)
31-40	26(10.4)	6(2.4)	3(1.2)	1(0.4)	36(14.4)
≥41	37(10.3)	5(1.4)	4(1.1)	4(0.8)	50(14.0)
Total	160(77.3)	21(10.1)	14(6.8)	12(5.8)	207
Males					
1-10	26(7.0)	5(1.3)	1(0.3)	3(0.8)	35(9.4)
11-20	44(11.8)	6(1.6)	1(0.3)	1(0.3)	52(13.9)
21-30	16(19.5)	2(2.4)	1(1.2)	4(4.9)	23(28.0)
31-40	14(15.9)	0	0	1(1.1)	15(17.0)
≥41	47(16.3)	4(1.4)	6(2.1)	1(0.3)	58(20.1)
Total	147(80.3)	17(9.3)	9(4.9)	10(5.5)	183

Further analysis was done to quantify microfilaria density with age. The greater proportion of infected individuals were in the 1-20 mff category and this was noted in all age groups. In this category there was a slight increase in proportions of

individuals as age increases from 7% to 15% (from age 1-10 to 21-30 years) and started to decrease thereafter. This is shown in Table 4.

Table 4: Distribution of microfilaria density by age.

Age (years)	Microfilaria counts / 200µl				Total
	1-20mff.	21-39 mff.	40-59mff.	≥60	
1-10	53 (7.0)	6 (0.8)	2 (0.3)	3 (0.4)	64
11-20	86 (10.7)	12 (1.5)	5 (0.6)	5 (0.6)	108
21-30	44 (15.1)	5 (1.7)	3 (1.0)	7 (2.4)	59
31-40	40 (11.8)	6 (1.8)	3(0.9)	2 (0.6)	51
≥41	84 (13.0)	9 (1.4)	10 (1.5)	5 (0.8)	108
Total	307 (78.7)	38 (9.7)	23 (5.9)	22 (5.6)	390

Prevalence of geohelminth infection:

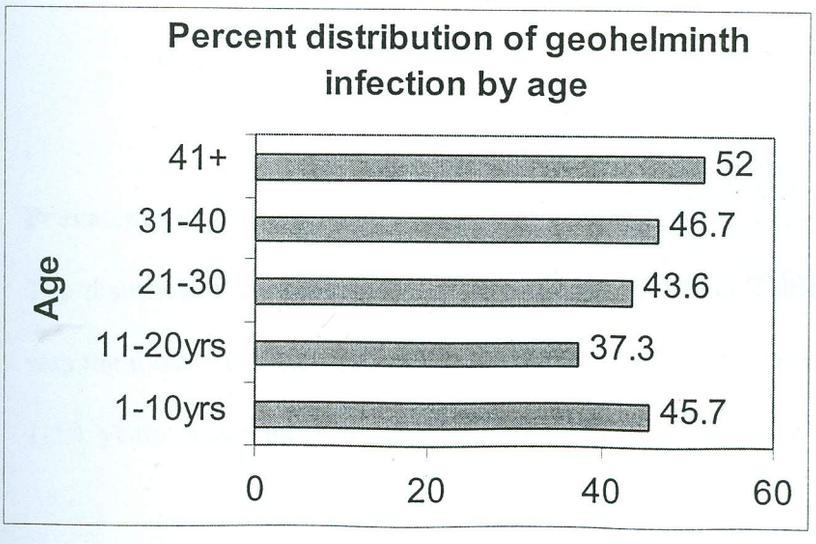
The overall prevalence of geohelminth infection in all the four areas (shehias) was 44.7%. Of these, females were 737 (45.1%) and males were 531 (44.1%). Analysis was done to determine sex differences in prevalence rates. The observed difference in prevalence rates by sex was not statistically significant (χ^2 =0.27, p=0.61) as illustrated in Table 5.

Table 5: Baseline prevalence of geohelminth infection by age and sex.

Age (years).	Females. n(%)	Males n(%)	Total n(%)
1-10	177 (45.6)	170 (45.7)	347 (45.7.)
11-20	166 (38.6)	134 (35.8)	300 (37.3)
21-30	100 (47.8)	27 (32.9)	127 (43.6)
31-40	110 (44.0)	48 (54.5)	158 (46.7)
≥41	184 (51.4)	152 (52.8)	336 (52.0)
Total	737 (45.1)	531 (44.1)	1268 (44.7)

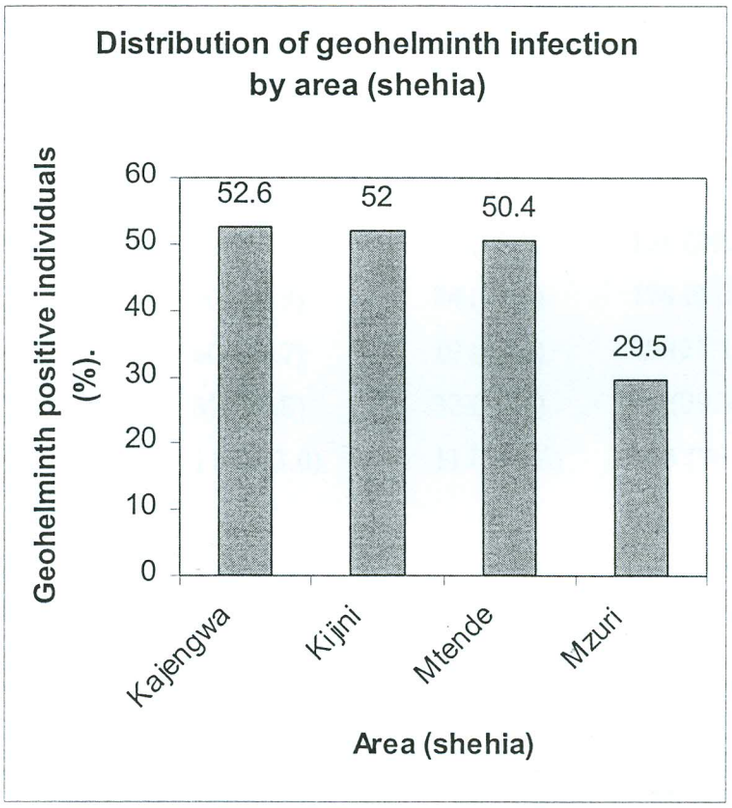
The overall prevalence rates of geohelminth infection by age group was relatively high (45.7%) in the 1-10 years age category, then there was a decline in prevalence in between 11-20 and started to rise thereafter as shown in figure 3.

Figure 3: Distribution of geohelminth infection by age



Analysis was also done to determine if there was any difference in the distribution of prevalence rates of geohelminth by area of residence. Prevalence was lowest at Mzuri (29.5%) and highest at Kajengwa (52.6%) as illustrated in fig.4.

Figure 4 : Distribution of geohelminth by area (shehia)



Prevalence of geohelminth infection by species:

The distribution of geohelminth by species is shown in Table 6. *Trichuris trichiura* was the most prevalent (32.2%) and there was a high prevalence (36%) in age group 1-10 years followed a decrease in prevalence (25.9%) in age group 11-20 and

stabilises thereafter. This was followed by Hookworm (26.2%) which shows increasing prevalence with increasing age (χ^2 trend=52.93, p<0.001) and the last was Ascaris (10.92%) which showed decreasing prevalence with increasing age (χ^2 trend=18.5, p=0.00002).

Table 6: Distribution of geohelminth species by age and sex:

