Lymphatic Filariasis in Zanzibar: Epidemiology, elimination and impact

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by

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TEXT BOUND INTO THE SPINE

ABSTRACT

The study is divided into four areas: a pre-treatment study focusing on the epidemiology of lymphatic filariasis (LF) and the monitoring of the impact of annual mass drug administration (MDA) using a combination of ivermectin (200µg/kg) and albendazole (400mg) against the filaria parasite *Wuchereria bancrofti*.

This study is one of the first to provide epidemiological evidence on the estimated number of rounds of mass administration needed to interrupt LF transmission in a country where the principal vector is *Culex quinquefasciatus*. At the sentinel site of Kizimkazi, microfilaraemia (mf) prevalence and density dropped gradually following five rounds of MDA from 17.8% and 356 mf/ml to zero with a drug coverage of above 75.0% (of the total population) in all rounds. At the sentinel site of Kwahani microfilaraemia (mf) dropped from 7.2% and 323 mf/ml to zero after four rounds of MDA. A decline in circulating filarial antigen (CFA) following MDA was observed when 100 individuals randomly selected from sentinel sites and twelve spot-check sites were examined following MDA. This study provides a model for other filariasis-endemic countries in sub-Saharan Africa currently undertaking or planning to start mass treatment campaigns under the Global Programme to Eliminate Lymphatic Filariasis (GPELF) where *Culex quinquefasciatus* is the vector.

Entomological surveys completed in both sentinel sites indicated the decline in LF microfilariae larvae in the mosquito population after four rounds of MDA using ivermectin and albendazole. This was demonstrated in Kizimkazi sentinel site when surveys completed prior to the start of MDA recorded infective rates (0.4%) of LF mf L3 larvae in the mosquitoes caught and dissected, but none of the mosquitoes caught later during the other proceeded surveys had LF microfilariae larvae. However, in Kwahani sentinel site none of the mosquitoes caught and dissected had LF microfilariae during both baseline surveys as well as other surveys completed after the MDA rounds. In PCR analysis of 5,184 recently-fed mosquitoes (*Culex quinquefasciatus)* caught in Kizimkazi sentinel site indicated a maximum likelihood of infection of 1.13% with a 95% confidence interval of 0.82%-1.52%. This suggests the existence of some mf carriers with potential to infect mosquitoes. However, the presence of *W. bancrofti* infective larvae (L3) in the vector population is a direct measure of transmission because only mosquitoes carrying the infective stage of the parasite are capable of contributing to transmission.

The second area was monitoring the impact of MDA on other parasitic diseases with a particular focus on soil-transmitted helminths and scabies in Zanzibar. A significant decline in patients with worms (soil-transmitted helminthiasis) and scabies was observed during a six year follow-up of records in 50 health facilities in the country. The decline in prevalence and intensity of *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm following MDA rounds was also recorded when 100 individuals were randomly selected from the sentinel sites and the twelve spot-check sites were examined. A third study monitored the impact of home based care on lymphoedema patients and hydrocelectomy on patients with hydroceles. The follow-up assessment data on the condition of 120 hydrocele surgery patients and 81 lymphoedema patients under home-based care showed an improvement and a decline in frequencies of attacks of adenolymphangitis.

A final study undertaken was to investigate triple combination therapy in the mass treatment of LF, schistosomiasis and soil-transmitted helminthiasis in a single treatment to reduce costs. This study combining the treatment of albendazole, ivermectin (Mectizan®) and praziquantel was designed as a safety study on a large population and was among the first studies to be conducted in sub-Saharan Africa where the diseases are co-endemic.

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DEDICATION

This thesis is dedicated to

My wife Nasra S. Salim and our children who endured numerous long periods of my absence from home during this study

My family in Zanzibar

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CHAPTER I

INTRODUCTION AND STUDY OBJECTIVES

1.0 Introduction

Lymphatic filariasis is an infectious disease caused by the parasitic nematode worms *Wuchereria bancrofti, Brugia malayi* and *Brugia timori.* The infective stage larvae (L3) are transmitted when an infected mosquito bites a person. This disease affects an estimated 120 million people throughout the tropics (Michael et al., 1996; Zagaria and Savioli, 2002). *Wuchereria* and *Brugia* are known to occur in some 81 countries (Table 1.1): 40 in Africa, 16 in Southeast Asia, 15 in the Western Pacific, 7 in the Americas and 2 in the Middle East (Anonymous, 2001). LF has also been previously reported, and may still occur, in more than 30 additional countries (Ottesen et al., 1997). *Wuchereria bancrofti* is found throughout the tropics and sub-tropics, and accounts for approximately 90% of the 120 million infections worldwide (Rajan and Gundlapalli, 1997; Ravidran, 2003). *Brugia malayi* and *Brugia timori* are responsible for the remaining 10% of infections and have much more restricted ranges, with *B. malayi* being endemic only in certain parts of India, South-east Asia (China, Indonesia, Malaysia, The Philippines, the Republic of Korea, Thailand and Vietnam) and the Western Pacific, whilst the *B. timori* is confined to specific Indonesian islands - Timor Leste (formerly Timori island) and Flores and Alor (Hamer and Despommier, 1998; Anonymous, 2001; Melrose, 2002; Fischer et al., 2004). Humans are the only known hosts for *W. bancrofti, w*hile *B. malayi* and *B. timori* have animal host species such as leaf monkeys (*Presbytis*) and domestic cats (Michael et al., 1996; Rajan and Gundlapalli, 1997; Kazura, 2002). However, the epidemiological significance of such hosts is not understood. LF causes debilitating genital disease in more than 26 million men, lymphoedema or elephantiasis of the leg in an estimated 16 million people, and lymphatic dysfunction in virtually all those infected hence WHO has ranked it as the

second leading cause of permanent disability worldwide (WHO, 1994; WHO, 1995; Michael et al., 1996; WHO, 2005). It is reported that more than 40 million of those infected are suffering from one or more of the overt manifestations caused by infection (Ottesen et al., 1997; Molyneux and Zagaria, 2002; Ottesen et al., 2008).

Lymphatic filariasis has been grouped with onchocerciasis, schistosomiasis, soil transmitted helminths, leprosy, African trypanosomiasis, leishmaniasis, dracunculiasis, trachoma and Buruli ulcer as one of the neglected tropical diseases prevailing in sub-Saharan Africa. These diseases affect the poorest people in the rural as well as urban areas of low-income countries in the world (Hotez et al., 2005). Using the Disability Adjusted Life Years (DALY) as a metric the burden of these diseases is equivalent to approximately half the disease burden of HIV/AIDS and equivalent to that of malaria (Hotez et al., 2005). Although neglected diseases cause great suffering and often life-long disabilities, the mortality rate associated with these diseases is relatively low and therefore does not receive the attention and funding of high-mortality diseases such as HIV/AIDs, tuberculosis and malaria (Molyneux, 2004). Most patients with neglected diseases live in developing countries and are amongst the poorest quintile unable to pay for health care because the pharmaceutical industry has traditionally ignored these diseases as they do not promise a good return on investment (Yamey, 2002). However, in the past two decades there has been significant achievements in the control of some of the tropical diseases including lymphatic filariasis through vertical interventions (Molyneux, 2004, Hotez et al., 2004; WHO 2004). The progress made to date provides promise that some of the neglected diseases including lymphatic filariasis could be controlled or even eliminated as public health problems in areas where they are endemic.

In 1988, the International Task Force for Disease Eradication (ITFDE) was formed to evaluate the potential for eradication of candidate diseases and

identify specific barriers to eradication or elimination (Molyneux et al., 2004). The ITFDE (1993) reviewed more than 80 diseases. Based on the criteria used to assess feasibility of disease eradication programmes they recommended six diseases - dracunculiasis, rubella, poliomyelitis, mumps, lymphatic filariasis and cysticercosis could be eradicated using existing technology, (ITFDE, 1993; Molyneux et al., 2004). The three broad criteria proposed to assess feasibility of disease eradication programmes were social and political considerations, biological and technical feasibility, and a full understanding of cost and benefit issues (Aylward et al., 2000). Theoretically, it is believed that if the right tools were available, some of the infectious diseases would be eradicable, but in reality there are distinct biological features of the organisms and technical factors that make potential eradicability more or less likely. At a meeting in Berlin in 1997 (a Dahlem workshop) on Eradication of Infectious Diseases the focus was on the science of eradication of diseases where four questions were addressed:

1. How should eradication be defined and what are the biological criteria?
2. What are the criteria for estimating the costs and benefits of disease eradication?
3. What are the societal and political criteria for eradication?
4. When and how should eradication programmes be implemented?

Eradication was defined as the permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; that is to say interventions are no longer needed. However, elimination refers to local reduction to zero of incidence of infection as a result of deliberate efforts. Since infection can be imported from other areas that remain endemic permanent intervention is required (Dowdle and Hopkins,1998; Dowdle, 1998; Molyneux et al., 2004). That workshop considered three indicators to be of primary importance in assessing eradicability of infectious diseases: an effective intervention is available to interrupt transmission of the agent; practical

diagnostic tools with sufficient sensitivity and specificity are available to detect levels of infection that can lead to cessation of transmission and humans are essential for the life-cycle of the agent, which has no other vertebrate reservoir and does not amplify in the environment (Dowdle, 1998).

In Africa, India and most other *Wuchereria bancrofti* endemic areas the levels of lymphatic filariasis infection remain high. The major reasons for persistence of the disease has been the lack of diagnostic and control tools and strategies that are cost-effective and appropriate for the endemic countries (Ottesen et al., 1997). However, recent advances in lymphatic filariasis research have led to a new understanding about the severity and impact of the disease, new diagnostic and monitoring tools have been developed and, most importantly, new treatment and control strategies introduced (Ottesen et al., 1997). The three available drugs diethylcarbamazine (DEC), ivermectin (Mectizan®) and albendazole have been shown by intensive investigation to be safe and effective anti-filaricides for mass treatment to control the transmission of *W. bancrofti* in several settings. Zanzibar decided to use the combination of ivermectin and albendazole as agreed for the whole of Tanzania.

The recognition that two-drug single dose treatment strategies are significantly more effective than treatment with either drug alone has been a major advance in the development of control regimens for lymphatic filariasis (Moulia-Pelat et al., 1995; Ottesen and Ramachandran,1995; Addiss et al., 1997; Ismail et al., 1998; Bockarie et al., 2002). Lymphatic filariasis was previously eliminated from several parts of the world - the mainland of China (WHO, 2001), Quemoy (Kinmen) Island in China by use of DEC-fortified salt (Fan, 1990), Republic of Korea (Chai JY et al., 2003), Solomon Islands by use of residual insecticide spraying for vector control (Webber, 1979), Suriname and small foci in Santa Catarina state, Brazil by use of DEC chemotherapy (Schlemper et al., 2000). On the basis of these advances, in 1997, the Fiftieth World Health Assembly (WHA) passed a resolution (50.29 which called for member states to support the

elimination of LF through the "Global Elimination of Lymphatic Filariasis as a public health problem" (WHO, 1997; Molyneux and Taylor, 2001), prompting the establishment of LF elimination programmes in many endemic countries including Zanzibar - Tanzania. However, it is important to note that previously elimination of filariasis was not achieved in some areas despite long-term control programmes (Esterre et al., 2001).

In 2000, the World Health Organization started a worldwide coalition of many organizations known as a "Global Alliance to Eliminate Lymphatic Filariasis" (GAELF) with the same aim at the Global Programme – the global elimination of LF as a public health problem (Anon. 2001). The current double – prolonged elimination strategy involves MDA to interrupt transmission of infection, and disability prevention and control to relieve suffering of individuals already afflicted with acute or chronic LF (WHO, 2000). Based on the centralization of health services, an LF- endemic country identifies the implementation unit (e.g. district, town) within its borders that will be responsible for implementing mass treatment. The nation's baseline geographic distribution of filarial infection is then assessed. If the prevalence of infection in a given administrative unit exceeds 1% everyone in the unit, regardless of infection status, is treated once a year with either diethylcarbamazine (DEC) or ivermectin (in areas where onchocerciasis is prevalent) in combination with albendazole (Ottesen,2000; Molyneux and Taylor, 2001; Molyneux and Zagaria, 2002). In countries where LF co-exists with onchocerciasis diethylcarbamazine (DEC) is contraindicated because of its association with anaphylactic reaction, severe itching and progression to ocular pathology due to the death of microfilaria in the eyes of individuals infected with *Onchocerca volvulus* (Ottesen et al., 1997; Greene et al., 1983). In countries which are co-endemic for LF and onchocerciasis, ivermectin and albendazole are the drugs of choice. The combination of two drugs has been shown to provide a long-lasting suppression of microfilariaemia than using one drug alone (Ismail et al., 2001). Hence, that suppression ensures that the vectors (mosquitoes) are deprived of the opportunity to continue

transmission. However, these drugs have a limited profile against the adult worms although some present evidence suggests that these drugs may adversely affect their survival and the female worm's ability to reproduce (Dreyer et al., 1995c; El Setouhy et al., 2004; Fox et al., 2005). It is recommended that annual mass treatment continues until transmission has been interrupted. For the MDA to be effective in the long term, a high percentage drug coverage (≈70%) of the total population of the at-risk community needs to treated every year for up to six consecutive years (Molyneux and Zagaria, 2002). This period corresponds to the estimated reproductive life-span of the adult female worm.

Early support in the task of eliminating lymphatic filariasis came from Ministries of Health of the endemic countries and a number of international organizations, including the Arab Fund for Economic and Social Development (AFESD), the United States Centers for Disease Control and Prevention (CDC) and the United Kingdom Department for International Development (DFID). In January 1998, the Programme was given its most powerful boost when SmithKlineBeecham (SB), later to become GlaxoSmithKline (GSK) announced its commitment to collaborate with WHO in a partnership between the private and public sector to support the Global Programme to Eliminate Lymphatic Filariasis by donating albendazole free of charge for as long as necessary. GSK decided to give that donation because most of LF endemic countries are economical poor and its people cannot afford to buy these drugs. Later that year, a further boost was given when Merck & Co. Inc. pledged to expand its Mectizan Donation Program for Onchocerciasis to cover treatment of LF in all African countries where the two diseases occur together (Molyneux et al., 2000; WHO, 2002). The GPELF has rapidly upscaled and by 2004, 38 of the 83 countries and territories classified as LF endemic had commenced elimination programmes. It is estimated that more than 76.5 million people were treated with the two-drug combination of ivermectin/albendazole or DEC/albendazole in 2004, while 171.6 million in Brazil, Guyana and India were treated with DEC alone or DEC-fortified

salt (WHO, 2005). In 2007, WHO reported 546 million people had been treated in a single year (WER, 2008).

1.1 Study site

Zanzibar is one of the political entities of the United Republic of Tanzania. It comprises two main islands, Unguja (mostly referred as Zanzibar) and Pemba, and a number of sparsely populated islets. It lies 35km off mainland Tanzania coast, 6°south of the Equator (Figure 1.1). Unguja Island is 87km by 35km while Pemba Island is 64km by 32km at the longest and widest points respectively. The land areas of Unguja and Pemba islands are 1,654sq km and 984sq.km respectively. The total population of Zanzibar is about 984,625 distributed as 622,459 and 362,166 on Unguja and Pemba respectively. The population growth rate is 3.1% (Population Census Report, 2002). On Unguja more than 40% of the population resides in Zanzibar town, the administrative and commercial centre of the two islands. On Pemba, on the other hand, there are three towns forming concentrated population centres namely Wete, Chake Chake and Mkoani on the North, Central and South Western coast of the island respectively (Figure 1.1). The life expectancy at birth for Zanzibar was estimated in 2002 to be 57 years (National Bureau of Statistics, 2002). The infant mortality rate is estimated at 83 per 1,000 live births; under five mortality 114.3 per 1,000 (TRCHS, 1999), while maternal mortality is estimated at 377 per 100,000 live births (UNICEF, 1998). Mortality and morbidity in Zanzibar continues to be dominated by preventable, communicable diseases such as malaria, tuberculosis and diarrhea. There has also been a recent increase in the number of cholera outbreaks. Conditions related to pregnancy and childbirth and respiratory infections in young children also contribute significantly to mortality. At the same time, Zanzibar has documented a marked increase in non-communicable diseases such as diabetes mellitus, cardiovascular disease and cancer. HIV prevalence is 0.6% among the sexually active adults (MOHSW, 2002) with a significant presence of predisposing risk factors.

Zanzibar has a hot and humid tropical climate with temperatures ranging from 19°C to 32°C. The hottest months are January to March and coolest months are July and August. There are two rainy seasons following the North East and South East monsoon winds. The long rains, called 'Masika' locally, begin in late-March and end in mid-May to early-June while short rains, called Vuli, occur in September to October. The islands receive adequate rainfall especially during the long rain season. The annual rainfall is 61" (1570mm) for Unguja and 75.9" (1928mm) for Pemba. However, the eastern coastline of both islands receives less rainfall. Zanzibar's economy is dependent on cloves which account for approximately 90% of its exports. About 70% of the labour force is engaged in agriculture. The government is now diversifying economic production to other sectors such as tourism and fisheries. Food sufficiency is one of the high priorities. Rice is the favoured food in Zanzibar and rice cultivation is being expanded by the government to ensure food security. However, rice fields are suitable breeding sites for mosquito species that

After the 1964 revolution, Zanzibar joined with the then Tanganyika to form the United Republic of Tanzania. However, Zanzibar has considerable autonomy in her domestic affairs administered through the Revolutionary Council and the House of Representatives. Administratively the two islands are divided into five regions, three on Unguja and two on Pemba. Each region consists of two districts and each district is divided into several Shehias. The Shehia is the lowest administrative level of the government structure. Each Shehia is headed by the community leader commonly referred as Sheha. The Shehia, district and regional structure are the main channels of communication between the population and higher government structures. The Health Service is one of the domestic affairs administered separately from the Union government although there is considerable collaboration with the mainland. The agency responsible for health services in Zanzibar is the Ministry of Health and Social Welfare transmit both malaria and filariasis in Zanzibar.

Figure 1.1 Map of Zanzibar and Pemba

Public Health in Zanzibar

The health system in Zanzibar enjoys a commendable infrastructure with more than 95% of Zanzibaris living within five kilometres or less of a health facility. Health services are delivered through Directorates of the MOHSW and specialized vertical programmes: AIDS and STD; malaria; diarrhea and ARI; schistosomiasis and intestinal helminths; filariasis, TB and leprosy; Expanded Programme of Immunisation; Safe Motherhood and Reproductive Health; Adolescent Health; Integrated Management of Childhood Illnesses; and Community Mobilization. The health budget in Zanzibar is approximately US$1 per person/year. Health services are decentralized, in the sense that they are planned and implemented at district and community levels.

Malaria has historically been the major cause of morbidity and mortality in Zanzibar, particularly among children. A new drug policy of artemisinin combination therapy (ACT) was introduced in 2002, and insecticide-treated nets (ITN) were scaled up resulting in an increase in coverage from 3.4% in 2002 to 45.8% in 2005 (ZMCP, 2005). As a result, there is some evidence that incidence of malaria, due to *Plasmodium falciparum*, is now falling (MSF, 2006). At the same time, the rapid fall in positive diagnoses in the health facilities involved in a pilot study to introduce rapid diagnostic testing indicates that the earlier presumptive diagnosis of all fever such as malaria exaggerates the true position (Reyburn H et al., 2007). The Zanzibar Malaria Control Programme is currently implementing its Strategic Plan for the period 2004 – 2008, the goal of which is "to significantly reduce morbidity and mortality due to malaria in the population of Zanzibar with special attention to the most vulnerable groups - children under five, pregnant women, and the poor – and in doing so promote socio-economic development." The core interventions/measures being prevention of malaria through promotion and targeted distribution of ITNs, together with other vector control methods (eg indoor residual spraying); access to effective case management (including the introduction of Rapid Diagnostic

Tests) and control and prevention of malaria in pregnancy through intermittent presumptive treatment, and expanding net use by pregnant women.

The Zanzibar HIV/STD prevalence survey carried out in 2002 indicated that overall HIV prevalence on the islands was relatively low (compared to the mainland Tanzania and neighboring countries) at 0.6%, with the figure being higher among young adults and women. Among specific risk groups, the prevalence is higher. For example, among those attending at antenatal clinics the rate was 0.9%, among STI patients it was almost 6%, for intravenous drug users 12%, and among TB patients, 25%. An estimated 4% of hospital beds were occupied by HIV/AIDs patients (ZACP 2003). The main transmission route is unprotected heterosexual sex, indicating the need for efforts to be maintained to prevent the spread to the broader population. The 2001 Africare study found that 78% of youths felt that condom use was socially unacceptable, thus presenting a challenge which has yet to be overcome. Vertical transmission, from mother to child, was estimated at about 4% of the overall total. The STD/HIV programme is currently implementing its strategic plan with the main focus being to achieve 1 VCT site per 20,000 people by 2010 and be able to attain 3,000 People Living With HIV/AIDs (PLWHA) on ARVs by 2011 using IEC and community mobilization, condom promotion and use; provision of VCT services at 26 sites with routine diagnostic testing; early diagnosis and treatment of sexually transmitted infections; management of opportunistic infections; provision of prevention of mother to child transmission (PMTCT) services at all referral facilities (Public Health Care Centre); comprehensive HIV/AIDs care for both adults and children, including the provision of anti-retroviral therapy (ART) at hospital level; ensuring availability of safe blood for transfusion throughout the islands; and home-based care for chronically ill patients as core interventions.

There has been a slow but steady increase in smear positive tuberculosis in Zanzibar in recent years, and there are concerns that among HIV positive persons TB incidence is rising much faster. The distribution of the TB burden

around the islands is not at uniform level, with cases more concentrated in urban areas. The TB programme is trying to expand access to early diagnosis and treatment by scaling-up core services throughout the country. However, multi-drug resistance has been noted and appropriate action is being planned to solve this problem. The programme is in the process of implementing its strategic plan targeting increasing case detection and cure rates of TB by 5%; reducing prevalence from 12% to 7%; reducing the death rate from 8% to 4%; establishing community-based DOTS in all districts by 2009; increasing the number of cases detected and cured under DOTS from 347 to 500; preventing a rise in multi-drug resistance through appropriate control strategies; and on implementing collaborative TB/HIV activities by 2010. Programme activities include early diagnosis and treatment; DOTS at both Public Health Community Units (PHCUs) and within the community and prophylaxis for HIV positive persons with Co-trimoxazole being the core interventions.

In Zanzibar it has been observed that the number of registered leprosy cases being treated has been increased in recent years, with over one hundred new cases being detected per year. In 2004, this was over 1 case per 10,000 population, ie above the WHO target for elimination. Late treatment seeking results in the unfortunate situation that patients have often already suffered disability by the time they report for medical help. However, multi-drug therapy (MDT) was introduced for the first time 1988, in line with the WHO strategy. The specific programme targets in fighting leprosy are to increase case detection and cure rates by 5%; increase diagnostic centres from 11 in 2004 to 40 by 2010; increase service points for MDT from 60 public health facilities to all of them together with selected private and institutional facilities and to expand access to MDT in health facilities by 100% using IEC for early recognition, case management at PHCU level and above, and if possible rehabilitation.

Schistosomiasis and soil-transmitted helminths are common public health problems in Zanzibar, affecting Pemba to a greater extent than Unguja. In

Unguja, the problems are localized largely in the North region and Central district. The prevalence of both schistosomiasis and soil-transmitted helminths in affected populations was more than 70%. However, the active mass treatment programme that has been going on in Pemba, and school-based treatment programme on Unguja, have significantly reduced prevalence rates, and associated morbidity. The programme is seeking to intensify its activities using health education on prevention and control of schistosomiasis and STH through Sheha, school teachers, and health workers, improving diagnosis and treatment at PHC levels.

Lymphatic filariasis has historically been a significant public health problem in Zanzibar with prevalence ranging between 5% and 30% in the southern districts of both islands which have high prevalence. The LF Programme under MOHSW was established in 1994 and an MDA campaign was initiated in all the eligible population in 2001 following the launch of GPELF. Since 2001 an annual MDA using a combination of ivermectin and albendazole has being in progress with the aim of stopping transmission. There has been good coverage in all rounds. District by district assessment identified several patients with lymphoedema and others with hydrocele (Mohammed et al., 2006). The Zanzibar PELF has introduced a home based care management intervention to all lymphoedema patients in the country with the intention of alleviating their suffering and improving their social and economic status. Males with hydrocele, have been recorded and some have already been operated on. The remaining patients have been identified for surgery when the MOHSW has acquired additional resources.

Zanzibar MOHSW is preparing a plan for Health Sector Reforms to ensure the availability of equitable health care services for the whole population. The plan will focus on priority diseases and address the burden of disease according to an essential health care package. The essential health care package focuses on the principles of primary health care (PHC), an approach based on the

community, PHCUs and "cottage" hospitals. However, these primary level facilities cannot provide particular specialized services, which are normally provided at secondary and tertiary levels, therefore the MOHSW put in place a mechanism of two way referral of patients from one level to another.

The overall goal of Zanzibar health policy is to "improve and sustain the health status of all Zanzibar people" (GOZ, 2002). The intermediate objective is the reduction of the absolute levels of morbidity and mortality from all major causes, and to reduce the health disparities between different population groups and geographical areas (MOHSW, 2002). Emphasis is given throughout to ensuring that vulnerable groups such as the poor, women of reproductive age, children, the disabled and the elderly are assured of access to high quality services. Strengthening of primary health care remains the primary strategy. A number of guiding principles underpin the MOHSW Health Sector Reform Strategic Plan:

- A multi-sectoral approach to the planning, implementation, monitoring and evaluation of health services;
- Political commitment and civil society involvement;
- A commitment to reduce stigma and discrimination in combating the HIV epidemic;
- Adoption of a human rights-based approach;
- Sensitivity to the culture and social context of Zanzibar. While firmly based on sound scientific evidence, health promotion strategies shall promote and protect positive aspects of the Zanzibari culture;
- Active seeking and promotion of community participation in health;
- Ensuring that comprehensive basic health services shall be accessible to all.

The district health system is the essential focus of the process of strengthening of Primary Health Care, which remains the cornerstone of the Zanzibar health sector. The majority of the contributing factors to the Zanzibar burden of disease are most cost-effectively and equitably handled at this level. The district

serves as the interface between the population, as beneficiary of health services, and the MOHSW as the overall steward of the sector, with responsibility for setting of standards and guidelines, and for assuring access and quality. Local responses to varying environmental and behavioural factors are better handled within the district health system. MOHSW places great emphasis on strengthening involvement of stakeholders at all levels from the household upwards, and in particular to strengthening the planning and management capacities at district level in support of a decentralized health service delivery.

The MOHSW has not only committed to the decentralization of responsibilities, articulated in the district health plans but also to identifying resources. At present government funding tends to flow, in kind, to the district level but the introduction of the Health Service Fund (HSF) is seen as a precursor for a possible multi-source grant for district health services. The needs-based allocation formula for the HSF resources has been refined in order to reflect varying under-five mortality and support costs (via district area), whilst budgetary restructuring will be pursued in order both to harmonize HSF and government funding modalities for district health services, as well as to facilitate improved reporting by geographical area.

Over the years, Zanzibar has developed an impressive public sector health infrastructure, based on a network of first and second line Primary Health Care Units in both urban and rural areas. There are six public hospitals in Zanzibar. The main Mnazi Mmoja hospital is a referral hospital in Zanzibar town with a capacity of about 400 beds, while there are three District hospitals on Pemba: Wete, Chake Chake and Abdulla Mzee in Mkoani with bed capacities of 110, 120 and 80 respectively. Other public hospitals are Mwembeladu Maternity Home with a bed capacity of 34 and the Kidongo Chekundu psychiatric hospital with 110 beds, both of which are on Unguja (Table 1.3). There is also a

burgeoning private health sector, although in contrast to the public facilities, this is largely concentrated in the urban areas, notably Zanzibar town (Table 1.4).

The presence of LF in Tanzania was first recorded in 1911. Since then a number of country wide studies have been carried out to delineate the extent and the magnitude of the disease in the country. The Islands of Unguja and Pemba have been identified as two of the major foci in Tanzania for this disease.

In Zanzibar LF has been documented as far back as 1911. The most common type of microfilaria species found is *Wuchereria bancrofti* although *M. persitans* has been documented, with *Culex quinqefaciatus, A. costalis* and *A. funestus* implicated as the main vectors for the transmission of bancroftian filariasis on the island (Mansfield-Aders, 1927).

Studies carried out in Zanzibar at the beginning of the twentieth century on the microfilaraemia rates in hospitalized patients irrespective of the cause of admission revealed high microfilaria prevalence. In Pemba in 1930, McCarthy recorded microfilaraemia rates as high as 30% in adults and 15% in children (McCarthy 1930). While in 1976, Kilama and his colleague found the following microfilaraemia (mf) rates in Unguja and Pemba: Konde-11.8%, Jambiani-12%, Chake Chake-16.2%, Makunduchi-39%, Kengeja-15.1%, and Zanzibar Town 15% (Kilama et al., 1975). In other studies by Maxwell and colleagues (1987–1991) in Unguja microfilaraemia prevalence was as follows: Pwani Mchangani - 0.3%, Konde-3%, Jambiani-12%, Moga-32% (in 1991), Makunduchi-49% (1987), Kengeja-13% (1989), Kizimkazi-26% (1988), Zanzibar town-8% (1991), and Makunduchi-12% (1989). However, in Pemba in 1999 microfilaria prevalence was found to be 9.7% (Pedersen et.al., 1999) while, Dahoma (2000) found that prevalence of *W. bancrofti* was 13.7% in Makunduchi, south district of Unguja.

The information from both community-based surveys and from hospital records clearly defines the magnitude of the problem of LF in Zanzibar. LF was confirmed to be highly endemic on both islands with microfilaraemia ranging between 5% and 30% in the population.

The Ministry of Health and Social Welfare recognised the public health problem of LF in Zanzibar and called for a major public health intervention based on strategies which included mass chemotherapy by using ivermectin and albendazole for a period of 5-6 years.

In 2001 Zanzibar embarked on the goal of eliminating lymphatic filariasis as a public health problem by the year 2020 through the Global Programme to Eliminate Lymphatic Filariasis (GPELF). In August 2005, Zanzibar implemented the fifth MDA to all the eligible population and the results of coverage in all districts were extremely encouraging. The ultimate goal of the MDA strategy is to eliminate transmission of *W. bancrofti* and hence LF in country. In 2002 activities related to controlling and preventing disability caused by LF through the process of community home-based long-term care commenced and hydrocele surgery commenced in 2004.

At the moment there is an international momentum for LF elimination. However, several important issues remain to be resolved before the disease can be eliminated from the major endemic areas. These include uncertainty about several critical elements of the elimination strategy, such as the required coverage and duration of annual treatment to achieve elimination and its relation to endemicity levels and vector/parasite complexes. There is an urgent need for appropriate tools, procedures and criteria for monitoring and evaluating the impact of elimination programmes. It is also becoming increasingly important to be able to predict and demonstrate the public health and socioeconomic impact of the elimination efforts.

It is clear that monitoring the impact of the different control and intervention strategies is of great importance before any conclusion on status can be reached. Hence, there is a compelling need to have longitudinal studies of the impact of treatment with current drug combinations on transmission and the human parasite reservoir, together with modeling to predict the required duration of treatment for elimination as well as cost–effective and sustainable management strategies for the management of lymphoedema and hydrocele. The level of transmission may be assessed by studying both the numbers of infective larvae of the human lymphatic filarial parasites in the mosquito population, and by measuring the prevalence and intensity of microfilaraemia in the human population (WHO 1987). Since vectoral capacity (especially the number of infective and innoculative bites) have a significant role in the transmission dynamics of *W .bancrofti*, then it is hypothesized that the lowering of the number of L3 larva in the vector (as a result of MDA) within sentinel sites will be a secondary benefit in mitigating the transmission of bancroftian filariasis. The current strategy based on the MDA campaign excludes the under-five children (height less than 90cm), pregnant women, women on one week of puerperal period and the chronically sick from taking drugs. Further reduction of coverage of the total population occurs if people refuse to take drugs (non-compliers) reducing the prospect of eliminating transmission completely (WHO, 1997).

Many studies have shown that even when all microfilariae have been eliminated from the blood and the successful interruption of transmission has been achieved, the residual lymphatic damage from the earlier infection will persist and facilitate invasion of the damaged skin and lymphatics by secondary microbial pathogens (bacteria and fungi) that cause local inflammation that can induce or exacerbate lymphoedema, elephantiasis and genital damage in those already infected or suffering from the manifestations of lymphatic filariasis. However, new advances in research have made treatment of such sufferers more feasible (Melrose, 2002; Lammie et al., 2002; Dreyer et al., 2000; Addiss

et al., 2007). It is now clear that with regular washing of the affected parts with soap, cleaning and drying between the toes; elevating the affected limbs at night; regular exercising of the limb to promote lymph flow; keeping nails clean; wearing protective footwear; using timely antiseptic or antibiotic creams locally or, in severe cases, systemic antibiotics to treat small wounds or abrasions, will not only stop progression of elephantiasis but also reverse the damage already present in many affected individuals (Melrose, 2002; Lammie et al., 2002; Dreyer et al., 2000; Addiss et al., 2007).

With these advances available to lymphoedema patients, WHO adopted a strategy to prevent disabilities associated with lymphatic filariasis to enable LF sufferers in the community to lead a better quality of life and ensure their full participation in the community both socially and economically. The MDA, which is directed towards at the "at–risk" population, prevents occurrence of new infection and disease while those who are already affected symptomatic relief can be achieved through disability management as part of home based long-term care and through changing the attitudes of communities. In view of hydrocele prevalence and public health perspective surgical intervention for morbidity management on hydrocele has also been considered to be an appropriate strategy under the Global Programme to Eliminate Lymphatic Filariasis (GPELF).

It has been documented that soil-transmitted intestinal parasites are equally as common as LF in Zanzibar (Mohammed et al., 2008). Both are diseases of poverty, as they occur in populations at the lowest levels of the socio-economic ladder and are perpetuated within communities. It has been well documented that soil transmitted helminths (STH) thrive in communities with poor housing, sanitation, water supplies, health care, education and low personal income (Crompton, 1999; Crompton & Savioli, 1993). Intestinal helminthic parasites cause serious health consequences and can cause serious intestinal problems, anaemia, can exacerbate malnutrition and stunt both mental and physical

growth in children found in LF endemic areas (Stoltfus et al., 2004; Albonico et al., 2006). In some areas up to 90% of children are infected with these intestinal parasites (WHO 2002a). Most of the coastal Tanzanian islands have childhood infection rates of over 80% (Albonico et al., 2002). However, the drugs that are being administered once yearly as the mainstay to eliminate LF are also the most effective drugs available for broad anti-parasite treatment of hookworm, roundworm, whipworm, lice, scabies and other parasitic infections (Horton, 2002). In other words, not only do LF and STH occur in the same geographical areas, but also the same drugs treat them both effectively. The combination of ivermectin and albendazole is shown to treat STH infections better than either drug alone (Beach, et al. 1999). Beach et al (1999) showed that treating intestinal helminths with a combination of ivermectin and albendazole not only reduces transmission but can also treat the retardation in cognitive and physical growth of infected school children (Stoltzfus et al., 2001). Treatment also increases the productivity of infected adults in the population (Ottesen et al., 1999).

The study described in this project seeks to provide information on the above issues in the context of the Zanzibar situation and GPELF as well as other sub-Saharan African countries and other countries where LF is endemic.

1.2 Study General Objective

The overall objective of this study is to monitor, evaluate and assess the impact of different control and intervention measures being implemented by the Zanzibar programme to eliminate LF and other prevalent parasitic diseases as well as assessing conditions of patients with LF after hydrocelectomy and lymphoedema management through community home based care.

Specific Objectives

(i) To determine whether 5–6 rounds of MDA campaigns using albendazole and ivermectin will arrest transmission of *W. bancrofti* filariasis in Zanzibar by monitoring and undertaking follow-up of

1. the MDA coverage for each district;
2. the microfilariae prevalence and density before each round of MDA in the sentinel and spot check sites;
3. the prevalence of circulating antigenemia in 2-4 year old children from selected communities with different levels of initial prevalence of LF (sentinel and spot check sites);
4. the evaluation of mosquito infection rates;
5. the records of different parasitic disease incidence in the different health facilities in the country.

(ii) To assess the relative contribution of hydrocelectomy and lymphoedema management through community home based care to the LF patients in the Zanzibar community, in terms of disease condition as well as psychosocial and economic status, by monitoring and making follow up of:

1. all LF hydrocele patients operated under the national elimination programme;
2. all lymphoedema patients within the Community Home Based Care in the selected sites.

(iii) To assess

1. the initial safety of the three drug treatment regimen of ivermectin, albendazole and praziquantel through a large scale medically supervised monitoring programme;
2. upscaling of treatment regimen if no adverse events are recorded to incorporate triple therapy on a national annual prevention programme;
3. to monitor the results of the trial programme

Table 1.1 Countries with endemic lymphatic filariasis (WHO WER (2008) – 81 countries)

REGION	COUNTRIES
AFRICA	Angola, Benin, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Cote d'Ivoire, Democratic Republic of Congo, Equatorial Guinea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritius, Mozambique, Niger, Nigeria Reunion, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Sudan, Togo, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
SOUTH EAST ASIA	Bangladesh, Brunei Darussalam, Cambodia, China, India, Indonesia, Lao PDR , Malaysia, Maldives, Myanmar, Nepal, Philippines, Republic of Korean, Sri Lanka, Thailand, Vietnam
THE WESTERN PACIFIC	American Samoa, Cook Islands, Fiji, French Polynesia, Kiribati, Micronesia, New Caledonia, Niue, Papua New Guinea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Wallis and Futuna, Marshall Islands
THE AMERICAS	Brazil, Costa Rica, Dominican Republic, Guyana, Haiti, Suriname, Trinidad and Tobago
THE MIDDLE EAST	Egypt, Yemen

Table 1.2 ZANZIBAR DEMOGRAPHIC DATA

Population	984.625 (2002 Tz census report) Male : 482,619 - Female :502,006
Age Structure	0-14years:44.3% 15-64 years: 53.1% 65 years and over: 2.6% (2003 est.)
Medium age	*total:* 17.5 years
Population growth rate	3.1% (2003 est.)
Birth rate	39.5 births/1,000 population (2003 est.)
Death rate	17.38 deaths/1,000 population (2003 est.)
Net migration rate	-4.91 migrant(s)/1,000 populations (2003 est.)
Sex ratio	At birth: 1.03 male(s)/female - Under 15 years: 1.01 male(s)/female - 15-64 years: 0.98 male(s)/female - 65 years and over: 0.77 male(s)/female Total population: 0.98 male(s)/female (2003 est.)
Infant mortality rate	Total : 103.68 deaths/1,000 live births Female: 93.78 deaths/1,000 live births (2003 est.) Male : 113.29 deaths/1,000 live births
Life expectancy at birth	Total population: 44.56 years Male: 43.33 years: Female: 45.83 years (2003 est.)

Health Indicators

Table 1.3: Number and distribution of Public Health infrastructure in Zanzibar

District	1st line PHC Units	2nd line PHC Units	PHC Centres	District Hospitals	Tertiary Hospitals	Special Hospitals
North A	17	3	1			
North B	7	2				
Central	9	3				
South	7	3	1			
West	9	2				
Urban	5	3			2	1
Micheweni	6	3	1			
Wete	16	2		1		
Chake Chake	13	2	1	1		
Mkoani	9	2		1		
Total	**98**	**25**	**4**	**3**	**2**	**1**

Table 1.4: Private Health Facilities in Zanzibar, 2006

Health Facilities	Unguja	Pemba
Dispensaries/Clinic	**74**	**7**
General hospitals	**3**	
Special hospitals	**1**	
Total	**78**	**7**

CHAPTER II

BACKGROUND AND LITERATURE REVIEW

2.1 History of LF disease

Lymphatic filariasis has afflicted humans for many centuries and elephantiasis of the leg and hydrocele are described in the historical records of Ancient China and Greece and featured in ancient statues from Egypt and West Africa. Microfilariae were first reported from hydrocele fluid of a human in Cuba in 1863 by a French physician, Jean-Nicolas Dermaquay (Pan American Health Organization, 2003). Dermaquay's findings went unnoticed until 1868 when Otto Wucherer reported microfilariae worms in the haematuric urine of a patient in Brazil (Routh and Bhowmik, 1993). In 1870 Thomas Lewis described microfilariae in both urine and peripheral blood from Indian patients (Routh and Bhowmik, 1993). However, Joseph Bancroft is honoured as being the first to identify adult worms in human tissue, which he published in 1877. Sir Patrick Manson incriminated a mosquito as the vector in 1878, describing the ingestion of larvae by mosquitoes and the subsequent larval metamorphosis, but the full life cycle was not determined until 1899 by Joseph Bancroft in Australia (Bancroft, 1877; Grove, 1990; Cox, 1996). Manson's discovery was the first demonstration of the transmission by an insect of an infectious agent. It was in 1958 when Brug for the first time reported the features that differentiate microfilariae of the genera *Wuchereria* species from those of *Brugia* species when he described the different morphology of microfilariae from patients in North Sumatra (Buckley, 1960).

2.2 Biology of Filarial worms

2.2.1 Human Lymphatic Filarial Worms

Filarial worms are tissue-dwelling roundworms belonging to several genera *Wuchereria* or *Brugia, Mansonella (and Acanthochilonera), Streptocerca*:

Nematoda, Superfamily: *Filarioidea* humans as definite hosts and arthropods as the intermediate hosts. Among the most significant lymphatic-dwelling worms found in humans are *Wuchereria bancrofti, Brugia malayi* and *Brugia timori* that cause lymphatic filariasis, the subcutaneous-dwelling *Onchocerca volvulus* that causes blindness, chronic dermatitis and subcutaneous nodules, and the connective tissue-dwelling *Loa loa,* the tropical eye worm which causes loaisis with the characteristic Calabar swellings. *Mansonella persitans, Mansonella ozzardi* and *Mansonella streptocerca* are also human filarial worms but are of relatively minor or unknown clinical significance. There are other several species that are zoonotic filarial worms that sometimes infect humans such as *Dirofilaria immitis*, the dog heart worm, which can lodge in the lungs and cause pulmonary symptoms, and *Meningonema peruzzi* of monkeys, which can cause symptoms in the central nervous system (McMahon and Simonsen, 1995; Southgate, 1995; Kazura, 1999). There are also many filaria parasites found in other mammals and birds

2.2.2 Life Cycle of Filarial Worms

Wuchereria bancrofti, is the most common of the filarial nematode species throughout tropics and subtropics, and accounts for approximately 90% of the 120 million infections of LF worldwide (Rajan and Gundlapalli, 1997; Ravidran, 2003). It is only in some parts of South East Asia (China, Indonesia, Malaysia, The Philippines, the Republic of Korea, Thailand and Vietnam) and the Western Pacific, Indonesia islands Timor Leste (formerly Timori island) and Flores and Alor where it is found to be co-endemic with other species *Brugia malayi and Brugia timori* (Hamer and Despommier, 1998; Anonymous, 2001; Melrose, 2002; Fischer et al., 2004).

The adult *W. bancrofti* are white thread-like worms, the female being up to 100mm long and 0.3mm wide, the male is shorter up to 40mm long (McMahon and Simonsen,1995). The *Brugia* species are only half of the size of the *W.*

bancrofti. The microfilariae (mf) measures approximately 250x10μm. *W. bancrofti* is transmitted by mosquitoes, which play an important role both as a vector and an intermediate host within which a portion of the parasite's life cycle occurs; *W. bancrofti* microfilariae undergo extensive development and transformation in the mosquito in order to become infective (Rajan and Gundlapalli, 1997). When a mosquito takes a blood meal from an infected human, *Wuchereria bancrofti* microfilariae (also known as first larval stage or L1 larvae) in the peripheral circulation are ingested. After a rapid transformation - a period of less than two hours - in the mosquito's stomach, L1 larvae penetrate the midgut and migrate to the thoracic flight muscles. In the flight muscles the microfilariae undergo a series of what are believed to be chemically programmed development changes (Scott, 2000). Depending on ambient temperature, the larvae first develop into a shorter "sausage" form which then undergoes two moults generating L2 larvae and subsequently L3 larvae forms. Upon completion of development, the L3 larvae, now measuring 1500x20μm migrates into the mosquito's head and proboscis and are deposited on the skin during the mosquito's next blood meal. Unlike other parasites, which are injected directly into the bloodstream as the mosquito feeds, the *Wuchereria bancrofti* larvae must locate and crawl through the puncture wound created by the mosquito during feeding or through other skin lesions. Once inside the body, the L3 larvae travel through subcutaneous tissues until they reach the peripheral lymphatic vessels. The larvae undergo another moult generating an L4 larval form that develops into adult worms within 9 to 14 days. The adult worms undergo sexual reproduction resulting in the production of large numbers of microfilariae, which migrate into bloodstream to start the cycle a new. The complete life cycle is shown in Figure 2.1. The adult worms begin producing microfilariae six to twelve months after the infective bite. The fecund life span of *W. bancrofti* in an endemic area is estimated to be 5 years (Vanamail et al., 1996) whereas the mean life-span of the parasite is estimated at about 10 years (Subramanian et al., 2004).

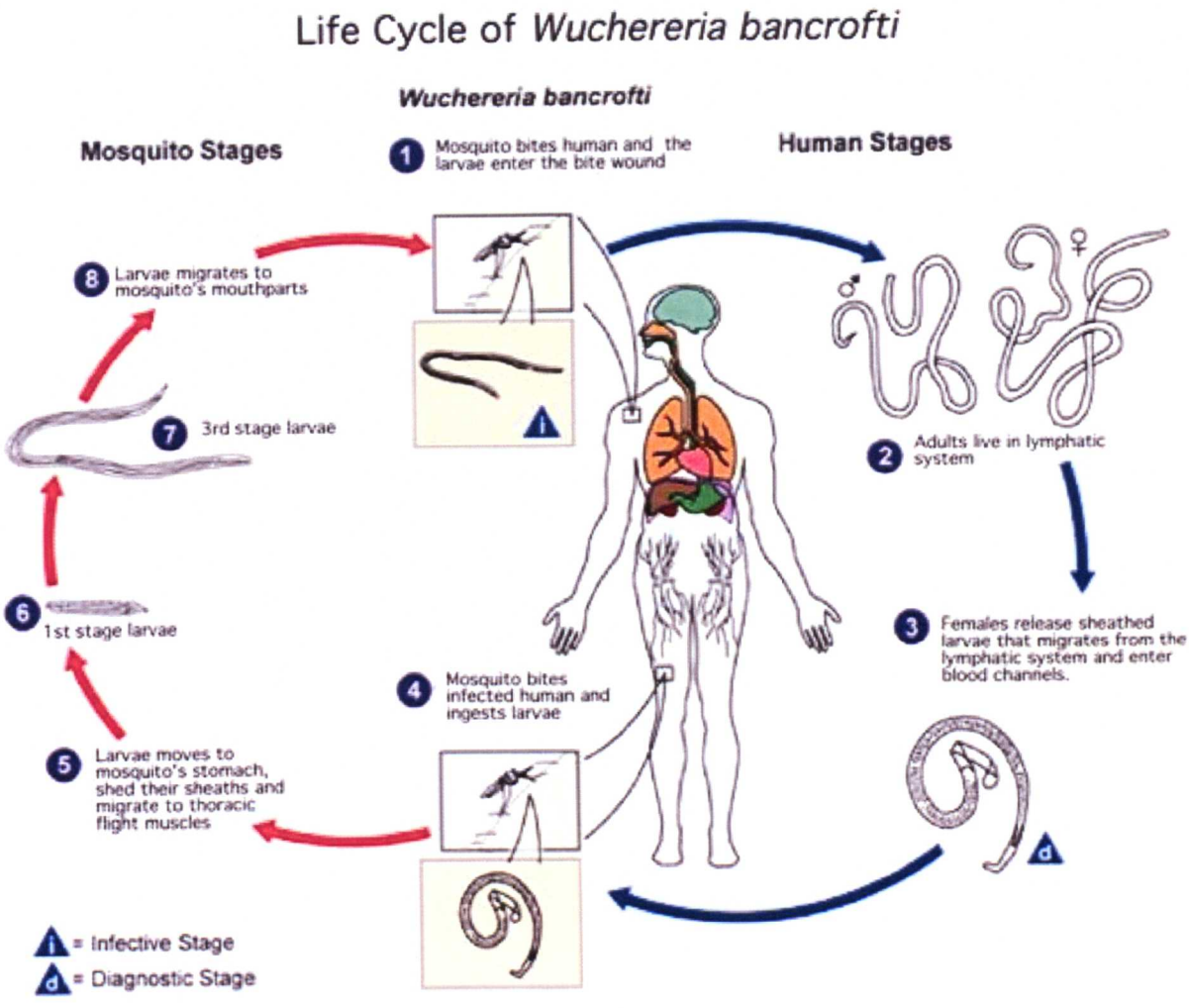

Figure 2.1 The life cycle of filarial nematodes in the human and mosquito hosts. *W. bancrofti*, *B. malayi*, and *B. timori* have a similar life-cycle. The adult parasites causing filarial disease live in the lymphatic system of the human body. The female worm produces offspring, known as microfilariae, which leave the lymphatic system to enter the blood where they may be taken up by mosquitoes during a blood-meal. The microfilariae undergo about 10 - 14 days of development in the mosquito to become infective, third-stage larvae which migrate to the mosquito's mouthparts. These larvae may be transmitted to humans at the time the mosquito takes its next blood-meal. Once transmitted to humans, the larvae take approximately 6-12 months to mature into adult worms. The adult female has the capacity to produce several million microfilariae in its approximate 4-6 year reproductive lifespan (Source: www.dpd.cdc.gov/dpdx/HTML/Filariasis.htm

2.2.3 Microfilarial periodicity

The major vectors of *W. bancrofti* vary with geographical, climatic and ecological factors. The parasite has apparently adapted to the biting habits of the major or vector for any specific location. The microfilariae appear in the peripheral blood in large numbers at a specific period of the 24-hour cycle. When the largest density of microfilariae is found in the peripheral blood at night they are said to have a nocturnal periodicity. In most parts of the world *W. bancrofti* microfilariae circulating in an infected human exhibit a marked nocturnal periodicity (Hamer and Despommier, 1998). Depending on the population surveyed, microfilariae density in the peripheral circulation peaks between 11pm and 3am with very few or no microfilariae detectable during daylight hours (Dreyer et al., 1996; Simonsen et al., 1997); the microfilariae congregate in vessels in the lungs and other deep blood vessels during the daytime (Manson, 1899). In areas where *W. bancrofti* exhibits nocturnal periodicity, infection is transmitted in the evening and night by biting *Anopheles, Culex* or *Mansonia* mosquitoes (Hamer and Despommier, 1998).

In sub-periodic filariasis, significant levels of microfilariae are found in peripheral blood throughout the 24 hour period, but density does increase at a specific period. In some parts of the eastern South Pacific, however, microfilariae are detectable in the blood throughout the day, with the peak density occurring during daylight hours (Rajan and Gundlapalli, 1997). This periodicity is known as diurnally sub-periodic type. In these areas, infection is transmitted primarily by the day- biting *Aedes* mosquitoes (Rajan and Gundlapalli,1997; Hamer and Despommier, 1998). In East Africa, including Zanzibar islands, *W. bancrofti* is the only known aetiologic agent of LF and the microfilariae show nocturnal periodicity. The nocturnal periodicity is by far the most common. It is reported that the average resident of *W. bancrofti* endemic areas receives tens or hundreds of thousands of mosquito bites per year, a proportion of which are

from infective mosquitoes and thus is exposed to hundreds, if not thousands, of infective larvae in that time period (Rajan and Gundlapalli, 1997). This indicates that most, if not all, individuals in endemic areas are exposed to infective larvae and that exposure begins in infancy. However, hundreds, or even thousands, of infective bites may be required to establish infection, indicating that children may not begin to become infected until they reach two years of age or become antigenaemic (Hairston and De Meillon, 1968; Roseboom et al., 1968; Gubler and Bhattacharya, 1974., Lammie et al., 1994). Despite uniform exposure to infective larvae, individual responses to this parasitologic challenge vary dramatically (Rajan and Gundlapalli, 1997).

2.3 Clinical manifestations of lymphatic filariasis

The clinical manifestations of LF have been reported to vary from one endemic area to another and also differ to some extent on the species of the parasite that is involved (Sasa, 1976). Bancroftian filariasis is characterized by a wide spectrum of clinical manifestations ranging from clinically asymptomatic microfilaria-positive individuals to patients with disfiguring chronic filarial disease. Based on those different clinical conditions those living in endemic areas are generally categorized into five broad groups.

2.3.1 Endemic "normals" group

These are those individuals without evidence of clinical or parasitological infection and have been living in a lymphatic filariasis endemic area for a long period. This group is generally referred to as "endemic normals" (WHO, 1992). Initially, this group is composed of only individuals who were negative for microfilariae and lacked clinical symptoms of filariasis. However, the development of sensitive and specific tests has led to a refinement of this group to include those who are also negative for circulating filarial antigen.

2.3.2 Asymptomatic microfilaraemic group

These are those individuals who are without evidence of clinical symptoms or signs of filariasis disease, but with circulating adult worm antigen and with or without microfilariae in the blood. This usually constitutes a large group of people living in LF endemic areas. A large proportion of these individuals remain asymptomatic for many years (Ottesen, 1992; WHO, 1992) although some may later develop clinical symptoms. Studies have shown that individuals in this group have subclinical lymphatic pathology (Amaral et al., 1994; Freedman et al., 1994). In addition to lymphatic pathology it was observed that up to 45% of microfilaraemic patients have renal pathology manifested as haematuria and/or proteinuria (Dreyer et al., 2000). The actual mechanisms leading to these renal abnormalities have not been well defined although it has been suggested that immunologic damage induced by immune complexes deposited in renal glomeruli is likely to be the cause. However, such complexes have been detected circulating in the blood of some clinically asymptomatic individuals with bancroftian filariasis (Prasad et al., 1983; Lunde et al., 1988; Kobayashi et al., 1997). In the past, the living worms themselves were not thought to cause pathology; instead, damage was believed to result from the immune system's response to resident worms. Recognition of the adult worms as foreign by the immune system was thought to disrupt the presumed harmonious relationship between adult worm and human host, leading to inflammation, secondary tissue damage and development of chronic clinical manifestations of LF. However, recent lymphoscintography and ultrasound evaluations of infected "asymptomatics" suggest that while they exhibit no outward signs of disease, such individuals in fact sustain extensive lymphatic damage that appears to progress as the duration of infection increases (Witte et al., 1993; Amaral et al., 1994; Freedman et al., 1995a and 1995b; Dreyer et al., 2002). Initially, this lymphatic damage was considered to be the result of either worm-related lymphatic obstruction or an inflammatory response to the adult worms; however, studies have shown no evidence of either obstruction or

inflammation, suggesting that the mechanism of damage is non-obstructive and unrelated to immune responses targeting the adult worms (Dreyer et al., 2000). It is now believed that some factors released by living adult worms cause local lymphatic vessel dilation that increases with duration of exposure to the worms (Dreyer et al., 2000). As vessel dilation progresses, the contraction of the vessel walls decreases, impairing the vessel's ability to transport lymph and causing lymphatic vessel dysfunction that results in local accumulation of interstitial fluid. Sites of vessel dysfunction and fluid accumulation reflect the most common adult worm nesting sites – the lymphatic vessels of the legs and spermatic cord.

2.3.3 Acute symptomatic group

In filariasis endemic areas, some infected individuals develop periodic episodes of acute filarial disease characterized by fever and accompanied by inflammation of the lymphatic vessels (lymphangitis) and lymph nodes (lymphadenitis). This clinical manifestation is generally referred to as adenolymphangitis (ADL) and is thought to be induced by adult worms located in the lymphatics (Ottesen, 1992). The recurrent episodes of ADL are believed to be a major risk factor for the development of lymphoedema of the legs (Pani et al., 1990; Das et al., 1994). There are two common types of acute attacks that are noticed to occur in residents of LF-endemic areas (Dreyer et al., 1999). The first being the acute attacks referred to as acute filarial lymphangitis (AFL) that are said to be triggered by body's inflammatory response to the death of one or more adult filarial worms in the lymphatic vessels. Studies have shown that death of the worms either spontaneously or as a result of treatment could trigger ADL (Noroes et al., 1997; Dreyer et al., 1998). Although AFL may be characterized by localized pain and redness centered on the location of the dead worm's nest, AFL episodes are often subclinical (Dreyer et al., 1999). Individuals experiencing AFL are generally febrile with mild systemic symptoms and no exfoliative dermatitis; oedema rarely occurs as a result of filarial acute attacks (Dreyer et al., 1999). About 3% of the reported acute attacks experience

AFL (Dreyer et al., 1999). The second syndrome is referred to as acute dermatolymphangitis or acute dermatolymphangioadenitis (ADLA) and is suggested to be a result of secondary bacterial infections. These episodes are often severe and can have visible and permanent negative consequences. ADLA is made possible by the damage live worms have inflicted on lymphatic vessels draining the skin (Dreyer et al., 1999). As adult worm-induced vessel dilation and damage progresses, protein-rich interstitial fluid accumulates in the lymphatic vessels of the foot, leg and scrotal wall. Skin lesions caused by fungal infections or breaks in the skin provide entry portals for bacteria, which find abundant nutrients readily available in the interstitial fluid under the skin. ADLA is characterized by fevers, prostration and other systemic manifestations of bacteremia, as well as pain, oedema (swelling), diffuse cutaneous and subcutaneous inflammation and exfoliative dermatitis (skin peeling) at, and radiating from, the site of infection (Dunyo et al., 1998; Dreyer et al., 1999). The symptoms of a bacterial acute attack can last for a week or more, with the oedema of the affected body part (foot, leg, scrotum) generally taking longer to subside and often not regressing completely. ADLA episodes recur at irregular intervals and the resulting oedema requires progressively longer periods of time to resolve. Eventually, the swelling no longer subsides, resulting in chronic lymphoedema of the affected part (Dreyer et al., 1999). Bacterial acute attacks, however, do not abate with the onset of chronic disease but rather increase in frequency as disease progresses, compounding existing lymphatic and skin damage and aggravating chronic manifestations. The syndrome is a common cause of lymphoedema both within and outside filariasis endemic areas.

2.3.4 Chronic lymphatic pathology group

In LF endemic areas there is always a group of individuals that develop chronic lymphatic pathology. The most common main clinical manifestations of chronic lymphatic filariasis are hydrocele, lymphoedema/elephantiasis, and chyluria (WHO, 1992).

Hydrocele is characterized by the accumulation of clear, sterile fluid inside the scrotal sac and the resultant swelling, without changes in the quality of the skin and underlying tissues. The tunica vaginalis, the membrane surrounding the testes, secretes lubricating fluid that allows the testes to move freely within scrotum. In healthy men, the lymphatic vessels of the spermatic cord take up this fluid, preventing its accumulation in the scrotum. In men infected with adult worm-induced damage to the spermatic cord lymphatics results in slow build-up of fluid in the scrotum due to inefficient drainage. When adult worms in the intrascrotal lymphatics die, the vessels are blocked by the body's inflammatory reaction to the disintegrating worms and fluid accumulates more rapidly in the scrotum, producing a hydrocele (Dreyer et al., 2000). Early in the natural history of infection, the vessel blockage is generally only temporary; re-canalization occurs, fluid drainage resumes and the hydrocele disappears (Dreyer et al., 2000). Later, however, as damage to the intrascrotal lymphatics becomes more extensive and the burden of repeated temporary obstructions increases, a chronic hydrocele may develop. Hydrocele is much more prevalent than lymphoedema and elephantiasis of either the leg or the scrotum, to the point that the prevalence of hydrocele in men in a given area has been found to be a relatively accurate surrogate for the prevalence of *W. bancrofti* microfilaremia in the general population in that area (Gyapong et al., 1998a). *Brugia* species are not associated with hydrocele (Partono, 1987). Chylocele is a chronic condition that resembles hydrocele but occurs when dilated lymphatic vessels in the spermatic cord rupture and cause leakage of milky coloured lymph fluid (rich in fat) into the cavity of tunica vaginalis (Dreyer et al., 1998b).

Lymphoedema occurs due to accumulation of lymph fluid in the tissues following damage of the lymphatic vessels (Ottesen, 1990). Lymphoedema is common in the lower limbs but can affect the arms, breasts, scrotum, penis and sometimes vulva. Lymphoedema develops gradually starting as pitting oedema that is reversible to later becoming a persistent swelling which is accompanied by

fibrotic changes of the skin. These changes can ultimately lead to gross pathology generally referred to as elephantiasis. Elephantiasis is characterized by profound fibrosis as well as profoundly thickened and leathery skin sometimes with wart-like growths and secondary microbial infections (Ottesen, 1990). Damaged and dilated lymphatic vessels near the surface of the skin may push outward, forming small pouches and vesicles that can leak protein-rich lymph fluid or even rupture, increasing the opportunity for bacterial infection and producing conditions known as "mossy foot" and lymph scrotum (depending on the location of the vesicles) (Dreyer et al., 2000).

Chyluria is a less common manifestation defined as the excretion of chyle (intestinal lymph) into urinary tract. The basic pathophysiology is related to blockage of the retroperitoneal lymph nodes below the cisterna chili with consequent reflux and flow of the lymph directly into renal lymphatic vessels, which may rupture and permit flow of chyle into the urinary tract (WHO, 1992). The urine often appears milky white in colour from the contents of lipoprotein or red when there is admixture of blood. Chyluria is frequently mono-symptomatic and self-limiting, the fistula closing spontaneously after a few days or weeks, but it occasionally persists and may lead to weight loss, lymphopaenia and anaemia that require nutritional and sometimes surgical intervention (Date et al., 1983; McMahon and Simonsen, 1995)

2.3.5 Tropical pulmonary eosinophilia (TPE)

Some individuals in LF endemic areas are reported to have an inflammatory response to microfilariae in the lungs resulting in development of tropical pulmonary eosinophilia (TPE). These comprise less than1% of all patients with lymphatic filariasis. Tropical pulmonary eosiniophilia presents a clinical picture of paroxysmal nocturnal cough (and sometimes wheezing) similar to asthmatic symptoms (Ottesen, 1992). Visualization of chest radiographs indicates nodular or diffuse pulmonary lesions. Other clinical features of TPE include elevated

peripheral blood eosinophilia (> 3000/mm*3), extraordinary high levels of serum IgE and very high levels of specific anti-filarial antibodies. Unlike all other forms of LF patients with TPE are extremely hyper-responsive to filarial antigens, especially those derived from the microfilarial stage of parasite (Ottesen, 1984). Untreated TPE produces lung disease and permanent lung damage.

Other chronic manifestations attributed to LF include mono-articular arthritis, glomerulonephritis and endomyocardial fibrosis (McMahon and Simonsen, 1995).

2.4 Pathogenesis of lymphatic filariasis

The pathogenesis of filarial disease remains poorly understood and has been a subject of controversial debate. Unlike most human diseases, human filariasis suffers from the lack of an appropriate animal model for research into the basic pathophysiology of the disease (Nelson et al., 1991). The most widely investigated animal models are the Mongolian jird (*Meriones unguiculatus*) (Ash and Riley, 1970) and the ferret (*Mustela putorius furo*) (Crandall et al., 1982). The major deficiency of these animal models, however, is that the infection does not mimic the human disease in the anatomic localization of adult worms, in the symptomatology, or in the immune effector mechanisms that may be involved (Nelson et al., 1991).

Abnormalities in the lymphatic vessels have been shown to occur in a variety of hosts with experimental filariasis (Schacher and Sahyoun, 1967; Denham and Rogers, 1975; Rogers et al., 1975; Vincent et al., 1980; Hines et al., 1985). In cats (*Felis catus*) infected with *B. pahangi* for example, lymphatic vessels begin to dilate as early as 10 days after larval inoculation (Denham and Rogers, 1975). Detailed examination of the nature and distribution of lymphatic and blood vascular abnormalities in ferrets infected with *B. malayi* demonstrated generalized vascular abnormalities (Case et al., 1991).

Dilation of lymphatic vessels (lymphangiectasia) is the most investigated of the lymphatic abnormalities. Investigations employing videomicroscopy (Case et al., 1991; Case et al., 1992) and ultrasonography (Noroes et al., 1996) demonstrated nests of wriggling live adult worms, which typically stretched and dilated lymphatic vessel walls. Histological examination of the tissues from infected ferrets revealed that dilated lymphatics, most prominent near living or dead adult worms, exhibited plump endothelium and thickened walls and valves with perilymphangitis and adjacent tissue fibrosis was frequently present. Histological examination of tissues obtained from patients with filariasis found that lymphatic vascular lesions parallel those seen in infected ferrets (Case et al., 1991).

Examination of clinically asymptomatic microfilaraemic persons using radionuclide lymphoscintography revealed varying degrees of structural lymphatic damage including lymph vessel dilation (Freedman et al., 1995). In addition to dilation of LF, lymph flow studies reported an enhanced pattern of rapid, increased lymph flow in asymptomatic microfilaraemic persons, which is thought to be due to increased lymph production in distal tissue (Freedman et al., 1995). Studies on the B and T lymphocyte immune-deficient mutant mouse called severely combined immunodeficiency (SCID) demonstrated that the presence of adult worms in the lymphatic vessels was associated with lymphangitis and lymphangiectasia and in some cases there were significant inflammatory changes and retention of lymph fluid (Nelson et al., 1991). Thus, in the absence of any immune response the parasite or its excretory/secretory products is able to induce lymphatic pathology.

The aetiology of abnormally increased lymph production seems to result from either structural damage to lymph vessel walls caused by the constantly motile adult worms (Case et al., 1992; Witte et al., 1993) or by the effect of unidentified parasite secretory products after endothelial cell function (Kaiser et al., 1990; Mupanomunda et al., 1997).

Earlier studies attribute pathogenesis to obstructed afferent lymph flow with truncal back pressure from nodal congestion and inflammatory or granulomatous responses to released products or calcified filariae. It was postulated that perilymphatic inflammation, such as that resulting from reactions to a dead adult worm might generate fibrosis and narrowing of lymphatics with gradual distal dilatation (Manson-Bahr, 1959). Formation of lymphatic granulomatous nodules and development of acute filarial lymphangitis as a result of death of the adult worms is observed in some patients, e.g. after administration of treatment (Noroes et al., 1997; Dreyer et al., 1998a). This has made some investigators propose that lymphangiectasia and inflammatory reactions are two independent components of lymphatic pathology that are triggered by 'toxins' of living adult worms and by host reactions to damaged or dead worms, respectively (Dreyer et al., 2000).

Studies in animal models have shown that secondary infections with bacteria and fungi may play an important role in the development of chronic lymphatic pathology. For example, secondary infection with *Streptococcus* bacteria in cats infected with *B. malayi* resulted in a more severe lymphatic pathology than in control animals (Bosworth and Ewert, 1975). Similar results were obtained when *B. malayi* infected cats were exposed to the yeast phase of the fungus *Sporothrix schenkii* (Barbee et al., 1977). Oedema and fibrosis tended to appear earlier, more consistently and progressed more rapidly in cats with dual infections than in controls.

Bacteriological investigations of patients with filarial lymphoedema found bacteria in skin, tissue and lymph fluids and lymph nodes of patients with chronic lymphoedema without recent episodes of filarial ADL (Olszewski et al., 1999). Further, 4.7% of patients with ADL or a recent episode (within the last 2 weeks) had positive blood cultures. Taken together, these results suggest that secondary infections may be responsible for filarial ADL and exacerbation of

lymphatic pathology. Improved foot care hygiene combined with appropriate use of topical antibiotics or anti-fungals reduces the number of ADL attacks (Shenoy et al., 1998) thus providing further evidence that secondary infections have a role to play in lymphatic pathology. The quality of life of lymphoedema patients after education or appropriate hygiene, skin care techniques and simple exercises that encourage lymph drainage was previously shown to improve using a Dermatology Life Quality Index (DLQI) questionnaire (McPherson, 2003).

2.5 Immunology of lymphatic filariasis

As in many parasitic diseases, anti-filarial immune responsiveness is correlated with filarial infection in humans (Ottesen, 1992). Following serologic assays conducted on samples collected from LF patients in endemic areas it has been shown that almost all individuals have been exposed to filarial parasites (Piessens et al., 1980b; Bailey et al., 1995). However, there are a large group of individuals, who despite lifelong exposure to infection have no detectable microfilaraemia and/or antigenaemia and clinical history or evidence of infection (Freedman et al., 1989; Day, 1991; King and Nutman, 1991; Mahanty et. al., 1992). These individuals are referred to as "endemic normals" or "putatively immune", and exhibit a greater degree of increased immune responsiveness than that of microfilaraemic individuals (Ottesen et al., 1997; Piessens et al., 1980a; Piessens et al., 1980b; Ottesen et al., 1982; Ottesen, 1984; King and Nutman, 1991; Dimock et al., 1994). The presence or absence of specific antibody and cellular responses actively generated by the host are important in determining the outcome of infection (Ottesen, 1984).

2.5.1 Cellular immune responsiveness

Initial studies showed that LF infection is associated with cellular immune hypo-responsiveness and limited almost exclusively to filarial antigens (Ottesen et al.,

1977; Piessens et al., 1980a; Piessens et al., 1980b). The patients with tropical pulmonary eosinophilia have been proved to be exceptions as they demonstrate a hyper-responsiveness condition to filarial antigens especially those derived from the microfilarial stage of the parasite, a feature that is not seen in other filarial patients (Ottesen, 1984). This observation led to the speculation that tropical pulmonary eosinophilia is a form of occult filariasis in which the absence of microfilariae reflects an immunologic hyper-responsiveness on that part of the host which results in effective clearance of the stage of the parasite from the blood (Ottesen, 1984). The existence of specific cellular immune unresponsiveness in human filariasis is presumably important for the successful persistence of the parasite within the host (Ottesen, 1984). It is recognized that unresponsiveness occurs not because the patients fail to become sensitized to filarial antigens, but because various modulating mechanisms develop that can specifically suppress responses to these antigens (Ottesen, 1984). The mechanisms involved in modulation of cellular immune responses to filarial antigens include, serum suppressor factors, suppressive adherent cells that are probably monocytes and T-lymphocyte suppressor cells (Piessens et al., 1980c; Piessens et al., 1982).

Cellular immune responses can be defined on the basis of cytokine production by T helper cells, with T helper 1 (Th1) and Th2 representing proposed subgroups (Mosmann and Coffman, 1989). Stimulation of peripheral blood mononuclear cells (PBMC) from individuals with active filarial infection using parasite antigen has been shown to result in increased Th2 cytokine production (IL-4, IL-5 and IL-10 responses) suggesting an active immunological cross-regulation response that inhibits pro-inflammatory responses to the parasite. In contrast, antigen-negative individuals characteristically have strong Th1 (IFN-γ responses) (Steel et al., 1994; de Almeida et al., 1996; Dimock et al., 1996).

2.5.2 Humoral immune responsiveness

Hyperglobulinaemia with elevated levels of specific antibody have long been recognized in filariasis, with only microfilaraemic patients having relatively deficient antibody responses which could reflect an element of specific humoral immune-suppression (Ottesen, 1984). Humoral immune response in human filariasis is generally dominated by the IgG4 isotype, when measured by enzyme-linked immune-sorbent assay (ELISA) against somatic adult worm antigen (Ottesen et al., 1985; Kwan-Lim et al., 1990; Egwang et al., 1993) and individuals harbouring adult worms have been found to have higher anti-filarial IgG4 levels than adult worm-free individuals (Nicolas et al., 1999).

For children living in filariasis endemic areas, anti-filarial IgG4 responses are higher in individuals with antigenaemia than in those without antigenaemia and increases in anti-filarial IgG4 are associated with acquisition of infection, as defined in antigen status. In contrast, anti-filarial IgG1 and IgG2 increase to the same extent among children who acquire infection (antigenaemia) and among those who remain antigen negative suggesting that these responses are driven by exposure to filarial larvae rather than infection (Lammie et al., 1998). Other investigators have postulated that IgG1 levels are more related to microfilarial status than to infection status (Simonsen et al., 1996). However, in adults, antifilarial IgG2 responses of antigen-negative persons are similar to those of antigen-positive (microfilaria negative) persons, but are significantly higher than those of microfilaria-positive individuals (Addiss et al., 1995; Dimock et al., 1996). The reason for decreased anti-filarial IgG2 responses in microfilaraemic persons is not clear, but may be related to shifts in cytokine production (King et al., 1990).

There are a few individuals that appear to be truly immune and never become infected at all in the endemic community. However, most of them become infected at some point in their lives. Studies have shown that even of those

infected some appear to be able to clear the infection without extensive lymphatic damage; it is unclear whether some of these individuals also develop resistance to re-infection in the process. Others are unable to clear the infection but manage to sustain very low parasite burdens (ie their circulating microfilariae levels are below the level of detection and only detection of the circulating adult worm antigen in their blood shows them to be infected) and outwardly, at least, remain free of any manifestations of LF. Another group, while demonstrably antigen-positive and microfilariae positive, also never show any outward signs of infection. Finally, certain proportions go on to exhibit clinical manifestations of LF. Even in these individuals, however, there is no simple progression of events; the clinical manifestations of *W. bancrofti* infection are not uniform but vary in different individuals.

2.6 Vectors of lymphatic filariasis

Sir Patrick Manson was the first person to demonstrate that mosquitoes were vectors of *W. bancrofti* in 1878 (Scott, 2000). However, studies have shown that not all mosquito species can transmit the parasites. The major mosquito species that transmit the lymphatic filariae of humans varies with geographical, climatic and ecological factors. Studies show that *Culex, Anopheles, Aedes* and *Mansonia* are the main mosquito genera responsible for LF transmission. These mosquito species have been found to be specific in the species of LF they transmit. *Culex* transmit *W. bancrofti* only while *Anopheles* transmit *W. bancrofti, B. malayi,* and *B. timori; Aedes* transmit *W. bancrofti,* and *B. malayi* and *Mansonia* transmit *W. bancrofti* and *B. malayi* (Sasa, 1976; Scott, 2000). This suggests that bancroftian filariasis can be transmitted by a wide range of mosquito species. The *Culex pipiens* complex that includes *Culex quinquefasciatus* as well as the *An. gambiae and An. punctulatus* are responsible for the nocturnally periodic form of *W. bancrofti* and *Aedes pseudoscutellaris* group are also involved in transmission (Sasa, 1976; Scott, 2000).

Entomological studies in East Africa reported that *Anopheles gambie sensu lato, Anopheles funestus* and *Culex quinquefasciatus* are the important vectors of filariasis in that region (Nelson et al., 1962; White, 1971; Wijers and Kiilu, 1977; Mwandawiro et al., 1997; Pedersen and Mukoko, 2002). A survey conducted in four coastal villages near Tanga, Tanzania, identified the principal vectors of LF, in order of importance, as *An. gambie s.l., Cx. quinquefasciatus* and *An. funestus* (McMahon et al., 1981). In most studies in East Africa *Cx. quinquefasciatus* was shown to be the main vector in the coastal towns and villages, while *An. gambie* and *An. funestus* were more important in inland areas.

The importance of the three mosquito vectors in transmission appears to depend on the prevailing ecological and socioeconomic factors. In rural areas, where there are no pit latrines, anophelines are often the only vectors of *W. bancrofti* whereas in urban areas *Cx. quinquefasciatus* is the principal vector (Mansfield-Aders, 1927; White, 1971; Hawking, 1977; Maxwell., 1999). Availability of breeding sites in urbanized areas leads to continuous transmission by *Cx. quinquefasciatus* mosquitoes throughout the year whereas transmission is interrupted in the dry season in rural areas due to the lack of availability of stagnant water bodies (Wijers and Kiilu, 1977; McMahon et al., 1981). *Cx. quinquefasciatus* mosquitoes are a major biting nuisance in many urban areas and their abundance appears to be increasing. This is mainly due to rapid urbanization without provision of proper sanitation leading to increased numbers of breeding sites in the form of wet pit latrines, cess pits and blocked open drains (Curtis and Feachem, 1981).

Mansonia species are said to be the major vectors of brugian filariasis in most parts of Asia. These include *Mansonia annulifera, Mansonia uniformis* and *Mansonia indiana*, but *Mansonia annulifera* is the major vector (Sabesan et al., 1991). *Anopheles barbirostris* has been reported to be the second potential vector (Raghavan, 1961).

In the 1930s in Sri Lanka studies on brugian filariasis transmission identified *M. uniformis, M. annulifera* and *M. indiana* to be the major mosquito vectors which were found in association with the water plant *Pistia stratiotes* (water lettuce). Based on these findings, campaigns for removal and destruction of *P. stratiotes*, initially by manual methods and later using herbicides, were undertaken (Dassanayake and Chow, 1954). A comprehensive survey of *B. malayi* infection carried out in 21 previously endemic foci in Sri Lanka concluded that the parasite has been eliminated mainly through destruction of aquatic vegetation, particularly *P.stratiotes*, through the use of a "weedicide" (Phenoxylene 30) and selective treatment of microfilaria- positive individuals with diethylcarbamizine (Gautamadasa, 1986). Table 2.1 gives summary of the major vectors of *W. bancrofti* in different geographical regions. Culex mosquitoes are the only reported potential vectors of LF in Zanzibar (Maxwell et al., 1990; Mawell et al 1991; Pedersen et al., 1999)

Table 2.1 Major vectors of *Wuchereria bancrofti* in different geographical regions

Geographical Region	Vector species
The Americas and Caribbean	Primary vector is *Culex quinquefasciatus*. Other vectors include members of subgenus *Nyssorhynchus* (*Anopheles darlingi, An. aquasalis, An. Albitarsis*)
East Mediterranean (Egypt)	Members of *Culex pipiens* group are the principal vectors.
South and East Asia	Nocturnally periodic *W. bancrofti* is mainly transmitted by *Culex pipiens* group. Other vectors include members of subgenus Anopheles (*An.barbirostris, An.nigerrimus)and subgenus Myzomyia (An. Philippinensis, An. Stephensi, An. vuruna)*
Pacific	The major vectors include Aedes (Stegomyia) *pseudoscutellaris* group (e.g. *Ae. Polynesiensis*) Anopheles (Myzomyia) *punctulatus* group, *Cx. Quinquefasciatus, Ochlerotatus vigilax*
Africa	*Cx. quinquefasciatus, An. gambiae s.l, An. funestus*

2.7 LF vector-parasite relationship

The ability of mosquitoes to ingest microfilariae of *W. bancrofti* and complete successful development of the ingested microfilariae to infective larvae (L3) are important determinants of transmission of infection. Studies on the vector-parasite relationship have identified two different patterns of infection that have important implications on the epidemiology and success of interruption of transmission LF. The relationship between culicine species and *W. bancrofti* is known as limited. As the number of ingested microfilariae increases, the success rate of the ingested microfilariae to yield infective filarial larvae decreases in limitation (Southgate and Bryan, 1992; Pichon, 2002). Previous entomologic studies have shown that a considerable proportion of ingested

microfilariae are damaged during uptake by the pharyngeal armatures of mosquitoes (Bryan et al., 1974; McGreevy et al., 1978). Studies have shown that *C. quinquefasciatus* ingest microfilariae from human blood very efficiently, are easily infected by parasite, and can harbour large numbers of microfilariae in their tissues. However, few microfilariae survive to infectivity – 50% of microfilariae are killed or inactivated in the mosquito gut within 20 hours of ingestion, and since the parasite's development from microfilariae to the L3 stage can take up to 14 days, many mosquitoes die before becoming infective. In addition, some mosquitoes feed on other mammals or birds after becoming infective, thereby "wasting" the L3 larvae they carry. Hence, the passage of *W. bancrofti* from human host to human host via *C. quinquefasciatus* is relatively inefficient. However, in culicine species such as *Aedes* and *Culex,* the pharyngeal armatures are less well developed and thus inflict less damage on ingested microfilariae (McGreevy et al., 1978). Thus, even at low microfilarial numbers parasite uptake by culicine mosquitoes occurs. It has been proposed that in areas where limitation occurs the total interruption of transmission will be difficult to achieve (Pichon, 2002).

The relationship between anopheline species and *W. bancrofti* is known as facilitation (Pichon, 2002). Investigations on *An. gambiae* and *An. arabiensis* revealed that the percentage of mosquitoes ingesting *W. bancrofti* microfilariae was strongly associated with microfilariae density in the host blood (Bryan and Southgate, 1988b). Conversely, the probability of microfilariae successfully penetrating the gut wall in *Anopheles* mosquitoes diminishes as the number of microfilariae ingested diminishes due to damage inflicted on the microfilariae. The pharyngeal armature is well developed in anopheline mosquitoes hence microfilariae are damaged when ingested and at low densities there are very few undamaged microfilariae left to infect the mosquito (Bryan and Southgate, 1988a). In facilitation there is a critical threshold below which the parasite population will die out spontaneously (Webber, 1991; Pichon, 2002). These findings have led to the conclusion that interruption of transmission is easier to

achieve when the local vectors are anopheline mosquitoes (Bryan and Southgate, 1988b).

2.8 Diagnostic Techniques of lymphatic filariasis

Currently, there are many different methods available to determine infection and disease status of an individual. Those include both parasitological as well as immunological techniques. However, new technological advances in immunological diagnosis and imaging has revolutionised our understanding of the pathophysiology of LF. Early methods of diagnosis of an active infection were based on the detection of microfilariae in the blood. The parasitological techniques employed include: Thick Blood Films, Counting Chamber, Membrane (Nucleopore) filtration technique, Knott's concentration technique and the Quantitative Blood Count (QBC) technique.

2.8.1 Parasitological diagnosis

2.8.1.1 Thick blood films

The most widely used method for detection of microfilariae is the examination of thick blood film stained with Giemsa (Eberhard and Lammie, 1991). This technique uses a thick smear made from a finger prick blood sample. The smear is air-dried, stained with Giemsa (1:10) for 30 minutes and examined under a microscope (McMahon et al., 1979a; Wamae, 1994). The staining allows the identification of *W. bancrofti* microfilaria based on size, presence of the sheath and lack of nuclei in the tip of the tail from other human filarial species. If a measured volume of the blood is used intensity of infection (per ml) can be determined. It is relatively cheap and requires minimal training for its use (Moulia-Pelat et al., 1992). However, its major limitations are; (i) low sensitivity owing to small amounts of blood used and loss of microfilariae during staining procedures (Sabesan et al., 1991; Simonsen, 2003) and (ii) the technique is often inconvenient, as a blood sample needs to be obtained at night (in areas

with nocturnal periodicity) to coincide with peak concentration of microfilariae, i.e. between 2100 hrs and 0200 hrs. This test can be modified by the administration of a low dose of diethylcarbamazine (DEC) prior to drawing the sample (provocative test). The DEC provokes microfilariae to leave the deep vasculature and move into the peripheral circulation and thus allowing use of the test during the day (McMahon et al., 1979b). The provocative test cannot be used in onchocerciasis endemic areas due to the side-effects of DEC on patients with onchocerciasis (severe Mazzoti reaction).

2.8.1.2 Counting Chamber technique

This is another method for examination and counting of microfilariae in the infected blood. The counting chamber technique is fast, quantitative and cheap (McMahon et al., 1979a). A 100µl of blood is added to 0.9ml of 3% acetic-acid and then transferred into a special chamber called "counting chamber" and examined for microfilariae under low power of a compound microscope. This technique is ideal for routine hospital diagnosis as well as field surveys in areas where only one species of filarial is known to exist. Many studies in East Africa use the counting chamber technique (McMahon et al., 1979).

2.8.1.3 Membrane (Nucleopore) filtration technique

This technique involves filtration of a known volume of venous blood (usually 1 ml) through a polycarbonate Nucleopore membrane (3µm pore size) (Eberhard, 1991). This is followed by a large volume of pre-filtered water (35ml) that lyses the red blood cells. The filter is then removed and placed on a glass slide for staining and subsequent examination. The staining allows species identification. This technique has proved to be highly sensitive and excellent for determining density of infection but due to high cost of filters and the need for venous blood makes it impractical for field surveys (Desowitz et al., 1973)

2.8.1.4 Knott's concentration technique

This test has been modified since its invention. In this method 1ml of anti-coagulated venous blood is mixed (lysed) with 10ml of 1-2% formalin or citrate-saponin solution depending on whether viable microfilariae are required (Melrose et al., 2000). The preparation is then centrifuged at 500g for a minute to sediment the microfilariae at the bottom of the tube. The supernant is removed and a drop of 1% methylene blue is added to the sediment. The resultant sediment is then transferred to a glass slide and examined under the microscope for microfilariae. The viscosity of the sediment may hamper microscopic examination of the sediment. Triton X-100 can be added to enhance visibility as it dissolves the proteingenous elements of the deposit (Melrose et al., 2000). However, this method is not favourable because the resulting precipitate makes examination of microfilariae difficult thus reducing its sensitivity.

2.8.1.5 The Quantitative Blood Count (QBC) technique

In this system heparin, EDTA and acridine orange are incorporated into a microhaematocrit tube (Freedman and Berry, 1992). Following centrifugation of blood sample, the buffy coat interface is examined by fluorescence microscopy, where the acridine orange stained DNA of the nuclei within the microfilariae can readily identified, and morphologic characteristics can be examined, allowing for differentiation of species (Bawden et al., 1994). Though this test is faster, its sensitivity is not superior to the thick blood film technique at low microfilarial densities.

2.8.2 Serological diagnosis

It is recognized that measurement of microfilaraemia is a relatively insensitive method especially if microfilaria density is very low (Eberhard and Lammie,

1991; Melrose et al., 2004). Additionally, a significant proportion of the population with active infection have no circulating microfilariae (Lammie et al., 1994) and although these people do not contribute to transmission, basing prevalence on microfilaria detection alone underestimates the burden of infection (Turner et al., 1993). Also the tests described above do not allow for determination of whether microfilariae negative status is due to true absence of adult worms, infection with single sex or non-fecund worms or asymptomatic infection with microfilarial densities below the limits of detection (More and Copeman, 1990). Another limitation is lack of the ability to accurately classify individuals according to their relative adult worm burden, as the precise correlation between microfilarial density and adult worm burden is unclear.

2.8.2.1 Circulating filarial antigen

In early 1990 a monoclonal antibody Og4C3 for detecting bancroftian filariasis circulating filarial antigen (CFA) by enzyme-linked immunosorbent assay (ELISA) was developed (More and Copeman, 1990). Studies with animal models showed that circulating filarial antigen levels correlate with the number of adult worms in the host (Weil et al., 1985; Weil et al., 1990) and the same is believed to be true in bancroftian filariasis (Ismail et al., 1998). It has been reported that if diagnosis using microfilaraemia measurement is used about 50% of infected children are missed as compared to CFA assay (Steel et al., 2001). In a study to determine the suitability of the Og4C3 assay for field studies, the assay was found to be 100% sensitive for patent infection as determined using Giemsa-stained thick blood films (Lammie et al., 1994). This new development offered the convenience of daytime testing and greater sensitivity than testing for microfilaria (Turner et al., 1993; Simonsen and Dunyo, 1999). These advances led to the development of two commercially available assays capable of detecting parasite antigen in whole blood or serum. The first to become available used the monoclonal antibody Og4C3 marketed as TropBio-test and manufactured by TropBio Pty Ltd, Australia (More and Copeman, 1990). This is

a semi-quantitative sandwich enzyme-linked immunosorbent assay (ELISA) that recognises a major protein moiety of a phosphorylcholine-containing circulating antigen of adult *W. bancrofti* worms. This assay has been shown to have no cross-reactivity to *Brugia* species or other common gastrointestinal helminths (Simonsen and Dunyo, 1999). In high intensity microfilaraemia its sensitivity approaches 100%, but falls to less than 75% in those with low level microfilaraemia (Chanteau et al., 1994; Rocha et al., 1996). This test can also be used on filter paper blood samples but its sensitivity has been reported to be as low as 50.3% when used on such preparations (Gyapong et al., 1998a). It has, however, a high specificity of between 99-100% (Chanteau et al., 1994; More and Copeman, 1990).

The second assay uses the monoclonal antibody AD12 developed recently (Weil et al., 1997). This has been marketed as a rapid-format immune-chromatographic card test (ICT), originally manufactured by ICT diagnosis (Balgowlah, New South Wales, Australia) and recently taken over by Binax, USA. The ICT utilises capillary as well as venous blood and thus is simple and can be used in the field at any time of the day by people with minimum training (Weil et al., 1997). Results are available within ten minutes and the test has now become the method of choice in community surveys for rapid assessment of endemicity. Studies evaluating the performance of ICT against thick films and filtration techniques have reported a sensitivity of 100%, specificity 96.3%, positive predictive value 70.7% and a negative predictive value of 100% (Phantana et al., 1999; Simonsen and Dunyo, 1999; Pani et al., 2000; Njenga and Wamae, 2001; Chandrasena et al., 2002). It has been reported that if diagnosis using microfilaraemia measurement is used about 50% of infected children are missed as compared to CFA assay (Steel et al., 2001). In a study to determine the suitability of the Og4C3 assay for field studies, the assay was found to be 100% sensitive for patent infection as determined using Giemsa-stained thick blood films (Lammie et al., 1994). This new development offered

the convenience of daytime testing and greater sensitivity than testing for microfilaria (Turner et al., 1993; Simonsen and Dunyo, 1999).

2.8.2.2 Filarial antibody detection technique

These methods, based on detection of filarial-specific antibodies, are usually used for epidemiological and diagnostic purposes. They are mostly based upon crude filarial antigens and have been available since 1960s (Harnett et al., 1998; Melrose et., 2004). By providing a cumulative measure of exposure to filarial infection, antibody assays may circumvent many of the limitations of methods based on direct detection of the parasite or its antigens (Lammie et al., 2004). In terms of the immunological response to lymphatic filarial infections, among populations living in endemic areas, isotype-specific antifilarial antibody responses against parasite antigens are characteristically correlated with infection status (Ottesen, 1992) and this feature has been exploited to develop antibody assays. For example, filarial-specific IgG4 levels are more related to antigenaemia (Addiss et al., 1995). Therefore, measurement of filarial IgG4 levels may be a useful strategy for assessing the impact of mass chemotherapy on filariasis infection. A method was also developed for the detection of anti-filarial IgG4 antibody in urine (Itoh et al., 2001). The method is desirable in certain situations eg young children because use of urine is less invasive than blood sampling. Although assays based on anti-filarial IgG4 antibody reduces cross-reactions with non-filarial helminths (Melrose et al., 2004) as they are limited by cross-reactivity with antibodies from other nematodes, especially with *Strongyloides* (Muck et al., 2003).

Recently a dip stick test called "Brugia Rapid" was devised to test for brugian filariasis. "Brugia Rapid" demonstrated high sensitivity (97%) and specificity (99%). The Brugia Rapid unlike the ICT detects anti-filarial IgG4 antibody, not CFA (Kumari et al., 1994). However, performance of the test requires several steps that make it less convenient as the ICT (Melrose et al., 2004).

A number of recombinant filarial antigens have been developed for use in antibody assays for filariasis (Wang et al., 1999; Rahma et al., 2001). Recombinant filarial antigens should, in principle, be more useful as the basis of diagnostic or exposure assays because of their greater specificity (Lammie et al., 2004). Assays conducted to examine the performance of antibody assays using 3 recombinant antigens, Bm14, WbSXP and BmR1 demonstrated good sensitivity (>90%) for field use and none of the assays demonstrated cross-reactivity with specimens from persons with non-filarial helminth infections. The Bm14 ELISA assay, however, demonstrated some antibody reactivity with sera from patients with *W. bancrofti, B. malayi, L. loa* and *O. volvulus*. The BmR1 assays are sensitive for *B. malayi* infection but relatively insensitive for *W. bancrofti* infection, making the assays suitable for areas with brugian filariasis (Lammie et al., 2004). The Bm14 ELISA assay may be useful in areas with exclusively one type of filariasis.

Antibody responses develop in the absence of demonstrable infection, and detecting incident antibody responses should provide a more sensitive measure of transmission than microfilaria or CFA. Children born after the cessation of transmission should be antibody-negative, while older adults may have evidence of residual antibody reactivity (Gao et al., 1994; Rodriguez-Perez et al., 1999; Weil et al., 2000). Since antibody responses provide an earlier indicator of infection, assays for anti-filarial antibodies should be useful for surveillance following initiation of LF elimination programmes (Lammie et al., 2004). These tests have been used to determine the impact of MDA in Egypt (Ramzy et al., 2006).

2.8.2.3 Molecular diagnosis

An alternative to the identification of the parasite, or parasite antigen is the identification of parasite DNA within the infected individual. The identification of

non-coding sequences from *B. malayi* and *W. bancrofti* has enabled the development of DNA-based techniques for these parasites (Siridewa et al., 1994; Zhong et al., 1996). By incorporation of a 3' biotin on one PCR primer, and using an internal fluorescein-labelled probe, these PCR-based diagnostic methods have subsequently been refined to allow for ELISA-based detection of PCR products (Nutman et al., 1994). In evaluation studies the method has been shown to be of equivalent or greater sensitivity compared to parasitological methods, detecting patent infection in almost all infected individuals (McCarthy et al., 1996). In addition the technique is able to detect cryptic infections. This technique can also be used on saliva and pathological specimens to detect parasite DNA (Abbasi et al., 1996).

2.8.2.4 Serodiagnosis using parasite extract

Although methods to detect humoral immune responses to filarial infection have been available for at least 60 years, the development of sero-diagnostic assays of sufficient sensitivity and specificity has proven problematic (Ambroise-Thomas, 1974; Fairley, 1937). The major difficulty has been their poor specificity. There is extensive cross-reactivity in the sera of individuals infected with closely related helminths, and even some protozoal parasites (Maizels et al., 1985). Further, it is difficult to distinguish previous infection, or exposure to the parasite (aborted infection), from current active infection. Notably most residents of endemic regions are antibody positive (Ottesen et al., 1982). However, these assays may have a role in making a diagnosis as a negative result effectively excludes past or present infection. The anti-filarial IgG4 antibody, which is produced in abundance during active infection, has been found to be the most useful (Chanteau et al., 1995; Terhell et al., 1996). It has been shown to be a good index of intensity and duration of infection in endemic populations (Mahanty et al., 1994). In addition it correlates well with microfilariae counts (Maizels et al., 1995). Despite the limitations cited above the newly introduced dipstick incorporating IgG4 antibody shows promise as an

epidemiological tool in *Brugia*-endemic areas (Rahmah et al., 1998; Rahmah et al., 2001). Another area that is showing diagnostic potential is the use of filarial-specific enzymes (such as filarial acetylcholinesterase) either as antigens for antibody assays or by the detection of the enzyme itself (Misra et al., 1993; Sharma et al., 1998).

2.8.3 Ultrasonographic techniques

The use of high-frequency ultrasound in conjunction with Doppler techniques has revolutionised our understanding of the location of adult worms in humans. These techniques have made it possible to visualise adult worms in the female breast, scrotum and spermatic cord (Ameral et al., 1994; Dreyer et al., 1996b; Noroes et al., 1996a). Live adult worms have a distinctive pattern of movement within the lymphatic channels (called "filarial dance sign") (Ameral et al., 1994). Adult worms seem to remain in a constant location referred to as a "nest" in the lymphatic channels (Dreyer et al., 1994). Sensitivity of detecting the adult worm nests by ultrasound has been shown to be approximately 80% in men who are microfilaria-positive (Noroes et al., 1996). The loss of the "filarial dance sign" has been used to monitor the efficacy of anti-filarial chemotherapy (Dreyer et al., 1996; Dreyer et al., 1995). Recent field trials of a novel approach to the treatment of *W. bancrofti* infection using the antibiotic doxycycline applied ultrasonography to assess the effect of the treatment on adult worms (Taylor et al., 2005).

2.8.4 Entomological methods for monitoring of lymphatic filariasis

There are two ways of determining the LF infection in the mosquitoes. The traditional one whereby female mosquitoes are collected and dissected then examined for infective larvae. This method has been used for assessment of active transmission of LF. The collection of wild-caught, blood-engorged vector mosquitoes to detect infection in human populations is defined as

"xenomonitoring". Indoor-resting collection of blood-fed females is considered most appropriate with the blood meals representing the human population (WHO, 2002). A major advantage of xenomonitoring is that it indirectly gives a 'real-time' assessment of the relative levels of infection in human population (Williams et al., 2002). Detection of *W. bancrofti* in mosquitoes requires time-consuming dissection and microscopic examination of individual mosquitoes. In addition, speciation of filarial larvae requires additional technical expertise. In terms of monitoring filariasis elimination programmes, dissection is the most ideal means detecting infection in vector populations but becomes increasingly costly and laborious when the prevalence of infection in the mosquito population drops below 1% (Ramzy, 2002; Goodman et al., 2003). The number of mosquitoes that can be processed using this technique was estimated to be about 35 per person-hour and is slower if mosquitoes are preserved in alcohol (Bockarie et al., 2000). Thus, the use of mosquito dissection for monitoring filariasis elimination programmes may be inappropriate when the prevalence of infection is low because of the need to collect and dissect thousands of mosquitoes. However, this technique may be more useful as a tool for baseline assessment of transmission.

New techniques using PCR assays based on the amplification of a highly repeated DNA sequence found in *W. bancrofti* (the 188bp SspI repeat) has been recently developed with the intention of addressing problems encountered with traditional diagnostic methods (McCarthy et al., 1996; Williams et al., 1996; Zhong et al., 1996; Ramzy et al., 1997). Detection of parasite DNA in human blood and mosquitoes by PCR has been shown to be a sensitive and specific method for determining infection rates in endemic areas and thus a powerful new tool for evaluation and monitoring of community-based filariasis control programmes (Fischer et al., 1999; Farid et al., 2001). Screening of pools of mosquitoes by PCR has been proposed to be a rapid non-invasive tool to monitor the success of elimination programmes and to detect re-establishment of transmission in post-intervention period (Bockarie et al., 2000). A method for

detection and quantification of SspI PCR amplification products by ELISA (PCR-ELISA) has been developed (Fischer et al., 1999). However, the PCR-ELISA assay is too laborious and expensive and offers few significant advantages over the standard SspI PCR assay (Ramzy, 2002).

The drawback of the *W. bancrofti* SspI PCR assay is that it does not differentiate infective larvae (L3) from the other stages of the parasites (microfilariae, L1 and L2) in the mosquito. The presence of *W. bancrofti* infective larvae in the vector population is a direct measure of transmission because only mosquitoes carrying the infective stage of the parasite are capable of contributing to transmission. Therefore, an ideal PCR assay for monitoring the level of transmission during a filariasis control programme would be one based on L3 specific primers.

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2.8.5 Rare cases of lymphatic filariasis detection

LF is rarely diagnosed by incidental finding of microfilariae or adult worms in cytologic and histopathologic specimens, e.g. hydrocele fluid (Gratama, 1970), cervical smears (Walter et al., 1983), breast nodules (Chen et al., 1981) and lymph nodes (Varghese., 1996)

Despite the widely held belief that transmission of lymphatic filariasis will cease once the microfilariae prevalence is reduced to 1%, there is little scientific evidence to support this view (Melrose et al., 2004). *Aedes polynesiensis,* a major vector in Pacific, can transmit parasites even when microfilaria prevalence and density are extremely low (Esterre et al., 2001). An important factor in the long-term success of GPELF is the availability of effective tools for diagnosis

and monitoring of transmission (Melrose et al., 2004) even when microfilariae prevalence is below 1% level by thick smear.

2.9 Chemotherapy (Treatment)

The diethylcarbamizine citrate (DEC) has been a drug of choice for the treatment of LF caused *W. bancrofti* and *Brugia* for the past 50 years (Ottesen, 1985, 2006).

DEC has been reported to clear LF microfilariae from the peripheral blood very rapidly. However, when the intensity of infection is high the clearance is delayed (Kimura et al., 1985). A 6mg/kg DEC dose daily for a period of 12 to 14 days has been the recommended dosage. However, studies have proved that a single-dose treatment with 6mg/kg of DEC has comparable macrofilaricidal and long-term microfilaricidal efficacy (Dreyer et al., 1995c). Although, the 12-day course provides more rapid short-term microfilaricidal suppression when other factors are considered such as cost, convenience and patient compliance it seems reasonable to recommend a single-dose regimen (Ottesen, 2000).

The microfilaricidal effect of DEC has been widely documented (Addiss and Dreyer, 1999). The macrofilaricidal effect of DEC, until recently, has been debatable and that was mainly due to the absence of direct methods for monitoring LF adult worms. The evidence of macrofilaricidal effect of DEC was mainly associated with prolonged suppression of microfilariaemia, development of local nodules and identification of degenerating worms in biopsies of nodules (Addiss and Dreyer, 1999; Figueredo-Silva et al., 1996). However, with the advent of ultrasound, recently investigators have been able to monitor the effect of DEC on adult LF worms *in vivo* (Dreyer et al., 1998). In one study 31 men examined before treatment had 53 individual adult worm nests detected by ultrasound and after treatment with DEC the filarial dance sign became undetectable in 22 (42%) of these nests. Thirty-nine percent of the men had

cessation of the dance sign in all their previously detectable adult-worm nests (Noroes et al., 1997). These observations have also been demonstrated in children from Haiti (Fox et al., 2005). Several investigators have reported a decrease in the incidence of filarial adenolymphangitis following treatment with DEC (Simonsen et al., 1995). This would be consistent with current knowledge that true acute adenolymphangitis is caused by the death of the adult worm in the lymphatic channels. Thus, by killing a number of adult worms, DEC may reduce the number of subsequent acute attacks. The evidence that DEC reverses chronic manifestations of LF is contradictory. Using ultrasound, investigators in Brazil reported no change in lymphatic function in persons with lymphoedema one year after treatment with DEC (Freedman et al., 1995a). However, several observations of resolution of early stage hydrocele and lymphoedema have been reported following community-wide mass treatment with DEC (Dunyo and Simonsen, 2002; Meyrowitsch et al., 1996). Lack of control groups in these studies makes conclusive inferences difficult. Of note, there is agreement, though not universal, that DEC has no effect on longstanding lymphoedema or hydrocele. This is not surprising as the majority of these cases usually do not have active infections.

The DEC treatment against LF is usually associated with relatively few side effects. The ultrasonographic findings, which confirm the variable macrofilariacidal effect of DEC, also confirm the clinical observations that up to 45% of infected men develop scrotal nodules after a single 6mg/kg dose of DEC (Dreyer et al., 1995b). Side effects of DEC may be systemic (eg fever, headache, myalgia, malaise and haematuria) related to the death of microfilariae or localised (eg nodules, pain, adenitis and retrograde lymphangitis) suggesting an inflammatory reaction due to the death of the adult worm at a particular anatomical site (Addiss and Dreyer, 1999). DEC is contraindicated in individuals co-infected with *O. volvulus* as it may lead to a worsening of ocular manifestations associated with onchocerciasis (Molyneux et al., 2003).

The ivermectin (Mectizan) is the second agent that is recommended for the LF treatment. Ivermectin is a macro-cyclic lactone and it is available in the form of 6mg tablets. Ivermectin is used extensively in veterinary medicine. Ivermectin is reported to cause paralysis in many species of nematodes and arthropods through the influx of chloride ions across cell membranes and by the disruption of nerve signal transmission, probably mediated by gamma-aminobutyric acid (Abalis *et al.*, 1986). Ivermectin is a drug of choice for the treatment and control of onchocerciasis (Ottesen and Campbell, 1994; Ottesen et al., 1997). It has also been shown to be a potent microfilaricidal agent against LF. Different studies have shown that a single dose of 200-400µg/kg ivermectin can suppress *W. bancrofti* microfilariae for periods of 6-24 months (Kazura et al., 1993; Richards et al., 1991). An effect of ivermectin on adult worms has been suggested but this has been disproved by recent ultrasonographic investigations even at total doses of 4800µg/kg over a 6 month period (Dreyer et al., 1998; Dreyer et al., 1995c; Ismail et al., 1996). The systemic side effects for ivermectin are similar to those of DEC and include fever, headache, myalgia and malaise but there are no local side effects associated with death of the adult worms as seen in DEC treatment (Cartel et al., 1991). However, serious adverse events have been reported where ivermectin is used for onchocerciasis control in *Loa loa* endemic areas (Gardon et al.,1997; Twum-Danso, 2003a; Twum-Danso, 2003b). *Loa loa* is a filarial worm that is transmitted by a tabanid fly of the genus *Chrysops* (Boussinesq and Gardon, 1997). Individuals with high intensity *Loa loa* microfilaraemia have an increased risk of developing *Loa loa* encephalopathy following ivermectin treatment (Boussinesq and Gardon, 1997; Twum-Danso, 2003a). *Loa* is endemic in West and Central Africa and manifests as an eye worm or Calabar swelling (transient subcutaneous oedema) when adult worms migrate through the eye and cutaneous tissues.

Albendazole is the third drug which is being used for the control of LF. Albendazole is a benzimidazole derivative and is available for the LF programme in the form of chewable tablets of 400mg – the single annual dose.

It has a broad spectrum of efficacy against a wide range of human and animal helminth parasites (Horton, 2000). The mechanism of action of albendazole is still unclear. However, it is said to bind nematode tubulin, inhibiting the tubulin polymerase, thus preventing the formation of microtubules and so stopping cell division. Also, the loss of cytoplasmic microtubules disturbs the uptake of glucose and causes depletion of glycogen, hampering the formation of ATP required for survival and reproduction of the worms and impairing nutrient uptake by the parasite (Lacey at al., 1987; Lacey, 1990). This contrasts with the mode of action of non-benzimidazole anthelminthics which act on the parasite neuromuscular pathways and paralyse them. Jayakody et al, (1993) conducted the first formal study on the effectiveness of albendazole in *W. bancrofti* infection. High dosages (400mg twice daily) were used for three weeks on 15 microfilaraemic men and the results were compared with those of 12 other microfilaraemic men of comparable age and weight who had received DEC (6mg/kg/day) for three weeks. Although clearance of microfilariae was more rapid with DEC there was no significant difference between the groups at 3, 6 and 18 months post treatment. However, this dramatic microfilaricidal effect was associated with pain and inflammation of the scrotal sac in these men presumably induced by dying adult worms. Though these reactions are also seen following DEC treatment they discouraged further study of high dose albendazole treatment in LF.

The studies undertaken on the combination of those drugs and their outcome opened a new chapter in the treatment of LF as such results identified the value of the two-drug combination regimen – the combination of either diethylcarbamazine (DEC) or ivermectin and albendazole given as a single dose. Studies showed that single doses of albendazole (400mg) given in combination with either ivermectin (400µg/kg) or DEC (6mg/kg), have both long-term effectiveness and safety in decreasing microfilaraemia in *W. bancrofti* infections (Ismail et al., 1998). These findings were corroborated at the lower drug dosages (albendazole 400mg and ivermectin 200µg/kg), commonly used in

the treatment of intestinal helminths and onchocerciasis, respectively (Addiss et al., 1997; Ismail et al., 2001). Furthermore the addition of albendazole did not result in an increase in frequency of adverse reactions compared with DEC treatment alone (Ismail et al., 2001). Studies also showed that in addition to the significant microfilaricidal activity induced by the two drug combinations, circulating filarial antigen levels, presumably reflecting the presence of viable adult worms, were seen to fall progressively. However, the combination with DEC had consistently lower antigen levels than the one with ivermectin probably reflecting the superior macrofilaricidal effect of DEC (Ottesen et al., 1999).

In most African countries the recommended combination is that of ivermectin and albendazole because of co-endemicity of LF with onchocerciasis in many areas. Those combinations are given annually for a period up to six years to all eligible populations. The effectiveness of albendazole in treating individuals with LF has recently been reviewed by the International Filariasis Review Group and published in the Cochrane Library (Addis et al., 2005). Two trials met the inclusion criteria for the meta-analysis; one from Ghana and the other from Haiti (Beach et al., 1999; Dunyo et al., 2000). There was no difference when albendazole was compared to placebo both in Ghana and Haiti in reductions on either microfilaraemia or antigenaemia. A meta-analysis of these trials suggested a statistically significant reduction in the prevalence of microfilariae when the analysis was restricted to microfilariae positive individuals at baseline, in favour of ivermectin. Beach et al (1999) reported that the combination of albendazole and ivermectin was better at reducing microfilaria loads than ivermectin alone after four months of follow-up, but in the Ghana trial the two regimens were not different at 12 months of follow-up. These inconsistent findings are probably due to differences in time-points, differences in evaluation techniques and also differences in dosages. These trials did not evaluate the effect of albendazole in MDA campaigns and thus should be extrapolated with caution. Recently, a less stringent review also found limited evidence to support the use of albendazole in a combination regimen in LF control programmes

(Tisch et al., 2005). Despite this assertion the authors recognise the potential peripheral benefits of albendazole such as broad spectrum anthelminthic action against co-occuring intestinal helminth infections, thus potentially enhancing the health benefits of filariasis control (Rajendran et al., 2006).

Although those drugs have been recommended and are being used in many public health programmes in community-wide drug treatment strategies a point of caution is the development of drug resistance. The increasing occurrence of resistance to anthelminthic drugs is well documented in animal nematodes and this raises concern that the frequent treatments used in chemotherapy-based programmes to control human STH and LF may select resistant worms that will impair the benefits of treatment at the individual and at the public health level.

Resistance to benzimidazole (e.g. albendazole) anthelminthics and to ivermectin have arisen relatively easily in nematode parasites of animals when repeated mass treatment has been used to control nematode populations with little refugia from drug selection (Wolstenholme et al., 2004). To date resistance to albendazole or ivermectin has not been unequivocally demonstrated in nematodes of humans (Schwab et al., 2005). This is because in contrast to animals, it is difficult to conduct controlled *in vivo* or *in vitro* studies of drug efficacy against filarial parasites in humans. However, there are reports of reduced parasitological and clinical responses to benzimidazole and ivermectin in nematode parasite of humans which could be indicative of drug resistance development and genetic changes in *W. bancrofti* and *O. volvulus* (Awadzi et al., 2004; McCarthy, 2005; Schwab et al., 2005). In view of this, efforts are currently underway to develop genetic tools to monitor for albendazole and ivermectin efficacy in human filariae.

Despite the above mentioned promise accorded by the two drug combinations used in MDA campaigns, there is broad recognition of the need for a macrofilaricide to enable programme closure. Recently the focus on the

potential of antibiotics as adult worm sterilants has become a subject of intense investigations (Molyneux and Taylor, 2001; Taylor et al., 2005). This was due to the realisation that *Wolbachia* endosymbionts are potential targets for a number of antibiotic compounds. In addition, *Wolbachia* have been shown to contribute to disease pathology and adverse reactions following treatment (Cross et al., 2001; Taylor et al., 2001). Thus, use of antibiotics to eliminate these endosymbionts offers a novel approach to the treatment of filarial nematodes (Hoerauf et al., 2000). Doxycycline, 100mg/day for 6 weeks, permanently sterilises *Onchocerca* adult female worms. Doxycycline seems to be effective against *Wolbachia* from *W. bancrofti.* Hoerauf et al, (2003a) using quantitative PCR, were unable to detect any *Wolbachia* ftsz genes within four months of starting doxycycline therapy in 26 out of 29 cases and more importantly there was no microfilariaemia a year after starting therapy. This would be consistent with complete block of embryogenesis observed in onchocerciasis. Recently data published from a randomised double blind controlled trial from Tanzania has shown that doxycycline, 200 mg per day for 8 weeks, almost completely cleared microfilaraemia within 8-14 months and that 22% versus 88% (in placebo group) still had adult worms detected by ultrasound at 14 months (Taylor et al., 2005; Debrah et al 2006).

2.10 Extra Benefits Associated with LF Chemotherapy

In most countries where LF is endemic the soil transmitted nematodes *Ascaris lumbricoides, Trichuris trichura* and the hookworms (*Ancylostoma duodenale* and *Necator americanus)* are also among the commonest chronic infections of resident communities. About a quarter of the world's population, most of them living in developing countries, are estimated to be infected with one or more species of these worms (Chan, 1997). Adult hookworms attach themselves to the mucosa of the upper small intestine, ingesting tissue and blood and changing their feeding site every 4-6 hours (Layrisse and Roche, 1964). Blood is primarily lost when it passes through the hookworm's intestinal tract and is

subsequently expelled during feeding, but secondary loss also occurs from bleeding of damaged mucosa. Thus, as with any other disease which causes chronic blood loss, hookworm infections invariably lead to iron-deficiency anaemia. The amount of blood loss is strongly correlated with the worm load and faecal egg count (Albonico et al., 1998). The correlation is basically linear, with no evidence for a threshold in relationship between hookworm infection intensity and intestinal blood loss (Stoltzfus et al., 1996). However, since the development of iron deficiency anaemia from hookworm depends on iron intake and iron stores in addition to the intensity and duration of infection, a threshold effect is sometimes observed in the development of anaemia. The threshold varies depending on the iron intake and stores in the affected community or population sub-group (Stoltzfus et al., 1996). In populations with poor iron status and iron store to buffer the losses caused by hookworms, decline in haemoglobin levels may be apparent even at the lowest levels of hookworm infection intensity (Stoltzfus et al., 1997c).

Hookworm infection intensities often continue to rise in adulthood unlike ascariasis and trichuriasis (Bradley et al., 1993). Thus, where hookworm infection is endemic, it is usually common in pregnant and lactating women, a group that is particularly vulnerable high prevalence of anaemia. It has been estimated that at any given time, about 44 million pregnant women around the world are infected with hookworm (Bundy et al., 1995). In sub-Saharan Africa alone, about 7.5 million women are considered to be both infected and pregnant and probably a million of these are likely to harbour 40 or more hookworms and so be at risk of clinical disease, i.e. developing iron-deficiency anaemia (Crompton, 2000). Those predictions are supported by a study carried out among pregnant women living in the plains of Nepal where 74.2% were infected with hookworms; 72.6% were anaemic, and hookworm infection intensity was the strongest predictor of iron status (Christian et al., 2004; Dreyfuss et al., 2000). Also 75% of pregnant women attending an antenatal clinic in coastal Kenya were infected with hookworm and 76% of this study population were

anaemic (Geissler et al., 1998). Hookworm egg output was a significant predictor of haemoglobin status among the multigravidae but not primigravidae in the Kenyan antenatal population. Olsen et al (1998), found 70% of adult women in Western Kenya to be infected with hookworm; even light hookworm infections contributed significantly to low haemoglobin levels in this adult population. Although the problem of iron deficiency is particularly prevalent and severe in pre-school children, and theoretical calculations suggest that hookworms could contribute to iron deficiency in pre-schoolers (Stoltzfus et al., 1997c), iron deficiency anaemia has been linked to lowered performance on development tests and school attainment. However, more research is needed to establish or reject the role of hookworms in this sphere of childhood development (Crompton, 2000).

The pathogenesis of *Ascaris lumbricoides* is linked both to its migration in the human body and to the adult worm stage. Larvae migrating to the lung may induce pulmonary hypersensitivity with eosinophilic inflammation, which can manifest as asthma. Complications of *Ascaris* infection during the period of larval migration through the lungs can include pneumonitis, called Löffler's syndrome. The intestinal phase is generally asymptomatic although has been shown to produce abnormalities of intestinal absorption. Moderate infections can produce lactose intolerance, protein-energy malnutrition, and decreased fat absorption leading to vitamin-A deficiency. Heavy infections may result in bowel obstruction. A bolus of entangled worms may cause intestinal obstruction in the terminal ileum, one of the most serious complications of ascariasis. Less common complications include perforation of the intestine, as well as cholangitis, pancreatitis, and appendicitis from migration of adult worms (Crompton, 2000).

T. trichura also causes blood loss but to a much lesser degree than hookworm infection (Stephenson et al., 2000a). Rarely it may take the form of gross haemorrhage (as a part of dysentery or of rectal prolapse), which would lead to

a severe, sometimes life-threatening anaemia. The question of whether whipworms actually suck and ingest blood remains controversial. More commonly the blood loss is believed to be part of an exudation from the superficial lamina propria and damaged epithelium and to be proportional to the parasite burden (Bundy and Cooper, 1989). It has also been suggested that the anaemia seen in trichuriasis may be due to a chronic reduction in food absorption and therefore iron intake, due to anorexia resulting from production of tumour necrosis factor (TNF) alpha (Stephenson et al., 2000a). In a follow up study of 658 Panamanian schoolchildren (6-12 years of age), haemoglobin levels were found to be significantly lower in children with heavier *T. trichiura* infections (>5000epg faeces, n=14) (Robertson et al., 1992). The incidence of anaemia was significantly more in children with mixed *T. trichiura* and hookworm infections than in those with single infections. However, at follow-up, 12 months later, there was no significant improvement in haemoglobin levels in children who had lost hookworm or *Trichuris* infections during the preceding year, or in those who had a significant reduction in the intensity of infection. Ramdath et al, (1995) also found that Jamaican children with heavy infection intensities of over 10,000epg faeces (n=21) had significantly lower haemoglobin levels, whereas those with lighter infections (n=400), had no evidence of iron deficiency or anaemia. Mahendra Raj (1999), however, failed to find evidence of significant occult gastrointestinal bleeding in Malaysian children with heavy *Trichuris* infections and no dysenteric syndrome. Forrester et al (1998) also failed to find a significant association between intensity of infection and haemoglobin levels in their Mexican study population.

These infections can interfere with appetite, decrease food absorption and cause intestinal blood loss (Stephenson et al., 2000b). Hence, STH infections are highly associated with under-nutrition, iron deficiency anaemia, growth stunting and impairment of learning (De Silva, 2003). In most studies it has been reported that STH infections have impacted on physical growth, iron status and cognitive function. All STH worms have been implicated in impaired

physical growth in school children as measured by weight gain, height, mid-upper arm circumference and skin-fold thickness (De Silva, 2003).

Many studies have been conducted in different regions to examine the impact of anthelminthic treatment on physical growth. In a study conducted in Kenya where school children (2-6 years) with high prevalence of ascariasis, hookworm and trichuriasis were provided with a single dose of albendazole (400mg) and followed up six months later were observed to have gained weight and height compared to those in the same locality who were given placebo (Stephenson et al., 1993a; Stephenson et al., 1989). The gains in weight and height were attributed more to decrease in hookworm egg counts than the two other parasites. Two subsequent studies in the same population provided further evidence of improved growth after albendazole treatment of children with multiple helminthic infection (Stephenson et al., 1993).

In a study involving 1,206 school children between 2-12 years of age with high prevalence of *A. lumbricoides* from 21 villages in Myanmar given levamisole every 3 months and followed for two years showed significant increments in height from the sixth month onwards, but weight gain became significant only at 24 months. By the end of the follow-up period, the height and weight gains per child were 0.65 cm and 0.93 kg respectively in the treated group as compared with the control group (Thein et al., 1991).

One of the largest reported intervention trial was undertaken in Zanzibar as part of the school based de-worming programme in children with very high prevalence rates of hookworm, *T. trichiura* and *A. lumbricoides* (Stoltzfus et al., 1997a). Children in four primary schools were given thrice-yearly mebendazole 500mg (n=1,019), and children from another set of four schools received twice yearly mebendazole 500mg (n=990), and finally children in four other schools did not receive an anthelminthic (n=1,054). At the end of the 12 month follow-up, children below the age of 10 years had gained more weight (0.27kg) in the

twice yearly group and significantly more height (0.3cm) in the thrice yearly group compared with controls. It was concluded that the deworming programme improved growth in school children, especially those who were young and less stunted. Overall improvements were small but among non-stunted children, the dewormed children gained about 20% more weight than the control group.

The Zanzibar study found that treatment improved growth of children under 10 years, whereas there were no improvements among the older children (Stoltzfus et al., 1997). The same study found that among the older children, girls grew less than boys in response to deworming (Stoltzfus et al., 1997). There was no correlation between the degree of malnutrition at the onset of the study and the incremental gains in height and weight after treatment in the Myanmar study (Thein et al., 1991), but Zanzibari children who were less stunted appeared to benefit more from gains in both height and weight than those with severe stunting at the time of the intervention (Stoltzfus et al., 1997). Among the Zanzibari schoolchildren who had very high baseline levels of hookworms and trichuriasis as well as malaria and poor iron intake, the deworming programme had no impact on haemoglobin levels (Stoltzfus et al., 1998). Twice yearly deworming with mebendazole 500mg did however improve iron status as measured by protoporphyrin (a measure of iron-deficient erythropoiesis) and serum ferritin (a measure of iron stores) and markedly reduced the incidence of moderate to severe anaemia in children with heavier hookworm infections at baseline (Stoltzfus et al., 1998). However, findings from the Zanzibar study are evidently variable and may be influenced by several factors which include the age and sex mix of the study population, baseline nutritional status, the relative prevalence and intensity of the three types of nematodes, the choice of drugs and dosage used and the time period between intervention and final assessment.

A study conducted in Kenyan school boys with mixed infections of hookworm, *T. trichiura* and *A. lumbricoides,* haemoglobin concentrations dropped significantly

by 6g/l in the placebo group (n=26) at the 4 month follow-up, whereas they showed a non-significant decrease of 2g/l in the group treated with a single dose of albendazole 600mg (n=27). The difference of 4g/l between the two groups was statistically significant (Stephenson et al., 1993). Similar results were found among Tanzanian schoolchildren infected with hookworm or *Trichuris* in addition to *S. haematobium*. At the 4 month follow-up, haemoglobin concentrations had dropped by 3.5g/l in the placebo group (n=123), whereas in the group treated with a single dose albendazole (400mg) with praziquantel (n=127), haemoglobin levels fell significantly less, by only 1.1g/l (Beasley et al., 1999). In South Africa significant increases in haemoglobin concentration were seen after 11 months when school children with moderate levels of trichuriasis and no hookworm were given 4-monthly albendazole along with a daily cup of iron-fortified soup for 6 months (Kruger et al., 1996). However, the results are somewhat difficult to interpret, since trichuriasis levels fell in the placebo group as well as the albendazole groups.

Many studies have reported an association between soil-transmitted nematode infections and impaired cognitive function and school performance, but reports of controlled intervention trials examining this relationship are few. Five of the eight reported studies have concentrated on trichuriasis in Jamaican children. Extremely severe infections of *T. trichiura* in the form of Trichuris Dysentery Syndrome (TDS) have an undoubted impact on cognitive function (Callender et al., 1992). Follow-up after 4 years showed that although these children showed catch-up growth in height, their intelligence quotients, school achievements and cognitive function remained significantly lower than those of controls (Callender et al., 1998). As many more children have mild to moderate trichuriasis, rather than heavy infections such as seen in TDS it is important to determine the level at which detrimental effects occur. This may, however, vary from area to area depending on other variables that also influence the detrimental effects measured.

A clinical trial carried out in Jamaican children with moderate to heavy infections of trichuriasis found that children who received albendazole 400mg daily for 3 days, improved more than the group receiving a placebo in three of eight tests of cognitive function at follow-up 9 weeks later (Nokes et al., 1992). However, the pattern of cognitive improvement was not consistent across specific functions and was therefore difficult to explain Baddeley (1992). A similar randomised clinical trial (using albendazole 400mg on each of 2 days) was carried out in a larger sample of 289 Jamaican children with mild to moderate infections of *Trichuris* (Simeon et al 1995). At follow-up, 12 weeks later, the investigators failed to find a consistent improvement in cognitive function following anthelminthic treatment. However, children with evidence of under-nutrition improved much more with treatment than the better nourished children in verbal fluency. In the same study population, followed up over a longer period of time, spelling and school attendance improved after treatment in more heavily infected and shorter children, respectively (Simeon et al., 1995). A third study carried out among Jamaican children with mild or moderate trichuriasis also failed to find significant improvements in cognitive function after albendazole therapy (Gardner et al., 1996). These findings suggest that *T. trichiura* infections of low to moderate intensity in children of adequate nutritional status are unlikely to have a substantial detrimental effect on cognitive function. Schoolchildren in Guatemala (infected with both *Ascaris* and *Trichuris*) also failed to show improvement in several tests of cognitive function and school performance 6 months after treatment with repeated doses of albendazole (Watkins et al., 1996); and Malaysian school children with moderately high levels of ascariasis and trichuriasis did not show any improvement in school attendance 4 months after treatment with albendazole (Mahendra Raj et al., 1997). One study carried out among 6-8 years old in Jakarta, Indonesia, found that children with ascariasis improved in two of six tests of cognitive function 5 months after treatment with single dose mebendazole when compared with controls. However, children subjected to health education in addition to mebendazole treatment failed to show a similar improvement, and subsequent

analyses showed that the treatment groups were not similarly matched in some important characteristics (Hadidjaja et al., 1998). In general, assessment of changes in cognitive performance is difficult due to lack of appropriate tools and those available are standardised for children in developed countries may not necessarily be applicable across cultures. In addition, malnutrition, anaemia and learning impairment are linked to poverty. The association is of vital importance in assessing effectiveness of helminth intervention programmes. In a recent Cochrane review, Dickson et al, (2000a; 2000b), did not find evidence for improvement in cognitive performance in children treated with chemotherapeutic agents but did find a small effect on growth.

In Sri Lanka, however, deworming in addition to iron-folate supplementation has been a routine part of public health antenatal care for many years (De Silva et al., 1999). A cross-sectional study carried out against this background found that mebendazole therapy is safe during pregnancy as it is not associated with a significant increase in major congenital defects (De Silva et al., 1999). The effect of deworming in addition to iron-folate supplementation during pregnancy has been evaluated in three published studies. The first involved 195 pregnant tea plantation workers in Sri Lanka where hookworm is known to be prevalent (Atukorala et al., 1994). Women received the intervention which was delivered by the public service; the investigators did not control the intervention in any way. Thus it appeared that some women received iron-folate tablets and some did not, but all the women who received deworming (mebendazole 200mg daily for 3 days) also received iron-folate tablets. Receiving the combination of mebendazole with iron-folate supplementation (n=51) was more effective in improving the women's iron status during pregnancy than receiving iron-folate supplementation alone (n=64), and resulted in a marked increase in haemoglobin and improved iron status as indicated by protoporphyrin and serum ferritin levels. A subsequent study conducted in Sierra Leone also measured the impact of a single dose albendazole with or without daily iron-folate supplements, on haemoglobin and serum ferritin concentrations during

pregnancy (Torlesse and Hodges, 2000). At baseline (during the first trimester of pregnancy), the prevalence of hookworm and trichuriasis were 66.5% and 71.9%, respectively; 58.7% of the 125 women were anaemic and 21.2% had low serum ferritin levels indicative of depleted iron stores. The haemoblobin and serum ferritin concentrations of the women who received albendazole along with iron-folate supplements did not change significantly from baseline to the third trimester. However, among women who received either anthelminthic or iron-folate supplements alone, or who received neither, these values decreased significantly. After controlling for baseline haemoglobin concentration and season, the authors found that the mean benefit of anthelminthic therapy relative to the control was 6.6g/l of Hb; the corresponding value for iron-folate supplements were additive. The third study conducted in Nepal assessed the impact of albendazole given in the second trimester and found a 59g gain in birth weight of infants born to mothers who had received two doses and similarly infant mortality fell by 41%. These gains were in addition to significant reductions in rates of moderate to severe anaemia amongst the treated group (Christian et al., 2004).

Where ascariasis is the major helminth infection, the choice of anthelminthic is of little consequence since all the commonly used anthelminthics give good egg reduction rates (De Silva et al., 1997). However, it is of more importance in dealing with hookworm infections and trichuriasis. Although pyrantel, levamisole, mebendazole and albendazole are all effective against hookworm, in a single dose formulation, albendazole probably achieves the best reductions in worm burden (De Silva et al., 1997).

Many studies have been conducted to check the effect of ivermectin on the gastrointestinal parasites (*Ascaris lumbricoides, Trichuris trichura*, hookworms, *Strongyloides stercoralis,*) as well as ectoparasites and cutaneous larva migrans.

A study report of approximately 50 patients assessed by stool examinations one month after treatment indicated that ivermectin was 100% effective in removing *Ascaris lumbricoides* infections at dosages of 50-200µg/kg (Richard –Lenoble et al., 1988; Freedman et al., 1989; Nacquira et al., 1989). No side- effects could be attributed to the ivermectin treatment (Ottesen et al., 1994).

In a study trial of 17 patients with trichuriasis treated with high–dose ivermectin (400µg/kg over 2 days) were all cured. At lower ivermectin dosages (50–200µg/kg) cure was reported in only 55% of patients; yet significant reductions in intensity of infection occurred even in those not cured completely (Richard–Lenoble et al., 1988; Freedman et al., 1989; Nacquira et al., 1989). No adverse reactions were attributed to the use of ivermectin in treating trichuriasis (Ottesen et al., 1994).

In a study with 74 patients with hookworm infection treated with ivermectin at dosages ranging between 50–400µg/kg, complete cure at one month was achieved in only 20%, and appeared independent of the ivermectin dose (Nacquira et al., 1989). However, in those not completely cured, approximately 60% reduction in stool egg count was reported. One study indicated that cure of *Ancylostoma duodenale* infections was almost twice as likely as cure of *Necator americanus* after ivermectin treatment. No specific side-effects have been attributed to the use of ivermectin in hookworm infection. At the dosages studied ivermectin is clearly less effective than other drugs currently available to treat human hookworm infections. Unless a more effective dosage or treatment strategy is defined, other drugs (e.g mebendazole, pyrantel, albendazole) will remain the agents of choice for human hookworm infection (Ottesen et al., 1994).

Studies conducted on 200 patients with strongyloidiasis indicate that ivermectin in dosages (of equal to or greater than) 150µg/kg given in either singly or as two doses up to 2 weeks apart has an efficacy of 90–95% (Richard–Lenoble et al.,

1988; Freedman et al., 1989; Nacquira et al., 1989; Shikiya et al., 1992). Only mild adverse reactions e.g borborygmus, diarrhea, constipation) were reported, in a small minority (less than 10%) of patients. Elsewhere albendazole has been successfully used (Ottesen et al., 1994). Although the effectiveness of ivermectin has been reported in a single patient who had not been responsive to multiple courses of albendazole (as well as thiabendazole, flubendazole, mebendazole and praziquantel) (Lyagoubi et al., 1992) comparative trials of ivermectin and albendazole will be required before deciding on the future drug of choice for strongyloidiasis.

In a single study of a population undergoing treatment with ivermectin (100-200µg/kg) or placebo for onchocerciasis, there were significantly fewer head lice (*Pediculus capitus)* infestations in children who received ivermectin (Dunne et al., 1991) though no such differences were seen with respect to scabies infestations (*Sarcoptes scabiei*) in that study. Another study (Kar et al., 1994) has indicated a good clinical response in patients with widespread scabies infections after treatment with ivermectin. Its role in these human ectoparasite infestations deserves further study.

A study trial of 20 patients with cutaneous larva migrans showed ivermectin was 100% curative at dosages of 150–200µg/kg (Caumes et al., 1992; Louis De Quincenet & Louis. 1992). No side-effects were noted in any patient. This is far superior to the earlier results achieved by oral or topical thiabendazole or other medications for treating cutaneous larva migrans. Recently albendazole has been reported to induce similar impressive responses (Ottesen et al 1994; Heukelbach J et al., 2005).

Public health programmes designed to decrease the prevalence of intestinal helminths have focused on two areas: (i) decreasing transmission through improved sanitation and handling of human waste and (ii) reduction of human infections through drug treatment. The potential advantage of drug treatment is

a rapid reduction in infections. The problem with this approach is that these effects may be temporary as the population is rapidly re-infected. In Japan, following the Second World War, an intensive drug treatment programme was implemented at the same time as sanitation conditions were improved (Yokogawa, 1985). Although this strategy proved successful in controlling helminth infections, the programme was both time and resource intensive and spanned several decades.

As discussed above, albendazole is an effective and safe drug for treating intestinal helminth infections (including hookworms) as any other available, and it has effects against other parasites such as *Ascaris* and *Trichuris* as well. Therefore, its inclusion in two-drug treatment regimens for the control or elimination of LF should result in a public health impact greater than the elimination of LF alone, especially because the filariasis elimination strategy calls for the community-wide treatment in endemic areas of all those 'at risk' of LF infection. A significant departure from the approach advocated by the Soil Transmitted Helminth Control Initiative of targeted bi-annual treatment in high prevalence communities (Hall et al., 1997; World Health Organisation, 2004). Furthermore, when albendazole is used in combination with ivermectin, the public health benefit might be even broader as has recently been demonstrated in Haiti (Beach et al., 1999; De Rochars et al., 2004). Not only is ivermectin itself effective against many intestinal nematodes, strongyloides and even ectoparasites, such as *Tunga*, scabies and lice (Heukelbach et al., 2004), it seems to synergise with albendazole such that activity of the two drugs in combination against *Trichuris* is far greater than that of either drug alone (Beach et al., 1999; Lawrence et al.,2005).

The extra benefits associated with ivermectin and albendazole in controlling other prevailing parasitic disease in the community will play a major role in achieving the highest drug coverage in LF MDA campaigns. The LF Programme has stopped MDA using ivermectin and albendazole against LF. These drugs

had a strong impact on soil-transmitted helminthiasis. We recommend that the Ministry of Health Zanzibar should improve surveillance approaches towards this disease and find an alternative for maintaining the delivery of either albdendazole or mebendazole so as to maintain and improve the decline in the prevalence of soil-transmitted helminthiasis to school children and the community at large.

CHAPTER III

EVOLUTION AND DEVELOPMENT OF LF CONTROL IN ZANZIBAR

3.1 Introduction

Lymphatic filariasis (LF), caused by the filaria parasite *W. bancrofti* is of medical and public health importance in Tanzania. In Zanzibar, on the islands of Unguja and Pemba, LF has historically been a significant public health problem with prevalence ranging between 5-30% with the southern districts of both islands having records of high prevalence. In 1990 Maxwell reported prevalences as high as 40% in some areas of Zanzibar (Maxwell et al, 1990). In May and June 1975 extensive surveys for bancroftian filariasis were undertaken in Zanzibar by Kilama and his team (Kilama et. al. 1975) with the aim of determining the status of, and the potential vector species. In Unguja the communities that were chosen to represent the northern, central, southern and urban parts of the island were Chaani, Makunduchi, Jambiani and Zanzibar Town respectively. However, on Pemba three communities were chosen: Konde (northern area), Chake Chake (central area) and Kengeja (southern area). The results of the 1975 surveys in Unguja showed the overall prevalence of clinical signs among men aged 15 years or more in four communities of Unguja was 29.6% for hydrocele and 7.9% for elephantiasis while the microfilarial (mf) rates determined by night blood film in those communities were Chaani 7%, Jambiani 7%, Makunduchi 39% and Zanzibar Town 20%. Of 656 mosquitoes caught only 34 *Culex quinquefasciatus (Cx. pipiens fatigans)* had filarial infection. In Pemba, the overall prevalence of clinical signs among men aged 15 years or more in three communities was 22.4% for hydrocele and 1.4% for elephantiasis. The microfilarial (mf) rates in those communities were as follows: Konde, 11.8%; Chake Chake, 16.2% and Kengeja, 15.1% (117/774). Only 23 mosquitoes were

caught on Pemba, of which 22 were *Culex quinquefasciatus (Cx. pipiens fatigans)* none of which had filarial infection (Kilama et al., 1975). In June 1990 cross-sectional clinical, parasitological and entomological study surveys were conducted in three urban and semi-urban communities on Pemba island - Konde, Chake Chake and Kengeja and results were compared with similar surveys done 15 years earlier. The overall prevalence of clinical LF manifestation among males aged 15 years or more (n=614) was remarkably similar to those recorded 15 years earlier: elephantiasis, 1.4% in 1975 and 1.1% in 1990; hydrocele, 22.4% and 21.8%, respectively. However, when the communities were compared individually, there was a reduction in hydrocele prevalence in Konde from 22.4% to 11.5% and an increase in Kengeja from 27% to 35.5%. The overall microfilarial prevalence found during night blood surveys of all individuals aged 1 year or more (n=2,687) was 9.7%, compared to 14.2% recorded in 1975. The reduction was most pronounced in Konde. Of 1,052 female mosquitoes caught with CDC light traps, 95% were *Culex quinquefasciatus* and 5% *Anopheles gambiae s.l.* Infective larvae of *Wuchereria bancrofti* were found only in *Culex quinquefasciatus.* These results showed that the LF situation in urban and semi-urban communities on Pemba appeared not to have changed significantly over the 15 years (Pedersen et al., 1999).

Between 1987 and 1991 several cross-sectional clinical, parasitological and entomological study surveys were conducted by Maxwell and her team on Unguja Island with the aim of determining the status of LF and the potential vectors. The 1987 survey results in Makunduchi, south of Unguja, showed a remarkable increase of microfilaria (mf) prevalence rate to 49% as compared to 39% recorded in 1975, while in Moga in the north of Unguja island the mf rate was 32% in 1991 and in Chaani (the village closest to Moga) the mf rate was 7% in 1975. Pwani Mchangani, a village north-east Unguja, with a very limited number of mosquito-breeding sites was found to have mf prevalence of 0.3 % in the 1987 survey. Kizimkazi had a 26% mf rate and Zanzibar Town was recorded to have a reduction from 20% in 1975 to 8% in 1991.

The prevalence of clinical LF manifestations among males aged 15 years or more in Makunduchi (1987) was elephantiasis 26.5%, hydrocele 32.4%; in Moga (1991) elephantiasis 16.1%, hydrocele 20.3%; in Pwani Mchangani (1987) elephantiasis 1.6%, hydrocele 4.2%; in Kizimkazi (1991) elephantiasis 25%, hydrocele 27.4% and in Zanzibar- town (1991) elephantiasis 7.5%, hydrocele 11.2%. However, the overall survey results record a large number of hydroceles compared to lymphoedema a situation similar to that found elsewhere in East Africa (Kilama et al. 1975; Maxwell et al., 1990, 1991) (Table 3.1). In addition, *Culex quinquefasciatus* was recorded as the principal vector of bancroftian filariasis on the islands of Zanzibar (Kilama et al. 1975; Maxwell et al., 1990, 1991).

Table 3.1 Records of Clinical manifestations of LF in surveyed areas in Zanzibar

Surveyed Area	District	Region	Year	Prevalence Rate	
				Elephantiasis	Hydrocele
Makunduchi	South	South	1987	26.5%	32.4%
Pwani Mchangani	North 'A'	North	1987	1.6%	4.2%
Kizimkazi	South	South	1991	25.0%	27.4%
Moga	North 'A'	North	1991	16.1%	20.3%
Zanzibar Town	Urban	Urban West	1991	7.5%	11.2%

Many attempts to control LF in Tanzania have been conducted using mass chemotherapy with Diethylcarbamazine (DEC) combined with either vector control and/or environmental management (Jordan 1958, Kolstrup et al 1981, Maxwell et al 1990). Most of these were small scale interventions or were localized to a few regions or zones as proof of concept. Unfortunately, the re-infection rate remained high after the termination of the control programmes. Hence, the microfilaraemic rates remains similar at the start of this study to the levels recorded earlier (Maxwell et al. 1999, Dahoma, 2000).

In 1994 Ministry of Health, Zanzibar established an LF Control Programme unit under the Director of Preventive Health Services and Health Education. By 1997, the MOH Zanzibar, with technical support from WHO, developed a Plan of Action for the Integrated Control of Filariasis, Intestinal helminths, Malaria and Schistosomiasis. In that document, one of the suggestions for filariasis control was the use of mass treatment with drug combinations.

In 1997, the World Health Assembly adopted Resolution WHA50.29 calling for the elimination of LF as a public health problem worldwide.

The principal strategy for interrupting transmission of infection is to identify the areas in which LF is endemic and then implement community-wide programmes to treat the entire at-risk population. The main goal of such treatment is to break the cycle of transmission between mosquitoes and humans thus protecting future generations from the disease.

To interrupt transmission, the essential strategy adopted by WHO is to treat the entire population at risk for a period long enough to ensure that levels of microfilariae in the blood remain below those necessary to sustain transmission. Annually a single dose of two drug regimes [albendazole (400mg) plus DEC (6mg/kg) OR albendazole (400mg) plus ivermectin (Mectizan®) (200μg/kg)] is advocated. The duration for treatment has been estimated to be 4-6 years corresponding to the reproductive lifespan of the parasite (Norman et al., 2000; Plaisier et al., 1998).

In 2000 small and large scale community trials to assess safety and efficacy of co-administration (ivermectin + albendazole) were undertaken in Zanzibar for bancroftian filariasis infections and observations showed that the combination regime to be safe and efficacious.

In 2001 Zanzibar was among the countries selected as part of the Mass Drug Administration (MDA) of the Global Programme to Eliminate Lymphatic Filariasis (GPELF) as a public health problem by 2020. Although Zanzibar is onchocerciasis free, mainland Tanzania is onchocerciasis endemic and because there is free movement of people between Zanzibar and the mainland it was agreed that the regime of ivermectin (200μg/kg) and albendazole (400mg) for an MDA campaign would be the appropriate choice as opposed to DEC/albendazole which is the combination used in the LF programme in the Comoros and Madagascar.

3.2 Assessment of LF prevalence at selected sentinel sites.

To monitor the progress of the MDA interventions according to the WHO LF Programme Managers Guidelines the identification of sentinel sites and the collection of baseline data was recommended before the start of the intervention (WHO, 1998). Therefore, the purpose of this study was to carry out baseline epidemiological investigations on LF in the selected sentinel sites of Zanzibar.

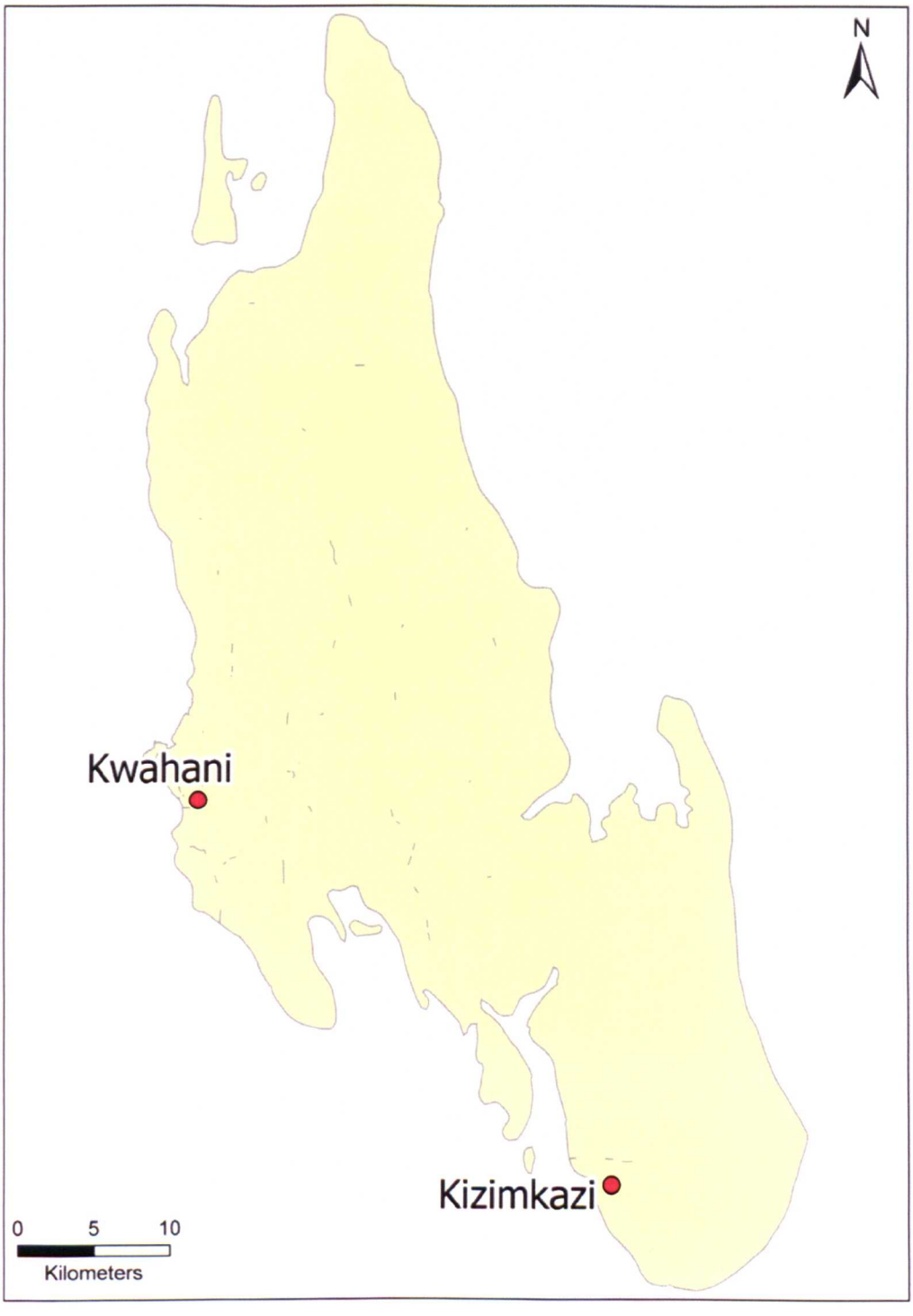
The surveys were carried out in September, 2001 in two sentinel sites of Zanzibar before the start of first community MDA the following month. All essential conditions for the selection of sentinel sites were followed (WHO, 1998). Zanzibar, because of its size, population and LF records was recommended to have two sentinel sites. The selected sites were Kizimkazi and Kwahani (See Figure 3.1). These were selected for a detailed baseline epidemiological study of bancroftian filariasis and monitoring of the impact of MDA.

3.2.1 Sentinel sites

Kizimkazi and Kwahani were selected as the two sentinel sites (Figure 3.1). These study sites receive the same pattern of rainfall depending heavily on the season related to the change of monsoon winds. The season of heavy rains which accounts for about 50% of the total annual rainfall lasts from March to May. The relatively cool, dry season covers the period from June to September. Periodically a small rainy season with about 20% of the total annual rainfall occurs during October to December. The North-East monsoon winds bring a dry season that lasts from January to March. The annual rainfall ranges from 1,500-2,000mm; temperature varies from 26.7°C to 32.5°C. The two sites, however, differ in physical features, vegetation, human settlement and economic activities.

Kizimkazi is located in the dry, arid stony area along the coast in the rural Southern district of Unguja Island. It is made up of two local administrative units referred locally as Shehias with a total population of 3,037 people. The main occupation is fishing and small scale farming. Houses made of stone and lime, and thatched with palm leaves are common in Kizimkazi although some of the less poor prefer to use bricks of cement with iron roofing in house construction. Most houses have pit latrines, some with cesspits and soakage pits that are good breeding sites for the *Culex* mosquitoes. Kizimkazi has a historically high prevalence of LF patients and drugs for treatment for lymphatic filariasis were not previously available.

Figure 3.1 Map of Unguja island with two selected sentinel sites



Kwahani, the second sentinel site, has a number of LF patients and is located in the urban district of Unguja Island and made up of one Shehia with a total population of 4,550 most of them are employed in different sectors. Most of the houses are made of bricks and cement, most have pit latrines, and some have pour-flush toilets, cesspits or soakage pits. The area is surrounded by many open drains which are potential breeding sites of mosquitoes.

In Pemba no sentinel site was selected because the site that had record of high prevalence of LF (Kengeja) had undergone drug trials of both ivermectin and albendazole in 1999-2000 and the LF prevalence record after that trial was below 2%.

3.2.2 Ethical issues

The study protocol was reviewed by the research council of the Ministry of Health and Social Welfare and ethical approval given. Community meetings were held to inform the public about the study and to emphasize the importance that community members participate. Records of participation in the study were outlined in the community meetings. Participants were also given the opportunity to enquire about the details of the study and all questions were answered.

3.2.2.1 Community mobilization

An official letter to the Ministry of Regional Administration and Local Government was sent requesting permission to conduct the study in the selected study sites and the benefits that would be gained after the completion of the study. With written consent from the local government community entry and sensitization sessions were organized using the following:

- Sensitization meetings with shehas (community leaders) together with shehias councils (an average of 12 members) was undertaken in each site;
- The shehias councils were briefed about the aims and the expected benefits of the study. This helped to reduce tensions and the suppress rumors that might have affected the study. The local council had a chance of exchanging views and ideas and thus assisted in planning for the larger community sensitization meetings. Furthermore, these sessions assisted in identifying community elders and other "gatekeepers" who might help especially in overcoming stigma and other negative effects that would have affected or hampered community participation;
- The meeting with shehias councils assisted in preparing community meeting plans for sensitization. The villagers identified locations where filaria night blood film and screening could occur;
- Issues that were stressed during the community sensitization sessions were:
  - information on the magnitude of LF as a national and international problem;
  - current national intervention strategies;
  - The objective of the study and the importance of their full participation.

Individuals were also informed of their rights to participate in the study; written informed consent was obtained from all the screened subjects. For any subject less than 15 years age consent was obtained from either the parent or the guardian (Annex 1).

After the team had been introduced to the local authorities, community leaders and villagers, and their permission to carry out surveys had been obtained, all the residents with their children were requested to come to appointed centres within the villages between 2000 and 0200 for clinical assessment and for sampling of night blood films.

3.2.3 Clinical examinations

All participants, both males and females, aged ≥1 year, who had lived in the sites for at least 1 year, were clinically examined for chronic manifestations of LF. They were examined for the presence, or absence, of lymphoedema (of the leg, upper limb, breast, arm, scrotum) and males were examined for hydrocele (scrotal swelling) and other scrotal involvement by a clinician in a private room. Lymphoedema was defined by the presence of non-pitting oedema, which corresponds to grades 2 and 3 of the International Society of Lymphology and soft but reversible pitting oedema, which corresponds to grade 1 (Keeley, 2000; Keely, 2000; Penzer, 2003; WHO, 1987a). Signs of current attacks of adenolymphangitis (ADL) and scarification were also recorded.

The staff performing the physical examination were qualified and trained to differentiate hydrocele from inguinal hernia. Clinical hydrocele was diagnosed based on the finding of a non-tender, soft, fluid-filled mass whose superior limit could be defined by the examining finger. Scrotal lymphoedema was differentiated from hydrocele as the internal scrotal contents remain normal on palpation. Chronic signs were graded as described by Estambale et al. (1994) A hydrocoele was considered to be true when its sise was equal or more than 6 cm with fluid acculation. For limb elephantiasis, this includes both limb lymphoedema and scrotal elephantiasis.

3.2.4 Microfilaraemia surveys

The surveys on microfilaraemia prevalence at sentinel sites were carried out to obtain baseline data for programme monitoring and evaluation.

3.2.4.1 Parasitological surveys

Parasitological surveys for filarial infection were carried through night blood film examination for prevalence and density of *Wuchereria bancrofti*. All participants, male or female, aged one year or more, were included as recommended for the programme by the WHO Monitoring and Evaluation Guidelines (WHO, 2005). Demographic data (name, age, sex) and treatment status were recorded. Participants also answered questions regarding previous treatment with anti-filarial drugs. The targeted population for each sentinel site was 500 individuals as recommended in the Guidelines for LF Programme Managers (WHO, 2000).

The microfilaraemia assessments took place in September 2001 and were progressively carried out in conjunction with each of the MDA rounds.

3.2.4.2 Collection of blood samples

Blood samples were collected between 2030h and 2400h, when the numbers of microfilariae approached peak levels in the peripheral blood circulation in this setting (Gatika et al., 1994). Finger prick blood was obtained by cleaning the tip of the middle finger with cotton swab containing 70% isopropyl alcohol and pricking with a sterile lancet. A 100µl blood sample, for microfilaria detection were collected from the prick into heparinized capillary tubes and then transferred into a tube containing 0.9 ml of 3% acetic acid solution and mixed gently. The acetic acid solution serves as a fixative/preservative as well as a lysing solution for the red blood cells. At the same time thick blood smears were also taken for species identification. The samples were kept at room temperature until the following day when microfilaria examination and counting was done under a microscope in the laboratory using the counting-chamber method (McMahon et al., 1979). The number of mf per 100µl blood was counted and the mf intensity per ml of blood calculated. The blood smears were dried, dehaemoglobinized, fixed, stained with Giemsa stain and examined under

a microscope. Microfilariae were identified to species based on morphological criteria (WHO, 1987).

3.2.5 Data analysis

All individual data were pre-coded and entered using EpiInfo 2000 (Centers for Disease Control and Prevention, Atlanta, GA) or Excel 2000 (Microsoft) and Access 2003 (Microsoft). Data were then processed and analysed using either EpiInfo 2000 or SPSS 11 software package (SPSS Inc, Chicago, IL) for statistical analyses. A P-value of 0.05 was considered indicative of a statistically significant difference.

Sample frequencies and cross tabulations were performed on the main variables of the data collection sheets. Chi-square tests were used to compare dichotomous variables; continuous variables were compared using the Kruskal-Wallis (non-parametric) test.

3.2.6 Results

3.2.6.1 Characteristic of the study population

A total of 1,000 participants were recruited in the baseline surveys carried out in the two sentinel sites. The Kizimkazi sentinel site was selected to be representative of rural districts while Kwahani was selected for the urban and peri-urban districts of the country. The majority of the study participants at Kizimkazi were in the age group category of 11-20 years 203 (40.6%) and in the 21-30 years 77 (15.4%) age groups respectively as shown in Table 3.1 and Figure 3.4. Of the recruited subjects, 46% were females while males made up the remaining 54% (Table 3.2). However, in Kwahani most of the study participants were also in the age group category of 11–20 years 198 (39.6%) and in the 21-30 years 79 (15.8%) (Table 3.3; Figure 3.4). In Kwahani out of 500 participants 56% were females and males 44% (Table 3.3).

Figure 3.2 **A technician taking a blood sample from a participant**

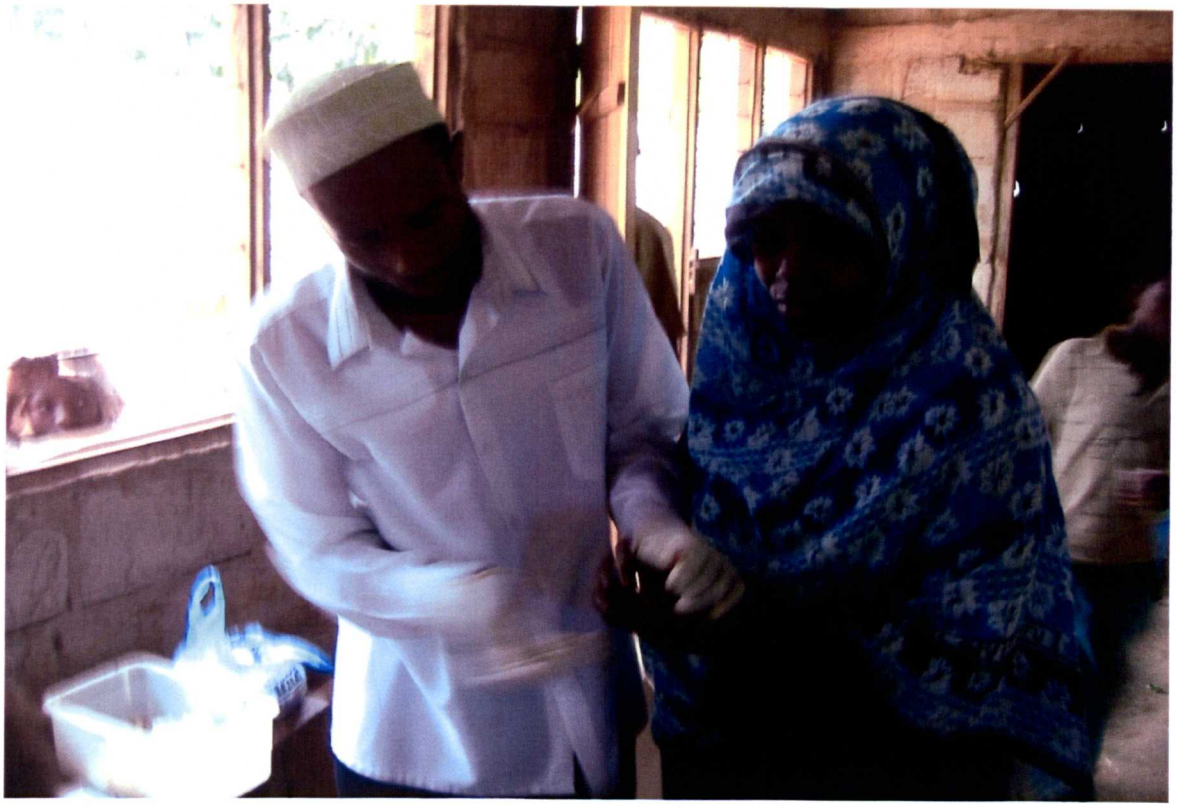


Figure 3.3 Examination of blood samples for microfilariae

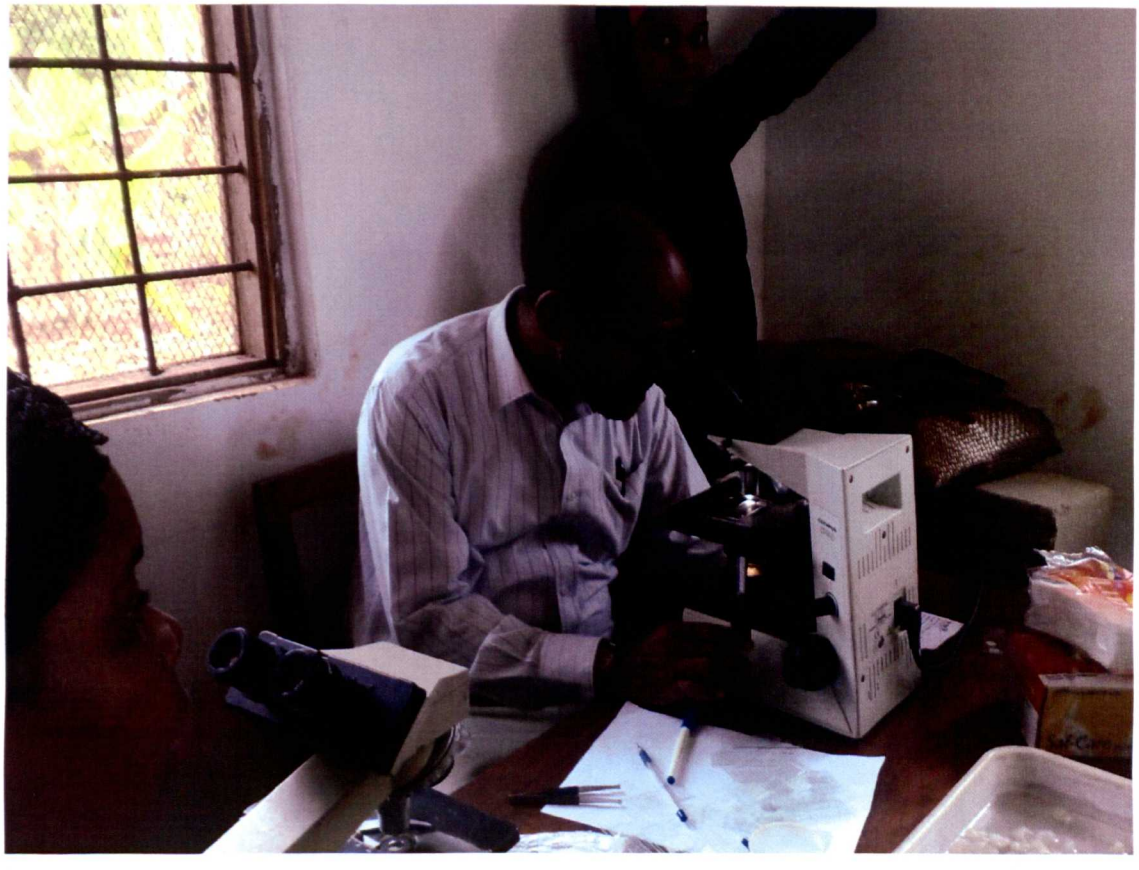


Table 3.2 Distribution of the screened population by age and sex in Kizimkazi

The majority of participants were between 11 years and 40 years in all groups. More males participated compared to females

Age (years)	Females N (%)	Males N (%)	Total n (%)
1 – 5	12(5.2)	18(6.7)	30(6.0)
6-10	15(6.5)	22(8.1)	37(7.4)
11-20	90(39.1)	113(41.9)	203(40.6)
21-30	39(17.0)	38(14.1)	77(15.4)
31-40	25(10.9)	30(11.1)	55(11.0)
41-50	23(10.0)	19(7.0)	42(8.4)
50+	26(11.3)	30(11.1)	56(11.2)
Total	**230 (46.0)**	**270 (54.0)**	**500 (100)**

Figure 3.4 Distribution of study participants by age and sex at the Kizimkazi Site

The highest number of participants was in the 11- 20 years age group.

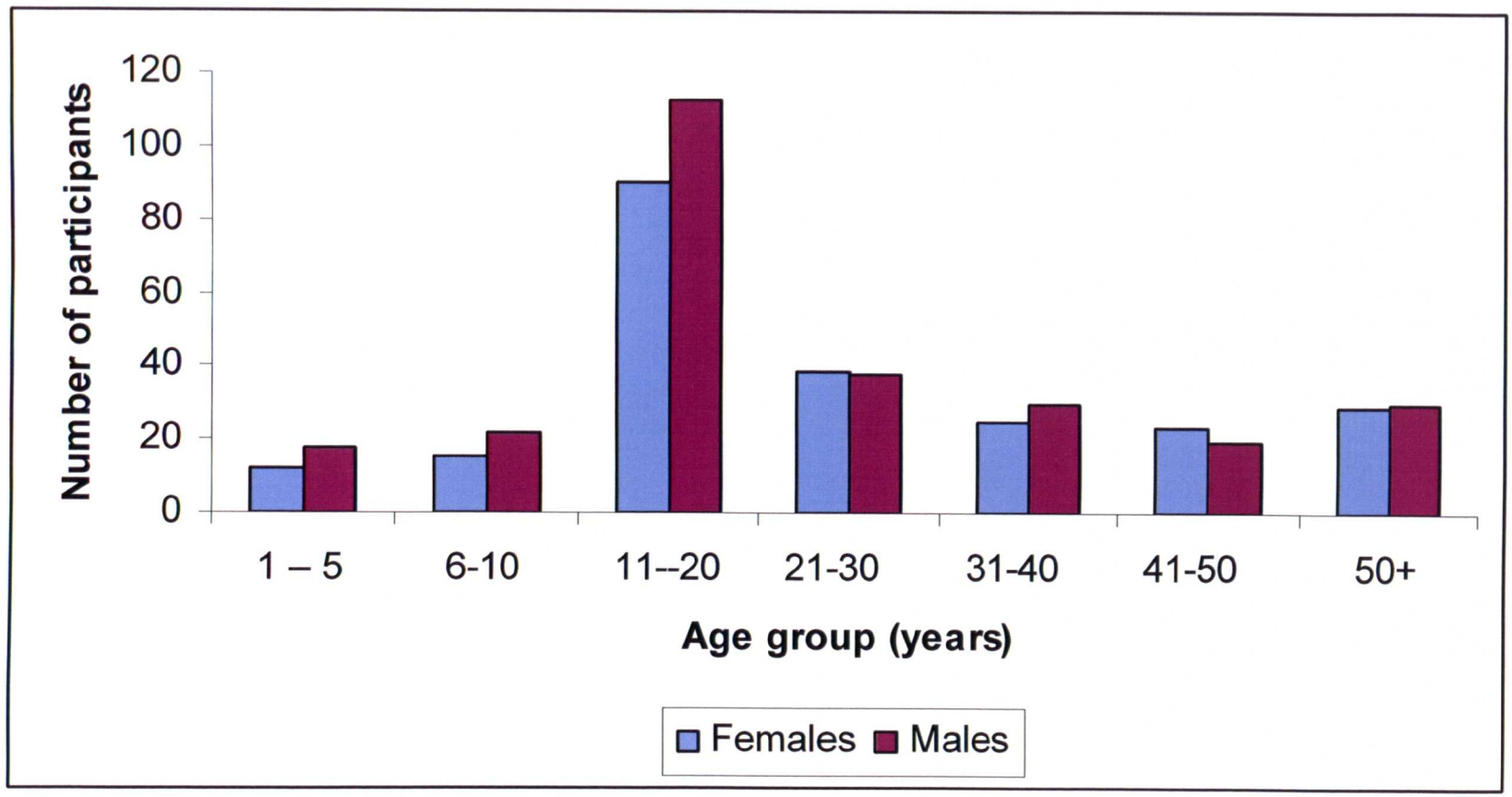


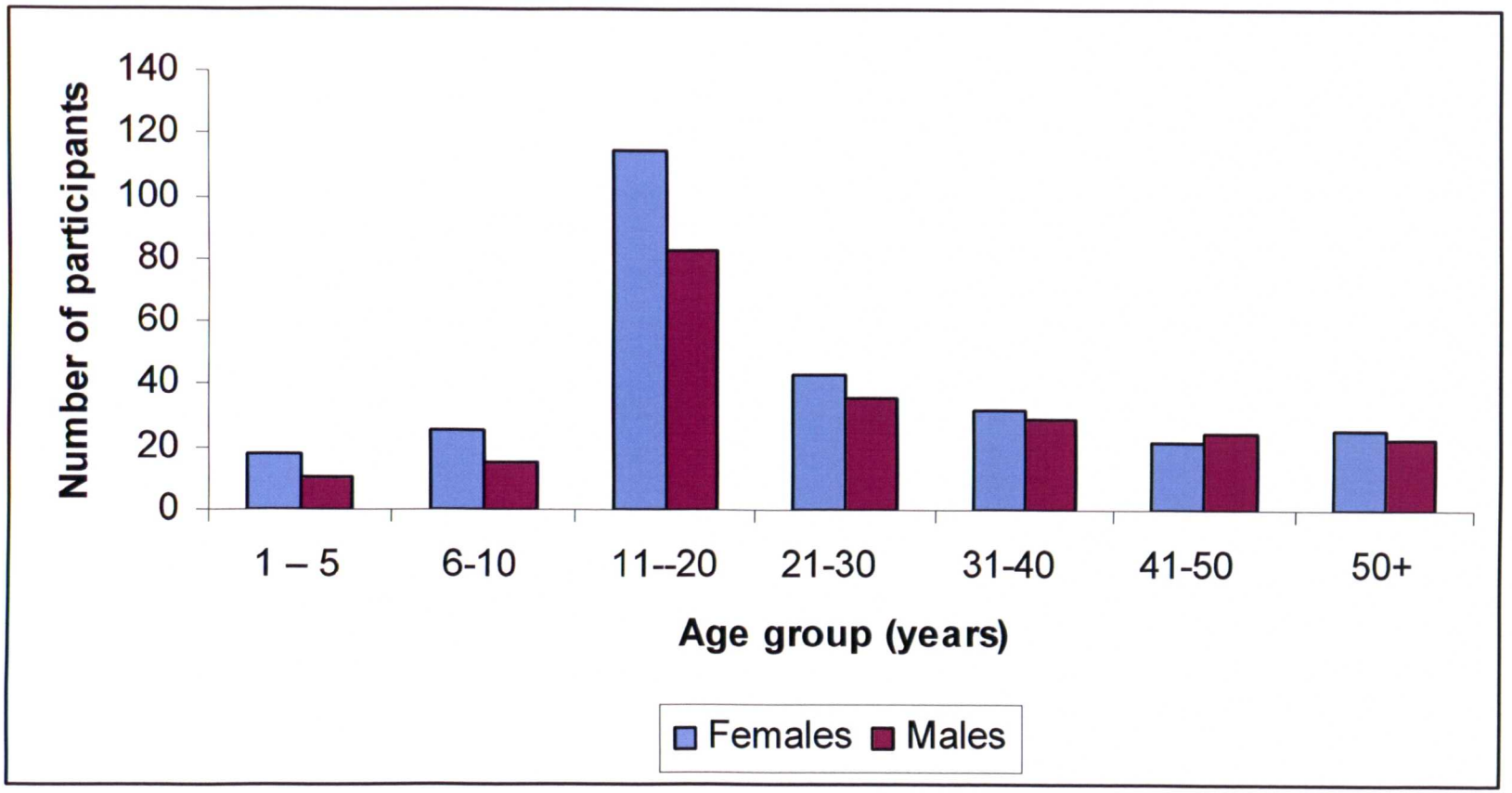
Table 3.3 Distribution of the screened population by age and sex at Kwahani

Majority of participants were between 11 years and 40 years in both groups. A larger number of females participated compared to the male group

Age (years)	Males n (%)	Females n (%)	Total N (%)
1 – 5	10(4.5)	18(6.4)	28(5.6)
6 -10	15(6.8)	25(8.9)	40(8.0)
11- 20	83(37.7)	115(41.1)	198(39.6)
21- 30	36(16.4)	43(15.4)	79(15.8)
31- 40	29(13.2)	32(11.4)	61(12.2)
41- 50	24(10.9)	22(7.9)	46(9.2)
50+	23(10.5)	25(8.9)	48(9.6)
Total	**220 (44.0)**	**280 (56.0)**	**500 (100)**

Figure 3.5 Distribution of study participants by age and sex at Kwahani site

The highest number of participants is in 11-20 years age group.



3.2.6.2 Prevalence results

The results in Kizimkazi revealed that 89 (17.8%) of individuals tested positive for *Wuchereria bancrofti* microfilaraemia. More males (47) than females (42) tested positive (17.4% vs 18.2%) but that difference was not significant (X^2=1.07; p=0.3). The sex ratio male/female was 1:1.2 in the infected individuals. The prevalence of *W. bancrofti* microfilaraemia was 17.4% amongst the males examined (47/270) and 18.2% in the females (42/230). The age of the positive participants ranged from 6 years to 90 years. The general distribution pattern of microfilaraemia positives increased with increasing age being 10 (11.2%) in those aged 6-10 years. The highest microfilaraemia positive 38 (42.7%) was in the 11-20 year age group in both sexes (Table 3.4). The mean age of the positive participants was 34.2 years, the variance 317.69, the standard deviation 17.58 and the median 36 years. In the females, the mean age of the positives was 34.5 and the median 35 years (range 8 to 72 years); and in males the mean was 38.5 and the median 38 (range 10 to 90 years). The positive females tend to be older than the positive males and that difference was significant (Anova t test = 3.77; p=0.0002).

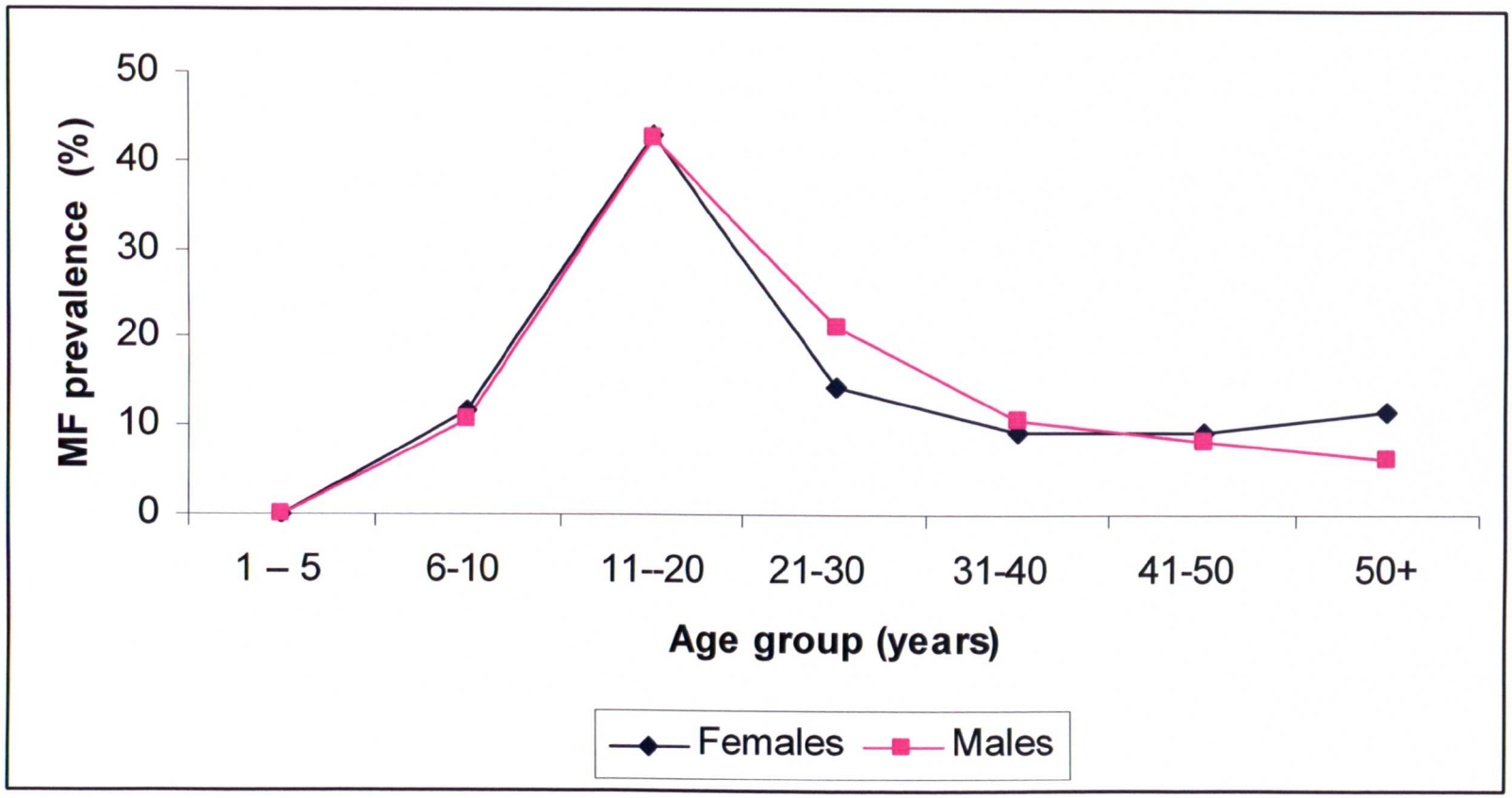
Table 3.4 Baseline prevalence of microfilaraemia by age and sex at Kizimkazi.

More males were mf positive than females. Individuals with mf prevalence were 6 years and above in both groups.

Age (Years)	Total Examined		MF-Positive individuals		
	Males (%)	Females (%)	Males n(%)	Females n (%)	Total N (%)
1- 5	18(6.7)	12(5.2)	0(0.0)	0(0.0)	(0.0)
6- 10	22(8.2)	15(6.5)	5 (10.6)	5 (11.9)	10 (11.2)
11-20	113(41.9)	90(39.1)	20 (42.6)	18 (42.9)	38 (42.7)
21-30	38(14.1)	39(17.0)	10 (21.3)	6 (14.3)	16 (18.0)
31- 40	30(11.1)	25(10.9)	5 (10.6)	4 (9.5)	9 (10.1)
41- 50	19(7.0)	23(10.0)	4 (8.5)	4 (9.5)	8 (9.0)
50+	3011.1)	26(11.3)	3 (6.4)	5 (11.9)	8 (9.0)
Total	**270 (54.0)**	**230 (46.0)**	**47 (17.4)**	**42 (18.2)**	**89 (17.8)**

Figure 3.6 ***Microfilaraemia prevalence rates by age and sex at Kizimkazi site***

Microfilaraemia prevalence rates by age and sex were not significantly different in age and sex. In the age group 21-30 years more males were mf positive than females



In Kwahani, 36 (7.2%) individuals tested positive for *Wuchereria bancrofti* microfilaraemia. More males (19) than females (17) tested positive in Kwahani. However, the number of females examined (280) was higher compared to the number of males (220). The prevalence of *W. bancrofti* microfilaraemia was 8.6% amongst the males examined (19/220) and 6.1% in females (17/280) but the difference was not significant (X^2=1.07; p=0.3). The sex ratio male/female was 1:11 in the infected individuals. The age of the positive participants ranged from 6 to 72 years. The general distribution pattern of the microfilaraemia positives was increased with increasing age being 2 (5.6%) in those aged 6-10 years to 13 (36.1%) in those aged 11-20 years and highest 8 (42.1% among males aged 11-20 years and in females 5 (29.4%) aged 11-20 years respectively (Table 3.5). The mean age of the positive participants was 33.5 years, the variance 317.69, the standard deviation 17.75 and the median 36 years. In the females, the mean age of the positives was 34.5 and the median 35 years (range 12 to 53 years) and in males the mean was 38.5 and the median 38 (range 6 to 72 years).

Table 3.5 Baseline prevalence of microfilaraemia by age and sex at Kwahani

Age (Years)	Total Examined		MF-Positive individuals		
	Males (%)	Females (%)	Males n(%)	Females n (%)	Total N (%)
1- 5	10(4.5)	18(6.4)	0(0.0)	0(0.0)	0(0.0)
6- 10	15(6.8)	25(8.9)	0 (0.0)	2 (11.8)	2 (5.6)
11-20	83(37.7)	115(41.1)	8 (42.1)	5 (29.4)	13 (36.1)
21-30	36(16.4)	43(15.4)	6 (31.6)	4 (23.5)	10 (27.8)
31- 40	29(13.2)	32(11.4)	2 (10.5)	3 (17.6)	5 (13.9)
41- 50	24(10.9)	22(7.9)	2 (10.5)	2 (11.8)	4 (11.1)
50+	23(10.5)	25(8.9)	1 (5.3)	1 (5.9)	2 (5.6)
Total	**220 (44.0)**	**280 (56.0)**	**19 (8.6)**	**17 (6.1)**	**36 (7.2)**

Figure 3.7 Microfilaraemia prevalence rates by age and sex at Kwahani site

In the age group 11-20 and 21-30 more males had higher mf prevalence than the females.

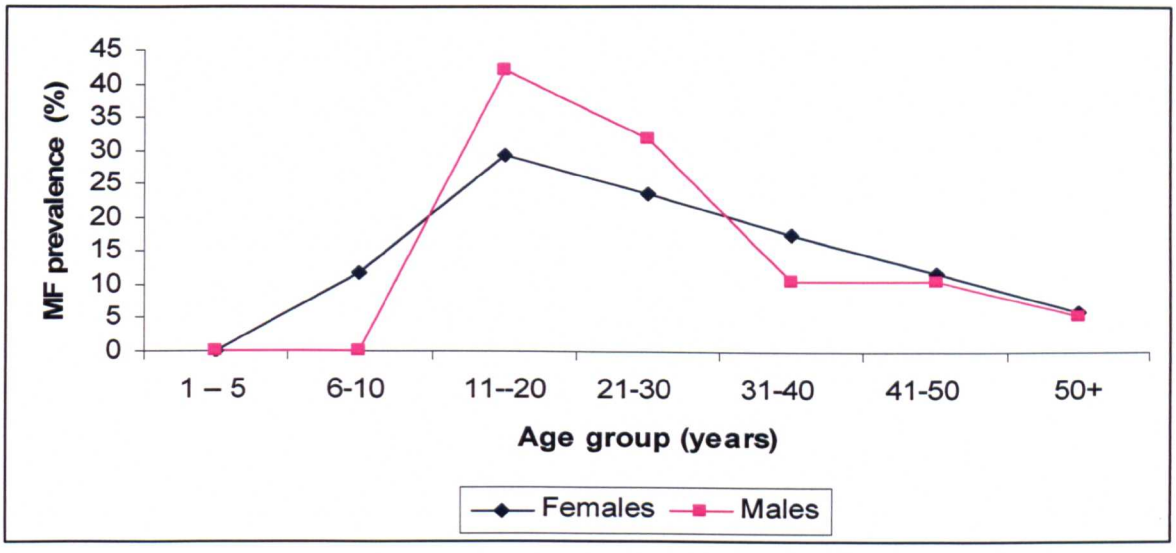
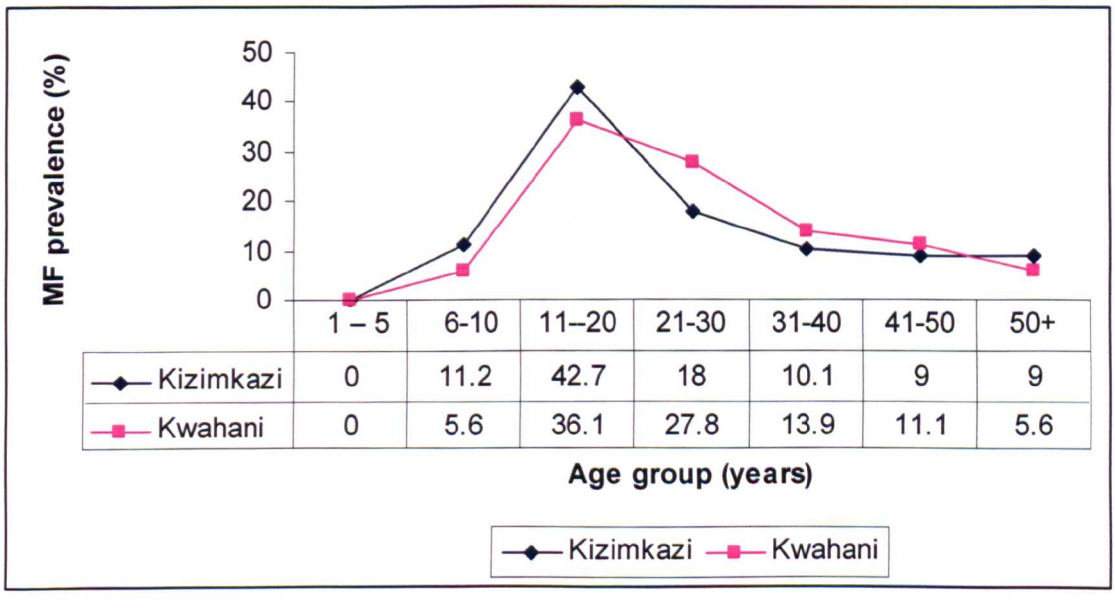


Figure 3.8 Microfilaraemia prevalence rates by age at two sentinel sites

The overall microfilaraemia prevalence in the Kizimkazi site is higher in all age groups 6 years and more.



	1 – 5	6-10	11–20	21-30	31-40	41-50	50+
Kizimkazi	0	11.2	42.7	18	10.1	9	9
Kwahani	0	5.6	36.1	27.8	13.9	11.1	5.6

Table 3.6 Microfilaraemia density (mf/ml) in the two sentinel sites

Site	Number Examined	Number mf positive	mf prevalence rate	mf density (mf/ml)
Kizimkazi	500	89	17.8%	356.0
Kwahani	500	36	7.2%	323.0

3.2.6.3 Clinical manifestations at sentinel sites

3.2.6.3.1 Lymphoedema of the limbs

500 individuals were examined at Kizimkazi and 92 were found to have lymphoedema of the legs. Out of those 92, two were young females aged only 8 years. The prevalence rates of lymphoedema of the legs in the Kizimkazi study site are summarized in Table 3.7. The overall prevalence rate of lymphoedema of the legs in 500 persons was 18.4%. Of the 500 persons examined at Kizimkazi 230 (46%) were females and 270 (54%) were males. The prevalence rate of lymphoedema in females (20.1%) was higher than in males (16.5%) (P=0.006). The age-specific prevalence of leg lymphoedema is summarized in Table 3.7 and Figure 3.8. The prevalence rate of lymphoedema of the legs increased with age in both males and females. In the age group below 10 years no male was found with lymphoedema, while in the same age group 2 female individuals had lymphodema. Out of 38 males with lymphoedema the prevalence in the age group 10–19 years was 15.8% and in 30-39 year group 23.7%. However, the age group of 50+ years had a significantly higher prevalence (47.4%) in males and the same was found in the same female age group (40.7%). A steady increase in the prevalence with age was noticed in the female age groups (Table 3.7 and Figure 3.8).

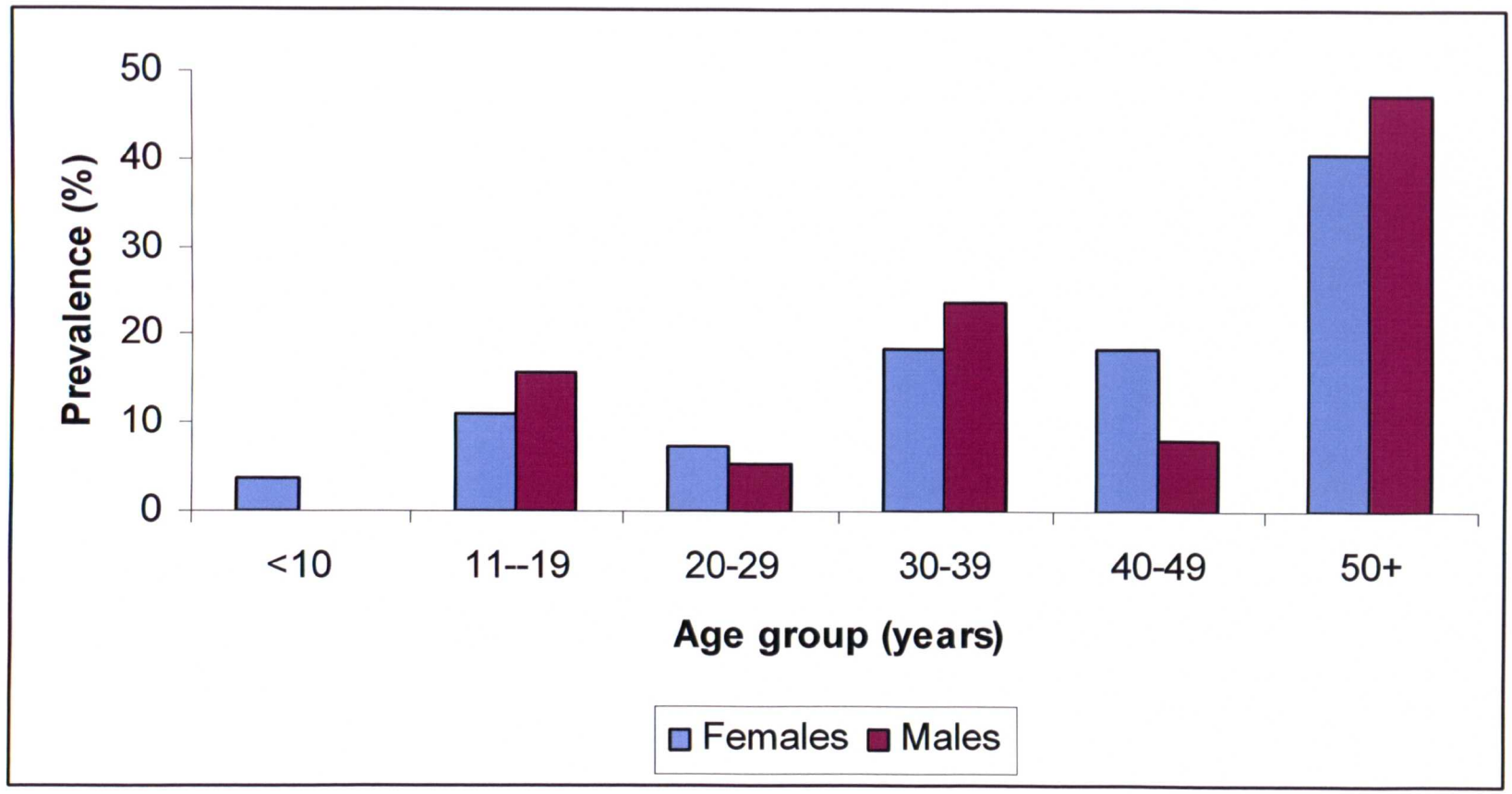
Table 3.7 Prevalence of lymphodema by age and sex at the Kizimkazi site

There is a steady increase in the lymphodema prevalence with age in the female age groups.