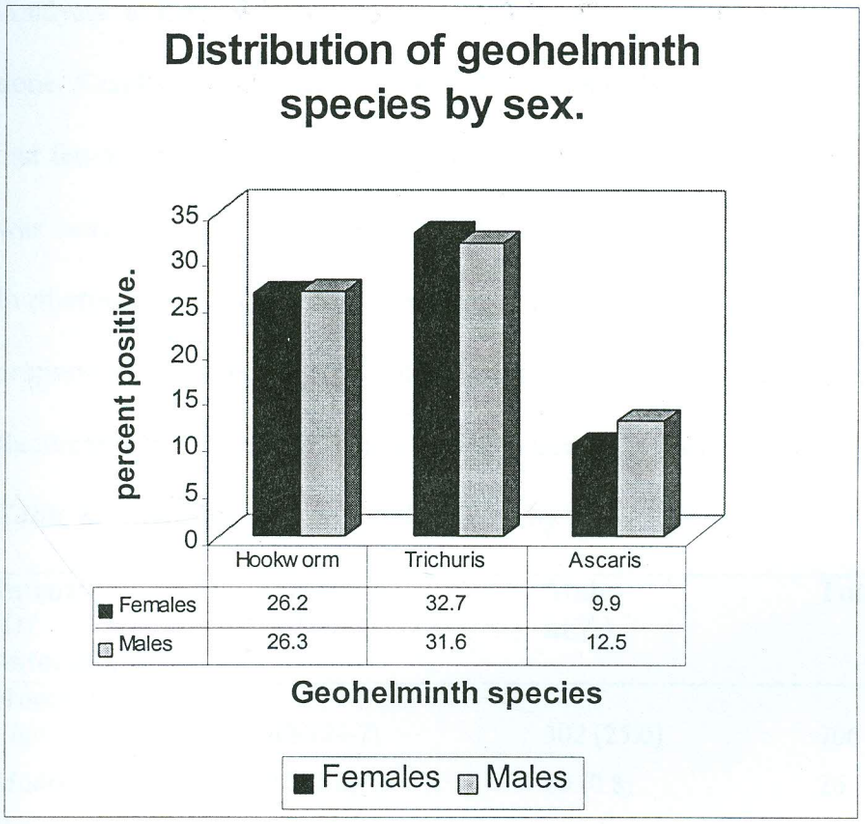
Age (years)	Geohelminth positive individuals		
	Females n(%)	Males N(%)	Total. n(%)
Hookworm			
1-10	93 (24.0)	65 (17.5)	158 (20.8)
11-20	90 (20.9)	84 (22.5)	174 (21.6)
21-30	60 (28.7)	19 (23.2)	79 (27.1)
31-40	67 (26.8)	32 (36.4)	99 (29.3)
≥41	118 (33.0)	117 (40.6)	235 (36.4)
Trichuris			
1-10	135(34.8)	139(37.4)	274 (36.0)
11-20	114 (26.5)	94 (25.1)	208 (25.9)
21-30	81 (38.8)	21 (25.6)	102 (35.1)
31-40	80 (32.0)	29(32.9)	109(32.2)
≥41	124 (34.6)	98 (34.0)	222(34.4)
Ascaris			
1-10	50(12.9)	81(21.8)	131(17.2)
11-20	38 (8.8)	27(7.2)	65(8.1)
21-30	19(9.1)	5(6.1)	24(8.2)
31-40	29 (11.6)	9(10.2)	38(11.2)
≥41	24 (6.7)	28 (9.7)	52(8.1)

Further analysis to quantify geohelminth infections was done for each parasite species by age and sex. Parasite densities were grouped in three categories, namely light, moderate, and heavy intensity infections. Generally for all the three species the highest prevalence was found in the light category. A high number of individuals in all age groups were with low egg counts. Analysis also showed that for all the three species there was no significant difference between males and females as shown in figure 5. The results are summarised in Table 7 and 8.

Table 7: Intensity of geohelminth species by age:

Intensity of infections	**Age (years).**					**Total**
	1-10 n(%)	**11-20 n(%)**	**21-30 n(%)**	**31-40 n(%)**	**≥41 n(%)**	
Hookworm						
Light	150 (19.7)	169 (21.0)	71 (24.4)	96 (28.4)	220 (34)	706
Moderate	8 (1.1)	4 (0.5)	3 (1.0)	3 (0.9)	8 (1.2)	26
Heavy	2 (0.3)	1 (0.1)	3 (1.0)	0	7 (1.0)	13
Trichuris						
Light	243 (32.0)	201 (25.0)	101 (34.7)	104 (30.8)	212 (32.8)	861
Moderate	31 (4.1)	7 (0.9)	1 (0.3)	5 (1.5)	10 (1.5)	54
Ascaris						
Light	103 (13.6)	61 (7.6)	20 (6.9)	37 (10.9)	46 (7.1)	267
Moderate	28 (3.7)	4 (0.5)	4 (1.4)	1 (0.3)	6 (0.9)	43

Figure 5: Distribution of geohelminth species by sex.



Hookworm infection by sex and age:

Results show that 95% of the males and 94.3% the females had low hookworm counts. There was no statistically significant sex difference in hookworm intensity infections (χ^2 = 0.16, p=0.688). However, within this category the proportions of infected individuals increased with increasing age. This trend was noted for both sexes particularly in light intensity infections (χ^2 trend=11.5, p<0.001for females and males χ^2 trend =50.99, p<0.001) .

Trichuris infection by sex and age:

Analysis to determine differences in Trichuris intensity distribution by age and sex was done. Results revealed that a greater proportion of infected individuals in males (94.2%) and females (94%) had light intensity infection. Infection in the high intensity category was zero. High prevalence (36.0%) was noted in the 1-10 year age category. Furthermore, results had also shown that in light intensity infections category the proportions of infected individuals decreases in the second decade followed by a fluctuant increase on prevalence as age increases. This was especially noted in male.

Table 8: Intensity of geohelminth species by sex

Intensity Of infection	Females n(%)	Males n(%)	Total
Hookworm			
Light	404(24.7)	302 (25.0)	706
Moderate	16 (1.0)	10 (0.8)	26
Heavy	8 (0.5)	5(0.4)	13
Trichuris			
Light	502 (30.7)	359 (29.8)	861
Moderate	32(1.9)	22(1.8)	54
Ascaris			
Light	139 (8.5)	128 (10.6)	267
Moderate	21 (1.5)	22 (1.8)	43

Ascaris infection by sex and age:

Further analysis to quantify Ascaris infection was done to determine differences in sex and age distributions. Results showed that high proportions of infected males

(85.3%) and females (86.9%) were in light intensity infection category and that there was no individual with heavy intensity infections. Similarly the results have also shown that in all intensities of infections (light and moderate) the proportions of infected individuals decreases with increasing age (χ^2 trend=18.6, p=0.00002). This was noted in both males and females.

3.2. Prevalence of concomitant infection between Microfilaria and geohelminthes:

Analysis was done to determine concomitant infection between geohelminth and microfilaria. Out of the 2839, 184 (6.48 %) had both parasites.

3.3 DRUG EFFICACY STUDY

Out of three hundred and ninety positive (390) microfilaraemic individuals two hundred and sixty-seven (68.5%) participated in the drug efficacy study. The main reason for the non- participation of the remaining 31.5% (123) was their unavailability. Of these, eight females turned out to be pregnant and were therefore not included. Two elderly males also died just before the commencement of the study. Almost sixty eight percent of these were either petty traders or students who were studying outside the study area and were travelling constantly to and from the study area and could therefore not participate. Another twenty percent were either fisherman or truck/passenger transport drivers and were similarly not available. Only five individuals did not give consent and were therefore not included in the study. The demographic characteristics and parasitological status (i.e.

microfilaraemia and geohelminth infection status) of those individuals who did not participate did not differ from those who did participate (data not shown).

Out of 418 recruited individuals 267 microfilaraemic individuals participated fully in the study while those 151 amicrofilaraemic only 140 individuals showed up for post treatment parasitological evaluation (Eleven participants (2.6%) did not turned up for post- treatment parasitological evaluation). Complete data was thus obtained from 267 microfilaraemic individuals and 140 amicrofilaraemic participants who were randomly divided into the two treatments arm regimes. Analysis on efficacy was done only on 407 participants who completed both parasitological evaluations.

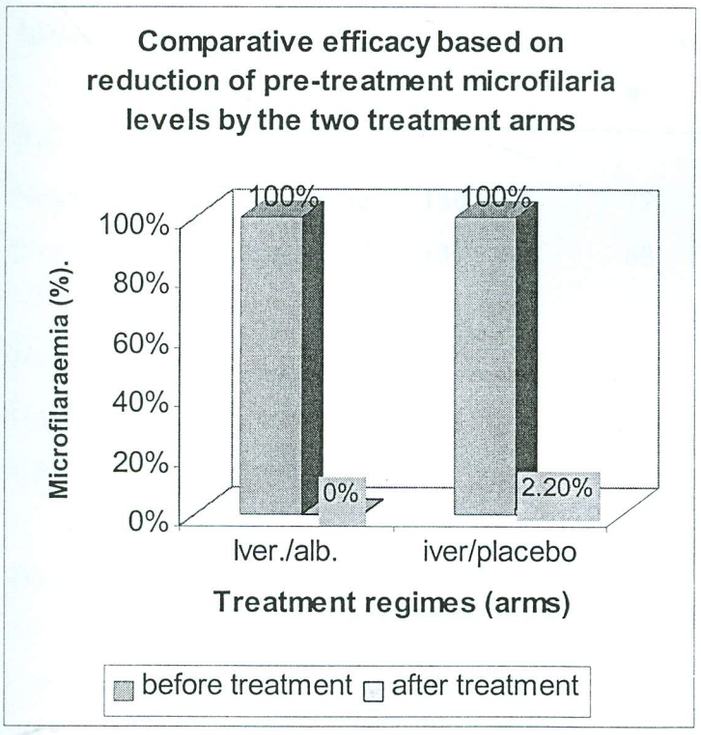
Efficacy of drugs combinations (ivermectin plus albendazole and ivermectin placebo) on reduction of microfilaria prevalence (positive proportions).

Analysis was done to determine differences between the two treatment arms on microfilaraemia prevalence and intensity reduction.

Results showed that out of 130 microfilaria positive individuals in the ivermectin plus albendazole treatment arm there was 100% reduction of the pre- treatment levels two weeks after drug administration, while there was 97.81% (3 microfilaraemic) reduction of the pre-treatment levels in the ivermectin placebo arm. The noted differences in microfilaria prevalence reduction were not statistically significant (Yate's corrected $\chi^2 = 2.23$, $p=0.14$) as shown in figure 6 and Table 9.

On further analysis to determine sex differences on microfilaria prevalence reduction by the two arms, results showed that there was 100% reduction of the pre-treatment microfilaraemia in both females and males in the ivermectin /albendazole treatment arm while the reduction in ivermectin/ placebo was by 97.2% and 98.5% for females and males respectively (as shown in Table 10). The observed differences were not statistically significant (Yates corrected χ^2 =0.30, p=0.58).

Figure 6: Microfilaria percent reduction by the two treatment regimes



Similarly analysis to determine differences in reduction potentials by age was done. Results have shown that in the ivermectin –albendazole treatment arm there was 100% reduction in all age groups and hence no difference in the proportion of

microfilaria reduction was noted with increasing age. However, in the ivermectin – placebo treatment arm there was less reduction in age groups 1-10 years, 85.7 (Yate's corrected χ^2 =7.65, p=0.006) and 95.45% in the age group 21-30 years (Yate's corrected χ^2 =0.51, p=0.475). The observed difference in the age 1-10 years category was statistically significant. This is detailed in Table 11.

Table 9: Distribution of microfilaraemic individuals into two-treatment regimes and percentage reduction.

Allocated drug	Microfilaria status		Total
	Presence	Absence	
	n	n	
Pre –treatment			
Ivermectin with albendazole	130	72	202
Ivermectin with placebo.	137	68	205
Post –treatment			
Ivermectin with albendazole	0	202	202
Ivermectin with placebo.	3	202	205
Percentage reduction			
Ivermectin with albendazole	100%		
Ivermectin with placebo.	97.81%		

Table 10: Percentage reduction of microfilaraemia by the two treatment arms by sex

Allocated drug	Microfilaria positive individuals.	
	Females n	Males n
Pre –treatment		
Ivermectin with albendazole	67	63
Ivermectin with placebo.	72	65
Post –treatment		
Ivermectin with albendazole	0	0
Ivermectin with placebo.	2	1
Percentage reduction		
Ivermectin with albendazole	100%	100%
Ivermectin with placebo.	97.2%	98.5

Table11: Percentage reduction of microfilaraemia by the two treatments arms by age:

Allocated Drug.	Microfilaria positive individuals				
	Age groups (years).				
	1-10	11-20	21-30	31-40	≥41
Pre –treatment					
Ivermectin with albendazole	22	37	21	20	30
Ivermectin placebo	14	34	22	21	46
Post –treatment					
Ivermectin with albendazole	0	0	0	0	0
Ivermectin -placebo	2	0	1	0	0
Percentage reduction					
Ivermectin with albendazole	100%	100%	100%	100%	100%
Ivermectin-placebo	85.7%	100%	95.5%	100%	100%

Efficacy of drug combination (ivermectin plus albendazole and ivermectin with placebo) on microfilaria intensity.

Further analysis was done to determine differences amongst the two treatment arms on reducing microfilaria intensities.

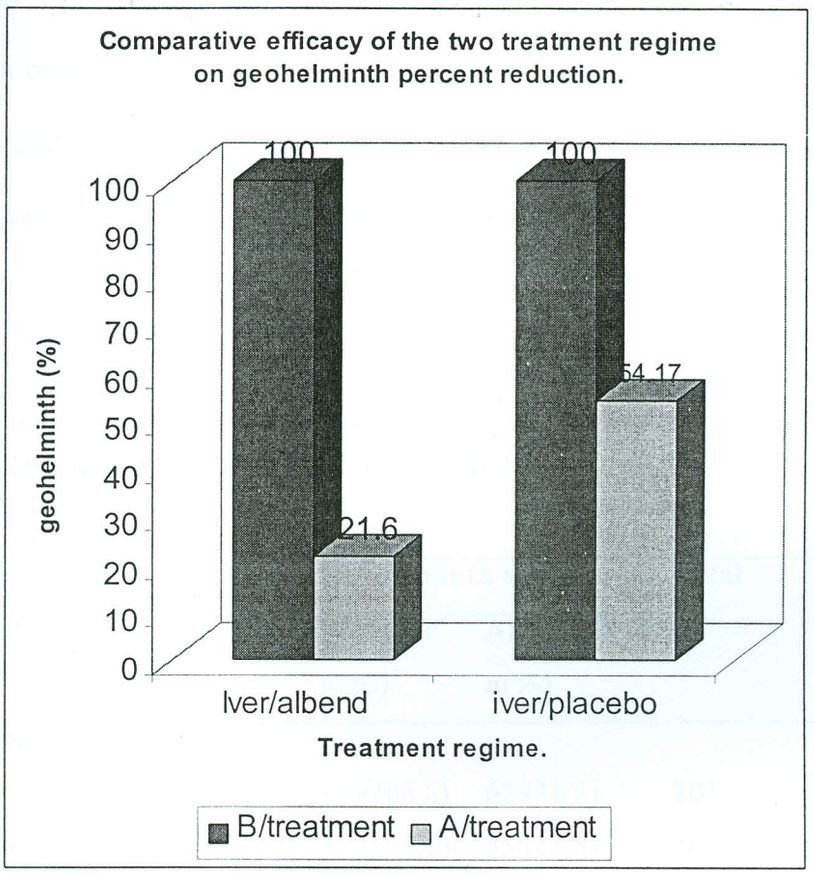
In the three intensity categories (21-39 mff. 40 –59mff. ≥60mff) both treatment arms had equal percentage reduction. However, in the 1-20 microfilaria category there was a difference in the percent reduction. Ivermectin /albendazole regime had 100% reduction of the pre- treatment levels while the ivermectin /placebo had 98.5% reduction. The observed difference on intensity was marginally significant (χ^2 =4.2, p=0.041).

Efficacy of drug combinations (ivermectin plus albendazole and ivermectin with placebo) on reduction of geohelminth prevalence:

Analysis to determine differences on geohelminth prevalence reduction between the two treatment arms (ivermectin /albendazole and ivermectin with placebo) was done.

Results on the overall geohelminth prevalence reduction revealed that ivermectin plus albendazole combination had 78.41% reduction of the pre-treatment levels compared to 45.83% geohelminth reduction by ivermectin placebo arm (figure 7). This marked observed difference on geohelminth reduction was statistically significant as shown in Table 12 (χ^2 =29.44, p<0.0001).

Figure 7: Comparative efficacy on geohelminth percent reduction.



Subsequent analysis to determine sex differences on geohelminth prevalence reduction by individual treatment arm was done. Between the two treatments, there was a significantly higher reduction in both males and females with the ivermectin /albendazole arm (χ^2 =23.41 and 23.22 respectively, p<0.001 in both cases). Furthermore, the percent reduction was slightly higher in males 78.9% than in females 77.9% but this was not statistically significant (χ^2 =0.08,p=0.78) as shown in Table 13.

Analysis was also done to determine differences in geohelminth prevalence reduction by age between the two treatment combinations. Within all age groups there was reduction on geohelminth prevalence and all were statistically significant ($p<0.01$). However, less reduction (60%) in the ivermectin-albendazole arm was observed in 21-30 years category while similar findings were noted in the 11-20 year age category.

Table 12: Geohelminth percent reduction by the drug combination (ivermectin/albendazole and ivermectin placebo)

Allocated drugs	**Geohelminth status**		**Total**
	Presence n(%)	**Absence n(%)**	
Pre- treatment			
Ivermectin with albendazole	139 (68.8)	63 (31.2)	202
Ivermectin with placebo.	120 (58.5)	85 (41.5)	205
Post- treatment			
Ivermectin with albendazole	30 (14.9)	172 85.1)	202
Ivermectin with placebo.	65 (31.7)	140 68.3)	205
Percentage reduction			
Ivermectin with albendazole	78.41%		
Ivermectin with placebo.	45.83%		

Table 13: Geohelminth percentage reduction by two treatments arms by sex

Allocated drugs	Geohelminth positive status	
	Females	**Males**
Pre- treatment		
Ivermectin with albendazole	68	71
Ivermectin with placebo.	68	52
Post- treatment		
Ivermectin with albendazole	15	15
Ivermectin with placebo.	37	28
Percentage reduction		
Ivermectin with albendazole	77.9%	78.9%
Ivermectin with placebo.	45.6%	46.1%

Table 14: Geohelminth percent reduction by the two treatments arms by age.