Age (Years)	Males n(%)	Females n(%)	Total n(%)
<10	0(0.0)	2(3.7)	2(2.2)
10-19	6(15.8)	6(11.1)	12(13.0)
20-29	2(5.3)	4(7.4)	6(6.5)
30-39	9(23.7)	10(18.5)	19(20.7)
40-49	3(7.9)	10(18.5)	13(14.1)
50+	18(47.4)	22(40.7)	40(43.5)
Total	**38(16.5)**	**54(20.1)**	**92(18.4)**

Figure 3.9 Prevalence of lymphoedema recorded during study survey at Kizimkazi, Zanzibar, 2001

There was a steady increase in the prevalence rates with ages.



At Kwahani, out of 500 individuals who were examined for lymphoedema, 13 of them were found to have lymphoedema of the legs, one of which was a young boy aged 15 years. The prevalence rates of lymphoedema of the leg in the Kwahani study site are summarized in Table 3.8. The overall prevalence rate of lymphoedema of the leg in 500 persons was 2.6%. Of the 500 persons examined at Kwahani 220 (44%) were males and 280 (56%) were females. The prevalence rate of lymphoedema in males (4.1%) was higher than in females (1.4%) (P=0.006). The age-specific prevalence of leg lymphoedema is summarized in Table 3.8. Although there were few cases of lymphoedema at Kwahani, the prevalence rate of lymphoedema of the legs increased with age in both males and females. In the age group below 10 years no cases of lymphoedema were found. The same trend was noticed with age group 10-19 and 20-29 in females although in the male groups there was one case in each age group. Among males, the highest prevalence of lymphoedema was in the age group of 50+ years (55.6%). However, the prevalence rate in males in age group 50+ years was significantly higher (55.6%) than in females in the same age group (50%) (P=0.005). There was no significant difference in the prevalence of lymphoedema in the female age groups 30-39 years (25%) and 40-49 years (25%) (P=0.400). As in Kizimkazi, in Kwahani there was also a steady increase in the prevalence of lymphoedema with age (Table 3.8).

Table 3.8 Lymphodema recorded by age and sex at Kwahani, 2001

Age (Years)	Males n(%)	Females n(%)	Total n(%)
<10	0(0.0)	0(0.0)	0(0.0)
10-19	1(11.1)	0(0.0)	1(7.7)
20-29	1(11.1)	0(0.0)	1(7.7)
30-39	0(0.0)	1(25.0)	1(7.7)
40-49	2(22.2)	1(25.0)	3(23.1)
50+	5(55.6)	2(50.0)	7(53.8)
Total	**9(4.2)**	**4(1.4)**	**13(2.6)**

The association between the prevalence of leg lymphoedema and microfilaraemia in Kizimkazi was determined in persons aged >10 years stratified into age groups to generate enough data to allow statistical analysis. The association between prevalence of leg lymphoedema and microfilaraemia was not significant (r=0.662, r2=0.440, P=0.152). Table 3.9 shows the distribution of lymphoedema of the leg by stage and median age of affected individuals. The majority of lymphoedema 46 (50%) was in stage1, which is mild and reversible. The number of individuals with lymphoedema stages 1 and 2 in the male and female groups was not significantly different. However, there were more females, 11 (20.4%) with lymphoedema stage 3 than males, 4 (10.5%). The prevalence of lymphoedema of the leg stage 4 was higher in males (7.8%) than in females (5.5%), but the difference was not significant (P=0.476). Similarly, in stage 6 the prevalence was much higher in males (2.6%) than in females (1.9%). The median age was similar for individuals with different stages of lymphoedema of the leg, both in males (P=0.287) and females (P=0.863). Leg lymphoedema was recorded in 92 cases. Of these 92 cases, 55 (60%) and 37(40%) individuals had bilateral and unilateral leg lymphoedema, respectively. In terms of stage, 69 individuals (75%) had lymphoedema below stage 3 whereas 23 persons (25%) had stage 3 and above. Of the 23 individuals with

lymphoedema stage 3 and above, 20 (87%) persons had bilateral lymphoedema. Of the 69 persons with leg lymphoedema <stage 3, 30 (43.5%) had bilateral involvement. For lymphoedema <stage 3, there was no significant difference in the proportion of persons with bilateral and those with unilateral involvement (P=0.785).

Table 3.9 Distribution of leg lymphoedema by stage, age and gender during baseline survey in 2001 at Kizimkazi

The majority of lymphoedema were in stage1. The median age was similar for individuals with different stages of lymphoedema of the leg.

Stage of leg lymphoedema	Males		Females		ALL	
	No.	Median age (range),years	No.	Median age (range),years	No.	Median age (range),years
1:Swelling reversible at night	20	45(13-76)	26	42(17-85)	46	43(13-85)
2:Swelling does not disappear	10	57(45-68)	13	39(8-75)	23	45(8-75)
3:Skin has shallow folds	4	51(25-70)	11	71(69-73)	15	57(25-73)
4:Skin has irregular growths	3	57(30-85)	3	79	6	79(30-83)
6:Skin has moss-like growth	1	66	1	76	2	66
All	38	51(13-83)	54	44(8-85)	92	48(8-85)
P value*		0.863		0.287		0.476

*Median test

Kwahani

Table 3.10 shows the distribution of lymphoedema of the leg by stage and median age of affected individuals at Kwahani in the 2001 survey. Although, cases of lymphoedema were few in Kwahani compared to the number in Kizimkazi. Of 13 recorded cases of lymphoedema the majority 6 (46.2%) were in stage1, 3 (23.1%) in stage 2, 2 (15.4%) in stage 3 and 1 (7.7%) in stages 4

and 6. The number of individuals with lymphoedema stage 1 and 2 in the male group was higher than in the female group. However, no case in both stages 4 and 6 were recorded in the female group unlike the male group. Of these 13 lymphoedema cases in Kwahani, 6 (46.2%) and 7 (53.8%) individuals had bilateral and unilateral leg lymphoedema, respectively. For lymphoedema <stage 3, there was no significant difference in proportion of persons with bilateral and those with unilateral involvement (P=0.785).

Table 3.10 Distribution of leg lymphoedema by stage, age and gender during baseline survey in 2001 at Kizimkazi

The majority of lymphoedema was in stage 1. The median age was similar for individuals with different stages of lymphoedema of the leg.

Stage of leg lymphoedema	Males		Females		ALL	
	No.	Median age (range), years	No.	Median age (range), years	No.	Median age (range), years
Swelling reversible at night	4	45(13-76)	2	42(17-85)	6	43(13-85)
Swelling does not disappear	2	57(45-68)	1	39(8-75)	3	45(8-75)
Skin has shallow folds	1	51(25-70)	1	71(69-73)	2	57(25-73)
Skin has irregular growths	1	57(30-85)	0	0	1	79(30-83)
Skin has moss-like growth	1	66	0	0	1	66
All	9	51(13-83)	4	44(8-85)	13	48(8-85)
P value*		0.863		0.287		0.476

*Median test

3.2.6.3.2 Hydrocele

A total of 270 males were examined for hydrocele in Kizimkazi during the survey conducted in the two sentinel sites in 2001. Hydroceles were detected in 21 males (7.8%) with 2 cases found in boys below 20 years old (18 and 19 years old). The prevalence rates of hydrocele in males in Kizimkazi are

summarized in Table 3.11 and Figure 3.9. The prevalence rates of hydrocele among the age group ranged from 9.5%–28.6% in males above 10 years old, but were not significantly different (P=0.543). The highest prevalence rates were observed in the age group 30-39 (28.6%) and in 50 years+ (28.6%). In Kwahani of 220 males examined only 3 (1.4%) had hydroceles, one was 42 years and 2 were over 50+ (65 years and 72 years). The prevalence of hydrocele increased steadily with increase in age. Males above 30 years old had a significantly higher prevalence of hydrocele than those in the 10-19 years (P<0.001) and 20- 29 year (P=0.003) age groups at Kizimkazi. However, in Kwahani hydrocele was found in only males above 40 years.

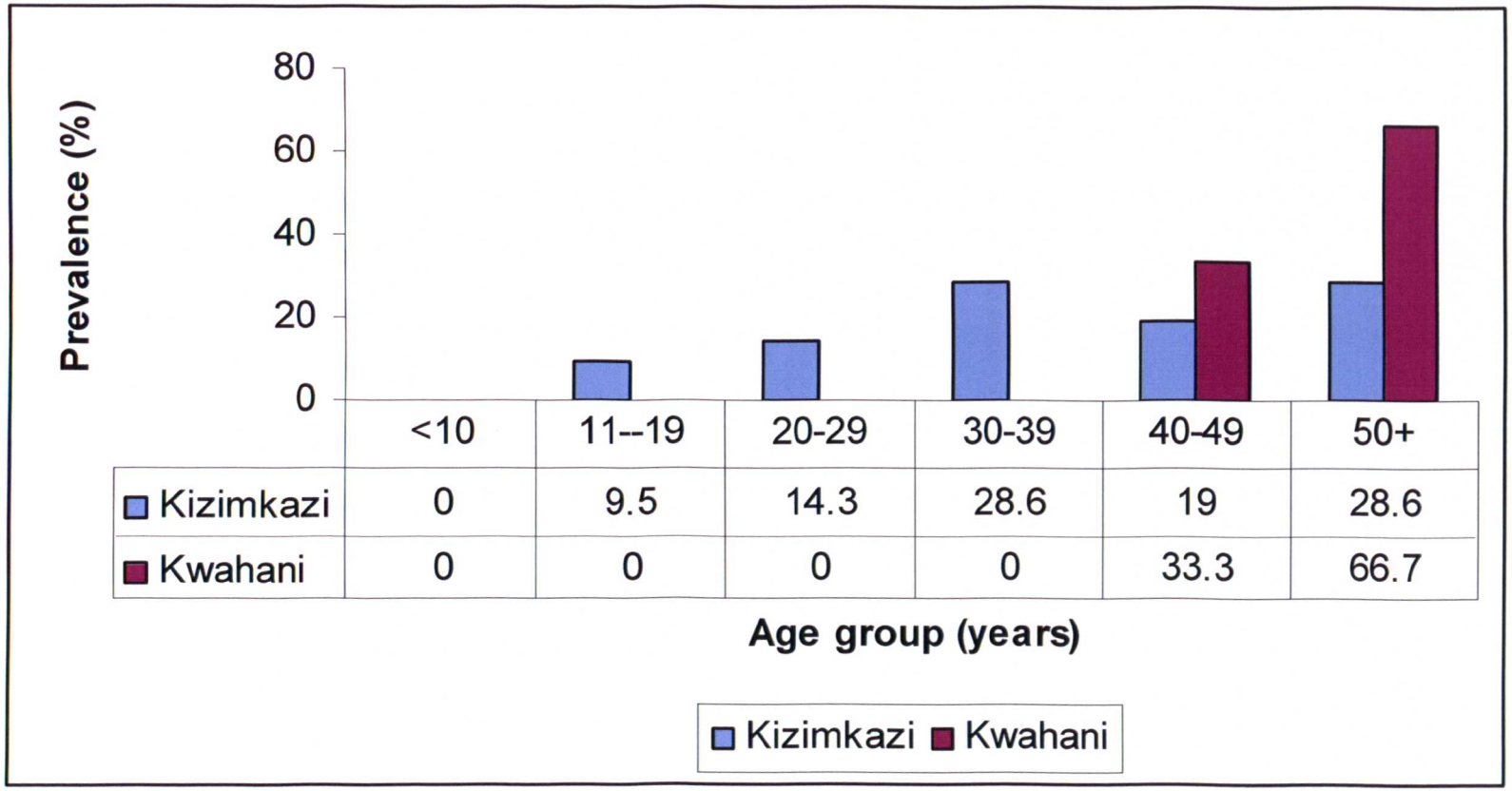
Table 3.11 Prevalence of hydrocele by age during a survey at two sentinel sites.

A stead increase in prevalence with age was noticed in both sites.

Age group	Kizimkazi Site		Kwahani Site	
	No. Examined	No. with Hydrocele (%)	No. Examined	No. with Hydrocele (%)
<10	40	0 (0.0)	25	0 (0.0)
10-19	113	2 (9.5)	83	0 (0.0)
20-29	38	3 (14.3)	36	0 (0.0)
30-39	30	6 (28.6)	29	0 (0.0)
40-49	19	4 (19.0)	24	1 (33.3)
50+	30	6 (28.6)	23	2 (66.7)
Total	**270**	**21 (7.8)**	**220**	**3 (1.4)**

Figure 3.10 Age-specific prevalence of hydrocele in males aged >10 years during baseline survey at Kizimkazi and Kwahani, Zanzibar in 2001

The prevalence of hydrocele increased steadily with age.



	<10	11--19	20-29	30-39	40-49	50+
Kizimkazi	0	9.5	14.3	28.6	19	28.6
Kwahani	0	0	0	0	33.3	66.7

The frequencies of hydrocele by stage in the two sentinel sites are summarized in Table 3.12. The majority of cases (50%) were in stage 1 (6-8cm, longitudinal axis). In general there were fewer hydroceles in the more advanced stages. The median age of persons with different stages of hydrocele were similar (P=0.540).

Table 3.12 Distribution of hydrocele cases by stage and median age of patients

The majority of hydroceles were in the earlier stages and the median age of persons with different stages of the manifestation was similar.

Stage of hydrocele	Number	Median age (range), years
1 (6-8cm)	12	49 (16-85)
2 (8-11cm)	7	45 (18–75)
3 (11-15cm)	3	52 (25-75)
4 (>15cm)	2	58 (53-62)
All	24	49 (12-85)
P value*		0.246

*Median test

Detection of microfilaria is a specific test for the presence of active infection. The prevalence of microfilaraemia in males with and without hydrocele at Kizimkazi was 1.7% and 18.2%, respectively, the difference was significant (P=0.0254).

In addition to comparing individuals with and without hydrocele for the presence of active infection, analyses were also undertaken on the intensity of infection in Kizimkazi. The geometric mean intensity of microfilariae in 4 microfilaraemic males with hydrocele was 828mf/ml. For 19 microfilaraemic males with no

hydrocele the intensity of microfilaraemia was 325mf/ml. However, the difference in intensity of microfilaraemia in microfilaraemic individuals with and without hydrocele was not significant (P=0.109).

3.2.6.3.3 Scrotal lymphoedema

During examination for hydrocele, males were also examined for scrotal lymphoedema. Of the 443 males examined in the two sites none of the males had scrotal lymphoedema.

3.2.6.4 Summary of the results.

In the results of LF baseline survey in the two sentinel sites selected Kizimkazi (rural area) the individuals recruited were 46.0% females and males 54.0%. However, in Kwahani (urban area) sites females were 56.0% and males 44.0%. This indicates that in the rural areas of Zanzibar men compared to women are more likely to participate in health study survey more than in urban areas (Table 3.2 &Table 3.3). In all the sites looking at the age and sex distribution most participants were in the age group category of 11-20 years in both sex (Table 3.2 & Table 3.3). As for the prevalence of *W.bancrofti* at Kizimkazi site the prevalence was 17.8% and the intensity 356 mf/ml while at Kwahani prevalence was 7.2% and the intensity 323 mf/ml and in both sites the greater number of males were found to be microfilariae positive than females (Table 3.4 & Table 3.5; Figure 3.7). In the general distribution of microfilaraemia positive increased with increasing age in both sites. However, it was noticed that the high number of individuals who were microfilariae positive were in the 11-20 age group category (Figure 3.5 & 3.6).

Most LF clinical manifestations noticed at both Kizimkazi and Kwahani sentinel sites were lymphoedema of the legs and hydroceles. At Kizimkazi lymphoedema prevalence rate was 18.4% and in females 20.1% and males 16.5%. As with

microfilaraemia an increase in prevalence rate of lymphoedema of the legs with increase in age was noted in both sex and in all sites. However, the age group of 50 years and above had higher prevalence rate recorded as compared to younger age group (Table 3.7 & Figure 3.8). Most lymphoedema cases were in the stage 1 and 2 in all sites. However, at Kizimkazi there were more cases of lymphoedema of the leg than Kwahani (Table 3.7; Table 3.8; Table 3.9 & Table 3.10). As for hydroceles at Kizimkazi the prevalence recorded was 7.8% and Kwahani 1.4% (Table 3.11). However, at Kizimkazi sentinel sites cases of hydroceles were recorded in all age group with the exception of age group of below 10 years unlike Kwahani where cases were only recorded in age group 40 years and above (Table 3.11).

CHAPTER IV

THE ZANZIBAR PROGRAMME TO ELIMINATE LYMPHATIC FILARIASIS

4.1 Background

Zanzibar adopted a national programme for the elimination of lymphatic filariasis in 2001. The entire country was found to be at risk of lymphatic filariasis according to the results of the disease surveys undertaken in the country. The Ministry of Health and Social Welfare (MOHSW) decided to place the LF elimination programme, like other parasitic diseases control programmes, under the Department of Preventive Health Services and Health Education in its MOHSW organogram. The District Medical Officers in collaboration with appointed members from the District Health Management Teams (DHMT) are responsible for the implementation of all programme activities at their respective levels of the health system.

The Zanzibar programme to eliminate lymphatic filariasis (PELF) has two main objectives: (i) to interrupt lymphatic filariasis transmission by 2015; and (ii) to eliminate lymphatic filariasis as a public health problem by 2020. The strategies advocated and implemented by the Zanzibar (PELF) are those recommended by the Global Programme to Eliminate Lymphatic Filariasis:

- Interruption of transmission through annual mass drug administration to endemic communities using ivermectin and albendazole for 4 – 6 years
- Morbidity control: prevention and alleviation of disability and suffering in individuals already affected by LF (hydrocele surgery, skin hygiene for elephantiasis and lymphoedema).

The other strategies deployed are surveillance, inter-sector and inter-country collaboration, operational research, capacity building and vector control in collaboration with malaria control programme.

The Zanzibar PELF has been implementing its activities since 2001. The treatment is organized through annual mass drug administration (MDA) campaigns at community level by the district teams. The objective is to deliver to all eligible members in the districts the combination of two drugs, albendazole and ivermectin (Mectizan®); the doses of ivermectin (Mectizan®) are determined by the height of the individual using dose poles. The drugs are administered by drug distributors, referred to as filarial prevention assistants (FPAs) selected from the community members with health services provision experience and based on a pre-set criteria. They are then trained for this purpose by the members of District Health Management Team. The criteria usually used for selecting community drug distributors are either that s/he should be:

- medical staff within the area concerned;
- a school teacher from the same locality;
- had worked in previous health campaign;
- physically active;
- from the shehia or village where he/she is expected to work;
- accepted by and acceptable to his/her community.

In addition to the MDA, Zanzibar PELF has an LF morbidity programme to manage the clinical manifestations of the disease, which affect up to 5% of the population with lymphoedema or elephantiasis and up to 20% of the men with hydrocele. Care for persons with lymphoedema includes such self help measures as exercise, improved skin hygiene (washing and drying), and application of anti-fungal or anti-bacterial ointments to reduce skin infections. The morbidity programme also includes surgery to correct hydrocele. This not

only alleviates the suffering of individuals and improves their physical, social and economic well-being but also gives credibility to the Programme in the country. The LF morbidity management programme is likely to continue long after transmission of LF has been interrupted.

4.1.1 Partnership/collaborative bodies

The Zanzibar PELF has, since its initial phase, received assistance from and is collaborating with different bodies both international and local. Among those organizations are WHO Headquarters, Geneva, WHO African Regional Office (WHO/AFRO) and the WHO country office for both financial and technical support; Izumi Foundation for financial support ; Liverpool LF-Support Centre for financial and technical support; DFID for financial and technical support; the pharmaceutical companies Merck & Co. Inc. and GlaxoSmithKline through the donation of Mectizan® and albendazole respectively including transport costs to and from the port of entry; the Zanzibar Ministries of Education, Information, Youth, Women and Children Affairs, the Ministry of Defense and Ministry of Home Affairs and others for social mobilization aspects.

4.2 Zanzibar PELF strategies for Mass Drug Administration (MDA)

4.2.1 Introduction

In most African countries the recommended combination for community MDA against LF is that of ivermectin (Mectizan®) and albendazole because of co-endemicity of onchocerciasis with LF in several areas. However, Zanzibar is onchocerciasis free but because it is part of Tanzania and the mainland is onchocerciasis endemic and there is free movement and settlement of the population in both island and mainland it was agreed to use the Mectizan®/albendazole combination. These combinations are given annually for a period up to six years to all eligible populations. One of the important barriers to the successful implementation and completion of filariasis elimination

programs based on annual treatment is the need to achieve high coverage levels. Obtaining the widest possible drug coverage (80-90%) in communities at risk is required for successful interruption of transmission (Sunish et al, 2003). Hence the most important operational challenge is to develop approaches to ensure broad drug coverage. Also one of the specific aims of the study is to determine whether 5-6 annual rounds of MDA using albendazole and Mectizan® is sufficient to stop transmission in Zanzibar. Therefore, the Ministry of Health, Zanzibar decided to adopt the following strategies with the intention of achieving the highest drug coverage in all its districts.

4.2.2 Operational units

Zanzibar consists of 10 administrative districts (see Maps Figure 4.1 & 4.2). In order to implement MDA and other PELF activities each district has been designated as an operational unit. However, the urban district of Unguja Island because of its settings was divided into 3 independent zones and each zone is taken as an independent operational unit. Hence, there are 12 PELF operational units in Unguja and Pemba Islands.

Special Institutions

The Ministry of Health decided, in agreement with those institutions concerned, to have them as independent operational units for the PELF activities. These included army and police camps and prisons which formed additional operational units for each of Unguja and Pemba Islands.

The District Medical Officers (DMOs) are responsible for all PELF activities in their respective districts. The DMOs selected one member of the health staff to be responsible for PELF in each district who was then responsible to select 4-5 trainers (depending upon the size of the district) from the DHMT for each district to attend a training of trainers course (TOT) for instruction on the MDA. The 4-5

trained health personnel from each district form the District PELF Team. In the case of the special institutions each selected one officer to attend the training of trainers. Each selected officer from a special institution is responsible to set up his/her plan for all issues related to PELF including MDA and submit it to the PELF office.

Figure 4.1 Map of Unguja island with six districts

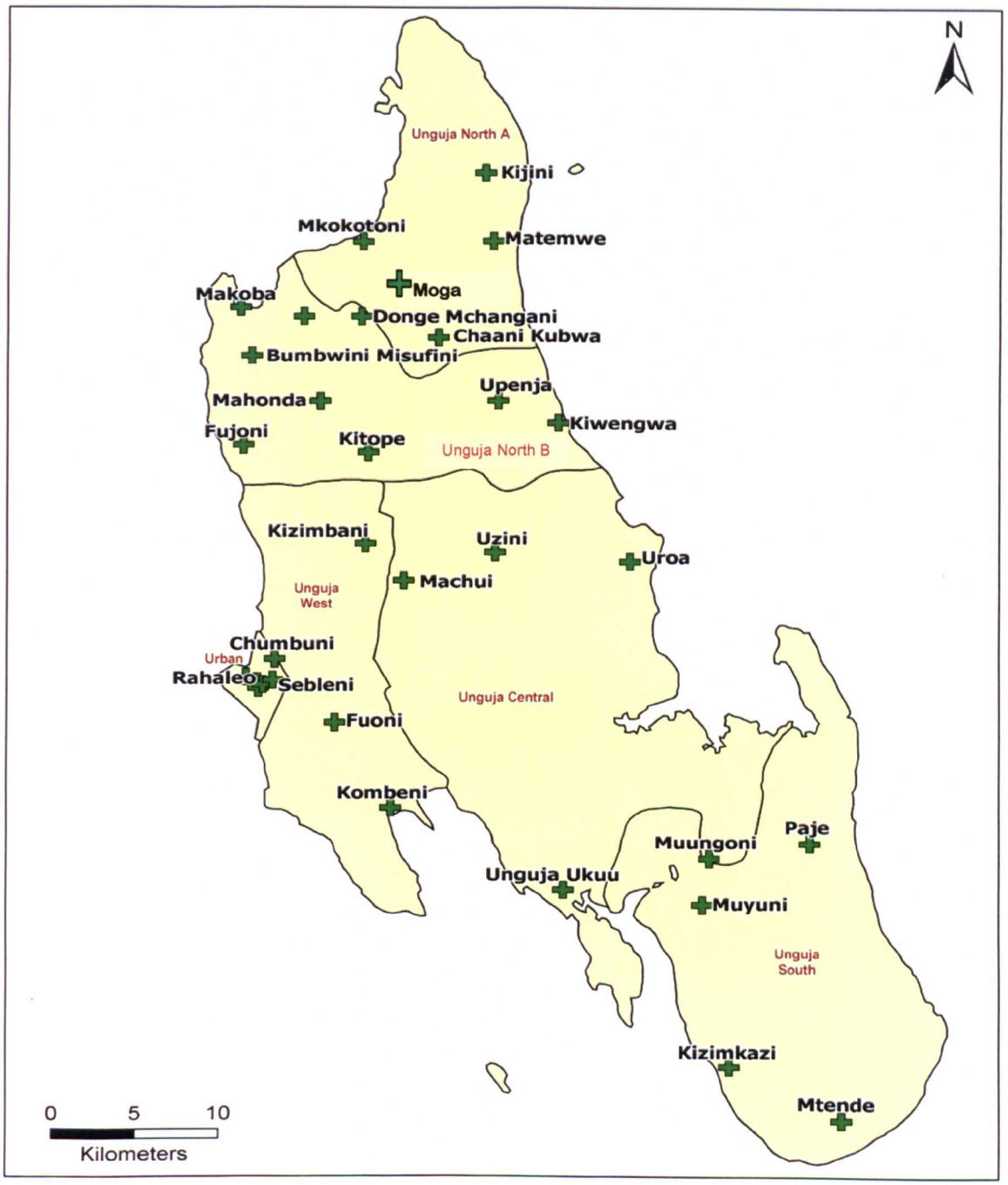
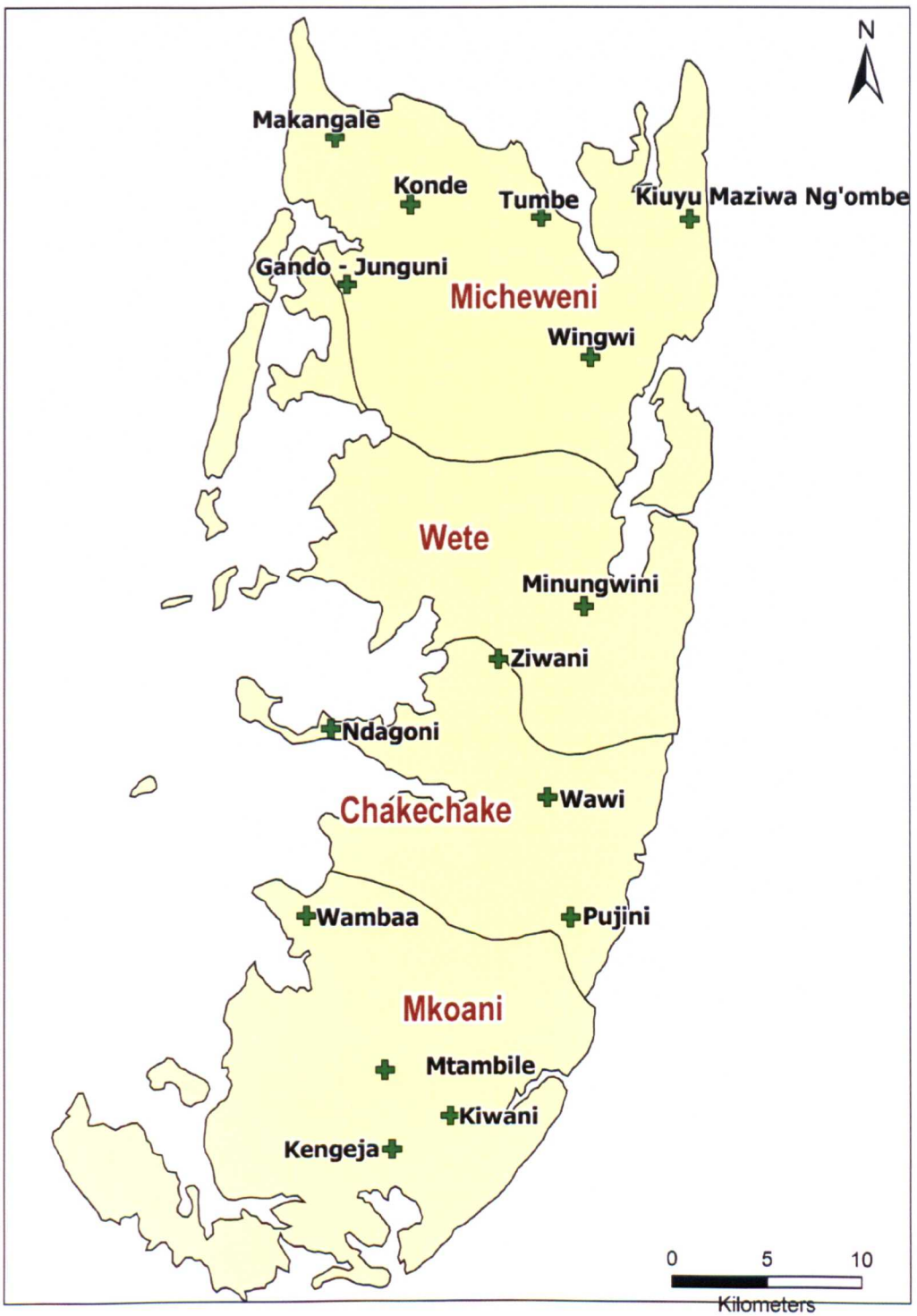


Figure 4.2 Map of Pemba island with four districts



4.2.3 Training

The national PELF personnel before each annual MDA had the responsibility of conducting training of trainers (TOT) on drug distribution. Two one day training courses for trainers on drug distribution were organized, one in Unguja Island and the other one in Pemba Island. The identified personnel from the national PELF level facilitated the training sessions. The TOT aimed at training 62 participants, 50 from 12 operational units and 12 from special institutions (i.e 6 from Unguja and 6 from Pemba). Those attending TOT training were given responsibility of training drug distributors or filarial prevention assistants (FPAs) in their respective operational units. It was realized that through the strategy of moving from house-to-house to distribute drugs and for each distributor to cover fifty households more than 4000 drug distributors (FPAs) needed to be trained. It was estimated that every trainer had to train about 70 drug distributors in 5 days in 5 different groups. All basic knowledge of LF disease, its transmission and different ways of interrupting transmission, how to determine the dosage of ivermectin (Mectizan®) using height via dose poles as well as the aspects of adverse drug reactions were covered in the training cascade.

Table 4.1 Dosage of Mectizan® in height

Height	No. of Mectizan® tablets
90-119cm	1
120-140 cm	2
141-158 cm	3
>158 cm	4

4.2.4 Time frame for MDAs

The implementation of the MDA for each round was planned for the Saturday of the last week of October when most of the people would be at their respective settlements and because a mop-up operation could be scheduled for the following Sunday in order to reach as many defaulters as possible. However, it was also agreed that if the day and date falls in the Holy month of Ramadan when most people would be fasting during the day, the MDA would be shifted to another month either before or after but the day should remain a Saturday with mop-up on the following Sunday. To cover the whole population of Zanzibar 4,161 drug distributors called Filaria Prevention Assistants (FPAS) were recruited. Each FPA was expected to cover approximately 50 households on the day of the MDA.

4.2.5 Social mobilization

The Zanzibar PELF realized that to achieve the highest drug coverage the social mobilization component was crucial. In collaboration with technical experts from WHO, the PELF designed a plan based on Communication for Behavioral Impact (COMBI) for the effective MDA to achieve the highest coverage for the Programme. To implement communication interventions several strategies were proposed.

1. Advocacy/public relations/administrative mobilization

The Zanzibar PELF in collaboration with MOH authority established a National Task Force, a Technical Committee for Unguja and a Technical Sub-Committee for Pemba. Following that the PELF carried out a programme of activities for administrative mobilization, consisting of staff meetings and consultation, and the issue of various memoranda Zanzibar PELF needed to:

- prepare a two page briefing paper on LF and the Zanzibar MDA- day; hold several meetings of National Task Force;
- hold meetings of Technical Committee;
- hold meetings of the Technical Sub-Committee in Pemba;
- hold meetings with District Commissioners;
- hold meetings between the MOH/PELF staff and Zonal and District Medical officers with the special attention of selecting FPAs;
- issue an official memorandum (copied to District Commissioners and Shehas) from the MOH to all health staff regarding the MDA campaign, explaining its importance on LF prevention and sharing a summary of the COMBI Plan;
- hold meetings between MOH and Ministry of Education (MOE) to share the briefing document and the COMBI Plan and explain school promotion efforts and secure commitment;
- issue a memorandum from the MOE to District Education Officers (copied to Shehas) emphasizing the role of teachers and school children and inviting active participation;
- issue a memorandum from District Education Officers to all primary and secondary school heads regarding the school promotion effort, its rationale, and inviting participation;
- hold meeting with Imams and other religious leaders in each island;
- hold a meeting with all Shehas on each island.

The Zanzibar PELF then coordinated a programme of press and media activities to put on the public agenda the issues surrounding LF and its prevention. This was done in collaboration with Zanzibar Television and Radio Zanzibar. To facilitate the distribution of all press materials to local media the Zanzibar PELF:

- prepared a two page press release (written in journalistic style) based as a briefing document announcing the MDA day and what was to be expected;

- prepared a two page press release on the schools campaign;
- held press conferences with MOH and MOE and the press on the effort in schools;
- prepared and distributed to print media a major press release of a 2000 word feature article on the endemic LF situation in Zanzibar based on the briefing document but written in journalistic style and featuring various quotes from MOH, PELF staff and others, including WHO;
- prepared and distributed for radio and television a 2-minute press release with sound/video bites covering some of the same themes as the feature article/press release above, for use in radio and television news programmes;
- maintained an on-going public relations/press effort for three months prior to MDA day issuing weekly press releases announcing the interventions during the campaign, and a news story of progress on the overall effort or some district related news story;
- produced and broadcast half-hour radio discussions aired 6 weeks before F-day and another 1 week before MDA-day;
- arranged for the "Mawiyo" morning radio show to cover news of MDA day activities.

2. **'Personal selling'/door-to-door communication**

This involved the establishment of a "personal selling" network of drug distributors or filaria FPAs with supporting materials. The PELF requested the staff at health facilities and District Health Management Team members with the help of a community leader (Sheha), to select temporary workers from their respective Shehia to serve as PELF drug distributors on MDA day and the mop-up day. Criteria for selection of the drug distributors were observed and followed. All selected distributors, underwent training in the substantive matters of the disease, the process of drug administration, and door-to-door communication techniques. After the training each distributor was provided with

Filaria Household Registers to enter the essential demographic information for each household member to which s/he had been assigned. Each distributor was required to make three home visits to each of his/her assigned houses. In the first visit s/he was expected to provide information pamphlets and explain rationale for the visit and what would be done on MDA day and also register and take height measurements of all members of each household. During the second visit they addressed issues related to LF disease, the drugs to be given as well as the timing of his/her third visit on the MDA day.

3. **Community mobilization and promotional activities**

The Zanzibar district PELF team was responsible for conducting LF and MDA day community meetings in collaboration Primary Health Care Unit staffs, Imams and other religious leaders and community leaders - Sheha for each Shehia. The same district PELF team was required to organize and execute School Promotion efforts for the MDA day.

4. **Massive advertising**

The national PELF team in collaboration with local TV and Radio stations planned and executed a massive, repetitive, intense and persistent radio and TV advertising campaign continuously for fifteen days prior to the MDA day.

4.2.6 Management of adverse reactions

The LF MDA was the first country wide community drug administration to take place in Zanzibar. In order to assure the safety of its people the Ministry of Health PELF prepared for any unwanted side events due the MDA. Hence the Zanzibar PELF involved the Director of Curative Services of the MOH addressing issues associated with management of adverse reactions related to the country-wide distribution of ivermectin (Mectizan®) and albendazole. This is

because within MOH all issues related to hospital management of patients are under the Director of Curative Services. A statement was made to the public before the MDA on the anticipated side effects of the drugs and on what to do in such an eventuality [WHO, 2000]. The statement was made by PELF personnel through mass media and sensitization meetings in the community. All public health facilities were kept open 24 hours on the MDA campaign days and on the mop-up day. All health facilities involved were stocked with adequate quantities of drugs for the management of adverse reactions before the MDA campaign started. Private health facilities were also provided with drugs for the management of adverse reactions to encourage full involvement in the MDA.

4.2.7 Strategies for surveillance

To assess the country achievement of the MDA objective, two sentinel sites for monitoring were identified before the commencement of first MDA. One sentinel site was selected from rural operational units (Kizimikazi) and one from urban operational units (Kwahani). Before the first MDA campaign started, base line data were collected from each of the sentinel sites, where 500 individuals of all ages were examined for lymphoedema and for microfilariaemia using night blood sample counting chamber technique and the baseline microfilaraemia prevalence, mean microfilaraemia density and lymphoedema prevalence and the hydrocele rate were determined (see Chapter III). It was agreed before another MDA round that the activities undertaken during the collection of baseline data would be repeated in the selected sentinel sites. In addition to the sentinel sites randomly selected spot check sites were added as the MDA rounds continued and the same procedures used in sentinel sites were repeated in the spot check sites. Besides data collection other activities that had been agreed to be undertaken in the sentinel and spot check sites after every round of drug distribution included: (i) monitoring the proportion and nature of adverse reactions encountered through interviews, (ii) Assessment of the reasons for drug compliance, (iii) compared coverage in gender and age groups, (iv) elicit

reasons for an inadequate or drop in coverage and find remedies and (v) submit a report of the findings, with a plan for improvement (WHO- Annex 2b). All these activities were conducted by members of PELF from national level and other MOHSW staff not involved in the drug distribution activity to avoid bias.

4.2.8 Results of PELF implementation

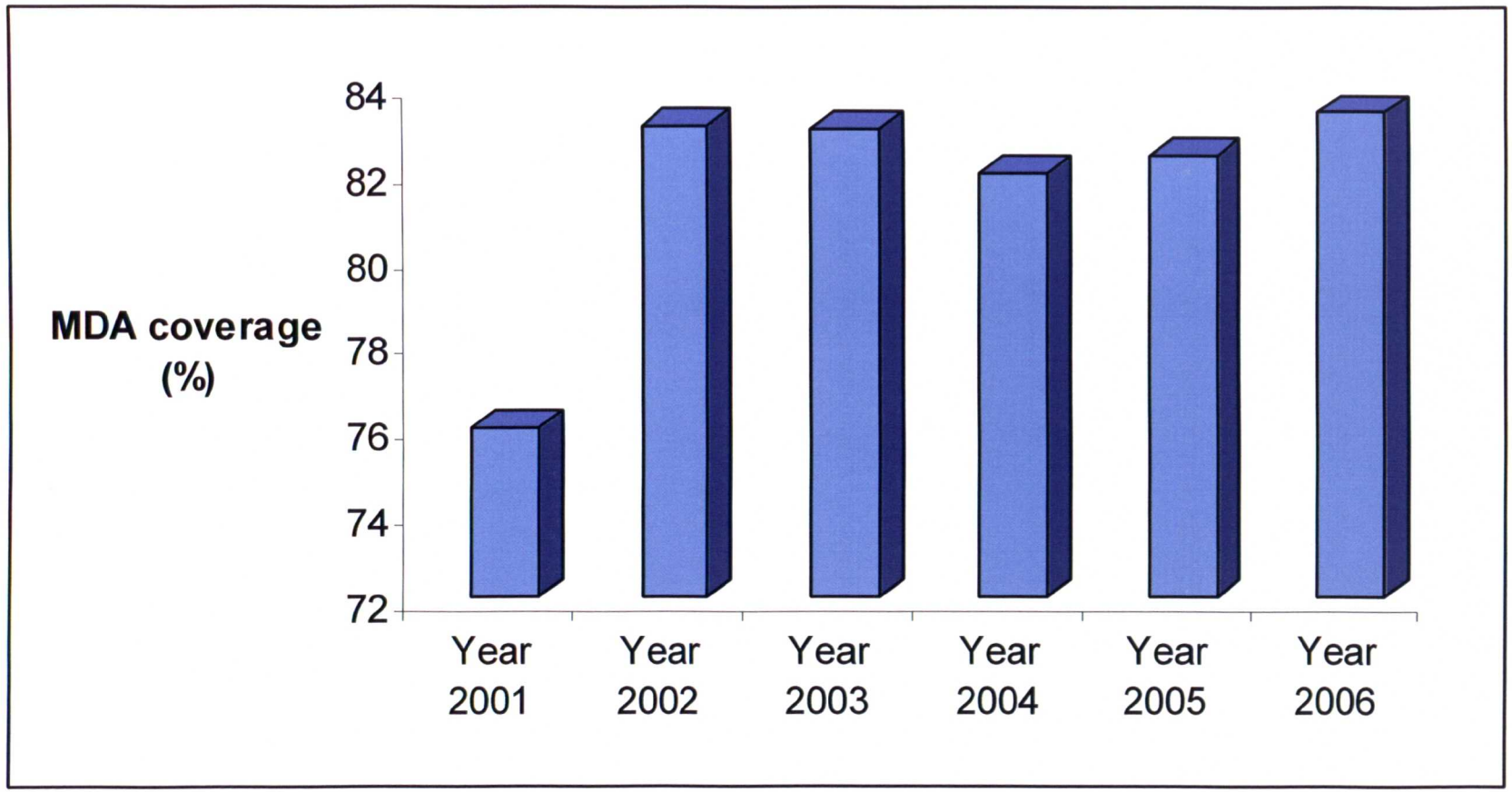
The MDA campaigns in all six rounds (2001,2002, 2003,2004,2005,2006) resulted in attaining good drug coverage in all the ten districts of Zanzibar. However, the coverage in the first round was only adequate in some districts. The table below shows overall drug coverage in all districts of Zanzibar in those six MDA rounds (Table 4.2).

Table 4.2 Zanzibar LF Mass Drug Administration coverage 2001–2006

Year	Districts covered	Total population	Treated population	Treatment coverage of total population (%)
2001	10	840,670	638,909	76.0
2002	10	984,625	818,155	83.1
2003	10	1,049,339	872,731	83.0
2004	10	1,096,796	899,373	82.0
2005	10	1,126,624	928,339	82.4
2006	10	1,161,629	968,992	83.4

In the first round of MDA in 2001 the overall drug coverage was below 80%. However, in the preceding MDAs the coverage achieved the level targeted.

Figure 4.3 Zanzibar LF Mass Drug Administration coverage 2001–2006



4.3 MDA COVERAGE ASSESSMENTS

4.3.1 Background

Zanzibar started annual MDA through the entire country in October 2001 and completed its sixth round in December 2006. The recommended drug combination for Zanzibar is albendazole and ivermectin (Mectizan®) and distributed through a door-to-door a strategy was believed to be the most appropriate to attain highest drug coverage in the country. The two important indicators for MDA for any LF endemic country are the therapeutic and the geographical coverage. However, in Zanzibar because the distribution covers the whole country the geographical coverage was not considered. These indicators were reported from the drug distributors to the Health Centre and then to district level; calculations are based on the population estimate. To determine the programme success treatment coverage has been identified to be crucial and independently surveyed coverage is recommended by the WHO Global Programme to Eliminate Lymphatic Filariasis (GPELF). The main objective of the assessment of surveyed coverage was to compliment the reported coverage by providing coverage estimates that are statistically likely to be representative for surveyed districts.

4.3.2 Methodology

The methodology used was based on the standard protocol developed by WHO 'A cluster-survey protocol for assessing MDA coverage for LF programmes' (WHO, 2005) which was modelled on immunization coverage surveys and other country experiences (Mathieu et al., 2003). The sampling methodology is designed to provide an estimate of actual coverage that is accurate to within plus or minus 6.5%. The survey is undertaken at the level of Implementation Unit (IU) which is commonly a district where 30 sub-units are selected randomly. From each of these, a cluster of individuals is selected. A population-proportionate sampling method is used to select the sub-units to take into

consideration the differences of populations. Once the 30 sub-units for the districts have been identified, 30 individuals will be selected from each sub-unit, resulting in an overall sample size for the survey of 900 individuals. Once a starting household has been randomly selected, data are collected from all individuals in this starting household. Once this is done, the next nearest is visited and data are collected from all individuals in that household. This process continues until data have been collected for 30 individuals. This methodology allowed additional information to be collected economically during coverage surveys by adding questions related to KAP and any side effects experienced. In the first survey questions related to KAP were added to the questionnaire and the results analysed and appropriate measures taken based on the recommendations of the study findings.

Zanzibar given its size and population was regarded as a single implementation unit with its districts and special units considered to be operational units. To obtain coverage data a simple coverage survey study was conducted after each round of MDA in 35 Shehias (20 from Unguja Island and 15 from Pemba). However, in the survey after first MDA a total of 39 Shehias were involved (24 in Unguja and 15 in Pemba). All surveys were undertaken by personnel, at least one at supervisory level above those who were responsible for drug distribution, according to WHO guidelines. The selection of those surveyed Shehias was done randomly for each district to achieve proper representation. For each of the selected Shehias 600-1,000 individuals of both sexes were interviewed using a questionnaire designed to check the coverage rate, as well as adverse reactions that had been experienced during the MDA campaign. The results showed that the drug distribution coverage of the total population of Zanzibar was between 70%-80% in all rounds. After the collection and analysis of the data from all the districts of Zanzibar the results of drug distribution coverage for the entire population showed variation between districts. However, the average coverage for all districts in all the six rounds was 76%, 83.1%, 83%, 82%, 82.4% and 83.4% (Table 4.2, Figure 4.3).

4.3.3 Results

4.3.3.1 Drug coverage assessment

Of the 26,143 people interviewed from 39 Shehias during the survey carried out one week after the first MDA (Table 4.3) an overall drug coverage rate of 76% (79% in Unguja island and 71% in Pemba island was recorded, which reflected the 92.1% and 85.6% of people who swallowed the drugs among the eligible population respectively.

The survey undertaken after the second round of MDA (2002) in 35 Shehias of Zanzibar showed no statistically significant difference between the reported treatment coverage by the drug distributors and the checked or observed/surveyed treatment coverage when compared as indicated in Table 4.4. However, the reported coverage was higher than surveyed coverage.

Table 4.3 Evaluation of drug coverage rate after first MDA round

Island	Number of sites (Shehias) surveyed	Number interviewed	Eligible among the interviewed	Number of interviewed who swallowed the drugs	Drug coverage rate among interviewed
Unguja	24	15,779	13,523 (85.7%)	12,461	79.0%
Pemba	15	10,364	8,649 (83.5%)	7,402	71.4%
Overall	39	26,143	22,172 (84.8%)	19,863	75.9%

Table 4.4 Districts reported and checked treatment coverage after 2nd. MDA round

District	Reported Treatment Coverage (%)	Checked treatment coverage		
		Population surveyed	Number treated	Coverage (%)
North A	84.0	2225	1769	79.5
North B	85.0	2120	1717	81.0
Central	81.0	2002	1568	78.3
South	82.0	2017	1593	79.0
West	80.0	2345	1841	78.5
Urban	83.0	2337	1872	80.1
Micheweni	84.0	2018	1647	81.6
Wete	85.0	2212	1838	83.1
Chake Chake	81.0	2301	1815	78.9
Mkoani	89.0	2041	1780	87.2

4.3.3.2 Drug compliance assessments

During the survey after the first round of MDA among 22,172 eligible 2,309 individuals (Unguja Island 1,062 and Pemba 1,247) were interviewed. Different reasons were given for the non-treatment of eligible individuals. In the areas where the majority of the inhabitants belonged to the opposition party the refusal rates were higher compared to other areas where majority were from ruling party. The main reason given by those who refused was because the drug distributors were selected from members of ruling party and therefore they had no faith in them. Other reasons for drug refusal as well as absenteeism were rumours that circulated saying the drugs being distributed were designed for family planning and most of the people have a negative attitude towards drugs related to family planning. However, the surveys that were done after the

second MDA and subsequent MDAs showed a significantly increased coverage in all districts. The reason for non-treatment among the eligible individuals was mainly attributed to absenteeism.

4.3.4 Side effects (adverse reactions) observed

It was necessary to assess and determine the distribution of side reactions following the LF MDA campaign in the country. Most of the adverse effects related to the MDA were observed during first round compared to other rounds. In the first survey the same population interviewed to assess the drug coverage rate (Table 4.3) was also asked about any side-effects they suffered after consuming the drugs. Only 1,589 (8%) individuals who swallowed the drugs reported side effects. These were mostly transient and minor such as abdominal discomfort, headaches, dizziness and scrotal pains. Among them 826 (52%) were females and 763 (48%) were males. 1,462 (92%) were reported to have taken their treatment in the morning while 127 (8%) had their treatment in the afternoon. Most of this group complained of abdominal discomfort 837 (4.2%), mild headache 439 (2.2%), dizziness 298 (1.5%) and scrotal pain 15 (0.1%). All reported their reactions disappeared within twenty four hours. Not a single severe adverse reaction was reported as defined by World Health Organization (WHO, 2003.)

The few reported mild side effects associated with the MDA indicated that a combination of albendazole and ivermectin (Mectizan®) is safe and well tolerated. Similarly, this combination has been reported to be safe for LF elimination by several authors in different settings (Addis et al., 1997; Bockarie et al., 2002b; Dunyo et al., 2000; Simonsen et al., 2004). However, the IEC messages in the LF elimination campaign should include messages about the potential side effects and measures to be taken when such effects are encountered. A higher frequency of side effects had been recorded in several countries in different settings during MDA – India, in the State of Orissa, 15.5%

during 2002 MDA and 16.5% during 2004 MDA (Babu et al., 2006); Haiti, 47% during third round MDA (Mathieu et al., 2006); Haiti 8% during fifth round MDA (Hochberg et al., 2006).

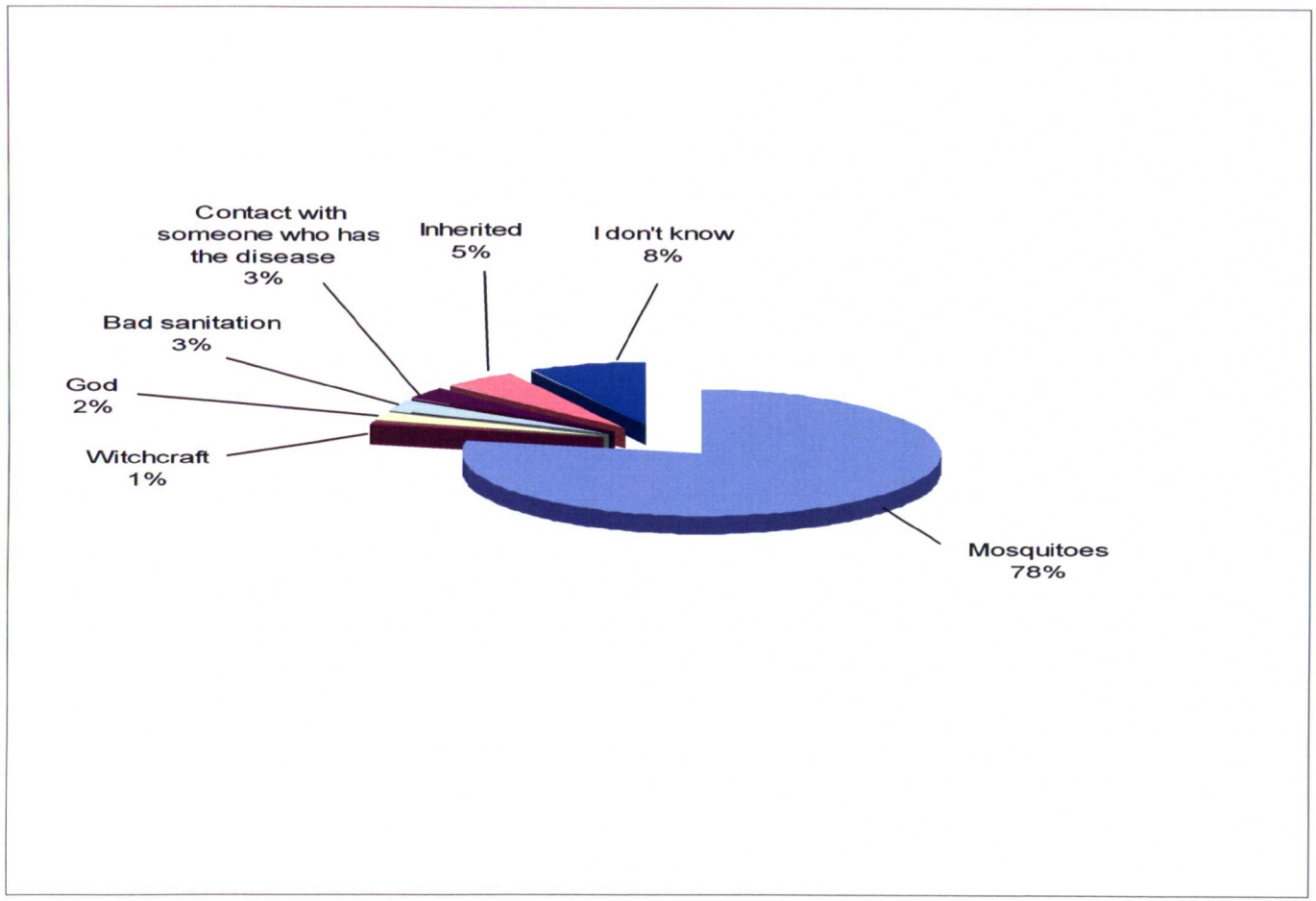
4.3.5 Knowledge, Attitude and Practice (KAP) study results

The aim of adding questions related to KAP within the designed questionnaire of the survey after the first MDA was to identify knowledge, attitude and perceptions towards LF in the Zanzibar community to be able to address appropriately the whole issue of PELF MDA. Three general questions were added:

(i) What people think causes LF - locally referred as 'Matende'?;
(ii) What was the source of information on MDA?;
(iii) What convinced people to take the drugs on MDA day?

Of the 1,901 individuals who responded to the question on what they think causes 'Matende' (LF) 1,483 (78%) replied mosquitoes, 19 (1%) replied witchcraft, 38 (2%) God's will, 57 (3%) bad sanitary conditions, 57 (3%) contact with someone who has the disease, 95 (5%) heredity and 152 (8%) they do not know what causes LF (Figure 4.4).

Figure 4.4 Results of KAP study on What people think causes Elephantiasis - locally referred as 'Matende'?; [1,901 responses]



Of the 2,158 persons who were interviewed by which means they received MDA information, 950 (44%) heard it on national radio; 43 (2%) read it in school information sheets, 65 (3%) heard it from sound trucks, 86 (4%) from health personnel in their respective areas, 108 (5%) when they attended community meetings, 108 (5%) heard it from either friends or family members, 108 (5%) from promotional materials, either leaflets or posters, 194 (9%) from their community leader (Sheha), 216 (10%) from drug distributors who visited their respective houses and 280 (13%) saw it local TV. About 1620 (75%) individuals claimed to have acquired information from a combination of those different sources (Figure 4.5).

Of the 1,637 individuals that were interviewed on what convinced them to take drugs during the campaign 589 (36%) said information from media (local radio, TV and newspapers), 262 (16%) from local community leaders (Shehas), 229 (14%) from drug distributors, 164 (10%) from friends or family members, 82 (5%) from home delivery of the drugs, 82 (5%) from the sound trucks that were passing around with LF messages, 65 (4%) from school information sheets that were brought home by their children with LF messages, 65 (4%) from fear of the disease and the whole issue of preventing themselves from contacting the disease, 33 (2%) because the drugs were free while most of the time people used to buy drugs, 16 (1%) from religious leader announcements, 17 (1%) from their political leaders in their speeches during political party meetings, 16 (1%). No one convinced them it was their personal decisions and 17 (1%) said the different government programmes convinced them to take LF drugs (Figure 4.6).

Figure 4.5 What was the source of information on MDA?

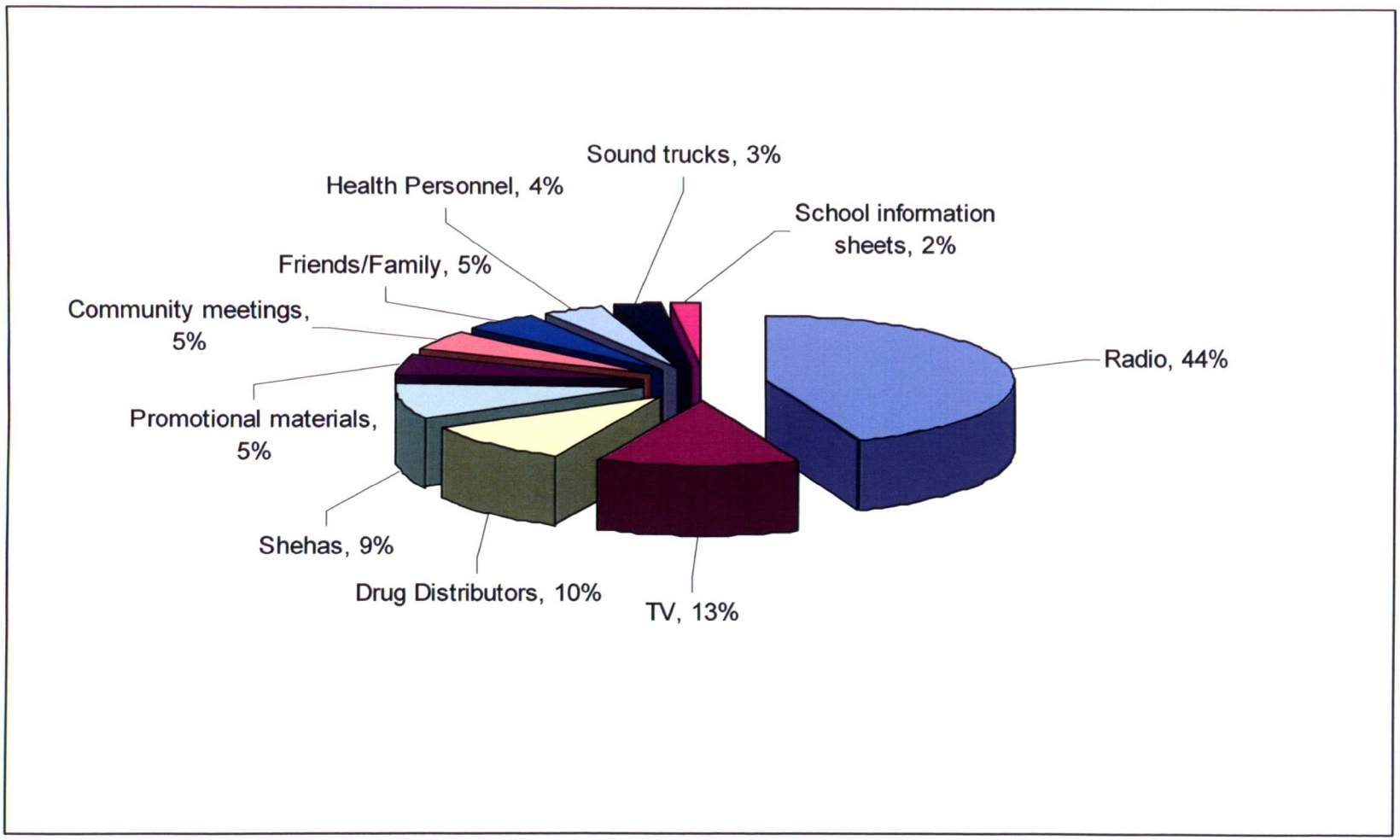
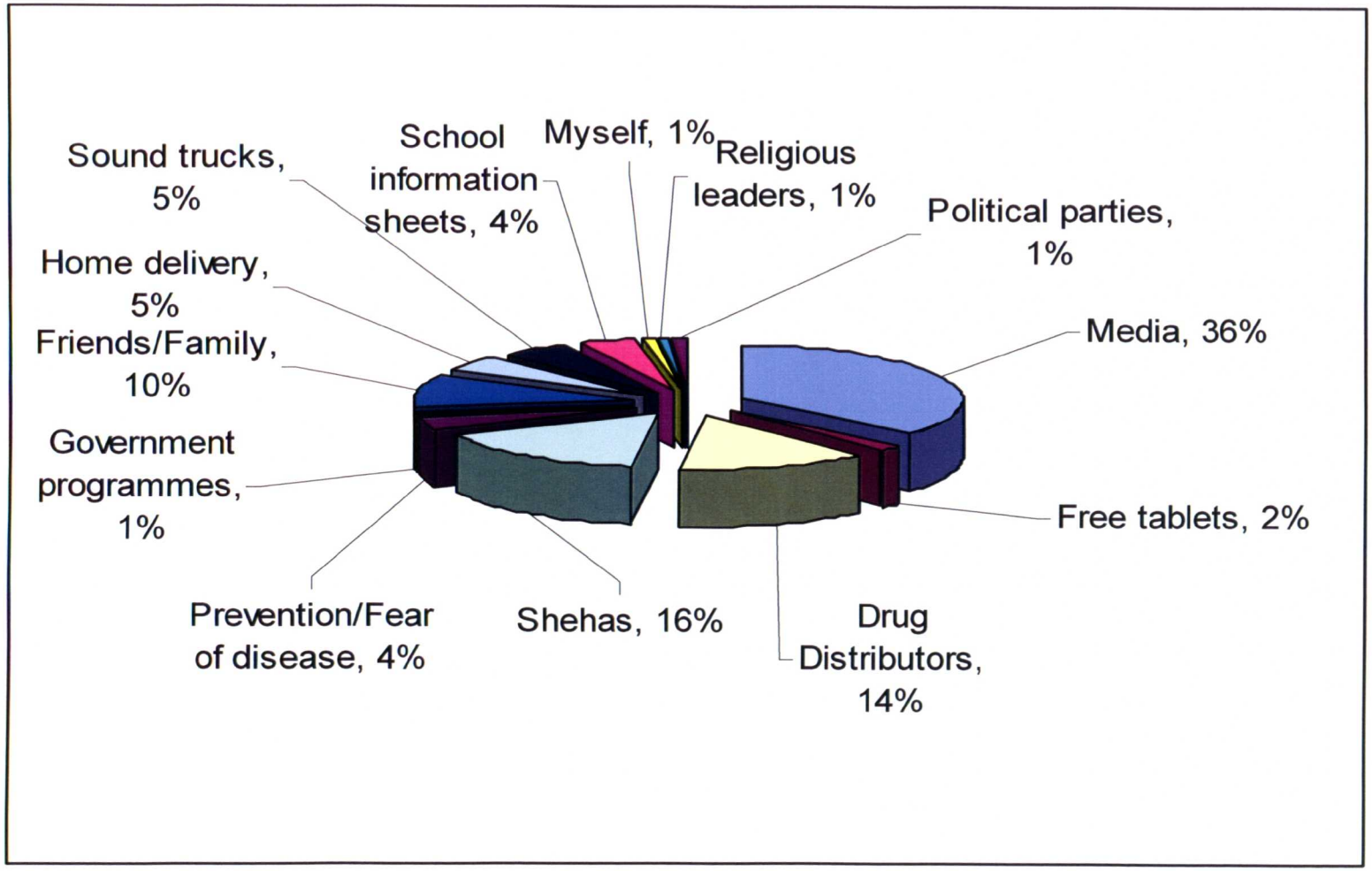


Figure 4.6 The condition that convinced people to take the drugs on MDA day



4.3.6 Discussion

The results of the surveys showed that reported and checked therapeutic coverage was consistent in all ten districts of Zanzibar. Although, both reported and checked coverage of the eligible population after the first MDA was below the recommended 80% in all districts except the South district of Unguja and Mkoani district of Pemba. However, the information gained from the survey after first MDA was crucial in adjusting subsequent social mobilization activities as well as distribution strategies. After MOHSW and PELF implementation of the recommendations of the study reports, both therapeutic reported and checked coverage reached the recommended therapeutic coverage target in all the districts.

KAP surveys showed that LF (Matende) as a disease is well known in all districts of Zanzibar. Similar results were reported in India (Babu et al., 2004), and Burkina Faso (Kyelem, 2007). As to how people acquire the disease, a good percentage of people were aware of the mode of transmission after the MDA through social mobilization activities. In Burkina Faso, where conditions were different from what was observed in Zanzibar there were fewer number of individuals aware of mode of the transmission of the disease even after first MDA round (Kyelem, 2007)

4.4 Impact of MDA rounds on filarial Infection

4.4.1 Introduction

The Zanzibar PELF aimed at following the global recommendation of interrupting LF transmission through annual MDA using ivermectin (Mectizan®) and albendazole for 4–6 years. The goal was set based on the estimated reproductive life span of *Wuchereria bancrofti* being 4-6 years (Norman et al., 2000; Plaisier et al., 1998). Zanzibar is using a combination of albendazole and

ivermectin (Mectizan®) hence the estimated required drug coverage should be 80% of the total population.

In PELF the monitoring and evaluation process is a crucial component of the programme to assess the treatment impact on the status of infection, transmission, disease, inability to detect ongoing transmission and recrudescence of infection or non-response to treatment and impact of treatment on the other prevailing helminth diseases in the country. Monitoring and evaluation are follow-up activities that allow assessment of the effectiveness of the programme and its findings can be adopted by countries in their respective LF programmes with a similar setting to those of Zanzibar.

In Zanzibar the impact of six rounds of MDA using albendazole and ivermectin (Mectizan®) on filarial infection on both the prevalence and intensity at selected sentinel sites and spot check sites was followed. The trend of infection of soil-transmitted helminthiasis in those sites was also investigated.

4.4.2 Methodology

The selected sentinel sites in Zanzibar were Kizimkazi and Kwahani (Chapter III). Baseline data of *Wuchereria bancrofti* were collected and recorded prior to the first MDA in 2001 (Chapter III). Post-MDA data to assess the impact of MDA on microfilaraemia were collected every year before each MDA campaign. However, the GPELF recommends impact evaluation is undertaken every two years – baseline, mid-term (before third MDA) and before fifth MDA (WHO, 2005). In Zanzibar all procedures used during baseline data collection were strictly followed. It has been reported that the drug effects decrease with time though their efficacy in controlling microfilaraemia remain effective up to 12 months following treatment (Bockarie et al., 1998; Dunyo et al., 2000; Moulia-Pelat et al., 1995; Ottesen et al., 1997). All surveys in Zanzibar were carried

out between 7-10 months after the previous MDA. The same period was reported in Egypt and elsewhere (Ramzy et al., 2006; WHO, 2006).

Before the third round of MDA, in addition to the sentinel sites three spot check sites were added to the survey as suggested by WHO. These spot check sites were selected from areas with previous records of high prevalence of LF. The selected spot check sites were Moga, located in the North A district of Unguja island (Figure 4.1) and the other two sites are Konde, located in the Micheweni district of Pemba island and Madungu which is located in Chake Chake district of Pemba island (Figure 4.2).

Before the fourth round of MDA in addition to the sentinel sites a further three spot check sites were added to the survey. As with the previous survey prior to the third round MDA spot check sites were selected from areas with records of high prevalence of *W. bancrofti* in the country. The selected spot check sites were Jambiani, located in the South district of Unguja Island (Figure 4.7), the other two sites were Kambini which is located in the Wete district of Pemba Island and Uweleni which is located in Mkoani district of Pemba Island (Figure 4.7).

In the fourth survey Antigen Detection Tests using ICT cards were added. This is a test where a finger prick blood is added to the sample pad of the ICT test card. The pad contains dried colloidal gold-labelled polyclonal anti-filarial antibodies that bind to adult worm antigen in the blood (Weil et al., 1997). When the card is closed, the antigen-antibody complexes, as well as unbound antigen, flow across the nitrocellulose strip and are trapped by a monoclonal antibody (AD 12) in the strip's coating. The results are read after 10-15 minutes. The resulting gold-labelled conjugates yield a pink line next to a control pink line that appears in all valid cards. Thus blood samples from antigen-negative individuals exhibit one pink line, whereas those from antigen-positive individuals display two pink lines. All the ICT cards used were from Binax Inc. (Portland,

ME, USA). However, before the fifth MDA, in addition to sentinel sites, twelve more sites were added and grouped in four different groups according to specific qualities with the intention of acquiring more technical information on the impact of MDA on microfilaria prevalence, microfilaria density, circulating filarial antigens (CFA) and STH prevalence and intensity in relation to MDA coverage. These sites were set into four main groups:

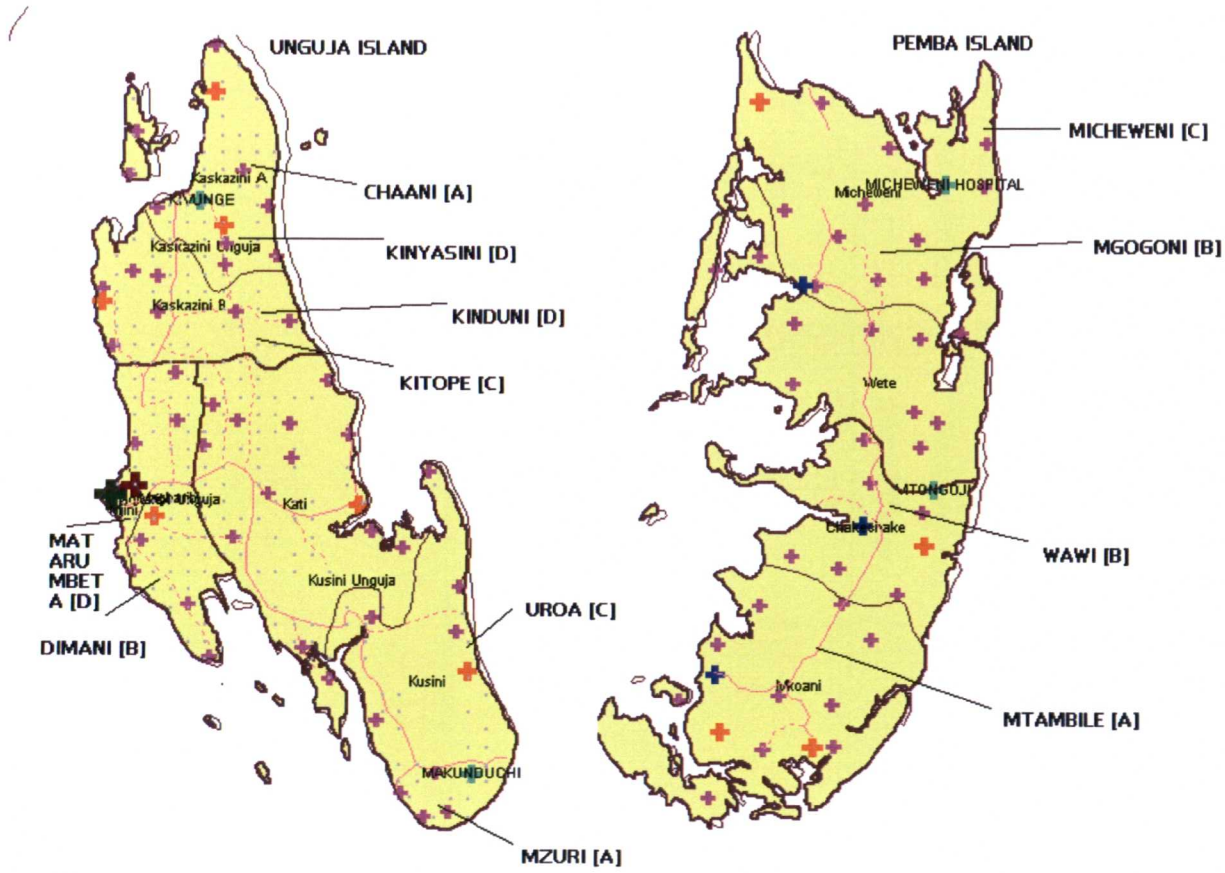
A: High mf prevalence and achieving high drug coverage during MDAs;
B: High mf prevalence and achieving low drug coverage during MDAs;
C: Low mf prevalence and achieving high drug coverage during MDAs;
D: Low mf prevalence and achieving low drug coverage during MDAs.

Also in the fifth and sixth surveys, antigen tests using ICT cards as well as stool sampling examination using the Kato Katz technique were added. The ICT cards were intentionally added from fourth survey and not the first three surveys mainly because they are expensive and have been proved to be very sensitive and appropriate when microfilaria densities are low.

Table 4.5 The group of selected sites and their locations

Group	Site	District	Region	Island
A	Mzuri Makunduchi	South	South	Unguja
A	Chaani	North 'A'	North	Unguja
A	Mtambile	Mkoani	South	Pemba
B	Dimani	West	Urban West	Unguja
B	Mgogoni	Micheweni	North	Pemba
B	Wawi	Chake Chake	South	Pemba
C	Kitope	North 'B'	North	Unguja
C	Uroa	South	South	Unguja
C	Micheweni	Micheweni	North	Pemba
D	Kinduni	North 'B'	North	Unguja
D	Kinyasini	North 'A'	North	Unguja
D	Matarumbeta	Urban	Urban West	Unguja

Figure 4.7 Map of Unguja and Pemba Islands showing selected sites



From each sentinel site, 500 individuals, and in the additionally selected sites, 300 individuals of both sex and all age groups were examined. Blood examination was done to determine microfilaraemia prevalence, microfilaraemia density using the counting chamber technique, thick blood smear and circulating filarial antigens (CFA) using ICT card test. As for soil-transmitted helminthiasis (STH) infections 100 individuals from each site had their stool samples examined using the Kato Katz technique. The survey was scheduled to be used as a routine yearly monitoring tool after the fifth MDA to identify areas in which MDA was still needed.

Table 4.6 Kizimkazi sentinel site treatment coverage during MDAs

Year	Total population	Treated population	Treatment coverage (%)
2001	3,005	2,639	87.8
2002	3,028	2,483	82.0
2003	3,084	2,711	87.9
2004	3,328	2,761	83.0
2005	3,364	2,859	85.0
2006	3,421	2,922	85.4

Table 4.7 Kwahani sentinel site treatment coverage during MDAs

Year	Total population	Treated population	Treatment coverage (%)
2001	4,435	2,895	65.5
2002	4,685	3,908	83.4
2003	4,805	3,832	79.8
2004	4,985	4,012	80.5
2005	5,473	4,668	85.3
2006	5,582	4,772	85.5

4.4.3 Results

4.4.3.1 Sentinel sites

4.4.3.1.1 Changes in microfilaraemia prevalence and density

The overall prevalence of microfilaraemia at the Kizimkazi sentinel site for 2001 was 17.8% before the first MDA; 4% in 2002 after the first MDA; 1.4% in 2003 after the second MDA; 1.2% in 2004 after third MDA; 1% in 2005 after the fourth MDA and 0% in 2006 after the fifth MDA. The changes in overall prevalence of microfilaraemia in Kizimkazi are shown in Table 4.8 and Figure 4.8. One year after the first MDA the overall prevalence of microfilaraemia decreased by 77.5% and was significantly lower than at baseline ($P < 0.001$). The overall prevalence of microfilaraemia decreased significantly by 92.1% in 2003 after two rounds of MDA ($P<0.001$). The same trend in the reduction of prevalence of microfilaraemia was recorded in the results after third, fourth and fifth round of MDAs. However, the microfilariae density decreased significantly from 356 mf/ml to188mf/ml ($P< 0.001$) post-first MDA and to 94mf/ml post-second MDA, but was noticed to increase again after third round MDA to 125mf/ml and 160mf/ml post-fourth MDA and then dropped to zero after fifth round.

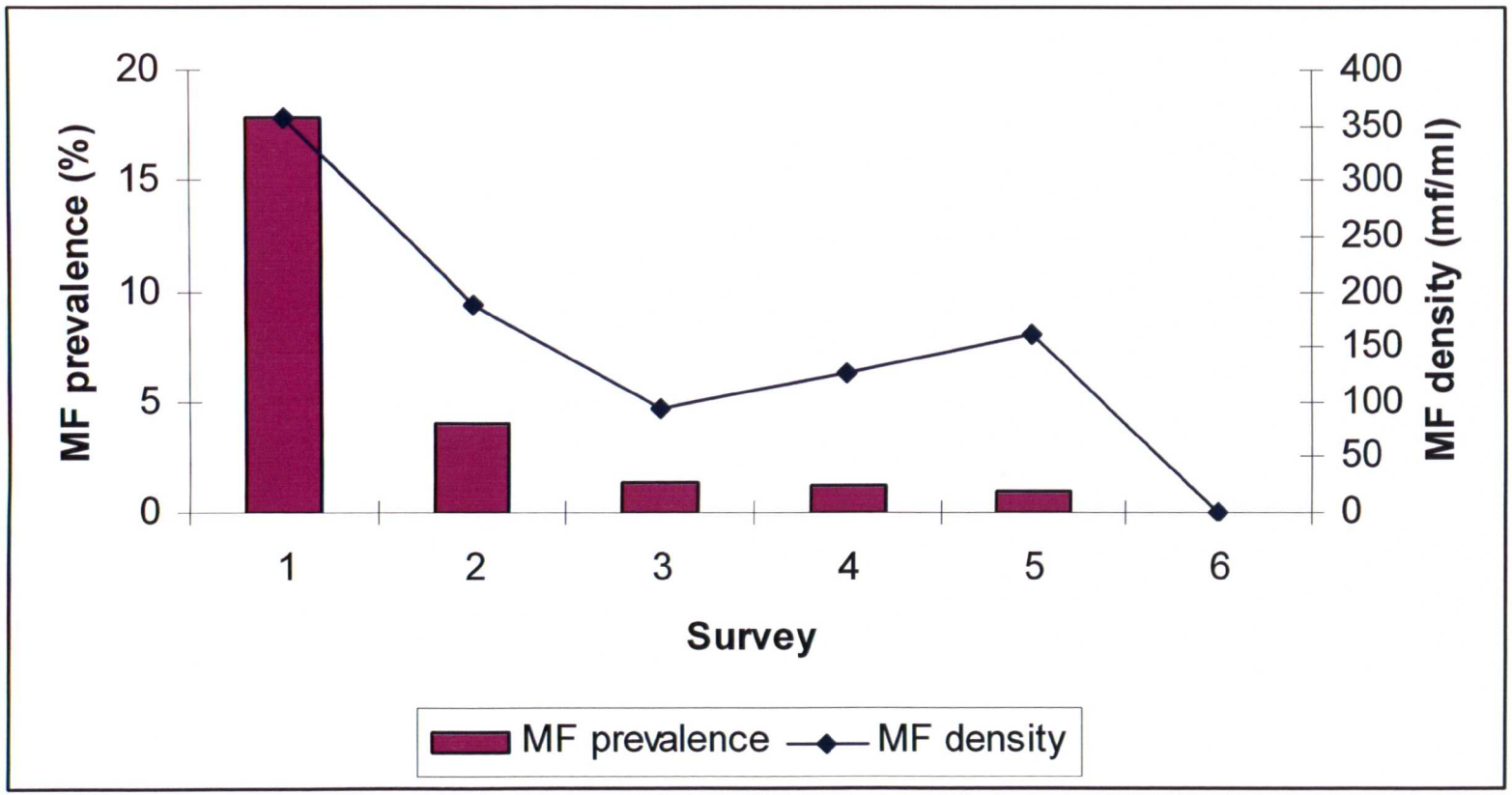
In the Kwahani sentinel site the overall prevalence of microfilaraemia in 2001 was 7.2% before the first MDA; 1.4% in 2002 after the first MDA, 0.4% in 2003 after the second MDA; 0.2% in 2004 after the third MDA; 0% in 2005 and 2006 after the fourth and fifth MDAs respectively. The changes in overall prevalence of microfilaraemia in Kwahani are shown in Table 4.9 and Figure 4.8. One year after the first MDA the overall prevalence of microfilaraemia decreased by 80.6% and was significantly lower than at baseline ($P<0.001$). The overall prevalence of microfilaraemia decreased significantly by 94.4% in 2003 after two rounds of MDA ($P<0.001$). The same trend in the reduction of prevalence of microfilaraemia was observed after the third, fourth and fifth rounds of MDA. However, in Kwahani the microfilariae density decreased significantly from 323mf/ml to 66mf/ml post first MDA ($P<0.001$) but was noticed to increase again after second and third rounds of MDA to 75mf/ml and 100mf/ml respectively and then dropped to zero after the fifth round MDA.

Table 4.8 MF Prevalence and density recorded at the Kizimkazi Sentinel site

Year	Survey	No. EXD	No. Positive	MF Prevalence	MF Density (Mf/ml)
2001	Baseline	500	89	17.8%	356
2002	Post 1st MDA	500	20	4.0%	188
2003	Post 2nd MDA	500	7	1.4%	94
2004	Post 3rd MDA	500	6	1.2%	125
2005	Post 4th MDA	500	5	1.0%	160
2006	Post 5th MDA	500	0	0.0%	0

The prevalence of microfilaraemia decreased post-MDA. The microfilaraemia density decreased post-first and second MDA but increased after third round of MDA and then dropped to zero after the fifth round.

Figure 4.8 Mf prevalence and density recorded at Kizimkazi Sentinel site.



The bars show mf prevalence decreasing with surveys done after MDA whilst the line graph shows the mf density decreasing in surveys 2 and 3 but increasing again in survey 4 and 5 after MDA.

Table 4.9 Mf prevalence and density recorded at the Kwahani Sentinel site

Year	Survey	No. EXD	No. Positive	MF Prevalence	MF Density
2001	Baseline	500	36	7.2%	323
2002	Post 1st MDA	500	7	1.4%	66
2003	Post 2nd MDA	500	2	0.4%	75
2004	Post 3rd MDA	500	1	0.2%	100
2005	Post 4th MDA	500	0	0.0%	0
2006	Post 5th MDA	500	0	0.0%	0

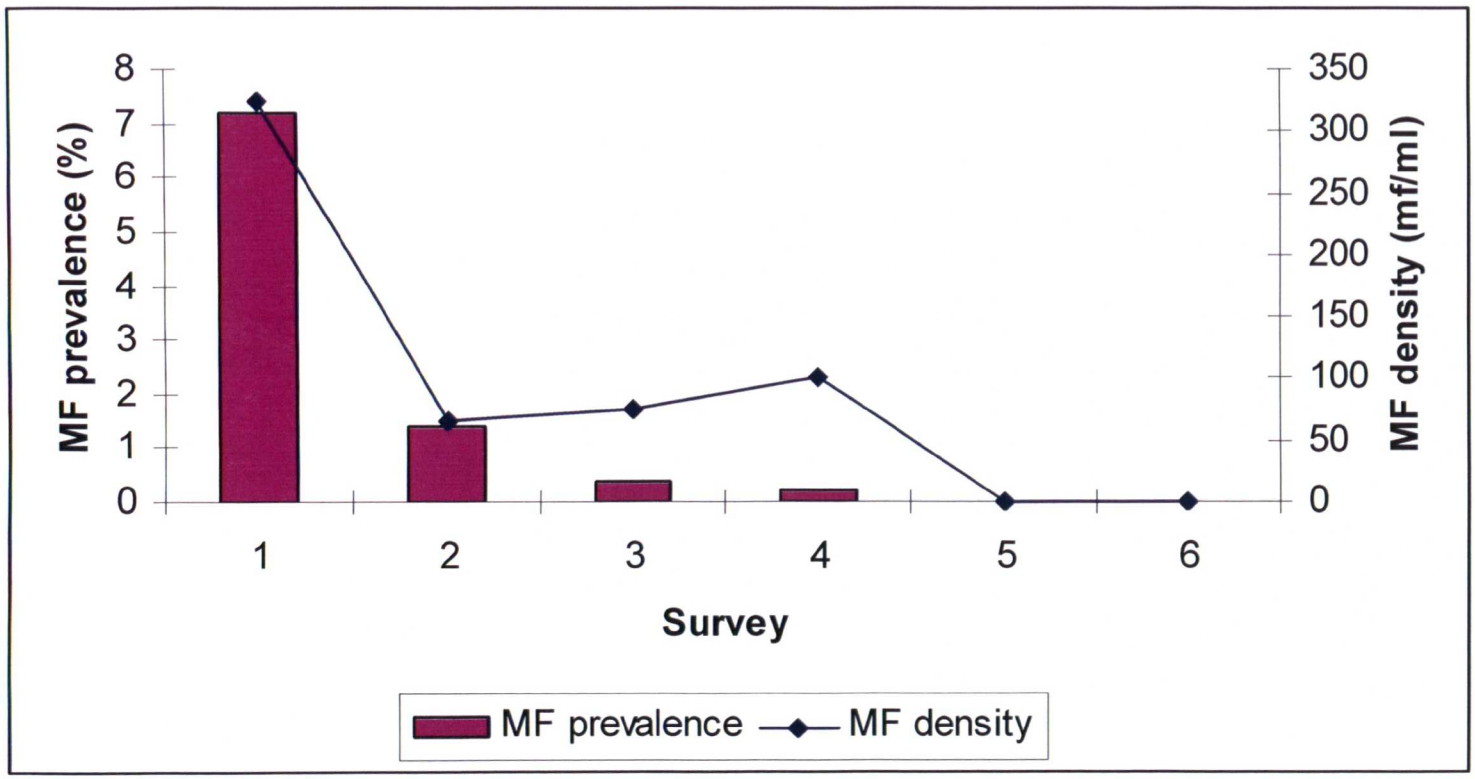
The prevalence of microfilaraemia decreased post-MDA. The microfilaraemia density decreased post-first MDA but increased after second and third rounds of MDA and then dropped to zero after fourth and fifth rounds.

Table 4.10 Prevalence of *W. bancrofti* in sentinel sites post 1st round MDA

	Baseline Data		Post 1st MDA data		% Reduction
Site	Tot. Exam	No. positive (%)	Tot. Exam	No. positive (%)	
Kizimkazi	500	89(17.8)	500	20(4.0)	77.5
Kwahani	500	36 (7.2)	500	7(1.4)	80.6

At the Kizimkazi sentinel site where the prevalence was high 17.8% of the baseline survey had a reduction of 77.5% after the first round of MDA. However, Kwahani which had a lower prevalence at the baseline experienced a greater reduction (80.6%).

Figure 4.9 Mf prevalence and density recorded at the Kwahani Sentinel site



The bars shows mf prevalence decreasing with surveys done after MDA whilst the line graph shows the mf density decreasing in the second survey and increasing in third and fourth surveys and decreasing to zero in fifth and sixth surveys.

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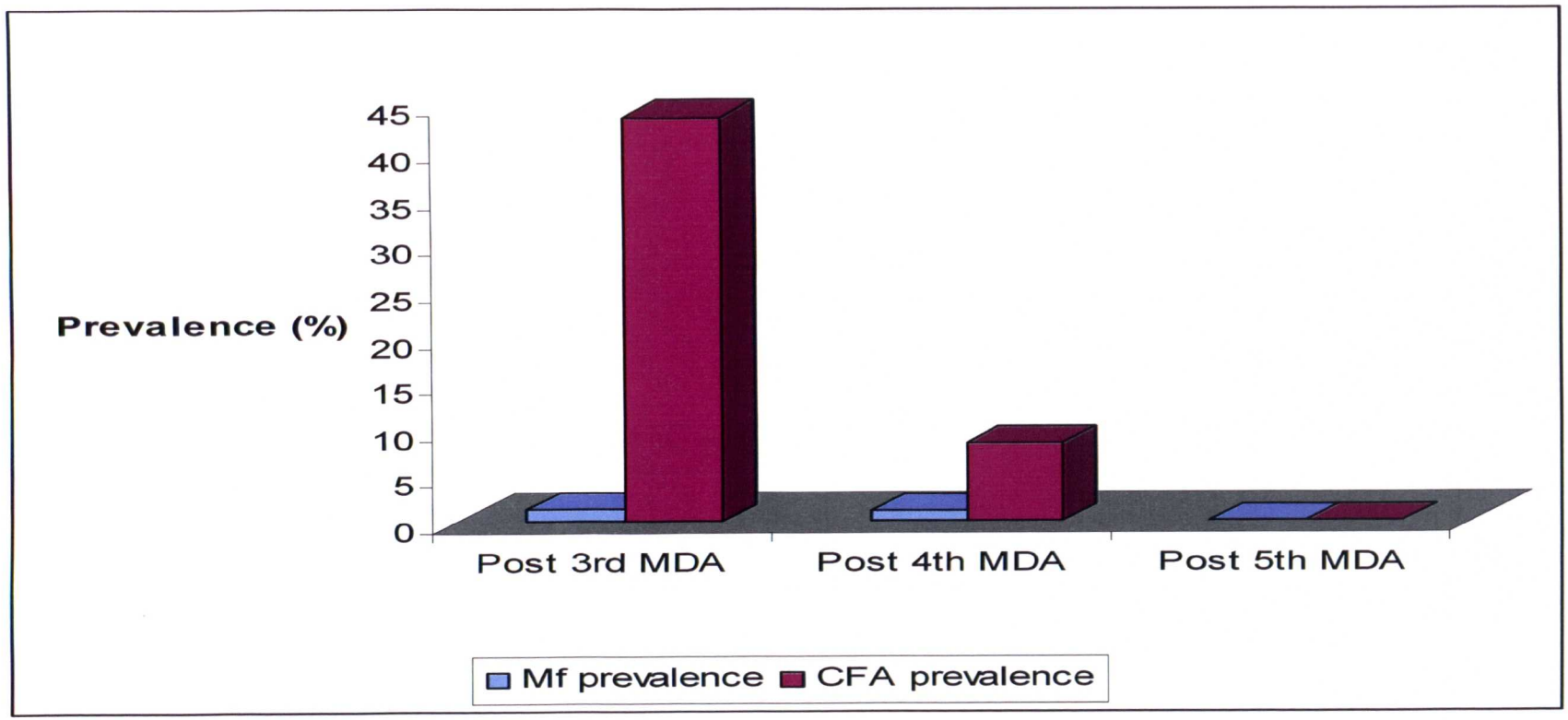
Figure 4.10 **Prevalence of *W. bancrofti* antigenaemia and mf prevalence in Kizimkazi post MDA.**



The circulating filarial antigen checked with ICT cards was high post-third MDA (43.6%) but dropped to 8.4% post-fourth MDA and zero after fifth MDA.

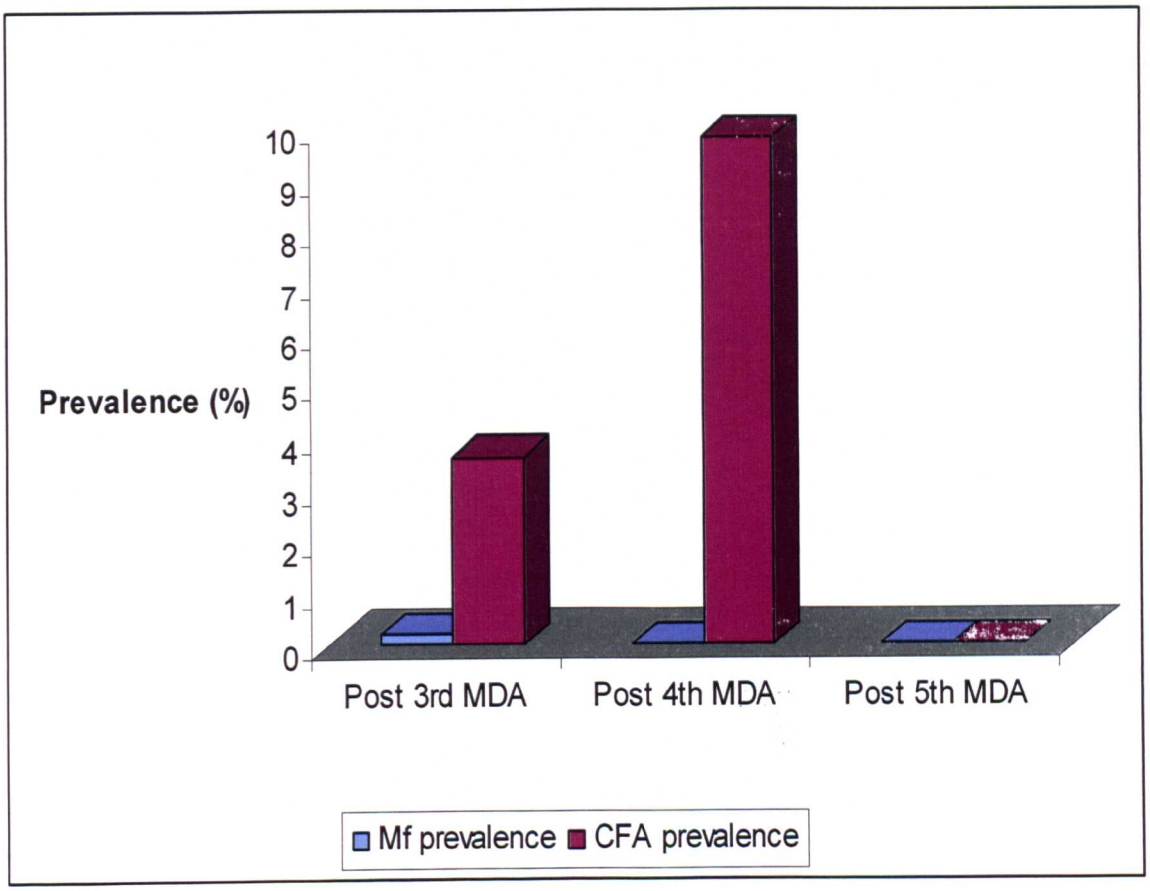
Of the 500 individuals tested for circulating *W. bancrofti* filarial antigenaemia (CFA) using ICT cards at Kwahani sentinel site after three rounds of MDA, 18 individuals were found to be positive with a prevalence rate of 3.6%. However, when the same number of individuals (500) were tested again after fourth MDA the number who tested positive with ICT increased to 49 (9.8%) and zero after fifth MDA (Table 4.14). When microfilariaemia prevalence was compared with circulating *W. bancrofti* filarial antigenaemia with low mf prevalence (0.2%) after three rounds of MDA the CFA it was 3.6% and when mf prevalence was zero after fourth round MDA the CFA was 9.8% (Figure 4.10)

Table 4.17 Prevalence of *W. bancrofti* antigenaemia in Kwahani post-MDA

Year	Survey	No. EXD	No. ICT Positive	C FA Prevalence rates
2004	Post 3rd MDA	500	18	3.6%
2005	Post 4th MDA	500	49	9.8%
2006	Post 5th MDA	500	0	0.0%

The circulating filarial antigen (CFA) was 3.6% after the third round MDA and 9.8% and zero post fourth and fifth rounds of MDA respectively.

Figure 4.11 Prevalence of *W. bancrofti* antigenaemia and mf prevalence post at Kwahani post MDA



4.4.3.2 Spot check sites

In Moga the microfilariae prevalence was 1.4% post second round MDA 2002, while in the survey undertaken in 1991 the prevalence was 32% (Table 4.18). The MDA has had a significant impact in reducing prevalence. In Konde the microfilariae prevalence was 1.6%, the survey done at the same site in 1999 recorded a prevalence of 11.8%. In Madungu the prevalence was 1.5%, the survey in 1999 at the same site showed a prevalence of 16.2% (Table 4.18). The overall results showed that two rounds of MDA had a great impact in the total reduction of microfilariae prevalence in both islands.

Table 4.18 Prevalence of *W. bancrofti* and mf density in spot check sites post 2nd MDA round

	Post 2nd MDA data		
Site	Total Examined	No. positive (%)	Mf density (mf/ml)
Moga	500	7(1.4)	157
Konde	500	10 (1.6)	181
Madungu	500	5(1.0)	180

In Jambiani the microfilariae prevalence was zero although the circulating filarial antigen was 8% after three rounds of MDA. In Jambiani a survey done in 1975 showed a microfilariae prevalence of 7%. In Kambini no microfilariae were detected and circulating filarial antigen prevalence was also zero. However, in Uweleni after three rounds of MDA, out of 500 individuals screened 6 were found to be microfilariae positive (1.2% prevalence) and the circulating filarial antigen was 10.2%. When those six individuals were interviewed on their record of taking drugs during MDA one had not taken any drug in three rounds and was found to be highly infected with microfilariae which was the reason why the microfilariae density was 1275 mf/ml in the Uweleni site (Table 4.19). The

overall results showed that three rounds of MDA had a significant impact in the total reduction of microfilariae prevalence in both islands.

Table 4.19 Prevalence of *W. bancrofti* and mf density in spot check sites post 3rd MDA round

	Post 3rd MDA data			
Site	Tot. Examined	No. positive (%)	Mf density (mf/ml)	CFA (using ICT cards) ICT+(%)
Jambiani	500	0(0.0)	0	40 (8.0%)
Kambini	500	0 (0.0)	0	0 (0.0%)
Uweleni	500	6(1.2)	1275	51(10.2%)

4.4.3.3 Grouped spot check sites

In grouped spot check sites the results of microfilaraemia survey which were undertaken post-fourth round of MDA showed that in group A the recorded prevalence and the treatment coverage was both high in all rounds. In Mzuri of the 300 individuals screened 5 were microfilaraemia positive with a prevalence of 1.7% and microfilaria density of 170mf/ml; in Mtambile 5 were positive with a prevalence rate of 1.7% and microfilaria density of 160mf/ml. However, in Chaani all the 300 individuals screened were negative (Table 4.20). After the fifth round MDA results showed no microfilariae positive individual in any of the three sites (Table 4.20). The CFA survey results post fourth MDA in Mzuri showed that of the 300 individuals tested for circulating *W. bancrofti* filarial antigenaemia (CFA) using ICT cards 201 were found to be positive with a prevalence rate of 67.0%. In Mtambile the CFA positives were 53 (17.5%) while in Chaani CFA positive individuals were 51(17%)(Table 4.21).

In group B where LF prevalence was high but with low treatment coverage both the Dimani and Mgogoni sites each had one individual who was microfilariae positive (prevalence of 0.3% and microfilaria density of 40mf/ml) in Dimani and 150mf/ml in Mgogoni. However, in Wawi 5 individuals were microfilariae positive out of 300 screened with a prevalence rate of 1.7% and density of 133mf/ml (Table 4.20).

After the fifth MDA survey there were no microfilariae positive individuals in any of the three sites (Table 4.21). In Dimani of the 300 individuals tested for circulating *W. bancrofti* filarial antigenaemia (CFA) using ICT cards 74 were found to be positive an ICT prevalence of 24.7%. In Mgogoni the CFA positivity was 30 (10%) while in Wawi CFA positive individuals were 25 (8.3%) (Table 4.21).

In group C where the prevalence was low but with high treatment coverage in all rounds, screened individuals were no microfilariae positive in three sites: Kitope, Uroa and Micheweni (Table 4.20). After the fifth MDA there were no microfilariae positive individuals in the three sites (Table 4.21). In Kitope of the 300 individuals tested for circulating *W. bancrofti* filarial antigenaemia (CFA) using ICT cards 33 were found to be positive with a prevalence rate of 11%. In Uroa the CFA positives were 35 (11.7%) while in Micheweni CFA positive individuals were 10 (3.3%) (Table 4.21).

In group D where records of the prevalence was low with low treatment coverage in all rounds microfilariae positive was found in Kinduni, Kinyasini and Matarumbeta (Table 4.20). After the fifth MDA the surveys showed no microfilariae positive individual in any site (Table 4.21). In Kinduni of the 300 individuals tested for circulating *W. bancrofti* filarial antigenaemia (CFA) using ICT cards, 38 were positive - a prevalence rate of 12.7%. In Kinyasini CFA positivity was 33 (11%) while in Matarumbeta CFA positive individuals were 64 (21.3%) (Table 4.21).

Table 4.20 Prevalence of *W. bancrofti* and mf density in grouped check sites post-4th MDA round

Group	Site	No. EXD.	MF prevalence	MF density (mf/ml)	CFA (ICT cards) Results
A	Mzuri	300	5 (1.7%)	170	201(67.0%)
A	Chaani	300	0 (0.0%)	0	51 (17.0%)
A	Mtambile	300	5 (1.7%)	160	53 (17.5%)
B	Dimani	300	1 (0.3%)	40	74 (24.7%)
B	Mgogoni	300	1 (0.3%)	150	30 (10.0%)
B	Wawi	300	5 (1.7%)	133	25 (8.3%)
C	Kitope	300	0 (0.0%)	0	33 (11.0%)
C	Uroa	300	0 (0.0%)	0	35 (11.7%)
C	Micheweni	300	0 (0.0%)	0	10 (3.3%)
D	Kinduni	300	0 (0.0%)	0	38 (12.7%)
D	Kinyasini	300	0 (0.0%)	0	33 (11.0%)
D	Matarumbeta	300	0 (0.0%)	0	64 (21.3%)

Table 4.21 Prevalence of *W. bancrofti* and mf density in grouped check sites post-5th MDA round

Group	Site	No. EXD.	MF prevalence	MF density (mf/ml)	CFA (ICT cards) Results
A	Mzuri	300	0 (0.0%)	0	0 (0.0%)
A	Chaani	300	0 (0.0%)	0	0 (0.0%)
A	Mtambile	300	0 (0.0%)	0	0 (0.0%)
B	Dimani	300	0 (0.0%)	0	0 (0.0%)
B	Mgogoni	300	0 (0.0%)	0	0 (0.0%)
B	Wawi	300	0 (0.0%)	0	0 (0.0%)
C	Kitope	300	0 (0.0%)	0	0 (0.0%)
C	Uroa	300	0 (0.0%)	0	0 (0.0%)
C	Micheweni	300	0 (0.0%)	0	0 (0.0%)
D	Kinduni	300	0 (0.0%)	0	0 (0.0%)
D	Kinyasini	300	0 (0.0%)	0	0 (0.0%)
D	Matarumbeta	300	0 (0.0%)	0	0 (0.0%)

4.4.4 Discussion

Zanzibar had six rounds of MDA with good coverage its ten districts. However, in the first rounds some sites did not attain the GPELF treatment coverage goal. The GPELF set the objective of treatment coverage as 80% of the population to be able to eliminate LF in an endemic country (Molyneux and Zagaria, 2002; Ottesen 2000a; Ottesen et al., 1997).

The microfilaraemia prevalence reported is community prevalence, not a cohort follow up of microfilaraemia rates. It was decided to use the community prevalence because this would reflect the real situation in the country as the aim of the programme is to interrupt transmission in all endemic communities. There

are several well designed studies showing the effectiveness of MDA using albendazole and ivermectin (Mectizan®) or DEC on infection after 4 to 5 rounds (Bockarie et al., 2002; Ottesen, 1985; Ramzy et al., 2006). Our objective was to assess the efficacy of the national health system to reach the goal of elimination within its routine activities. It is likely that a well founded project or a project not using the regular public health system with its known weaknesses and high levels of bureaucracy would have a better chance to attain the goal of the GPELF as the goal was based on research which therefore was well monitored and founded.

The surveys showed that the MDA delivered within the national health system had impact on *W. bancrofti* prevalence and intensity though the ideal coverage was not reached; an observation by Ramaiah et al. (2003) in India after 6 years of MDA at 54-75% coverage rates. Indeed, the sites assessed after two, three and four rounds of MDA had a statistically significant decline in *W. bancrofti* prevalence and intensity and such findings are reported by several authors (Bockarie et al., 2002; de Rochars et al., 2005; Diallo et al., 2006; Dunyo et al., 2000; Fraser et al., 2005; Gyapong, 2000; Meyrowitsch et al., 1996a; Simonsen et al., 2004b; WHO, 2006b). We found that the initial prevalence and density might have an influence on the impact of MDA; the site of Kizimkazi (Table 4.8 and Figure 4.6) with the highest prevalence showing a low mf decrease as compared to Kwahani which had low prevalence and intensity of mf. It is interesting to note that in Kizimkazi where the prevalence was high initially (17.8% at the baseline survey) had a reduction of 77.5% after the first round of MDA. However, in Kwahani which had a lower baseline prevalence experienced a higher reduction of 80.6% (Table 4.9, Figure 4.7). The role played by the initial prevalence on elimination has been pointed out in several studies (Michael et al., 2004; Stolk et al., 2003).

The children seem to be protected from transmission by the MDAs. There was no difference in the impact of MDA on *W. bancrofti* according to sex in all the visited sites.

Results after 6 rounds of MDA report sufficient impact on infection as in Egypt where MDA was based on DEC and albendazole. However, in India where a single drug (DEC) is used for elimination a persistent microfilaraemia was reported after 6-10 rounds of treatment (Ramaiah et al., 2002; Ramaiah et al., 2003., Ramaiah et al., 2007)

4.4.5 Conclusion

In a resource constrained settings, obtaining good treatment coverage is a key objective for national programmes. The use of a health system with full community involvement enables good treatment coverage of the eligible population by MDA to be achieved. Monitoring the impact of the MDA in randomly selected surveillance sites is essential to check if the programme is on track. In Zanzibar, the impact of 5 MDA rounds resulted in a significant decline of *W. bancrofti* infection. However, results of our surveys indicate that achieving high coverage of the population requires careful attention to appropriate strategies of social mobilization. There is also a need for xenomonitoring to be included in monitoring and evaluation of the impact of MDA in relation to disease transmission. It is important to select high risk sites for programme surveillance while spot check sites should be randomly selected.

4.5 Impact of MDA on STH at sentinel and spot check sites

Before the fifth MDA during the night blood survey at sentinel and spot check sites 100 individuals were selected randomly from each site and each provided with a container for stool sample to provide stool samples the following morning. The stool samples were collected, processed and examined using Kato Katz

technique in the laboratory by well trained and experienced technicians. This process was repeated before each MDA starting from fifth round onwards in all sites. The main intention of this survey was to determine the STH (*Ascaris*, Hookworm and *Trichuris*) prevalence and intensity in relation to MDA coverage.

4.5.1 Results of soil-transmitted helminths at sentinel sites

Table 4.22 Results of STH in the Kizimkazi and Kwahani sentinel sites in 2005

STOOL EXAMINATION	KIZIMKAZI SITE			KWAHANI SITE		
	Trichuris	***Ascaris***	**Hookworm**	***Trichuris***	***Ascaris***	**Hookworm**
No. Males examined	39 (1)	39 (0)	39 (0)	32 (0)	32 (0)	32 (0)
No. Females examined	61 (4)	61 (0)	61 (0)	68 (0)	68 (0)	68 (0)
Tot Samples examined	100 (5)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)
Percentage (%)	**5%**	**0%**	**0%**	**0%**	**0%**	**0%**

At both sentinel sites (Kizimkazi and Kwahani), after four rounds of MDA, the prevalence of STH was 5% in Kizimkazi and zero in Kwahani (Table 4.22). However, in Kizimkazi out of the 5 individuals found having STH eggs 4 (6.6%) were females below ten years old and all had eggs of *Trichuris trichura* and the intensity of infection was light with egg count per gram of faeces (1<EPG<999).

Table 4.23 Results of STH in the Kizimkazi and Kwahani sentinel sites in 2006

STOOL EXAMINATION	KIZIMKAZI SITE			KWAHANI SITE		
	Trichuris	***Ascaris***	**Hookworm**	***Trichuris***	***Ascaris***	**Hookworm**
No. Males examined	33 (1)	33 (0)	33 (0)	35 (0)	35 (0)	35 (0)
No. Females examined	67 (1)	67 (0)	67 (0)	65 (0)	65 (0)	65 (0)
Tot Samples examined	100 (2)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)
Percentage (%)	**2%**	**0%**	**0 %**	**0%**	**0%**	**0%**

After the fifth round of MDA the prevalence of STH was low at both sites. In Kizimkazi prevalence was 2% and zero in Kwahani (Table 4.23). However, in Kizimkazi, 2 individuals were found with STH eggs (a boy of 6 years and a girl of 4 years), *Trichuris trichura,* and the intensity of infection was light with egg count per gram of faeces (1<EPG<999) (Table 4.23).

Table 4.24 Results of STH in the Kizimkazi and Kwahani sentinel sites in 2007

STOOL EXAMINATION	KIZIMKAZI			KWAHANI		
	Trichuris	***Ascaris***	**Hookworm**	***Trichuris***	***Ascaris***	**Hookworm**
No. Males examined	38 (0)	380 (0)	38 (0)	37 (0)	37 (0)	37 (0)
No. Females examined	62 (0)	62 (0)	62 (0)	63 (0)	63 (0)	63 (0)
Tot Samples examined	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)
Percentage (%)	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**

After six rounds of MDA the prevalence of STH was zero at both sites (Table 4.24).

4.5.2 Results of soil-transmitted helminths at the spot check sites

Table 4.25 Prevalence of STH in GROUP A - sites 2005

	MZURI			CHAANI KUBWA			MTAMBILE		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	31	69	100	68	52	120	60	69	129
Trichuris	0(0.0%)	0(0.0%)	0(0.0%)	2(2.9%)	7(13.5%)	9(7.5%)	27(45%)	24(34.8%)	51(39.5%)
Ascaris	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	0(0.0%)	1(0.8%)	5(8.3%)	5(7.2%)	10(7.8%)
Hookworm	0(0.0%)	0(0.0%)	0(0.0%)	5(7.4%)	1(1.9%)	6(5.0%)	4(6.7%)	2(2.9%)	6(4.7%)

Of all three sites of group A the prevalence of STH in Mzuri was zero in surveys before the fifth round MDA. However, at Chaani Kubwa and Mtambile the prevalence of *Trichuris trichura* was 7.5% and 39.5% respectively. The prevalence of *Ascaris* in Chaani Kubwa was 0.8% but in Mtambile it was 7.8%. Hookworm prevalence in Chaani Kubwa was 5% and Mtambile 4.7%. In Mtambile out 51 individuals with *Trichuris* infection 27 (45.0%) were males and 24 (34.8%) females. The intensity of infection of all species in all sites was low as for egg counts per gram EPG (Table 4.25).

Table 4.26 Prevalence of STH in GROUP A - sites 2006

	MZURI			CHAANI KUBWA			MTAMBILE		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	35	71	106	65	61	126	63	71	134
Trichuris	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2(3.3%)	2(1.6%)	8(12.7%)	5(7.0%)	13(9.7%)
Ascaris	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Hookworm	0(0.0%)	0(0.0%)	0(0.0%)	1(1.5%)	0(0.0%)	1(0.8%)	1(1.6%)	0(0.0%)	1(0.7%)

In all three sites of group A the prevalence of STH at Mzuri was zero in a survey before six round MDA. However, at Chaani Kubwa and Mtambile the prevalence of *Trichuris trichura* was 1.6% and 9.7% respectively. The prevalence of *Ascaris* was zero in all three sites. However, prevalence of hookworm in Chaani Kubwa prevalence was 0.8% and Mtambile 0.7%. In Mtambile out 13 individuals with *Trichuris* infection 8 (12.7%) were males and 5 (7%) females. The intensity of infection of all species in all sites was low as for egg counts per gram (Table 4.26).

Table 4.27 Prevalence of STH in GROUP A - sites 2007

	MZURI			CHAANI KUBWA			MTAMBILE		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	33	73	106	65	63	128	62	71	133
Trichuris	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	3(4.8%)	1(1.4%)	4(3.0%)
Ascaris	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Hookworm	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)

In two sites of group A, the prevalence of STH was zero in the survey after the sixth MDA. However, in Mtambile the prevalence of *Trichuris trichura* was 3% and the intensity of infection was low. The prevalence of *Ascaris* and hookworm was zero in all three sites (Table 4.27).

Table 4.28 Prevalence of STH in GROUP B - sites 2005

	DIMANI			WAWI			MGOGONI		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	60	59	119	97	25	122	83	41	124
Trichuris	5(3.0%)	6(10.2%)	11(9.2%)	23(23.7%)	11(44.0%)	34(27.9%)	40(48.2%)	15(36.6%)	55(44.4%)
Ascaris	0(0.0%)	0(0.0%)	0(0.0%)	5(5.2%)	0(0.0%)	5(4.1%)	6(7.2%)	1(2.4%)	7(5.6%)
Hookworm	2(3.3%)	2(3.4%)	4(3.4%)	0(0.0%)	3(12.0%)	3(2.5%)	11(13.3%)	1(2.4%)	12(9.7%)

In the group B sites, surveys before fifth round MDA only Dimani had no *Ascaris*. In Dimani, Wawi and Mgogoni the prevalence of *Trichuris trichura* was 9.2%,

27.9% and 44.4% respectively. The prevalence of *Ascaris* in Wawi was 4.1% and Mgogoni 5.6%. The prevalence of hookworm in Dimani was 3.4%, Wawi 2.5% and Mgogoni 9.7%. However, the intensity of infection of all species in all sites was low as for egg counts per gram (Table 4.28).

Table 4.29 Prevalence of STH in GROUP B - sites 2006

	DIMANI			WAWI			MGOGONI		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	62	55	117	65	41	106	78	50	128
Trichuris	1(1.6%)	2(3.6%)	3(2.6%)	7(10.8%)	3(7.3%)	10(9.4%)	9(11.5%)	5(10.0%)	14(10.9%)
Ascaris	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Hookworm	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2(2.6%)	0(0.0%)	2(1.6%)

In the two sites of group B, Dimani and Wawi, the prevalence of *Ascaris* and hookworm was zero in surveys done before the sixth round of MDA. In Dimani, Wawi and Mgogoni the prevalence of *Trichuris trichura* was 2.6%, 9.4% and 10.9% respectively. The prevalence of *Ascaris* was also zero in Mgogoni. However, the prevalence of hookworm found in two adult males in Mgogoni was 2.6% (Table 4.29). The intensity of infection of all species in all sites was low in terms of egg counts per gram.

Table 4.30 Prevalence of STH in GROUP B - sites 2007

	DIMANI			WAWI			MGOGONI		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	58	63	121	61	40	101	72	49	121
Trichuris	0(0.0%)	0(0.0%)	0(0.0%)	1(1.6%)	0(0.0%))	1(1.0%)	2(2.8%)	0(0.0%))	2(1.7%)
Ascaris	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Hookworm	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)

In all three sites of group B the prevalence of *Ascaris* and hookworm was zero in surveys after the sixth round of MDA. However, in Wawi and Mgogoni the

prevalence of *Trichuris trichura* was 1% and 1.7% respectively but the intensity of infection was low in egg counts per gram (Table 4.30).

Table 4.31 Prevalence of STH in GROUP C - sites 2005

	KITOPE			UROA			MICHEWENI		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	95	26	121	71	47	118	80	45	125
Trichuris	10(10.5%)	2(7.7%)	12(9.9%)	7(9.9%)	2(4.3%)	9(7.6%)	16(20.0%)	6(13.3%)	22(17.6%)
Ascaris	2(2.1%)	0(0.0%)	2(1.7%)	1(1.4%)	0(0.0%)	1(0.8%)	7(8.8%)	1(2.2%)	8(6.4%)
Hookworm	8(8.4%)	2(7.7%)	10(8.3%)	0(0.0%)	0(0.0%)	0(0.0%)	2(2.5%)	0(0.0%)	2(1.6%)

In group C sites surveys before fifth round of MDA only Uroa had no hookworm infection. However, at Kitope, Uroa and Micheweni the prevalence of *Trichuris trichura* was 9.9%, 7.6% and 17.6% respectively. The prevalence of *Ascaris* in Kitope was 1.7%, Uroa 0.8% and Micheweni 6.4%. Hookworm prevalence in Kitope was 8.3%, and in Micheweni 1.6%. However, the intensity of infection of all species in all sites was low as for egg counts per gram (Table 4.31).

Table 4.32 Prevalence of STH in GROUP C - sites 2006

	KITOPE			UROA			MICHEWENI		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	79	48	127	69	54	123	78	49	127
Trichuris	2(2.5%)	0(0.0%)	2(1.6%)	1(1.4%)	0(0.0%)	1(0.8%)	3(3.8%)	1(2.0%)	4(3.1%)
Ascaris	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2(2.6%)	0(0.0%)	2(1.6%)
Hookworm	1(1.3%)	0(0.0%)	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)

In surveys before sixth round MDA at group C sites both Kitope and Uroa had no *Ascaris* infection. However, in Micheweni the prevalence of *Ascaris* infection was 1.6%. In Kitope, Uroa and Micheweni the prevalence of *Trichuris trichura* was 1.6%, 0.8% and 3.1% respectively. Hookworm infection was only found in Kitope with a prevalence of 0.8%. However, the intensity of infection of all species in all sites was low as egg counts per gram (Table 4.32).

Table 4.33 Prevalence of STH in GROUP C - sites 2007

	KITOPE			UROA			MICHEWENI		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	75	43	118	73	51	124	78	51	129
Trichuris	1(1.3%)	0(0.0%)	1(0.8%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Ascaris	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Hookworm	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)

Two sites of group C showed an STH prevalence of zero in surveys after the sixth round of MDA. However, at Kitope the prevalence of *Trichuris trichura* was 0.8% and the intensity of infection was low in terms of for egg counts per gram. The prevalence of *Ascaris* and hookworm was zero in all three sites (Table 4.33).

Table 4.34 Prevalence of STH in GROUP D - sites 2005

	KINDUNI			KINYASINI			MATARUMBETA		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	59	61	120	92	28	120	63	60	123
Trichuris	4(6.8%)	6(9.8%)	10(8.3%)	3(3.3%)	1(3.6%)	4(3.3%)	1(1.6%)	0(0.0%)	1(0.8%)
Ascaris	5(8.5%)	2(3.3%)	7(5.8%)	1(1.1%)	1(3.6%)	2(1.7%)	0(0.0%)	0(0.0%)	0(0.0%)
Hookworm	3(5.1%)	3(4.9%)	6(5.0%)	5(5.4%)	0(0.0%)	5(4.2%)	0(0.0%)	0(0.0%)	0(0.0%)

Of the three sites in group D the prevalence of both *Ascaris* and hookworm was zero in Matarumbeta in surveys before the fifth round of MDA. However, in Kinduni, Kinyasini and Matarumbeta the prevalence of *Trichuris trichura* was 8.3%, 3.3% and 0.8% respectively. The prevalence of *Ascaris* in Kinduni was 5.8% while in Kinyasini it was 1.7%. As for hookworm in Kinduni, prevalence was 5% and in Kinyasini, 4.2%. The intensity of infection of all species in all sites was low in egg counts per gram EPG (Table 4.34).

Table 4.35 Prevalence of STH in GROUP D - sites 2006

	KINDUNI			KINYASINI			MATARUMBETA		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	63	65	128	78	45	123	67	62	129
Trichuris	1(1.6%)	1(1.5%)	2(1.6%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Ascaris	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Hookworm	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)

In the two sites of group D in Kinyasini and Matarumbeta the prevalence of *Trichuris trichura, Ascaris* and hookworm was zero in the survey before the sixth round of MDA. However, in Kinduni the prevalence of *Trichuris trichura* was 1.6% found in a boy of 6 years and a girl of 4 years but the intensity of infection was in egg counts per gram. Also in Kitope prevalence of both *Ascaris* and hookworm was zero (Table 4.35).

Table 4.36 Prevalence of STH in GROUP D - sites 2007

	KINDUNI			KINYASINI			MATARUMBETA		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Tot. Exam.	65	68	133	74	45	119	66	69	135
Trichuris	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Ascaris	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Hookworm	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)

After six rounds of MDA the prevalence of *Trichuris trichura* was zero in all sites of group D (Table 4.36).

4.5.3 Discussion

The results of soil-transmitted helminth infections at the Kizimkazi and Kwahani sentinel sites were very low as compared to the previous data of a school survey undertaken before MDA started. In Kizimkazi the prevalence of *A. lumbricoides* was 42.5%, *T. trichiura,* 54.7% and hookworm, 22.3% and in Kwahani *A. lumbricoides was 28.5%, T. Trichiura, 34.5%* and hookworm, 12.4% in 2001

(unpublished data MOH, Zanzibar). The four rounds of MDA have played a major role in reducing the prevalence of STH as well as the intensity of infection in the sentinel sites. However, the four female children below ten years found with eggs of *Trichuris trichura,* in Kizimkazi, when egg counts were undertaken on intensity were low. The prevalence and intensity of *A. lumbricoides* and *T. trichiura* infections tended to rise rapidly in pre-school children, peak in primary school age group and then slowly come down toward adulthood (Padmasiri et al., 2006). Kizimkazi is a rural village where sanitation facilities are not as developed compared with Kwahani which is close to an urban area. The results of surveys done after fifth and sixth round showed a marked reduction in both the prevalence and intensity of STH infection in both the two sites as indicated in the tables (Table 4.22).

As for the grouped spot check sites the conditions of STH before the fifth round was not bad in most of the sites. In the group A sites that had a record of high drug coverage both the prevalence and intensity of STH decreased compared to the previous data collected in those sites before the MDA started (unpublished MOH report). Where the prevalence was found to be high, such as in Mtambile and Chaani Kubwa they represent areas where sanitation facilities and conditions are not good and also the soil is loamy. In those sites the infection was mainly that of *Trichuris trichura.* In Chaani Kubwa and Mtambile hookworm infection was recorded in 6 (5%) and 6 (4.7%) in adults respectively. Hookworm infections rose steadily throughout childhood reaching a peak in adulthood (Padmasiri et al., 2006). However, in both sites the intensity of infection was low. In the results obtained after fifth and sixth rounds of MDA a marked reduction in both the prevalence and intensity of infection was observed (Tables 4.26, 4.27). In group B sites after four rounds of MDA the prevalence of *Trichuris trichura* was 27.9% and 44.4% in Wawi and Mgogoni, both rural villages in Pemba, with poor sanitation facilities. However, the intensity was low in both villages. As in other sites the results after the fifth and sixth MDA round dropped both in prevalence and intensity of infection of STH (Table 4.29; Table 4.30). In

both groups C and D sites the prevalence and intensity of STH was low after four rounds of MDA. However, in Micheweni the prevalence of *Trichuris trichura* was 17.6% but the intensity of infection was low. Micheweni is a rural village where sanitation facilities are of very low quality. In groups C and D sites after the fifth and sixth rounds MDA, a drop in both prevalence and intensity of infection of STH was observed (Tables 4.32, 4.33, 4.35, 4.36). The overall results obtained after the fourth, fifth and sixth rounds of MDA suggest a significant impact on the prevalence and intensity of soil-transmitted helminthiasis in Zanzibar. It has already been reported that in several MDA programmes that included albendazole for LF control resulted in significant, sustained declines in the prevalence of STH infections (De Rochars et al., 2004; Mani et al., 2004; Oqueka et al., 2005; Rajendran et al., 2003).

4. 6 Impact of MDA rounds on transmission (entomological component)

4.6.1 Introduction

The principal vectors of *Wuchereria bancrofti* in Zanzibar are *Culex quinquefasciatus* mosquitoes (Mansfield-Aders, 1927; Maxwell et al., 1990; Maxwell et al., 1999; Pedersen et al., 1999). Their potential breeding places are wet pit latrines, cess pits, blocked open drains, polluted puddles (Maxwell et al., 1990). When MDA started in 2001 there was no organized vector control programmes in the rural areas identified for monitoring the prevalence of microfilaraemia rate annually. Evaluation of filaria density/rate in the mosquito population was not considered as primary or secondary indicators in selected sentinel sites. Since vectorial capacity (especially the infective bites) have a significant role in the bancroftian disease dynamics, then it was hypothesized that the lowering of L3 larva in the vector (as a result of MDA) within those sentinel sites will be a secondary benefit in mitigating the transmission of bancroftian filariasis. Hence, there was a need for monitoring of the impact of MDA in the vector to determine if six rounds of MDA were enough to stop

transmission of bancroftian filariasis in the country. It is clear that monitoring of infection rates in the vector is important before any conclusion on the effect of the intervention (Ramaiah et al., 2007).

4.6.2 Entomological Surveys at Sentinel sites

4.6.2.1 Baseline survey (before country-wide MDA starts).

Before MDA started in 2001 in both two sentinel sites (Kizimkazi and Kwahani) a two week entomological survey was conducted to determine the *W. bancrofti* infection rate in the vectors. Adult mosquitoes were collected using CDC light traps in 10 randomly selected houses in each site. All female adult mosquitoes collected were morphologically identified and counted. All live female mosquitoes were dissected for infective filariae.

4.6.2.1.1 Results of baseline survey

In Kizimkazi sentinel site (17.8% mf baseline) a total of 1,135 female mosquitoes were caught in 2001 during the base line survey before the first MDA started 955 (84%) were Cx *quinquefasciatus* and 180 (15.6%) were *Anopheles spp.* (Table 4.37). Of the 807 dissected 4 (0.4%) were found with infective larvae (L3) of *W. bancrofti* (Table 4.38). However, in Kwahani (17.2% mf baseline) 1857 female mosquitoes were caught; 1,505 (81%) were *Cx quinquefasciatus* and 352 (19%) were *Anopheles spp.* (Table 4.37). Of the 1,331 dissected none were found with infective larvae (L3) (Table 4.38). The difference in the number of mosquitoes caught between these two sites is mainly due to high breeding sites in Kwahani compared to Kizimkazi as described before.

Table 4.37 Adult mosquitoes caught from two sentinel sites before first MDA

Sentinel site	Total Mosquitoes caught	Culex spp.	Anopheles spp.
Kizimkazi	1,135	955	180
Kwahani	1,857	1,505	352

Table 4.38 L3 infective rate of mosquitoes in Kizimkazi and Kwahani sentinel sites before 1st MDA

Sentinel site	No. mosquitoes Dissected	No. mosquitoes with L3	Percentage infective
Kizimkazi	807	3	0.4%
Kwahani	1,331	0	0.0%

4.6.2.2 Entomological surveys (after four rounds of MDA).

In Zanzibar the impact of MDA on transmission was examined by collection and dissection of indoor mosquitoes for filarial infection. Adult mosquitoes were collected from 20 randomly selected houses from Kizimkazi and Kwahani (Figure 4.39). Mosquito collections were carried out after obtaining the verbal consent of the household members. The collection was done about every 2 weeks. Mosquitoes were collected using CDC light traps run by rechargeable batteries. The light traps were hung approximately 1m above the ground outside

an untreated bednet, placed around a bed occupied by a person sleeping alone in the room. The catch of anophilines and *Cx. quinquefasciatus* with light traps used in this way has been shown to be correlated with the indoor human biting catch (Lines et al., 1990). The traps operated from 1800-0600h. In each household, one insect collector spent 30 minutes searching all the resting places such as hanging objects, walls, roof and beneath the surfaces of fixed objects collecting them using torches and aspirators. All collected mosquitoes were immediately transported to the laboratory and processed on the same day. All live mosquitoes caught were identified on morphological criteria, counted, then dissected (Annex I). Each mosquito was the cut into three parts (head, thorax and abdomen) and placed in three separate drops of normal saline. The parts were gently macerated with needles and examined under a compound microscope for the presence of filarial larvae. The entomological survey took place from September 2005 to July 2008.

4.6.2.2.1 Results

In Kizimkazi 1,184 female mosquitoes were caught in 2005 of which 1,141 (96%) were *Cx quinquefasciatus* and 43 (3.6%) were Anophelines. Of the 831(70.2%) collected and dissected none was found with infective larvae of *W. bancrofti* (Table 4.40). In the second year (2006) a total of 6,407 female mosquitoes were caught of which 6,292 (98.2%) were *Cx quinquefasciatus* and 115 (1.8%) were Anophelines and none of the 4,165 (65%) dissected was positive infective larvae. However, in 2007 and 2008 only *Cx quinquefasciatus* were caught. This could have been due to the indoor residual spraying programme against vectors of malaria that had been ongoing since July 2006. Of 4,219 caught 3,038 (72%) when dissected for infective larvae were found to be negative in 2007. In 2008 of the 2,393 females caught 1,628 (68%) when dissect had no infective larvae (Table 4.40).

In Kwahani, a total of 1,389 female mosquitoes were caught in 2005 of which 1,223 (88%) were *Cx quinquefasciatus* and 166 (12%) were Anophelines. Of the 861 (62%) collected alive and dissected none were found with infective larvae of *W. bancrofti* (Table 4.42). In the second year (2006) a total of 3,524 female mosquitoes were caught of which 3,160 (89.7%) were *Cx quinquefasciatus* and 364 (10.3%) were Anophelines and none of the 2,403 (68.2%) dissected were positive with filarial infection. However, in 2007 and 2008 only *Cx quinquefasciatus* were caught. Out of 3,117 caught 2,057 (66%) when dissected for infective larvae were found to be negative in 2007. In 2008, out of 2,206 females caught 1,401 (63.5%) when dissected none had filarial infection (Table 4.42).

Table 4.39 Mosquito collection at the Kizimkazi sentinel site

	2005			2006			2007			2008		
	Cx	Anophs	Tot	Culex	Anophs	Tot	Cx	Anophs	Tot	Cx	Anophs	Tot
Jan.				256	5	261	209	0	209	355	0	355
Feb.				338	3	341	248	0	248	245	0	245
March				403	5	408	435	0	435	389	0	389
April				732	4	736	556	0	556	275	0	275
May				970	22	992	353	0	353	379	0	379
June				867	35	902	401	0	401	426	0	426
July				859	29	888	322	0	322	324	0	324
Aug.				543	12	555	401	0	401			
Sept.	209	18	227	341	0	341	329	0	329			
Oct.	375	12	387	337	0	337	375	0	375			
Nov.	302	9	311	345	0	345	302	0	302			
Dec.	255	4	259	301	0	301	288	0	288			
Total	**1141**	**43**	**1184**	**6292**	**115**	**6407**	**4219**	**0**	**4219**	**2393**	**0**	**2393**

Table 4.40 Results of dissected mosquitoes from the Kizimkazi site

Year	Total Mosquitoes caught	Mosquitoes dissected n (%)	Results of Filarial Larvae
2005	1184	831(70.2)	00
2006	6407	4165(65.0)	00
2007	4219	3038(72.0)	00
2008	2393	1628(68.0)	00

Table 4.41 Mosquito collection at the Kwahani sentinel site

	2005			2006			2007			2008		
	Cx	Anophs	Tot	Culex	Anophs	Tot	Cx	Anophs	Tot	Cx	Anophs	Tot
Jan.				67	17	84	81	0	81	243	0	243
Feb.				129	21	150	101	0	101	302	0	302
March				230	15	245	195	0	195	279	0	279
April				402	32	434	278	0	278	353	0	353
May				319	59	378	345	0	345	316	0	316
June				453	65	518	298	0	298	344	0	344
July				396	81	477	322	0	322	369	0	369
Aug.				334	74	408	356	0	356			
Sept.	232	68	300	264	0	264	332	0	332			
Oct.	431	55	486	198	0	198	267	0	267			
Nov.	292	29	321	201	0	201	301	0	301			
Dec.	268	14	282	167	0	167	241	0	241			
Total	1223	166	1389	3160	364	3524	3117	0	3117	2206	0	2206

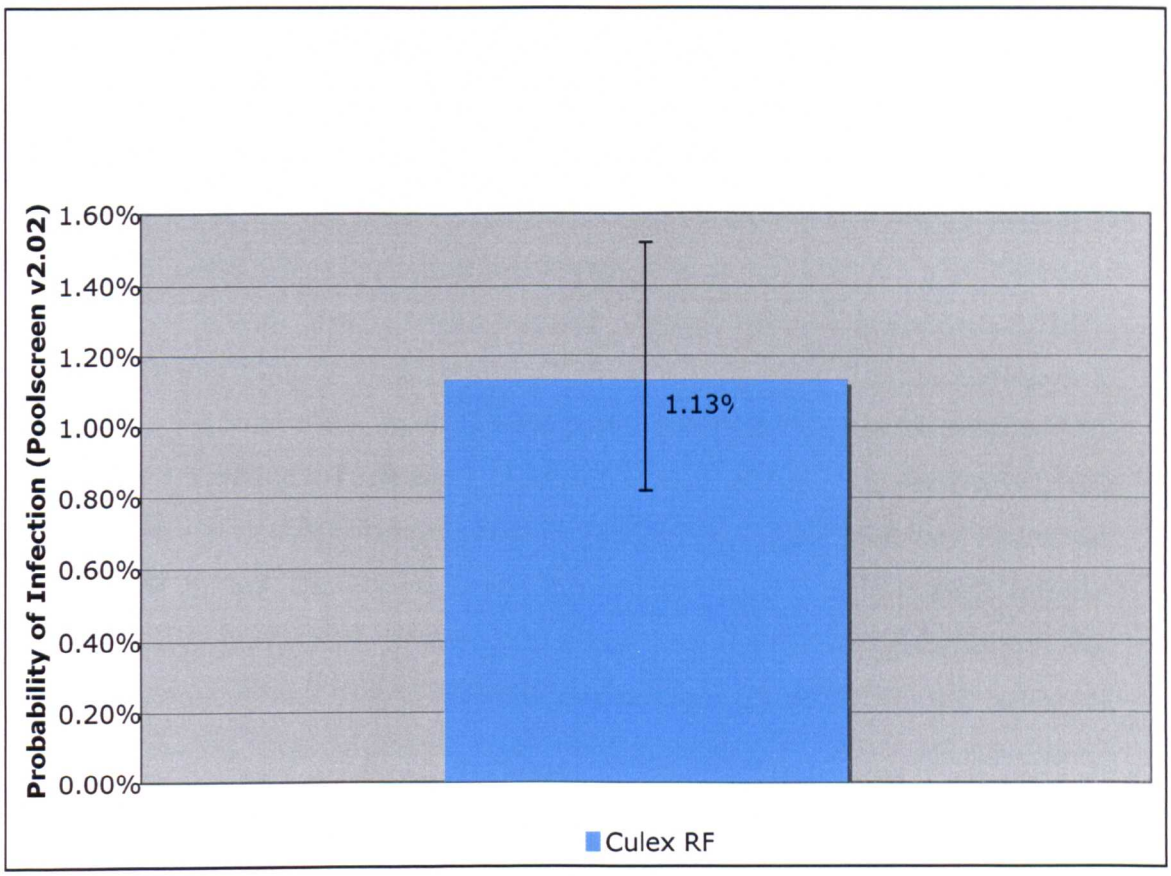
Table 4.42 Results of dissected mosquitoes from the Kwahani site

Year	Total Mosquitoes caught	Mosquitoes dissected n (%)	Results of Filarial Larvae
2005	1389	861(62.0)	00
2006	3524	2403(68.2)	00
2007	3117	2057(66.0)	00
2008	2206	1401(63.5)	00

4.6.3 *Culex quinquefasciatus* collected at Kizimkazi and tested for PCR

At the Kizimkazi site between November 2007 and February 2008 an additional mosquito collection was done. This time collection of female *Culex* mosquitoes was undertaken outdoors using gravid traps placed at the sites where human specimens were collected. The traps were baited with a mixture of straw, manure, powdered milk and Brewer's yeast in water and left to infuse for 4-5 days. All mosquitoes collected were identified, isolated, dried, packed and then sent to CDC Atlanta, USA for analysis. A total of 5,184 recently-fed vector (RFV) were packed and transferred to CDC Atlanta for molecular xenomonitoring using qPCR RFV PCR analysis and this was because the Zanzibar laboratory lacked facilities for PCR. All 5,184 RFV mosquitoes were tested in 280 pools. The mean pool size was 19 with a range of 5-20 mosquitoes per pool and a median of 20. Fifty-three of the 280 pools tested positive for *W. bancrofti* DNA. The Poolscreen (v. 2.02) calculation indicates a maximum likelihood of infection of 1.13% with a 95% confidence interval of 0.82% -1.52% (Figure 4.10).

Figure 4.12 Molecular Xenomonitoring of *W. bancrofti* Infection in Zanzibar, Tanzania



4.6.4 Discussion

The results obtained in all the sites during the whole period of indoor vector surveys after four rounds of MDA and good drug coverage indicated that not a single caught mosquito dissected was found with filarial larvae. However, before the MDA started the entomological results showed that in Kizimkazi the infective rate was 0.4% indicating transmission was ongoing (Table 4.38). The results after four rounds MDA indicated that transmission had been reduced in these sites. This was no doubt because after MDA the chances of a mosquito imbibing microfilariae were greatly reduced. Before MDA commenced in 2001, the microfilariae prevalence rate was 17.8% in Kizimkazi and 7.2% in Kwahani. However, in Kizimkazi the results of the blood survey in the community in 2005 before fifth MDA the microfilariae prevalence was 1% and in Kwahani it was zero. Traditionally, collection of mosquitoes which are dissected and examined for infective larvae had been used for assessment of active transmission. Detection of *W. bancrofti* in mosquitoes requires time-consuming dissection and microscopic examination of individual mosquitoes. In addition, speciation of filarial larvae requires additional technical expertise. In terms of monitoring filariasis elimination programmes, dissection is the ideal means for detecting infections in vector populations but becomes increasingly costly and laborious when the prevalence of infection in the mosquito population drops below 1% (Ramzy, 2002; Goodman et al., 2003; Ramaiah et al., 2003; Richards et al., 2005). The number of mosquitoes that can be processed using this technique was estimated to be about 35 per/person/hour and is slower if mosquitoes are preserved in alcohol (Bockarie et al., 2000). Thus, the use of mosquito dissection for monitoring filariasis elimination programmes may be inappropriate when the prevalence of infection is low because of the need to collect and dissect thousands of mosquitoes. However, this technique may be more useful as a tool for baseline assessment of transmission. In recent years, however, a PCR assay based on the amplification of a highly repeated DNA sequence found in *W. bancrofti* (the 188 bp SspI repeat) has been developed to address

the shortcomings of traditional diagnostic methods (McCarthy et 41 al., 1996; Nicolas et al., 1996; Williams et al., 1996; Zhong et al., 1996; Ramzy et al., 1997). Detection of parasite DNA in human blood and mosquitoes by PCR has been shown to be a sensitive and specific method for determining infection rates in endemic areas and thus a powerful new tool for evaluation and monitoring of community-based filariasis control programmes (Fischer et al., 1999; Farid et al., 2001). Screening of pools of mosquitoes by PCR has been proposed to be a rapid non-invasive tool to monitor the success of elimination programmes and to detect re-establishment of transmission in post-intervention period (Bockarie et al., 2000). A method for detection and quantification of the SspI repeat PCR amplification products by ELISA (PCR-ELISA) has been developed (Fischer et al., 1999). However, the PCR-ELISA assay is laborious and expensive and offers few significant advantages over the standard SspI PCR assay (Ramzy, 2002). The results of 5,184 recently-fed vector (RFV) *Culex quinquefasciatus* mosquitoes caught in Kizimkazi and tested with PCR 53 of the 280 pools tested positive for *W. bancrofti* DNA. The results indicate a maximum likelihood of infection of 1.13% with a 95% confidence interval of 0.82%-1.52%. This suggests the existence of some mf carriers with potential to infect mosquitoes. One major concern for LF elimination programmes is the role of these residual mf carriers as a source of recrudescent infection (Ramaiah et al., 2007). Although recrudescence was a major hindrance to LF control in the South Pacific region where *Aedes spp* is the vector, studies in various provinces of China showed that very low-density microfilaraemia, achieved after chemotherapeutic intervention, disappears gradually (Kimura et al., 1985; Sun and Chen, 1992). The residual mf carriers turn negative at a rate of 61%, 87% and 99% after 3, 4-5 and 7 years, respectively, following cessation of control measures (Shi, 1994). However, *W. bancrofti* SspI PCR assay does not differentiate infective larvae (L3) from the other stages of the parasite (microfilariae, L1 and L2) in the mosquito. The presence of *W. bancrofti* infective larvae in the vector population is a direct measure of transmission because only mosquitoes carrying the infective stage of the parasite are capable of

contributing to transmission. Therefore, an ideal PCR assay for monitoring the level of transmission during a filariasis control programme would be one based on L3 specific primers (WHO, 2002).

CHAPTER V

IMPACT OF MDA ON THE CLINICAL MANIFESTATIONS OF LF

5.1 Introduction

Zanzibar commenced MDA using ivermectin (Mectizan®) and albendazole in 2001 with the aim of interrupting *W. bancrofti* transmission. However, there is little information on the impact of MDA on clinical manifestations (adenolymphangitis, lymphoedema and hydrocele) due to infection. In this chapter the impact of MDA on clinical manifestations of bancroftian filariasis is assessed in individuals examined pre and post-MDA.

To monitor the progress of MDA interventions according to the WHO LF Programme Managers' Guidelines the establishment of sentinel sites and the collection of baseline and ongoing data was recommended (WHO, 1998). In the two sentinel sites selected, Kizimkazi and Kwahani, surveys were conducted before each MDA to check the impact of the previous MDA for both prevalence of and clinical manifestations of the disease in 500 individuals of both sexes and different age groups from each site. The baseline data collected in 2001 were compared with data collected after each MDA. The communities of both sites had not received any anti-filarial treatment prior to October 2001.

This study enabled us to examine individuals pre and post-MDA with and without chronic disease, a condition which is a useful way to accurately document both resolution and incidence of clinical manifestations, thus giving an insight into the dynamics of filarial disease during MDA.

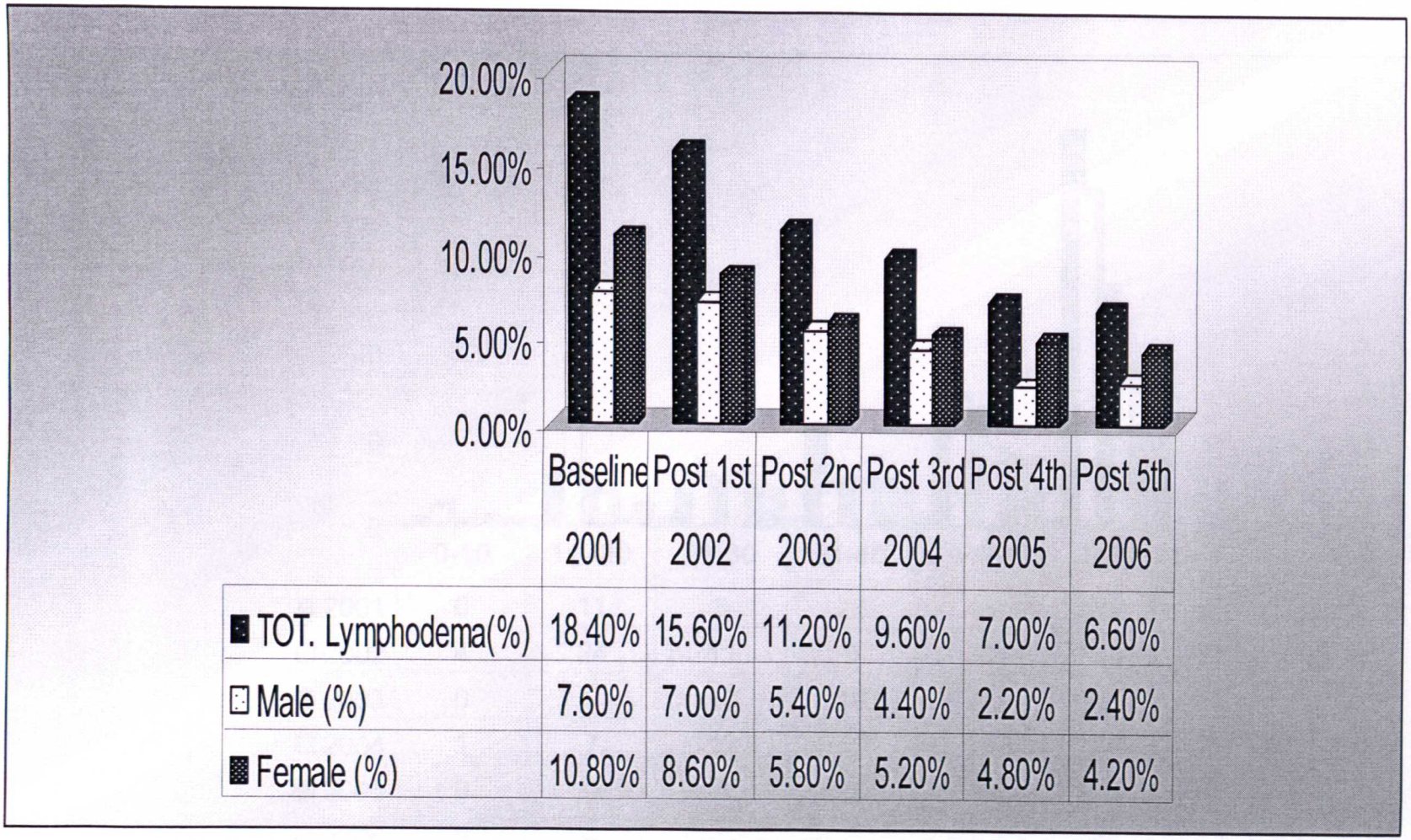
5.2 Impact of MDAs on lymphoedema of the limbs

At Kizimkazi sentinel site 500 individuals were examined after the first MDA and 78 (15.6%) of them were found to have lymphoedema of the legs. Of the 78 one was a young female aged 9 years. The prevalence rates of lymphoedema of the legs in the Kizimkazi study site after five MDAs are summarized in Table 5.1. After five years the prevalence of lymphoedema of the legs dropped gradually post-MDA in Kizimkazi from 92 (18.4%) at baseline to 78 (15.6%), 56 (11.2%), 48 (9.6%) and 35 (7%) respectively (Table 5.1). Children under ten years were excluded from the analyses of the impact of MDA on leg lymphoedema because this manifestation was not common in this group. The number of females with lymphoedema was higher than in males in all surveys (Table 5.1). The number of individuals who were examined and found to have lymphoedema of the legs before and after the first round of MDA was 19 (10 males and 9 females) and their ages ranged from 16-71 years. Following the second and third MDAs most of those with stage I and II lymphoedema before the first MDA found their lymphoedema had resolved. In a survey of 500 individuals in Kizimkazi to determine the prevalence of lymphoedema of the limbs after four MDAs a decline in the records of individuals with leg lymphoedema was reported compared to the survey undertaken before the first MDA. In the age group 30-39 years 19 individuals were recorded to have leg lymphoedema in 2001 (Table 3.6). However, in the same age group the number with leg lymphoedema dropped to 9 in 2005 survey. The drop in the number of individuals with leg lymphoedema was recorded in the age group of above 50 years when 15 individuals were found to have lymphoedema of the leg in 2005 survey as compared to 40 individuals recorded in the same age group in survey done in 2001 (Tables 3.6, 5.1) (Figure 5.1).

Table 5.1 Lymphoedema and mf prevalence by sex post-MDA at the Kizimkazi sentinel site

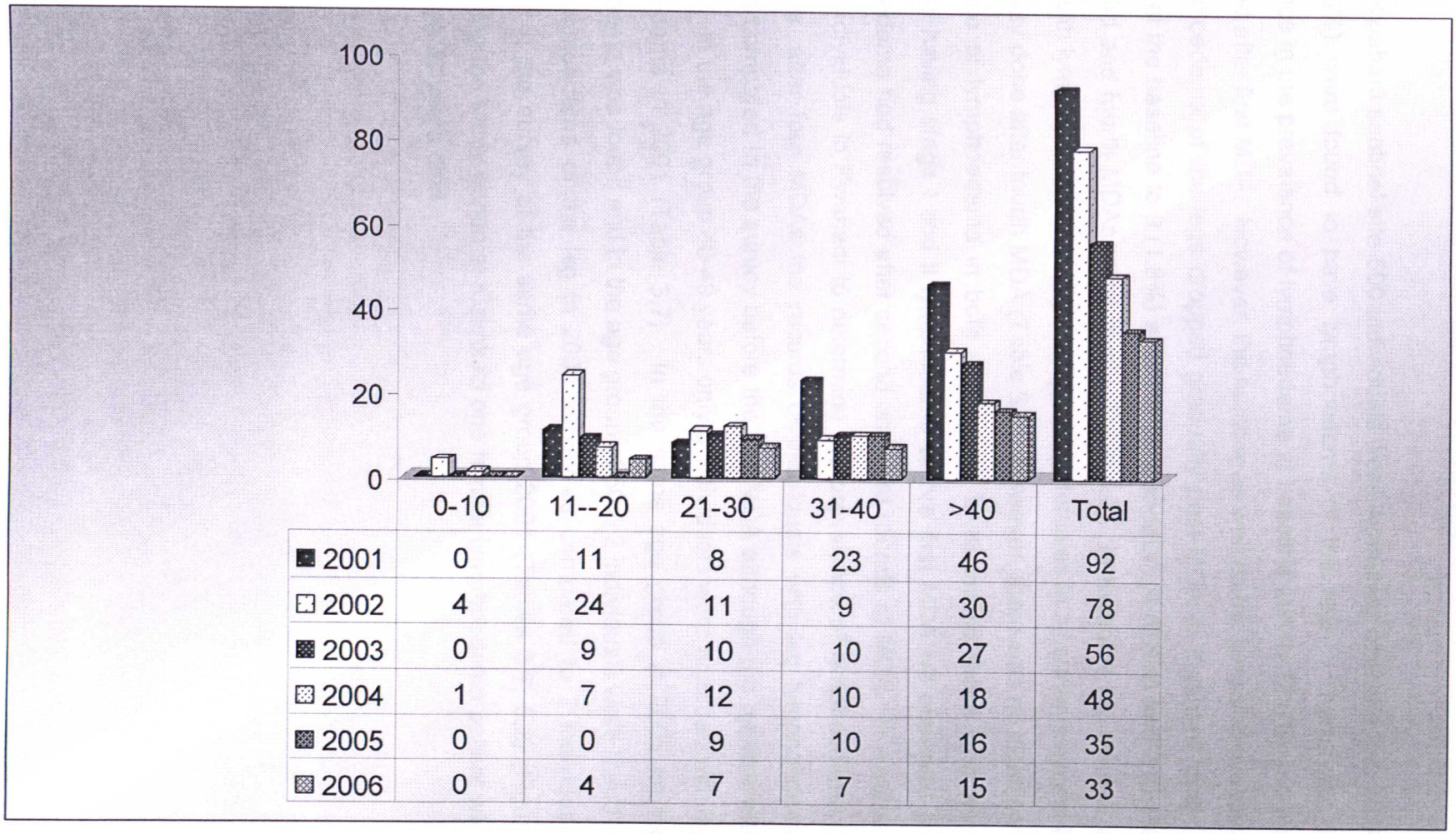
Year	Survey	No. EXD	No. (%)	Male (%)	Female (%)	MF prevalence
2001	Baseline	500	92(18.4%)	38(7.6%)	54(10.8%)	17.8%
2002	Post 1st MDA	500	78(15.6%)	35(7.0%)	43(8.6%)	4.0%
2003	Post 2nd MDA	500	56(11.2%)	27(5.4%)	29(5.8%)	1.4%
2004	Post 3rd MDA	500	48(9.6%)	22(4.4%)	26(5.2%)	1.2%
2005	Post 4th MDA	500	35(7.0%)	11(2.2%)	24(4.8%)	1.0%
2006	Post 5th MDA	500	33 (6.6%)	12(2.4%)	21(4.2%)	0.0%

Figure 5.1 Lymphoedema patients in Kizimkazi post-MDA



	Baseline 2001	Post 1st 2002	Post 2nd 2003	Post 3rd 2004	Post 4th 2005	Post 5th 2006
TOT. Lymphodema(%)	18.40%	15.60%	11.20%	9.60%	7.00%	6.60%
Male (%)	7.60%	7.00%	5.40%	4.40%	2.20%	2.40%
Female (%)	10.80%	8.60%	5.80%	5.20%	4.80%	4.20%

Figure 5.2 Lymphoedema patients by age and sex post-MDAs in Kizimkazi



	0-10	11--20	21-30	31-40	>40	Total
2001	0	11	8	23	46	92
2002	4	24	11	9	30	78
2003	0	9	10	10	27	56
2004	1	7	12	10	18	48
2005	0	0	9	10	16	35
2006	0	4	7	7	15	33

At the Kwahani sentinel site 500 individuals were examined after the first MDA, 13 (2.6%) were found to have lymphoedema of the legs. There was no difference in the prevalence of lymphoedema at baseline survey (2.6%) and that obtained after first MDA. However, the number as well as the overall prevalence of lymphoedema of the legs dropped gradually post-MDA in Kwahani from 13 (2.6%) at the baseline to 9 (1.8%) after the second MDA, 4 (0.8%) and 2 (0.4%) after third and fourth MDAs respectively (Table 5.2). In Kwahani the number of males with lymphoedema was high compared to females in all surveys except in the survey done after fourth MDA (Table 5.2). However, there was no significant difference of lymphoedema in both sexes. As in Kizimkazi those who were recorded having stage I and II lymphodema before first MDA we observed the lymphoedema had resolved after second and third rounds of MDA. In a survey of 500 individuals in Kwahani to determine the prevalence of lymphoedema of the limbs, after four MDAs the records of individuals with leg lymphoedema declined compared to the survey before the first MDA although the number was very low. In the age group 40-49 years only 3 individuals were recorded with leg lymphoedema in 2001 (Table 3.7). In the same age group in 2005 no leg lymphodema was found and in the age group of 50+, 2 individuals were found to have lymphoedema of the leg in 2005 survey as compared to 7 individuals recorded in the survey of the same age group 2001 (Tables 3.7, 5.2) (Figure 5.3). During the study period at Kizimkazi one female lymphoedema patient who was above 70 years died.

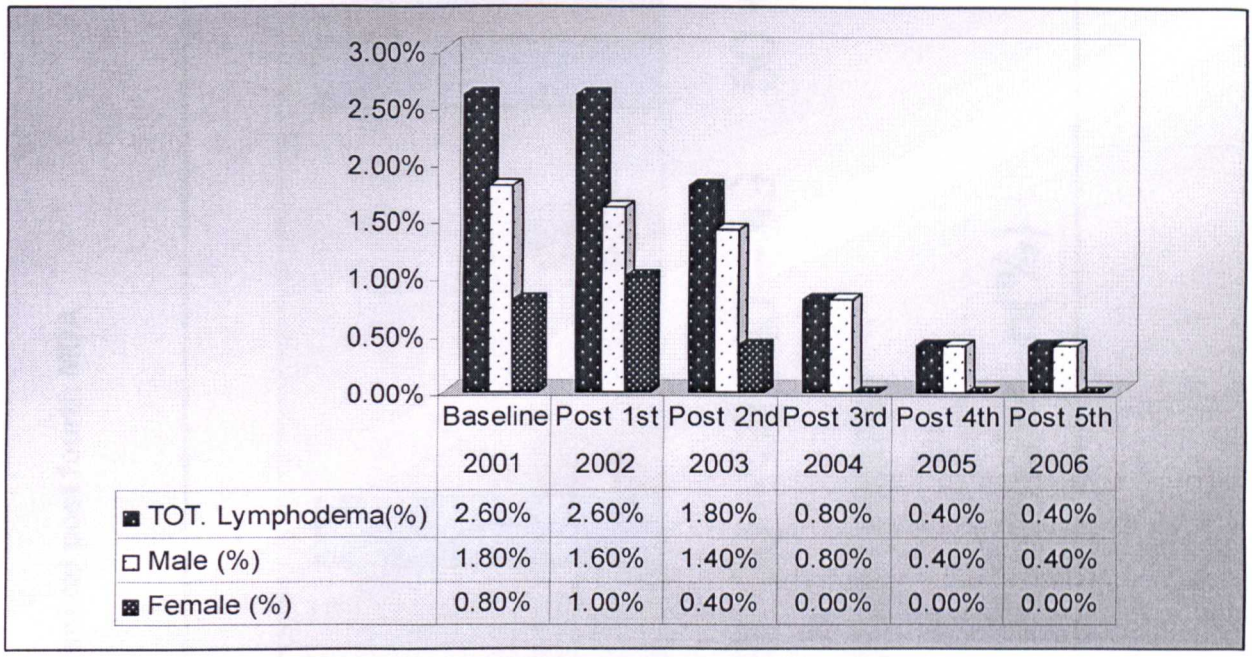
Table 5.2 Lymphoedema and mf prevalence by sex post-MDA at the Kwahani sentinel site by cross-sectional survey

Year	Survey	No. EXD	No. (%)	Male (%)	Female (%)	MF prevalence
2001	Baseline	500	13 (2.6%)	9(1.8%)	4 (0.8%)	7.2%
2002	Post 1st MDA	500	13 (2.6%)	8(1.6%)	5 (1.0%)	1.4%
2003	Post 2nd MDA	500	9 (1.8%)	7(1.4%)	2 (0.4%)	0.4%
2004	Post 3rd MDA	500	4 (0.8%)	4(0.8%)	0 (0%)	0.2%
2005	Post 4th MDA	500	2 (0.4%)	2(0.4%)	0 (0%)	0%
2006	Post 5th MDA	500	2 (0.4%)	2(0.4%)	0 (0%)	0%

Table 5.3 Prevalence of lymphoedema by age and sex in Kizimkazi site post fourth MDA

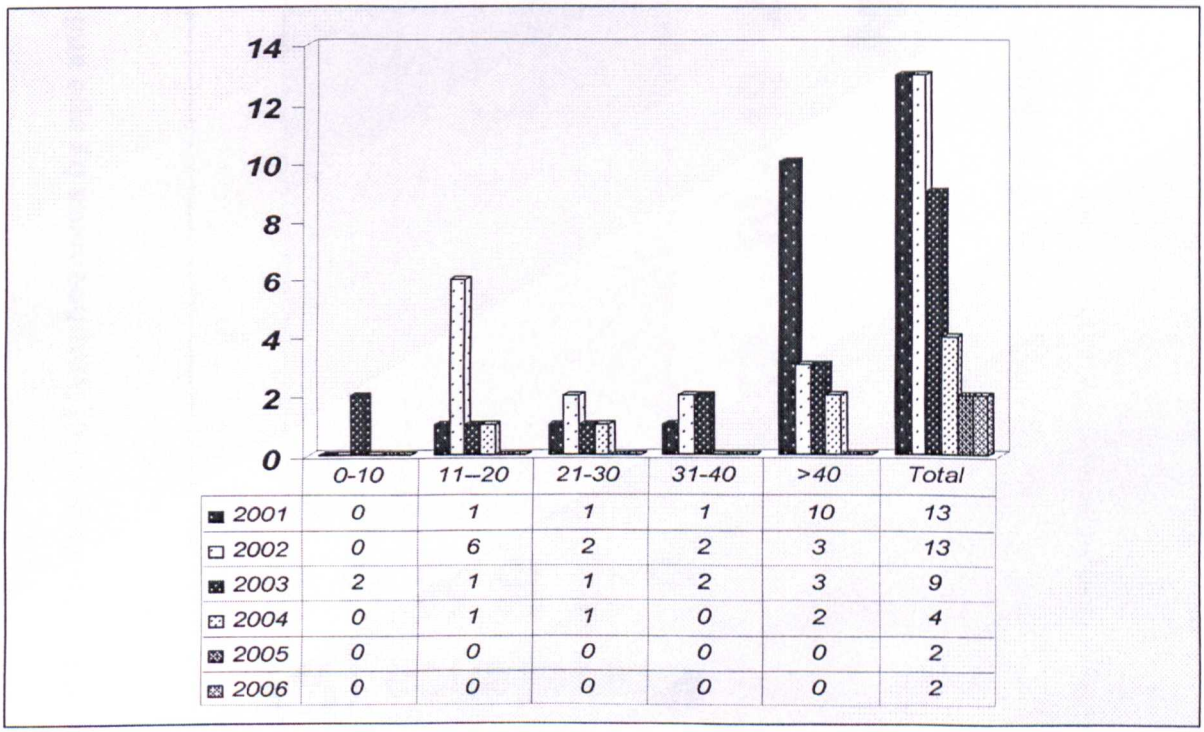
Age (Years)	**Males N (%)**	**Females N (%)**	**Total N (%)**
<10	0 (0%)	0 (0%)	0 (0%)
10–19	0 (0%)	0 (0%)	0 (0%)
20–29	1 (9.1%)	6 (25%)	7 (20%)
30–39	5 (45.5%)	4 (16.7%)	9 (25.7%)
40–49	0 (0%)	4 (16.7%)	4 (11.4%)
50+	5 (45.5%)	10 (41.7%)	15 (42.9%)
Total	**11 (5.2%)**	**24 (8.3%)**	**35 (7%)**

Figure 5.3 Lymphoedema patients in Kwahani post-MDA



	Baseline 2001	Post 1st 2002	Post 2nd 2003	Post 3rd 2004	Post 4th 2005	Post 5th 2006
TOT. Lymphodema(%)	2.60%	2.60%	1.80%	0.80%	0.40%	0.40%
Male (%)	1.80%	1.60%	1.40%	0.80%	0.40%	0.40%
Female (%)	0.80%	1.00%	0.40%	0.00%	0.00%	0.00%

Figure: 5.4 Lymphoedema patients by age and sex post-MDA in Kwahani



	0-10	11–20	21-30	31-40	>40	Total
2001	0	1	1	1	10	13
2002	0	6	2	2	3	13
2003	2	1	1	2	3	9
2004	0	1	1	0	2	4
2005	0	0	0	0	0	2
2006	0	0	0	0	0	2

Figure 5.5 Prevalence of lymphoedema by age and sex in Kizimkazi post fourth MDA

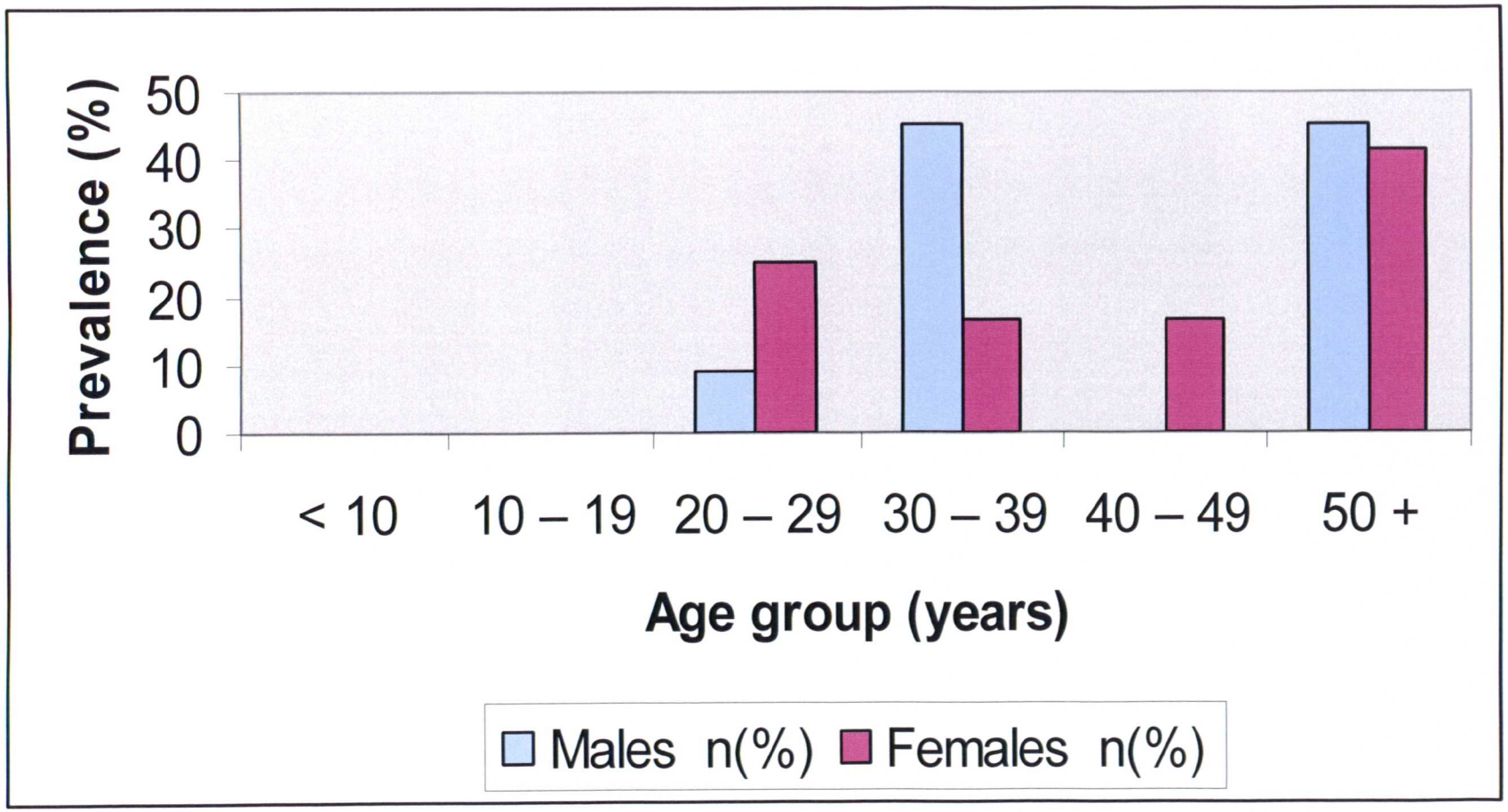
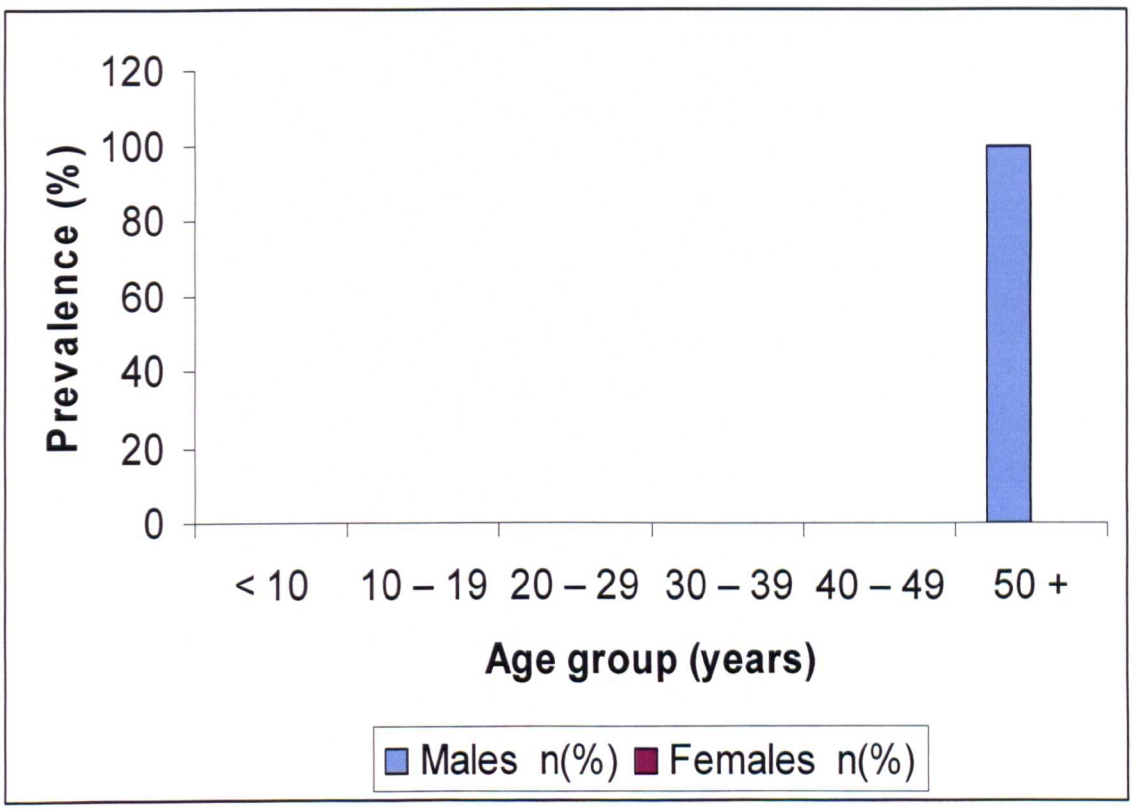


Table 5.4 Prevalence of lymphoedema by age and sex in Kwahani post fourth MDA

Age (Years)	Males N (%)	Females N (%)	Total N (%)
<10	0 (0%)	0 (0%)	0 (0%)
10–19	0 (0%)	0 (0%)	0 (0%)
20–29	0 (0%)	0 (0%)	0 (0%)
30–39	0 (0%)	0 (0%)	0 (0%)
40–49	0 (0%)	0 (0%)	0 (0%)
50+	2 (100%)	0 (0%)	2 (100%)
Total	**2 (0.9%)**	**0 (0%)**	**2 (0.4%)**

Figure 5.6 Prevalence of lymphoedema by age and sex in Kwahani post fourth MDA



In Kizimkazi there was resolution of lymphoedema of the legs in 14 of 92 adults (15.2%) after the first MDA and 57 of 92 after four MDAs with ivermectin (Mectizan®) and albendazole. In Kwahani the resolution of lymphoedema of the legs was recorded in 4 of 13 adults (30.8%) after two MDAs. However, in the Papua New Guinea study resolution of lymphoedema of the legs was reported in 62 of 90 adults (69%) and that resolution was not correlated to the drug regimen (Bockarie et al., 2002). In a clinical trial using DEC, Kenney and his colleagues reported a decrease in prevalence of lymphoedema in the 1–3 months of follow-up (Kenney et al., 1949). However, Pani noticed no decrease in prevalence of lymphoedema in a clinical trial using DEC in the one year follow-up at Pondicherry India (Pani, 1995). Moore et al (1996) reported a decrease in size of lymphoedema following use of DEC in the 1 week–7 month follow-up on a peace corps volunteer who developed acute lymphatic dysfunction within 3 months of arriving in an area that was endemic for filariasis. Previous investigations have shown that all cases of pitting lymphoedema could be resolved within one year after treatment with DEC, but the more advanced patients required two-four years to resolve (Partono et al., 1981). Partono et al (1981) reported a decrease of both acute attacks and prevalence of lymphoedema following MDA using DEC alone in an eleven year follow-up in West Flores, Indonesia. While Malecela and Mackenzie reported in Tanzania the decrease in frequencies of acute attacks and prevalence of lymphoedema after MDA using a combination ivermectin (Mectizan®) and albendazole in 1- 2 years period of the follow-up (WHO/TDR/SWG/ 2005).

5.3 Impact of MDAs on prevalence of hydrocele

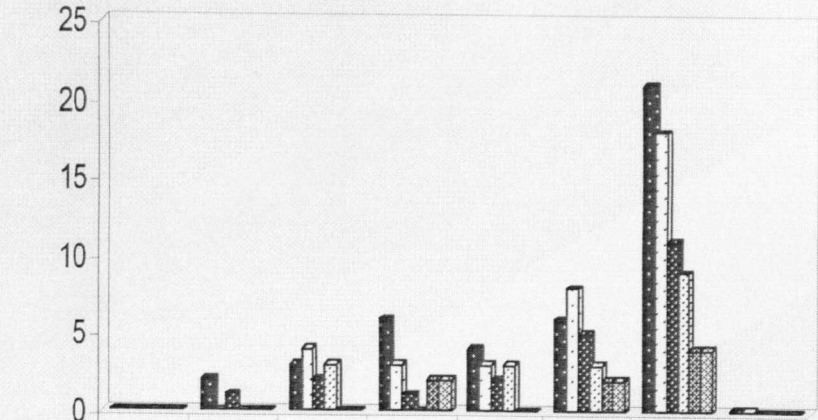
During the 2001 survey out of 270 males examined for hydrocele in Kizimkazi, 21 (7.8%) males were found with hydrocele. Out of those 21 found with hydrocele 2 were below 20 years old (18 and 19 years old). However, a decline in cases of hydroceles was recorded in surveys after the MDAs (Table 5.5) (Figure 5.7). The number as well as the overall prevalence of hydrocele

declined gradually over the five years of MDA in Kizimkazi from 21 (7.8%) at baseline to 18 (6.5%), 11 (4.2%), 9 (4.1%), 4 (1.9%) and 4 (1.4%) respectively (Table 5.5) (Figure 5.7). In Kwahani of 220 males examined before the first MDA only 3 (1.4%) had hydrocele, one was 42 years old and 2 were over 50 years old (65 years and 72 years). However, following MDA a small decline in the number and prevalence of hydrocele 3 (1.4%), 2 (0.8%), 2 (0.8%), 1 (0.6%), 1 (0.4%) and 1 (0.4%) was recorded. After the second and third rounds of MDA the prevalence of hydrocele did not change in Kwahani. However, a slight change was recorded after the fourth MDA although not statistically significant (Table 5.6) (Figure 5.8).

Table 5.5 Prevalence of hydrocele by age post MDA in Kizimkazi

Age group	2001	2002	2003	2004	2005	2006
<10	0	0	0	0	0	0
10-19	2	0	1	0	0	0
20-29	3	4	2	3	0	0
30-39	6	3	1	0	2	2
40-49	4	3	2	3	0	0
50+	6	8	5	3	2	2
ToT	21	18	11	9	4	4
No. EXD.	**270**	**275**	**265**	**220**	**210**	**294**
Prev. rate	**7.8%**	**6.5%**	**4.2%**	**4.1%**	**1.9%**	**1.4%**

Figure 5.7 Records of individuals with hydrocele in Kizimkazi post-MDA

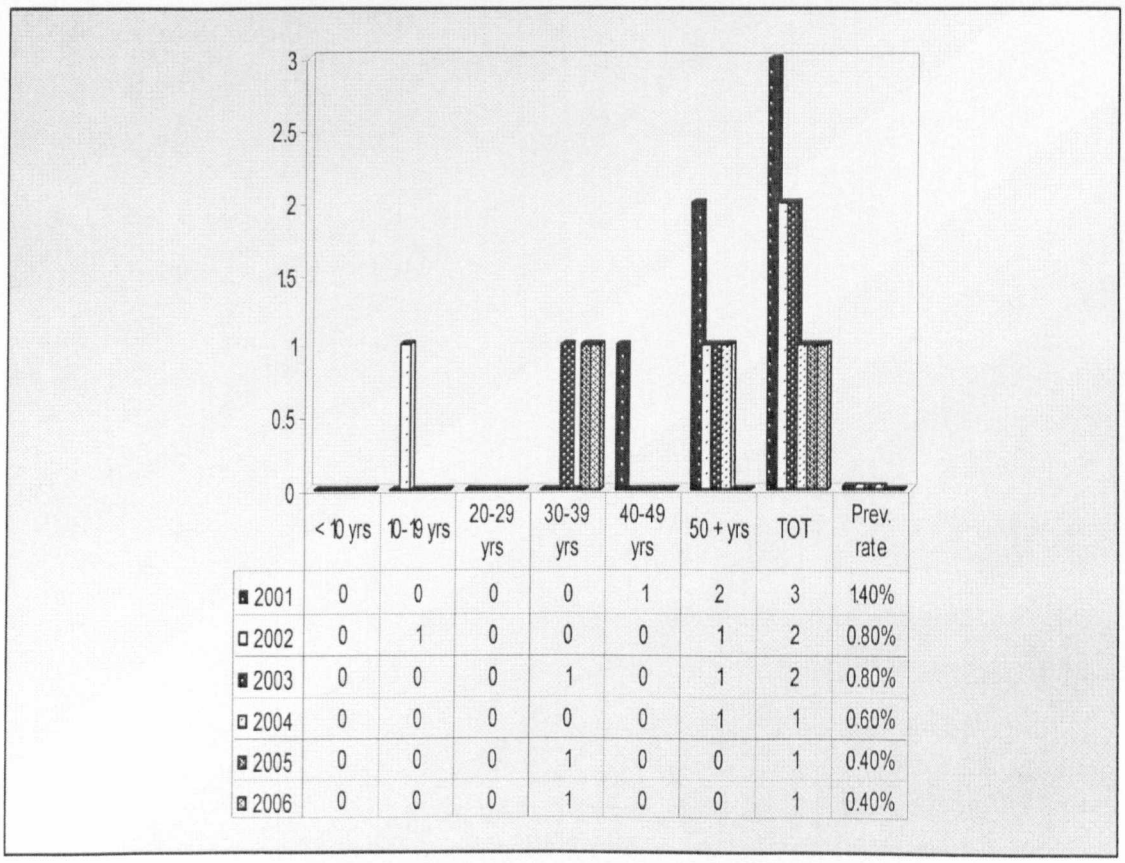


	< 10 yrs	10-19 yrs	20-29 yrs	30-39 yrs	40-49 yrs	50 + yrs	TOT	Prev. rate
2001	0	2	3	6	4	6	21	7.80%
2002	0	0	4	3	3	8	18	6.50%
2003	0	1	2	1	2	5	11	4.20%
2004	0	0	3	0	3	3	9	4.10%
2005	0	0	0	2	0	2	4	1.90%
2006	0	0	0	2	0	2	4	1.40%

Table 5.6 Records of individuals with hydrocele in Kwahani post-MDA

Age group	2001	2002	2003	2004	2005	2006
<10	0	0	0	0	0	0
10-19	0	1	0	0	0	0
20-29	0	0	0	0	0	0
30-39	0	0	1	0	1	1
40-49	1	0	0	0	0	0
50+	2	1	1	1	0	0
ToT	3	2	2	1	1	1
No. EXD.	**220**	**254**	**261**	**159**	**230**	**206**
Prev. rate	**1.4%**	**0.8%**	**0.8%**	**0.6%**	**0.4%**	**0.4%**

Figure 5.8 Records of individuals with hydrocele in Kwahani post-MDA



Previous studies in India showed a dramatic impact by MDA on the frequency of hydrocele which constituted about 60% of the total chronic disease burden (TDR, 1994). The proportion of people with hydrocele was 20.5% prior to intervention, compared to 5.1% (a 75% reduction) after seven cycles of DEC mass administration. The impact was more appreciable in the <40-year age group, in which the frequency of hydrocele cases declined from 13.6%-1.5% (a 90% reduction). In villages administered seven cycles of ivermectin (Mectizan®), the overall frequency of hydrocele decreased from 23.9%-10.4% (a 56% reduction) and the frequency in the <40-year age group decreased from 15.8%-6.0% (a 62% reduction) (Vector Control Research Centre, annual report 2003). Studies conducted in Tanzania indicated DEC administered in different regimens resulted in complete resolution or reduction in hydrocele. However, complete resolution of hydrocele was observed in 25%, 36.8%, 45.5% and 46.2% of males treated with DEC-fortified salt, a 12-day course of DEC, semi-annual DEC and monthly low-dose DEC, respectively (Meyrowitsch et al., 1996a; Meyrowitsch et al., 1996b). In Papua New Guinea a study reported resolution of hydrocele in 91 of 105 males (87%) after four annual MDAs with DEC alone or DEC plus ivermectin (Mectizan®) (Bockarie et al., 2002). Simonsen and his group reported resolving in hydroceles following mass treatment of DEC and a one year follow-up (Simonsen et al., 1995). However, Beye et al (1952) reported no decrease in prevalence of hydrocele and lymphoedema following both MDA and selective distribution of DEC in the sixteen months of follow-up. Also Bernhard et al (2001) noticed no decrease in prevalence of hydrocele following both MDA and in a clinical trial using DEC in one year follow-up.

5.4 Acute attacks after MDA

In both sites in surveys after the first MDA the decrease in the frequency of acute attacks was reported by lymphoedema patients. However, in those with advanced chronic stage lymphoedema the decrease in frequency of acute

attack was noticed after the second and third rounds of MDA. Ciferri et al (1969) reported the decrease in frequency of acute attacks following MDA using DEC alone in a 2 year follow-up. Partono et al (1981) reported a decrease in both acute attacks and prevalence of lymphoedema following MDA using DEC alone in an eleven year follow-up. While Malecela and Mackenzie reported a decrease in frequency of acute attack and prevalence of lymphoedema after MDA using a combination ivermectin (Mectizan®) and albendazole in a 1-2 year period of follow-up (WHO/TDR/ SWG/ 2005).

5.5 Discussion

Most of the previous reports on the impact on MDA on the clinical manifestations of the LF were mainly on MDA using DEC and albendazole or DEC alone. However, very few studies explained the impact of using ivermectin (Mectizan®) and albendazole. These experiences in Kizimkazi and Kwahani relate to an area where MDA using a combination of ivermectin (Mectizan®) and albendazole was used. It is not known if additional cycles of MDA or better treatment compliance would further reduce the prevalence of hydrocele, or if MDA 'cure' of hydrocele is irreversible. Because of the close association between the chronic and acute disease, such a drastic reduction in the proportion of people with hydrocele should also lead to some relief for the patients from acute disease episodes. However, as indicated data on the impact of MDA on filarial morbidity are inconsistent (WHO, TDR/ SWG/ 2005). Several studies report reductions in adenolymphangitis, lymphoedema, and/or hydrocele following MDA, but others report no such association. March et al (1960) reported a decrease in acute attacks, reduced prevalence of hydrocele and lymphoedema following monthly MDA using DEC alone in the 10 years follow-up. Meyrowitch et al (1996a) reported a decrease in the prevalence of both hydrocele and lymphoedema following MDA using DEC salt in a two year follow-up. However, Fan et al (1995) reported no decrease in the prevalence of either

hydrocele or lymphoedema following MDA using DEC salt in a 16–19 years follow-up.

Assessing the public health impact of MDA with anti-filarial drugs is an important issue for programme advocacy and for morbidity control strategies.

CHAPTER VI

IMPACT OF MDA ON SOIL-TRANSMITTED HELMINTHS AND SCABIES

6.1 INTRODUCTION

Zanzibar's Programme to Eliminate Lymphatic Filariasis (PELF) for six years administered ivermectin (Mectizan®) and albendazole to all eligible individuals in the community. Eligible recipients had to be over and above five years, and be in relatively good health. Pregnant women or women who had just given birth, the elderly or extremely ill were not eligible to receive the drugs. The Zanzibar PELF programme has been successful, as each of the six rounds of MDA had coverage of over 90% of the eligible population, with approximately an 80% average of the total population. Zanzibar has been a model for MDA success because of the utilization of existing social, religious and political networks to distribute drugs and education (Mohammed et al., 2006). Studies show that MDA dramatically decreased the prevalence of infection, with an added impact on hookworm, whipworm, roundworm, and scabies, easily treated with the same drugs noted to be likely.

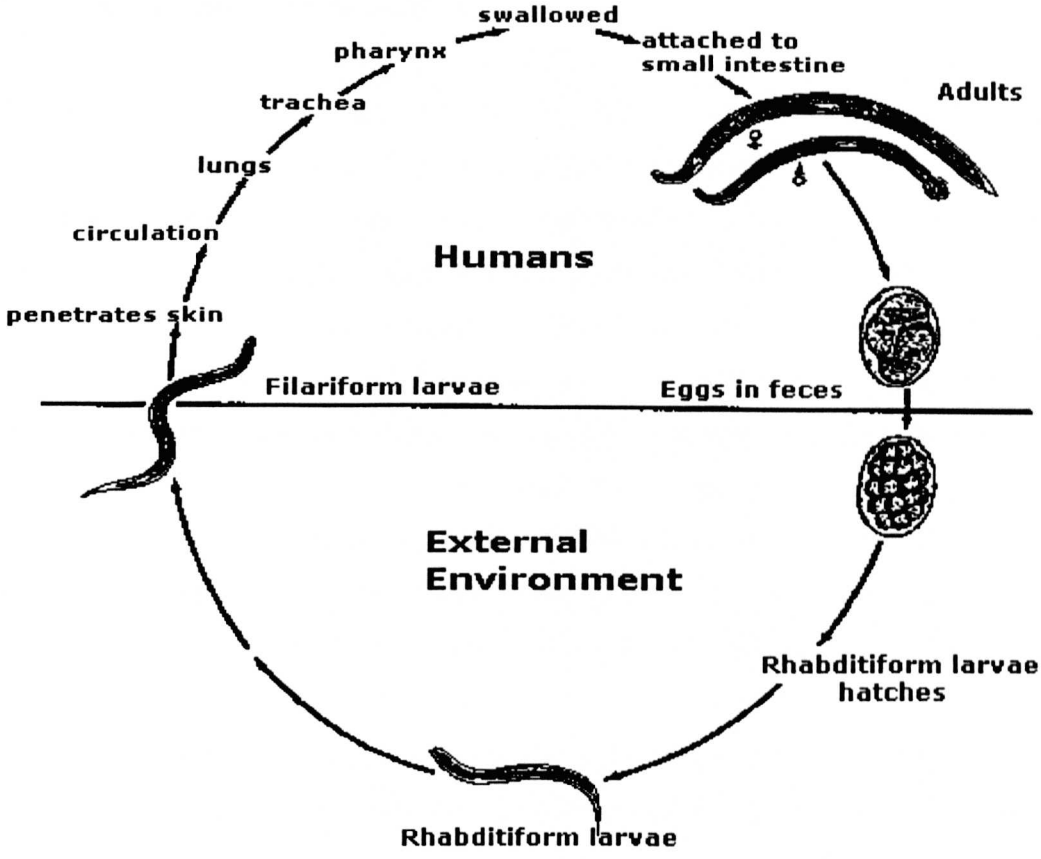
The question became how to maximize the benefits of such a programme by utilizing existing social and political networks to treat other conditions. The opportunity to receive the support of WHO and pharmaceutical donors in collaboration with PELF's efforts go far beyond reducing, and possibly eliminating the devastation of LF.