Allocated Drug.	Geohelminth positive infected individuals				
	Age groups (years).				
	1-10 n(64)	**11-20 n(82)**	**21-30 n(53)**	**31-40 n(66)**	**≥41 n(142)**
Pre –treatment					
Ivermectin with albendazole	29	24	15	22	49
Ivermectin/placebo	19	16	12	19	54
Post –treatment					
Ivermectin with albendazole	5	5	6	3	11
Ivermectin -placebo	9	12	8	12	24
Percentage reduction					
Ivermectin with albendazole	82.8%	79.2%	60%	86.4%	77.6%
Ivermectin-placebo	52.6%	25%	33.3%	36.8%	55.6%

Efficacy of drug combinations (ivermectin plus albendazole and ivermectin with placebo) on geohelminth species.

3.5.1 Hookworm infection.

Analysis to determine differences in hookworm prevalence reduction between the two treatment arms (ivermectin plus albendazole and ivermectin with placebo) was done.

Results show that ivermectin albendazole combination reduced the hookworm prevalence by 75.8% while ivermectin –placebo reduced hookworm by 30.3 % of the pre-treatment levels. This noted difference was statistically significant

(χ^2 =84.52, p< 0.0001) as shown in Table 15.

Further analysis was done to determine differences between the two treatment arms on reduction of hookworm intensities from the pre –treatment levels.

Results showed that both two treatment arms have no difference on hookworm reduction at moderate and heavy intensities infections categories, where reduction in both arms were 100% of the pre-treatment levels. However there were differences in the light intensity category where percent reduction was 73.6% in the ivermectin plus albendazole combination compared to 23.2% reduction of the pre- treatment levels on ivermectin placebo arm. This marked observed difference was statistically significant

(χ^2 = 103.27, p<0.0001) as shown in Table 16.

Table 15: Pre –and post treatment proportions of individuals with specific geohelminth species.

Allocated drug	Proportion of geohelminth species.		
	Hookworm species n (%)	Trichuris infections n (%)	Ascaris infections n (%)
Pre –treatment			
Ivermectin with albendazole	95 (47.0)	95 (47.0)	41 (20.3)
Ivermectin with placebo.	76 (37.1)	87 (42.4)	34(16.6)
Post –treatment			
Ivermectin with albendazole	23 (11.4)	8 (4.0)	2(1.0)
Ivermectin with placebo.	53 (25.9)	21 (10.2)	5 (2.4)
Percentage reduction			
Ivermectin with albendazole	75.8%	91.6%	95.1%
Ivermectin with placebo	30.3%	75.9	85.3%

Table 16: Percentage reduction on hookworm intensity (infection) by the two treatments arms:

Allocated drug	Light intensity infection	Moderate intensity infection	Heavy intensity infection
Pre –treatment:			
Ivermectin with albendazole	87	6	2
Ivermectin with placebo	69	5	2
Post –treatment			
Ivermectin with albendazole	23	0	0
Ivermectin with placebo	53	0	0
Percentage reduction			
Ivermectin with albendazole	73.6%	100%	100%
Ivermectin with placebo.	23.2%	100%	100%

3.5.2 Trichuris infection:

Analysis was done to determine differences between the two treatment arms on reducing the prevalence of trichuris infections.

Results revealed that ivermectin albendazole combination reduced *T. trichiura* infection by 91.6% compared to 75.9% reduction by ivermectin placebo combination of the pre- treatment levels. The observed differences were statistically significant (χ^2 =17.96, p<0.0001) as illustrated in Table 15.

Further analysis was carried out to determine if there were differences on percentage reduction of Trichuris intensity between the two treatment arms.

Results showed that in both levels of Trichuris infections, i.e. light and moderate intensity infection, ivermectin and albendazole combination reduced (from the pre-treatment levels) 90.7% of the light and 100% of the moderate infections respectively, while ivermectin placebo combination had reduced 73% of the light and 92.3% of the moderate intensity infection. The difference on the reduction between the two treatment arms at moderate intensity infection was statistically significant (χ^2= 16.41, p<0.0001). Similarly the noted differences in the light intensity category was also statistically significant (χ^2 =20.76, p<0.0001). This is summarised in Table 17.

Table 17: Percentage reduction on Trichuris intensity infections by the two treatment arms.

Allocated drug	Light intensity infection n	Moderate intensity infection. n
Pre –treatment		
Ivermectin with albendazole	86	9
Ivermectin with placebo.	74	13
Post treatment:		
Ivermectin with albendazole	8	0
Ivermectin placebo.	20	1
Percent reduction		
Ivermectin with albendazole	90.7%	100%
Ivermectin with placebo.	73%	92.3%

ASCARIS INFECTIONS:

Analysis was done to determine differences between the two treatment arms on reduction of prevalence of Ascaris infections.

Results revealed that ivermectin albendazole combination had reduced Ascaris infection by 95.12% (of the pre-treatment levels) compared to the 85.3% reduction by ivermectin placebo combination as shown in Table 15. The noted differences between the two treatment arms were found to be statistically significant (χ^2 = 10.77, p=0.001).

Results on percent reduction potentials of Ascaris intensity showed that at moderate levels of infection the two treatment arms had no difference in percentage reduction where both treatment arms (ivermectin-albendazole and ivermectin –placebo) had 100% reduction. However differences in percentage reductions were noted in light intensity infections where ivermectin-albendazole combination had 93.5% reduction of the pre-treatment levels of Ascaris infection compared to 78.3% of the ivermectin placebo combinations. The observed difference was statistically significant (χ^2 =20.04, p<0.0001). This is shown in Table 18.

Table 18: Percentage reduction of the two treatments arms on Ascaris intensity.

Allocated drug	**Light intensity infection n**	**Moderate intensity infection n**
Pre- treatment		
Ivermectin with albendazole	31	10
Ivermectin with placebo.	23	11
Post -treatment		
Ivermectin with albendazole	2	0
Ivermectin with placebo.	5	0
Percentage reduction		
Ivermectin with albendazole.	93.5%	100%
Ivermectin with placebo.	78.3%	100%

3.4. SAFETY STUDY:

Four hundred and eighteen (418) of the recruited individuals were randomly treated by ivermectin plus albendazole combination and ivermectin with placebo allocation. Females constituted 52.2% of this study group (which is the same cohort with that of the drug efficacy study) with a population mean weight of 44.92 kgs (SD± 16.31). Dosage on drug administered depended on individual body weight. Individuals weighing 45-64 kgs. constituted 49.5% of the study population. Distribution of weight is shown in Table C in the appendix B.

Participant's follow-up was done at 6 hours, 24 hours, 48 hours, 72 hours and 96 hours after the drug administration. Monitoring for the development of adverse effects was done. Three (0.72%) of those recruited were not available for the study during the 96 hours follow-up. The noted signs and symptoms were then analysed for each treatment arm. At each point of follow-up (6, 24, 48, 72 and 96 hours) symptoms and signs were compared to their correspondent proportions at baseline for those that had values greater than zero. When the prevalence was zero comparison was done with six hours record.

3.4.1 Symptoms:

Analysis revealed that symptoms started to be reported from six hours post treatment and rose markedly between 24 hours and 48 hours. However these started to decline with time from 72 hours to 96 hours. The proportions of individuals who developed symptoms were then grouped into those ranging from 1.0 to 3.9% and those with values

greater than 4%. Further statistical analysis was only carried out for those reported symptoms that had affected more than 4% of the study population. Symptoms were reported on the basis of the treatment arm and the following symptoms were reported to have prevalence between 1-3.9%:

Reported symptoms in the Ivermectin plus albendazole treatment regime

- **At six hours post treatment**: participants complained to have started observing increased palpitations.
- **At 24 hours post-treatment**: reported symptoms included anorexia, light headedness, epigastric pain, testicular tenderness, constipation, vomiting, increased appetite, abdominal discomfort, facial swelling, insomnia, palpitations and visible urticuria.
- **At 48 hours post treatment**: reported symptoms included anorexia, light-headedness, testicular tenderness, constipation, vomiting, abdominal discomfort, palpitations, and excessive urination.
- **At 72 hours post treatment**: reported symptoms included light-headedness and palpitations.

Reported symptoms in the Ivermectin with placebo treatment regime:

- **At six hours post –treatment**: light -headedness, vomiting, and lethargy.

- **At 24 hours post –treatment:** anorexia, light-headedness, epigastric pain, constipation, abdominal discomfort, insomnia, lethargy, visible urticuria and increased sexual desire.
- **At 48 hours post –treatment:** reported symptoms included: light - headedness, constipation, abdominal discomfort and palpitations.
- **At 72 hours post –treatment:** reported symptoms included –light headedness, palpitations.

3.5. OBSERVED SYMPTOMS WITH TIME

Within the drug observations

Analysis to determine the significance of symptoms occurrence with time was done for each treatment regime (using either baseline or 6 hours post –treatment information). Comparison of symptoms was done for each drug. The noted symptoms included: fever, headache, body pain, cough, chills, athralgia, nausea, abdominal pain, dizziness, chest pain, loose stool, itching and wheezing.