6.2 Hookworm

Hookworm infection, ancylostomiasis, is a parasite of the intestine caused by the *Necator americanus* in tropical areas of Africa. Worldwide, it is estimated that

over 1 billion people are infected with hookworm. The parasite thrives in warm, moist places where sanitation is poor. An infected individual passes the eggs in the stool, where they hatch in the soil. Other individuals then contact the infection by walking barefoot or sitting on contaminated soil. After entering the body, the larvae migrate through the lymphatic vessels and bloodstream into the lungs. The larvae pass into the air spaces, climb the respiratory tract into the throat, and are swallowed, reaching the intestine about one week after penetrating the skin. Adult worms then attach themselves by the mouth to the lining of the small intestine and live on blood from the host. Itchy rashes may occur where larvae penetrated the skin, and movement of the larvae through the lungs can cause fever, coughing, and respiratory infection. Anaemia then develops as blood is lost to the parasite and the host becomes iron deficient. In children, slow growth, heart failure, and widespread tissue swelling may develop when the resulting anaemia is severe (Stoltzfus, et al. 1997). The diagnosis is made by identifying hookworm eggs in a stool sample. The infection is successfully treated with albendazole, mebendazole, or pyrantel pamoate (WHO, 2004; Horton, 2000, Urbani and Albonico, 2003).

Figure 6.1 Life cycle of hookworm



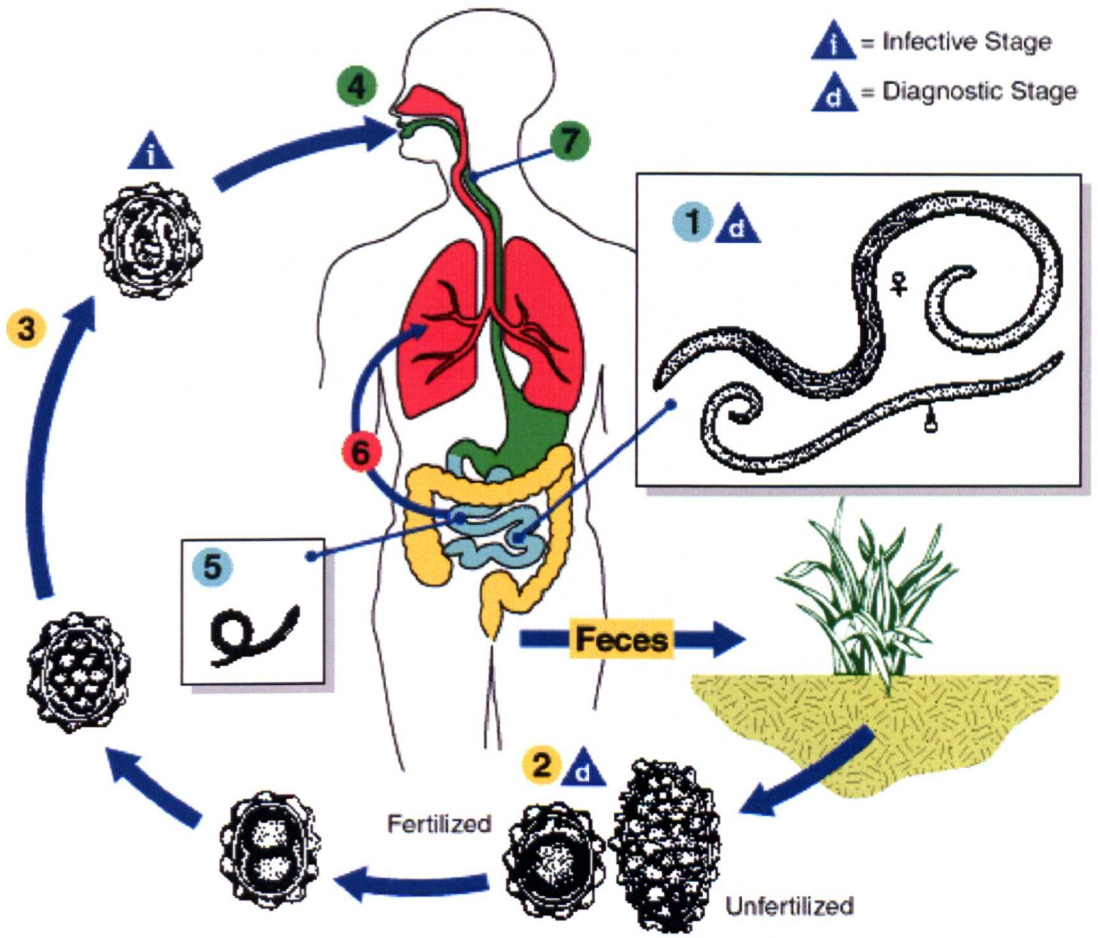
The hookworm life cycle:

- Adult worms live in the lumen of the small intestine, where they attach to the intestinal wall with resultant host blood loss;
- Eggs are passed in the stool, and under favorable conditions (moisture, warmth, shade), hatch in 1-2 days;
- Larvae are released, grow in the feces and/or the soil, and after 5-10 days (and two molts) have become filariform (L-3) larvae that are infective;
- These infective larvae can survive 3-4 weeks in favorable environments;
- On contact with the human host, the larvae penetrate the skin and are carried through the veins and the heart to the lungs;
- They penetrate into the pulmonary alveolae, ascend the bronchial tree to the pharynx, and are swallowed;
- Upon reaching the small intestine, they undergo two more molts yielding fourth stage larvae (L4) and then adult worms;
- Five weeks or more are required from invasion by the L3 to oviposition by the adult female;
- Most adult worms are eliminated in 1-2 years, but longevity records can reach several years;
- Some *A. duodenale* larvae, following penetration of the host skin, can become dormant (in the intestine or muscle!);
- In addition, infection by *A. duodenale* may probably also occur by the oral and transmammary route (*N. americanus*, however, requires a transpulmonary migration phase.)

6.3 Roundworm or Ascariasis

Ascariasis is an infection caused by *Ascaris lumbricoides*, an intestinal roundworm. Ascariasis is the most common roundworm infection in humans, occurring in over 1 billion worldwide. The infection is found mostly in areas with poor sanitation. Infection begins when a person swallows food contaminated with eggs that have been passed in the stool from an infected person and incubated in the soil. Once swallowed, the eggs hatch and release larvae into intestine where they migrate through the wall, through the lymphatic system and bloodstream to the lungs. Once inside the lungs, the larvae move up the respiratory tract and are swallowed. Adult female worms range from 20 - 49 cm in length while adult males range from 15 – 31cm in length and males are distinctly more slender than females. The migration of larvae through the lungs can cause fever, coughing, and wheezing. Severe *Ascaris* infections cause abdominal cramps and can even result in a blockage of the intestine. Diagnosis of ascariasis is made by identifying eggs or adult worms by microscope in a stool sample. Prevention of ascariasis is easily accomplished by adequate sanitation and the avoidance of uncooked foods. As a treatment, mebendazole, albendazole, or pyrantel pamoate are effective drugs (WHO, 1999; Bennet and Guyat, 2000; WHO, 2004; Horton, 2000, Urbani and Albonico, 2003).

Figure 6.2 Life cycle of roundworm

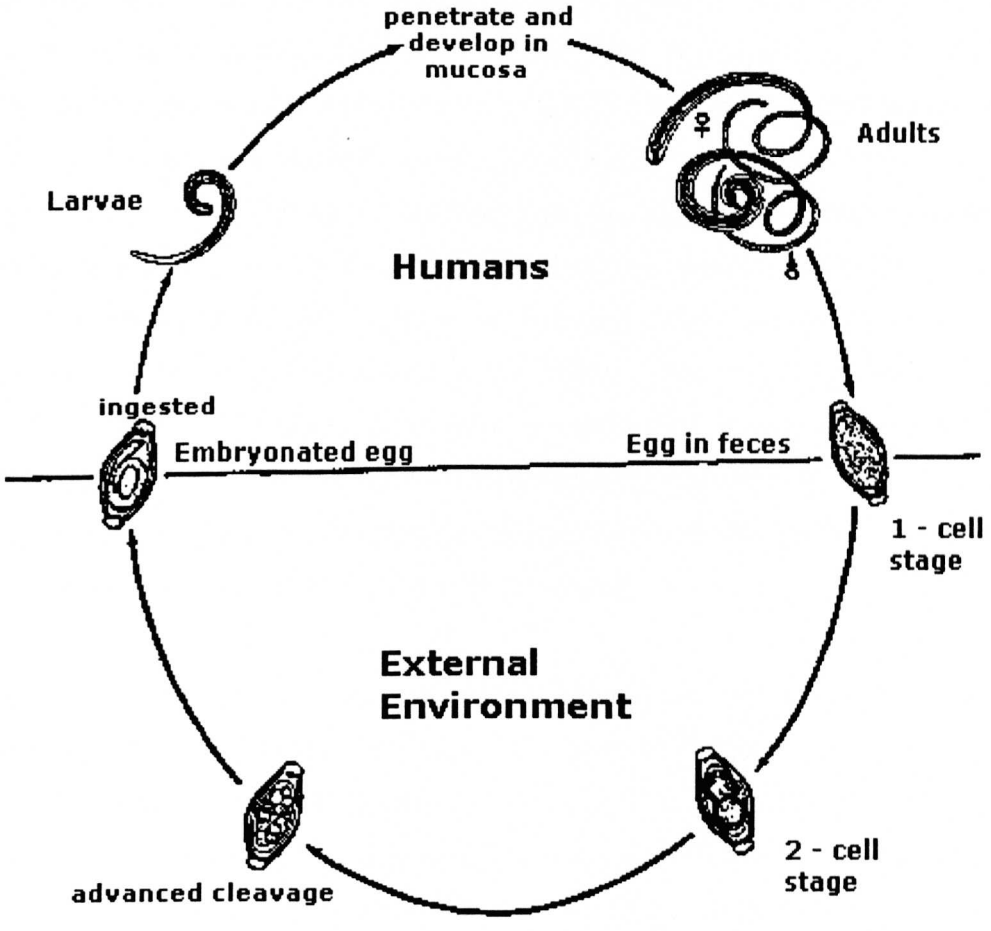


6.4 Whipworm (*Trichuris trichiura*)

Whipworm infection (trichuriasis) is caused by the roundworm *Trichuris trichiura*. Whipworm infection is very common in the tropics, where poor sanitation and a warm, moist climate provide the relevant condition for eggs to incubate and develop in the soil. The parasite is acquired by swallowing food that contains eggs that have been passed in the stool of an infected person and incubated in the soil. The larvae hatch in the small intestine, migrate to the large intestine, and embed themselves into the intestinal lining. Each larva grows into a worm that is about 4.5cm long. A severe whipworm infection can lead to abdominal pain, chronic diarrhea, weight loss, bleeding from the intestine, and anaemia. A whipworm infection is diagnosed by identifying eggs in stool samples examined under a microscope. This parasitic infection can be prevented by maintaining sanitary toilet facilities, good personal hygiene (namely hand washing), avoiding unwashed vegetables.

Albendazole or mebendazole are effective medications for treating the infection (WHO, 2004; Horton, 2000, Urbani and Albonico, 2003).

Figure 6.3 Life cycle of Trichuris trichura



The life cycle of *Trichuris trichiura*:

- The adult worms (approximately 4cm in length) live in the cecum and ascending colon;
- Female worms in the cecum shed between 3,000 and 20,000 eggs per day;
- The unembryonated eggs are passed with the stool;
- In the soil they embryonate and become infective in 15 to 30 days;
- After ingestion (soil-contaminated hands or food), the eggs hatch in the small intestine, and release larvae that mature and establish themselves as adults in the colon.
- The adult worms are fixed in that location, with the anterior portions threaded into the mucosa.
- The females begin to oviposit 60 to 70 days after infection.
- The life span of the adults is about 1 year.

Source: CDC's Parasite & Health page about trichuriasis

6.5 Scabies

Scabies is a mite infestation that causes rashes and severe itching. It is caused by the mite *Sarcoptes scabiei*. The infestation spreads easily from person to person by physical contact. The mite tunnels in the uppermost layer of the skin and deposits eggs, which hatch several days later. It takes 4-6 weeks after infection for the allergic reaction to develop (Bockarie MJ et al., 1999). Usually, itching and the appearance of burrows are all that are needed to make a diagnosis of scabies. However, confirmation of the diagnosis can be made by taking a scraping from the bumps or burrows and examining it under a microscope to confirm the presence of mites, their eggs or their faeces. Ivermectin (Mectizan®) taken by mouth in two doses given a week apart is effective against severe infestations. Occasionally, the skin irritation and deep scratches lead to a bacterial infection, which may require antibiotics given by mouth (Carapetis et al., 1997; Glaziou et al., 1993).

The effect the two drugs, ivermectin (Mectizan®) and albendazole, used in Zanzibar for PELF at no cost and with successful distribution networks in place had on intestinal helminth and scabies infections was explored. The aim of the study was to examine the impact that the combined ivermectin (Mectizan®) and albendazole treatment, administered by the Zanzibar PELF annually to combat LF, had on children infected with STH or scabies.

6.6 Study on records of STH and Scabies at Health Facilities

To determine the added impact of MDA on other conditions a study was conducted by involving 50 primary health care units (PHCU) in the ten districts of Zanzibar by checking the trend of registered cases of STH and scabies during the six years period (2000–2005) at each selected heath facilities. In each district 5 PHCUs were randomly selected. All 50 PHCUs for both islands were surveyed to obtain data from the respective registers. Registers contain a list of

names, age, sex, complaint and treatment of each patient who visits the clinic. Six years data were collected (2000-2005). The data in 2000 was included as a baseline sample of the number of cases registered before MDA commenced.

6.6.1 Methodology

The PHCU sampled was decided randomly. Each of the ten regional districts on Zanzibar has several health facilities. Each facility was assigned a number and five facilities were randomly selected. For Unguja Island a total of 30 health facilities were sampled. While for Pemba Island in 20 health facilities were sampled.

After the PHCUs were chosen, permission was obtained from the Ministry of Health and Social Welfare, regional medical officers were notified, and the health facilities (PHCUs) were asked to prepare for the study. It was decided to extract data from the patient registers, listing name, age, sex, complaint, and treatment of each patient who visited the PHCU. Six years were surveyed (2000-2005). The year 2000 was included to collect a baseline sample of the number of cases before MDA was implemented. The five subsequent years after the initiation of the MDA were also examined.

Before the first visit to the health facilities, a data sheet was constructed to tabulate information to be taken from the patient registers (See Annex II). Each register for each year and each health facility was systematically examined by the same two individuals together to account for any human error that might occur. This was because each entry in the patient registers is handwritten by a doctor or nurse, often hurriedly. Having two individuals involved in the data analysis facilitated deciphering any illegible handwriting and prevented any omission or double counting. A pair of data extractors also provided a guideline for what conditions to count or to discard in the data set.

The data collected was divided into four age sets. These included birth to five years, 6-10 years, 11-15 years and 16-20 years of age. Though children from birth to five years are ineligible to receive the medication from the LF programme, they are included in the study to provide a baseline indicator for the prevalence of STH in untreated children. For this, we can obtain a measure of the transmission rates. Individuals under 20 years of age were chosen because they have long been the focus of past studies on STH infection rates. Also the majority of benefits from the treatment and prevention of these infections fall within the childhood population (Stephenson et al. 2000).

Guidelines were established for data collection within the patient registers. To calculate the number of STH cases treated, listings of worms, helminths, abdominal pain treated with albendazole, and any other afflictions in which mebendazole or albendazole were prescribed secondarily were counted. In cases of scabies and skin diseases, incidents of scabies, skin disease, rashes, and all afflictions treated with Scabex.

6.6.2 Location of health facilities

During the study, five PHCUs were chosen from each district of Unguja Island and Pemba Island as data collection areas. Each health facility selected caters for a wide range of geographical areas and population densities. The PHC Units selected were:

Unguja districts (Figure 6.4)

North 'A':	Kidoti, Mkokotoni, Kijini, Matemwe and Chaani Kubwa;
North 'B':	Fujoni, Bumbwini, Donge, Mahonda and Upenja;
Central:	Unguja Ukuu, Machui, Uzini, Mwera and Uroa;
South:	Muungoni, Paje, Kiz/Dimbani and Mtende ; Muyuni
West:	Matrekta, Kombeni , Selem, Kizimbani; Fuoni
Urban:	Rahaleo,Chumbuni, Kidongo Chekundu, Matarumbeta and Sebleni.

Pemba districts (Figure 6.5)

Micheweni:	Wingwi, Konde, Makangale, Tumbe and Kiuyu Maziwangombe;
Wete:	Jadida, Mzambarauni, Kiungoni, Minungwini, and Junguni;
Chake Chake:	Ziwani, Gombani, Wawi, Ndagoni and Pujini;
Mkoani:	Mtambile, Kengeja, Wambaa, Kiwani and Bogoa PHC Units.

Figure 6.4 Unguja Map showing PHC Units surveyed for STH and scabies (2000-2005)

Figure 6.5 Pemba Map showing PHC Units surveyed for STH and scabies (2000-2005)

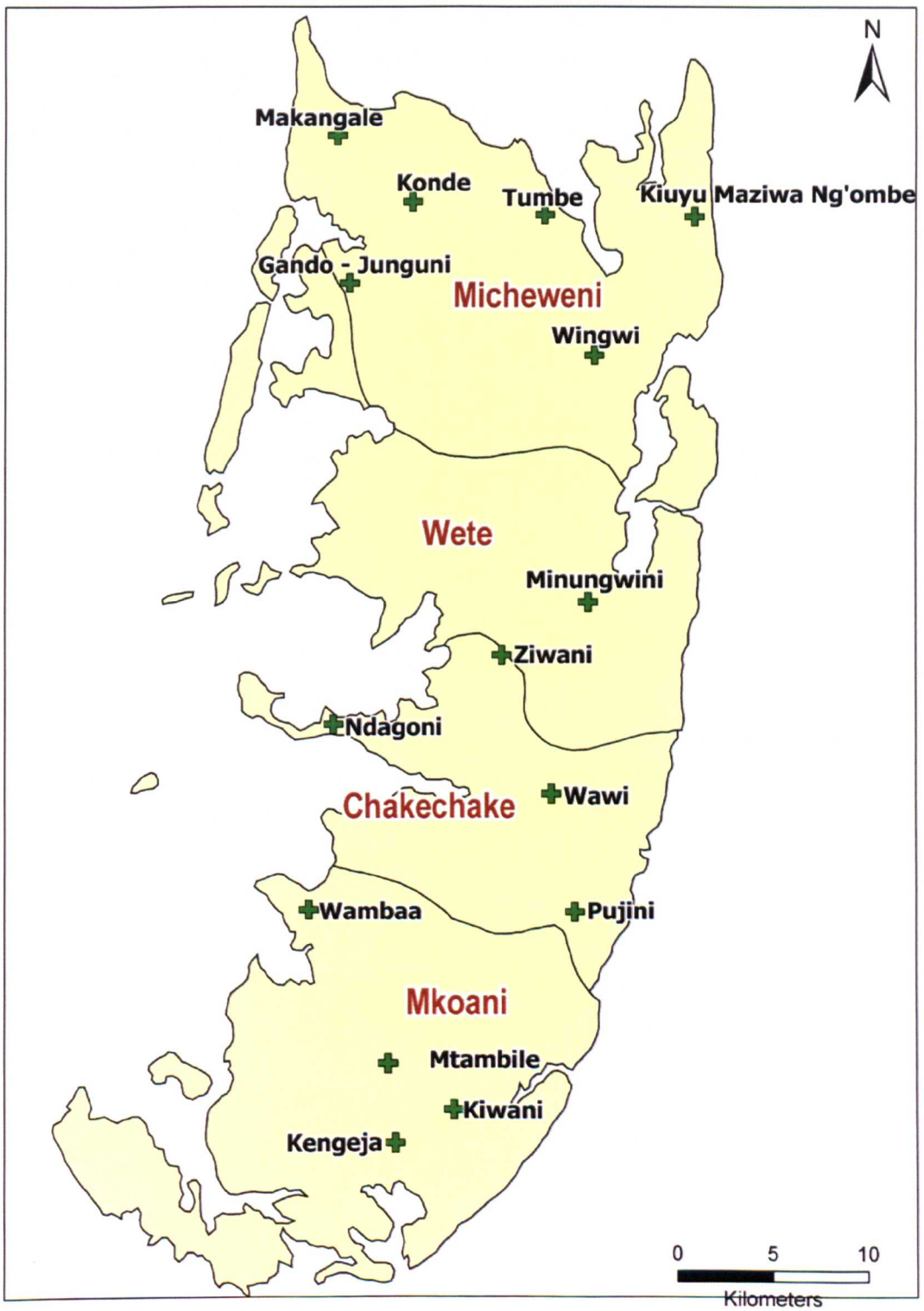


Figure 6.4 Unguja Map showing PHC Units surveyed for STH and scabies (2000-2005)

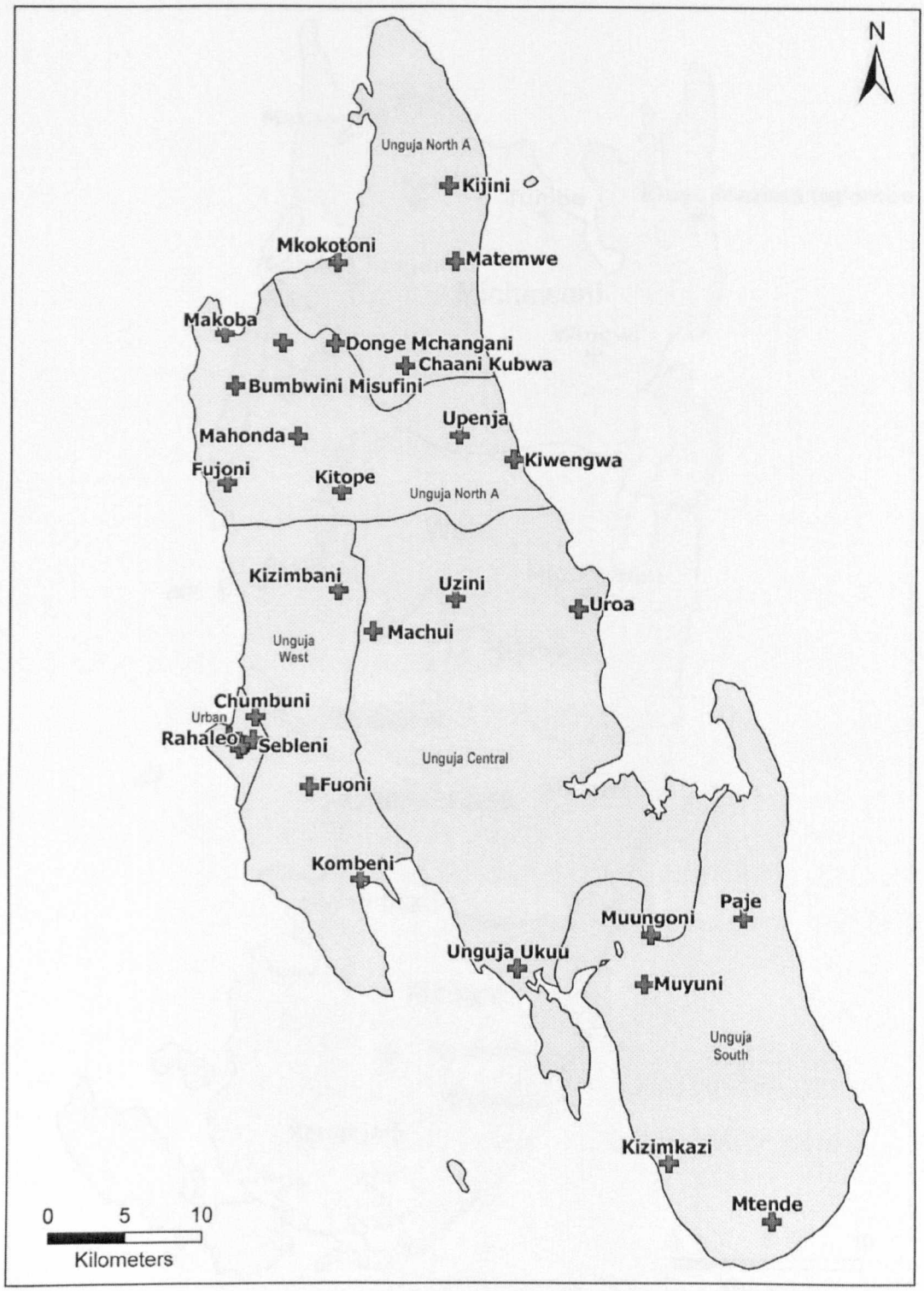
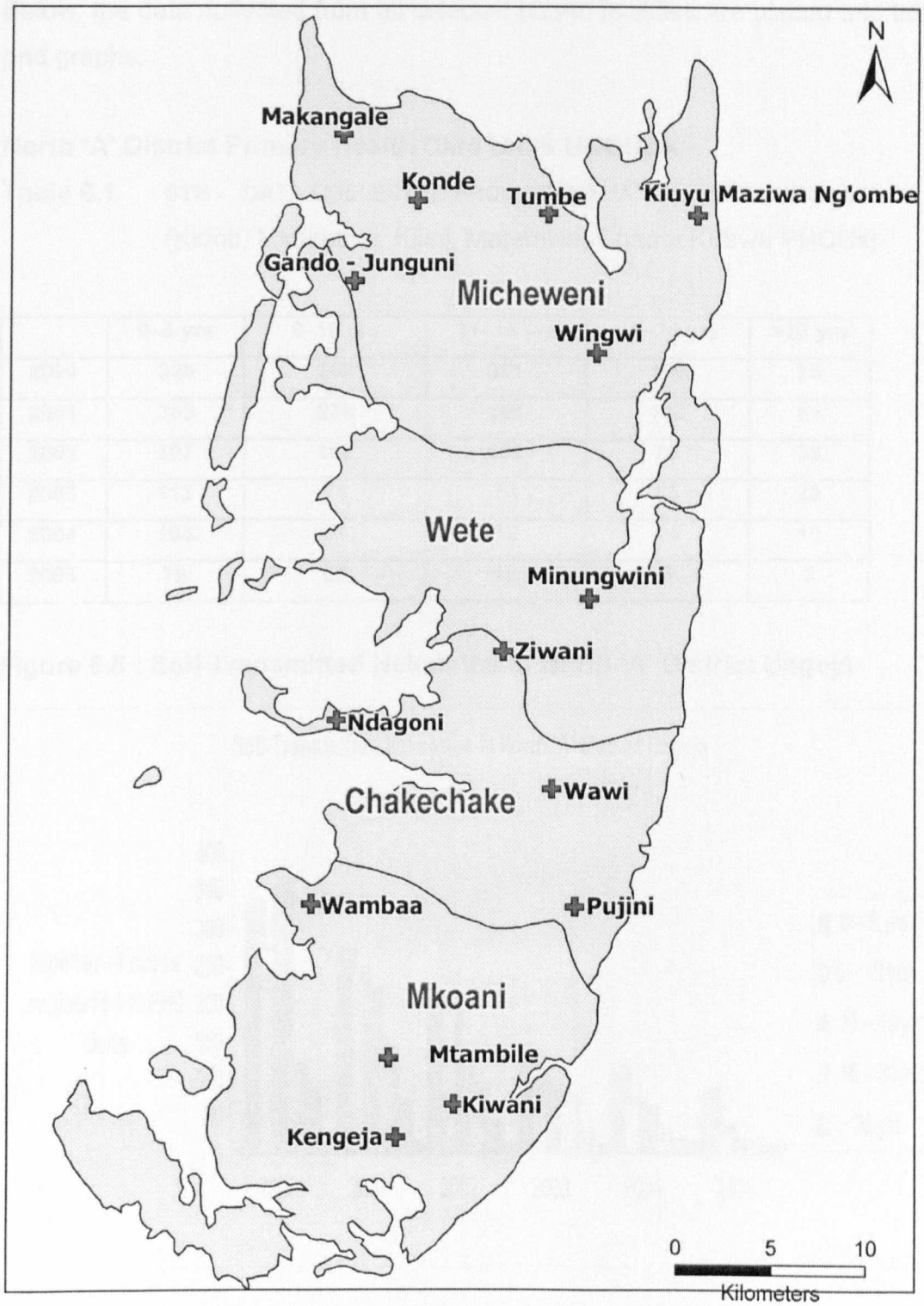


Figure 6.5 Pemba Map showing PHC Units surveyed for STH and scabies (2000-2005)



6.6.3 Results

Below, the data collected from all selected health facilities are placed into tables and graphs.

North 'A' District Primary Health Care Units UNGUJA

Table 6.1 STH - DATA COLLECTED FROM NORTH 'A' DISTRICT UNGUJA
(Kidoti, Mkokotoni, Kijini, Matemwe, Chaani Kubwa PHCUs)

	0–5 yrs	6–10 yrs	11–15 yrs	16–20 yrs	>20 yrs
2000	326	268	351	106	75
2001	260	236	207	133	61
2002	197	186	102	75	32
2003	113	81	73	65	23
2004	105	61	52	14	10
2005	75	25	10	5	3

Figure 6.6 : Soil-Transmitted Helminths in North 'A' District Unguja

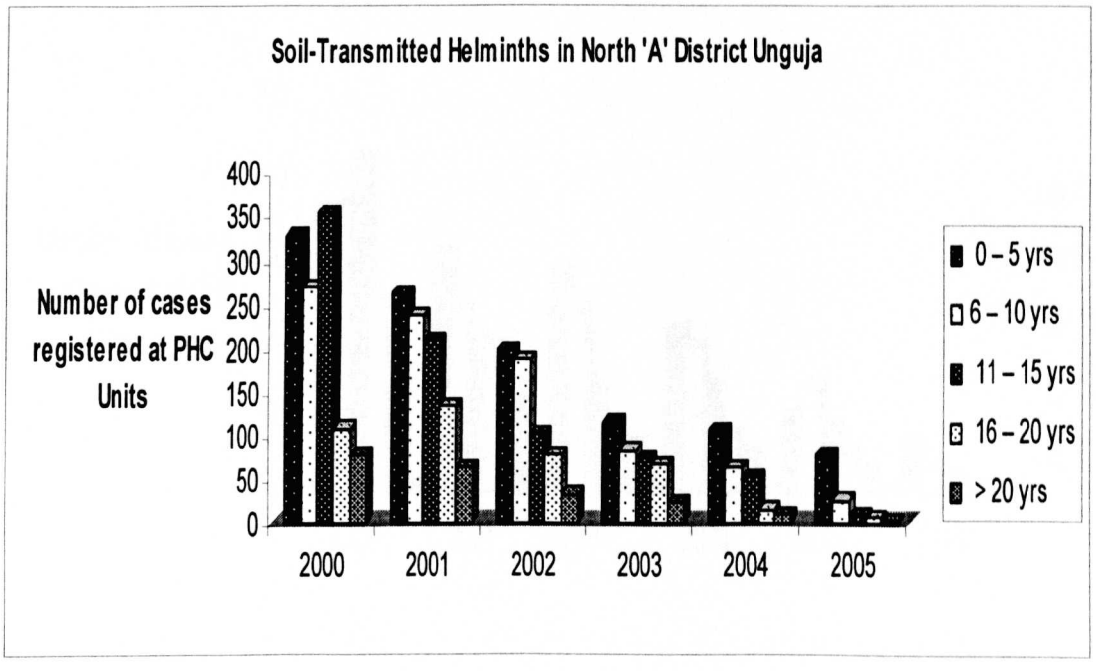
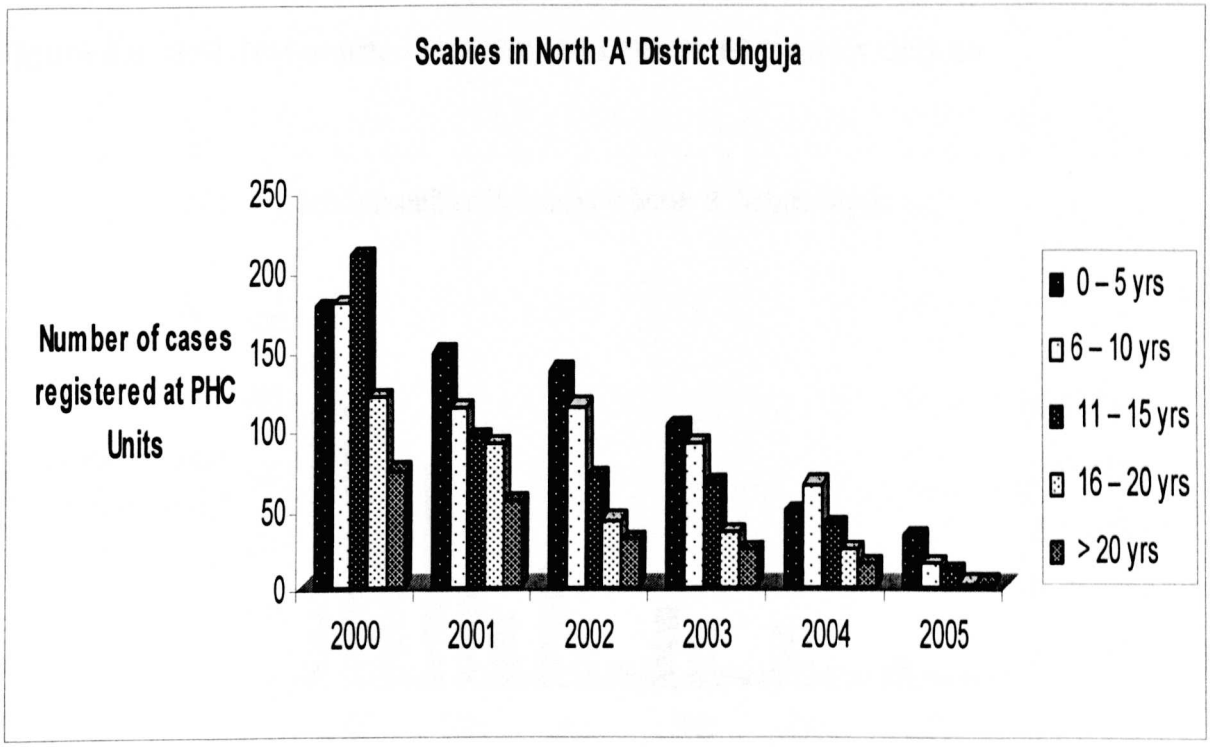


Table 6.2 SCABIES – DATA COLLECTED FROM NORTH 'A' DISTRICT UNGUJA (Kidoti, Mkokotoni, Kijini, Matemwe, Chaani Kubwa PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	176	178	209	119	73
2001	146	111	94	90	54
2002	135	113	70	42	30
2003	101	90	65	35	23
2004	48	64	38	23	15
2005	32	15	10	2	2

Figure 6.7 Scabies in North 'A' District Unguja



North 'B' District Primary Health Care Units Unguja Island

Table 6.3 STH - DATA COLLECTED FROM NORTH 'B' DISTRICT UNGUJA (Fujoni, Bumbwini, Donge, Mahonda, Upenja PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	452	381	279	184	163
2001	300	134	139	95	91
2002	152	65	31	20	16
2003	93	41	25	11	7
2004	68	21	11	7	3
2005	33	13	8	4	2

Figure 6.8: Soil-Transmitted Helminths in North 'B' District Unguja

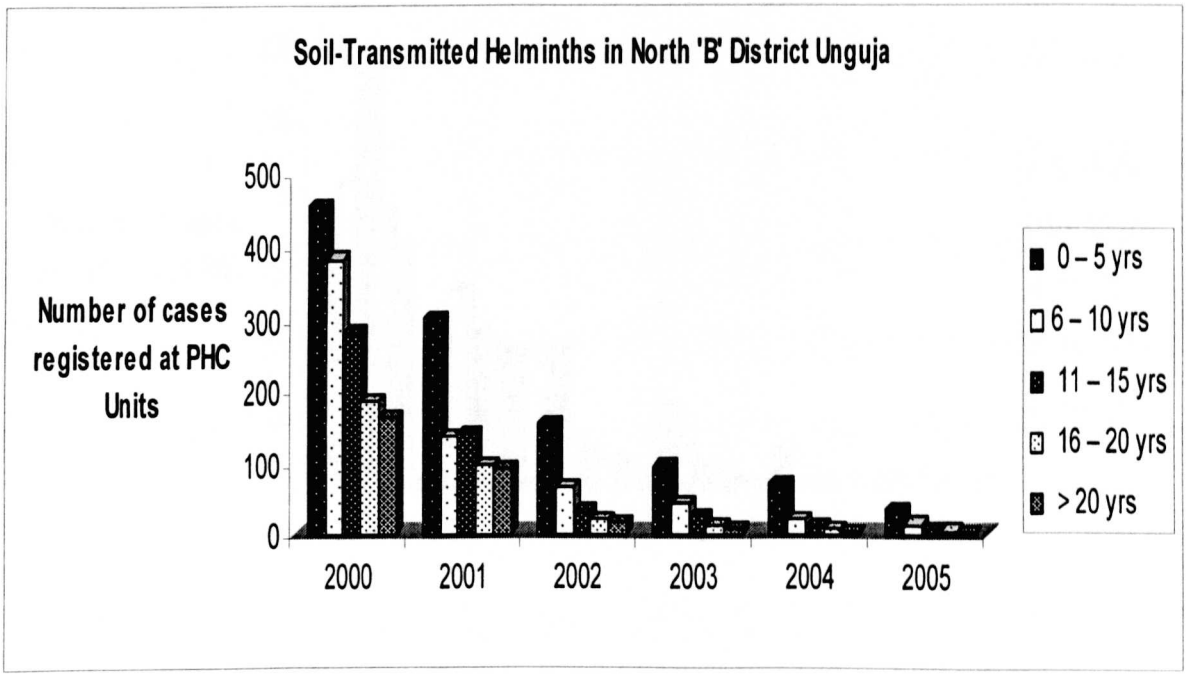
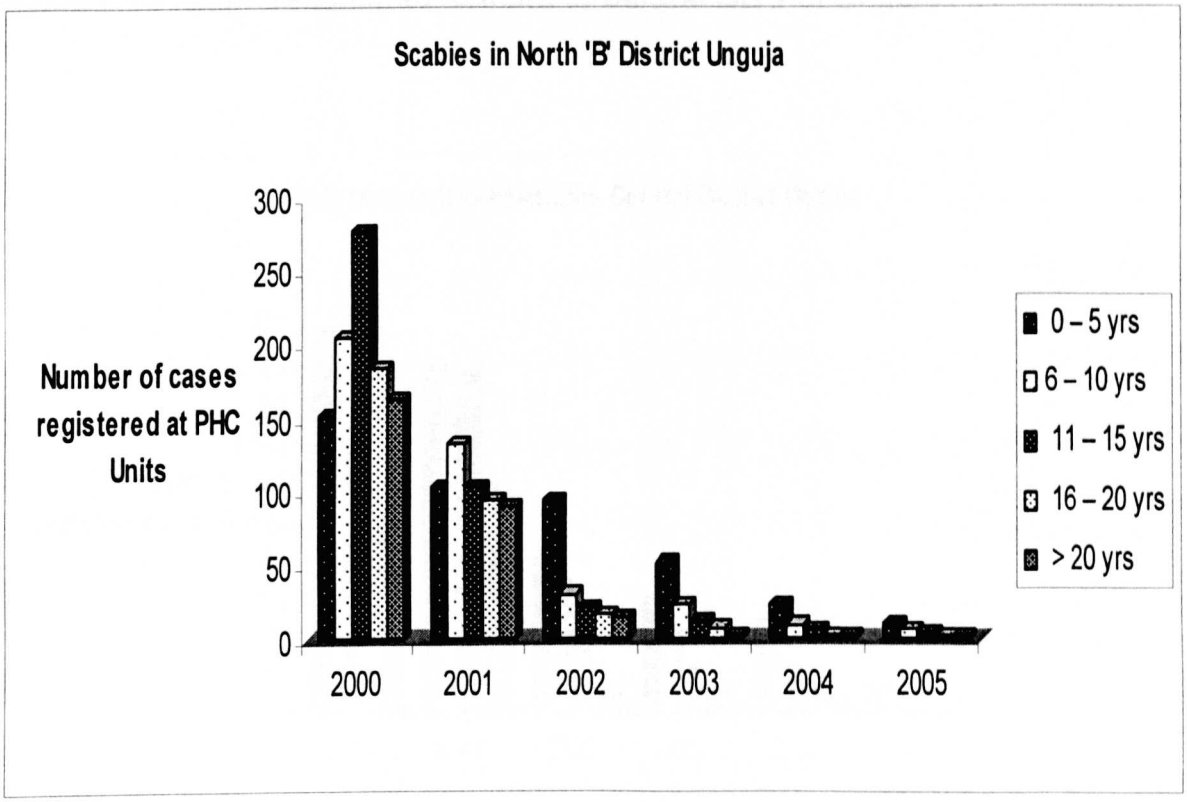


Table 6.4 SCABIES – DATA COLLECTED FROM NORTH 'B' DISTRICT UNGUJA (Fujoni, Bumbwini, Donge, Mahonda, Upenja PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	152	205	279	184	163
2001	103	134	104	95	91
2002	95	31	21	18	16
2003	52	23	12	8	3
2004	24	10	6	3	2
2005	11	6	4	2	2

Figure 6.9: Scabies in North 'B' District Unguja



Central District Primary Health Care Units Unguja Island

Table 6.5 STH DATA COLLECTED FROM CENTRAL DISTRICT UNGUJA (Unguja Ukuu, Machui, Uzini, Mwera, Uroa PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20 yrs
2000	196	138	115	100	78
2001	176	143	171	116	56
2002	78	65	42	23	15
2003	56	41	21	12	9
2004	45	23	15	8	6
2005	13	9	4	2	0

Figure 6.10 Soil-Transmitted Helminths Central District Unguja

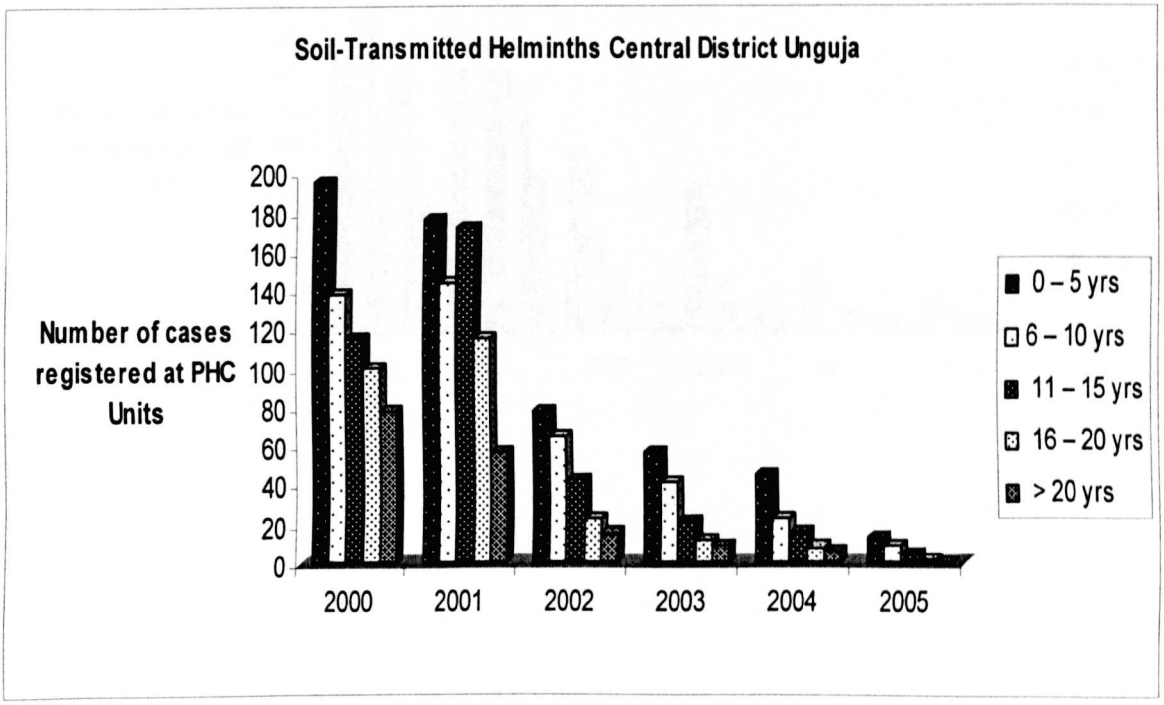
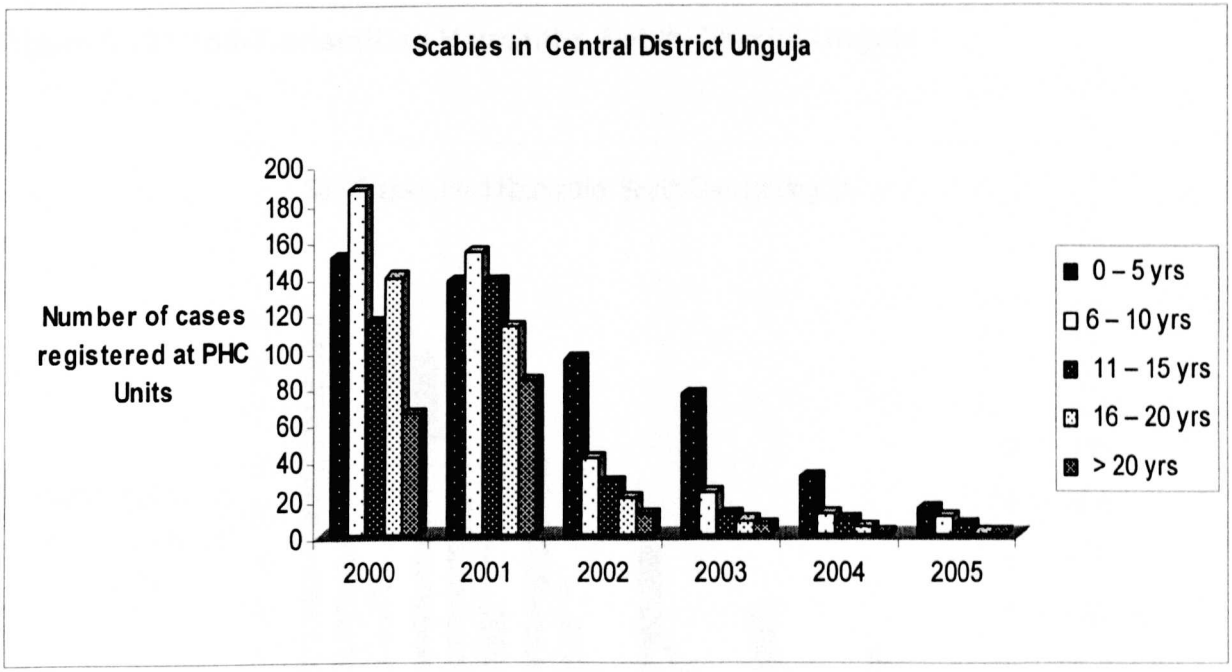


Table 6.6 SCABIES – DATA COLLECTED FROM CENTRAL DISTRICT UNGUJA (Unguja Ukuu, Machui, Uzini, Mwera, Uroa PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	150	187	116	140	65
2001	138	153	138	113	83
2002	95	41	28	20	12
2003	76	23	11	8	6
2004	31	12	8	4	2
2005	14	10	6	1	1

Figure 6.11: Scabies in Central District Unguja



South District Primary Health Care Units Unguja Island

Table 6.7 STH DATA COLLECTED FROM SOUTH DISTRICT UNGUJA

(Muungoni, Paje, Kiz/Dimbani, Mtende, Muyuni PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	90	57	43	36	33
2001	83	65	51	43	29
2002	60	34	25	16	10
2003	63	35	20	15	9
2004	30	16	9	5	3
2005	21	11	4	1	1

Figure 6.12: Soil-Transmitted Helminths South District Unguja

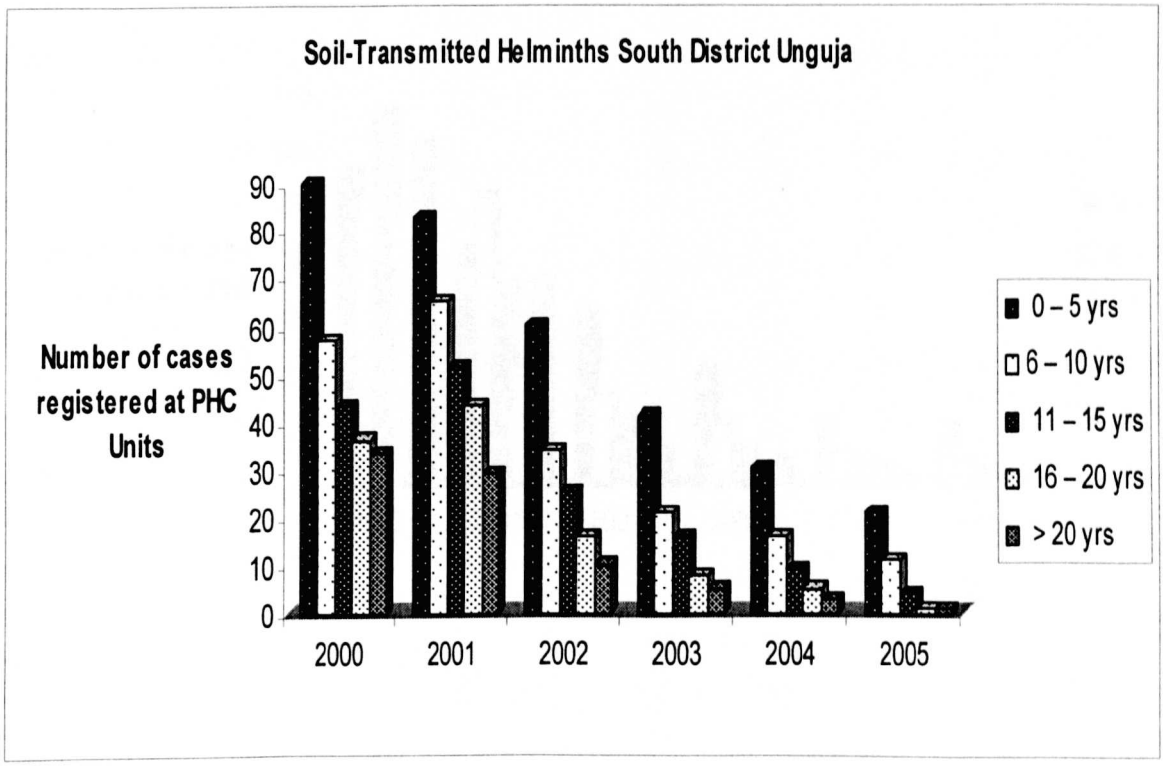
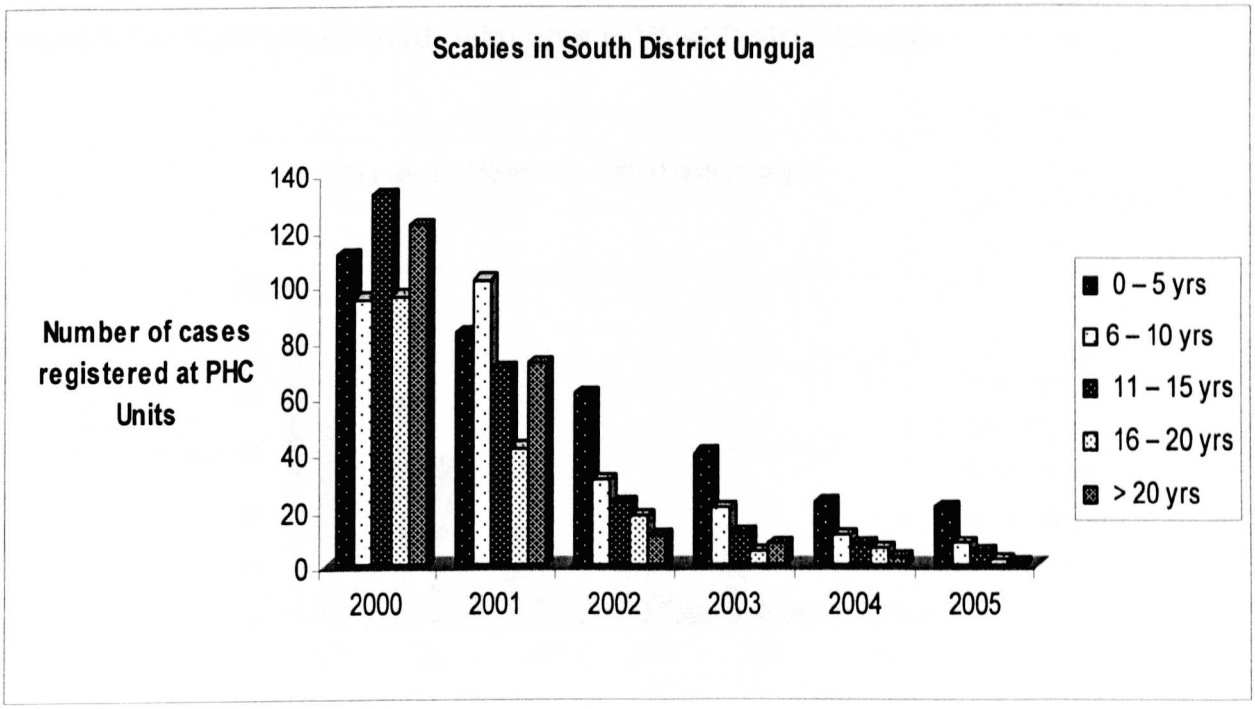


Table 6.8 SCABIES – DATA COLLECTED FROM SOUTH DISTRICT UNGUJA

(Muungoni, Paje, Kiz/Dimbani, Mtende, Muyuni PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	111	95	133	96	122
2001	83	102	70	42	72
2002	61	31	23	18	11
2003	40	21	12	5	8
2004	23	11	8	6	3
2005	21	8	5	2	1

Figure 6.13 Scabies in South District Unguja



West District Primary Health Care Units Unguja Island

Table 6.9 STH DATA COLLECTED FROM WEST DISTRICT UNGUJA

(Matrekta, Kombeni , Selem, Kizimbani, Fuoni PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	298	171	176	114	53
2001	194	110	142	95	20
2002	78	52	31	20	16
2003	65	41	20	12	9
2004	55	20	13	8	6
2005	32	10	8	6	3

Figure 6.14 Soil-Transmitted Helminths in West District Unguja

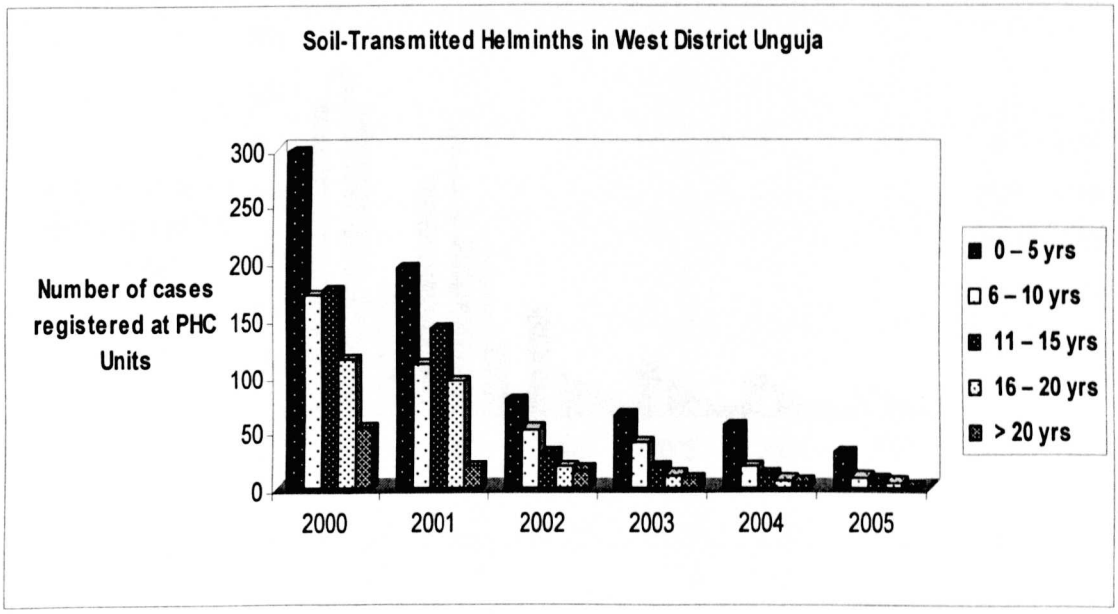
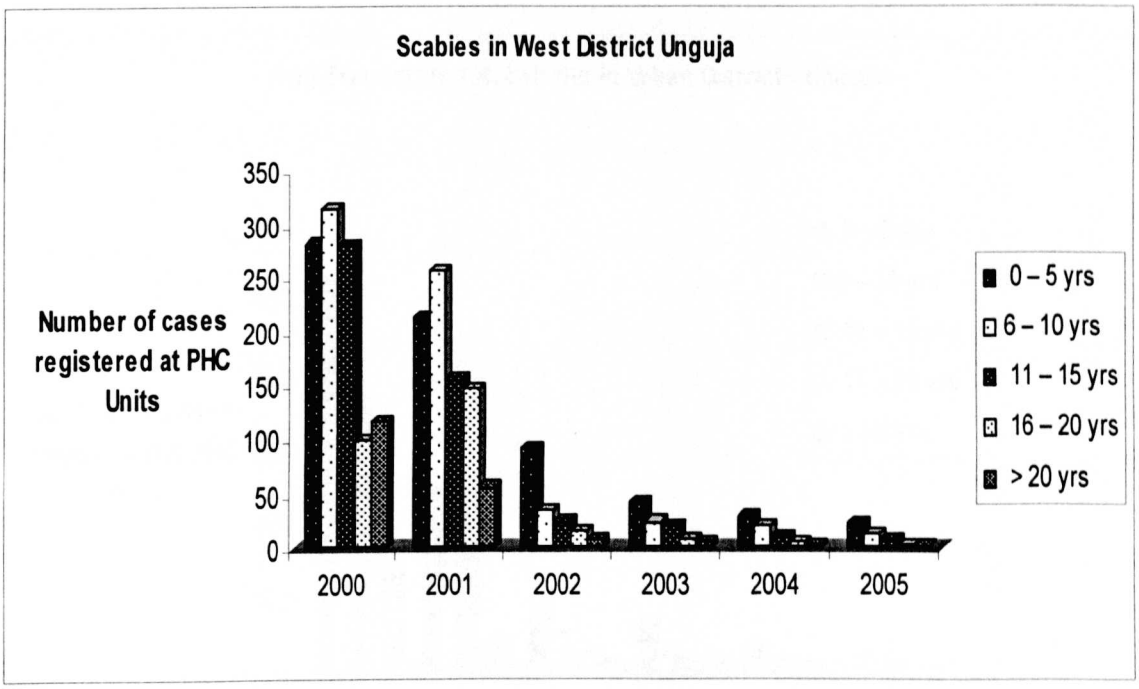


Table 6.10 SCABIES DATA COLLECTED FROM WEST DISTRICT UNGUJA

(Matrekta, Kombeni , Selem, Kizimbani, Fuoni PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	282	316	280	99	117
2001	211	257	154	146	56
2002	92	35	24	15	8
2003	42	24	20	9	5
2004	29	20	11	6	4
2005	23	13	7	4	2

Figure 6.15 Scabies in West District Unguja



Urban District Primary Health Care Units Unguja Island

Table 6.11 STH DATA COLLECTED FROM URBAN DISTRICT UNGUJA
(Rahaleo, Chumbuni, Kidongo Chekundu, Matarumbeta, Sebleni PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	519	370	366	175	145
2001	238	113	238	29	42
2002	85	43	21	18	12
2003	65	20	12	7	9
2004	35	12	8	7	5
2005	21	9	4	3	1

Figure 6.16 Soil-Transmitted Helminths in Urban District Unguja

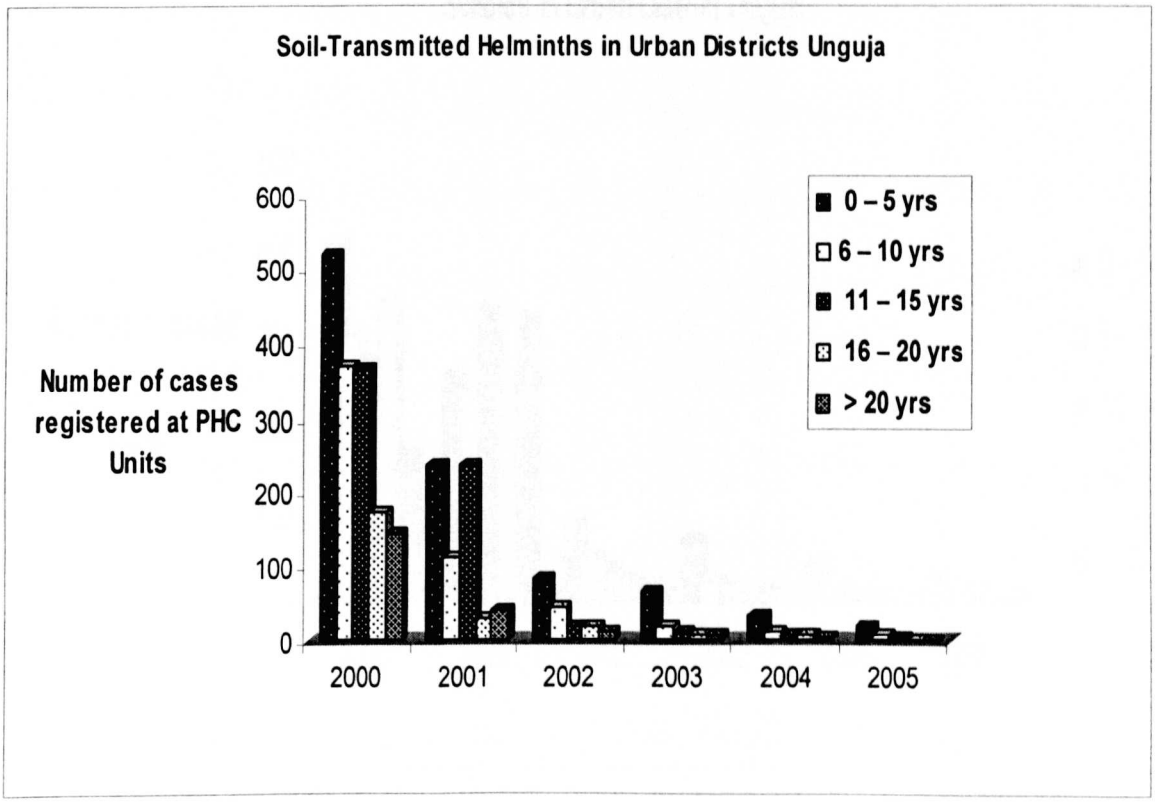
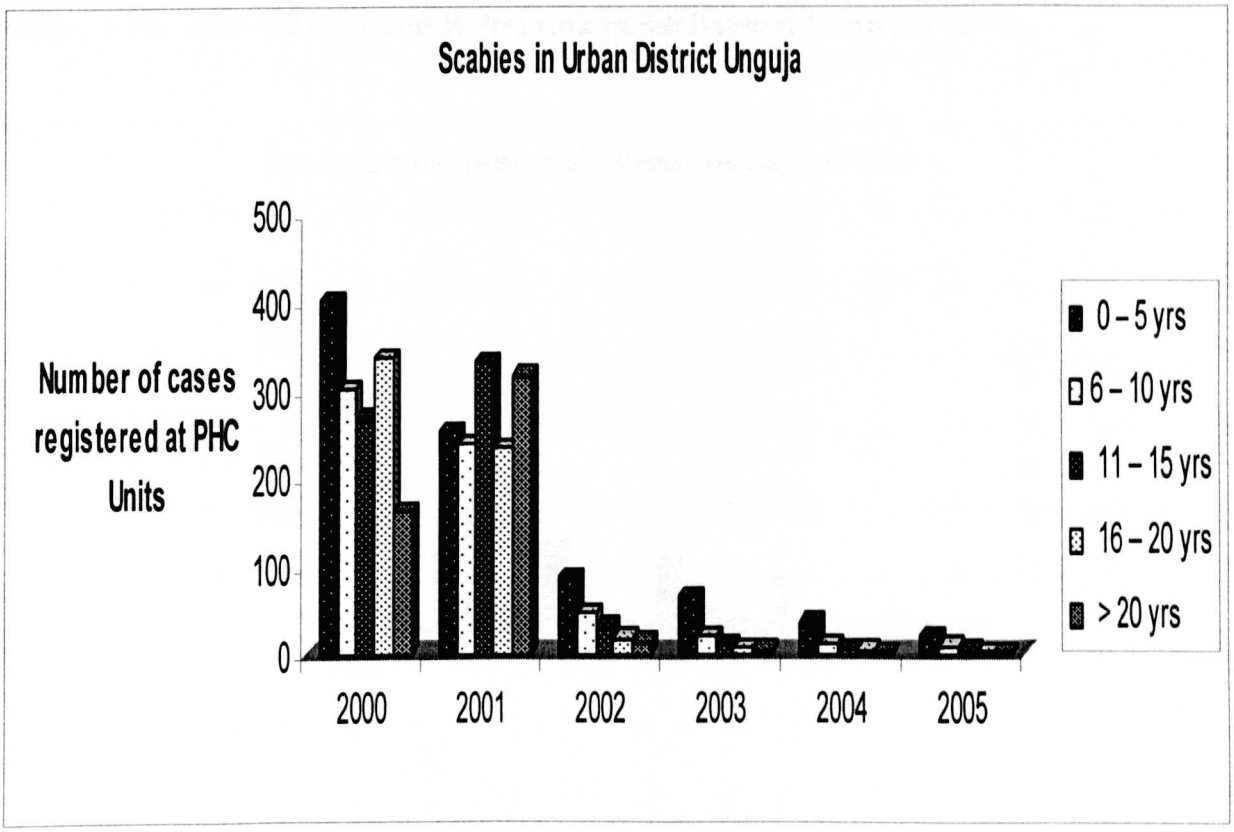


Table 6.12 SCABIES DATA COLLECTED FROM URBAN DISTRICT UNGUJA

(Rahaleo, Chumbuni, Kidongo Chekundu, Matarumbeta, Sebleni PHCUs)

	0 – 5 yrs	6 – 10 yrs	11 – 15 yrs	16 – 20 yrs	> 20 yrs
2000	402	300	265	335	163
2001	249	238	329	232	314
2002	85	46	31	18	13
2003	65	20	12	7	5
2004	35	12	8	5	3
2005	21	9	4	3	1

Figure 6.17 Scabies in Urban District Unguja



Micheweni District Primary Health Care Units Pemba Island

Table 6.13 STH DATA COLLECTED FROM MICHEWENI DISTRICT PEMBA
(Wingwi, Konde, Makangale, Tumbe, Kiuyu Maziwangombe PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20 yrs
2000	519	370	366	175	145
2001	238	113	238	29	25
2002	144	40	23	18	11
2003	113	22	20	11	8
2004	82	17	12	8	5
2005	29	8	5	2	2

Figure 6.18 Soil-Transmitted Helminths in Micheweni District Pemba

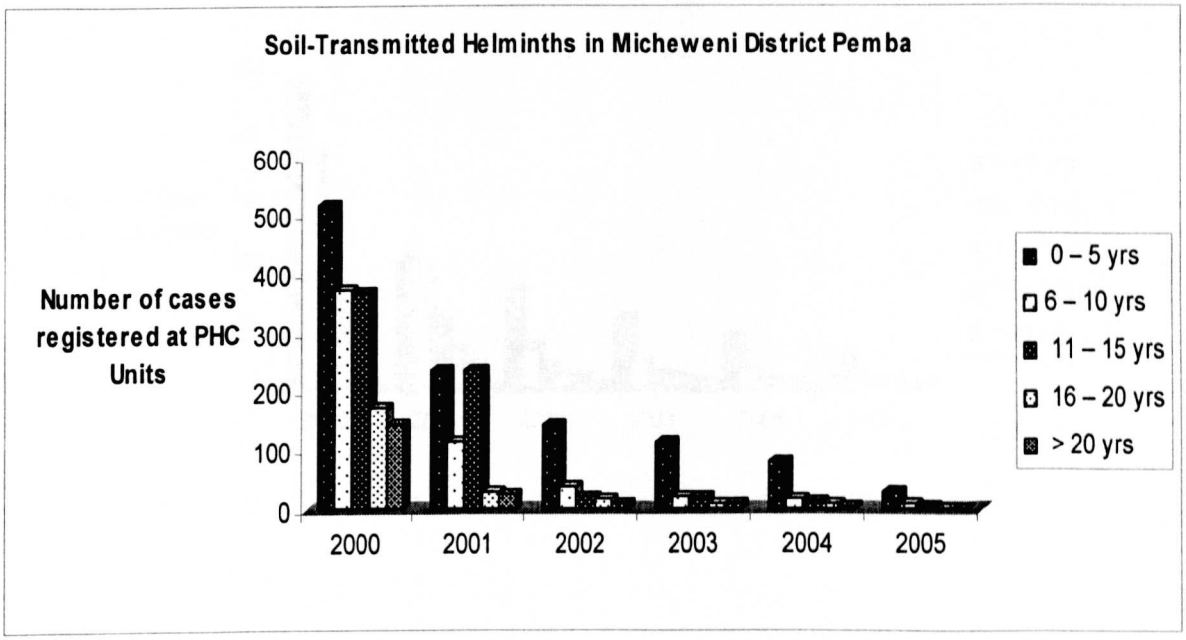
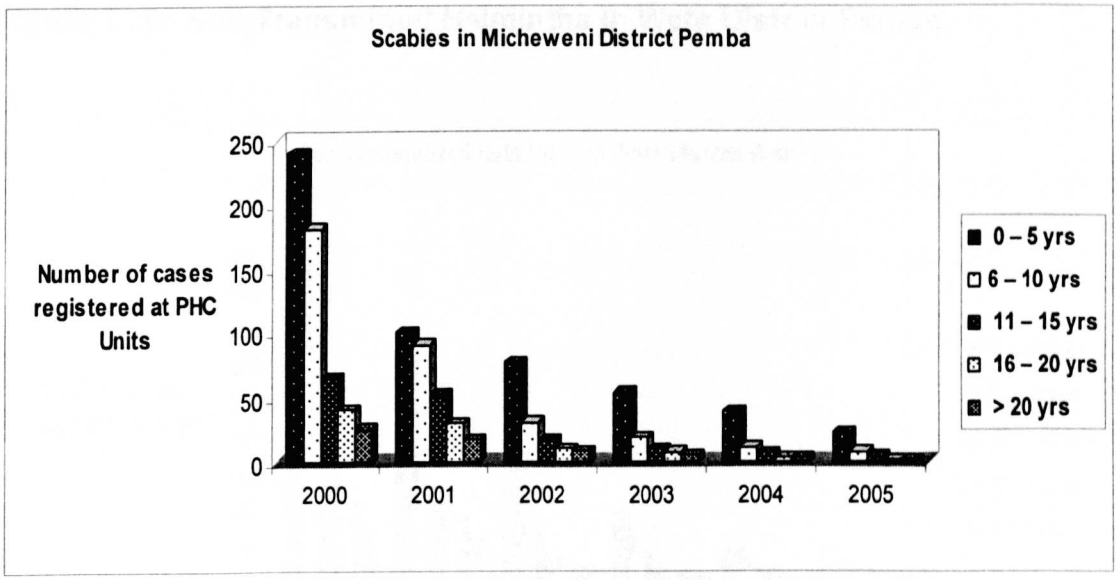


Table 6.14 SCABIES DATA COLLECTED FROM MICHEWENI DISTRICT PEMBA

(Wingwi, Konde, Makangale, Tumbe, Kiuyu Maziwangombe PHCUs)

	0 – 5 yrs	6 – 10 yrs	11 – 15 yrs	16 – 20 yrs	> 20 yrs
2000	241	182	65	41	26
2001	101	91	52	30	18
2002	78	31	18	11	9
2003	54	20	11	8	6
2004	39	12	7	4	4
2005	23	8	5	2	2

Figure 6.19 Scabies in Micheweni District Pemba



Wete District Primary Health Care Units Pemba Island

Table 6.15 STH DATA COLLECTED FROM WETE DISTRICT PEMBA
(Jadida, Mzambarauni, Kiungoni, Minungwini, Gando- Junguni PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	435	320	186	101	62
2001	312	128	113	82	54
2002	152	65	31	20	16
2003	93	35	23	11	7
2004	42	21	10	7	3
2005	25	13	7	4	2

Figure 6.20 Soil-Transmitted Helminths in Wete District Pemba

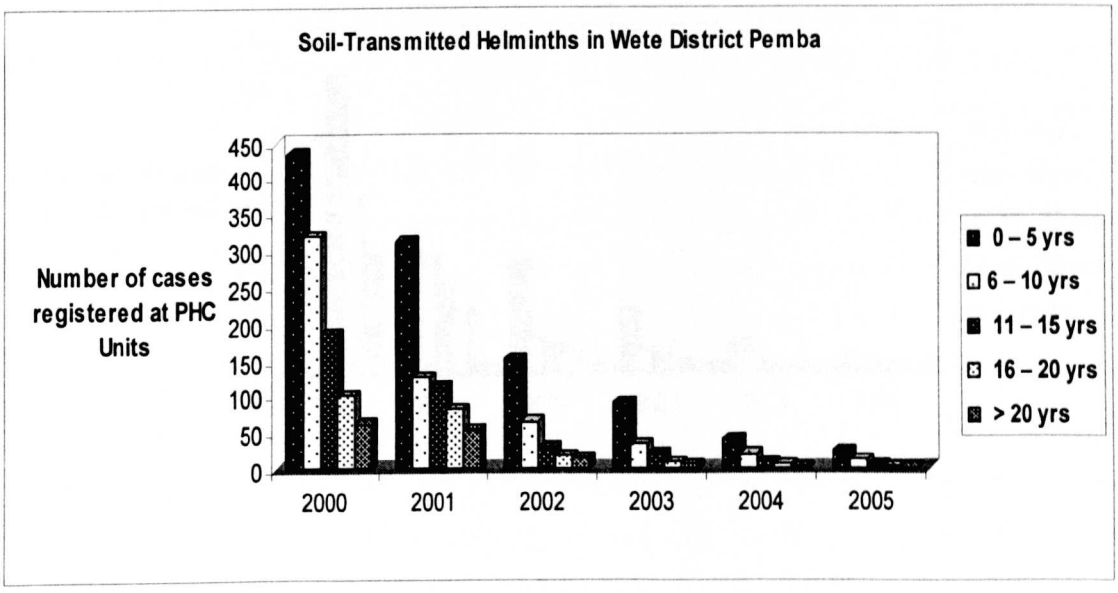
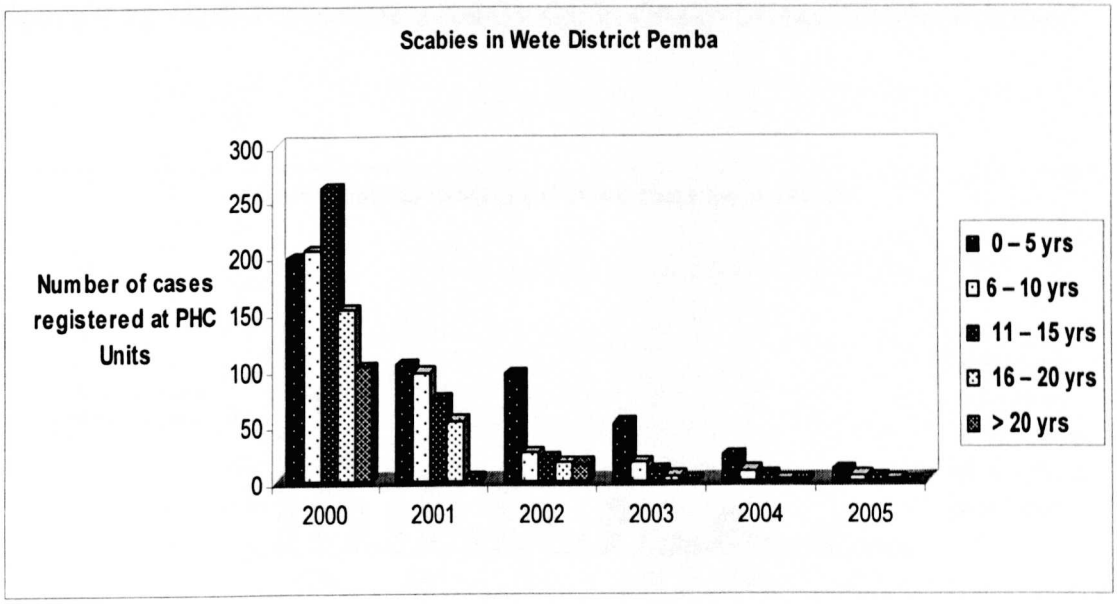


Table 6.16 SCABIES DATA COLLECTED FROM WETE DISTRICT PEMBA

(Jadida, Mzambarauni, Kiungoni, Minungwini, Gando- Junguni PHCUs)

	0 – 5 yrs	6 – 10 yrs	11 – 15 yrs	16 – 20 yrs	> 20 yrs
2000	198	205	261	152	101
2001	103	96	73	54	4
2002	95	25	21	18	16
2003	52	18	10	6	3
2004	24	10	6	3	2
2005	11	6	4	2	1

Figure 6.21 Scabies in Wete District Pemba



Chake Chake District Primary Health Care Units Pemba Island

Table 6.17 STH DATA COLLECTED FROM CHAKE CHAKE DISTRICT PEMBA

(Ziwani, Gombani, Wawi, Ndagoni, Pujini PHC Us)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	251	171	141	114	53
2001	194	132	122	95	20
2002	79	50	31	20	14
2003	61	35	20	13	9
2004	45	20	13	8	6
2005	30	10	8	5	3

Figure 6.22 Soil-Transmitted Helminths in Chake Chake District Pemba

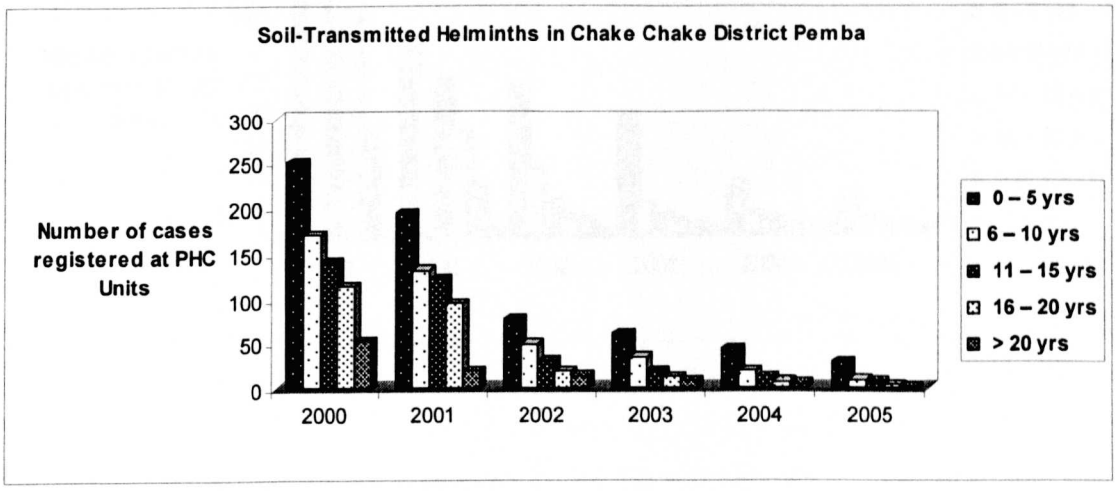
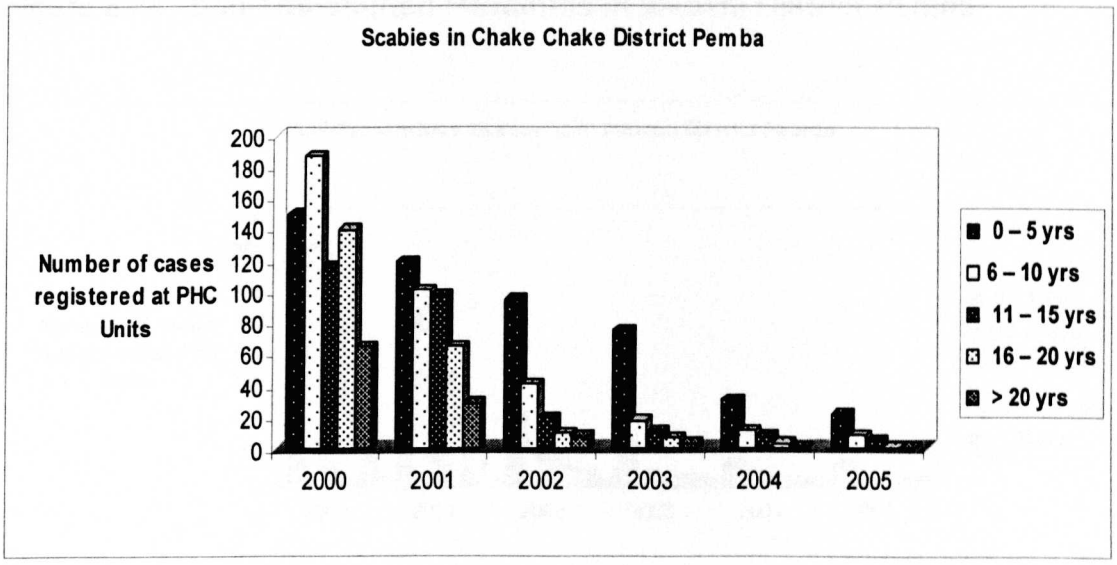


Table 6.18 SCABIES – DATA COLLECTED FROM CHAKE CHAKE DISTRICT PEMBA

(Ziwani, Gombani, Wawi, Ndagoni, Pujini PHCUs)

	0 – 5 yrs	6 – 10 yrs	11 – 15 yrs	16 – 20 yrs	> 20 yrs
2000	150	187	116	140	65
2001	120	101	98	65	29
2002	95	41	20	10	8
2003	76	18	11	7	4
2004	31	12	8	4	2
2005	22	9	6	1	1

Figure 6.23 Scabies in Chake Chake District Pemba



Mkoani District Primary Health Care Units Pemba Island

Table 6.19 STH DATA COLLECTED FROM MKOANI DISTRICT PEMBA

(Mtambile, Kengeja, Wambaa, Kiwani, Bogoa PHCUs)

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	334	351	245	106	78
2001	252	225	158	132	60
2002	101	51	31	23	18
2003	65	21	15	11	9
2004	31	12	9	5	3
2005	27	7	4	2	2

Figure 6.24 Soil-Transmitted Helminths in Mkoani District Pemba

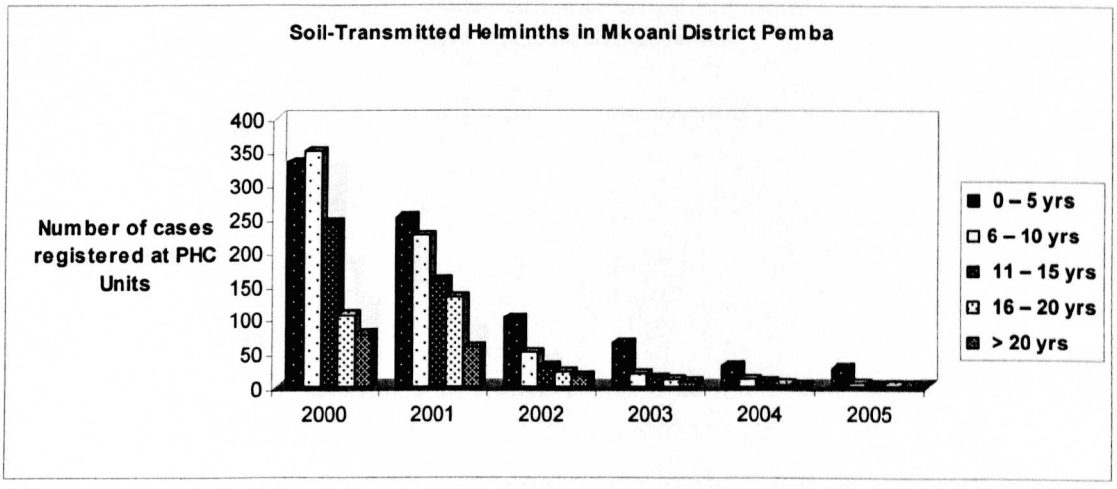
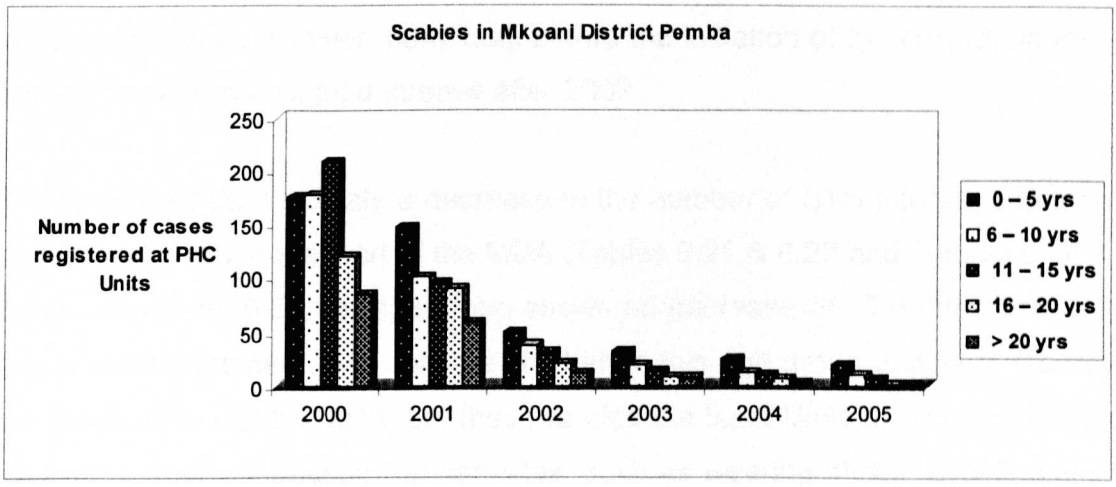


Table 6.20 SCABIES DATA COLLECTED FROM MKOANI DISTRICT PEMBA

(Mtambile, Kengeja, Wambaa, Kiwani, Bogoa PHCUs)

	0 – 5 yrs	6 – 10 yrs	11 – 15 yrs	16 – 20 yrs	> 20 yrs
2000	176	178	209	120	85
2001	148	101	95	90	58
2002	49	38	31	21	13
2003	32	20	15	9	8
2004	25	13	11	7	4
2005	20	11	7	2	2

Figure 6.25 Scabies in Mkoani District Pemba



6.7 Discussion

The soil-transmitted helmithiasis (STH) and scabies results in all ten districts of Zanzibar showed a gradual decrease in cases registered at the health facilities after the MDA in all age groups. Within the age group 0-5 years only those children who were five years received the drugs. However, in this group a decline in cases of both STH and scabies was noticed after the MDA rounds.

The combined data from the eligible 50 health facilities in this study showed a decrease in the occurrence of STH within all age groups eligible who received drugs during the MDA. The prevalence of scabies shows both decreases and increases over the study period, with the total number of cases being lower today than when the MDA started in 2001.

When only those age groups eligible to receive the drugs from the LF programme were examined in an aggregate over the last five years, a clear decrease is shown in the prevalence of STH. In addition, the total number of scabies infections is lower today than before the initiation of the LF programme, though there was a slight decrease after 2002.

The combined data indicate a decrease in the number of STH infections treated by age group since the start of the MDA (Tables 6.21 & 6.22 and Figures 6.26 & 6.27). However, 0-5 year age group shows no decrease of STH infections, but this is to be expected. Not only are children in this age group unable to receive the medication via the MDA, but they are also the least likely to take preventive measures from contracting the parasites, such as wearing shoes, avoiding soil-contaminated foods, etc. All eligible recipients of the drugs are found in the age groups where decrease occurs.

Table 6.21 STH Combined data from 30 PHCUs in Unguja

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	1881	1385	1330	715	547
2001	1251	801	948	511	299
2002	650	445	252	172	101
2003	455	259	171	122	66
2004	388	153	108	49	33
2005	195	77	38	21	10

Figure 6.26 Soil-Transmitted Helminths in Unguja (2000-2005)

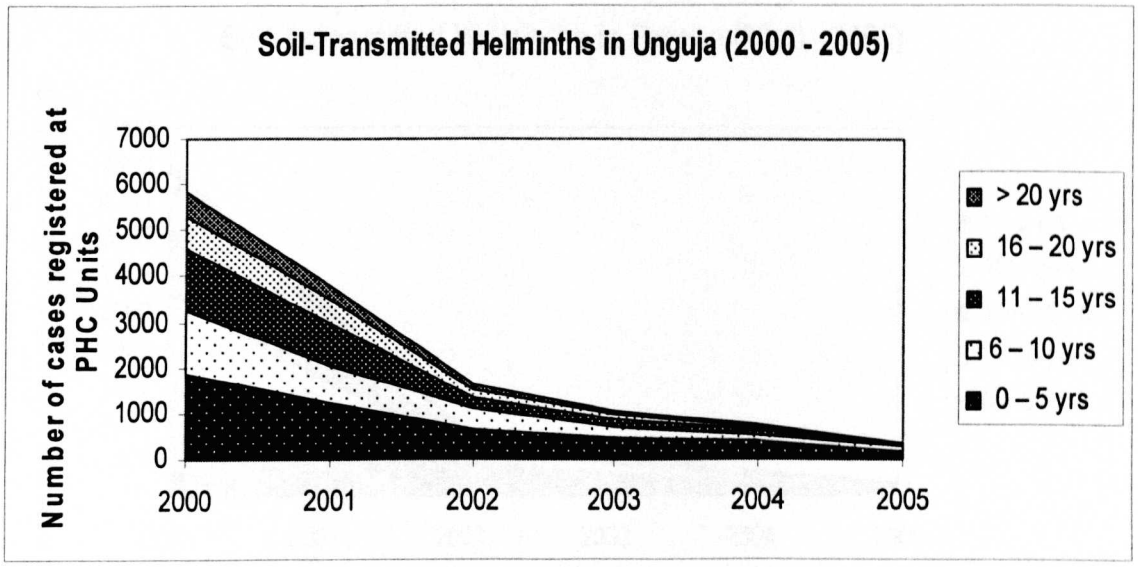


Table 6.22 STH Combined data from 30 PHCUs in Pemba

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	1539	1212	938	496	338
2001	996	598	631	338	159
2002	476	206	116	81	59
2003	332	113	78	46	33
2004	200	70	44	28	17
2005	111	38	24	13	9

Figure 6.27 Soil-Transmitted Helminths in Pemba (2000-2005)

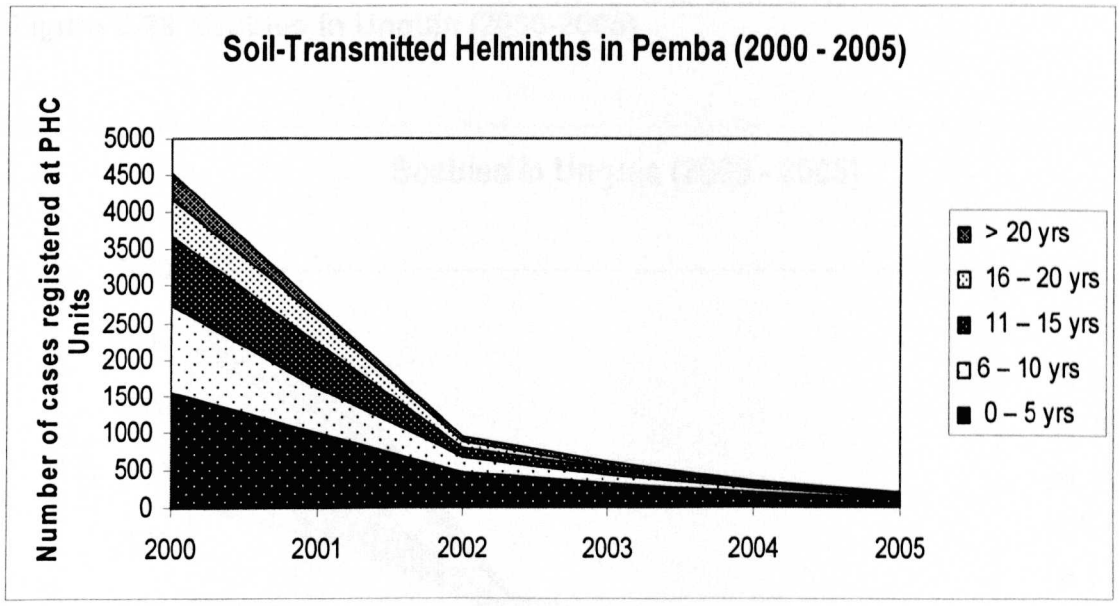


Table 6.23 Scabies combined data from 30 PHCUs in Unguja

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	1273	1281	1282	973	703
2001	930	995	889	718	670
2002	563	297	197	131	90
2003	376	201	132	72	50
2004	190	129	79	47	29
2005	122	61	36	14	9

Figure 6.28 Scabies in Unguja (2000-2005)

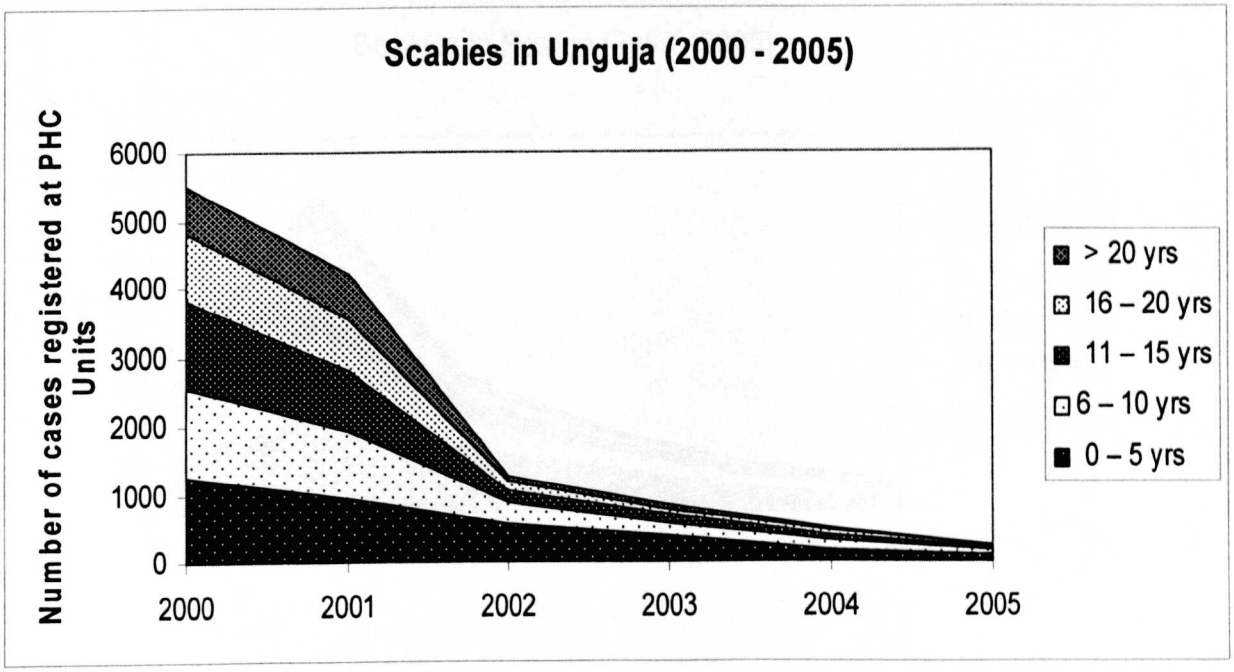
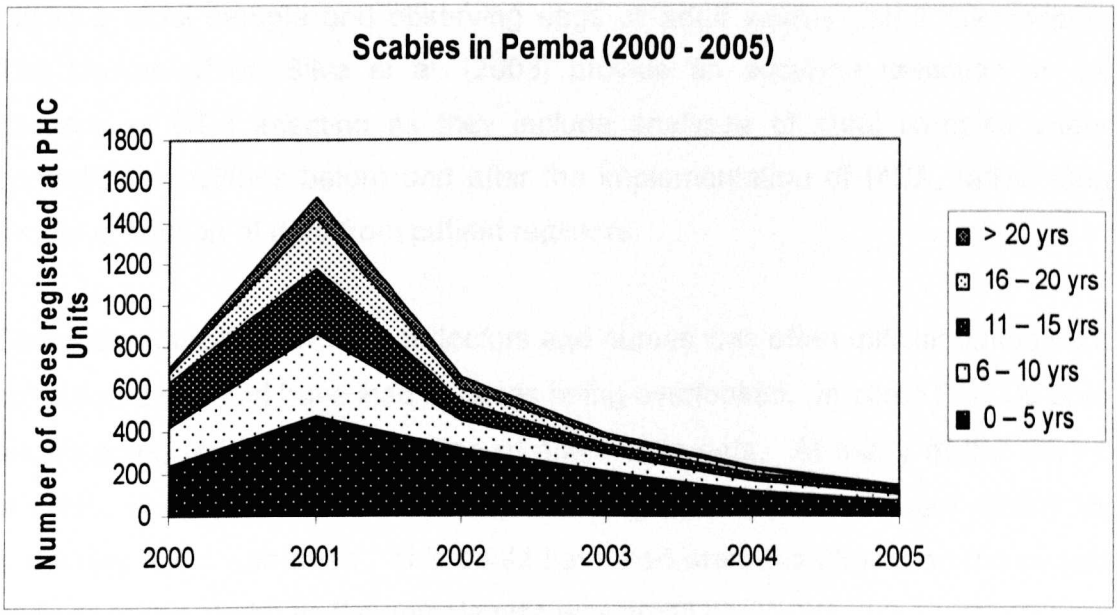


Table 6.24 Scabies combined data from 20 PHCUs in Pemba

	0–5yrs	6–10yrs	11–15yrs	16–20yrs	>20yrs
2000	241	182	209	41	26
2001	472	389	318	239	109
2002	317	135	90	60	46
2003	214	76	47	30	21
2004	119	47	32	18	12
2005	76	34	22	7	6

Figure 6.29 Scabies in Pemba (2000 – 2005)



As with the figure of the prevalence of STH by age group, this chart (Figure 6.29) shows a slight decrease in age groups in scabies infections treated. Only one age group (6-10 years) from those eligible to participate in MDA shows a slight decrease in the number of scabies infestations treated at the clinics. The cause behind this is unknown.

Similarly, de Silva, et al. (2003) in Sri Lanka also showed only a slight decrease in the overall intensity of STH infection, though their results indicate that over the lifetime of the filariasis control programme there, a further reduction or possible elimination could be expected. This proves that albendazole treatment of any kind can interrupt the transmission rate of helminths.

The study findings reported are all subject to human error on many levels. Often clinics are overcrowded and conditions are treated at first glance. In all of the health facilities, clinical symptoms are the first line for diagnosing helminth infections. Under normal circumstances, helminth infections are diagnosed by taking a stool sample and observing eggs or adult worms under microscope. The studies of de Silva et al. (2003) provide an accurate reflection of the intensity of STH infection as they include analyses of stool samples under controlled conditions before and after the implementation of MDA, rather than simple collection of data from patient registers.

Deciphering the handwriting of doctors and nurses was often difficult during data collection and could have lead to cases being overlooked. In some PHCUs poor bookkeeping led to the elimination of entire data sets. At many of the sites it was also unclear as to whether the patient registers contained every patient for every day clinic was open. This could have had dramatic effects on the overall findings of the study, as the sample size was small.

Another aspect that must be factored in is the possibility for natural cycles that may occur in the transmission of STH and scabies. The decrease in cases, if

any, may not be conclusively linked to the LF programme solely, though, it is likely that the MDA of ivermectin (Mectizan®) and albendazole did play a major role in the decrease of the infections. In any event, the MDA has not lead to an increase of any of these conditions.

CHAPTER VII

DISABILITY PREVENTION AND CONTROL

7.1 Introduction

Lymphatic filariasis is the second leading causes of chronic disability worldwide (WHO 1995). In its most obvious manifestations, LF causes enlargement of the leg or arm, the genitals, vulva and breasts (Krishna Kumari et al., 2005). Globally, there are an estimated 120 million affected persons, 25 million of whom have hydrocele, 15 million suffer from lymphoedema and elephantiasis mainly of the lower limbs, more than 90% of them with *Wuchereria bancrofti* (Michael et al. 1996; (Ravindran, 2003; WHO 2004).

In recent years, understanding of the clinical manifestations has become clearer following a series of new findings and the use of tools to study the lymphatics and examine the adult worm in the lymph nodes. However, the most significant discovery has been in the area of chronic disease, with understanding of the key role of bacterial infections in the occurrence of acute attacks and progression of the disease (WHO, 2004). The clinical features of LF are caused by the living adult worms, by inflammatory reactions resulting from the death of adult worms, by secondary bacterial infections occurring in damaged lymphatics or by microfilariae. The adult worms cause lymphangiectasia, even in asymptomatic persons (WHO, 2004). Dilatation of the lymphatic vessels eventually leads to lymphatic dysfunction and the chronic clinical manifestations, including lymphoedema and hydrocele. Death of adult worms causes an acute inflammatory response that is manifested clinically as acute filarial adenolymphangitis. Secondary bacterial infections cause an acute syndrome of dermatolymphangioadenitis, which occurs much more commonly than filarial adenolymphangitis and plays an important role in the progression of the disease. However, recent studies also have indicated a possible role for

Wolbachia in the pathogenesis of lymphoedema (Taylor, 2003; Debrah et al., 2006). The chronic urogenital manifestations include lymphoedema and elephantiasis, lymph scrotum, hydrocele, chylocele, and chyluria. The disease causes permanent and long-term disability, deforming, and damaging limbs and genitals causing not only malfunction but serious psycho-social consequences (WHO, 2004). Patients with LF face considerable physical, psychological and social disability (Krishna Kumari et al. 2005). Hydrocele, a condition that results from the accumulation of fluid in the tunica vaginalis of the scrotum, is the most commonly observed chronic presentation in *Wuchereria* endemic regions of the world (Ahorlu et al. 2001). Hydrocele is rarely fatal, and patients are usually not in pain, but it may carry grave social and economic consequences for those affected (Evans et al., 1993; Dreyer et al., 1997; Coreil et al., 1998; Ahorlu et al., 1999; Gyapong et al., 2000; Ahorlu et al., 2001; Perera et al., 2007). Studies in Ghana have revealed a negative impact of hydrocele in terms of work performance, sexual function and everyday social interaction and relationships (Ahorlu et al., 1999). The only definitive treatment for hydrocele is surgery (hydrocelectomy) (Ahorlu et al., 2001). The World Health Assembly resolved to eliminate LF disease by 2020 (Resolution for the Global Programme to Eliminate Lymphatic Filariasis - GPELF). The GPELF aims to prevent disability through primary, secondary and tertiary prevention approaches. Primary prevention of disability is achieved through interruption of transmission through MDA. Secondary prevention includes disease management to prevent its progression or worsening, through limb hygiene and skin care to prevent adenolymphangitis (ADL) attacks and reduces risk of lymphoedema progression (Pani & Lall 1998; Krishna Kumari et al. 2005). Tertiary prevention measures include counselling of patients to help them cope with the psychological stress associated with disease and educating families and communities to allow them to fully participate in society (Krishna Kumari A et al. 2005). Home-based care management of lymphoedema patients is one of the proposed approaches for the lymphoedema patients. Home based care is carried out in the patient's home as opposed to a health facility and aims at promoting, maintaining and

restoring health. WHO recommends the home based care because it is the most appropriate strategy for implementing disability prevention whereby the principal carer is the patient. This is also because (a) care and prevention techniques can be carried out in the home by the patient, aided or unaided and (b) management of chronic manifestations warrant long-term care so home-based care is particularly appropriate.

In Zanzibar during the MDA campaign the community drug distributors were asked to register all lymphoedema patients and those with hydrocele in their respective working areas. A total of 1,824 cases of lymphoedema were recorded and 1,577 cases of hydrocele in all ten districts of Zanzibar. In 2003 the Zanzibar LF programme started planning for the management of individuals with LF disease using the community home based management approach as recommended by WHO (WHO. 2004). Although hydrocele surgery was conducted in some district hospitals the Zanzibar PELF undertook a special initiative by conducting a ten-day workshop on hydrocelectomy involving ten medical doctors one from each district. It was recommended that the hospitals from the southern districts of both islands should place more emphasis on this operation as cases recorded in their respective districts were found to be high in comparison to other areas. In this chapter the objective is to determine the impact of both the interventions of home based care management and hydrocelectomy with the intention of assessing their status in the community. Two sites were selected for this study (Kizimkazi and Makunduchi) (Figure 7.1).

7.2 Home-based care on lymphoedema patients

7.2.1 Methodology

7.2.1.1 Study Area

The subjects investigated lived in Kizimkazi and Makunduchi both situated in the southern district of Unguja island. These sites are less than five kilometers apart. Both areas have high number of individuals with lymphoedema and

elephantiasis (Maxwell et al., 1990; Mohammed et al., 2006). The sites are rural and its inhabitants are mostly fishermen or small scale farmers. The Zanzibar PELF initiated the home based care management in these areas (Figure 7.1).

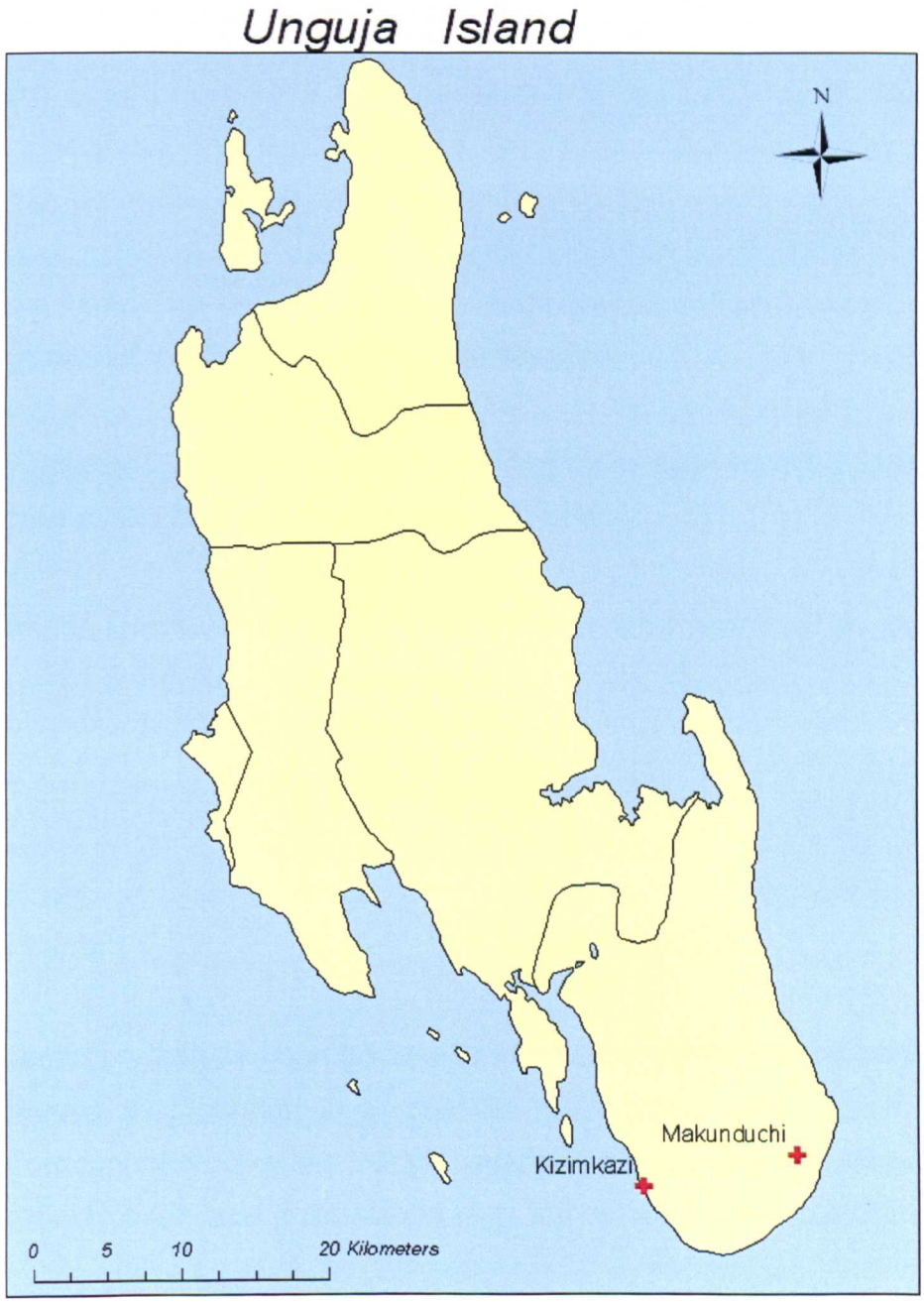
7.2.1.2 Study Population

7.2.1.2.1 Selection of lymphoedema patients

The MDA registers of Kizimkazi and Makunduchi were used to identify patients for enrollment into the study. The enrolment of each lymphoedema patient was undertaken, after verbal informed consent was obtained, through interview at his or her own house using a specially designed questionnaire form. The participants were asked about:

- the duration of their condition;
- when they first observed the appearance of swelling;
- any reasons associated with their swelling;
- any previous history of lymphoedema in family members;
- how frequently do they experience episodes of limb pain with fever;
- their current treatment and limb-care practices;
- the physical difficulties they experienced in daily activities due to their condition;
- treatment-seeking behaviour - the kind of medication they had received, and the expenditure they incurred;
- bathing habits and care of the affected limbs while bathing, their use of water and soap, whether they use cold or warm water;
- how they normally deal with acute attacks.

Figure 7.1 **A Map of Unguja Island indicating sites selected for the study of home based Care management of the lymphoedema patients in Zanzibar.**



In addition to the questions on page 245 all participants were asked about their own feelings about having lymphoedema or elephantiasis towards other people without lymphoedema and whether they had family problems associated with their conditions. They were also asked about any support they received and attitudes of their carers towards them. For each lymphoedema patient enrolled in the study a detailed examination was done. The severity of the lymphoedema seen in each case was graded I–IV, as described by Dreyer et al. (2002). During the interviews, the hygiene of the lymphoedema-affected limbs was categorized as described by Yahathugoda et al. (2005) as:

Poor - when there was dust on the limb, entry lesions (wound), odour and eczema, and the individual did or did not wear shoes;

Moderate - when there was dust on the limb but there were no entry lesions, odour or eczema, and if the individual did have shoes;

Good - when the limbs were devoid of dust, there were no entry lesions, odour or eczema, and the individual had shoes.

A total of 81 lymphoedema patients were enrolled in both sites.

7.2.1.3 Training of home based care management for lymphoedema patients

The Zanzibar PELF in 2004 organized training on community home based care on lymphoedema management to all districts of Zanzibar. However, in this chapter the concentration is on the training undertaken in the southern district of Unguja where Kizimkazi and Makunduchi sites are situated. The training was organized in two sections – The first for the informal carers and the second for the lymphoedema patients and their families. In collaboration with District Health Management Team and Community leaders informal carers were

selected from each site. Their selection was based on either being community-based MDA distributors/family planning workers; traditional birth attendants; traditional healers; other available community workers or even patients themselves. Also they could be members of the community of either sex, young or old (over 18 years of age); literate or illiterate, but with a certain degree of LF understanding. Each informal carer was responsible for 5-15 patients provided they lived within a reasonable distance of the patient's home to enable them to make home visits and continue to carry out their normal daily activities. All selected informal carers received intensive practical training on how to screen and train patients and their families on basic rules of hygiene, hygienic care of the affected limb with stress being placed on washing of the affected limb with soap and water, the importance of keeping the affected limb dry between washes, raising the affected limb at night, regular exercising of the limb to promote lymph flow, the periodic clipping of nails, use of protective footwear, use of cool water to reduce temperature during acute attacks, application of antiseptic or antibiotic creams locally or, in severe cases, systemic antibiotics to treat small wounds or abrasions especially between the toes or sides of the feet, carrying out health education in the family and community, referring patients when necessary, collecting monthly data and counseling LF patients according to the WHO Training module on community home based prevention of disability due to lymphatic filariasis (WHO/CDS/CPE/CEE/2005.35, Parts 1-4). The informal carers were then asked to train their respective patients and family members and were observed to see that they trained them properly according to the WHO Training module on community home-based prevention of disability due to lymphatic filariasis (WHO/CDS/CPE/CEE/2005.35, Parts 1-4).

7.2.1.4 Follow-up of lymphoedema patients

The most relevant indicator for monitoring lymphoedema management through home based care is the frequency of acute attacks. At the start of activities, baseline data on the frequency of acute attacks was established by asking

patients if they had suffered an acute attack in the previous 12 months. Each informal carer was then asked to visit their respective patients in their homes on a weekly/fortnightly basis to provide information to the patients, their families, friends and neighbours on home care and simple steps to follow and prevent and alleviate disability, how to manage an acute attack and if necessary attend the PHCU. Each visit was recorded on the patient's recording form and was delivered each week to the PHCU. All informal carers were provided with recording and follow-up forms (Annex IIIa & IIIb) and were asked to visit their allotted patients, complete the follow-up form and hand it in to the PHCU each week. They were also asked to refer any patient with an acute attack to the closest PHCU if recorded on their forms.

In all sites PHCUs, the Public Health Nurse or other health personnel responsible for PHCU were trained on home based care procedures, on how to manage lymhoedema patients in their unit, on supervision of informal carers, how to check the completion of a patient's record, how follow up the form completed by the informal carers and collect and retain the forms on a monthly basis at the PHCU. Supervision was on weekly basis. In all monitoring and supervision the designed supervisory tools used were based from both the WHO Tutor's Guide and Learner's Guide of the Training Module on Community Home-Based Prevention of Disability due to Lymphatic Filariasis.

7.2.2 Results

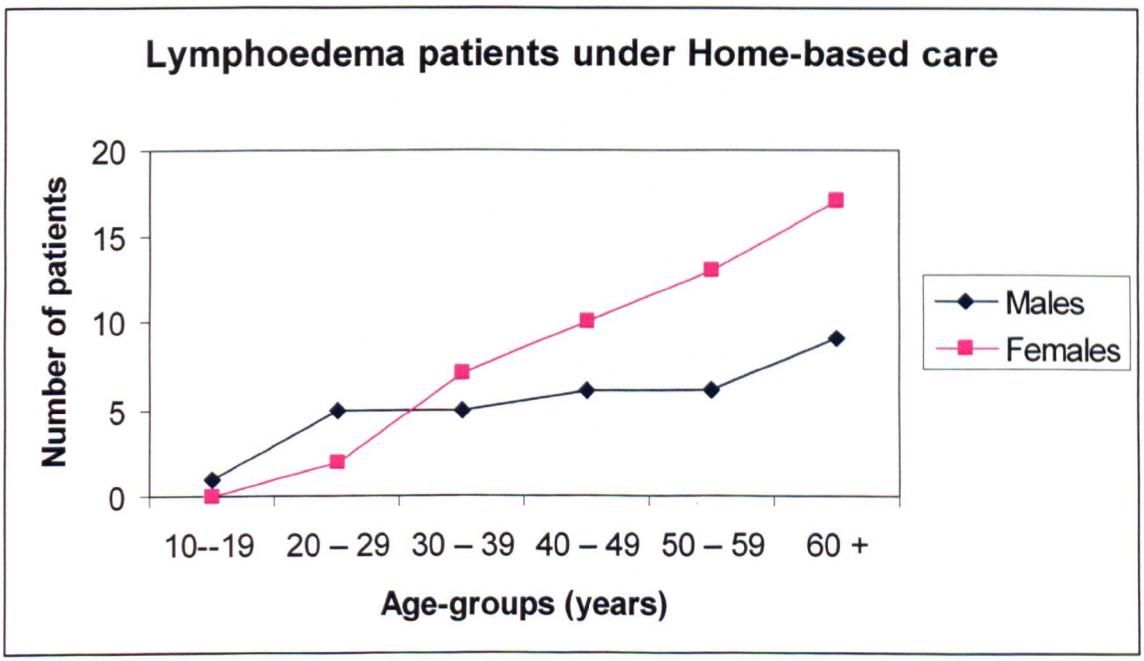
7.2.2.1 Pre-intervention results

The results that are presented in this chapter are results of a follow-up of 81 lymphoedema patients who received home based care training and were under supervision by informal carers in Kizimkazi and Makunduchi between 2004-2006.

Table 7.1 Lymphoedema patients enrolled for Home-based care management at Kizimkazi and Makunduchi

Age group (years)	Males n (%)	Females n (%)	Total n (%)
10–19	1 (3.1%)	0 (0.0%)	1 (1.2%)
20–29	5 (15.6%)	2 (4.1%)	7 (8.6%)
30–39	5 (15.6%)	7 (14.3%)	12 (14.8%)
40–49	6 (18.8%)	10 (2.4%)	16 (19.8%)
50–59	6 (18.8%)	13 (26.5%)	19 (23.5%)
≥60	9 (28.1%)	17 (34.7%)	26 (32.1%)
Total	**32** (39.5%)	**49** (60.5%)	**81**(100%)

Figure 7.2 Lymphoedema patients enrolled for home based care management in age-groups and sex



A total of 81 lymphoedema patients (49 females and 32 males) were enrolled in the two sites of Kizimkazi and Makunduchi. 59 patients (34 females and 25 males) are residents of Kizimkazi, while 22 patients (15 females and 7 males) live in Makunduchi. The overall male: female ratio was 1:1.53. There was only one patient below 20 years (a young boy of 15 years). However, most of the patients were aged 30 years and above. The oldest patient was a woman of 100 years in Kizimkazi. In all age groups the number of females was higher than males, and in the age groups 50–59 years and >60 years the number of females was double the number of males (Table 7.1) (Figure 7.2). Most of the female patients 30 (61.2%) did not work for a living but stayed at home and were dependent on other members of the families for food, clothing, shelter and medicine. However, most of the males 27 (84.4%) worked for their living; only 5 (15.6%) remained at home and were dependent on other family members for their daily necessities. Sixty nine (85%) of the individuals were married and those who developed lymphoedema after marriage remained married despite their condition. Three out of twelve of those who were single believed that they had not married because of their lymphoedema.

Of the 81 patients, 67 (82.7%) said that their oedema had appeared after several bouts of fever attacks. However, 14 (17.3%) related their oedema to incidence of injuries to their limbs. Of the 81 patients, 25 (30.9%) said that they had a family history of lymphoedema. Most patients 65 (80.2%) had lymphoedema in one limb. However, 14 (17.3%) had lymphoedema in both legs. Of the 81 patients 2 (2.5%) had lymphoedema in three limbs (2 legs and an arm). Of the 81 individuals 2 (2.5%) males had grade–I lymphoedema, 52 (64.2%) (31 females and 21 males) had grade–II, 21(26%) (12 females and 9 males) had grade–III, 4 (4.9%) (3 females and 1 male) had grade–IV, and two males grade–V and grade-VI respectively (Table 7.2).

Table 7.2 Characteristics of the 81 lymphoedema patients enrolled for home based care

DESCRIPTION	Number of cases
SEX	
Male	32 (39.5%)
Female	49 (60.5%)
AGE (years)	
10–19	1 (1.2%)
20-29	7 (8.6%)
30–39	12 (14.8%)
40–49	16 (19.8%)
50–59	19 (23.5%)
≥60	26 (32.1%)
MARITAL STATUS	
Single	12 (15.0%)
Married	69 (85.0%
LOCATION OF LYMPHOEDEMA	
Right or left lower limb	65 (80.2%)
Both lower limbs	14 (17.3%)
Both lower limbs and an arm	2 (2.5%)
All four limbs	
LYMPHOEDEMA GRADE	
I	2 (2.5%)
II	52 (64.2%)
III	2126%)
IV	4 (4.9%)
V	1 (1.2%)
VI	1 (1.2%)
DURATION OF LYMPHOEDEMA (years)	
<5	5 (6.1%)
6–10	8 (9.9%)
>10	68 (84%)

7.2.2.1.1 Pre-intervention records of acute dermatolymphangioadenitis (ADLA) (Limb Pain and Fever)

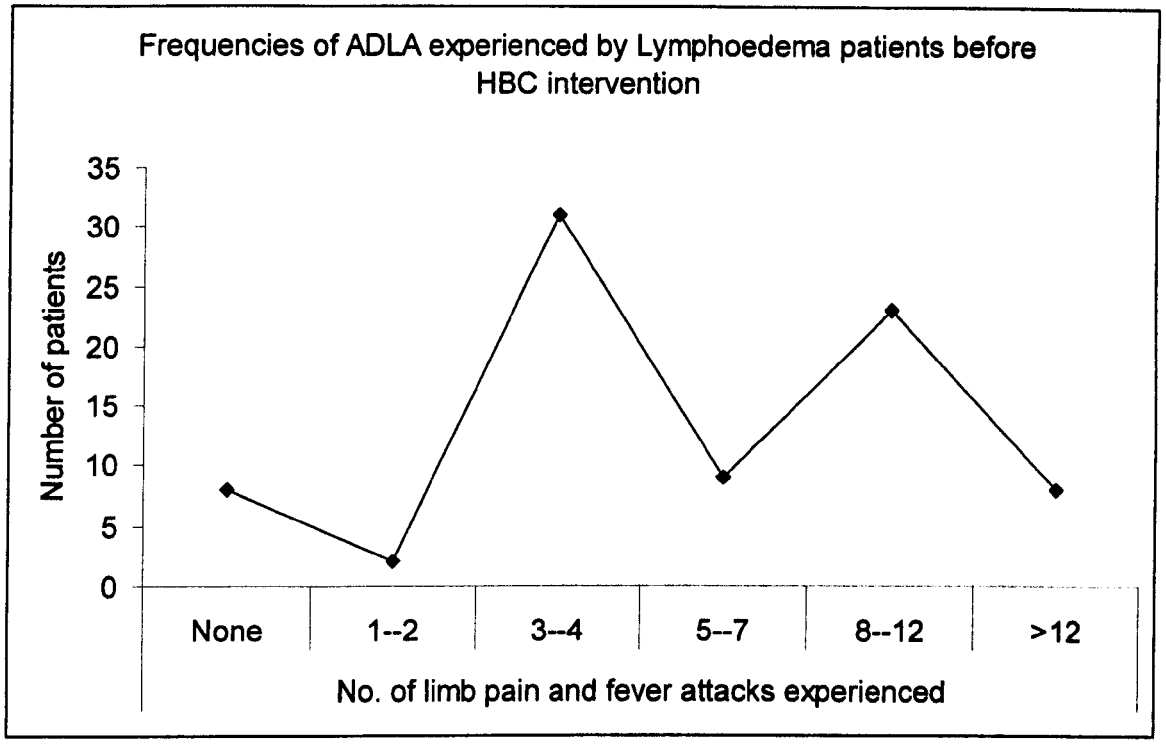
Of the 81 patients 73 (90.1%) said they had experienced episodes of limb pain with fever in the previous year. ADLA episodes were recorded in 73 individuals (29 males and 44 females). The average number of ADLA episodes per person was 3.4 (range 1-14) per month. The mean age of the individuals was 39 years (range <10-100 years). There was no statistically significant difference in ADLA occurrence between the sexes, nor was ADLA occurrence significantly associated with age. There was no significant relationship between age, frequency or temporal distribution of ADLA episodes. The number of episodes experienced by the patients in the previous year and the number of individuals found to have wounds (entry lesions) are shown in the Table 8.3. About 8 (9.9%) individuals said they had never experienced episodes of limb pain with fever in the previous year. However, those who experienced episodes some complained of repeated attacks of more than three times in the previous year. More complaints were from those with wounds in their affected limbs (Table 7.3) (Figure 7.3). Individuals with chronic lymphoedema experienced ADLA significantly more often than individuals without chronic lymphoedema, the average number of episodes being 3.5 and 1.6, respectively (Mann-Whitney U-test, $p<0.001$). Of the 81 patients 21 (25.9%) (9 females and 12 males) were found with wounds in their affected limbs. In both females and males the wounds were located in their toe webs and skin creases. On examination, 7 individuals with wounds had grade–II lymphoedema, 9 had grade-III and 3 had grade-IV (Table 7.3). Although the data regarding acute attacks may not be precisely accurate as it was based on a one-year recall, there is still reason to believe that the recall data reliably reflects the burden imposed by ADLA attacks on the affected population (Sabesan et al. 1992; Evans et al. 1993; Nilmini Chandrasena et al. 2004).

As for treatment seeking behavior, most of the patients (95%) sought treatment from PHCUs in their areas during the acute attacks. Patients were usually given paracetamol and sometimes antibiotics - mostly penicillin. About 3% of the patients had taken traditional herbal medicines, and 2% had treated themselves mainly with paracetamol. None of the patients when interviewed was found to use home based care management practices for their affected limbs. However, most of them said that when they take bath they also wash their affected limbs.

Table 7.3 Frequencies of ADLA during previous 12 months in relation to grade of lymphoedema before HBC intervention

Grade of Lymphoedema	Number of Patients	No. of limb pain and fever attacks experienced						Cases with entry lesions (wounds)
		None	1-2	3-4	5-7	8-12	>12	
I	2	1	1	0	0	0	0	0
II	52	5	1	20	6	16	4	7
III	21	2	0	9	2	6	2	9
IV	4	0	0	2	1	1	0	3
V	1	0	0	0	0	0	1	1
VI	1	0	0	0	0	0	1	1
Total	**81**	**8**	**2**	**31**	**9**	**23**	**8**	**21**

Figure 7.3 Frequencies of ADLA during previous 12 months in relation to grade of lymphoedema before HBC intervention



7.2.2.2 Records of ADLA during HBC intervention (2004-2006)

During the first 12 months with HBC management intervention, 76 (93.4%) individuals declared they no longer experienced ADLA episodes. However, 5 (6.2%) individuals reported reduced the frequency of ADLA episodes, the average number of episodes per person being 1.2. In the same period when patients were examined for wounds 73 (90.1%) no longer had wounds on their affected limbs. In the record of the second year after the HBC management intervention, 79 (97.5%) individuals reported no ADLA episodes. Of 81 patients only 2 (2.5%) individuals reported they had an ADLA episode for the whole year. During the same period patients examined for wounds 79 (97.5%) had no wounds on their affected limbs (Tables 8.4; 8.5; 8.6) (Figure 7.5).

Figure 7.4a Follow-up of LF lymphoedema patient under home-based care management at Kizimkazi

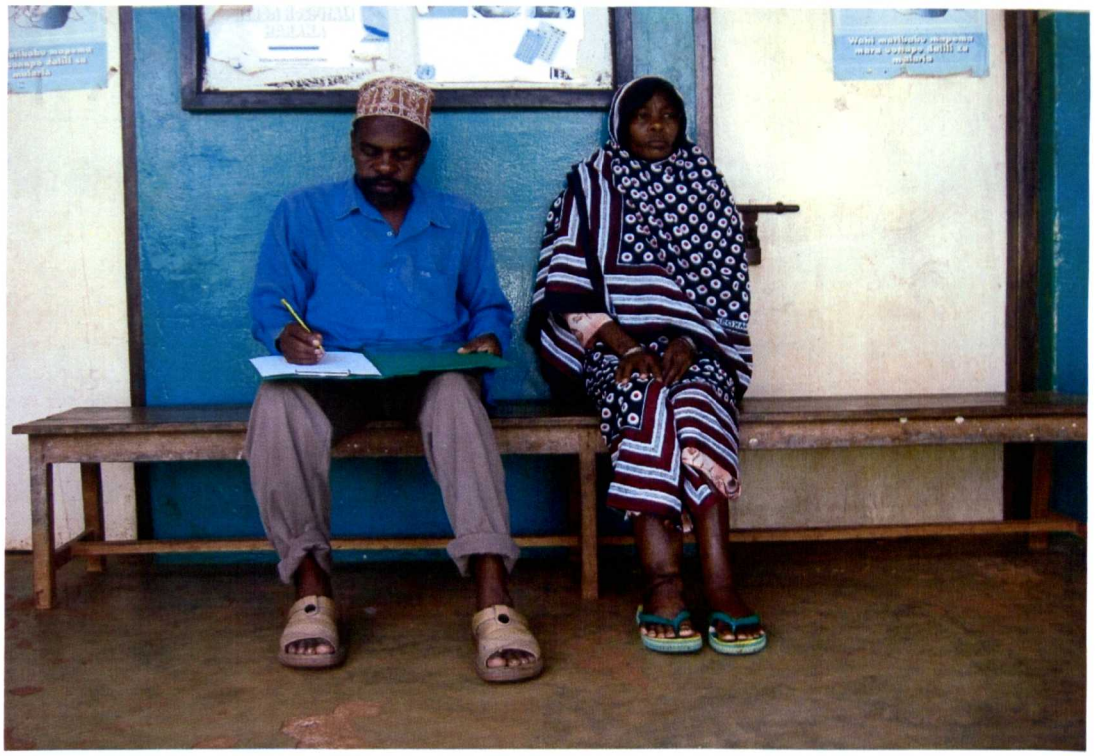


Figure 7.4b Follow-up of LF lymphoedema patient under home-based care management at Makunduchi

Table 7.4 Records of acute attacks after HBC management of lymphoedema patients on a monthly basis in Kizimkazi and Makunduchi

RECORDS OF ACUTE ATTACKS AFTER HOME-BASED MANAGEMENT ON LYMPHOEDEMA PATIENTS ON MONTHLY BASIS			
	2004 n (%)	**2005** n (%)	**2006** n (%)
Baseline	35 (43.2%)	0 (0%)	0 (0%)
1st Month	16 (19.8%)	0 (0%)	0 (0%)
2nd Month	14 (17.3%)	3 (3.7%)	2 (2.5%)
3rd Month	10 (12.3%)	2 (2.5%)	0 (0%)
4th Month	5 (6.2%)	0 (0%)	0 (0%)
5th Month	4 (4.9%)	0 (0%)	0 (0%)
6th Month	2 (2.5%)	0 (0%)	0 (0%)
7th Month	0 (0%)	0 (0%)	0 (0%)
8th Month	0 (0%)	0 (0%)	0 (0%)
9th Month	0 (0%)	0 (0%)	0 (0%)
10th Month	0 (0%)	0 (0%)	0 (0%)
11th Month	0 (0%)	0 (0%)	0 (0%)
12th Month	0 (0%)	0 (0%)	0 (0%)

Table 7.5 Frequencies of ADLA during the first 12 months in relation to grade of lymphoedema after HBC intervention

Grade of Lymphoedema	Number of Patients	No. of limb pain and fever attacks experienced						Cases with entry lesions (wounds)
		None	1-2	3-4	5-7	8-12	>12	
I	2	2	0	0	0	0	0	0
II	52	52	0	0	0	0	0	0
III	21	19	2	0	0	0	0	5
IV	4	3	1	0	0	0	0	1
V	1	0	1	0	0	0	0	1
VI	1	0	1	0	0	0	0	1
Total	**81**	**76**	**5**	**0**	**0**	**0**	**0**	**8**

Figure 7.5 Frequencies of ADLA during the first 12 months in relation to grade of lymphoedema after HBC intervention

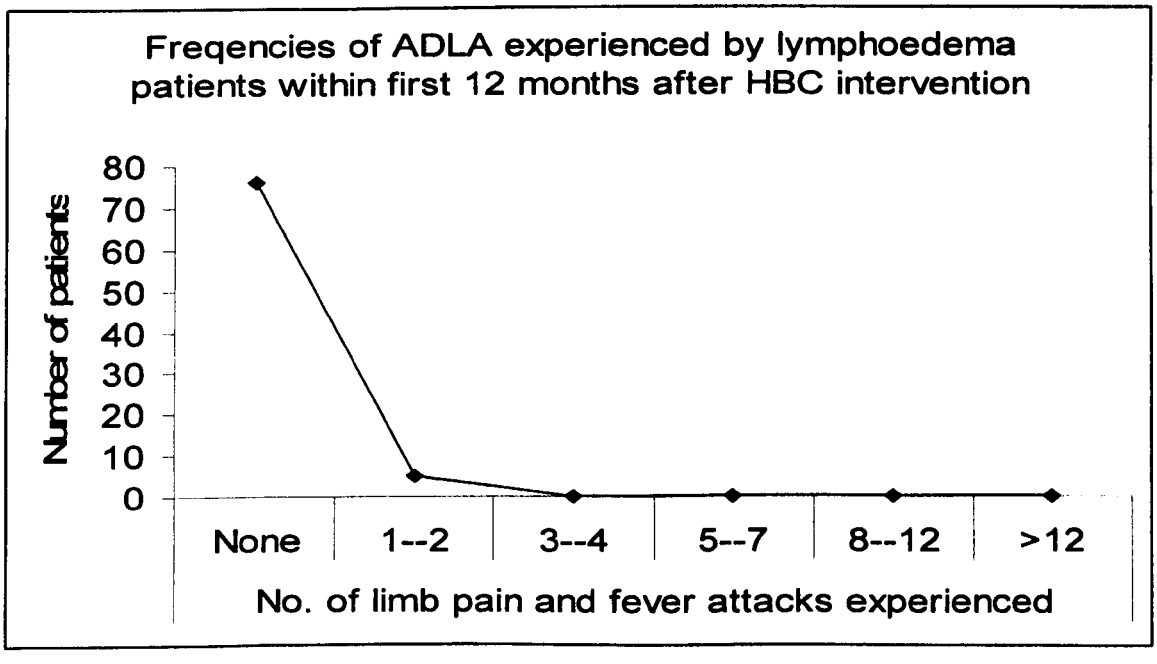


Table 7.6 Frequencies of ADLA during the second 12 months in relation to grade of lymphoedema after HBC intervention

Grade of Lymphoedema	Number of Patients	No. of limb pain and fever attacks experienced						Cases with entry lesions (wounds)
		None	1-2	3-4	5-7	8-12	>12	
I	2	2	0	0	0	0	0	0
II	52	52	0	0	0	0	0	0
III	21	21	0	0	0	0	0	0
IV	4	3	1	0	0	0	0	1
V	1	1	0	0	0	0	0	0
VI	1	0	1	0	0	0	0	1
Total	**81**	**79**	**2**	**0**	**0**	**0**	**0**	**2**

Figure 7.6 Frequencies of ADLA within the second 12 months in relation To grade of lymphoedema after HBC intervention

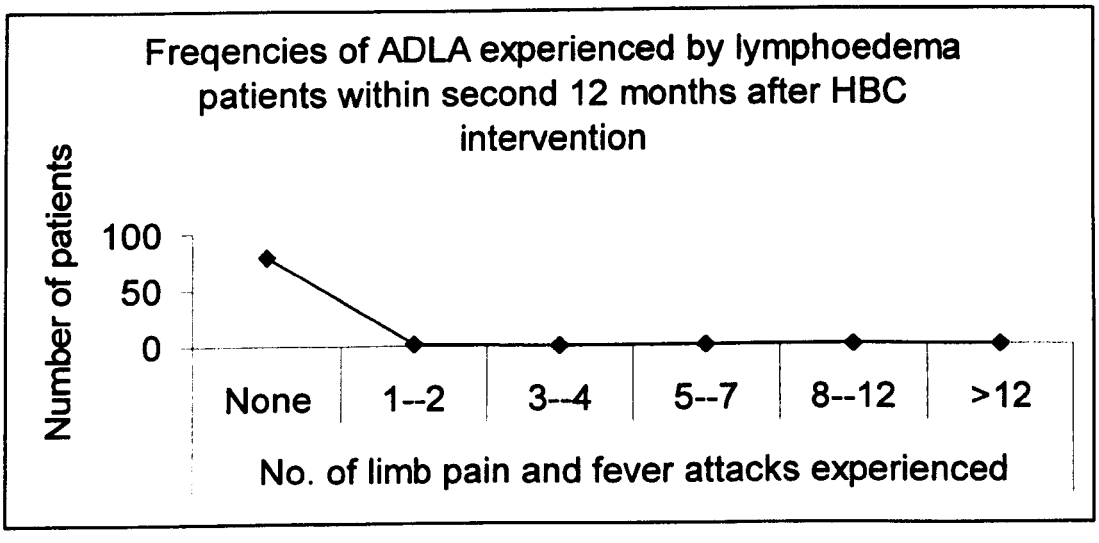
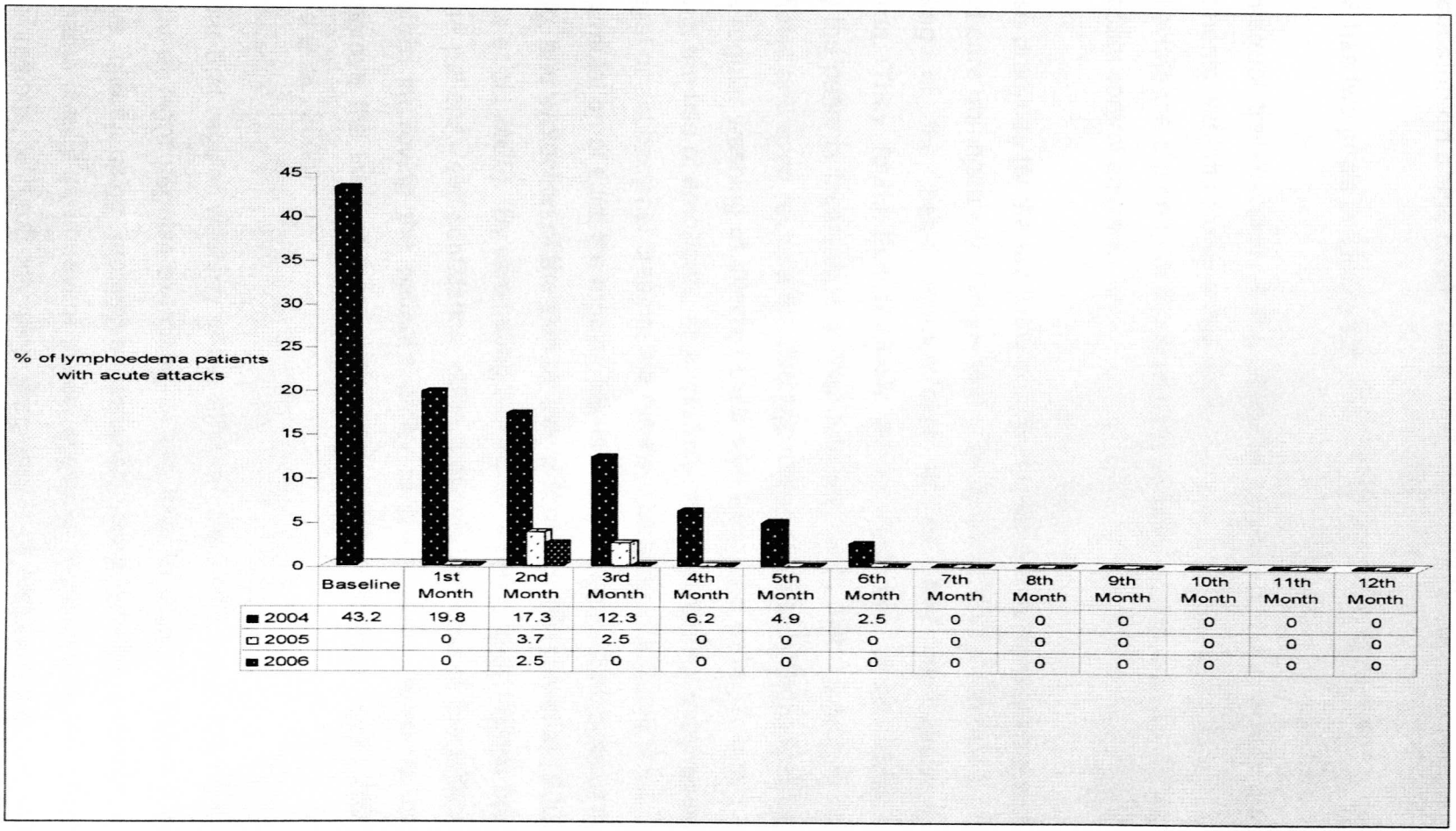


Figure 7.7 Frequencies of Acute Attacks after HBC 2004 -2006



	Baseline	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month	7th Month	8th Month	9th Month	10th Month	11th Month	12th Month
2004	43.2	19.8	17.3	12.3	6.2	4.9	2.5	0	0	0	0	0	0
2005		0	3.7	2.5	0	0	0	0	0	0	0	0	0
2006		0	2.5	0	0	0	0	0	0	0	0	0	0

7.2.3 Discussion on home based care

The GPELF has two goals in fighting LF:

1. to interrupt transmission of the parasites causing LF, by annual mass treatments with anti-filarial drugs and
2. to alleviate the suffering of those already afflicted by the disease through morbidity control activities.

One of those practices for the morbidity control related with lymphoedema is the home based care management. Dreyer and colleagues (2002) pioneered a new understanding of the basic management of LF and the associated lymphoedema. They found that relatively simple methods, which could be followed by the patients themselves or their families, could halt the progression of elephantiasis and even reverse the damage already present. These methods include: the regular washing of affected parts with soap and water, followed by careful drying; the use of emollients, as necessary; the treatment of entry lesions with antifungal or antibacterial creams; the regular elevation of afflicted limbs, to prevent accumulation of fluid; the regular, low-intensity movement of joints of the affected limb; and protection of the skin by use of footwear (Dreyer et al., 2002; Yahathugoda et al., 2005). By eliminating bad odour, helping entry lesions heal, improving the patient's self-confidence, often reducing the size of the afflicted limb, and often improving the patient's ability to work, such measures can markedly improve the lives of those with lymphoedema (Dreyer et al., 2002; Yahathugoda et al., 2005).

It is now clear that regular washing of the affected parts with soap; raising the affected limbs at night; regular exercising of the limb to promote lymph flow; keeping nails clean; using protective footwear; using timely antiseptic or antibiotic creams locally or, in severe cases, systemic antibiotics to treat small wounds or abrasions, will not only stop progression of elephantiasis but also

reverse the damage already present in many affected individuals. The overall results presented in Kizimkazi and Makunduchi during two years of follow-up after the introduction of home based care to lymphoedema patients shows that self- care of lymphoedema patients, after training through the informal carers' network, is useful and effective and significantly reduces the occurrence of acute attacks (ADLA) (Tables 7.4; 7.5; 7.6)(Figures7.5; 7.6; 7.7). Results were the same whether the patient was monitored at home by an informal carer or by medical personnel at a health facility. The patients who were monitored in both Kizimkazi and Makunduchi in addition to reporting the effectiveness of home based care on the frequency of acute attacks also reported its effectiveness in reducing entry lesions (wounds), reducing odour of the affected limbs and reducing the size of the lymphoedema. Most of the patients have reported satisfaction with the results of the home based care intervention as it has enabled them to improve their quality of life. Similar results have been reported in other places (Dreyer et al., 2002; Addiss et al., 1999; Dahl, 2001; Shenoy et al., 2003).

Earlier studies have shown that absenteeism because of frequent ADLA episodes, social stigma and shame associated with lymphoedema and hydrocele compelled many students with LF to give up education or led to poor educational achievements (Ramaiah et al. 2000, Perera et al., 2007).

7.3 Hydrocelectomy

Hydrocele is known to be a cause of physical disfigurement, social stigma, loss of self-esteem, lowered employment opportunity, interference in sexual activity, family discord and a cause of economic loss due to loss of work due to episodic attacks of ADLA (Ahorlu et al., 1999; Ahorlu et al., 2001; Muhondwa, 1983, Perera et al., 2007).In view of the hydrocele prevalence and public health perspective surgical intervention for morbidity management on hydrocele has been considered to be an appropriate strategy for GPELF (Addiss et al., 2000).

7.3.1 Methodology

In the follow-up to the MDA campaign a report of a higher prevalence of hydrocele in the south district of Unguja required the Zanzibar LF programme to appeal to MOH and WHO for financial assistance to conduct a hydrocelectomy workshop and then perform surgery on those affected.

7.3.1.1 Study area

A hydrocelectomy workshop in Makunduchi hospital decided that hydrocelectomy of individuals around Makunduchi and Kizimkazi should start at Makunduchi Hospital. This was because both these sites had a high number of individuals with hydrocele, as compared to other areas in the southern district of Unguja island.

7.3.1.2 Study population

7.3.1.2.1Selection of patients with hydrocele for hydrocelectomy

The MDA registers of Kizimkazi and Makunduchi were used to identify individuals with hydrocele for operation and enrolment into the study. The enrolment of each hydrocele patient took place after verbal informed consent was obtained, through an interview at home and at Makunduchi hospital, Unguja using a specially designed questionnaire form. The participants were asked about duration of their condition; when they first observed the appearance of the swelling, any reasons associated with their swelling; if they experience pain in their scrotum and fever; the physical difficulties they experienced on a daily basis due to their conditions and any treatment seeking behaviour. The participants were also asked about their social life and if they encountered any problems. All participants were also asked about their own feelings of having hydrocele, their attitude towards other people without hydrocele and if they had

family problems associated with their condition. For each individual enrolled for the operation and the study a detailed examination was done. A total of 45 individuals from both Kizimkazi and Makunduchi were enrolled in the study and were followed for two years.

The Zanzibar LF programme in collaboration with the District Health Management Team of the southern district of Unguja and the Public Health Nurses in charge at the PHCU in Kizimkazi and Makunduchi arranged the clinical examination and counselling of the patients in their respective areas, and arranged surgery in the district hospital (Makunduchi Hospital). A total of 45 males benefited from hydrocelectomy in both Kizimkazi (20) and Makunduchi (25). However, other males with hydrocele did not register during MDA campaign because they felt their condition was not serious and did not warrant 'self-exposure' to public "ridicule". None of the 45 hydrocele patients enrolled had scrotal or penile lymphoedema.

7.3.1.3 Surgical operation of individuals with hydrocele

All enrolled individuals (45) had hydrocele operations at Makunduchi hospital performed by a medical doctor who participated in the hydrocelectomy workshop conducted at the same hospital. Prior to the operation all subjects were thoroughly examined and requested to return at the hospital for follow-up.

7.3.1.4 Follow up of hydrocelectomy patients

Monitoring the condition of the hydrocelectomy patients to assess the impact of this intervention was taken as indicator that could be linked with DALYs and economic impact. All enrolled individuals (45) who received surgery were asked to return to Makunduchi Hospital for follow up 10 days post- surgery when clinical examination was undertaken as well as being questioned in accordance with the patient's follow-up form. Six months after surgery all enrolled subjects

were visited at home and the tenth day follow-up post-surgery examination repeated. One year after their surgery patients were again visited at home and previous procedures repeated. The final follow-up was two years after surgery at home. However, in the final follow-up in addition to questions of the hydrocelectomy patients, interviews were conducted with different members in the community including the wives of hydrocelectomy patients, co-workers and community leaders.

7.3.1.5 Results

7.3.1.5.1 Results prior hydrocelectomy intervention

7.3.1.5.1.1. Perceptions about hydrocele

In the results of interviews with the participants 32 (55%) believed the hydrocele condition to be enhanced by hard work. However, some 5 (10%) believed that condition was due to excessive sexual activity, a finding reported in Ghana (Ahorlu et al., 2001). Two (4%) believed that excessive drinking of coconut water was a cause. Of the 52 patients 4 (8%) believed the condition was due to witchcraft. However, 9 (17.3%) believed it to be a disease not knowing the cause. As for treatment several options were mentioned but mostly used analgesics and/or antibiotics, surgical operation at hospitals and consultation of spiritualists or traditional healers.

7.3.1.5.1.2. Effect of hydrocele on physical activity and social life

In most studies hydroceles were reported to result in impairment of productive capacity and especially large ones could have a disastrous effect on the work performance of the patients (Ahorlu et al., 2001). In this study most of the patients particularly those with large hydroceles revealed that were unable to go about their daily activities. They said that condition did not only affect

themselves but also their families and the whole community. The same experience was reported in the Ghana study (Ahorlu et al., 2001). Although patients with hydrocele were allowed to fully participate and were free to contribute during discussions in all community functions those with large hydroceles did not attend those functions because of ridicule and the teasing they usually suffered from some individuals in the community. Few patients expressed sexual problems. However, as reported in Ghana due to strong community sanction against divorce, most of the patients who were married before developing hydrocele or before their disease reached an advanced stage were still married (Gyapong M et al., 2000; Ahorlu et al., 2001; SWG 2005).

7.3.1.5.1.3 Perception about surgical operation (hydrocelectomy)

Most patients especially those with large hydroceles were willing to have surgery, but the fear of death and the cost of surgery prevented them from doing so. The cost was around US$80-100 and this varied between public and private hospitals an amount beyond the reach of most patients.

7.3.1.5.2 Results after hydrocelectomy intervention

7.3.1.5.2.1 Experience of complications during and after hydrocelectomy

Of the 45 hydrocelectomy patients that were followed-up there were no complications during and after the surgery. All patients recovered well. All patients spent only one day in hospital after surgery and were discharged in the following day.

7.3.1.5.2.2 Impact of hydrocelectomy on physical activity and social life

All 45 hydrocelectomy patients reported major improvements in their health, work capacity and sexual performance after the surgical operation. The family

members, wives and co-workers of the patients were satisfied with the condition of patients after hydrocelectomy. The district authorities and community leaders were also pleased with the condition of patients after the hydrocelectomy and appreciative of the support provided.

7.3.1.6 Discussion

In Zanzibar especially in the southern districts of both islands about 20-30% of adult males had hydrocele (Kilama et al., 1975; Pederson et al., 1999). A similar figure has been reported in many LF endemic communities of Africa (Gypong et al., 1994; Meyrowitsch et al., 1995; Simonsen et al., 1995; Dunyo et al., 1996). Little is known about the natural history of hydrocele in filariasis-endemic areas, although there is increasing evidence suggesting that it is much more than previous realized. Recent observations from Brazil, Egypt, and Haiti indicate that many acute hydroceles resolve spontaneously (Noroes et al., 2003; Hussein et al., 2004; Addiss et al., 2001; Addiss et al., 2007). However, despite the heavy public health burden, the physical and social wellbeing of those affected has received little attention in the past. In most studies, hydrocele patients and their families were teased and in some cases patients could not find marriage partners. In some cases women married to hydrocele patients were 'silent sufferers' of their husbands by being imposed upon to undertake extra work and living in a marriage without sexual satisfaction (Gypong et al., 1996, 2000; Ahorlu et al., 1999; Dreyer et al., 1997; Coreil et al., 1998). The impact of hydrocelectomy on 45 hydrocele patients of Kizimkazi and Makunduchi suggests that the intervention not only corrected their hydrocele condition but also improved the physical and social status of the patient, increasing capacity to work, improved sexual function and active participation in communal activities. The study on hydrocele patients revealed that many hydrocele patients who wanted to undergo surgery were hesitant to go to hospital because of the fear of 'temporary death' while under anaesthesia and because of the cost of surgery (Gyapong et al. 2000). The same views were

expressed both in Kizimkazi and Makunduchi by patients during interview. LF patients with gross deformity caused by lymphoedema and hydrocele benefited from counseling to come to terms with deformity and also to overcome fear and undergo necessary treatment.

7.4 General Discussion on home base care and hydrocelectomy

The two main objectives of GPELF from the beginning were to interrupt transmission of the parasite through MDA and initiate morbidity control through providing care for those who suffer the devastating clinical manifestations of the disease. In the context of morbidity control, acute inflammatory episodes (acute dermato-lymphangioadenitis - ADLA), lymphoedema, and hydrocele are the major conditions considered.

Several studies have confirmed the importance of bacteria as a cause of ADLA in filariasis-endemic areas (Pani et al., 1995; Olszewski et., 1993; Olszewski et., 1997; Vijayalakshmi, 1997; Suma et al., 1997; Baird et al., 2002; Suma et al., 2002). Studies suggest that the rate of ADLA is higher in persons with chronic disease principally lymphoedema. The mean reported incidence of ADLA ranges from 1.5 to more than 7 episodes per patient /year (Pani et al., 1995; Suma et al., 2002; Ramaiah et al., 1996; Ananthakrishnan et al., 2004; Richard et al., 2007). In Ghana, studies indicate that patients with ADLA are incapacitated for 3 of 5.1 days of ADLA duration (Gyapong et al., 1996), while in Tanzania, patients are incapacitated for 3.7 of the 8.6 days of ADLA (Gasarasi et al., 2000). However, in Haiti and Togo the number of work days lost exceed the duration of ADLA episodes (Kanda, 2004; Richard et al., 2007). Among the risk factors for ADLA are increasing patient age, poor hygiene, illiteracy, gender (females tend to experience higher rates than males), lymphoedema severity and presence of entry lesions (Gasarasi et al., 2000; Ramaiah et al., 1996; Ananthakrishnan et al., 2004; Addiss et al., 1999). However, the association between ADLA frequency and stage, as well as extensive clinical experience

from filariasis-endemic areas strongly suggests that ADLA episodes are likely the most important factor in lymphoedema progression (Addiss et al., 2007). Little is known about what triggers the onset of clinical lymphoedema or about what factors cause lymphoedema, once triggered, to persist. The clinical model proposed by Dreyer emphasizes that lymphoedema is a multi-factorial process (Dreyer et al., 2000). However, after lymphoedema is established, recurrent episodes of ADLA are thought to be major factors associated with disease progression (Addiss et al., 2007). The simple intervention packages including home based care that are in use have resulted in dramatic reductions in ADLA rates, lower prevalence of chronic inflammatory cells in the dermis and sub-dermis, and improvement in quality of life (Addiss et al., 2007). The two years follow up of 81 lymphoedema patients who were under home based care in Kizimkazi and Makunduchi demonstrated the effectiveness of this intervention in reducing the incidence of ADLA episodes in lymphoedema patients. Similar results were reported in studies in Madagascar, Sri Lanka and Zanzibar (WHO. 2004). In Haiti, the reported incidence of ADLA during the year before beginning treatment was 2.1 episodes per year; this decreased to 0.6 episodes after hygiene and skin care was initiated (Addiss et al., 1999). The incidence and duration of ADLA episodes has a significant economic implication on individuals, their families and community. There was a substantial loss of work during episodes and subsequent economic loss (Babu et al. 2005). However, meticulous hygiene including use of footwear, regular washing of affected limbs, the use of the whole package of home-based care and also the prevention of injuries and infections (Babu et al. 2005) reduced ADLA incidence. Unlike MDA to interrupt transmission, which needs to be repeated once a year for 4-6 years (WHO 2001), lymphoedema care is a life-long and requires individual motivation and discipline, available clean water, supplies such as soap, topical anti-fungal and antibacterial agents and systemic antibiotics. The experience in many studies including Kizimkazi and Makunduchi shows that one of the keys to successful lymphoedema management for most patients is their commitment to daily self examination for inter-digital skin lesions and disciplined incorporation

of hygiene and skin care into a daily routine and adhering to all home based care management principles and procedures.

Of the clinical manifestations targeted by GPELF, hydrocele has been the focus of the least attention. In several studies on hydrocele, this condition has been reported to have great impact on different aspects. In terms of productivity hydrocele has been associated with reducing individual working hours, individual output as well as national output (Wijers et al., 1997; Evans et al., 1993; Lu et al., 1988; Ramu et al., 1996; Ramaiah et al., 2000; Gyapong et al., 1996). Stigma, emotional impact, male identity and sexual function have all been associated with hydrocele patients in many studies carried out in different countries (Lu et al., 1988; Wijers et al., 1997; Gyapong et al., 1996; Dreyer et al., 1997). Higher grades of lymphoedema and hydrocele interfere with the social life of the individual. Patients with a large hydrocele or elephantoid legs with massive skin folds and odour are victims of teasing and social stigmatization. Individuals with gross deformity were dejected, avoided all social activities and led an isolated life within the family. Individuals with lower grades of lymphoedema restricted their social activities to essential and unavoidable contacts, for fear of inadvertently eating foods that would induce ADL attacks (Krishna Kumari et al., 2005). However, most filariasis-endemic countries that are advanced in their MDA programmes, such as Zanzibar, have started to pay attention to hydrocele patients. In the two year follow-up of 45 hydrocele operated patients in Kizimkazi and Makunduchi all patients expressed their satisfaction with the intervention because it had improved their quality of life. Most of them have experienced significant improvement in self esteem, capacity for work, sexual function and were now fully participating in all community functions. However, the financial support given for their operation was limited and more patients are requesting hydrocelectomy as they cannot personally afford to pay.

Promoting and supporting improved access to health facilities for hydrocelectomy in endemic communities is an important adjunct to repeated drug treatments, which would further help to increase and sustain local interest in LF control activities. It could also be an important entry point for health education to improve local understanding about the biological aetiology and consequences of LF. Since patients often cannot afford it, policy-makers and civil society organizations and NGDOs should be encouraged to assist by subsidising the cost of hydrocelectomy. As expressed by Ramaiah although our knowledge of filariasis-related morbidity and its treatment has expanded in recent years, much work remains to be done to address the needs of more than 40 million persons who suffer worldwide from these conditions (Ramaiah et al., 2007; Addiss et al., 2007).

CHAPTER VIII

CO-ADMINISTRATION OF IVERMECTIN, ALBENDAZOLE AND PRAZIQUANTEL

8.1 Introduction

In Zanzibar, LF, schistosomiasis and STH are the major public health problems. Control of schistosomiasis and STH through large-scale preventive chemotherapy interventions distributing praziquantel and albendazole commenced in 1994. Schools represent the main delivery channel and schoolchildren the main target population, however occasionally whole communities have been also targeted for treatment. This strategy is still on-going with a period of interruption of two years (2000-2001) during which activities did not take place due to problems in securing the drugs. There has been a marked reduction in the prevalence and intensity of both schistosomiasis and STH (Ministry of Health and Social Welfare, unpublished data). However, such indicators show that continuation of treatment of schoolchildren is still necessary in some areas. The last distribution prior to the implementation of the activities described in this study was carried out in August 2005. Although the evaluation of the impact of MDA showed an overall decline in prevalence and intensity of microfilaraemia, the mean prevalence of infection in all age groups (adults and children) at one sentinel and in some randomly selected spot-check sites before the 5th round remained at 1% and above. The MoHSW therefore decided to implement a further (6th) round of MDA. This followed the WHO recommended processes leading to a decision to stop MDA only after interruption of transmission (prevalence of microfilaraemia <1% in the general population) (WHO, 2005). It was decided that the opportunity offered by the necessity to implement the 6th round of MDA throughout Zanzibar would be used to combine distribution of ivermectin (Mectizan®) and albendazole with the

distribution of praziquantel to the entire communities where LF, STH and schistosomiasis are co-endemic.

The three drugs (ivermectin (Mectizan®), albendazole and praziquantel) used in national LF elimination programmes, the control of STH and schistosomiasis are considered extremely safe, especially when administered individually as a single-dose or in combination (albendazole and ivermectin (Mectizan®) or albendazole and praziquantel). At the recommended once-yearly dosages (albendazole 400 mg; ivermectin (Mectizan®) 200µg/kg; praziquantel 40mg/kg) no toxic reactions to the drugs have been noted. Adverse reactions do sometimes occur following treatment with anthelminthic drugs, especially with ivermectin (Mectizan®) or praziquantel, primarily as a result of the individual's immune inflammatory response to dying parasites; the greater the infection load in the patient - the greater are the frequency and severity of such reactions. These can include systemic responses (headache, myalgia, light-headedness, anorexia, malaise, nausea, vomiting and wheezing, abdominal discomfort, dizziness, drowsiness, rectal bleeding); or, less commonly, localized reactions (including lymphadenitis, funiculitis, epididymitis, lymphangitis and even abscesses); in the case of schistosomiasis rarely are there hypersensitivity reactions but fever, pruritus and eosinophilia may occur. Only very rarely (in heavily infected individuals) are these post-treatment reactions severe or require more than just symptomatic treatment (Loukas and Hotez, 2006).

Pharmacokinetic studies carried out with the combination of albendazole, ivermectin (Mectizan®) and praziquantel when administered to healthy individuals indicate that there are no pharmacological interactions between the three drugs and that co-administration does not enhance their toxicity (Na-bangchang et al, 2006).

WHO (2006) recommended that co-administration of the three drugs is carried out only following some precautions. As a first step it is advisable that in a

population that has never been subjected to MDA with any of these drugs, the initial 1-2 rounds of treatment with praziquantel should be given separately from albendazole and/or ivermectin (Mectizan®); additionally, in a population that has previously been subjected to (separate) MDA with praziquantel and ivermectin (Mectizan®) or praziquantel and ivermectin (Mectizan®) + albendazole, extra safety monitoring should be carried out during the initial rounds of large-scale combined treatment to monitor for any unanticipated adverse reactions.

Since, in Zanzibar, separate MDA had already been conducted in the past, it was decided to implement co-administration of the three drugs under such precautionary measures. Before co-administering the drugs to the entire eligible population, equivalent to about 1 million individuals, it was considered imperative that such intervention took place in a pilot population and that active and passive surveillance measures be implemented during and after treatment for any occurrence of adverse events.

Results of the pilot intervention were considered crucial and acted as a decision indicator to proceed with a country-wide intervention. It was agreed that if no serious adverse experiences occurred during the pilot intervention co-administration would take place throughout Zanzibar and that active and passive surveillance measures would be also implemented during a countrywide intervention.

8.2 The pilot Intervention

8.2.1 Study area

The pilot intervention was conducted in 2 sites, one from each of the two islands Kinyasini on Unguja (resident population about 4,000) and Mtambile on Pemba (resident population about 3,000). In both sites the prevalence of LF, schistosomiasis and STH was high. Field assessments conducted before the survey showed that in Kinyasini the prevalence of LF (assessed by ICT) was

4%, of urinary schistosomiasis (assessed by urine filtration) it was 63.5% and of STH infections (assessed by Kato-Katz method) it was 76.8%; at Mtambile, the prevalence of LF was 13%, of urinary schistosomiasis it was 43%, and of STH, 73%. The major occupations of the communities in both sites were linked to agriculture. Both sites are surrounded by permanent water bodies.

8.2.2 Study Population

A total of 5,055 individuals were recruited in the study (Table 8.3), 2,509 from Kinyasini on Unguja (Table 8.1) and 2,546 from Mtambile on Pemba island (Table 8.2). There was good representation from both age and sex groups in both sites. In Mtambile, however, there were more females, 1,647 (64.7%) who participated in the study as compared to 899 (35.3%) males (Tables 8.1, 8.2) (Figures 8.1, 8.2).

There was a good representation for both age and sex groups in both sites. However, overall females were more prevalent than males and the age-group 10-19 years old was the most represented (Table 8.3 & Fig. 8.3)

Table 8.1 Study population by age group in Kinyasini, Unguja

		Treated population	
Age group	**Total**	**Female**	**Male**
<10	412	251 (60.9%)	161 (39.1%)
10-19	802	439 (54.7%)	363 (45.3%)
20-29	463	275 (59.4%)	188 (40.6%)
30-39	291	187 (64.3%)	104 (35.7%)
40-49	242	150 (62%)	92 (38%)
50+	299	202 (67.6%)	97 (32.4%)
Total	2,509	1,504 (59.9%)	1,005 (40.1%)

Figure 8.1 Study population in Kinyasini by sex and age

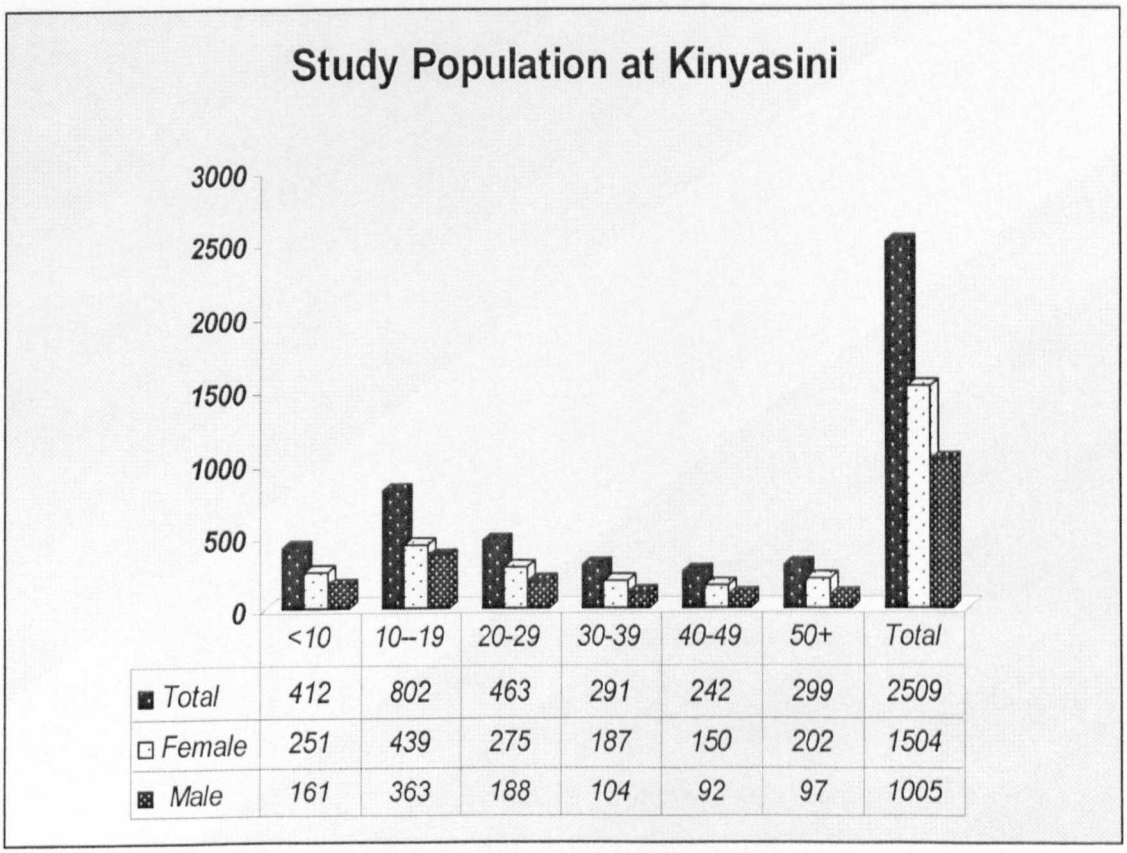


Table 8.2 Study population by age group in Mtambile

		Treated population	
Age group	**Total**	**Female**	**Male**
<10	351	204 (58.1%)	147 (41.9%)
10-19	746	446 (59.8%)	300 (40.2%)
20-29	427	334 (78.2%)	93 (21.8%)
30-39	405	290 (71.6%)	115 (28.4%)
40-49	296	177 (59.8%)	119 (40.2%)
50+	321	196 (61.1%)	125 (38.9%)
Total	2,546	1,647 (64.7%)	899 (35.3%)

Figure 8.2 Study population by sex and age in Mtambile

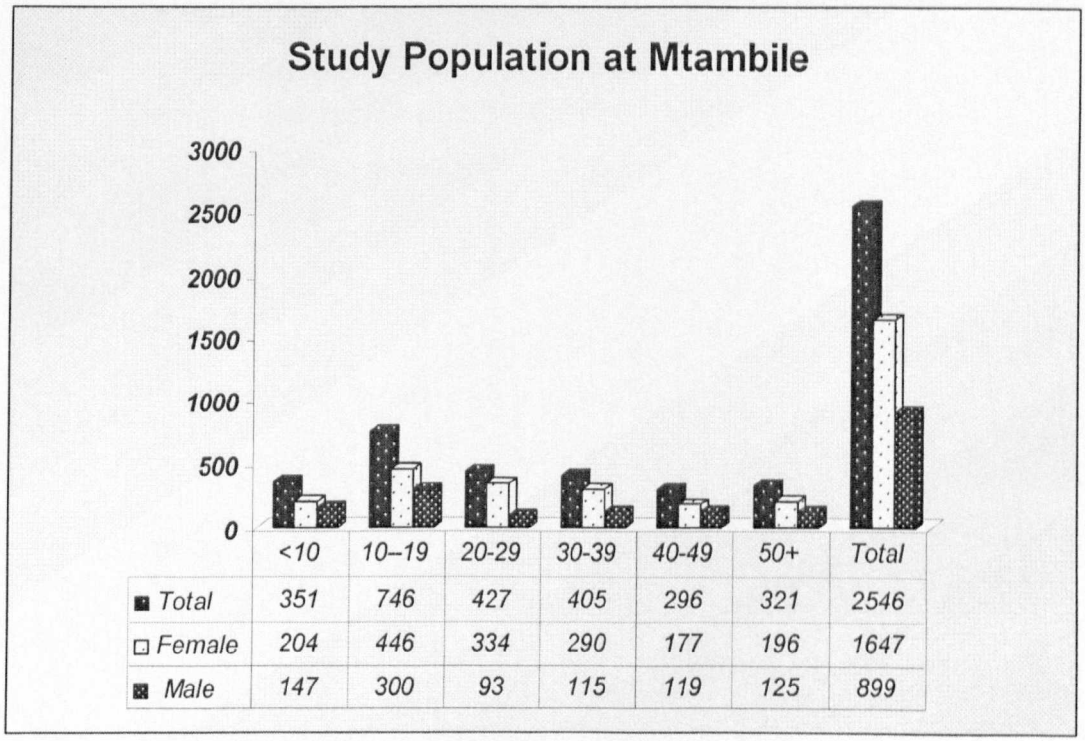


Table 8.3 Study population for both Kinyasini and Mtambile

		Treated population	
Age group	**Total**	**Female**	**Male**
<10	763	455	308
10-19	1548	885	663
20-29	890	609	281
30-39	696	477	219
40-49	538	327	211
50+	620	398	222
Total	**5,055**	**3,151 (62.3%)**	**1,904 (37.7%)**

Figure 8.3 Study population by sex and age in Kinyasini

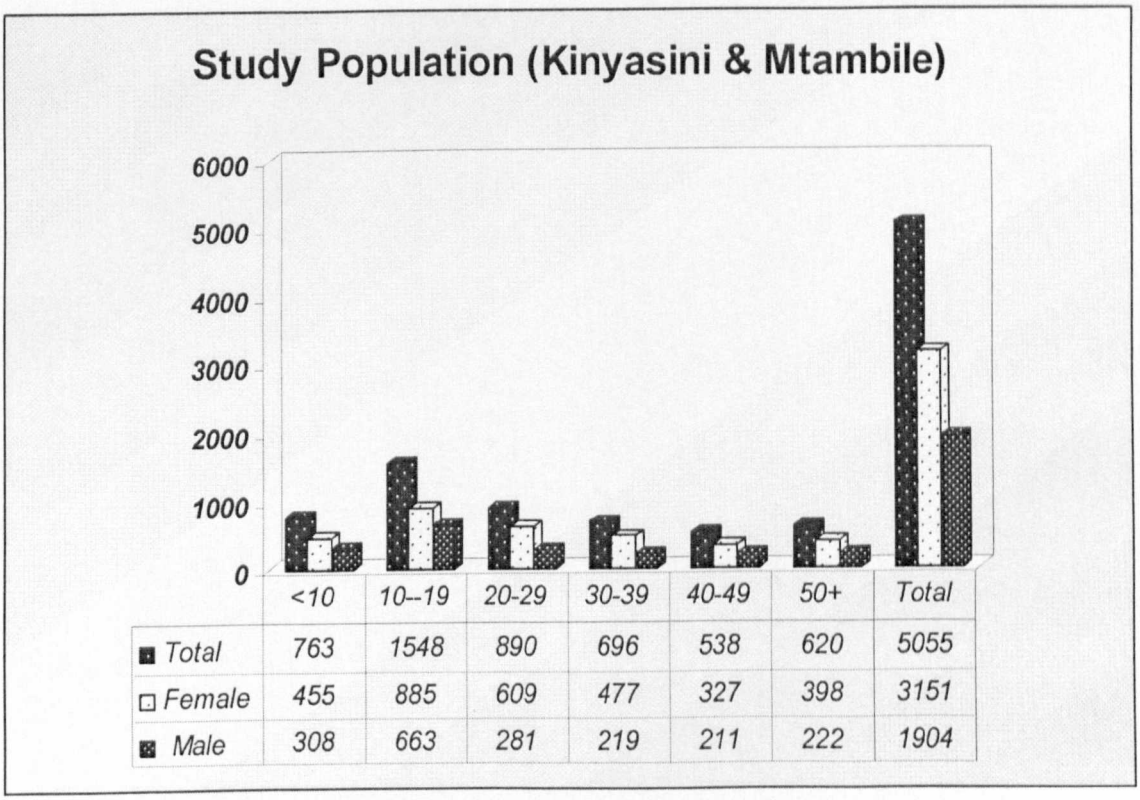
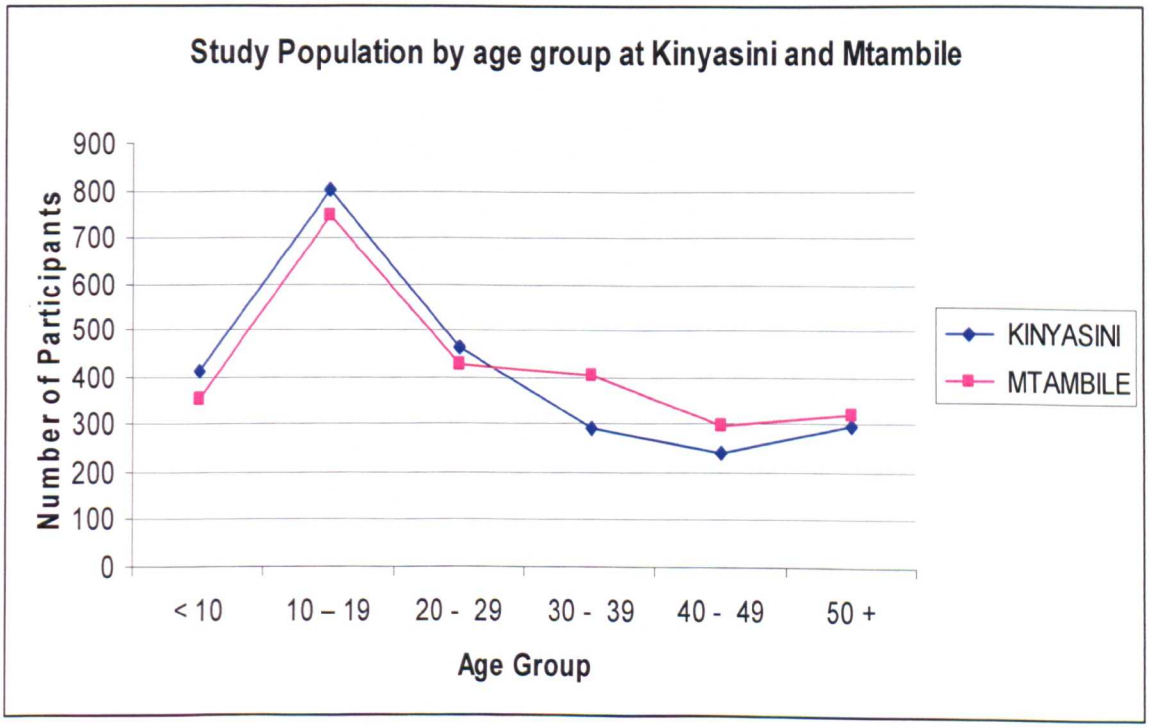


Table 8.4 Study population by age group in both sites

		Treated population	
Age group	**Total**	**Kinyasini**	**Mtambile**
<10	763	412	351
10-19	1548	802	746
20-29	890	463	427
30-39	696	291	405
40-49	538	242	296
50+	620	299	321
Total	5,055	2,509	2,546

Figure 8.4 Study population by age-group in Kinyasini and Mtambile



8.2.3 Treatment plan

All participants in the study were given their respective dosages of ivermectin (Mectizan®) (200μg/kg), albendazole (400mg) and praziquantel (40mg/kg); treatment was directly observed by the drug distributors to ensure the tablets were swallowed. The dosage for ivermectin (Mectizan®) and praziquantel was calculated using a two-faced tablet (height) pole: one side for determination of number of ivermectin (Mectizan®) tablets and the other side for the number of praziquantel tablets. One tablet of albendazole (400mg) was used as the standard dose for everybody irrespective of age or height.

8.2.3.1 Criteria for eligibility

The whole eligible population of Kinyasini and Mtambile was enrolled in the survey. Criteria for eligibility were the most restrictive to those used in disease-specific interventions against one of the three infections (i.e. those of LF, Schistosomisis and Soil-transmitted helminthiasis). As such all the residents, with the exception of the sick or infirm, children <15kg in weight or <90cm in height and pregnant and lactating women, of Kinyasini and Mtambile were considered eligible. Each eligible individual or their parent/guardian in the case of children was asked to give an informed consent (Annex V). Those who accepted were interviewed in order to determine their health status prior to the drug distribution, and all information was recorded.

Figure 8.5 **A woman taking ivermectin, praziquantel and albendazole tablets together in Kinyasini**

8.2.4 Surveillance measures

Both passive and active surveillance measures were implemented during the pilot intervention. Passive measures were put in place to ensure rapid medical assistance for any individuals experiencing adverse reactions after treatment. Measures to elucidate the nature of and quantify any adverse reactions were also developed.

Passive measures were established on the treatment day and the day after: two health centres in Kinyasini and two in Mtambile were kept open without interruption and equipped with first-line emergency drugs (anti-inflammatory and anti-histaminic drugs, cortisone, intravenous fluids). Treated individuals were invited to report to these centres in the event of any adverse reactions ("anything abnormal occurring in your body") arising; health centre personnel were trained on how to complete the record forms and were instructed to refer to main hospitals any individual presenting with serious adverse experiences (SAEs). In addition, watch vehicles/motor bikes patrolled around the area to facilitate a speedy response in the case of need.

Active surveillance measures were also carried out between the 5^{th} and the 7^{th} day after treatment: all treated individuals were interviewed to ascertain the occurrence of adverse reactions following the ingestion of the three drugs. A structured questionnaire including questions about specific symptoms or signs was developed for this purpose (Annex VI)

8.2.5 Results

8.2.5.1 Passive surveillance measures

Not a single serious adverse experience (an event that is fatal, life-threatening, disabling or incapacitating or that results in hospitalization after drug intake) was recorded or reported at any health facilities in either Kinyasini or Mtambile or at

the designated referral hospitals. Overall, of all the treated individuals only one was reported whose symptoms were mild and were successfully managed.

8.2.5.2 Active surveillance measures

The results of participant interviews on one day between the 5th and 7th day post- triple therapy using the combination of ivermectin (Mectizan®), praziquantel and albendazole showed that in Kinyasini, out of the 2,509 individuals who received treatment, 223 (8.9%) reported having experienced one or more symptoms of mild adverse reaction after taking the drugs but symptoms subsided within 24 hours (Table 8.5, Figure 8.5).

Very few side reactions were reported on the second day (Table 8.6). Most of the reported symptoms were dizziness 65, abdominal pain 68, nausea 26, body fatigue 18, diarrhoea 16, headache 29, fever 15, vomiting 8, joint/muscle pain 6, itching 4 and a single case of scrotal pain (Table 8.6, Figure 8.6). In all age groups the incidence of side reactions was higher in females compared to males. Many reported cases were reported in the age group 10-9 and 20-29 in both sexes (Table 8.5, Figure 8.5).

Table 8.5 Records of symptoms in Kinyasini

Age Group	Female	Male	Total
<10	15	10	35 (15.7%)
10–19	40	31	71 (31.8%)
20-29	34	14	48 (21.5%)
30-39	27	5	32 (14.3%)
40-49	9	7	16 (7.2%)
50+	22	9	31 (13.9%)
Total	147 (65.9%)	76 (34.1%)	223 (100%)

Figure 8.6 Records of symptoms of side reactions in Kinyasini

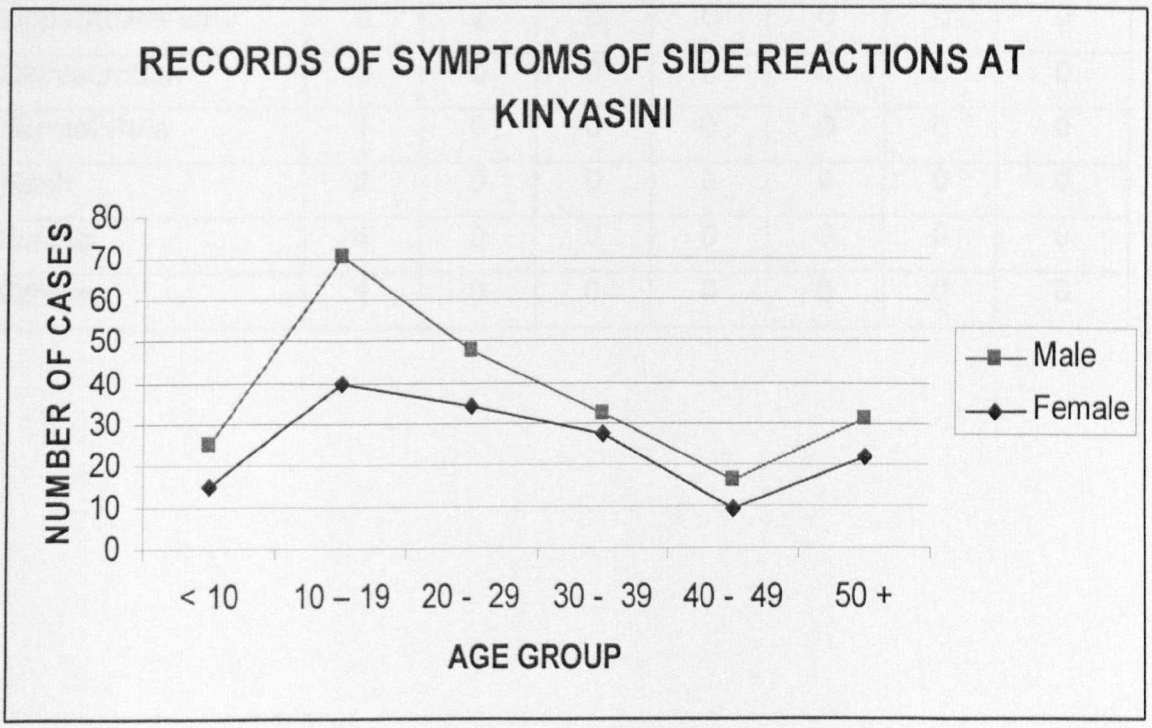
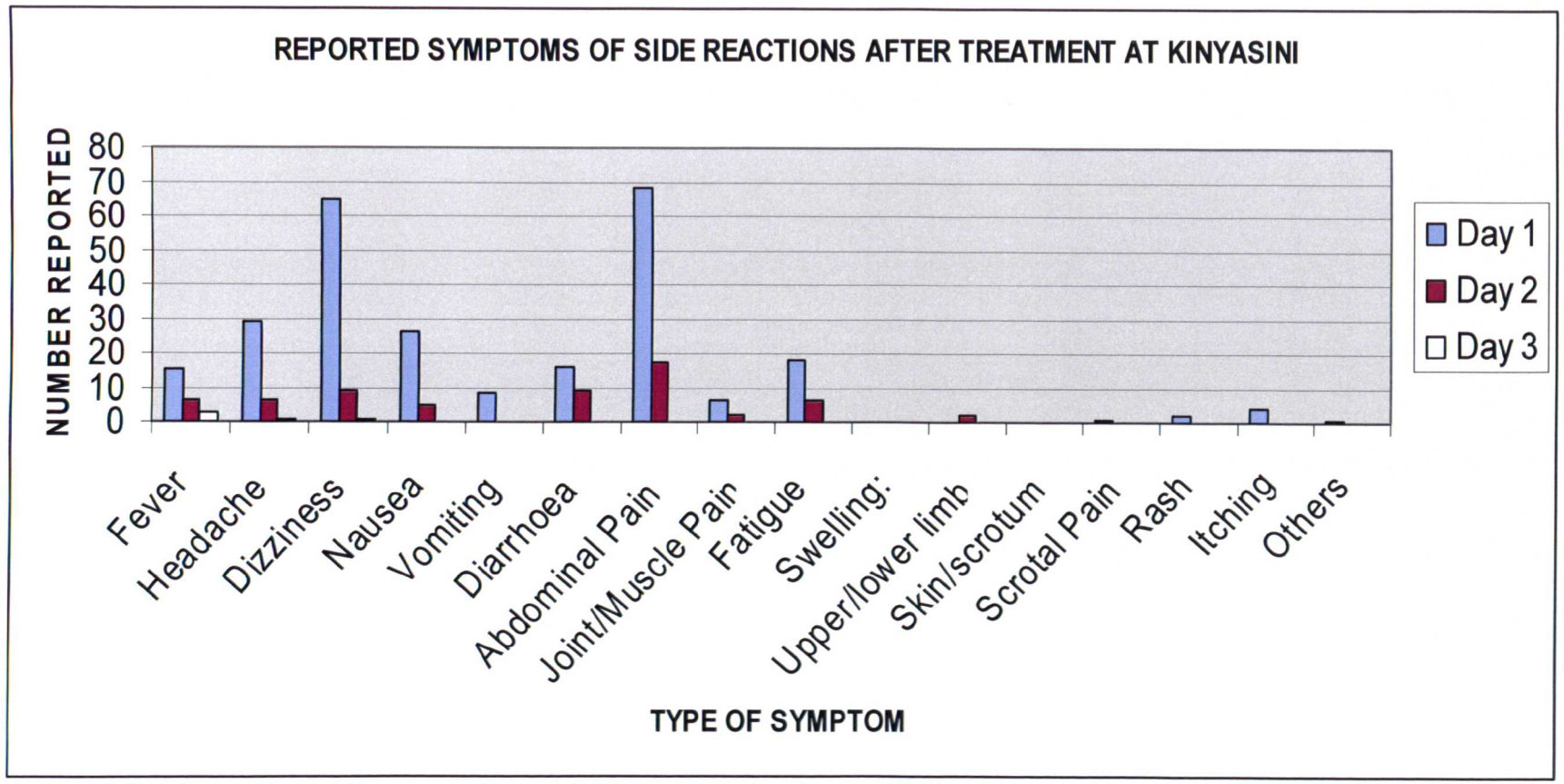


Table 8.6 Reported symptoms in Kinyasini

SYMPTOMS	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Fever	15	6	3	0	0	0	0
Headache	29	6	1	0	0	0	0
Dizziness	65	9	1	0	0	0	0
Nausea	26	5	0	0	0	0	0
Vomiting	8	0	0	0	0	0	0
Diarrhoea	16	9	0	0	0	0	0
Abdominal Pain	68	17	0	0	0	0	0
Joint/Muscle Pain	6	2	0	0	0	0	0
Fatigue	18	6	0	0	0	0	0
Swelling:	0	0	0	0	0	0	0
Upper/lower limb	0	2	0	0	0	0	0
Skin/scrotum	0	0	0	0	0	0	0
Scrotal Pain	1	0	0	0	0	0	0
Rash	2	0	0	0	0	0	0
Itching	4	0	0	0	0	0	0
Others	1	0	0	0	0	0	0

Figure 8.7 Reported symptoms of side reactions in Kinyasini



In Mtambile out of 2,546 treated and interviewed, 281 (11%) reported experiencing mild side reactions after triple therapy. 167 (59.4%) were females and 114 (40.6%) males (Table 8.7). The highest incidence was recorded in the age group 30-39 (31%) with more females (58) compared to males (29) and very little incidence in the age group below ten years (Table 8.7, Figure 8.7). All the symptoms were mild and subsided within 24 hours.