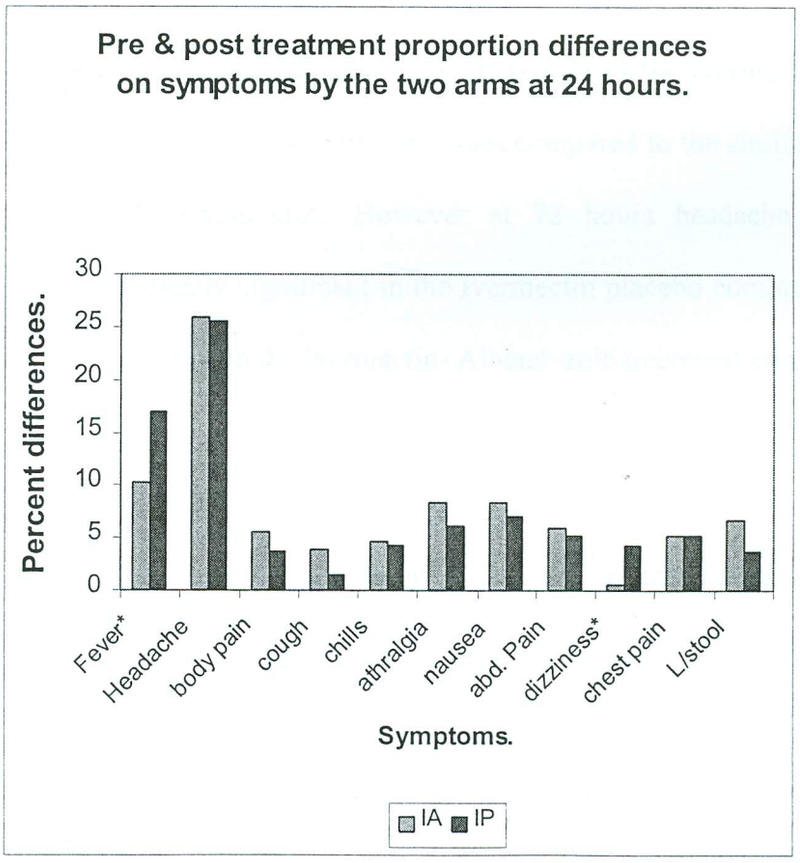
At twenty four hours:

The following symptoms were reported and were significant when compared to the baseline prevalence for each treatment arm and were thus associated to allocated drug combinations.

Fever was significantly associated with Ivermectin-albendazole regime (p=0.000) and also to Ivermectin placebo combination (p=0.000). Headache was also significantly associated with Ivermectin Albendazole regime (p=0.000) and with Ivermectin and

placebo regime (p=0.000). Other symptoms with significant prevalence in ivermectin – albendazole regime includes; Chills (p=0.035), chest pain (p=0.007) and itching (p=0.012). The same symptoms were also noted in the ivermectin placebo regime with significant values i.e. chills (p=0.031), Chest pain (p=0.003) and Itching (p=0.039).

Figure 8: Pre- and post treatment proportion differences between ivermectin Albendazole (IA) and Ivermectin placebo (IP) 24 hours after drug administrations.



*p<0.05

In addition results also showed that there were some symptom, which were only significant for one treatment regime as shown below:

Ivermectin plus Albendazole combination was associated with Athralgia which was prevalently observed (P=0.001), similar observations were noted for abdominal pain (p=0.017) and loose stool (p=0.001). However, dizziness (p=0.049) was highly observed at 24 hours in the ivermectin- placebo treatment arm. Other symptoms recorded were not significant as shown in the Table 19 and in figure 8.

At 48 hours headache was highly prevalent (p=0.003) in the ivermectin –albendazole combination and had statistical significant values compared to the similar observation in ivermectin -placebo combination. However at 72 hours headache (p=0.001) and wheezing were statistically significant in the Ivermectin placebo combination compared to the similar observations in the Ivermectin- Albendazole treatment arm.

Between drugs observations.

Further analysis was done to determine differences in association of the reported symptoms between the two treatment arms.

Result have shown that there were marked difference in reported symptoms between the two treatment arms in fever. However, the values were low for Ivermectin –Albendazole (IA) combination compared to Ivermectin –placebo (IP) treatment arm, revealing that IA caused less fever when compared to IP arm. The observed difference was statistically

significant (χ^2=4.01, p=0.045). Similarly differences were noted in headache (after 48 hours) where more headache was reported in IA arm then in IP arm. The observed differences in reported headache was statistically significant (χ^2=6.35, p=0.012).

Analysis was also done to observe differences and association of treatment arms to dizziness. High associations were noted in IP combination than in IA combination. The noted differences were statistically significant (χ^2=4.78, p=0.03). Results are shown in Table 20.

3.6: VITAL SIGNS:

Analysis on the recorded signs was done for temperature in all individuals, while pulse, respiratory, systolic and diastolic blood pressure were analysed only to those individuals aged 12 years and above. The general presentation of signs followed similar course as to those observed in symptoms.

Multivariate analysis of variances showed that the course of events as expressed by signs within each treatment arm was statistically significant (p<0.0001) in all the five analysed signs as shown in Table 21. However, when the two treatment arms were compared respiratory rate was the only sign which had statistical significant observation (p=0.033). This is shown in Table 22.

Analysis of variance on temperature had shown that within each treatment arm there was a gradual rise in temperature from 6 hours to twenty-four hours and followed by a

gradual decrease from 48 hours on wards. These observed trends in both treatment arms were statistically significant (p=0.000). Similar presentations on signs by both treatment arms were also noted in analysis of pulse rate; respiratory rate and all were statistically significant (p=0.000).

Further analysis on blood pressure parameters, systolic and diastolic, showed that in both treatment regimes the mean values for systolic blood pressure decreased from 129.5-mm hg at baseline to 120.6-mm hg (after 96 hours) in the ivermectin albendazole arm while in the ivermectin –placebo arm reduction was from 129.6 to 119.9mm hg. Similar results were found in diastolic blood pressure where in the ivermectin albendazole arm there was a decrease from 81.3-mm hg at baseline to 79.5-mm hg while in the ivermectin placebo arm the reduction was from 81.8mm hg at baseline to 77.4-mm hg after 96 hours. This gradual decrease continued with time (for the observation period) and was statistically significant in each treatment arm (p=0.000).

Further analysis of variances showed that respiratory rate in the Ivermectin – Albendazole combination was slightly higher than that observed in ivermectin placebo combination. This observed difference was statistically significant (p=0.033).

Table 19: Proportion of reported symptoms with values greater than 4%.
1. Within drug testing:

Symptoms	Baseline hour	Compared time	Drug used & Mcnemar's p-values	
			Ivermectin-albendazole	Ivermectin-placebo.
Fever	6hrs.	24hrs.	0.000	0.000
Headache	Day 0	6hrs	0.503	0.701
		24.hrs.	0.000	0.000
		48hrs.	0.003	0.324
		72hrs.	0.648	0.001
Body pain	Day 0	24hrs.	0.061	0.280
Cough	Day 0	24hrs	0.229	0.678
Chills	Day 0	24 hrs.	0.035	0.031
Athralgia	Day 0	24hrs	0.001	0.060
Nausea	6hrs.	24hrs.	0.006	0.003
		48hrs	0.503	0.189
Abdominal pain	Day 0	24hrs.	0.017	0.052
		48hrs	0.581	1.000
Dizziness	Day 0	6hrs.	0.210	0.754
		24hrs.	1.00	0.049
Chest pain	Day 0	24hrs.	0.007	0.003
Loose stool	6hrs.	24hrs.	0.001	0.096
		48hrs.	0.002	0.143
Itching	Day 0	24hrs.	0.012	0.039
Wheezing	Day 0	24hrs.	0.125	0.039

Table 20: Between drug group testing:

Symptoms.	Compared time.	Drug used.	Post treatment Proportions	Pre treatment proportions	Differences	Chi-square and p-values.
Fever	6 &24 hr	IA	10.7	0.5	10.2	χ^2 –4.01
		IP	17.9	0.9	17.0	p-0.045
Headache	0 &24hr	IA	32.2	6.3	25.9	*
		IP	34.4	8.9	25.5	
	0&48hrs.	IA	15.6	6.3	9.3	χ^2= 6.35
		IP	12.3	8.9	3.4	P=0.012
Body pain	0 &24hr	IA	9.8	4.4	5.5	*
		IP	12.7	8.9	3.8	
Cough	0 &24hr	IA	11.2	7.3	3.9	*
		IP	7.1	5.6	1.5	
Chills	0 & 24hr	IA	6.6	1.9	4.7	*
		IP	6.3	2.0	4.3	
Athralgia	0 & 24hr	IA	12.7	4.4	8.3	*
		IP	15.1	8.9	6.2	
Nausea	6 &24 hr	IA	14.6	6.3	8.3	*
		IP	11.3	4.2	7.1	
Abdomin	0 & 24hr	IA	8.8	2.9	5.9	*
al pain		IP	9.0	3.8	5.2	
Dizziness	0 &6hr	IA	5.4	2.4	3	*
		IP	2.8	1.9	0.9	
	0 & 24hr	IA	2.9	2.4	0.5	χ^2=4.78
		IP	6.1	1.9	4.2	P=0.029
Chest	0 &24hr	IA	6.3	1.0	5.3	*
pain		IP	5.7	0.5	5.2	
Loose	6 &24hr	IA	7.8	1.0	6.8	*
stool		IP	6.1	2.3	3.8	
	6 &48 h	IA	7.3	1.0	6.3	*
		IP	5.7	2.3	3.4	
Itching	0 &24hr	IA	6.3	2.0	4.3	*
		IP	4.7	0.9	3.8	
Wheezing	0 &24 hr	IA	2.9	0.5	2.4	*
		IP	4.2	0.9	3.3	

KEY: IA-Ivermectin/albendazole, **IP**- Ivermectin/placebo, *p>0.05.