Table 8.7 Records of symptoms in Mtambile

Age Group	Female	Male	Total
< 10	4	7	11 (3.9%)
10–19	36	19	55 (19.6%)
20- 29	25	18	43 (15.3%)
30- 39	58	29	87 (31%)
40- 49	18	21	39 (13.9%)
50+	26	20	46 (16.4%)
Total	**167 (59.4%)**	**114 (40.6%)**	**281 (100%)**

Figure 8.8 Records of symptoms of side reactions in Mtambile

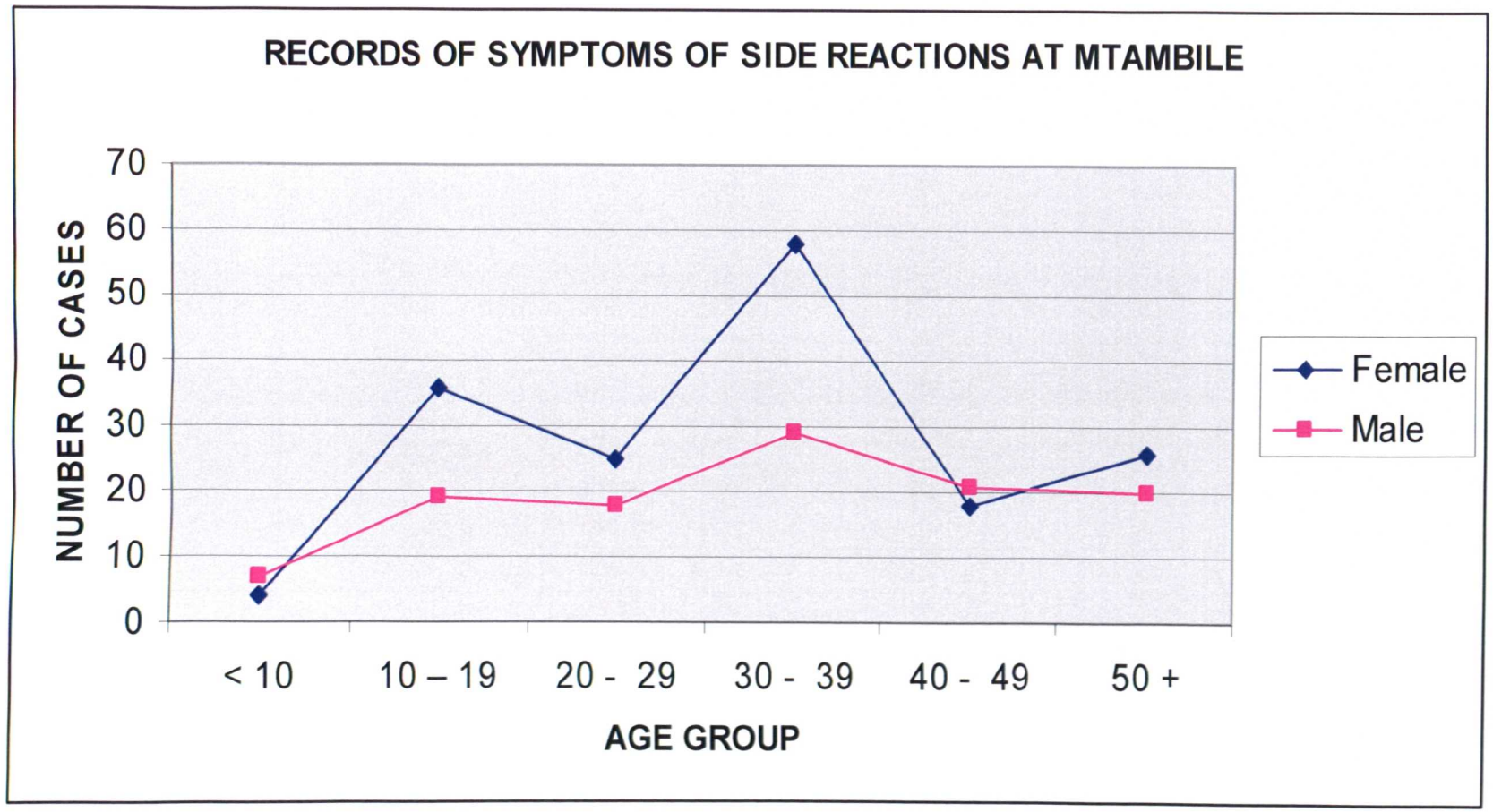
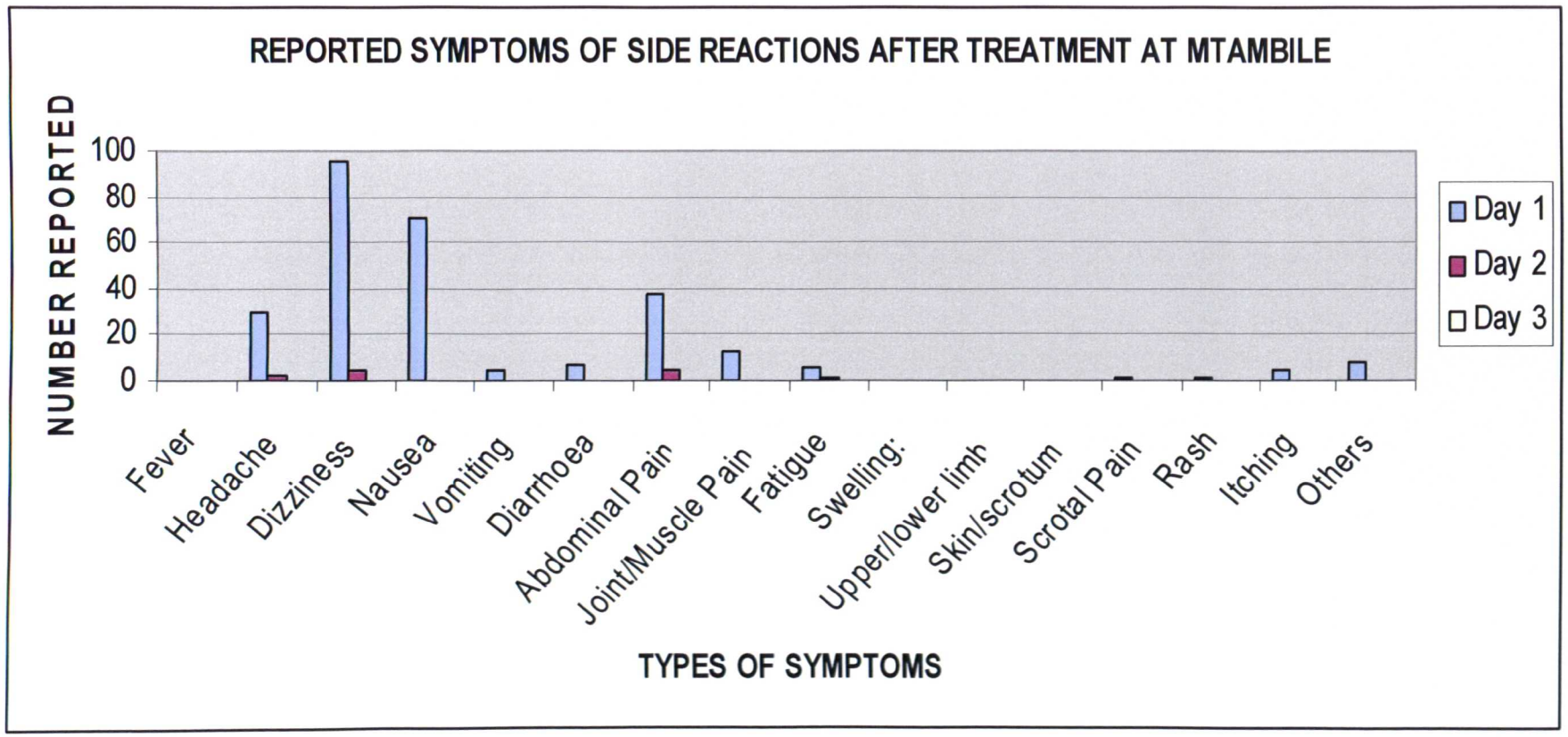


Table 8.8 Reported cases in Mtambile

SYMPTOMS	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Fever	0	0	0	0	0	0	0
Headache	30	2	0	0	0	0	0
Dizziness	95	4	0	0	0	0	0
Nausea	71	0	0	0	0	0	0
Vomiting	4	0	0	0	0	0	0
Diarrhoea	7	0	0	0	0	0	0
Abdominal Pain	38	4	0	0	0	0	0
Joint/Muscle Pain	13	0	0	0	0	0	0
Fatigue	6	1	0	0	0	0	0
Swelling:	0	0	0	0	0	0	0
Upper/lower limb	0	0	0	0	0	0	0
Skin/scrotum	0	0	0	0	0	0	0
Scrotal Pain	1	0	0	0	0	0	0
Rash	1	0	0	0	0	0	0
Itching	4	0	0	0	0	0	0
Others	8	0	0	0	0	0	0

Figure 8.9 Records of symptoms of side reactions at Mtambile



The results of the interviews with participants on one day between the 5th and 7th day post-triple drug administration are shown in Table 8.9. Overall, a total of 615 events were reported by 504 individuals. The number of individuals who reporting adverse reactions was less than 10% (504/5055) of those treated. The occurrence of adverse reactions is overall comparable in different sexes but peaks in the age-group 30-39 (Table 8.9). 87.3% of symptoms occurred within 24 hours post-treatment, while a few were also reported to have occurred on the second day (11.9%) and on the third day (0.8%). No symptoms were reported to have occurred thereafter (Table 7.10). The symptom most frequently reported was dizziness. All symptoms were reported to be mild and all of them subsided within a period of less than 24 hours after onset.

Table 8.9 Age distribution of individuals reporting adverse reactions

Age Group	Female	Male	Total
<10	19/455 (4.2%)	17/308 (5.5%)	36/763 (4.7%)
10-19	76/885 (8.6%)	50/663 (7.5%)	126/1548 (8.1%)
20-29	59/609 (9.7%)	32/281 (11.4%)	91/890 (10.2%)
30-39	85/477 (17.8%)	34/219 (15.5%)	119/696 (17.1%)
40-49	27/327 (8.3%)	28/211 (13.3%)	55/538 (10.2%)
50+	48/398 (12%)	29/222 (13%)	77/620 (12.4%)
Total	**314/3151 (10%)**	**190/1904 (10%)**	**504/5055 (10%)**

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Total	**314/3151 (10%)**	**190/1904 (10%)**	**504/5055 (10%)**

Table 8.10 Nature and timeline of adverse reactions

SYMPTOMS	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	TOTAL
Fever	15	6	3	0	0	0	0	24
Headache	59	8	1	0	0	0	0	68
Dizziness	160	13	1	0	0	0	0	174
Nausea	97	5	0	0	0	0	0	102
Vomiting	12	0	0	0	0	0	0	12
Diarrhoea	23	9	0	0	0	0	0	32
Abdominal Pain	106	21	0	0	0	0	0	127
Joint/Muscle Pain	19	2	0	0	0	0	0	21
Fatigue	24	7	0	0	0	0	0	31
Swelling:	0	0	0	0	0	0	0	0
Upper/lower limb	0	2	0	0	0	0	0	2
Skin/scrotum	0	0	0	0	0	0	0	0
Scrotal Pain	2	0	0	0	0	0	0	2
Rash	3	0	0	0	0	0	0	3
Itching	8	0	0	0	0	0	0	8
Others	9	0	0	0	0	0	0	9
TOTAL	**537**	**73**	**5**	**0**	**0**	**0**	**0**	**615**

8.3 Country-wide intervention

As the active surveys for adverse events did not indicate any concern for SAEs in the pilot phase, two weeks after co-administration of the three drugs had taken place in the pilot cohort on December 2-3, 2006 Zanzibar conducted its first triple MDA. This campaign was conducted under the newly established Lymphatic Filariasis, Schistosomiasis and Soil-transmitted helminthiasis Integrated Programme of the Ministry of Health and Social Welfare – Zanzibar.

Every eligible individual in Zanzibar was targeted to receive the three drugs at the same time with the exception of those living in areas which are schistosomiasis-free, where only ivermectin (Mectizan®) and albendazole were administered. Such areas include the urban district of Stone Town and the south district of Unguja island. The same criteria for eligibility and ineligibility applied in the pilot intervention were also applied during the country-wide intervention. Overall, about 700,000 individuals were administered three drugs (ivermectin (Mectizan®), albendazole and praziquantel) and 300,000 two drugs (ivermectin (Mectizan®) and albendazole).

A door-to- door strategy was chosen as the method of drug administration. For effective coverage 4,161 drug distributors, the same number used by previous LF-MDA campaigns, were employed and given extra training on how to use a double-faced drug pole in determining the number of tablets. Each drug distributor was responsible for 50 households. All drug distributors were previously identified through a participatory process starting from villages or the city divisions, so as to guarantee their full acceptance by the community. Many of them were health personnel or school teachers.

Similarly as in the pilot study, both passive and active surveillance measures were taken during and after the MDA. Passive surveillance, initiated during the intervention through the network of health centres on both islands to monitor and respond to potential side-effects, did not detect any SAEs.

One week after the drug distribution, active surveillance measures were carried out to quantify the occurrence of adverse reactions in a sub-sample of the target population; such activity was incorporated into the routine survey intended to assess and check drug coverage. 35 out of the 250 communities (shehias) which form Zanzibar were randomly selected and 600-1,000 people per site were interviewed, a total of some 30,000 individuals. Each interviewer was randomly assigned to one of the 35 evaluation sites and entered houses

following a random route in their area. Each individual visited was interviewed to investigate both drug intake and side-effects experienced.

Overall, only 266 individuals, equivalent to 1.4% of the interviewees who swallowed the drugs reported any side-effects; all of them were transient and minor, the most frequent being headache, dizziness, and abdominal discomfort. These side-effects were readily accepted and managed, as they were self-limiting.

8.4 Discussion

The results of the pilot study in Kinyasini and Mtambile made it possible to implement, for the first time, an MDA of ivermectin (Mectizan®), albendazole and praziquantel to all eligible individuals of Zanzibar.
Passive and active surveillance measures implemented during both the pilot phase and the nationwide intervention showed that these were mild and self-limiting events, not different in nature and frequency from those observed when any of the drugs are given individually or when ivermectin (Mectizan®) and albendazole or praziquantel and albendazole are given together.

Data from such a large population suggests that co-administration of the three drugs is a safe intervention when carried out in an area where LF, schistosomiasis and soil-transmitted helminthiasis are endemic and where several rounds of treatment with one or two drugs have been implemented in the past.

However, due to the limited information still available on this subject it is important to stress the need for maintaining passive surveillance measures during similar interventions, and to remind that detection, management and reporting of serious adverse experiences should be a key component of any health intervention administering drugs on a mass scale.

There are opportunities arising from a coordinated approach to tackle such diseases. It is expected that drug distribution costs will be lower when implementing two or more single disease interventions. Currently many control/elimination programmes in Africa are constrained not so much by drug availability but by lack of the financial resources necessary to meet drug distribution costs. Apart from praziquantel which is not donated, ivermectin (Mectizan®) is provided to endemic countries free of charge for as long as it is needed by Merck & Co. Inc. and albendazole by GSK. In many countries there is a significant geographic overlap between schistosomiasis, LF and STH hence triple drug co-administration can be an option to cut down costs especially in those countries where previous de-worming interventions have reduced the worm burden in the community. Co-administration of anthelminthic drugs also offers a good opportunity for integration of the parasitic disease control programmes in Africa and elsewhere - a common wish of most partners and donors.

In this study Zanzibar communities, endemic for *Wuchereria bancrofti* transmitted by *Culex quinquefasciatus*, showed that six rounds of mass administration of a combination of ivermectin and albendazole with a treatment coverage of 76 – 83%, were able to reduce microfilaria prevalence and intensity and transmission in both sentinel and spot check sites to < 1% microfilaria (mf) rate, the level currently considered appropriate to have interrupted transmission and hence to stop MDA (Mohammed et al., 2006; WHO, 2005). Zanzibar was able to attain high drug coverage through intensive social mobilization using the Communication for Behavioral Impact (COMBI) strategy with full commitment of government, political, religious, community leaders and community members at large. The Zanzibar programme of lymphatic filariasis elimination involved all stakeholders including community leaders, from initial planning to programme implementation. It is recommend that this approach be used when planning for any mass drug campaign for disease elimination or control in the community. At the Kizimkazi sentinel site microfilaraemia (mf) prevalence and density dropped gradually following five rounds of mass drug administrations (MDA) from 17.8% and 356 mf/ml to zero with a drug coverage of above 75.0% (of the total population) in all rounds (Table 4.8 & Figure 4.6). While at the Kwahani site microfilaraemia (mf) dropped from 7.2% and 323 mf/ml to zero after four rounds of MDA (Table 4.9 & Figure 4.7). The difference in number of MDA rounds which lead to zero microfilaraemia (mf) prevalence in Kizimkazi and Kwahani sentinel sites suggests that when initial LF prevalence is higher the number of MDA rounds with high coverage need to be more as compared to an area where initial LF prevalence is low. However, in Zanzibar a decline in circulating filarial antigen (CFA) following MDAs was observed when 100 individuals randomly selected from sentinel sites and twelve spot-check sites were examined. Zanzibar now is among the several countries that has started detailed evaluation and surveillance to assess whether transmission has stopped and to assess the risk of recrudescence.

In most developing countries, individuals infected with lymphatic filariasis are also at high risk of other neglected tropical diseases, such as hookworm, ascariasis, trichuriasis, schistosomiasis and trachoma. The geographical and epidemiological overlap of these diseases is particularly extensive in sub-Saharan Africa and Brazil, where the incidence of polyparasitism is high (Raso et al., 2004; Molyneux et al., 2005). During this study other parasitic diseases, the soil-transmitted helminths and scabies were monitored in conjunction with LF prevalence following MDA rounds. A significant decline in patients with worms (soil-transmitted helminthiasis) and scabies was observed during a six year follow-up of records in 50 health facilities in the country. The decline in prevalence and intensity of *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm following MDA rounds was also recorded when 100 individuals were randomly selected from the sentinel sites and the twelve spot-check sites were examined.

The high MDA coverage has been shown to lead to decreased transmission of soil-transmitted helmithiasis (STH), suggesting that MDA for LF reduces anaemia, enhance physical fitness and growth, improves cognition, school performance and work capacity, and provides important nutritional benefits (Stephensonet al 2000; Hotez et al 2004; Brooker, et al. 2004). Hence, the LF elimination programmes through mass drug administration provides an opportunity for the development of integrated public health programmes because of the ancillary benefits of ivermectin and albendazole against intestinal nematodes infections (Utzinger and Keiser. 2004 ; Gyapong et al 2005; Mani et al 2004) and the much reduced itching from scabies and lice (Gyapong et al., 2005). Hence, Zanzibar needs to conduct a community study survey focusing particularly with school-age children to determine haemoglobin levels and other health indicators after six rounds of MDA that has been implemented with high coverage.

Although mass drug administration has a significant impact on LF transmission drug treatment does not have obvious short-term effects existing chronic clinical manifestations. Additional measures of morbidity management are essential to provide immediate benefits to the patients. In this respect, management of leg lymphoedema/elephantiasis by simple hygiene measures, which had shown to halt or even reverse this condition, has been recommended (Ottesen et al., 1997; Dreyer and Piessens, 2000). In Zanzibar study the home based care of lymphoedema patients using simple hygiene measures, elevation of the infected limbs and simple exercises showed a great improvement of conditions and a decline in frequency of attacks of adenolymphangitis in 81 patients who were under home based care of lymphoedema. What has been observed in this study is that lymphoedema patients after receiving training on home based care of their affected limbs still need constant follow up to remind them on the different steps that are to be followed. However, it is suggested programmes could prepare posters to demonstrate the steps to be followed and leave the poster with patients to promote LF morbidity control. As with hydrocele the only definitive intervention available is surgery. In Zanzibar follow-up assessment data on the condition of 45 hydrocele surgery patients showed a significant improvement of their condition. The results of follow up of patients suggested that hydrocelectomy not only corrected the hydrocele but also improved the physical and social status of the patients, his household (in terms of increased capacity to work and improved sexual function) and the community (in terms of active participation in communal activities) as was observed in Ghana (Collins et al., 2001). As also pointed out by Collins et al., (2001) we suggest that in any lymphatic filariasis endemic country during MDA rounds promoting, supporting and improving access to facilities for hydrocelectomy is an important activity to increase and sustain local interest in lymphatic filariasis control activities. This could also be an important entry point for health education to improve local understanding about the biological aetiology and consequences of lymphatic filariasis (Collins et al., 2001).

Efforts towards greater integration of schistosomiasis and STH control became manifest through the 2001 WHA resolution, and practical recommendations on how to implement such a strategy were articulated by WHO expert committee (WHO. 2002). However, one of the challenges that considered to might limit integrated chemotherapy is the safety of co-administered drugs. Even before combination therapy with albendazole plus either ivermectin or DEC was implemented on a wide scale by the GPELF, enhanced surveillance for adverse events was carried out in pilot studies in different epidemiological settings (Horton et al. 2000) and results proved the safety of those combinations. Although pharmacokinetic studies suggest that ivermectin and albendazole can be safely co-administered with praziquantel, it was recommended that similar surveillance is needed before this three-drug combination can be used widely (Na-Bangchang et al., 2006). Zanzibar during its sixth's MDA round used three drugs combination at the same time. This was a study to investigate triple combination therapy in the mass treatment of lymphatic filariasis, schistosomiasis and soil-transmitted helminthiasis in a single treatment to reduce costs. In this study combining the treatment of albendazole, ivermectin (Mectizan®) and praziquantel was designed as a safety study on a large population and was among the first studies to be conducted in sub-Saharan Africa where the diseases are co-endemic (Mohammed et al., 2008). In Zanzibar this triple therapy study conducted by LF elimination programme provided a good framework for the synergy of control activities for other neglected tropical diseases (soil-transmitted helminthiasis and schistosomiasis) prevailing in Zanzibar and resulted in the Ministry of Health establishing an integrated helminthes control programme to address all neglected tropical diseases prevailing in the country. An important point for integration is the belief that significant cost savings can accrue from combining mapping activities, training and social mobilization, logistics and project management (Lammie et al. 2006; Ottesen et al. 2008; Molyneux et al 2009). As recommended by WHO in communities where LF programmes are ongoing and where schistosomiasis and soil-transmitted helminthiasis are co-endemic community-based treatment

for schistosomiasis and soil-transmitted helminthiasis could be warranted even when the prevalence of infection is below an arbitrarily set threshold (e.g. 50%) (WHO. 2002). Similar arguments for community MDA apply where the distribution of schistosomiasis and soil-transmitted helminthiasis overlap (Lammie P.J. et al. 2006).

However, when planning for integration it is very important that each disease-specific goal be considered. This needs to be done right at the planning stage. As expressed by Lammie P.J. et al. 2006 if integration efforts are undertaken in a systematic way and can be shown to strengthen existing health systems, it is plausible that a major step will be made towards achieving both health and poverty-related millennium goals.

REFERENCES

Abaru DE MJ, Marshall TF, Hamilton PJ, Vaughan JP, and Wegesa P.1980. Tanzania filariasis project: studies on microfilaraemia and selected clinical manifestations of Bancroftian filariasis. *Acta Trop. 37*: 63-71.

Abbasi I., Humburger J., Githure JJ., Ochola J., Agure R., Koech DK., Ramzy R., Gad A and Williams SA.1996. Detection *Wuchereria bancrofti* DNA inpatients' sputum by the polymerase chain reaction. *Trans R Soc Trop Med Hyg.* 90: 531-2

Abdel-Hameed AA DW, and Alkhalife IS., 2004. An inguinal mass with local vascular lesions induced by a lymphatic filaria. *Saudi Med. J. 25*: 1106-8.

Addis DG and Dreyer G. 1999. Treatment of Lymphatic filariasis in "Lymphatic filariasis". *Imperial College Press, London.*: 151-199.

Addis DG and Dreyer G. 2000. Treatment of Lymphatic Filariasis. In Lymphatic Filariasis. T.B. Nutman, editor. *Imperial College Press, London.*: 15-199.

Addis DG and Mckenzie C, 2004. LF Disease-Clinical Management. *Am J Trop Med Hyg. 71*: 12-15.

Addis DG. Dimock KA, Eberhard ML & Lammie PJ.,1995. Clinical,parasitolgic and immunologic observations of patients with hydrocele and elephantiasis in area with endemic lymphatic filariasis. *J Infect Dis. 171*: 755-758.

Addis DG.,Ejere H., Garner P., Gelband H., Gamble C. 2005. Albendazole for lymphatic filariasis (Review). *The Cochrane Collaboration.*

Addis DG, and Brady MA. 2007. Morbidity management in the Global Programme to Eliminate Lymphatic Filariasis: a review of the scientific literature. *Filaria Journal.* 6:2.

Albonico M, Bickle Q, Haji HJ, Ramsan M, Khatib JK, Savioli L, Taylor M. 2002. Evaluation of the efficacy of pyrantel–oxantel for the treatment of soil-transmitted nematode infections. *Trans. R. Soc. Trop. Med. Hyg. 96*: 635-690.

Albonico M, Montresor A, Crompton DWT and Savioli L. 2006. Intervention for the Control of Soil-Transmitted Helminthiasis in the Community. *Advances in Parasitology. 61*: 311-348.

Albonico M., Stoltzfus RJ., Savioli L., Tielsch JM., Chwaya HM., Ercole E., Cancrini G. 1998. Epidemiological evidence for a differential effect of hookworm species, Ancylostoma duodenale or Necator americanus, on iron status of children. *Int J Epidemiology. 27*: 530-7.

Alexander N D., 2000. Wuchereria bancrofti infection and disease in rural area of Papua New Guinea. *P N G Med J. 43*: 166-71.

Amaral F, Dreyer G, Figueredo-Silva J, Noroes J, Cavalcanti A, Samico SC, Santos A, and Countinho A. 1994. Live adult worms detected by ultrasonography in human Bancroftian filariasis. *Am J Trop Med Hyg. 50*: 753-7.

Ambroise-Thomas P.1974. Immunological diagnosis of human filariasis. Present possibilities, difficulties and limitations. *Acta Trop.* 31:108-28.

Anderson R, and Bain O. 1976. Keys to Genera of Spirurida. Part 3. Diplotriaenoidea, Aproctoidea and Filaroidea. In CIH keys to nematode parasites of vertebrates. R. Anderson, G. Chabaud, and S. Willmott, editors. *Commonwealth Agricultural Bureaux, London, England.*

Anonymous, 2001. Lymphatic filariasis. Weekly epidemiological record. *20*: 149 156.

Ash LR, and Riley JM. 1970. Development of subperiodic *Brugia malayi* in the jird, *Meriones unguiculatus,* with notes on infections in other rodents. *J Parasitol. 56*: 969-73.

Aylward B, Hennessey KA, Zagaria N, Olive JM, and Cochi S. 2000. When is a disease eradicable? 100 years of lessons learned. *Am J Public Health. 90*: 1515-20.

Bailey JW, Hightower AW, Eberhard ML, and Lammie PJ. 1995. Acquisition and expression of humoral reactivity to antigens of infective stages of filarial larvae. *Parasite Immunol. 17*: 617-23.

Bancrofti J. , 1877. Discovery of the adult representative of microscopic filariae. *Lancet 2*: 70-71.

Barbee WC, Ewert A, and Folse D. 1977. The combined effect of a cutaneo lymphatic fungus, *Sporothrix schenckii* and a lymphatic-dwelling nematode, *Brugia malayi. Trop Geogr Med. 29*: 65-73.

Bawden M., Slaten D. and Malone J. 1994. QBC: rapid filarial diagnoses from blood *Mansonella ozzardi* and *Wucheria bancrofti. Trans R Soc Trop Med Hyg.88:66.*

Beach MJ., Streit, TG., Addis,DG., Prospere, R., Roberts JM., Lammie, PJ. 1999. Assessment of combined ivermectin and albendazole for treatment of intestional helminth and Wuchereria bancrofti infections in Haitian schoolchildren. *Am J Tropical Medicine and Hygiene. 60*: 479-86.

Beaver P, Jung R, and Cupp E. 1984. Clinical parasitoloy. Lea & Febiger, Philadelphia, PA.

Bennet, A and Guyatt, H. 2000. Reducing intestinal nematodes infection:efficacy of albendazole and mebendazole. *Parasitology Today 2*: 71-74.

Bernhard P, Magnussen P, Lemnge MM. 2001. A randomized, double-blind, placebo-controlled study with diethylcarbamazine for the treatment of hydrocele in an area of Tanzania endemic for lymphatic filariasis. *Trans R Soc Trop Med Hyg 95*: 534-536.

Beye, 1952. Preliminary observations on the prevalence, clinical manifestations, and control of filariasis in Society Islands. *American Journal of Tropical Medicine and Hygiene 1*: 637-661.

Binoy C., Rao, Y.G., Ananthakrishnan, N., Kate, V., Yuvaraj, J. & Pani, S.P. 1998. Omentoplasty in the management of filarial lymphoedema. *Trans R Soc Trop Med Hyg 92*: 317-319.

Bockarie MJ, Alexander NDE, Kazura JW, Bockarie F, Griffin L, and Alpers MP. 1999. Treatment with ivermectin reduces the high prevalence of scabies in a village in Papua New Guinea. *Acta Trop. 75*: 127-130.

Bockarie MJ, Fischer P, Williams SA, Zimmerman PA, Griffin L, Alpers MP, and Kazura JW. 2000. Application of a polymerase chain reaction-ELISA to detect *Wuchereria bancrofti* in pools of wild-caught *Anopheles punctulatus* in filariasis in Papua New Guinea. *Am J Trop Med Hyg. 62*: 363-7.

Bockarie MJ, Fischer P, Williams SA, Zimmerman PA, Griffin L, Alpers MP, and Kazura JW. 2002. Mass treatment to eliminate filariasis in Papua New Guinea. *New England Journal of Medicine 347*: 1841-1848.

Bosworth W, and Ewert A.1975. The effect of *Streptococcus* on the persistence of *Brugia malayi* and on the production of elephantiasis in cats. *Int J Parasitol. 5*: 583-9.

Boussinesq M, Gardon J, Gardon-Wendel N, and Chippaux JP. 2003. Clinical picture, epidemiology and outcome of Loa-associated serious adverse events related to mass ivermectin treatment of onchocerciasis in Cameroon. *Filaria J. 2 Suppl 1:S4.*

Brabin L., 1990. Sex differentials in susceptibility to lymphatic filariasis and implications for maternal child immunity. *Epidemiol Infect. 105*: 335-53.

Brooker S., Bethony J, and Hotez PJ. 2004. Hookworm infection in the 21st century. *Adv Parasitol.* 58:197-288.

Bryan JH, and Southgate BA.(1988b) Factors affecting transmission of *Wuchereria bancrofti* by anophiline mosquitoes. 1. Uptake of microfilariae. *Trans R Soc Trop Med Hyg 82*: 128-37.

Bryan JH, Oothman P, Andrews BJ, and McGreevy PB. 1974. Proceedings: Effects of pharyngeal armature of mosquitoes on microfilariae of *Brugia pahangi. Soc Trop Med Hyg. 68*: 14.

Buckley JJ. 1960. On Brugia gen. nov. for *Wuchereria spp.* of the 'malayl' group, i.e., *W.malayi* (Brug,1927). *W.pahangi* Buckley and Edeson,1956, and *W.patei* Buckley, Nelson and Heisch, 1958. *Ann Trop Med Parasitol 54*: 75-7.

Burkot T, and Ichimori K. 2002. The PacELF programme: will mass drug administration be enough? *Trends Parasitol. 18*: 109-15.

Carapetis JR., Connors C., Yarmirr D., Krause V., Currie BJ. 1997. Success of scabies control program in an Australian aboriginal community. *Pediatr. Infect. Dis. J. 16*: 494-499.

Case T, Leis B, Witte M, Way D, Bernas M, Borgs P, Crandall C, Crandall R, Nagle R, Jamal S, et al. 1991. Vascular abnormalities in experimental and human lymphatic filariasis. *Lymphology. 24*: 174-83.

Case T, Leis B, Witte MH, Way DL, Crandall CA, Crandall RB. 1992. Videomicroscopy of intralymphatic-dwelling *Brugia malayi. Ann Trop Med Parasitol 86*: 435-8.

Casley-Smith JR, Morgan, R.G. & Piller, N.B., 1993. Treatment of lymphoedema of the arms and legs with 5, 6-benzo-[alpha]-pyrone. *New England Journal of Medicine 329*: 1158-1163.

Casley-Smith, J.R. & Casley-Smith, J.R. 1997. Modern treatment for lymphoedema. *5th edition. The Lymphoedema Association of Australia, Inc.*

CDC., 1993. Recommendations of the International Task Force for Disease Eradication. In Morbidity and Mortality Weekly Report. Vol. 42, Centers for Disease Control and Prevention.: 1-38.

Chabaud G., 1974. Keys to subclasses, order and superfamilies. In CIH keys to nematode parasites of vertebrates. R. Anderson, G. Chabaud, and S. Willmott editors. Commonwealth Agricultural Bureaux, London, England.

Chadee DD, Williams SA, and Ottesen EA. 2002. Xenomonitoring of *Culex quinquefasciatus* mosquitoes as guide for detecting the presence or absence of lymphatic filariasis: a preliminary protocol for mosquito sampling. *Ann Trop Med Parasitol*: S45-53.

Chai JY, Lee SH, Choi SY, Lee JS, Yong TS, Park KJ, Yang KA, Lee KH, Park HR, Kim MJ, Rim HJ. 2003. A survey of Brugia malayi infection on the Heuksan island, Korea. Korea J Parasitol 41:69-73.

Chandrasena TG, Premaratna R, Abeyewickrema W, and de Silva NR. 2002. Evaluation of ICT whole-blood antigen card test to detect infection due to *Wuchereria bancrofti* in Sri Lanka. *Trans R Soc Trop Med Hyg 96*: 60-3.

Chanteau S, Glaziou P, Plichart C, Luquiaud P, Moulia-Pelat JP, N'Guyen L, and Cartel JL. 1995. Wuchereria bancrofti filariasis in French Polynesia: age-specific patterns of microfilaremia, circulating antigen, and specific IgG and IgG4 responses according to transmission level. *Int J Parasitol. 25*: 81-5.

Chanteau S, Moulia-Pelat JP, Glaziou P, Nguyen NL, Luquiaud P, Plichart C, Martin PM, and Cartel JL. 1994. Og4C3 circulating antigen: a marker of infection and adult worm burden in *Wuchereria bancrofti* filariasis. *J Infect Dis. 170*: 247-50.

Chulerek P, and Desowitz R. 1970. A simplified membrane technique for the diagnosis of microfilaremia. *J. Parasitol. 56*: 23.

Ciferri, 1969. A filariasis-control program in American Samoa. *American Journal of Tropical Medicine and Hygiene 18*: 369-378.

Cox EF., 1996. Illustrated history of tropical diseases, 1 edn. *The Wellcome Trust, London.*

Crandall RB., McGreevy PB., Connor DH., Crandall CA., Neilson JT & McCall JW . 1982. The ferret (Mustela putorius furo) as an experimental host for Brugia malayi and Brugia pahangi. *Am J Trop Med Hyg. 31*:752-9.

Crivelli PE. 1986. Non-filarial elephantiasis in Nyambene range: a geochemical disease. *East Afr Med J 63*: 191-194.

Crompton DWT, Savioli L. 1993. Intestinal parasitic infections and Urbanization. *Bulletin of the World Health Organization.71:* 1-7

Crompton DW. 2000. The public health importance of hookworm disease. *Parasitology.12i Suppl:* S39-50.

Crompton DW, Savioli L. 1999. How much helminthiasis is there in the World?. *Journal of Parasitology. 85:* 397-403.

Curtis CF and Feachem RG.1981. Sanitation and *Culex pipiens* mosquitoes: a brief review. *J Trop Med Hyg.* 84: 17-25.

Dahoma MJU. 2000. MSc Thesis. UDSM.

Dandapat MC, Mohapatro SK, & Mohanty SS. 1986. Filarial Lymphoedema and elephantiasis of lower limb: a review of 44 cases. *British Journal of Surgery 73*: 451-3.

Das PK., Srividya A., Pani SP., Ramaiah KD., Vanamail P &Dhanda V. 1994. Cummulative exposure and its relationship with chronic filarial disease in bancroftian filariasis. *Southeast Asian Journal Trop Med Public Health 25*: 516-21.

Dassanayake WL, and Chow CY. 1954. The control of *Pistia stratiotes* in Ceylon by means of herbicides. *Ann Trop Med Parasitol.* 48:129-34.

Date A, Chandy M, and Pulimood,BM.1983. Filarial chyluria with opportunistic infections. *Trans R Soc Trop Med Hyg 77*: 112-113.

Day PK.1991. The endemic normal in lymphatic filariasis: A static concept. *Parasitol Today.*7:341-3.

de Almeida AB., Maia e Silva MC., Maciel MA & Freedman DO. 1996. The presence or absence of active infection, not clinical status, is most closely associated with cytokine responses in lymphatic filariasis. *J Infect Dis. 173*: 1453-9.

De Rochars MB, Direny AN, Roberts JM, Addiss DG, Radday J, Beach MJ, Streit TG, Dardith D, Lafontant JG, Lammie PJ. 2004. Community-wide reduction in prevalence and intensity of intestinal helminths as collateral benefit of lymphatic filariasis elimination programs. *Am J Trop. Med. Hyg. 71:* 466-470.

Debrah AY, Mand S, Specht S, Marfo-Debrekyei Y, Batsa L, Pfarr K, Larbi J, Lawson B, Taylor M, Adjei O, Hoerauf A. 2006. Doxycycline Reduces Plasma VEGF-C/sVEGFR-3 and Improves Pathology in Lymphatic Filariasis. PLoS Pathogen. 2 : (9) . e92.

Denham DA., & Rogers R. 1975. Structural and functional studies on the lymphatics of cats infected with Brugia pahangi. *Trans R Soc Trop Med Hyg 69*: 173-6.

Desowitz RS, Southgate BA, and Mataika JU.1973. Studies on filariasis in the Pacific. 3. Comparative efficacy of the stained blood-film, counting – chamber and membrane-filtration techniques for the diagnosis of Wuchereria bancrofti microfilaraemia in untreated patients in areas of low endemicity. *Southeast Asian J Trop Med Public Health*. 4:329-35.

Dimock KA., Addiss DG., Eberhard ML & Lammie PJ. 1994. Differential proliferative and interleukin-10 responses to fractionated filarial antigens: preferential recognition by patients with chronic lymphatic dysfunction. *J Infect Dis. 170*: 403-12.

Dimock KA., Eberhard ML & Lammie PJ. 1996. Th1-like antifilarial immune responses predominate in antigen-negative persons. *Infect Immun. 64*: 2962-7.

Dowdle WR. 1998. The principles of disease elimination and eradication. *Bull World Health Organ. 76 Suppl* 2:22-5.

Dreyer G., Santos A., Noroes J., Rocha A, and Addis D. 1996c. A microfilaraemic carriers of adult *Wuchereria bancrofti. Trans R Soc Trop Med Hyg*. 90:288-9.

Dreyer G., Addiss, D., Noroes,J., Amaral, F., Rocha, A., & Coutinho, A. (1996a). Ultrasonographic assessment of the adulticidal efficacy of repeat high-dose ivermectin in bancroftian filariasis. *Trop Med Int Health 1*: 427-32.

Dreyer G., Addiss, D., Santos A., Figueredo-Silva J & Noroes J 1998. Direct assessment in vivo of the efficacy of combined single-dose ivermectin and diethylcarbamazine against adult Wuchereria bancrofti.(1998a). *Trans R Soc Trop Med Hyg 92*: 219-22.

Dreyer G., Addiss, D., Roberts J., Noroes J. 2002. Progression of lymphatic vessel dilation in the presence of living adult Wuchereria bancrofti. *Trans R Soc Trop Med Hyg 96*: 157-161.

Dreyer G., Figueredo-Silva J., Neafie RC & Addiss DG. 1998. Lymphatic filariasis. In Pathology of emerging infections. A.M.Nelson and J.C.R. Horsburgh, editors. (1998b). *American Society for Microbiology, Washington, D.C.*: 317-342.

Dreyer G., Medeiros Z., Netto MJ., Leal NC., de Castro LG., & Piessens WF. 1999. Acute attacks in the extremities of persons living in an area endemic for bancroftian filariasis: differentiation of two syndromes. *Trans R Soc Trop Med Hyg 93*: 413-417.

Dreyer G., Noroes J., Figueredo-Silva J., Piessens WF. 2000. Pathogenesis of lymphatic disease in bancroftian filariasis:A clinical perspective. *Parasitology Today 16*: 544-548.

Eberhard ML, and Lammie PJ.1991. Laboratory diagnosis of filariasis. *Clin Lab Med.* 11: 977-1010.

Dunyo SK., Nkrumah FK., Ahorlu CK & Simonsen PE. 1998. Exfoliative skin manifestations in acute lymphatic filariasis. *Trans R Soc Trop Med Hyg 92*: 539-540.

Egwang TG., Nguiri C., Kombila M., Duong TH., & Richard-Lenoble D. 1993. Elevated antifilarial IgG4 antibody levels in microfilaremic and microfilaridermic Gabonese adults and children. *Am J Trop Med Hyg. 49*: 135-42.

ElSetouhy M., Ramzy RM., Ahmed ES., Kandil AM., Hussain O., Farid HA., Helmy H & Weil GJ. 2004. A randomized clinical trial comparing single and multi-dose combination therapy with diethylcarbamazine and albendazole for treatment of bancroftian filariasis. *Am J Trop Med Hyg. 70*: 191-6.

Esterre P, Inzan CK, Ramarcel, ER., Andriantsimahavandy, A., Ratsioharana,M., Pecarrere, JL., & Roig, P. 1996. Treatment of chromomycosis with terbinafine: preliminary results of an open pilot study. *British Journal of Dermatology, 134 Supplement 46,*: 33-36.

Esterre P., Plichart C., Sechan Y, and Nguyen NL. 2001. The impact of 34 massive DEC chemotherapy on *Wuchereria bancrofti* infection and transmission: the Maupiti cohort. *Trop Med Int Health.* 6: 190-5.

Fairley NH. 1937. Serological and intradermal tests in filariasis. *R Soc Trop Med Hyg.* 24: 635- 648.

Fan PC. 1990. Eradication of bancroftian filariasis by diethylcarbamazine medicated common salt on Little Kinmen (Liehyu district),Kinmen (Quemoy) Islands, Republic of China. *Ann Trop Med Parasitol.* 84: 25-33.

Fan PC, Peng HW, Chen CC. 1995. Follow-up investigations on clinical manifestations after filariasis eradication by diethylcarbamazine medicated common salt on Kinmen (Quemoy) Islands, Republic of China. *The Journal of Tropical Medicine and Hygiene 98*: 461-464.

Fenwick A. 2006. New initiatives against Africa's worms. Trans R Soc Trop Med Hyg. 100:200-207.

Fischer P., T.Supali, and R.M.Maizels. 2004. Lymphatic filariasis and Brugia timori: prospects for elimination. *Trends Parasitol. 20*: 351-5.

Foldi E., Foldi, M. & Clodius, L. 1989. The lymphoedema chaos: a lancet. *Annals of Plastic Surgery 22*: 505-515.

Fox LM., Furnace, BW., Haser, JK., Brissau,JM., Louis-Charles, J., Wilson, SF., Addis, DG., Lammie PJ & Beach, MJ. 2005. Ultasonographic examination of Haitian children with lymphatic filariasis: a longitudinal assessment in the context of antifilarial drug treatment. *Am J Trop Med Hyg. 72*: 642-8.

Freedman DO., Nutman TB and Ottesen EA. 1989. Protective immunity in bancroftian filariasis. Selective recognition of 43 kD larval stage antigen by infection-free individuals in an endemic area. *J Clin Invest.* 43: 14-22.

Freedman DO, and Berry RS. 1992. Rapid diagnosis of Bancroftian filariasis by acridine orange staining of centrifuged parasites. *Am J Trop Med Hyg.* 47:787-93.

Freedman DO., Almeido-Filho PJ., Besh S., Silva MC., Braga C., Maciel A., & Furtado AF (1995a). Abnormal lymphatic function in presymptomatic bancroftian filariasis. *J Infect Dis. 171*: 997-1001.

Freedman DO., Bui T., Almeido-Filho PJ., Braga C., Silva MC., Maciel A., & Furtado AF (1995b). Lymphoscintigraphic assessment of the effect ofdiethlycarbamazine treatment on lymphatic damage in human bancroftian filariasis. *American Journal of Tropical Medicine and Hygiene 52*: 258-261.

Freedman DO, de Almeido-Filho PJ, Besh S, Maia e Silva MC, Braga C., Maciel A. 1994. Lymphoscintigraphic analysis of lymphatic abnormalities in symptomatic and asymptomatic human filariasis. *J Infect Dis. 170*: 927-33.

Gautamadasa CH.1986. A historical review of Brugian filariasis and its present status in Sri Lanka (MD Thesis). In Postgraduate Institute of Medicine. University of Colombo, Colombo.

Gao CL., Cao WC and Chen XX. 1994. Changes in anti-filarial antibody after control of filariasis in Shangdong Province. Chin Med J(Engl).107: 360-3.

Gardon J · Gardon-Wendel N, Demanga-Ngangue TSSP, Kamgno J, Jean-Philippe Chippaux and Boussinesq M. 1997. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for *Loa loa* infection. *The Lancet.* 350: (9070): 18-22.

Glaziou P., Cartel JL., Alzieu P., Briot C., Moulia-Petal JP., Martin PM. 1993. Comparison of ivermectin and benzyl benzoate for treatment of scabies. *Trop. Med. Parasitol. 44*: 331-332.

GOZ ,Zanzibar Ministry of Health and Social Welfare 2000 Report.

Greene BM., Taylor HR., Brown EJ.,Humphrey RL & Lawley TJ. 1983. Ocular and systemetic complications of diethylcarbamazine therapy for onchocerciasis: association with circulating immune complexes. *J Infect Dis. 147*: 890-7.

Grove DI. 1990. A history of Human Helmithology. 1 edn. *C.A.B. International, Wallingford.*

Gubler D.J, Bhattacharya NC. 1974. A quantitative approach to the study of bancroftian filariasis. *Am J Trop Med Hyg. 23*: 1027-1036.

Gyapong JO., Webber RH., Morris J., Bennet S. 1998. Prevalence of hydrocele as a rapid diagnostic index for lymphatic filariasis (1998a). *Trans R Soc Trop Med Hyg 92*: 40-43.

Gyapong JO., Kumaraswami V., Biswas G, and Ottesen EA. 2005. Treatment strategies underpinning the global programme to eliminate lymphatic filariasis. *Expert Opin Pharmacother.* 6: 179-200.

Gyapong M., Gyapong JO., Weiss M, and Tanner M. 2000. The burden of hydrocele on men in Northern Ghana. *ActaTrop.*77: 287-94.

Gyapong M., Gyapong JO, and Owusu-Banahene G. 2001. Community-directed treatment:the way forward to eliminating lymphatic filariasis as a public – health problem in Ghana. *Ann Trop Med Parasitol.*95: 77-86.

Hairston N.G, De Meillon B. 1968. On the ineffeciency of transmission of Wuchereria bancrofti from mosquito to human host. *Bull World Health Organization , 38*: 935-941.

Hamer DH, Despommier DD. 1998. Tissue nematodes. In:Infectious Diseases,. *Gorbach SL, JG Bartlett, Blacklow NR, eds. Philadelphia: W.B. Saunders Company,*: 2466-2475.

Harnett W., Bradley JE, and Garate T.1998. Molecular and immunodiagnosis of human filarial nematode infections. *Parasitology.*117 *Suppl* :S59 – 71.

Hawking F.1967. The 24-hours periodicity of microfilariae: biological mechanisms responsible for its production and control. *In Royal Society Series B. Vol.* 169 (1014).59-76.

Hawking F.1977. The distribution of human filariasis throughout the world. Part III. Africa. *Trop Dis Bull.* 74:649-79.

Heukelbach J , Walton SF, Feldmeier H. 2005. Ectoparasitic infestations. Current Infectious Diseases. 7: (5): 373-380.

Hines SA., Williams JL., Doyle TJ., Crandall RB., Crandall CA & Nayar JK. 1985. Lymphangiography in ferrets infected with Brugia malayi. *Lymphology. 18*: 173-4.

Horton J, 2000. Albendazole: a review of antihelminthic efficacy and safety in humans. *Parasitology 121*: S113-S132.

Horton J., Witt C., Ottesen EA., Lazdins JK., Addis DG.,Awadzi K.,Beach MJ., Belizario VY., Dunyo SK., Espinel M., Gyapong JO., Hossain M., Ismail MM., Jayacody RL., Lammie PJ., Makunde W., Richard-Lenoble D., Selve B., Shenoy RK., Simonsen PE., Wamae CN , and Weerasooriya MV. 2000. An analysis of the safety of a single dose, two drug regimens used in programmes to eliminate lymphatic filariasis. *Parasitology.121 Suppl*: S 147-60.

Hotez PJ., Buss P., Alleyne G., Morel C.,and Breman JG. 2004. Combating tropical infectious diseases: report of the Disease Control Priorities in Developing Countries Project. *Clin Infect Dis.*38:871-8.

Hotez PJ, Bethony, J., Bottazzi, M.E., Brooker,S., Buss,P. 2005. Hookworm: "the great infection of mankind". *PLoS Med. 2:e67.*

Hotez PJ. 2008. Hookworm and poverty. *Ann N Y Acad Sci.*1136:38-44.

Ismail MM, Jayakody, RL., Weil, GJ., Fernando, D., DeSilva,MS., DeSilva, GA., & Balasooriya, WK. 1998. Efficacy of single dose combinations of albendazole,ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis. Trans R Soc Trop Med Hyg. 92 : 94-97

Ismail MM, Jayakody, RL., Weil, GJ., Fernando, D., DeSilva,MS., DeSilva, GA.,& Balasooriya, WK. 2001. Long-term efficacy of single-dose combinations of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis. *Trans R Soc Trop Med Hyg 95*: 332-5.

Itoh M., Weerasooriya MV., Qiu G., Gunawardena NK., Anantaphuriti MT., Tesana S., Rattannaxay P., Fujimaki Y, and Kimura E. 2001. Sensitivity and specific enzyme-linked immunosorbent assay for the diagnosis of *Wuchereria bancrofti* infection in urine samples. *Am J Trop Med Hyg.* 65: 362-5.

Jungmann P., Figueredo, Silva J. & Dreyer, G.1991. Bancroftian lymphadenopathy: a histopathologic study of fifty-eight cases from northeastern Brazil. *American Journal of Tropical Medicine and Hygiene 45*: 325-331.

Kaizer L., Tithof PK & Williams JF. 1990. Depression of endothelium-dependent relaxation by filarial parasite products. *Am J Physiology 259*: H648-52.

Kazura JW. 1999. Filariasis. In: Tropical infectious diseases: principles,pathogens, and practice. (eds. Guerrant, R.L., Walker, D.H., & Weller, P.F.),. *Churchill Livingstone, Philadelphia.*: 852-902.

Kazura JW. 2002. Lymphatic Filariasis infections:an introduction to the filariae. In World Class parasites:The filaria. Vol.5. R.T.Klei TR, editor. *Kluwer Academic Publishers, London.*: 1-8.

Kenney M, Hewitt R. 1949. Treatment of Bancroftian filariasis with Hetrazan in British Guiana. *American Journal of Tropical Medicine and Hygiene 29*: 89-114.

Kilama WL, Swai ABM, Kihamia CM & Rwiza H. 1975. Bancroftian Filariasis in Zanzibar. *Mimeographed report, Ministry of Health, Zanzibar.*

King BG. , 1944. Early filariasis diagnosis and clinical findings: a report of 268 cases in American troops. *American Journal of Tropical Medicine and Hygiene 24*: 285-298.

King CL., Nutman TB.1991. Regulation of the immune response in lymphatic filariasis and onchocerciasis. *Parasite Today. 7*: 54-8.

King CL., Ottesen EA & Nutman TB. 1990. Cytokine regulation of antigen-driven immunoglobin production in filarial parasite infections in humans. *J Clinical Invest. 85*: 1810-5.

Kobayashi M. NM, Kanazawa T., Husky MK., Malagueno E & Santana JV, 1997. Detection of microfilarial antigen in circulating immune complex from sera of Wuchereria bancrofti-infected individuals. *Am J Trop Med Hyg. 57*: 200-4.

Kwan-Lim GE., Forsyth KP., Maizels RM. 1990. Filarial-specific IgG4 response correlates with active Wuchereria bancroftian infection. *J Immunology 145*: 4298-4305.

Lammie PJ., Hightower, AW., Eberhard ML. 1994. Age-specific prevalence of antigenemia in a Wuchereria bancrofti-exposed population. *Am J Trop Med Hyg. 51*: 348-55.

Lammie PJ, Reiss MD, Dimock KA, Streit TG, Roberts JM, Eberhard ML 1998. Longitudinal analysis of the development of filarial infection and antifilarial immunity in a cohort of Haitian children. *Am J Trop Med Hyg. 59*: 217-221.

Lammie PJ., Cuenco KT, and Punkosdy GA. 2002. The pathogenesis of filarial lymphoedema: is it the worm or is it the host? *Ann N Y Acad Sci.* 979: 131- 42.

Lammie PJ., Fenwick A, and Utzinger J. 2006. A blueprint for success: integration of neglected tropical diseases control programmes. *Trends Parasitol.22:* 313-321.

Lunde MN., Paranjape R., Lawley TJ & Ottesen EA. 1988. Filarial antigen in circulating immune complexes from patients with Wuchereria bancrofti filariasis. *Am J Trop Med Hyg. 38*: 366-71.

Mahadevan R, 1978. Surgical aspects of filariasis. *Tropical Doctor 8*: 28-35.

Mahanty S., Abrams JS., King CL., Limaye AP, Nutman TB.1992. Parallel regulation of IL-4 and IL-5 in human helminth infections. *J Immunolo.*148: 3567-71

Mani TR, Rajendran R, Sunish IP, Munirathinam A, Arunachalam N, Satyanarayana K, Dash AP. 2004. Effectiveness of two annual, single-dose mass drug administrations of diethylcarbamazine alone or in combination with albendazole on soil-transmitted helmithiasis in elimination programme. *Trop Med Int Health. 9*: 1030-1035.

Mansfield-Aders W., 1927. Notes on malaria and filariasis in the Zanzibar Protectorate. *Trans R Soc Trop Med Hyg 21*: 207-214.

Manson P. 1899. On filarial periodicity. *Bmj.2:* 644-646.

Manson-Bahr P. 1959. The Story of Filaria Bancrofti. II. Metamorphosis of W. bancrofti in the mosquito and filarial periodicity. *J Trop Med Hyg.*62:85-94 contd.

March, 1960. Reduction in the prevalence of clinical filariasis in Tahiti following

adoption of a control program. *American Journal of Tropical Medicine and Hygiene 9*: 180-184.

Maxwell CA, Curtis CF, Haji H, Kisumku S, Talib AI & Yahya SA. 1990. Control of bancroftian filariasis by integrating therapy with vector control using polystyrene beads in wet pit latrines. *Trans R Soc Trop Med Hyg 84*: 709 - 714.

Maxwell CA, Muchi J & Curtis CF. 1991. Transfer of vector control technology from a small town to a large one. *Trans R Soc Trop Med Hyg 85*: 314.

Maxwell CA., Mohammed K., Kisumku U & Curtis CF. 1999. Can vector control play a useful supplementary role against bancroftian filariasis ? *Bull World Health Organization 77*: 138-143.

McCarthy JS., Zhong M., Gopinath R., Ottesen EA., Williams SA , and Nutman TB.1996. Evaluation of polymerase chain reaction-based assay for diagnosis of *Wuchereria bancrofti* infection. J Infect Dis. 173: 1510-4.

McGreevey PB., Brayan JH., Oothuman P, and Kolstrup N.1978. The lethal effects of cibarial and pharyngeal armatures of mosquitoes on microfilariae. *Trans R Soc Trop Med Hyg.*72: 361-8.

McGregor A, 1994. Washing off elephantiasis [News]. *The Lancet 344, 121.*

McMahon JE., Marshall TF., Vaughan JP and Abaru DE. 1979. Bancroftian filariasis: a comparison of microfilariae counting techniques using chamber standard slide and membrane (nuclepore) filtration. *Ann Trop Med Parasitol.* 73:457- 64.

McMahon JE., Magayauka SA., Kolstrup N., Mosha FW., Bushrod FM., Abaru DE, and Bryan JH.1981. Studies on transmission of Bancroftian filariasis in four coastal villages of Tanzania. *Ann Trop Med Parasitol.* 75: 415-31.

McMahon JE, Simonsen,PE., 1995. Filariasis. In: Manson's Tropical Diseases. (ed. Cook, G.C.),. *WB Saunders Company Ltd., London.*: 1321-1368.

McPherson T, 2003. Impact on the quality of life of lymphoedema patients following introduction of hygiene and skin care regimen in a Guyanese community endemic for lymphatic filariasis: A preliminary clinical intervention study. *Filaria Journal 2*: 1-5.

Melrose WD., 2002. Lymphatic filariasis:new insights into an old disease. *Int J Parasitol. 32*: 947-60.

Merelo-Lobo AR, McCall PJ, Perez MA, Spiers AA, Mzilahowa T, Ngwira B, Molyneux DH, Donnelly MJ, 2003. Identification of the vectors of lymphatic filariasis in the Lower Shire Valley, southern Malawi. *Trans R Soc Trop Med Hyg 97*: 299-301.

Meyrowitsch DW, Simonsen, P.E. & Makunde, W.H., 1995. Bancroftian filariasis: analysis of infection and disease in five endemic communities of north-eastern Tanzania. *Ann Trop Med Parasitol 89*: 653-663.

Meyrowitsch DW, Simonsen PE, Makunde WH. 1996. Mass diethylcarbamazine chemotherapy for control of bancroftian filariasis through community participation: comparative efficacy of low monthly dose and medicated salt. *Transactions of the Royal Society of Tropical Medicine and Hygiene 90*: 74-79.

Michael E., Bundy DA., Grenfell BT. 1996. Re-assessing the global prevalence and distribution of lymphatic filariasis. *Parasitology 112(Pt.4)*: 409-28.

Michael E.,Malecela-Lazaro MN.,Simonsen PE.,Pedersen EM.,Baker G., Kumar A, and Kazura JW. 2004. Mathematical modelling and the control of lymphatic filariasis. *Lancet Infect Dis.*4:223-34.

Mohammed KA., Molyneux DH., Albonico M, and Rio F. 2006. Progress towards eliminating lymphatic filariasis in Zanzibar: a model programme. *Trends Parasitol.* 22: 340-4.

Mohammed KA., Haji HJ.,, Gabrielli AF.,, Mubila L.,Biswas G., Chitsulo L., Bradley MH., Engels D., Savioli L, and Molyneux DH. 2008. Triple Co Administration of Ivermectin, Albendazole and Praziquantel in Zanzibar: A Safety Study. *PLoS Neglected Tropical Diseases. 2:(1):* e171.

MOHSW, Ministry of Health and Social Welfare, Zanzibar. Annual Report 2002.

Molyneux DH, and Zagaria N. 2002. Lymphatic filariasis elimination: progress in global programme development. *Ann Trop Med Parasitol 96 Suppl 2:S15-40.*

Molyneux D H., Bradley M., Hoerauf A.,Kyelem D,and Taylor,MJ. 2003. Mass drug treatment for lymphatic filariasis and onchocerciasis. *Trends Parasitol. 19*: 516-22.

Molyneux D H. Hotez, P.J., & Fenwick ,A., 2005. "Rapid - impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. *PLoS Med. 2:e336.*

Molyneux D H, and Nantulya VM, 2004. Linking disease control programmes in rural Africa: a pro-poor strategy to reach Abuja targets and millennium development goals. *Bmj. 328*: 1129-32.

Molyneux D H., Neira M., Liese B, and Heymann D. 2000. Lymphatic filariasis: setting the scene for elimination. *Trans R Soc Trop Med Hyg 94*: 589-91.

Molyneux D H, and Taylor MJ, 2001. Current Status and future prospects of the Global Lymphatic Filariasis Programme. *Curr Opin Infectious Diseases 14*: 155-9.

More SJ, and Copeman DB. 1990. A highly specific and sensitive monoclonal antibody-based ELISA for the detection of circulating antigen in bancroftian filariasis. *Trop Med Parasitol.* 41:403-6.

Moore,1996. Diethylcarbamazine-induced reversal of early lymphatic dysfunction in a patient with bancroftian filariasis: assessment with use of lymphoscintigraphy. *Clinical Infectious Diseases 23*: 1007-1011.

Mortimer PS., 1995. Managing lymphoedema. *Clinical and Experimental Dermatology 20*: 98-106.

Mosmann TR. CR, 1989. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol. 7*: 145-73.

Moulia-Pelat JP., Glaziou P., Nguyen-Ngoc L., Cardines D.,Spiegel A, and Cartel JL. 1992. A comparative study of detection methods for evaluation of microfilaraemia in lymphatic filariasis control programmes. *Trop Med Parasitol.* 43: 146-8.

Moulia-Pelat JP., Glaziou P., Weil GJ., Nguyen LN., Gaxotte P, and Nicolas L. 1995. Combination of ivermectin and diethylcarbamazine, a new effective tool for control of lymphatic filariasis. *Trop Med Parasitol.* 46: 9-12.

Mupanomunda M. WJ, Mackenzie CD & Kaiser L, 1997. Dirofilaria immitis: heartworm infection alters pulmonary artery endothelial cell behavior. *J Appl Physiol. 82*: 389-98.

Mwandawiro CS., Fujimaki Y., Mitsui Y, and Katsivo M.1997. Mosquito vectors of bancroftian filariasis in Kwale district, Kenya. *East Afr Med J.* 74:288-93.

National Bureau of Stastistics Tanzania 2002.

Nelson GS., Heisch RB, and Furlong M.1962. Studies in filariasis in East Africa. II. Filarial infections in man, animals and mosquitoes on the Kenya Coast. *Trans R Soc Trop Med Hyg.*56:202-17.

Nelson FK. GD, Shultz LD & Rajan TV, 1991. The immunodeficient scid mouse as a model for human lymphatic filariasis. *J Exp Med. 173*: 659-63.

Ngwira BM., Jabu CH, Kanyongoloka H, Mponda M, Crampin AC, Branson K, Alexander ND, Fine PE, 2002. Lymphatic filariasis in the Karonga district of northern Malawi: a prevalence survey. *Ann Trop Med Parasitol 96*: 137-44.

Nicolas L. LS, Plichart C & Deparis X., 1999. Filarial antibody responses in *Wuchereria bancrofti* transmission area are related to parasitological but not clinical status. *Parasite Immunol. 21*: 73-80.

Noroes J. A, D., Santos, A., Medeiros, Z., Coutinho, A. & Dreyer, G., 1996. Ultrasonographic evidence of abnormal lymphatic vessels in young men with adult Wuchereria bancrofti infection in the scrotal area. *Journal of Urology, 156*: 409-412.

Noroes J. A, D., Amaral F., Coutinho A., Medeiros, Z., Coutinho, A. & Dreyer, G., 1996. Occurrence of living adult Wuchereria bancrofti in the scrotal area of men with microfilaraemia. *Trans R Soc Trop Med Hyg 90*: 55-56.

Noroes J. DG, Santos A., Mendes VG., Medeiros Z & Addiss D, 1997. Assessment of the efficacy of diethlycarbamazine on adult Wuchereria bancrofti in vivo. *Trans R Soc Trop Med Hyg 91*: 78-81.

Nutman TB., Zimmerman PA., Kubofcik J and Kostyu DD.1994. A universally applicable diagnostic approach to filarial and other infections. *Parasitology Today.*10:239-43.

Olszewski W.L. J, S., Manokaran, G., Lukomska, B. & Kubicka, U., 1993. Skin changes in filarial and non-filarial lymphoedema of the lower exttremities. *Tropical Medicine and Parasitology 44*: 40-44.

Olszewski WL. JS, Manokaran G., Pani S., Kumaraswami V., Kubicka U., Lukomska B., Tripathi FM., Swoboda E., Meisel-Mikolajezyk F., Stelmach E & Zaleska M, 1999. Bacteriological studies of blood, tissue fluid, lymph and lymph nodes in patients with acute dermatolymphangioadenitis (DLA) in course of 'filarial' lymphedema. *Acta Trop. 73*: 217-224.

Organization WH, (1999). Report of the WHO Informal Consultation on Monitoring Drug Efficacy in the Control of Schistosomiasis and Intestinal Nematodes. Geneva. *WHO, WHO/CDS/CPC/SIP 99.1.*

Organization WH, (2004a). WHO Model Formulary. Based on the 13th Model List of Essential Medicines 2003. Geneva:. *WHO*: 82-85.

Ottesen EA . 1990. The filariasis and tropical pulmonary eosinophilia. In: Tropical and Geographical Medicine,. *Warren, K.S. & Mahmoud, AAF (editors), 2nd edition. New York: McGraw-Hill,*: 407-428.

Ottesen EA . 1999. Towards Eliminating Lymphatic Filariasis. In Lymphatic filariasis. N. TB, editor. Imperial College Press. London. 201- 215.

Ottesen EA . 2000. The global programme to eliminate lymphatic filariasis. *Trop Med Int Health 5*: 591-4.

Ottesen EA . WP, Lunde M.N., & Hussain R., 1982. Endemic filariasis on a Pacific Island. II. Immunologic aspects: immunoglobulin, complement, and specific antifilarial IgG,IgM, andIgE antibodies. *Am J Trop Med Hyg. 32*: 953-61.

Ottesen EA DB, Karam M, and Behbehani K., 1997. Strategies and tools for the control/elimination of lymphatic filariasis. *Bull World Health Organization 75*: 491-503.

Ottesen EA., 1984. Immunological aspects of lymphatic filariasis and onchocerciasis in man. *Trans R Soc Trop Med Hyg 74 Suppl:*: 9-18.

Ottesen EA., 1985. Efficacy of diethylcarbamazine in eradicating infection with lymphatic-dwelling filariae in humans. *Rev Infect Dis 7*: 341-56.

Ottesen EA. , 1992. The Wellcome Trust Lecture. Infections and disease in lymphatic filariasis:an immunological perspective. *Parasitology. 104 Suppl*: S71-9.

Ottesen EA., 2006. Lymphatic filariasis: Treatment, control and elimination. Adv Parasitol, 61:395-441.

Ottesen EA ., Hooper PJ., Bradley M, and Biswas G. 2008. The Global Programme to Eliminate Lymphatic Filariasis: health impact after 8 years. PLoS Negl Trop Dis 2008;2:e317.

PAHO, 2003. Lymphatic Filariasis Elimination in the Americas:4th Regional Program manager's meeting, Washington,D.C.: 52-53.

Pani, 1995. Clinical manifestations of bancroftian filariasis with special reference to lymphoedema grading. *Indian Journal of Medical Research 102*: 114-118.

Pani S.P. Y, J., Vanamail, P., Dhanda, V., Michael, E., Grenfell, B.T & Bundy, D.A., 1995. Episodic adenolymphangitis and lymphoedema in patients with bancroftian filariasis. *Trans R Soc Trop Med Hyg 89*: 72-74.

Pani SP. KK, Rao AS & Prathiba J., 1990. Clinical manifestations in malayan filariasis infection with special reference to lymphoedema grading. *Indian J Med Res. 91*: 200-7.

Partono F MR, Purnomo, 1989. Towards a filariasis-free community: evaluation of filariasis control over an eleven year period in Flories, Indonesia. *Transactions of the Royal Society of Tropical Medicine and Hygiene 83*: 821-826.

Partono F. , 1987. The spectrum of disease in lymphatic filariasis. *Ciba Foundation Symposium 127*: 15-31.

Pedersen EM KW, Swai ABM, Kihamia CM, Rwiza H & Kisumku UM, 1999. Bancroftian filariasis on Pemba Island, Zanzibar, Tanzania: An update on the status in urban and semi-urban communities. *Tropical Medicine and International Health 4*: 295-301.

Pedersen EM and Mukoko, 2002. Impact of insecticide-treated materials on filarial transmission by various species of vector mosquito in Africa. Ann Trop Med Parasitol. 96. Suppl 2:S91-5.

Pichon G. 2002. Limitation and facilitation in the vectors and other aspects of dynamics of filarial transmission: the need for vector control against *Anopheles* transmitted filariasis. Ann Trop Med Parasitol. 2: S143-52.

Piessens WF. MP, Piessens PW., McGreevy M., Koiman I., Saroso JS & Dennis DT, 1980. Immune responses in human infections with Brugia malayi:specific cellular unresponsiveness to filarial antigens. 1980a. *J Clinical Invest. 65*: 172-9.

Piessens WF. MP, Ratiwayanto S., McGreevy M., Piessens PW., Koiman I., Saroso JS & Dennis DT, 1980. Immune responses in human infections with Brugia malayi:correlation of cellular and humoral reactions to microfilarial antigens with clinical status.(1980 b). *Am J Trop Med Hyg. 29*: 563-70.

Piessens WF. PF, Hoffman SL., Ratiwayanto S., Piessens PW., Palmieri JR., Koiman I., Dennis DT and Carney WP., 1982. Antigen-specific suppressor T lymphocytes in human lymphatic filariasis. *N Engl J Med. 307*: 144-8.

Piessens WF. RS, Tuti S., Palmieri JH., Piessens PW., Koiman I., & Dennis DT, 1980. Antigen-specific suppressor cells and suppressor factors in human

filariasis with Brugia malayi.(1980c). *New England Journal of Medicine 302*: 833-7.

Prasad GB. KIHB, 1983. Detection of antimicrofilarial ES antigen-antibody in immune complexes in Bancroftian filariasis by enzyme immunoassay. *Trans R Soc Trop Med Hyg 77*: 771-2.

Rahma N., Taniawati S, Shenoy RK., Lim BH., Kumaraswami V., Anuar AK., Hakim SL., Hayati MI., Chan BT., Suharni M. and Ramachandran CP 2001. Specificity and sensitivity of a rapid dipstick test (Brugia Rapid) in the detection of *Brugia malayi* infection. Trans R. Soc Trop Med Hyg. 95:601-4.

Ramaiah KD., Das PK., Michael E, and Guyatt H. 2000. The economic burden of lymphatic filariasis in India. *Parasitol Today.* 16:251-3.

Ramaiah KD., Das PK., Vanamail P, and Pani SP. 2003. The impact of six rounds of single-dose mass drug administration of *Wuchereria bancrofti* by *Culex quinquefasciatus* and its implications for lymphatic filariasis elimination programmes. *Trop Med Int Health.* 8:1082-92.

Ramaiah KD.,Guyatt H., Ramu K., Vanamail P., Pani SP,and Das PK. 1999. Treatment costs and loss of work time to individuals with chronic lymphatic filariasis in rural communities in south India. *Trop Med Int Health.* 4:19-25.

Ramaiah KD.,Kumar KN., Ramu K., Pani SP, and Das PK. 1997. Functional impairment caused by lymphatic filariasis in rural areas of south India. *Trop Med Int Health.* 2:832-8.

Ramaiah KD.,Ramu K., Guyatt H. Kumar KN and Pani SP. 1998. Direct and indirect costs of the acute form of lymphatic filariasis to households in rural areas of Tamil Nadu ,south India. *Trop Med Int Health.3*:108-15.

Ramaiah KD., Vanamail P., Pani SP., Yuvaraj J,and Das PK. 2002. The effects of single-dose mass treatment with diethylcarbamazine or ivermectin on *Wuchereria bancrofti* and its implications for lymphatic filariasis elimination. *Trop Med Int Health.* 7:767-74.

Ramaiah KD., Vanamail P, and Das PK. 2007. Changes in *Wuchereria bancrofti* infection in highly endemic community following 10 rounds of mass administration of diethylcarbamazine. *Trans R Soc Trop Med Hyg.*101:250-5.

Ramaiah KD., Das PK.,Vanamail P, and Pani SP. 2007. Impact of 10 years of diethylcarbamazine *and ivermectin mass administration on infection and transmission of lymphatic filariasis. Trans R Soc Trop Med Hyg.*101:555-563.

Ramzy RM., El Setouhy M., Helmy H., Ahmed ES., Abd Elaziz KM.,Farid HA., Shannon WD, and Weil GJ. 2006. Effect of yearly mass drug administration with diethlycarbamazine and albendazole on bancroftian filariasis in Egypt: A comprehensive assessment. *Lancet* 367. 992-9.

Ramzy RM.,Goldman AS, and Kamal HA. 2005. Define the cost of the Egyptian lymphatic filariasis elimination programme. *Filaria J* 4:7.

Raghavan NG. 1961 The vectors of human infections by Wuchereria species in endemic areas and their biology. *Bull World Health Organ.* 24:177-95.

Rajan TV GA, 1997. Lymphatic filariasis. *Chem Immunol 66*: 125-158.

Raso G., Luginbuhl A.,Adjoua CA.,Tian-Bi NT.,Silue KD et al. 2004. Multiple parasite infections and their relationship to self-reported morbidity in a community of rural Cote d'Ivoire. Int J Epidemiology. 33:1092-1102.

Ravindran B., 2003. Aping Jane Goodall:insights into human lymphatic filariasis. *Trends Parasitol. 19*: 105-9.

Rodriguez-Perez MA., Danis-Lozano R., Rodriguez MH, and Bradley JE. 1999. Comparison of serological and parasitological assessments of *Onchocerca volvulus* transmission after 7 years of mass ivermectin treatment in Mexico. *Trop Med Int Health.* 4:98-104.

Rogers R. DD, Nelson GS., Guy F & Ponnudurai T., 1975. Studies with Brugia pahangi. III: Histological changes in the affected lymph nodes of infected cats. *Ann Trop Med Parasitol 69*: 77-84.

Routh HB. aKRB, 1993. History of elephantiasis. *Int J Dermatol. 32*: 913-6.

Rozeboom L.E BNC, Gilotra S.K., 1968. Observations on the transmission of filariasis in urban Calcutta. *Am J Epidemiol 87*: 616-632.

Sebasan S., Kumar NP., Krishnamoorthy K, and Panicker KN. 1991. Seasonal abundance & biting behaviour of *Mansonia annulifera, M. uniformis* & *M. indiana* & their relative role in the transmission of malayan filariasis in Shertallai (Kerala state). *Indian J Med Res.* 93:253-8.

Sasa M., 1976. Human filariasis - A Global Survey of Epidemiology and Control. *University Park Press, Baltimore.*

Schacher JF. SP, 1967. A chronological study of the histopathology of filarial disease in cats and dogs caused by Brugia pahangi (Buckley and Edeson, 1956). *Trans R Soc Trop Med Hyg 61*: 234-43.

Schlemper BR., Steindel M., Crisard EC., Carvalho-Pinto CJ., Bernardini OJ., de Castilho CV., Rosa G., Kilian S., Guarneri AA., Rocha A., Medeiros Z, and Ferreira Neto JA. 2000. Elimination of bancroftian filariasis (*Wuchereria bancrofti*) in Santa Catarina state, Brazil. *Trop Med Int Health*. 5:848-54

Scott A.L. , 2000. Lymphatic-dwelling Filariae. In Lymphatic Filariasis. *Vol.1.T.B. Nutman, editor. ImperialCollege Press, London.*: 5-39.

Shenoy RK, Suma, T.K., Rajan, K. & Kumaraswami, V., 1998. Prevention of acute adenolymphangitis in brugian filariasis: comparison of efficacy of ivermectin and diethlycarbamazine, each combined with local treatment of the affected limb. *Ann Trop Med Parasitol 92*: 587-594.

Shenoy RK, 1998. Prevention of acute adenolymphangitis in brugian filariasis: Comparison of the efficacy of ivermectin and diethylcarbamazine, each combined with local treatment of the affected limb. *Ann Trop Med Parasitol 92*: 587-594.

Shenoy RK, Kumaraswami V, Suma TK, Rajan K, Radhakuttyamma G, 1999. A double-blind, placebo-controlled study of the efficacy of oral penicillin, diethylcarbamazine or local treatment of the affected limb in preventing acute adenolymphangitis in lymphoedema caused by brugian filariasis. *Ann Trop Med Parasitol 93*: 367-77.

Simonsen P.E, 1995. Selective diethylcarbamazine chemotherapy for control of Bancroftian filariasis in two communiies of Tanzania: compared efficacy of standard dose treatment and two semi-annual single dose treatments. *American Journal of Tropical Medicine and Hygiene 53*: 267-272.

Simonsen P.E NL, Meyrowitsch D.W., Makunde, W.H. & Magnussen, P., 1995. Bancroftian filariasis: the pattern of microfilaraemia and clinical manifestations in three endemic communities of Northern Tanzania. *Acta Trop. 60*: 179-187.

Simonsen P.E NL, Meyrowitsch D.W., 1997. Wuchereria bancrofti in Tanzania: microfilarial periodicity and effect of blood sampling time on microfilarial intensities. *Trop Med Int Health 2*: 153-158.

Simonsen P.E. L, M.M., Msangeni, H.A., Jakobsen, P.H. & Bygbjerg, I.C., 1996. Bancroftian filariasis: the patterns of filarial-specific immunoglobulin G1 (IgG1), IgG4, and circulating antigens in an endemic community of Northeastern Tanzania. *American Journal of Tropical Medicine and Hygiene 55*: 69-75.

Siridewa K., Karunanayake EH., Chandrasekharan NV., Abeyewickreme W., Franzen L., Aslund L, and Pettersson. 1994. Cloning and characterization of a repetitive DNA sequence specific for *Wuchereria bancrofti. Am J Trop Med Hyg.* 51:495-500.

Southgate BBJ, 1992. Factors affecting transmission of *Wuchereria bancrofti* by anophiline mosquitoes. 4. Facilitation, limitation, proportionality and their epidemiological significance. *Trans R Soc Trop Med Hyg 86*: 523 - 530.

Southgate VR, 1995. Medical Helminthology. In: Manson's Tropical Diseases, (ed. Cook, G.C.),. *WB Saunders Company Ltd., London.*: 1580-1649.

Steel C. GA, McCarthy JS & Ottesen EA., 1994. Long-term effect of prenatal exposure to maternal microfilaraemia on immune responsiveness to filarial parasite antigens. *Lancet. 343*: 890-3.

Steel C., Ottesen EA., Weller PF, and Nutman TB. 2001. Worm burden and host responsiveness in *Wuchereria bancrofti* infection: use antigen detection to refine earlier assessments from the South Pacific. *Am J Trop Med Hyg.* 65:498- 503.

Stoltzfus RJ., Albonico M., Chwaya HM., Tielsch JM., Schulze KJ, and Savioli L. 1998. Effects of the Zanzibar school-based deworming program on iron status of children. *Am J Clin Nutr.* 68:179-86.

Stoltzfus RJ., Albonico M., Tielsch JM., Chwaya HM., Schulze KJ, and Savioli L. 1997a. School-based deworming program yields small improvement in growth of Zanzibari school children after one year. *J Nutr.* 127:2187-93.

Stoltzfus RJ., Dreyfuss ML., Chwaya HM, and Albonico M. 1997b. Hookworm control as a strategy to prevent iron deficiency. *Nutr Rev.* 55:223-32.

Subramanian S. SW, Ramaiah KD., Plaisier AP., Krishnamoorthy K., Van Oortmarssen GJ., Dominic Amalraj D., Habbema JD & Das PK., 2004. The dynamics of Wuchereria bancrofti infection: a model-based analysis of longitudinal data from Pondicherrry, India. *Parasitology 128*: 467-82.

Taylor MJ.,Bandi C.,Hoerauf AM, and Lazdins J. 2000. Wolbachia bacteria of filarial nematodes: atarget for control? *Parasitol Today.*16:179-80.

Taylor MJ.,cross HF., Ford L., Makunde WH., Prasad GB, and Bilo K. 2001. Wolbachia bacteria in filarial immunity and disease. *Parasite Immunol.*23:401-9.

Taylor MJ.,cross HF., Makunde WH., McGarry HF.,Turner JD., Mand S, and Hoerauf A. 2005. Microfilaricidal activity after doxycycline treatment of Wuchereria bancrofti: a double-blind, randomized placebo-controlled trial. *Lancet.*365:2116-21.

Turner P., Copeman B., Gerisi D, and Speare R. 1993. A comparison of the Og4C3 antigen capture ELISA, the Knott test, an IgG4 assay and clinical signs, in the diagnosis of Bancroftian filariasis.*Trop Med Parasitol.*44:45-8.

UNICEF, Report 1998.

Urbani CaA, M., 2003. Anthelminthic drug safety and drug administration in the control of soil-transmitted helminthiasis in community campaigns. *Acta Trop. 86*: 215-221.

Vanamail P. Ramaiah K, Pani SP., Das PK., Grenfell BT & Bundy DA, 1996. Estimation of the fecund life span of Wuchereria bancrofti in an endemic area. *Trans R Soc Trop Med Hyg 90*: 119-21.

Vincent AL. AL, Rodrick GE., & Sodeman WA, Jr., 1980. The lymphatic pathology of Brugia pahangi in the Mongolian jird. *J Parasitol. 66*: 613-20.

Wamae CN, 1994. Advances in the diagnosis of human lymphatic filariasis: a review. *East Afr Med J 71*: 171-82.

Wang S., Xiong M., Liu T, and Tang L. 1999. Evaluation of recombinant chitnase antigen in serological diagnosis and surveillance of lymphatic filariasis. *Southeast Asian J Trop Med Public Health.* 30:567-71.

Webber RH.1979. Eradication of *Wuchereria bancrofti* infection through vector control. Trans R Soc Trop Med Hyg.73:722-4.

Webber RH. 1991. Can anophiline-transmitted filariasis be eradicated? *Journal of Tropical Medicine and Hygiene.*94:241-244.

Weil GJ., Malane MS., Powers KG, and Blair LS. 1985. Monoclonal antibodies to parasite antigens found in the serum of *Dirofilaria immitis*-infected dogs. *Journa Immunol.* 134:1185-91.

Weil GJ., Chandrashekar R., Liftis F., McVay CS., Bosshardt SC, Klei TR.1990. Circulating parasite antigen in *Brugia pahangi*-infected jirds. Journal Parasitol.76:78-84.

White GB. 1971. Studies on transmission of Bancroftian filariasis in Northern-Eastern Tanzania. *Trans R Soc Trop Med Hyg.*65:819-29.

WHO, 1987a. Control of lymphatic filariasis. A manual for health personnel. World Health Organization. 89pp.

WHO, 1992. Lymphatic filariasis: The disease and its control. Fifth report of the WHO Expert Committee on filariasis. Geneva: World Health Organization, Technical Report Series No. 821.

WHO, 1992. Informal consultation on evaluation of morbidity in filariasis Geneva: World Health Organization, TDR/FIL/MAD/92.3 (1992a).

WHO, 1992. Lymphatic filariasis: the disease and its control. Fifth report of the WHO Expert Committee on Filariasis. World Health Organization Technical Report Series,. *WHO(1992b) 821*: 1-71.

WHO, 1994. Lymphatic filariasis infection and disease:Control Strategies. Report of a consultative meeting held at the Universiti Sains Malaysia, Penang, Malaysia, Aug 1994. Geneva: World Health Organization, 1994. (TDR/CTD/FIL/PENANG/94.1).

WHO, 1995. The world health report 1995: Bridging the gaps. Geneva:. *World Health Organization.*

WHO, 1997. World Health Assembly resolution 50.29.

WHO, 2000. Preparing and implementing a national plan to eliminate lymphatic filariasis. *World Health Organization (WHO/CDS/CPD/CEE/2000.15 and 2000.16).*

WHO, 2002. Global Programme to Eliminate Lymphatic Filariasis: Annual Report on Lymphatic Filariasis .2002a. WHO/CDS/CPE/CEE/2003.38. *World Health Organization.*

WHO, 2005. Monitoring and epidemiological assessment to eliminate lymphatic filariasis at implementation unit level, Geneva.: 1-3.

WHO, Weekly Epidemiological Record, 2008; 83:333-48.

Wijers DJ, and Kiilu G.1977. Bancroftian filariasis in Kenya III. Entomological investigations in Mambrui, a small coastal town, and Jaribuni, a rural area more inland (Coastal Province). *Ann Trop Med Parasitol.*71:347-59.

Wijers DJ, and Kinyanjui H.1977. Bancroftian filariasis in Kenya II. Clinical and parasitological investigations in Mambrui, a small coastal town, and Jaribuni, a rural area more inland (Coastal Province). *Ann Trop Med Parasitol.*71:333-45.

Witte HM. JS, Williams WH., Witte CL., Kumaraswami V., McNeill GC., Can TC., Panicher TM, 1993. Lymphatic abnormalities in human filariasis as depicted by lymphangioscintighraphy. *Arch Int Medicine 153*: 737-744.

Yahathugoda TC, Wickramasinghe D, Weerasooriya MV, Samarawickrema WA, 2005. Lymphoedema and its management in cases of lymphatic filariasis: the current situation in three suburbs of Matara, Sri Lanka, before the introduction of a morbidity-control programme. *Annals of Tropical Medicine and Parasitology 99*: 501-510.

Zanzibar Aids Control Programme Report, 2003.

Zagaria N aSL, 2002. Elimination of lymphatic filariasis: a public-health challenge. *Ann Trop Med Parasitol 96 Suppl 2:S3-13.*

Zanzibar Malaria Control Programme Report, 2005.

Zhong M., McCarthy J., Bierwert L., Lizotte-Waniewski M., Chanteau S., Nutman TB., Ottesen EA,and Williams SA. 1996. A polymerase chain reaction assay for detection of the parasite *Wuchereria bancrofti* in human blood samples. *Am J Trop Med Hyg.*54:357-63.

APPENDICES

Annex 1: Dissection Record Form

Date of Dissection .....Village/Shehia ..... District..... Region .....

Name of Dissector .....

House Number ..... Name of House Holder .....

Mosquito Collection Method .....

	UF				F				HG				G				TOTAL			
	L1	L2	L3	-V	L1	L2	L3	-V	L1	L2	L3	-V	L1	L2	L3	-V	L1	L2	L3	INFECTION RATE
An. gambiae (s.l.)																				
An. funestus																				
C. quinque																				
Others																				
Total																				

Annex II: Data Collection Form

Date:..... **Health Facility: .....**

District:..... **Region:.....**

YEAR	AGE	SOIL TRANSMITED HELMINTH (STH)		SCABIES		LICE	
		Males	Females	Males	Females	Males	Females
2000	0 - 5						
	6 -10						
	11–15						
	16–20						
	> 20						
2001	0 - 5						
	6 -10						
	11–15						
	16–20						
	> 20						
2002	0 - 5						
	6 -10						
	11–15						
	16- 20						
	> 20						
2003	0 - 5						
	6 -10						
	11–15						
	16–20						
	> 20						
2004	0 - 5						
	6 -10						
	11–15						
	16–20						
	> 20						

Annex III a: Patient Form (English version)

Name of Informal Care _____

Date _____ **Shehia**_____ **Village**_____

Patient Name _____**Sex** ___ **Age**_____

LYMPHOEDEMA		ACUTE ATTACK		HYDROCELE	
YES(Y)	*NO(N)*	*YES(Y)*	*NO(N)*	*YES(Y)*	*NO(N)*
WOUNDS					
PATIENT REFERRAL					

ANNEX: III b

LYMPHOEDEMA PATIENT FOLLOW UP FORM (English version)

Date																								
Visit	1		2		3		4		5		6		7		8		9		10		11		12	
Lymphoedema																								
Acute Attack (Fever)	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Hydrocele																								
Wounds																								
Wounds Healed																								
Referral																								

ANNEX: IV a

(Patient's Form – Swahili version)

FOMU YA MGONJWA

Jina la Mhudumu _____

Tarehe _____ **Shehia**_____ **Mtaa**_____

Jina la mgonjwa _____**Jinsia** ____**Umri**_____

MATENDE		**HOMA YA MATENDE**		**MSHIPA/BUSHA**	
Ndio(N)	*Hapana(H)*	*Ndio(N)*	*Hapana(H)*	*Ndio(N)*	*Hapana (H)*
VIDONDA					
RUFAA YA MGONJWA					

ANNEX : IV b

FOMU YA UFUATILIAJI MGONJWA WA MATENDE (Swahili version)

Tarehe																								
Ziara ya	1		2		3		4		5		6		7		8		9		10		11		12	
Matende																								
Homa ya Matende	**N**	**H**	**N**	**H**	**N**	**H**	**N**	**H**	**N**	**H**	**N**	**H**	**N**	**H**	**N**	**H**	**N**	**H**	**N**	**H**	**N**	**H**	**N**	**H**
Busha																								
Vidonda																								
Vimepona																								
Rufaa ya mgonjwa																								

ANNEX V a **CONSENT FORM** (English version)

PARTICIPANT INFORMATION

Lymphatic filariasis, worms and schistosomiasis are among the endemic diseases in your locality. People may harbour the infection unknowingly. With the support of World Health Organisation (WHO) and other international organizations, the Program for Elimination of Lymphatic Filariasis (PELF) in collaboration with Schistosomiasis and Soil Transmitted Helminths Control programme which are under the Ministry of Health and Social Welfare Zanzibar, asks your assistance so as to gain new knowledge about the cost effective ways of treating these infections. The PELF has been campaigning for the people in the community to take drugs against lymphatic filariasis during Mass Drug Administration day each year through different strategies. The drugs that are being distributed by PELF are combination of ivermectin and albendazole and studies have elicited that the combination of Ivermectin and Albendazole are safe and potential against Lymphatic filariasis and worms infections. The Schistosomiasis and Soil Transmitted Helminths programme has been distributing Praziquantel and Albendazole, in its School programme and selected communities, against schistosomiasis and worms. Therefore, the purpose of this study is to establish the possibility of distributing IVERMECTIN, ALBENDAZOLE and PRAZIQUANTEL together at the same time to the eligible population in the community so that we can be able to determine the most cost effective system of delivering those drugs against lymphatic filariasis, schistosomiasis and worms infections. There is possibility of minor side reactions occurrence such as headache, myalgia, anorexia, malaise, nausea, vomiting and wheezing, abdominal discomfort, dizziness, drowsiness, rectal bleeding, lymphadenitis, funiculitis, epididymitis, lymphangitis ,abscess formation, fever and pruritus. All health facilities around you have been prepared to manage those anticipated side events. We want to be sure that there is no adverse reaction related to multiple therapy of these drugs during community mass drug administration campaign.

We kindly ask you to answer few questions on these issues. This information will help us to understand how treatment will affective. Necessary physical examination will also be performed by our medical team to check any clinical problem.

You do not expect to pay any charge with your voluntarily participation.