Table 21: Observed signs in safety study:

Vital signs.	Time in hours.	Ivermectin/albendazole arm.		Ivermectin/Placebo arm.	
		mean	SD	Mean	SD
Temperature	Day 0	36.2	0.5	36.2	0.6
	6hrs.	36.4	0.5	36.4	0.5
	24hrs.	36.5	0.7	36.4	2.6
	48hrs.	36.2	0.5	36.0	2.54
	72hrs.	36.0	0.5	35.9	2.52
	96hrs.	35.8	2.55	35.6	3.5
Pulse rate.	Day 0	75.3	7.9	75.0	8.7
	6hrs.	76.4	9.6	75.9	8.9
	24hrs	76.9	9.2	76.6	10.7
	48hrs.	74.5	8.2	75.2	9.7
	72hrs.	74.01	7.0	73.9	9.5
	96 hrs.	73.3	6.5	71.5	10.2
Respiratory rate	Day 0	15.8	2.6	15.8	2.7
	6hrs.	16.4	3.0	17.1	4.0
	24hrs.	16.0	2.6	15.9	3.3
	48 hrs.	15.9	2.3	15.7	2.5
	72hrs.	15.7	2.3	15.7	2.6
	96 hrs.	15.9	2.5	15.8	2.8
Systolic BP	Day 0	129.5	28.6	129.6	28.1
	6hrs.	128.5	27.0	127.5	25.4
	24hrs.	123.2	22.8	123.1	25.8
	48hrs.	121.0	20.6	121.6	23.8
	72hrs.	121.3	20.3	121.4	21.9
	96hrs.	120.6	20.2	119.9	23.4
Diastolic BP	Day 0	81.3	17.4	81.8	15.0
	6hrs.	80.4	16.5	81.0	14.9
	24hrs.	77.6	16.4	78.3	15.9
	48hrs.	79.0	14.4	78.2	14.2
	72hrs.	79.0	12.7	77.9	13.0
	96hrs.	79.5	13.7	77.4	13.9

Table 22: Degree of significance within the drugs and between the treatment combinations

Signs	Evaluated sample	Within the drug significance levels	Between the drugs significance levels.
Temperature	418	0.000	0.871
Pulse rate	343	0.000	0.347
Respiratory rate	343	0.000	0.033
Systolic BP	343	0.000	0.975
Diastolic BP	343	0.000	0.241

4.0 Discussions:

Baseline information:

This was a community based study involving night blood sample collection (twice, before and after treatment) and follow up for adverse effects after treatment. Despite this the community participation was high in all stages of the investigations with few dropouts (0.72% in safety and 2.9% in efficacy studies respectively). This could possibly be due to previous mass treatment campaign together with other filaria control activities especially health information messages which could have motivated the community. The studied community comprised of homogenous participants of both sexes and age groups. However the 2-4 years age group was least represented (4.6%).

The overall prevalence rate of bancroftian filariasis found in the south district was 13.7%. This prevalence rate is lower than those found in other studies. Mansfield-Aders (1927), found the prevalence of bancroftian filariasis in rural Zanzibar to be 26.3%. . In 1930 McCarthy reported the prevalence of 16.6% while Kilama et. al in 1976 found the prevalence to be 16%. Furthermore in 1988 the prevalence of bancroftian filariasis (before the mass treatment with DEC) at Makunduchi was 49.5% . However, in 1989 at Makunduchi, the prevalence (after treatment) had been reduced to 10.0% (Maxwell et. al, 1999).

It was expected that the microfilaria prevalence would have been much higher after the mass treatment was stopped more than five years now. However in the control program

by Maxwell, apart from mass treatment with DEC, they also applied vector control measures using polystyrene beads. They covered all the potentials breeding sites like pit latrines, cesspits which were the main mosquito breeding sites (Maxwell et. al, 1999). This perhaps could explain the low prevalence rate of microfilaria we found and in addition rural urban migration has been on the increase and thus could possibly contribute as a stabilising factor.

This study also found the overall microfilaria prevalence to be lower in females (12.7%) than in males (15.2%). This study therefore concurs with the study done in Lindi by Mwita (1996) where the prevalence rate in males was 13.3% compared to 11.1% in females. Similarly a study in Tanga by Simonsen et. al. (1995) found the prevalence to be high in males than in females. However in all these two studies the findings indicated that the differences by sex were of no statistical significance.

However, when age was considered, males aged 21-30 years were found to have high microfilaria prevalence in comparison to females in the same age category. A possible explanation for this difference may be due to the higher exposure of males to infective mosquito bites especially during community gatherings in the evenings.

Furthermore, results showed an increasing pattern of microfilaria prevalence with increasing age and later on levels off (plateaus) in later ages. A possible explanation could be as age increases also the exposure increases i.e. increased occupational and social exposures. In addition, passive immunity from the mother to the under fives

could possibly prevent (in endemic areas the young age groups from filariasis). Simonsen et. al. (1995) reported similar observations.

The microfilaria prevalence in the 1-10 years category could have resulted from the strong transmission pressure within the household in the peri-domestic vicinity where human carriers are in high proportions. Das et. al (1997) forwarded similar suggestions on the fact that parental infection might be an important risk factor together with household exposures.

The microfilaria prevalence showed a wide variation in the four areas, whereas Kajengwa had low prevalence (6.3%), Mtende had the highest, 22.4%. This observed difference could possibly be due to the fact that Makunduchi and its adjacent areas were formerly exposed to the mass treatment campaigns with DEC. In addition vector control activities using polystyrene beads was also applied in these areas whereas Mtende was not part of the control project.

In this study, a higher proportion (78.7%) of infected subjects was found to have low microfilaria density of 1-20 mff. While the remaining proportions had microfilaria density of moderate to severe levels. Out of those individuals with moderate and higher intensities 44.7% were originating from Mtende. A possible explanation for observing larger proportions in the 1-20 mff. category might be due to the fact that the former antifilaria campaigns (using DEC or polystyrene beads interventions) did not include Mtende.

The study also found out that there were small differences in microfilaria densities at this low intensity category by sex, but the differences in percentage by sex on proportion of individuals with 1-20 mff. intensity category was of no statistical significance. This concurs with the findings in Lindi by Mwita (1996) and by Simmonsen et. al. (1995) in Tanga.

Results of this study have shown that the overall geohelminth prevalence in the south district was 44.7%. Previous studies in other areas of Zanzibar have reported almost twice the prevalence observed in this study. The Ministry of Health report - Zanzibar (WHO[g], 1996) showed that in a school –based survey of 54 schools in Unguja, 85% of pupils were found to have geohelminthes infections. In addition other studies have noted similar observations as those detailed in the MOH-report,1994. Marti et. al in 1996, found out that only 1.1% (14/1204) of the examined children were free of intestinal geohelminth infection and Albonico et. al (1997) found the overall geohelminth prevalence to be 87.4%. However, in all these studies the sampled population was from the school children with an age range from 9-22 years and this could be the reason for the high prevalence they found. This study in comparison has recorded lower geohelminth prevalence rate. A possible explanation for this lower prevalence rate in this area could possibly be due to the nature of soil which is not homogenous as most parts are stony (rocky) and dry. However, these dry areas do interchange with clay and sand especially in agricultural and residential areas. Furthermore the school –health

based deworming campaigns could have contributed to this low observed geohelminth prevalence rate. This noted dilution on geohelminth prevalence rate might have also been due to the fact that low infection load and thus the transmission pressures in dry areas are low when compared with areas of high moistures.

The results also show that geohelminth infection in both sexes to be similar and that the observed difference was of no statistical significance. Furthermore, the overall prevalence rates were found to increase with increasing age . A possible explanation might be due to increase exposures in occupational activities such as agriculture, which increases the risk of infection. In addition the overall geohelminth infection is highest in the low-density category.

The prevalence of Trichuris infection was found to be higher (32.2%) than those observed for hookworm and Ascaris. This relatively high prevalence of Trichuris was also reported by Pampiglione et. al (1987) in Pemba where a prevalence of 87.9% was reported. The probable reason attributed to this high infection includes the high soil moisture and the annual rain distribution patterns. Also Trichuris infection is more resistant to routine chemotherapy. Albonico et. al (1994) in the mebendazole efficacy study in Pemba reported the lower cure rates of 25.6% for trichuris, however the noted egg reduction was 47%. Similar observations were found by Norhayati et. al. (1997) and by Ismail et. al, 1998.

Furthermore, results have shown the lower age category to have high prevalence of trichuris infection. This could be due to the fact that the younger age category are unaware of the hygiene practices and were highly exposed within their peri domestic areas. However in later age groups the prevalence were relatively similar (refer Table 6). Demographic information of this population had shown that about 27.5% the households use wells as their source of domestic water supply. Issues on water storage and latrine use might be contributory to this reported high infection by Trichuris.

When infection densities by area of residence was considered 43.6% of those infected were from Kajengwa where 92.3% of the population uses wells as their source of domestic water (figure 9 in appendix C) . Trichuris infection densities were limited between light and moderate intensity categories and larger proportions were found in the light intensity infections. These were of no significant differences in trichuris infection when age and sex were considered. This could probably be due to the facts that they were equally exposed. Tarimo (1999) reported similar observation in Temeke District.

The second geohelminth specie to be prevalent was hookworm infection (26.2%). The prevalence is relatively lower than expected possibly due to the on going deworming activities in the community. Furthermore results show that the proportion of hookworm infected individuals increased with increasing age in both sexes. This observed trend by age might be due to the increased occupational exposure, which increases with age. About 60.5% of these individuals in this community are peasant hence have increased risks of being exposed to hookworm infections.

Prevalence of hookworm infection has been shown to differ by area. Prevalence was high in areas with sandy soil or those, which are along the coastal areas. Prevalence was high for Kijini (31.7%) and Mtende (29.7%) where the nature of soil is relatively sandy. Sandy soil provides ideal condition for the rapid development and migration of infective stage larvae.

The prevalence rates of Ascaris infection was lowest (10.9%). As for Trichuris infection, the greater proportion of infected individuals 85.3% males and 86.9% females were in the light intensity category with no sex differences. The results also indicate the pattern of decreasing proportions of infected individuals with increasing age. This could possibly be due to the human behaviour pattern. Tarimo (1999) in Temeke noted similar observation of decreased infection by ascaris with increasing age. In addition the nature of soil may facilitate the transmission of this specie resulting in differences of prevalence by geographical area. Mtende and Mzuri being just along the southern coast have much lower prevalence of Ascaris infection (figure 10 in appendix C) than those observed at Kajengwa (18.3%). This suggests that soil pH (salinity) might not favour the development of Ascaris. Furthermore the common source of domestic water (e.g. contaminated well) may perhaps contribute to the noted higher prevalence of Ascaris infection.

Previous studies have not looked at the co-infection of microfilaria and geohelminth. Both the infections in this area are endemic and we expected a higher proportion of

people would have both these infections. May be the mass chemotherapy used in the past could account for the low co-infection prevalence. This is especially true for microfilaria because multiple infective mosquito bites are needed to lead to infection with adult male and female. Also the incubation period is relatively long.

Drug efficacy:
The primary aim of this study was to evaluate the efficacy of drug combinations. This was done at two levels. First, the efficacy against prevalence of microfilaraemia and microfilaraemia density. Secondly, the efficacy to reduce the prevalence of geohelminth infections and their load. The same cohort was used to evaluate all these levels and was also used to determine the safety of the drugs.

The percent reduction on microfilaraemia prevalence was higher in the ivermectin – albendazole regime (100%) while the reduction in ivermectin placebo combination was slightly lower. However the differences observed between these two treatment regimes were of no statistical significance. The findings of this study differ from those noted by Kar et. al 1993 (with the sample of sixty males with high-density microfilaraemia) where only 77% of those in the ivermectin treatment arm became amicrofilaraemic two weeks after treatment. Individuals in the Kar et. al (1993) study was later on followed at the third and sixth month of treatment and there was a rise of microfilaria geometric means. This observed difference could have resulted from the differences in the microfilaria densities, which were probably high in the Kar et. al (1993) study. A possible explanation for the noted non-significant observations in between the two

treatment regimes could have been due to the fact that the post treatment evaluation was done two weeks after treatment.

With such short duration the macrofilaricidal and static impact of albendazole on adult worms may have not yet been established. Probably at this stage, the major observed impact might have resulted only from the ivermectin component, which might have temporarily incapacitated the adult worm thus minimise the amount of sheded microfilaria or only the circulating microfilaria were cleared. This then impedes the chances of drawing immediate inferences. In other studies evaluations were conducted at either three or six months after treatment.

At this point of evaluation, the study had found that there was similar prevalence reduction in both sexes. Only in the age 1-10 years the two treatment arms had significant difference. Hormonal differences and host defence system differs as age increases. These observed differences in percent by each treatment arm were not statistically significant.

At higher microfilaria levels (>21mff./200µl), both treatment arms had 100% reduction of their pre-treatment levels. In addition individuals in this category constituted a lesser proportion of the infected individuals. This perhaps could explain the high clearance potentials at moderate and higher intensity levels.

The overall geohelminth (based on egg count) reduction was found to be higher in the ivermectin –albendazole combination (78.4%) whereas the ivermectin –placebo arm had 45.8% percent reduction. The observed differences on the geohelminth prevalence reductions was statistically significant. This indicates that the ivermectin –albendazole combination to be more efficacious than the ivermectin–placebo combination on reducing the prevalence of geohelminth.

Further observation has shown that despite differences in percent reduction by individual treatment regime, there was no influence of sex in the reduction of geohelminth infections. The observed difference was of no statistical significance.

When age was considered, it was found that the noted difference between the two treatment regimes at different age categories were of no statistical significance. In addition the study has also shown that in the ivermectin-placebo arm there was a low reduction in the 21-30-age category while in the ivermectin placebo category the lowest reduction was in the 11-20-age category. This could possibly be due to infection with multiple geohelminth species. Similarly relatively higher reduction were noted in higher age groups. This observed differences could perhaps be due to other host factors such as immune status (host defence mechanism) which might have assisted in the clearance of geohelminth infections.

In addition, the results have also shown that the ivermectin –albendazole combination to have higher geohelminth prevalence reduction on each species than the reduction observed in the ivermectin –placebo regimes.

The ivermectin –albendazole treatment combination had higher reduction on the prevalence of Hookworm, Trichuris and Ascaris respectively. These observations differ from those done by Beach et.al in Haiti (1999) where highest reduction was observed in Trichuris infection.

A study by Marti et. al. (1996) in Zanzibar showed that ivermectin alone did not reduce hookworm parasitoses, but had impact on ascaris and trichuris infections. This present study has observed similar findings. The ineffectiveness of Ivermectin on Hookworm could possibly be due to the fact that the drug has mild to no effect on adult worm (especially on ovulation/egg production). Similar observations have also been reported by Richards et. al (1995). However, this present study had revealed a marked reduction in hookworm followed by trichuris and ascaris in the Ivermectin–Albendazole combination. This noted reduction could be attributed to the synergistic effects of albendazole combination. In hookworm endemic areas the association of iron deficiency anaemia has been established (Stoltzfus et. al 1998) and iron deficiency anaemia is a major public health problem. With such background the combination treatment regime if effectively used might address this problem significantly and perhaps reduces iron deficiency anaemia associated with hookworm infection. However, this study was not designed to evaluate the impact on anaemia. In addition the study by Beach et. al (1999)

found out that the combined therapy had resulted in significantly greater gains in height (in hookworm – infected children) and weight (in the trichuris infected children) when compared to the placebo arm.

Furthermore, this study has shown that the ivermectin –albendazole combination treatment arm to be more efficacious in reducing the load in all the three species. At moderate and higher intensity infection both treatment arms had equal reduction on the load of infection. This was especially observed in Ascaris and Hookworm infection where there was 100% reduction at moderate and high intensity infections. In addition the ivermectin albendazole combination had 100% reduction while the ivermectin-placebo regime had 92.3% reduction of the Trichuris infections at moderate intensity infection category.

The study have also found out that those individuals with moderate and high parasite load in the ivermectin-albendazole treatment arm at post-treatment two weeks evaluation were still positive but with lighter infection. This change of status from heavy to light infection was more marked in the ivermectin-albendazole combination. These reductions at higher and moderate intensities are probably due to the immediate synergistic (static and cidal) effects of both drugs to adult worm resulting in individuals to have lighter infections. This has public health implication since disease due to helminths are strongly associated with the intensity of parasite; hence probably periodic treatment may have more complimentary effects.

In general, despite the short term post treatment evaluation there was substantial efficacy by the drug combination on the secondary outcome compared to the primary outcome i.e. there was marked difference in reduction of geohelminth (32.6%) while the reduction on microfilaria was only 2.2%.

Drug safety:

The primary aim of the safety component of this study was to observe differences of reported signs and symptoms in between the two treatment regimes.

Results on safety have also found that in general side effects were reported from six hours after the institution of treatment (in both two-treatment arms) and peaked between 24 and 48 hours. However, there was a general decline in magnitude of these side effects from 72 hours onwards and were almost over by 96 hours. Most of these side effects were manageable by using basic Primary Health Care Unit drugs like paracetamol, hydrocortisone and antihistamines etc. Prevalence rates for side effects ranged from zero in some symptoms to 34.4% in the two treatment arms. Majorities of these symptoms were in the mild and moderate category and were later on (during analysis) considered as one.

The patterns of symptoms presentations observed in this study are similar to those observed by Kar et. al. (1993) where similar dosage (200-microgram/kg.body weight) was used and found that the presentation of adverse effects were similar to all patients. In addition, Kar et. al. (1993), also noted that the intensities of these reactions peaked

between 24-48 hours and started to decline thereafter. Similar observations were noted by Nguyen et. al (1996) where much higher dosage was used. Despite this increased dosage, the course of events did not differ from those found in this study and the one reported by Kar et. al (1993). Furthermore, the present study have also observed side effects in both treatment arms and they were irrespective of the individuals microfilaria status.

Since signs and symptoms were recorded in both treatment arms and for the simplicity of reporting, they were grouped (during analysis)into those with prevalence values between 1-3.9% in each treatment arm and for those with prevalence values greater than 4% in each treatment arm. Recruited individuals in both treatment arms irrespective of their microfilaria status had reported side effects. Hence it may appear that the pre-treatment levels of microfilaraemia are not the only thresholds to the production and development of side effects but active clinical disease might have also contributed to the development of the recorded side effects.

Facial swelling (cellulitis), testicular tenderness, vomiting, excessive urination and lacrimation, palpitations, insomnia, which have been described in this study were not reported in earlier safety observations. However their prevalence ranged from 1.0-3.9%. These observations could have possibly been due to the reactions resulting from the interaction between the drugs and lymphatic filariasis together with geohelminth within the susceptible individuals.

In addition study results have also shown that symptoms with prevalence of ≥4% were common in both treatment arms and these included: fever, headache, body pain, cough, chills, athralgia, nausea, abdominal pain, dizziness, chest pain, loose stool, itching and wheezing. These observations concurs to those found by Kar et. al (1993) and Nguyen et. al (1996). However, the present study describes the development of side effects on each treatment arm against time.

Observations at 24 hours after treatment noted that the prevalence of side effects in both treatment regimes were significantly high when compared to the baseline data. These included headache, chills, chest pain and itching. The developments of these side effects were statistically significant in both treatment arms. A possible explanation may lie on the fact that both treatment arms had homogeneous representations of both microfilaria positive and clinical active diseased individuals. This therefore suggest that microfilaraemia threshold is not the only pre-requisite to the development of side effects but also active clinical disease might have a contributory role towards the development of side effects. Furthermore, within the same time the prevalence of athralgia, abdominal pain and loose stool were significantly recorded in the ivermectin albendazole combination while the prevalence of dizziness was significantly high in ivermectin placebo combinations.

Results have further revealed that at forty-eight hours, the prevalence of headache was markedly higher in the Ivermectin –Albendazole combination than in the ivermectin placebo arm. The contrast was also noted at 72 hours where Ivermectin-Placebo

combinations was associated with more headaches. This study has shown that each treatment arm to be significantly associated with certain symptoms at given point in time and that the observations were statistically significant.

When comparison between the two regimes against the development of symptoms with magnitude ≥4 % was done, the two treatment regimes differed in only three recorded symptoms. Headache was the only symptom, which was significantly associated with the Ivermectin –Albendazole combination. However, high fever and dizziness was strongly associated with the ivermectin placebo combination. All these observed differences in symptoms were statistically significant.

The findings have shown show that as far as symptom are concerned ivermectin albendazole combination had fewer reported symptoms than the ivermectin placebo arm when the two regimen were compared. The former regime is relatively safer when compared to the latter when symptoms are taken in consideration. These observed differences could probably be due to the fact that the combined regime basing on its synergistic effects acts much more faster by killing the infective parasites resulting in developing side effects which are short lived. In contrast the ivermectin placebo regime could perhaps be having static activities with prolonged slow antigen release from the dying parasite.

Analyses on signs have also shown that within each treatment arm there was a gradual increase in temperature, pulse rate and respiratory rate from six hours to 24 hours post drugs administration . however , these then started to decline from 48 hours onwards.

These noted changes in vital signs, which were diminishing with time, suggest that the observed sign to be self-limiting. These observations were statistically significant.

Furthermore within both treatment arms there was gradual decrease in systolic BP where the Ivermectin –albendazole combination had reduced the systolic pressure by a factor of 8.9 mm.hg while ivermectin placebo combination had reduced by a factor of 9.7 mm.hg. Similarly there was reduction on diastolic blood pressure (ivermectin – albendazole by 1.76 mm.hg and ivermectin placebo arm by 4.35 mm.hg) from the baseline in the 96 hours course of follow up with statistically significant values suggesting that both treatment arms have to influenced these reductions. However the reduction noted in both signs was higher in the ivermectin –placebo treatment arm compared to the values similarly observed in ivermectin-albendazole combinations and that all reductions were within the normal blood pressure parameters (normal systolic values 140/90 mm hg to 95/55mm hg when taken at rest, Macleod et. al, 1987). The only sign that was significantly raised in the ivermectin – albendazole combination was respiratory rate. This was transiently raised at six hours and declined after 72 hours. Individually both these drugs are not known to raise respiratory rate. There is no pharmacological reason however, one could speculate that the increased antigen biomass from dying geohelminthes and microfilariae could possibly lead to mild hypersensitive reactions raising the respiratory rate.

The current global agenda aims at eliminating lymphatic filariasis in endemic areas by using mass chemotherapy campaigns complemented by vector control activities. WHO has recommended the use of drug combination (Ivermectin-Albendazole or DEC-Albendazole) as one of the strategies to attain this goal.

The efficacy levels observed in this study together with safety levels noted justifies the potentials and hence the possibility of using this tool to attain the global goal. Furthermore the secondary benefits observed on geohelminth reduction (on both prevalence and intensity) together with those of weight and height gains in children reported in Haiti by Beach et. al, (1999) enlarges the scope of using this tool in control of other human nematode infections. Where lymphatic filariasis and geohelminth are endemic, ivermectin –albendazole may be more beneficial than ivermectin alone.

Despite the fact that the observed prevalence of co-infection (geohelminth & lymphatic filariasis) was found to be relatively low (6.48%) there is still a need to have more duration data especially on the sustainable reductions of microfilaraemia at six and 12 months period. However, at this level basing on observations noted in other studies, Mass treatment using drug combination is recommended.

However, currently the availability of ivermectin is restricted to lymphatic filariasis endemic areas or in follow up studies through donation programs. In addition the burden on the added cost on drug combination after the termination of the elimination campaign

will be left to individuals and affected countries. This then raises the question of affordability and the cost benefits of using this drug combination in other nematodes of public health importance as among one of the control strategies. Henceforth, cost benefits analysis is another area, which also needs investigations.

5.0 Conclusion and recommendations:

Bancroftian filariasis and geohelminth infections are both diseases of public health importance in Zanzibar and Tanzania at large. Both diseases contribute largely to morbidity and to the economic loss either directly through expenditures (patient care and medicaments) or indirectly through loss of participation in productive activities and routine works.

The current available antifilaria drug (DEC) in the country requires a long treatment schedule and is accompanied by a lot of side effects. This study has shown that the drug combination (Ivermectin –Albendazole) to be more efficacious than Ivermectin – placebo regime on reducing both the magnitude and intensity of geohelminth and microfilaria infections.

Furthermore, the combined therapy was accompanied by fewer side effects than the Ivermectin –Placebo regime indicating that the combination therapy is safe.

These short-term observations on safety and efficacy of the drug combination provide a strategy for future control activities on both bancroftian and geohelminth infections in endemic areas.

The short-term measures that are recommended are:

1. To evaluate the sustainability of the reduced microfilaria and geohelminth prevalence and load at three, six and twelve months after drug administration.

2. Updating drug filaria policy
3. Strengthening of the Filaria Control Unit and identify sources of ensuring availability of this drug combination.

Long term recommendations includes:

1. Update strategies on filaria elimination campaigns through mass chemotherapy using drug combinations.
2. To evaluate cost benefits gains from the drug combination especially on the impact on reducing iron deficiency anaemia and other related areas.

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