In case of inquiry, you can contact the research team who will be available during all study period or contact

Khalfan A. Mohammed, Programme of Elimination of Lymphatic Filariasis, Ministry of Health and Social Welfaref Zanzibar, P.O. box 236 Zanzibar, United Republic of Tanzania, Tel +255 777 432370, e-mail <kamsharjy@hotmail.com or <k.a.mohammed@liv.ac.uk>.

Your participation is entirely voluntary. The results of the study will be kept confidential and will not be made public. If the results of the trial are published, the subject's identity will remain confidential. By signing a written informed consent form, you also authorize the access of your medical records and trial data to the extent permitted by the applicable laws and regulations (e.g. the trial monitors, the auditors, Ethical Committees, and regulatory agencies).

If you agree you can anyhow stop your further participation whenever you wish.

For healthy participants, there may not be any direct benefit to your health. However, if you are infected, it is possible that your diseases may be treated by the drugs. More importantly, your participation can help us know how co effective can we stop LF transmission, Schistosomiasis and worms infection in Zanzibar. We are expecting to invite a total of 5000 participants in this trial. Information given and observations noted will be highly valued.

ADULTS: "Do you agree to participate by answering some questions ?"

PARENTS /GUARDIAN. " Since your child is too young to decide you are asked to decide for him /her. Do you on behalf of your child agree to answer some questions ?

Verbal informed consent provided:

1. Yes ( ) 2. No ( )

NAME OF PARTICIPANT:_____

SIGNATURE:_____DATE _____/_____/_____

WITNESSED BY NAME:_____

FUNCTION: _____

SIGNATURE:_____DATE _____/_____/_____

ANNEX: V b

CONSENT FORM (Swahili version)

TAARIFA NA RIDHAA YA WASHIRIKI WA UTAFITI

Maradhi ya matende, minyoo na kichocho ni miongoni mwa maradhi sugu katika maeneo mnayoishi.watu wanaweza kuwa na vimelea vya maradhi haya bila ya kujitambua. Kwa mashirikiano ya Shirika la afya Duniani (WHO) pamoja na mashirika mengine ya Kimataifa Mpango wa Kupambana na Kutokomeza Matende (PELF) ukishirikiana na Mpango wa Kupambana na Kichocho na Minyoo ambayo ipo chini ya Wizara ya Afya na Ustawi wa Jamii wanakuomba ushirikiane nao ili taarifa juu ya ya njia bora na rahisi ya utowaji wa dawa za kupambana na maradhi haya thakili. Mpango wa Kupambana na Kutokomeza Matende umekuwa ukifanya kampeni kwa kutumia mbinu mbali mbali kuwa taka wananchi kula dawa wakatika wa zoezi la ugawaji wa dawa dhidi ya matende kila mwaka. Dawa ambazo huwa zinatolewa ni mchanganyiko wa dawa mbili Ivermectin na albendazole. Tafiti zilizofanywa zinaonesha kuwa matumizi ya dawa za aina mbili za minyoo (Ivermectin na Albendazole) kuwa zina uwezo mkubwa/zaidi wa kuuwa vimelea vya maradhi yote haya mawili na zipo salama. Mpango wa Kupmbana na Kichocho na Minyoo umekuwa na utaratibu wa kutowa dawa za Praziquantel na Albendazole katika kupambana na maradhi hayo katika mpango wake wa mashuleni na katika baadhi ya jamii. Madhumuni hasa ya Utafiti huu ni kutafuta njia ambayo ni salama, bora na rahisi katika utowaji wa dawa zote tatu IVERMECTIN, ALBENDAZOLE and PRAZIQUANTEL kwa pamoja kwa walenga katika jamii kwa lengo la kupambana na maradhi ya matende, kichocho na minyoo katika jamii. Upo uwezekano wa kupata usumbufu baada ya kutumia dawa hizi, kama kuumwa na kichwa, kichefuchefu,kutapika, kuumwa na tumbo, kizungunzungu. Tunataka tuhakikishe kuwa hakuna tatizo lolote litokanalo na kutowa dawa hizo kwa pamoja wakati wa zoezi la utowaji wa dawa hizo katika jamii.

Kwa ridhaa yako tunaomba ushirikiane nasi katika kujibu masuali ambayo tutakuuliza.

Pindi ukitaka kujua taarifa yoyote ya zoezi hili unaweza kuwaona wahusika wakati wo wote au unaweza kuwasiliana moja kwa moja na

Khalfan A. Mohammed, Wizara ya Afya na Ustawi wa Jamii, S.L.B 236 Zanzibar, Tanzania, Simu +255 777 432370, Barua pepe <kamsharjy@hotmail.com au <k.a.mohammed@liv.ac.uk>.

Una hiari ya kukubali kushiriki kwenye utafiti huu ambao hautaambatana na malipo yoyote. Pia taarifa zako zitahifadhiwa na kubakia siri na kutumika pale tu ambapo zitaleta manufaa ya ziada kwa jamii .Utakuwa na hiari ya kujiondoa kwenye utafiti huu wakati wowote utapopenda , na kwa kufanya hivyo hutotengwa . Muhimu zaidi katika kushiriki kwako katika Utafiti huu kutatusaidia kuelewa vizuri namna na njia gain za kutumia ambazo ni salama na rahisi katika utowaji wa matibabu dhidi ya maradhi ya matende, kichocho na minyoo visiwani Zanzibar na kwengineko duniani.

Tunategemea kuwa na jumla ya watu 5000 mtaoshiriki na kutusaidia ili tufikie lengo letu hili.

KWA WATU WAZIMA: jee umekubali kushiriki kwa kipindi chote hichi pamoja na kujibu masuali tukayo kuuliza ?

KWA WAZAZI/ WALEZI WA WATOTO: Kwa niaba ya mtoto wako jee utamruhusu ashiriki kwa kipindi chote hichi na pia utakuwa tayari kumjibia masuali tutakayo muuliza ?

Nimekubali( ) nimekataa( )

JINA LA MHUSIKA:_____

SAHIHI: _____

TAREHE _____/_____/_____

IMESHUHUDIWANA
JINA:_____

SHEHIA/KAZI: _____

SAHIHI:_____

TAREHE _____/_____/_____

ANNEX:VI

QUESTIONNAIRE

PATIENT MONITORING FORM

Albendazole/Mectizan/Praziquantel Co-administration

Date_____ **Form Number**_____

Subject Initials_____ **Village**_____

Age: ____|____**(years)** **Sex:** M F *[Height:* ___.___*(m)* *Weight:* ____*(kg)]*

Date of Treatment: ____/____/____

Day Month Year

This form is being filled out on: Day 5 Day 6 Day7 Post Treatment

(Mark one)

Patient's response to:

1. When did you take the tablets? **Morning** **Afternoon** **Night**

Before meal **After meal**

2. How many tablets did you take? **Mectizan** ☐

Albendazole ☐

Praziquantel ☐

3. How have you been feeling since taking the treatment?

Indicate any symptoms in boxes below using the following codes.
1 = mild, **2** = moderate, **3** = intense. **DO NOT** mark boxes if **no** symptoms occur.

	Days post treatment when symptoms were present						
Symptom	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Fever							
Headache							
Dizziness							
Nausea							
Vomiting							
Diarrhoea							
Abdominal Pain							
Joint/Muscle Pain							
Fatigue							
Swelling:							
Upper/lower limb							
Skin/scrotum							
Scrotal Pain							
Rash							
Itching							
Other (specify below)							

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PLoS NEGLECTED TROPICAL DISEASES

Triple Co-Administration of Ivermectin, Albendazole and Praziquantel in Zanzibar: A Safety Study

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Abstract

Background: Public health interventions based on distribution of anthelminthic drugs against lymphatic filariasis (LF), onchocerciasis, soil-transmitted helminthiasis (STH) and schistosomiasis have been implemented separately to date. A better use of available resources might be facilitated by a more coordinated approach to control such infections, including the possibility of co-administering the three recommended anthelminthic drugs through a single, large-scale intervention.

Methodology/Principal Findings: Ivermectin, albendazole and praziquantel were co-administered to 5,055 children and adults living in areas endemic for LF, STH and schistosomiasis in Zanzibar, United Republic of Tanzania, during a pilot intervention aimed at elucidating and quantifying possible side-effects. Subsequently, these drugs were co-administered to about 700,000 individuals during a countrywide intervention targeting a large part of the total population of Zanzibar. Passive and active surveillance measures carried out during both interventions showed that side-effects attributable to the three drugs given at the same time were mild and self-limiting events.

Conclusions/Significance: Our data suggest that co-administration of ivermectin, albendazole and praziquantel is safe in areas where lymphatic filariasis, soil-transmitted helminthiasis and schistosomiasis are co-endemic and where several rounds of treatment with one or two drugs have been implemented in the past. Passive surveillance measures, however, should be continued and detection, management and reporting of possible side-effects should be considered a key component of any health intervention administering drugs.

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Introduction

Lymphatic filariasis (LF), soil-transmitted helminthiasis (STH) and schistosomiasis are diseases of considerable public health importance in tropical and sub-tropical countries. Globally, 1.2 billion people live in areas endemic for LF [1] and nearly one-fourth of them may already have infection [2]. LF is a leading cause of long-term disability [3]. Schistosomiasis occurs in over 70 countries in the tropics and sub-tropics; 779 million are estimated to be at risk of infection and 207 million to be infected [4–6]. 2 billion are estimated to be infected with STH, namely the roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*), and the hookworms (*Ancylostoma duodenale* and *Necator americanus*), worldwide and several million suffer from the chronic debilitating morbidity [7–10].

In most endemic countries, these infections often occur in the same individual [11]. This is especially true in poorest sectors of the population. Helminth infections have a substantial impact on the physical and intellectual development and on the overall health status of infected populations, as well as on the quantity and quality of their productive work [12–16]. Interventions to tackle helminth infections and their associated morbidity have been taken by national programmes in different countries including Zanzibar, in the United Republic of Tanzania; however such activities are implemented in a vertical fashion, with different diseases being addressed separately.

Control of LF, STH and Schistosomiasis in Zanzibar

Zanzibar comprises 2 main islands, Unguja and Pemba, with a population of around 1.2 million. LF, caused by *Wuchereria bancrofti*, and STH and schistosomiasis are considered major public health problems by the Zanzibar Ministry of Health and Social Welfare (MoHSW). Transmission of *W. bancrofti* occurs in both Unguja and Pemba [17]. Such an epidemiological situation justifies the inclusion of both islands among the areas eligible for mass drug administration (MDA) with ivermectin and albendazole at yearly intervals. Data show that the whole archipelago is also at

Author Summary

This paper describes how the use of three drugs which are used separately in mass drug distribution programmes when given together appear safe for use in large populations which have been previously treated with the same drugs separately (Mectizan [ivermectin], albendazole and praziquantel). The target diseases—lymphatic filariasis, soil-transmitted worms and schistosomiasis—were prevalent in Zanzibar up to 2000 but have been largely controlled by mass drug administration. The Ministry of Health and Social Welfare, with the support of WHO, initiated a small scale trial in a population of triple therapy in over 5,000 people initially in two sites, and having found there were no severe adverse events associated with the combined treatment then upscaled to treat the whole of the eligible population of over 700,000. Similarly, there were no severe adverse events. This is the first time the three drugs have been used together at the same time at scale in Africa and provide a basis for expansion of integrated preventive chemotherapy of helminths (worms). The next steps need to be initiated in populations which have heavier worm loads and such interventions need to be subject to close monitoring and ethical review.

high risk for STH; with the exception of a limited area on Unguja where the infection is not transmitted, it is also at high risk for urinary schistosomiasis caused by *Schistosoma haematobium* (MoHSW unpublished data, [18–21]). Control of schistosomiasis and STH through large-scale preventive chemotherapy interventions distributing praziquantel and albendazole started in 1994. Schools represented the main delivery channel and schoolchildren the main target population, however, occasionally whole communities have been also targeted for treatment. This strategy is still ongoing with a period of interruption of two years (2000 and 2001) during which activities did not take place due to problems in securing the drugs. There has been a reduction in prevalence and intensity of both schistosome and STH infections over the years (MoHSW unpublished data), however such indicators suggest that continuation of treatment of schoolchildren is still required. The last school-based drug distribution before the implementation of the activities described in this survey was carried out in May 2006.

In 2001 Zanzibar adopted the WHO recommended strategy against LF, consisting of MDA for elimination as a public health problem, coupled with disability prevention and management. MDA in Zanzibar involves administering a once-yearly dose of a combination of ivermectin (Mectizan, 200 μg/kg) and albendazole (400 mg) to its entire population, with the exception of those who are sick or infirm, of children <90 cm in height, of pregnant women, and of lactating women in the first week after birth. The last round before the implementation of the activities described in this article was conducted in August 2005 (5th round of MDA) [17].

W. bancrofti was highly endemic in both Unguja and Pemba before MDAs, with a prevalence of microfilaraemia in all age groups (children and adults) ranging between 5% and 30% [17]. Whilst the evaluation of the impact of MDAs showed an overall decline in both prevalence and intensity of microfilaraemia, mean prevalence of infection in all age groups (adults and children) at one sentinel and in some randomly selected spot-check sites after the 5th round was still 1% and above. The MoHSW therefore decided to implement a further round (6th) of MDA. This follows the WHO recommended processes leading to decision to stop MDA only after interruption of transmission (prevalence of microfilaraemia <1% in the general population) [22].

Triple Drug Co-Administration

The 6th round of MDA for LF offered the opportunity to evaluate the feasibility and safety of triple drug co-administration with ivermectin, albendazole and praziquantel in communities where LF, STH and schistosomiasis are co-endemic.

Ivermectin, albendazole and praziquantel are well suited for large-scale distribution in helminth control or elimination when administered individually or in double combination (ivermectin and albendazole *or* albendazole and praziquantel) at the recommended dosages (ivermectin 200 μg/kg; albendazole 400 mg; praziquantel 40 mg/kg). Combination of ivermectin and albendazole is highly efficacious after a single administration for LF, and treatment rarely results in side-effects outside those commonly associated with a therapeutic effect [23]. Similarly, co-administration of praziquantel and albendazole is an efficacious and safe tool to control morbidity due to schistosomiasis and STH in areas where both infections are endemic [24].

However, side-effects do sometimes occur following administration of anthelminthic drugs, primarily as a result of the individual's immune inflammatory response to dying parasites; the greater the infection load in the patient, the greater are the frequency and severity of such reactions. These can include systemic responses (e..g. headache, myalgia, light-headedness, anorexia, malaise, nausea, vomiting and wheezing, abdominal discomfort, dizziness, drowsiness, rectal bleeding); or, less commonly, localized reactions (including lymphadenitis, funiculitis, epididymitis, lymphangitis and even abscess formation); rarely, in case of administration of praziquantel for schistosomiasis, hypersensitivity reactions, fever, pruritus and eosinophilia may occur. Only seldom (in heavily infected individuals) are these post-treatment reactions severe or do they require more than just symptomatic treatment [25].

Triple co-administration of ivermectin, albendazole and praziquantel has never been carried out in large-scale interventions, however, pharmacokinetic studies performed in healthy (i.e. non-infected) individuals indicate that there are no pharmacological interactions between the three drugs and that triple co-administration does not enhance their toxicity [26].

However, because of the lack of documentation on such triple co-administration in real epidemiological scenarios, and considering that in those settings some of the individuals receiving drugs may carry high burden of multiple parasites, it is recommended that triple co-administration is carried out with caution and with adequate monitoring of potential side-effects [1]. As a first step it is advisable that in a population that has never been subjected to MDA with any of these drugs, the initial 1–2 rounds of treatment with praziquantel should be given separately from ivermectin and/or albendazole treatment; additionally, in a population that has previously been subjected to (separate) MDA with either ivermectin plus praziquantel or ivermectin+albendazole plus praziquantel, the three drugs should be co-administered in conjunction with additional safety monitoring for any unanticipated side-effects during the initial rounds.

Since in Zanzibar separate MDAs had already been conducted in the past, it was decided to implement co-administration of the three drugs with the requisite precautionary measures. Before co-administering the drugs to the entire eligible Zanzibar population of around 1 million, it was therefore considered imperative that such intervention take place in a pilot population and that active and passive surveillance measures be implemented during and after treatment.

Results of the pilot intervention were considered crucial to the initiation of a country-wide intervention. It was agreed that if side effects during the pilot intervention were mild and transitory, co-

administration would take place throughout Zanzibar and that active and passive surveillance measures would be also implemented during such a country-wide interventions.

The aim of the present paper is to report on the outcome of passive and active surveillance measures carried out to elucidate and quantify any side-effects experienced after co-administration of ivermectin, albendazole and praziquantel by a sample population of 5,055 and subsequently by about 700,000 individuals living in areas endemic for LF, STH and schistosomiasis in Zanzibar.

Methods

The Pilot Intervention Study Area

The pilot intervention was conducted in 2 highly endemic sites, one from each of the two islands forming Zanzibar: Kinyasini on Unguja (resident population of approximately 4,000) and Mtambile on Pemba (resident population of approximately 3,000).

Field assessments conducted in all age-groups before the survey in early November 2006 showed that at Kinyasini prevalence of LF antigenaemiaia (assessed by an ImmunoChromatographic Test ICT) [27]) was 4.0%, of urinary schistosomiasis (assessed by urine filtration) was 63.5% and of STH infections (assessed by Kato-Katz method) [28] was 76.8%; at Mtambile, these figures were 13.0%, 43.0% and 73.0%, respectively (MoHSW unpublished data). The major occupations of the community in both sites are linked to agriculture [29]. Both sites are surrounded by permanent water bodies.

Criteria for Eligibility

The whole population of both Kinyasini and Mtambile was considered for enrolment in the pilot intervention. Criteria for enrolment coincided with criteria for eligibility for administration of ivermectin and albendazole in LF disease-specific interventions, which are the most restrictive among the criteria used in interventions against one of the three diseases (LF, STH, and schistosomiasis) taken singularly. As such, we considered eligible all consenting residents of both sites, with the exception of those who were sick or infirm, of children <90 cm in height, of pregnant women, and of lactating women in the first week after birth. All consenting participants (written and oral) were interviewed in order to determine their health status before the intervention, and all their information were recorded.

Drugs and Their Administration

All participants in the study were given their respective dosages of ivermectin (200 μg/kg), albendazole (400 mg) and praziquantel (40 mg/kg) at the same time; treatment was directly observed by drug distributors to ensure that tablets were actually swallowed. The dosage for ivermectin and praziquantel was calculated using a two-sided tablet (height) pole that was the combination of the two poles currently used for separate administration of such drugs [1,30–32]: one side for determination of the number of ivermectin tablets and the other side for the number of praziquantel tablets. The two sides were clearly made distinguishable by the presence of the Kiswahili (local language) text "kichocho" (schistosomiasis) on one side and "matende" (elephantiasis, LF) on the other. One tablet of albendazole (400 mg) was used as the standard dose for everybody irrespective of age or height [1].

Theoretical and practical training sessions were held during the weeks preceding the intervention so as to train drug distributors - who were familiar with single-drug poles - on the use of the two-sided poles and on the shape and strength of each drug administered, so as to avoid any risk of miscalculation of the dose of ivermectin and praziquantel to be administered.

The strategy of drug distribution and the individuals responsible for drug distribution were the same used in those two sites during previous interventions of MDA with ivermectin and albendazole for elimination of LF.

The pilot intervention took place on 18 November at Kinyasini 2006 and on 19 November 2006 at Mtambile.

Surveillance Measures

Both passive and active surveillance measures were implemented during the pilot intervention. Passive measures were aimed at ensuring rapid medical assistance for any individuals who might experience side-effects after treatment, while active measures were in place to elucidate the nature of and quantify any such event.

Passive measures were established on the treatment day and the day after; two health centres at Kinyasini and two at Mtambile were kept open round the clock and equipped with first-line emergency drugs (non-steroid anti-inflammatory drugs, anti-histaminic drugs, cortisone, intravenous fluids). Individuals who received drugs were invited to report to these first-line centres in the event of any side-effects ("anything abnormal occurring in your body"), health centre personnel were trained on how to fill in the record forms and instructed to refer to second-line hospitals any individual presenting with side effects that they could not manage. In addition, vehicles/motor bikes patrolled the area to facilitate a rapid response should it be needed.

Active surveillance measures were also carried out between the 5th and the 7th day after treatment. All treated individuals were interviewed on occurrence of side-effects by experienced professional health staff and/or researchers who had participated in previous health survey studies done in the country and who were not resident either in Kinyasini or Mtambile. The occurrence of any side-effects following the ingestion of the three drugs was investigated. A side-effect was defined as any abnormal event experienced by a treated individual within period of observation. A structured questionnaire listing the most common symptoms and signs usually reported after administration of anthelminthic drugs was used to record events, but these events were not read to the interviewee who was asked the following question: "How have you been feeling since taking the treatment?" and left free to answer and to grade the possible event as mild, moderate or severe. For standardization of the approach to be used when administering the questionnaires,health staff/ researchers received one day training, on how to ask the questions and fill up the form.

Ethical Clearance

The protocol of the pilot intervention was reviewed and approved by the Ethical Committee of the Liverpool School of Tropical Medicine, United Kingdom, and by the MoHSW, Zanzibar. All individuals participating in the pilot intervention or their parent/guardian in case of children provided a written informed consent to treatment. All records are available for scrutiny in the MoHSW, Zanzibar. The procedure regarding the administration of questionnaires to designated interviewees was the same for the pilot project and the nationwide intervention. The individuals gave consent prior to being interviewed for adverse events. It is the policy of the MOHSW to obtain consent from involved communities or involved individuals before carrying out activities in the field.

Results

Population under Study

A total of 5,055 individuals of both sexes aged 5 years and above, participated in the pilot intervention: 2,509 from Kinyasini

Table 1. Population participating in the pilot intervention.

		Treated population	
Age group	**Total**	**Female**	**Male**
<10	763 (15.1%)	455	308
10–19	1548 (30.6%)	885	663
20–29	890 (17.6%)	609	281
30–39	696 (13.8%)	477	219
40–49	538 (10.6%)	327	211
50+	620 (12.3%)	398	222
Total	**5055 (100%)**	**3151 (62.3%)**	**1904 (37.7%)**

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and 2,546 from Mtambile. The age-group 10–19 years old was the most represented, in line with current demographic trends in Tanzania and most developing countries [27]. The number of females was higher than that of males (Table 1, Figure 1). This can be mainly explained by the fact that both Kinyasini and Mtambile are rural areas where young males are either farmers or have employment in town. Hence, they usually leave their houses early in the morning and return back late in the evening.

Passive Surveillance Measures

Only 1 treated individual reported to a first-line health centre (in Kinyasini) complaining about vomiting that started following treatment; symptoms were, however, mild and successfully managed on spot without requiring referral to a second-line hospital facility.

Active Surveillance Measures

The results of the interviews carried between day 5 and 7 post triple drug administration are shown in Table 2. Overall, a total of 615 events were reported by 504 individuals, i.e. by approximately 10% (504/5055) of those treated. Occurrence of side-effects was the same (10%) in different sexes and peaked in the age-group 30–39 (Table 2). 87.3% of symptoms occurred within 24 hours of treatment, while a few were also reported to have occurred on the second (11.9%) and on the third day (0.8%). The symptom most frequently reported was dizziness (Table 3). All symptoms were reported to be mild and subsided within a period of 24 hours after onset.

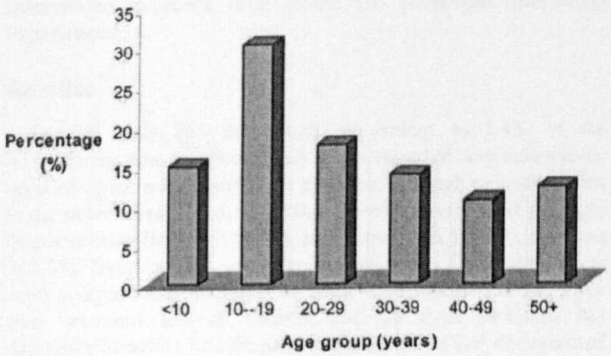

Figure 1. Population participating in the pilot intervention.
doi:10.1371/journal.pntd.0000171.g001

Table 2. Age distribution of individuals reporting side-effects.

Age Group	Female	Male	Total
<10	19/455 (4.2%)	17/308 (5.5%)	36/763 (4.7%)
10–19	76/885 (8.6%)	50/663 (7.5%)	126/1548 (8.1%)
20–29	59/609 (9.7%)	32/281 (11.4%)	91/890 (10.2%)
30–39	85/477 (17.8%)	34/219 (15.5%)	119/696 (17.1%)
40–49	27/327 (8.3%)	28/211 (13.3%)	55/538 (10.2%)
50+	48/398 (12.0%)	29/222 (13.0%)	77/620 (12.4%)
Total	**314/3151 (10%)**	**190/1904 (10%)**	**504/5055 (10%)**

doi:10.1371/journal.pntd.0000171.t002

The Country-Wide Intervention

As active surveillance for side-effects during the pilot intervention did not indicate any concern, two weeks after co-administration of the three drugs had taken place in Kinyasini and Mtambile, on December 2–3, 2006, the first large-scale triple drug co-administration was carried out in Zanzibar. This intervention was conducted under the newly established "Lymphatic Filariasis, Schistosomiasis and Soil-Transmitted Helminthiasis Integrated Programme" of the MoHSW. Every eligible individual in Zanzibar was targeted to receive the three drugs at the same time with the exception of those living in areas without transmission of schistosomiasis where only ivermectin and albendazole were administered. Such areas are restricted to Unguja island and include the whole Urban district of Stone Town, the whole South district, and some communities (shehias) in the North A district [18–20]. The same criteria for eligibility and ineligibility were applied as in the pilot intervention. Overall, about 700,000 individuals were administered three drugs (ivermectin, albendazole and praziquantel) and another 300,000 two drugs (ivermectin and albendazole).

Table 3. Nature and timeline of side-effects during the pilot intervention.

Symptoms	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Total
Fever	15	6	3	0	0	0	0	24
Headache	59	8	1	0	0	0	0	68
Dizziness	160	13	1	0	0	0	0	174
Nausea	97	5	0	0	0	0	0	102
Vomiting	12	0	0	0	0	0	0	12
Diarrhoea	23	9	0	0	0	0	0	32
Abdominal Pain	106	21	0	0	0	0	0	127
Joint/Muscle Pain	19	2	0	0	0	0	0	21
Fatigue	24	7	0	0	0	0	0	31
Swelling of the limbs	0	2	0	0	0	0	0	2
Swelling of scrotum	0	0	0	0	0	0	0	0
Scrotal Pain	2	0	0	0	0	0	0	2
Rash	3	0	0	0	0	0	0	3
Itching	8	0	0	0	0	0	0	8
Others	9	0	0	0	0	0	0	9
Total	**537**	**73**	**5**	**0**	**0**	**0**	**0**	**615**

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As in the pilot intervention, the door-to-door strategy was chosen as the method of drug administration. For effective coverage, 4,161 drug distributors, used in previous LF-MDA interventions, were deployed and given extra training on how to use the two-sided drug pole in determining number of tablets. Each drug distributor was responsible for 50 households. All drug distributors were previously identified through a community-based participatory process, so as to guarantee their full acceptance by populations targeted. Many of them were health personnel or school teachers.

Zanzibar was divided into 14 MDA operational units – 9 of the units followed the administrative divisions (districts); 3 were the result of subdividing the urban districts into more manageable units; and the remaining 2 units targeted special groups within special institutions (SI) (soldiers, policemen, prisoners, etc.).

The social mobilization component was given high priority in the campaign. Three important areas were emphasized:

1. The use of drug distributors to carry out social mobilisation through two preparatory visits to the households. The distributor explained the rationale of the programme and prepared people for any potential side-effects; in addition, these visits were also intended to build rapport and confidence between the distributors and the household members.
2. The proactive involvement of the religious and political leaders of different parties, at national, regional, district and community level.
3. The effective use of mass media and other communication tools.

Similar to what had happened for the pilot intervention, both passive and active surveillance measures were taken during and after the country-wide drug administration. Passive surveillance was established during the intervention through the network of health centres and referral hospitals in both islands to monitor and respond to potential side-effects.

One week after the drug distribution, active surveillance measures were carried out to quantify the occurrence of side-effects in a sub-sample of the target population; the activity was incorporated into the routine survey intended to assess and check drug coverage. 35 communities (shehias) out of the 250 that form Zanzibar were randomly selected (20 in Unguja and 15 in Pemba), and 600–1000 people per site were interviewed, for a total of 19,043 individuals. A researcher was randomly assigned to each of the 35 evaluation sites and entered houses following a random route in their area. The same questionnaire as in the pilot intervention was used, and each individual visited was interviewed to check drug intake and investigate side-effects experienced.

Results

Overall, only 266 individuals, equivalent to 1.4% of the interviewees who swallowed the drugs reported any side-effects, none of which was judged to be significant enough to justify a visit to the nearest health centre. All the side-effects were mild, the most frequent being fatigue (n = 102), abdominal pain (n = 67), dizziness (n = 57), fever (n = 27) and vomiting (n = 13). These side-effects were accepted and managed by those who reported them. They were transient and all counted for less than 24 hours. No difference in nature and frequency of side-effects was documented during the country-wide intervention between areas where ivermectin and albendazole only were distributed and areas where praziquantel was also added to the package.

Discussion

The results of the pilot intervention in Kinyasini and Mtambile were considered representative of the worst possible epidemiological scenarios in Zanzibar and as such were deemed sufficient to justify the implementation of the first nationwide intervention, in which ivermectin and albendazole currently recommended for elimination of LF and praziquantel for control of schistosomiasis were administered at the same time. The first national scale triple therapy carried out in Africa or indeed globally.

Passive and active surveillance measures implemented during both the pilot and the country-wide intervention showed that side-effects experienced by individuals co-administered with the three drugs were mild and self-limiting events. It was not possible or feasible to obtain individual data on parasitological status hence this data does not allow us to establish a clear relationship between infection status and side-effects experienced. However, we believe that our data show that triple drug co-administration is a feasible option in real epidemiological scenarios such as those exemplified by Kinyasini and Mtambile, where pre-intervention prevalence rates for schistosomiasis and STH infections were high and where *W. bancrofti* micrfilaria prevalence remained above the 1% cut off point for MDA [17]. The studies using the ICT cards to measure antigenaemia have limited value at this stage of an LF programme as they only measure the presecnec of adult worm antigen. Their use and value in post MDA evaluation is in measuring the transmission to children born since the first MDA commenced.

The proportion of individuals reporting any side-effects in the pilot intervention phase (10%) is higher than that in the nationwide intervention phase (1.4%). This can be explained by the fact that Kinyasini and Mtambile are both sites with particularly high prevalence of helminthic infections, while the nationwide intervention also covered areas with lower prevalence. The two sites were specifically selected in order to assess the occurrence of side-effects in places where they are expected to be most frequent and most severe, so as to use the results of the pilot intervention as indicators and make a judgment before the implementation of the nationwide intervention. It is also possible, however, that the sensitivity of the surveillance system during the pilot intervention was higher than during the nationwide intervention: individuals responsible for surveillance during the pilot intervention - which had a research-like outlook - might have paid more attention to recording side-effects.

Overall, both in the pilot and the nationwide intervention, the number of individuals reporting side-effects following treatment registered a significant decline from that reported for distribution of ivermectin and albendazole only by 2002 (24%) [33], which could be explained by considering that the average wormload in infected individuals in 2002 may have been higher due to the fact that only two rounds of LF treatment had taken place, and in the two previous years (2000 and 2001) the second yearly round of albendazole for STH had not been implemented due to shortage of drugs.

Data from such a large population under study in Zanzibar therefore suggests that co-administration of the three drugs is a safe intervention when carried out in an area where LF, STH and schistosomiasis are co-endemic and where several rounds of treatment with one or two drugs have been implemented in the past.

However, it is necessary to emphasize the need for maintaining passive surveillance measures during similar interventions, and to ensure that detection, management and reporting of potential side-effects are a key component of any health intervention administering drugs [34].

There are opportunities arising from a coordinated approach to tackle multiple tropical diseases simultaneously. Currently many

control/elimination programmes in Africa are constrained not by drug availability but by lack of the financial resources necessary for drug distribution, and it is expected that distribution costs will be lower when drugs are co-administered than in the case when several "vertical" interventions are conducted separately [35–38]. Meeting distribution costs would mean being able to implement control activities, since ivermectin and albendazole for LF elimination are donated. Praziquantel is not at presented donated on adequate scale to cover all the current needs.

In countries where there is a significant overlap between LF, STH and schistosomiasis [1], triple drug co-administration can be an option to cut down costs, boost control activities and improve the health status of neglected populations. Co-administration of anthelminthic drugs also offers an opportunity for integration of parasitic disease control programmes into the regular health system activities in Africa and elsewhere which has an appeal for most partners or donors. These interventions provide many benefits beyond purely disease elimination or control as they are relevant to the millennium development goals. MDA is a pro- poor non – discriminatory, and hence equitable intervention which reaches all eligible people irrespective of socio-economic status. This paper demonstrates co – administration of three highly efficacious antihelminthic drugs can be achieved at scale with very limited but acceptable side-effects. This work will pave the way for the next stage of studies in more intensely infected populations. This result will permit further expansion of the WHO policy of preventive chemotherapy [1] to needy populations for the control of neglected tropical diseases in sub Saharan Africa where extensive co-endemicity is the norm rather than the exception.

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Author Contributions

Supervised the implementation of the pilot intervention and of the country-wide intervention: DE LS DM. Participated in the development and review of the present manuscript: KM AG. Participated in the implementation of the pilot intervention and of the country-wide intervention: KM HH. Participated in the implementation of the pilot intervention: AG. Contributed to develop the protocol for the pilot intervention: KM HH LM GB LC MB DE LS DM. Reviewed the present manuscript: HH LM GB LC MB DE LS DM.

References

1. World Health Organization (2006) Preventive chemotherapy in human helminthiasis. Coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers. Geneva: World Health Organization. 62 p.
2. Das PK, Ramaiah KD, Augustin DJ, Kumar A (2001) Towards elimination of lymphatic filariasis in India. Trends Parasitol 10: 457–460.
3. World Health Organization (1995) World Health Organization Report 1995: Bridging the Gaps. Geneva: World Health Organization. 118 p.
4. Fenwick A (2006) New initiatives against Africa's worms. Trans R Soc Trop Med Hyg 100: 200–207.
5. Chitsulo L, Engels D, Montresor A, Savioli L (2000) The global status of schistosomiasis and its control. Acta Trop 77: 41–51.
6. Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J (2006) Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. Lancet Infect Dis 6: 411–425.
7. Crompton DWT (1999) How much helminthiasis is there in the world? J Parasitol 85: 397–403.
8. Bethony J, Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, Hotez PJ (2006) Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet 368: 1521–1532.
9. Crompton DWT (2000) Ascaris and ascariasis. Adv Parasitol 48: 285–375.
10. de Silva NR, Brooker S, Hotez PJ, Montresor A, Engels D, et al. (2003) Soil-transmitted helminth infections: updating the global picture. Trends Parasitol 19: 547–551.
11. Raso G, Luginbuhl A, Adjoua CA, Tian-Bi NT, Silue KD, et al. (2004) Multiple parasite infections and their relationship to self-reported morbidity in a community of rural Côte d'Ivoire. Int J Epidemiol 33: 1092–1102.
12. Babu BV, Swain BK, Rath K (2006) Impact of chronic lymphatic filariasis on quantity and quality of productive work among weavers in an endemic village from India. Trop Med Int Health 11: 721–717.
13. Crompton DWT, Nesheim MC (2002) Nutritional impact of intestinal helminthiasis during the human life cycle. Annu Rev Nutr 22: 35–59.
14. Gryseels B, Polman K, Clerinx J, Kestens L (2006) Human schistosomiasis. Lancet 368: 1106–1118.
15. Stephenson LS, Latham MC, Ottesen EA (2000) Malnutrition and parasitic helminth infection. Parasitology 121 Suppl: S23–S38.
16. Stoltzfus R, Albonico M, Tielsch J, Chwaya HM, Savioli L (1997) Linear growth retardation in Zanzibari schoolchildren. J Nutr 127: 1099–1105.
17. Mohammed KA, Molyneux DH, Albonico M, Rio F (2006) Progress towards eliminating lymphatic filariasis in Zanzibar: a model programme. Trends Parasitol 22: 340–344.
18. Savioli L, Dixon H, Kisumku UM, Mott KE (1989) Control of morbidity due to S. haematobium on Pemba Island: selective population of school children to identify high risk localities. Trans R Soc Trop Med Hyg 83: 805–810.
19. Stothard JR, Mgeni AF, Khamis S, Seto E, Ramsan M, Hubbard SJ, Kristensen TK, Rollinson D (2002) New insights into the transmission biology of urinary schistosomiasis in Zanzibar. Trans R Soc Trop Med Hyg 96: 470–475.
20. Stothard JR, Mgeni AF, Khamis S, Seto E, Ramsan M, Rollinson D (2002) Urinary schistosomiasis in schoolchildren on Zanzibar island (Unguja), Tanzania: a parasitological survey supplemented with questionnaires. Trans R Soc Trop Med Hyg 96: 507–14.
21. Renganathan E, Ercole E, Albonico M, De Gregorio G, Alawi KS, Kisumku UM, Savioli L (1995) Evolution of operational research studies and development of a national control strategy against intestinal helminths: the Pemba Island experience (1988–1992). Bull World Health Organ 73: 183–190.
22. World Health Organization (2005) Monitoring and epidemiological assessment of the programme to eliminate lymphatic filariasis at implementation unit level. Geneva: World Health Organization. 48 p.
23. Horton J, Witt C, Ottesen EA, Lazdins JK, Addiss DG, et al. (2000) An analysis of the safety of single dose, two drug regimens used in programmes to eliminate lymphatic filariasis. Parasitology 121(supplement): S147–S160.
24. Olds GR, King C, Hewlett J, Olveda R, Wu G, et al. (1999) Double-blind, placebo-controlled study of concurrent administration of albendazole and praziquantel in schoolchildren with schistosomiasis and geohelminths. J Infect Dis 179: 996–1003.
25. Loukas A, Hotez PJ (2006) Chemotherapy of helminth infections. In: Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's The pharmacological basis of therapeutics, 11th Edition. New York: McGraw-Hill. pp 1073–1093.
26. Na-bangchang K, Kietinun S, Pawa KK, Hanpitakpong W, Na-bangchang C, et al. (2006) Assessments of pharmacokinetic drug interactions and tolerability of albendazole, praziquantel and ivermectin combinations. Trans R Soc Trop Med Hyg 100: 333–345.
27. Weil GJ, Lammie PJ, Weiss N (1997) The ICT filariais test: a rapid-format antigen test for diagnosis of Bancroftian filariasis. Parasit. Today 13: 401–404.
28. Booth M, Vounatson P, N'goran EK, Tanner M, Utzinger J (2003) The influence of sampling effort and the performance of the Kato-Katz technique in diagnosing Schistosoma mansoni and hookworm co-infections in rural Cote d'Ivoire. Parasitology 103: 525–531.
29. Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat (2007) World Population Prospects: The 2006 Revision. New York: United Nations.
30. Alexander ND, Cousens SN, Yahaya H, Abiose A, Jones BR (2006) Ivermectin dose assessment without weighing scales. Bull World Health Organ 71: 361–366.
31. Montresor A, Engels D, Chitsulo L, Bundy DA, Brooker S, et al. (2001) Development and validation of a "tablet pole" for the administration of praziquantel in sub-Saharan Africa. Trans R Soc Trop Med Hyg 95: 542–544.
32. Montresor A, Engels, Ramsan D, Foum A, Savioli L (2002) Field test of the "dose pole" for praziquantel in Zanzibar. Trans R Soc Trop Med Hyg 96: 323–324.
33. World Health Organization (2003) Report on active surveillance for adverse events following the use of drug co-administrations in the Global Programme to Eliminate Lymphatic Filariasis. Wkly Epidemiol Rec 36: 313–320.
34. Dodoo A, Adjei S, Couper M, Hugman B, Edwards R (2007) When rumours derail a mass deworming exercise. The Lancet 370: 465–466.

35. Lammie PJ, Fenwick A, Utzinger J (2006) A blueprint for success: integration of neglected tropical diseases control programmes. Trends Parasitol 22: 313–321.
36. Brady MA, Hooper PJ, Ottesen EA (2006) Projected benefits from integrating NTD programs in sub-Saharan Africa. Trends Parasitol 22: 285–291.
37. Hotez PJ, Molyneux DH, Fenwick A, Ottesen EA, Sachs SE, Sachs JD (2006) Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med: e102.
38. Richards FO Jr, Eigege A, Miri ES, Jinadu MY, Hopkins DR (2006) Integration of mass drug administration programmes in Nigeria: the challenge of schistosomiasis. Bull World Health Organ 84: 673–6. Erratum in: Bull World Health Organ 84:760.

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Progress towards eliminating lymphatic filariasis in Zanzibar: a model programme

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Programmes to eliminate lymphatic filariasis are underway in ten countries of sub-Saharan Africa, and in several programmes outside Africa five rounds of mass drug administration (MDA) are being completed. In Africa, Egypt and Zanzibar have completed five rounds of MDA. Zanzibar was the first country to complete five rounds of treatment using a combination of albendazole and ivermectin, reducing both the prevalence and intensity of *Wuchereria bancrofti*. Characteristics of the Zanzibar programme serve as a model for other countries: factors crucial to its success include high-level political commitment, the development of appropriate social mobilization strategies, the involvement of communities in drug distribution, and the introduction of morbidity management for individuals with lymphoedema.

Introduction

Lymphatic filariasis, a major public health problem, is widely distributed in tropical and subtropical areas of the world. The predominant causative organism, *Wuchereria bancrofti*, is estimated to have infected more than 100 million people in 73 countries in total, and more than 50 million people in sub-Saharan Africa alone [1]. Lymphatic filariasis is recognized as a leading cause of disability [2] that exerts a heavy social and economic burden, although the associated chronic complications are stigmatizing and are often hidden. In males, genital pathology is a severe handicap leading to physical limitations, poor self-image and social exclusion. Individuals affected by lymphoedema also have severely reduced prospects of marriage, which is normally an essential source of societal security.

In 1993, the International Task Force on Disease Eradication considered lymphatic filariasis to be one of only six diseases that potentially could be eradicated [3]. In 1997, the World Health Assembly passed resolution 50.29, calling on member states to eliminate lymphatic filariasis as a public health problem on the basis of new diagnostic tools and a simple mass treatment strategy. This resolution was rapidly followed by generous donations of albendazole and ivermectin (Mectizan®) by GlaxoSmithKline (http://www.gsk.com) and Merck and Co., Inc. (http://www.merck.com), respectively, and a catalytic grant from the Bill and Melinda Gates Foundation (http://www.gatesfoundation.org) to the Global Alliance (http://www.theglobalalliance.org), a public–private partnership. Since then, there has been a major international effort in mobilizing, promoting and supporting elimination activities in endemic areas [4]. This review highlights the progress of a national programme and identifies the components required to ensure success through the phases of conception, resource mobilization, implementation and monitoring. The steps in this process are summarized in Box 1.

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Strategy for eliminating lymphatic filariasis

The Global Programme to Eliminate Lymphatic Filariasis is based largely on interrupting transmission through annual mass drug administration (MDA) to the 'at-risk' population in areas where lymphatic filariasis is endemic, and initiating a programme of care for individuals already suffering the consequences of infection. The goal of annual treatment is to break the cycle of transmission between mosquitoes and humans, thereby protecting future generations from the disease. To interrupt transmission, the essential strategy adopted by the World Health Organization (WHO) is to treat the whole at-risk population for a period long enough to ensure that levels of microfilariae in the blood remain below those necessary to sustain transmission.

Annual single doses of two drug regimens, albendazole (400 mg) plus either diethylcarbamazine (6 mg kg^{-1}) or ivermectin (200 mg kg^{-1}), are advocated. In African countries where onchocerciasis is co-endemic with filariasis, diethylcarbamazine cannot be used because it causes severe reactions in individuals with onchocerciasis; thus, albendazole and ivermectin is the predominant combination used in Africa. To interrupt transmission, mass treatment is thought to be necessary for 4–6 years, corresponding to the reproductive lifespan of the parasite. The success of this programme depends, however, on achieving and sustaining high levels of treatment coverage (65–80%) in endemic communities over this time.

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Box 1. Essential components of an elimination programme

- Map the distribution of lymphatic filariasis and identify implementation units with a prevalence of >1%
- National decision to implement programme
- Develop national plan
- Approve plan and submit request for donated drugs
- Develop financing plan from national and/or external resources
- Mobilize interest from non-governmental development organizations
- Identify the need for morbidity control implementation (including policy on hydrocele surgery)
- Select sentinel sites and acquire baseline data
- Define priority implementation units
- Establish time frame for mass drug distribution and select mass drug administration strategy
- Initiate training for drug distributors and design strategy for social mobilization
- Establish system for monitoring adverse events
- Distribute drugs
- Develop plan for monitoring and initiating mid-term evaluation and final evaluation (if possible including impact on intestinal helminths)

A recent publication on the impact of five rounds of mass drug distribution in Egypt in a population of 2.5 million using the albendazole–diethylcarbamazine combination suggests that transmission has been arrested, leading to cautious optimism that five rounds of treatment will be sufficient to eliminate transmission [5].

Whereas diethylcarbamazine has a modest adulticidal effect, the ivermectin–albendazole combination is thought to have a limited effect on the adult worms; however, both diethylcarbamazine and ivermectin clear microfilariae from infected subjects and thus deprive mosquito vectors of the opportunity to continue transmission [6,7]. Although ivermectin and diethylcarbamazine are the main antifilarial drugs, the addition of albendazole has been reported to give better clearance of microfilariae and other benefits, such as clearance of intestinal helminths in treated communities [6–8], and ivermectin has a positive effect on scabies and decrease in skin disease [9].

Countries have developed different strategies to distribute the drugs and to achieve programme success. As we describe below, the programme in Zanzibar represents an excellent model for other countries contemplating the development of a programme to eliminate lymphatic filariasis (see Box 1).

The Zanzibar context

Zanzibar is part of the United Republic of Tanzania, but it maintains its own government. It has a population of nearly 1 million people (984 625 in the 2002 census) and is growing at an annual rate of ~3%. Zanzibar was one of the earliest governments to develop and to implement a national programme to eliminate lymphatic filariasis (PELF). Lymphatic filariasis represents a major public health problem in Zanzibar and is endemic on both of the main islands (Unguja and Pemba) and all of the approximately 50 smaller islands. During the process of mapping the distribution of lymphatic filariasis in Zanzibar, the prevalence of microfilaraemia in the adult population was found to range from 5 to 30%. Hydrocele and lymphoedema were also recognized as significant clinical problems.

The Zanzibar Ministry of Health designed its national PELF on the basis of protocols recommended by the WHO [10]. The goal of Zanzibar's PELF is to interrupt lymphatic filariasis transmission by conducting MDA with a single combined dose of ivermectin and albendazole once a year for 4–6 years. The intervention is directed towards the whole population with the exception of children under 5 years, pregnant women, women in the first week after childbirth and severely ill people. Zanzibar has conducted five rounds of MDA since 2001, reaching the whole at-risk population. The decision to use ivermectin, as opposed to diethylcarbamazine, was based on the fact that onchocerciasis is endemic on the mainland of Tanzania and thus the use of diethylcarbamazine would pose a potential risk for individuals with onchocerciasis who migrate from Tanzania to Zanzibar.

In addition to MDA, Zanzibar has an lymphatic filariasis morbidity programme to manage the clinical manifestations of the disease that affect up to 5% of the population with lymphoedema or elephantiasis and up to 20% of adult men with hydrocele. Care for persons with lymphoedema includes self-help measures such as exercise, improved skin hygiene (washing and drying), and the application of antifungal or antibacterial ointments to reduce skin infections. The morbidity programme also includes surgery to correct hydrocele. These features not only alleviate the suffering of individuals and improve their physical, social and economic well-being, but also give credibility to the lymphatic filariasis programme in the country. Morbidity programmes are generally thought to increase community support for and hence participation in MDA, thereby enhancing coverage. Lymphatic filariasis morbidity management programmes will need to be continued long after the transmission of lymphatic filariasis has been interrupted because of the chronic nature of the disease.

One of greatest challenges to the successful implementation and completion of filariasis elimination programmes based on annual treatment is the need to achieve high coverage levels. Obtaining the widest possible drug coverage (80–90%) in at-risk communities is required to interrupt transmission successfully [11] and to control morbidity – the twin pillars of lymphatic filariasis elimination. Thus, the most important operational challenge is to develop mechanisms to ensure consistent and high drug coverage and compliance.

To implement MDA, Zanzibar's PELF established a plan of action based on six strategies with the goal of attaining the highest coverage possible. The strategies set forward were (i) dividing the country into operational units; (ii) establishing a time frame for an annual MDA campaign and designating an MDA day ('F-day'); (iii) identifying the training requirements for drug distributors and health staff in the districts and community; (iv) creating measures of preparedness to address anticipated adverse reactions to the drugs; (v) selecting sentinel and spot-check sites to monitor the impact of the program interventions; and (vi) initiating measures of social

mobilization to encourage the full participation of communities in F-days.

Social mobilization

In all five rounds of MDA, before F-day itself, campaign meetings were held with the National Task Force – an advisory board of Zanzibar's PELF derived from the leadership of different ministries, partner agencies such as the WHO, the United Nation's Children's Fund (UNICEF), non-governmental organizations, relevant national institutions, religious organizations and political parties. Information sheets were produced by the PELF and distributed through schools. TV and radio programs were designed, produced and aired, and local newspapers produced articles on PELF activities and F-Day [12]. Posters, leaflets and slogans carrying health messages were produced and distributed throughout the country. Activities towards social mobilization were undertaken in the districts and at community level.

Much of the success of the Zanzibar MDA campaign can be attributed to the drug distributors or 'filarial prevention assistants (FPAs).The FPAs were selected on the basis of their experience with public health activities, their residence in the community where the work was to be done, and their acceptance as an FPA by the community.

The MDA campaign

F-day

The last Saturday of October was established as the annual F-day with a 'mop-up day' on the Sunday. Before MDA, the FPAs made at least three visits to each household to build awareness and community support. The FPAs undertook door-to-door distribution, covering about 50 households each. All of the distributors had T-shirts with a logo of the PELF to identify themselves as representatives of the programme. Monitoring and supervision of the MDA were carried out by PELF staff and health and administrative officers from national, regional, district and shehia (the smallest administrative unit) levels. Good supervision and monitoring made it possible to address quickly any problem that occurred.

Coverage surveys are a key component of lymphatic filariasis elimination programmes because programme success requires consistently high coverage, particularly in places such as Zanzibar where not all treatment was directly observed. [12]. Drug distribution coverage for the total Zanzibar population averaged from 70 to 80% in all rounds, differing little from the coverage reported on tally sheets. The ability to maintain high coverage was attributed to the investment made by the programme in social mobilization. This is an important lesson for all lymphatic filariasis control programmes being implemented elsewhere. Distribution was undertaken to ensure that drugs were consumed at the time that they were made available to the household to maintain a 'semi-observed' treatment approach.

Adverse reactions management

Mass drug administration is known to be associated with adverse reactions, including vomiting, nausea, stomach cramps, headache, itching and diarrhoea, that are typically associated with the presence of microfilaraemia [13]. It is important that communities recognize such adverse events as evidence of the therapeutic action of the drugs, and this point should be emphasized as part of the social mobilization activities.

In Zanzibar, health facilities in the country were provided with drugs and guidelines for managing any anticipated adverse reactions. In addition, PELF and the Ministry of Health issued a statement through the mass media (TV and Radio Zanzibar) and conducted several sensitization meetings in the community before MDA to inform everyone about adverse reactions. As a result, the public was satisfied that these issues were appropriately addressed.

Monitoring and evaluation

The WHO guidelines for programme managers outline strategies for monitoring the progress of the lymphatic filariasis programme. Collecting parasitological data to demonstrate the impact of the programme also helps to maintain political and popular support for lymphatic filariasis. Before the MDA in Zanzibar, data were collected – in accordance with the WHO protocol – from sentinel sites selected to be representative of Unguja. The prevalence and intensity of microfilaria dropped markedly after the first round of MDA in both the urban and rural sites, documenting the effectiveness of MDA in Zanzibar and other endemic settings [14]. In Zanzibar, these declines continued after subsequent rounds of MDA (Figure 1).

At this stage of the programme, some individuals have residual microfilaraemia and it is not clear whether they can act as a renewed focus of transmission. In Zanzibar and other programme settings, operational research is needed to determine whether additional cycles of MDA or adjunctive vector control are needed as a strategy to eliminate transmission [15].

Disability control and management

In collaboration with the WHO, the management of individuals with lymphatic filariasis started in 2003 with the preparation and pre-testing of a 'home-based care' training module on lymphoedema management using simple procedures of regular washing, careful drying and treatment with antifungal, antibiotic or emollient creams of the affected limbs, as well as limb elevation, exercise and use of footwear [16,17]. This programme was implemented by health workers in the districts and at health centres or facilities, by informal caregivers in the community, and by individuals with lymphatic filariasis themselves and members of their families. Affected individuals showed clinical improvement with a decrease in the frequency of acute dermatolymphangioadenitis attacks and an improvement in measures of quality of life [17].

Lymphoedema management programmes help to maintain community support for MDA by addressing the needs of the individuals in the community with the most visible manifestations of lymphatic filariasis. Similarly, hydrocelectomy alleviates problems suffered by men disabled by lymphatic filariasis, improving their work capacity and

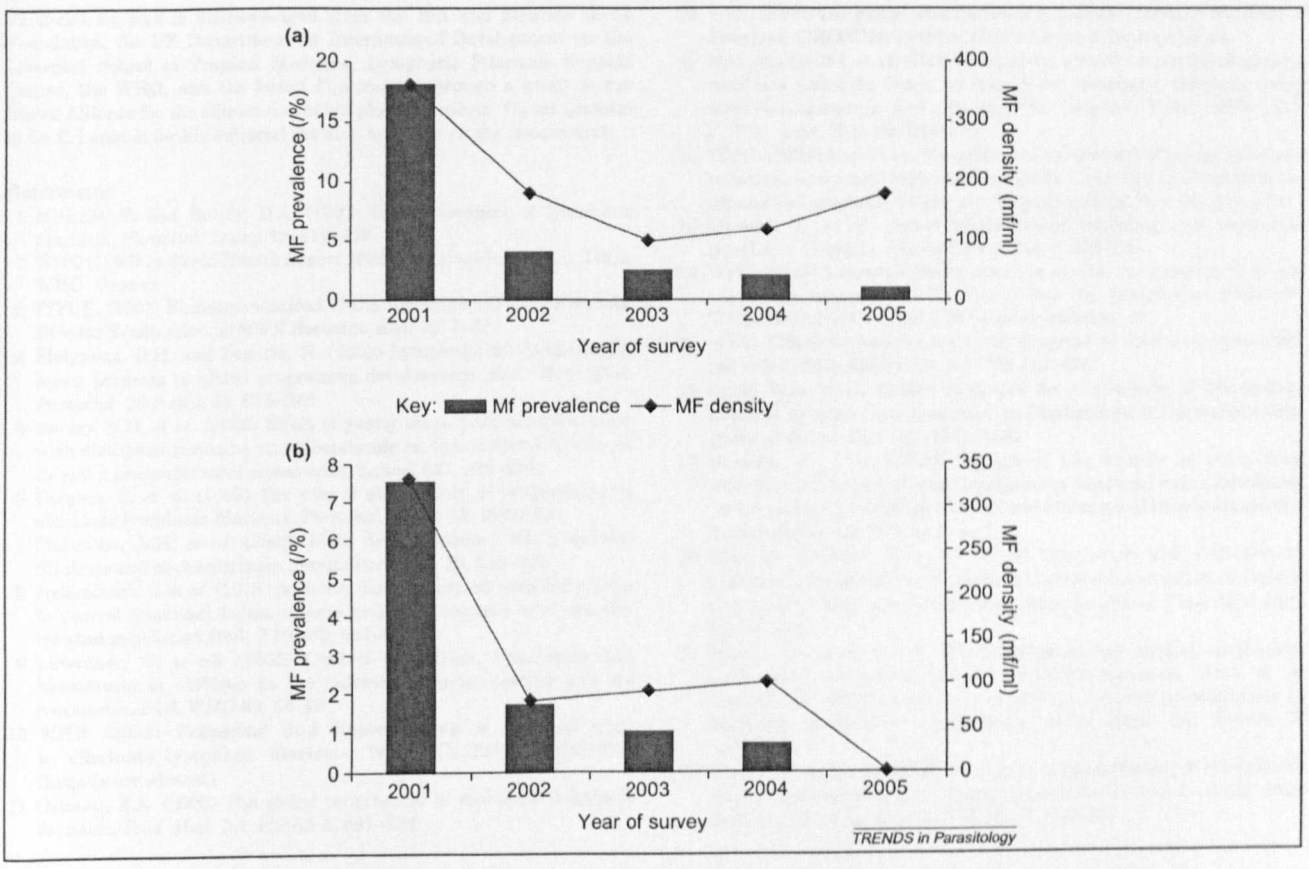

Figure 1. The prevalence of microfilariae (MF) in the adult population (bars) and density of microfilariae in the blood (diamonds) were determined according to a WHO protocol [8] in **(a)** rural (Kizimkazi) and **(b)** urban (Kwahani) sentinel sites. Data adapted, with permission, from Ref. [18].

sexual function and restoring their self-esteem, thereby enabling them to participate more actively in community activities.

Formula for success

The success of lymphatic filariasis elimination programmes will be judged by their impact on the prevalence, intensity and transmission of microfilariae. To achieve this impact, however, high coverage must be maintained [15,18]. In five rounds of MDA to the eligible population using a combination of ivermectin and albendazole and a house-to-house strategy of drug distribution with intensive social mobilization and the full commitment of all government and community bodies, Zanzibar has been able to achieve consistently high coverage in all five of its MDA rounds. The impact of high-coverage MDA is demonstrated by the marked drop in microfilaria prevalence and density [14] (Figure 1). As documented elsewhere, MDA has been also shown to provide secondary benefit through a decrease in the prevalence of geohelminths (soil-transmitted helminths) [19–22].

Disability prevention and control have been integrated into the routine activities of the health system. Such integration is probably essential if care is to be provided for individuals with filarial disease after the completion of MDA. In follow-up surveys, affected individuals reported that their conditions improved, in terms of both a decrease in the severity of acute attacks and an increase in their quality of life and ability to function in their communities [17].

Perspective

Annual MDA using either albendazole plus diethylcarbamazine or ivermectin is a global strategy adopted to stop the transmission of lymphatic filariasis. In 2001, Zanzibar was among the first countries to start country-wide community MDA using a combination of albendazole and ivermectin. Five rounds of treatments were accomplished in all ten administrative districts. High coverage was achieved through the collaboration and commitment of all sectors, partners and stakeholders. A marked decrease in the prevalence of microfilariae was noted as the number of rounds of MDA increased.

Drug distribution strategies for MDA vary by country: some programmes have elected to use a rally post for MDA, whereas others have used community-directed treatment strategies developed by onchocerciasis control programmes or house-to-house distribution [7]. Regardless of the approach used, our experience indicates that achieving high coverage of the population requires careful attention to appropriate strategies of social mobilization.

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References

1 Michael, E. and Bundy, D.A. (1997) Global mapping of lymphatic filariasis. *Parasitol. Today* 13, 472–476
2 WHO (1995) In *World Health Report 1995: Bridging the Gaps*, p. 118.2, WHO, Geneva
3 ITFDE. (1993) Recommendations of the International Task Force for Disease Eradication. *MMWR Recomm. Rep.* 42, 1–25
4 Molyneux, D.H. and Zagaria, N. (2002) Lymphatic filariasis elimination: progress in global programme development. *Ann. Trop. Med. Parasitol.* 96(Suppl. 2), S15–S40
5 Ramzy, R.M. *et al.* (2006) Effect of yearly mass drug administration with diethylcarbamazine and albendazole on bancroftian filariasis in Egypt: a comprehensive assessment. *Lancet* 367, 992–999
6 Ottesen, E. *et al.* (1999) The role of albendazole in programmes to eliminate lymphatic filariasis. *Parasitol. Today* 15, 382–386
7 Molyneux, D.H. *et al.* (2003) Mass drug treatment for lymphatic filariasis and onchocerciasis. *Trends Parasitol.* 19, 516–522
8 Heukelbach, J. *et al.* (2004) Selective mass treatment with ivermectin to control intestinal helminthiases and skin diseases in a severely infected population Bull. *WHO* 82, 563–571
9 Lawrence, G. *et al.* (2005) Control of scabies, skin sores and haematuria in children in the Solomon Islands: another role for ivermectin. *Bull. WHO* 83, 34–42
10 WHO (2002) Preparing and implementing a national plan to eliminate lymphatic filariasis. WHO/CDS/CPE/CEE/2000.15 (http://www.who.int)
11 Ottesen, E.A. (2000) The global programme to eliminate lymphatic filariasis. *Trop. Med. Int. Health* 5, 591–594
12 WHO (2002) The global elimination of lymphatic filariasis: the story of Zanzibar. WHO/CDS/CPS/SMT/2002.15 (http://www.who.int)
13 McLaughlin, S.I. *et al.* (2003) Frequency, severity and costs of adverse reactions following mass treatment for lymphatic filariasis using diethylcarbamazine and albendazole, Leogane, Haiti, 2000. *Am. J. Trop. Med. Hyg.* 68, 568–573
14 WHO. (2004) Report on the mid-term assessment of microfilaraemia reduction in sentinel sites of 13 countries of the Global Programme to Eliminate Lymphatic Filariasis. *Wkly Epidemiol. Rec.* 79, 358–365
15 Michael, E. *et al.* (2004) Mathematical modeling and control of lymphatic filariasis. *Lancet Infect. Dis.* 4, 223–234
16 WHO (2003) Learner's guide: training module on community home-based prevention of disability due to lymphatic filariasis. WHO/CDS/CPE/CEE/2003.35 (http://www.who.int)
17 WHO. (2004) Lymphatic filariasis, progress of disability prevention activities. *Wkly Epidemiol. Rec.* 79, 417–424
18 Stolk, W.A. *et al.* (2003) Prospects for elimination of bancroftian filariasis by mass drug treatment in Pondicherry, India: a simulation study. *J. Infect. Dis.* 188, 1371–1381
19 Oqueka, T. *et al.* (2005) Impact of two rounds of mass drug administration using diethylcarbamazine combined with albendazole on the prevalence of *Brugia timori* and of intestinal helminths on Alor Island. *Indonesia. Filaria J.* 4, 5
20 Beau De Rochars, M. *et al.* (2004) Community-wide reduction in prevalence and intensity of intestinal helminths as a collateral benefit of lymphatic filariasis elimination programs. *Am. J. Trop. Med. Hyg.* 71, 466–470
21 Mani, T.R. *et al.* (2004) Effectiveness of two annual, single-dose mass drug administrations of diethylcarbamazine alone or in combination with albendazole on soil-transmitted helminthiasis in filariasis elimination programme. *Trop. Med. Int. Health* 9, 1030–1035
22 Mani, T.R. *et al.* (2002) Efficacy of co-administration of albendazole and diethylcarbamazine against geohelminthiases: a study from South India. *Trop. Med. Int. Health* 7, 541–548

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Spatial distribution of soil-transmitted helminths, including *Strongyloides stercoralis*, among children in Zanzibar

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Abstract. A programme periodically distributing anthelminthic drugs to school-aged children for the control of soil-transmitted helminthiasis was launched in Zanzibar in the early 1990s. We investigated the spatial distribution of soil-transmitted helminth infections, including *Strongyloides stercoralis*, in 336 children from six districts in Unguja, Zanzibar, in 2007. One stool sample per child was examined with the Kato-Katz, Koga agar plate and Baermann methods. The point prevalence of the different helminth infections was compared to the geological characteristics of the study sites. The observed prevalences for *Trichuris trichiura*, *Ascaris lumbricoides*, hookworm and *S. stercoralis* were 35.5%, 12.2%, 11.9% and 2.2%, respectively, with considerable spatial heterogeneity. Whilst *T. trichiura* and hookworm infections were found in all six districts, no *A. lumbricoides* infections were recorded in the urban setting and only a low prevalence (2.2%) was observed in the South district. *S. stercoralis* infections were found in four districts with the highest prevalence (4.0%) in the West district. The prevalence of infection with any soil-transmitted helminth was the highest in the North A district (69.6%) and the lowest in the urban setting (22.4%). *A. lumbricoides*, hookworm and, with the exception of the North B district, *S. stercoralis* infections were observed to be more prevalent in the settings north of Zanzibar Town, which are characterized by alluvial clayey soils, moist forest regions and a higher precipitation. After a decade of large-scale administration of anthelminthic drugs, the prevalence of soil-transmitted helminth infections across Unguja is still considerable. Hence, additional measures, such as improving access to adequate sanitation and clean water and continued health education, are warranted to successfully control soil-transmitted helminthiasis in Zanzibar.

Keywords: soil-transmitted helminths, *Strongyloides stercoralis*, spatial distribution, soil type, Zanzibar.

Introduction

Unguja and Pemba, the two islands belonging to the Zanzibar archipelago offshore Tanzania in East Africa, are highly endemic for worm infections (Albonico et al., 1997; Mohammed et al., 2008; Stothard et al., 2008). Indeed, filaria (*Wuchereria bancrofti*), schistosomes (*Schistosoma haematobium*) and the common soil-transmitted helminths (i.e. *Ascaris lumbricoides*, hookworm and *Trichuris trichiura*) co-exist and multiple infections of different helminth species are common (Mohammed et al., 2008; Rudge et al., 2008). Additionally, *Strongyloides stercoralis*, the most

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neglected of the soil-transmitted helminths (Bethony et al., 2006; Steinmann et al., 2007), is also endemic (Marti et al., 1996; Stoltzfus et al., 1997; Knopp et al., 2008).

The tropical climate of the Zanzibar archipelago and the poor hygienic conditions under which the socio-economically deprived rural dwellers live facilitate the development and transmission of these helminth infections. Whilst lymphatic filariasis and soil-transmitted helminthiasis are endemic across Unguja (Mohammed et al., 2008), urinary schistosomiasis is geographically restricted. The focality of urinary schistosomiasis is governed by the distribution of its intermediate host, i.e. *Bulinus globosus* (Stothard and Rollinson, 1997). This snail species, and hence urinary schistosomiasis, is absent in the south of the island (Stothard et al., 2002). New research has revealed that soil-transmitted helminth infections also show considerable spatial heterogeneity; indeed an elevated prevalence of *A. lumbricoides* and *T. trichiura* has been reported in the northern parts of Unguja (Stothard et al., 2008). One possible explanation is that the eggs of these soil-transmitted helminths remain infective for a long period of time in the alluvium and clayey sands that are the predominant soil type in North Unguja (Stothard et al., 2008). Clayey sands can be considered as a composite matrix of coarse and fine grains where the interaction between coarser and finer grain matrices affects the overall stress-strain behaviour of the soil (Monkul and Ozden, 2007). For the transmission of hookworm, a poverty-related lifestyle in combination with environmental factors such as a sandy soil type with a high moisture content, a suitable temperature, rainfall and sun exposure are key factors (Brooker et al., 2004; Saathoff et al., 2005b; Hotez, 2008). The ecological and epidemiological features that might explain the spatial heterogeneity of hookworm and *S. stercoralis* distribution in Unguja, however, remain to be investigated.

Due to the high prevalence of *S. haematobium* and soil-transmitted helminth infections in Zanzibar and their negative health impacts, especially among children, a national control programme was initiated by the Zanzibar Ministry of Health in the early 1990s (Renganathan et al., 1995). Since 1994, single-dose oral praziquantel (40 mg/kg) against schistosomiasis, and single-dose oral mebendazole (500 mg) against soil-transmitted helminthiasis, were administered, mainly through the existing education sector (Mohammed et al., 2008). From 2003 onwards, mebendazole has been replaced by single-dose oral albendazole (400 mg) (Stothard et al., 2008). In 2001, a programme to eliminate lymphatic filariasis was established, distributing once yearly single-dose oral albendazole (400 mg) plus ivermectin (200 µg/kg) to the whole eligible population of Unguja (Mohammed et al., 2006). Ivermectin is not only effective against filaria and *A. lumbricoides*, but is also the drug of choice to treat *S. stercoralis* infections (Gann et al., 1994), and hence is likely to have an ancillary effect against strongyloidiasis.

Despite *S. stercoralis* being endemic in Unguja and Pemba (Marti et al., 1996; Stoltzfus et al., 1997), only one of the recently published articles discussing different aspects of soil-transmitted helminthiasis focussed on *S. stercoralis* (Knopp et al., 2008). The aim of the present study was to assess the prevalence and intensity of infection of soil-transmitted helminth infections, placing particular emphasis on *S. stercoralis*, among children from selected "madrassas" (Koran-schools) and primary schools in the six districts of Unguja. Finally, the spatial distribution of soil-transmitted helminth infections was considered in relation to known geological features.

Materials and methods

Study area

This study was carried out in Unguja, the main island of Zanzibar, in June 2007. Unguja has two annual wet seasons: the "Masika rains" from the south, lasting usually from mid-March to mid-June, and the "Vuli rains" from north-east, occurring during November and December. The average annual

rainfalls for north Unguja are 1,800 mm and for South Unguja 1,500 mm (MDG-Centre, 2007). The average annual temperature in Unguja is 27°C. The pedeology of Unguja soils range from alluvium to clayey sands with subordinate limestone (Kent et al., 1971). In the north-east of Unguja various soil-types constitute the ground whereas, at the western coastline and in the south, coral limestone areas are predominant (Calton et al., 1955; Hettige, 1990).

Study population

Stool samples were obtained from children visiting the "madrassas" of five villages, namely Banda-Maji, Mahonda, Kitumba, Dole and Pete. These villages are situated in the North A, North B, Central, West and South districts, respectively, and were geographically localized using Google™-Earth 2008. All villages are quite remote, have a similar socio-economic status with houses usually built with clayey walls and thatched coconut leafs. The majority of houses have no access to the power grid.

Additionally, stool samples were collected from children visiting five peri-urban primary schools (i.e. Nyerere, Rahaleo, Fuoni, Mwenge and Regeza Mwendo) belonging to the Urban district around Zanzibar Town. All surveyed villages were located between 5 and 40 km from Zanzibar Town.

Field and laboratory procedures

One day before visiting the Koran-schools, the respective "shehas" (heads) of the communities were informed about the purpose and procedures of the study and asked for permission. Stool containers, a marker-pen and a pre-numbered form to fill in the name, sex and age of the children attending school were given to the teachers who were instructed to ask each child, attending the afternoon class, to write down his/her name on the pre-numbered list and to record his/her unique identification number on the designated stool collection container. The containers were handed out to the children and they were invited to return the containers with a lime-sized sample of their next morning stool.

To minimize the risk of sample mix-up, a member of the Helminth Control Laboratory Unguja (HCLU) visited the Koran-schools early in the morning and called each child by name and compared the number on their filled container with the number on the list. The stool samples were transferred to the HCLU in Mianzini, Zanzibar Town. A similar stool collection procedure was implemented in the five urban primary schools, readily integrated in the so-called 24-school-survey, as part of an ongoing study on the epidemiology and control of soil-transmitted helminthiasis and urinary schistosomiasis (French et al., 2007).

Once the stool samples reached HCLU, they were promptly processed and examined by an experienced laboratory technician. In brief, stool samples of sufficient quantity were examined with three different methods according to the following priorities. First, a Kato-Katz thick smear (Katz et al., 1972) was prepared using 41.7 mg templates. Second, a groundnut-sized portion of each stool sample (~1g) was subjected to the Koga agar plate method (Koga et al., 1990). Third and finally, the Baermann technique (García and Bruckner, 2001) was performed. Further details pertaining to these three methods for helminth diagnosis have been presented elsewhere (Steinmann et al., 2007; Knopp et al., 2008).

Kato-Katz thick smears were examined quantitatively, i.e. the number of eggs for each helminth species was counted and recorded separately. The Koga agar plate was used to determine the presence, or absence, of larvae of *S. stercoralis* and hookworm. The Baermann method was used for diagnosis of *S. stercoralis* larvae. For quality control purposes, random samples amounting to 5% of the Kato-Katz thick smears, were re-examined by a senior laboratory technician.

Data management and analysis

Data were double-entered in Microsoft Excel version 10.0 and checked for consistency using EpiData version 3.1 (EpiData Association, Odense,

Table 1. Thresholds issued by the WHO for distinguishing light, moderate and heavy infection intensities.

Infection intensities	Thresholds for each soil transmitted helminth (EPG)		
	A. lumbricoides	*T. trichiura*	Hookworm
Light	1-4,999	1-999	1-1,999
Moderate	5,000-49,999	1,000-9,999	2,000-3,999
Heavy	≥50,000	≥10,000	≥4,000

Denmark). Statistical analyses were made with STATA version 9.2 (StataCorp., College Station, USA). The number of eggs per gram of stool (EPG) was obtained by multiplying the species-specific egg-count in a single Kato-Katz thick smear by 24. We used thresholds issued by the World Health Organization (WHO) for distinguishing light, moderate and heavy infection intensities (Montresor et al., 1998), as showed in the following table 1.

The geometric mean EPG was calculated for the children in the respective settings, using the following formula: $\exp(\sum \log(EPG + 1) / n) - 1$.

Ethical considerations and treatment

One part of this study was embedded in the island-wide parasitological surveys that are carried out in Unguja by the HCLU as part of their routine activities. Moreover, two schools were part of the 24-school survey that have been conducted once every year, starting in 2004, as a collaborative activity between the HCLU and the Natural History Museum (London, UK).

The institutional research commission of the Swiss Tropical Institute (Basel, Switzerland) and the institutional review board of the National Health Service Local Research Ethics Committee (application 03.36) of St. Mary's Hospital (London, UK), on behalf of the Natural History Museum/Imperial College, approved the study. The WHO (Geneva, Switzerland), and the Ministry of Health and Social Welfare (Stone Town, Zanzibar) cleared the study protocol.

Detailed information about the study was provided to the "shehas" of the villages, the teachers of the Koran-schools and the headmasters of the urban primary schools. A member of the HCLU explained the study to the children. Written informed consent to all anticipated medical interventions, including parasitological surveys done at schools, was given by parents and/or legal guardians upon enrolment of their children at school. At the end of the study, children were treated regardless of their infection status with a single oral dose of albendazole (400 mg). Those children found positive for *S. stercoralis* were also treated with a single oral dose of ivermectin (200 µg/kg).

Results

Study compliance

In total, 336 children from the six districts of Unguja submitted one stool sample each. The samples were subjected to three different methods for helminth diagnosis. As records of age and/or sex were not available for all children, sex was only recorded for 309 (92.0%) children out of which 51.8% were girls and 48.2% were boys and age from 244 (72.6%) children. The median age was 11 years with a range from 3 to 19 years. For all remaining children, hookworm diagnosis was performed on 334 (99.4%) stool samples examined either with the Kato-Katz, or the Koga agar plate, or both methods. Results for *A. lumbricoides* and *T. trichiura* were available for 327 (97.3%) children who had their stool samples examined with the Kato-Katz method. Finally, 319 (94.9%) stool samples were subjected

both to the Baermann and the Koga agar plate method for diagnosis of *S. stercoralis*.

Helminth infections

Table 2 shows that helminth infections are still prevalent among children in Unguja. With regard to the three common soil-transmitted helminths, *A. lumbricoides* was the only species that was absent in one of the surveyed settings, namely in the Urban district. *S. stercoralis* was the least common helminth infection. It was found in four of the six districts with an overall prevalence of 2.2% according to combined results from the Koga agar plate and the Baermann methods. The highest prevalence (4.0%) was observed in Dole in the West district. Larval counts were usually low; the two highest counts (i.e. 4 and 9 larvae) were observed in stool samples from the two infected children in Dole in the West district.

In Banda-Maji village in the North A district, more than two-thirds of the children were infected with at least one helminth species (69.6%). The second highest prevalence of helminth infection was observed in Kitumba village located in the Central district (52.0%). Considerably lower prevalences were found in Mahonda village in the North B district (40.0%), in Pete village in the South district (39.1%), in Dole village in the West district (30.8%) and, finally, in the primary schools surveyed in the Urban district (22.4%). Taken together, almost half of the children surveyed were infected with at least one helminth (166/336, overall prevalence: 49.4%). Moreover, 47 (28.3%) children harboured two or more helminth species concurrently.

T. trichiura was the predominant helminth with an overall prevalence of 35.5% as assessed by a single Kato-Katz thick smear per child. The infection prevalence ranged from 16.1% (the Urban district) to 55.2% (the North A district). The large majority of infections (111/116, 95.7%) were of light intensity with EPGs below 1,000 (Table 3). The remaining five children (4.3%) had a moderate infection intensity and attended the "madrassas" of either Pete (n = 3) or Banda-Maji (n = 2). The overall prevalence of *A. lumbricoides* infection was 12.2% according to the Kato-Katz method with the highest prevalence (40.4%) observed in Banda-Maji in North A district. Most infections (32/40, 80%) were of light intensity with EPGs below 5,000. The remaining eight children (20.0%) had a moderate infection intensity and they were diagnosed either in Banda-Maji in the North A district (n = 6) or in Dole in the West district (n = 2). The combined results from the Kato-Katz and the Koga agar plate methods revealed an overall hookworm prevalence

Table 2. Prevalence (number of children positive/number of children examined) of soil-transmitted helminth infections in 336 children from the 6 districts of Zanzibar, Tanzania.

Village	District	Parasite (Method)			
		A. lumbricoides (K-K[a])	*T. trichiura* (K-K[a])	Hookworm (K-K[a], KAP[b])	*S. stercoralis* (BM[c], KAP[b])
Banda-Maji	North A	40.3 (27/67)	55.2 (37/67)	14.5 (10/69)	2.9 (2/68)
Mahonda	North B	8.3 (2/24)	29.2 (7/24)	16.0 (4/25)	0 (0/21)
Kitumba	Central	9.1 (7/77)	44.2 (34/77)	11.7 (9/77)	2.8 (2/74)
Dole	West	5.9 (3/51)	19.6 (10/51)	15.4 (8/52)	4.0 (2/50)
Pete	South	2.2 (1/46)	39.1 (18/46)	6.5 (3/46)	0 (0/39)
—	Urban	0 (0/62)	16.1 (10/62)	7.7 (5/65)	1.5 (1/67)
Total		12.2 (40/327)	35.5 (116/327)	11.9 (39/334)	2.2 (7/319)

[a] K-K: Kato Katz thick smear; [b] KAP: Koga agar plate; [c] BM: Baermann

Table 3. Characteristics of the three common soil-transmitted helminth infections among the 327 school-aged children from Unguja who had one stool sample quantitatively examined by the Kato-Katz method.

Characteristics	Parasite		
	T. trichiura	*A. lumbricoides*	Hookworm
Number (%) of children infected	116 (35.5)	40 (12.2)	32 (9.8)
Infection intensity			
Light	111 (95.7%)	32 (80.0%)	32 (100%)
Moderate	5 (4.3%)	8 (20.0%)	0
Heavy	0	0	0
Geometric mean EPG (95% CI)	1326 (962-1829)	104 (86-125)	143 (98-207)

CI, confidence interval; EPG, eggs per gram of stool

of 11.9%, ranging between 6.5% (Pete, the South district) and 16.0% (Mahonda, the North B district). According to the quantitative Kato-Katz thick smear results, all infections were of light intensity with EPGs below 2,000.

The geometric mean EPGs of the three common soil-transmitted helminths are summarised in Table 2.

Geological features and soil types

The geographical location of the six study sites where the study was carried out were superimposed onto a Google™-Earth satellite image of Unguja (Fig. 1A) and juxtaposed to the underground composition and predominant soil types of the island (Fig. 1B), according to geological investigations published by Kent and colleagues in the early 1970s (Kent et al., 1971). The geographical coordinates of the study sites are as follows: Banda-Maji (5° 57' 0" S longitude and 39° 19' 0" E latitude); Mahonda (5° 59' 0" S, 39° 15' 0" E); Kitumba (6° 07' 0" S, 39° 17' 0" E); Dole (6° 06' 0" S, 39° 14' 0" E); and Pete (6° 17' 0" S, 39° 25' 0" E). The urban area is located in Zanzibar Town (6° 09' 0" S, 39° 12' 0" E).

The ground in Banda-Maji in the North A district and in Kitumba in the Central district consists of fossiliforous limestone and marly sand lithology. In Mahonda in the North B district and in Dole in the West district, the ground is characterized by clayey sands with subordinate limestone. In Pete in South district, reefal limestone constitutes the ground. In the urban area around Zanzibar Town, the ground consists primarily of limestone and soft sandstone or alluvium.

Discussion

Despite considerable efforts to control helminth infections on the islands of Unguja and Pemba over the past decade (Renganathan et al., 1995; Mohammed et al., 2008), surprisingly little is known about the spatial distribution of different helminth species, including underlying demographic, environmental and socio-economic factors. Our study sheds light on the distribution of helminth infections (among children) in the six districts of Unguja, five of them characterized as rural and the sixth in Zanzibar Town being urban. Emphasis is placed on the geological composition and soil types of the study locations, since these environmental factors have been shown to play an important role in the transmission of soil-transmitted helminthiasis (Brooker et al., 2004; Saathoff et al., 2005a). Particular consideration was given to *S. stercoralis* because this helminth species is often neglected in epidemiological investigations, which is partially explained by the need of particular diagnostic methods that are seldom used (Bethony et al., 2006; Steinmann et al., 2007).

In the present study, we screened over 300 children from six environmentally-distinct settings and

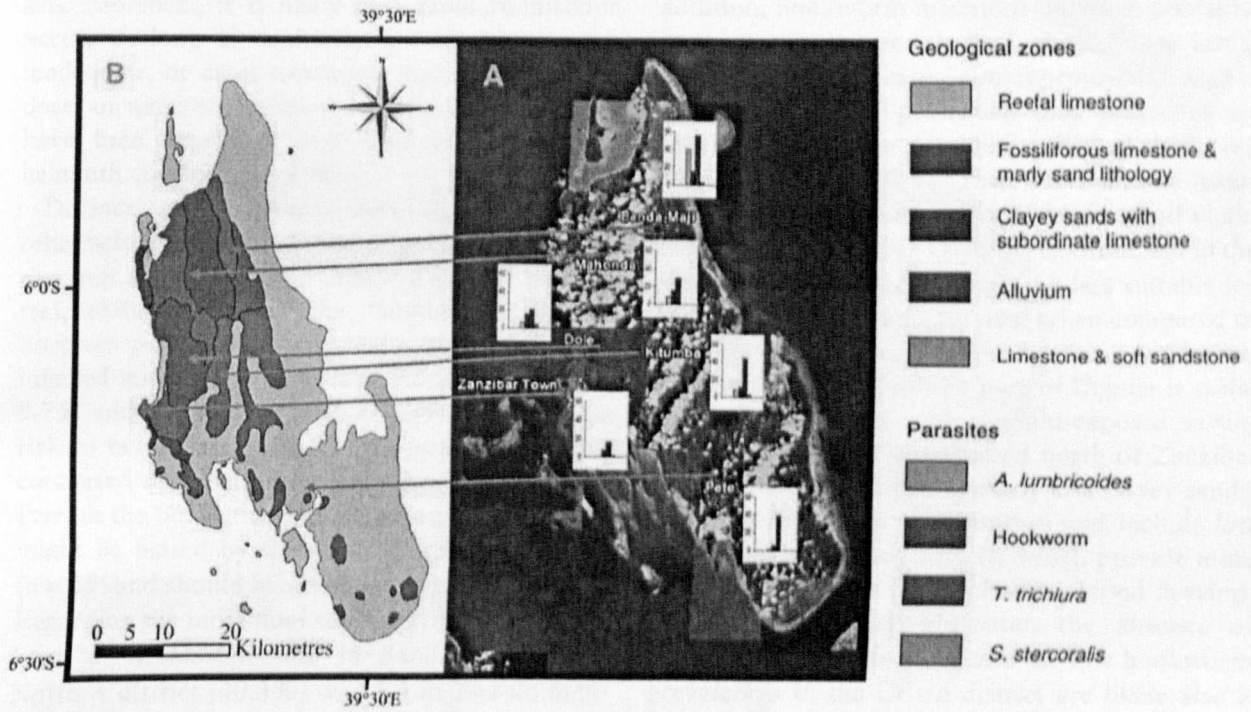

Fig. 1. Satellite image of Zanzibar from Google™-Earth (A) indicating the surveyed settings, and map showing the geological zones of Zanzibar adapted from Kent et al. (1971) (B).

subjected a single stool sample per child to the Kato-Katz, Koga agar plate and Baermann methods. We achieved a high compliance; more than 77% (259/336) of the children supplied stool samples of sufficient quantity to perform all three tests. Our findings underscore the feasibility and efficiency of epidemiological studies carried out in school environments, which in turn further strengthen the collaborative links between the health and education sectors (Lengeler et al., 2002). Approximately half of the children were infected with at least one helminth species with *T. trichiura* being the predominant one. Importantly, helminth infections were primarily of light intensity according to WHO thresholds (Montresor et al., 1998), which show the ability of a rigorously implemented national helminth control programme to reduce morbidity. Whilst *T. trichiura* and hookworm infections were observed in children from all six districts, no *A. lumbricoides* infections were diagnosed in the urban setting, and *S. stercoralis* infections were not detected in Mahonda in the North B district and Pete in the South district. However, the latter findings have to be interpreted with care, as the sample sizes in Mahonda and Pete were small (21 and 39 children, respectively) and only one stool sample per child was examined. Of note, *A. lumbricoides* and hookworm infections were considerably more often diagnosed in the northern part of Unguja than in the South.

We speculate that the high point-prevalence of *T. trichiura* infections in all districts (i.e. 16-55%) is, at least partially, explained by the low efficacy of the anthelminthics albendazole and ivermectin against this parasite (Marti et al., 1996; Keiser and Utzinger, 2008). The national control programme, emphasising repeated administration of anthelminthic drugs to school-aged children and other high-risk groups in Unguja, might therefore only have a limited effect on the transmission of trichuri-

asis. Moreover, it is likely that rapid re-infection occurs as long as sanitation on Unguja remains inadequate, or other treatment regimens (e.g. triple dose) or more efficacious drugs against trichuriasis have been developed and used in the national helminth control programme.

Distinct spatial patterns were observed for the other helminth species. From a north-south perspective (not considering the Urban district in the centre), children visiting the "madrassas" in the northern part of the island had a higher risk to be infected with *A. lumbricoides* (odds ratio (OR) = 9.75) and hookworm (OR = 2.31) but a similar risk to be infected with *T. trichiura* (OR = 1.05) compared to the children from the "madrassa" in Pete, in the South district. However, these findings might be biased by the small sample size in Pete (n = 39) and should hence be interpreted with care. Regarding the individual study-settings, the prevalence of *A. lumbricoides* in Banda-Maji in the North A district (40.3%) was 4.4 to 20-fold higher than in the other districts. This observation confirms that Banda-Maji has an elevated risk for soil-transmitted helminthiasis (Mohammed et al., 2008; Stothard et al., 2008). The high *A. lumbricoides* prevalence in Banda-Maji gives rise to concerns about whether in this area school-aged children had indeed been treated regularly with anthelminthic drugs and, if so, whether our findings might be an early sign of albendazole resistance development. Interestingly, a recent study carried out in this setting reported a low cure rate (42%) when *A. lumbricoides*-infected children were given single oral dose of albendazole (Stothard et al., 2008). On the other hand, the fact that no or only very few *A. lumbricoides* infections were observed in Pete in South district and among children attending peri-urban schools might be explained by the predominant soil types (i.e. limestone and sandstone) in those areas. It is conceivable that these soil types do not provide conducive microenvironments for sustaining the longevity of *A. lumbricoides* eggs, and that transmission of this infection is hence compromised. In addition, hookworm infections were less prevalent in these two settings. Indeed, the infective larval stages of hookworm require appropriate warmth, humidity and UV protection (e.g. facilitated by vegetation coverage providing sufficient shade and moisture of the soil) for their survival, and hence transmission (Brooker et al., 2004; Saathoff et al., 2005b; Hotez, 2008). Thus, the environment in the Unguja's South districts might be less suitable for their development and survival when compared to the North districts. The predominant geological formation in the southern part of Unguja is reefal limestone with dry and sunlight-exposed savannah, whereas the areas studied north of Zanzibar Town consist of alluvium, marly and clayey sands, have higher annual precipitation and include lots of streams and shady forests, which provide more suitable conditions for hookworm larval development and survival. However, the absence of *A. lumbricoides* infections and the low hookworm prevalences in the Urban district are likely also a result of improved socio-economic status leading to behavioural changes (e.g. wearing shoes) and improved hygienic conditions, and hence a reduced risk of infection. Of note, the stool samples obtained in the Urban district were provided by children attending primary schools, which are regularly subjected to screenings and anthelminthic drug distributions conducted by the national helminth control team. The stool samples obtained from the other districts of Unguja stemmed from children visiting "madrassas" which are not specifically part of the periodic school-based mass-drug administrations as children also visit public schools and anthelminthics are additionally distributed to the whole eligible island population in the frame of the programme to eliminate lymphatic filariasis. However, confounding factors such as lower coverage of treatment in the respective study population cannot be excluded.

The highest prevalence of *S. stercoralis* was found in Dole in the West district (4.0%), but infections were absent in Mahonda in the North B district and Pete in the South district. Bearing in mind that the

absence of an infection might be explained by the low sample sizes there, an additional factor to note is that, in Pete, the environment is drier than elsewhere, which might therefore be less suitable for the development of infective *S. stercoralis* larvae or free-living adult stages. However, one has to keep in mind that autoinfection can perpetuate *S. stercoralis* transmission for an extended period of time (Keiser and Nutman, 2004; Vadlamudi et al., 2006). It follows that this helminth is less closely linked to environmental factors than, for example, hookworm larvae. Autoinfection of *S. stercoralis* also imposes a considerable problem on copro-diagnostics. As larvae are not necessarily excreted in the stool, it is exceedingly difficult to identify infected individuals. Our recent work, focussing on the diagnosis of *S. stercoralis* among schoolchildren in Unguja, showed that the observed prevalence of this worm was more than double when three instead of a single stool sample were examined with a combination of the Koga agar plate and Baermann method (Knopp et al., 2008). Hence, the 'true' overall prevalence of *S. stercoralis* in the present study might well be 4% or even higher.

We conclude that soil-transmitted helminth infections are still prevalent across Unguja, but infection intensities are generally low, demonstrating the positive effect of the national control programme on morbidity. *T. trichiura* infections seem to be hardest to reduce with the current single-dose anthelmintic treatment campaigns. Although the observed prevalence of *S. stercoralis* was low, the 'true' prevalence might be considerably higher were more sensitive diagnostic approaches employed, and hence this parasite should not be neglected. Our findings call for continuation of the national control programme especially in the rural areas, but chemotherapy should be complemented by improved access to clean water and adequate sanitation, coupled with sound health education.

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References

Albonico M, Chwaya HM, Montresor A, Stolfzfus RJ, Tielsch JM, Alawi KS, Savioli L, 1997. Parasitic infections in Pemba Island school children. East Afr Med J 74, 294-298.

Bethony J, Brooker S, Albonico M, Geiger SM, Loukas A, Diemert D, Hotez PJ, 2006. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. Lancet 367, 1521-1532.

Brooker S, Bethony J, Hotez PJ, 2004. Human hookworm infection in the 21st century. Adv Parasitol 58, 197-288.

Calton WE, Tidbury GE, Walker GF, 1955. A study of the more important soils of the Zanzibar protectorate. East Afr Agricult J 21, 53-60.

French MD, Rollinson D, Basanez MG, Mgeni AF, Khamis IS, Stothard JR, 2007. School-based control of urinary schistosomiasis on Zanzibar, Tanzania: monitoring microhaematuria with reagent strips as a rapid urological assessment. J Pediatr Urol 3, 364-368.

Gann PH, Neva FA, Gam AA, 1994. A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. J Infect Dis 169, 1076-1079.

García LS, Bruckner DA, 2001. Diagnostic medical parasitology. American Society for Microbiology, Washington, DC, USA, pp. 1-791.

Hettige PML, 1990. Evaluation of land resources in Zanzibar Phase I and Phase II. Part I main volume, land evaluation and land sustainability classification - Unguja and Pemba Islands. Food and Agricultural Organization (FAO), Rome, Italy.

Hotez P, 2008. Hookworm and poverty. Ann N Y Acad Sci 1136, 38-44.

Katz N, Chaves A, Pellegrino J, 1972. A simple device for

quantitative stool thick-smear technique in schistosomiasis mansoni. Rev Inst Med Trop São Paulo 14, 397-400.

Keiser PB, Nutman TB, 2004. *Strongyloides stercoralis* in the immunocompromised population. Clin Microbiol Rev 17, 208-217.

Keiser J, Utzinger J, 2008. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. JAMA 299, 1937-1948.

Kent PE, Hunt JA, Johnstone DW, 1971. The geology and geophysics of coastal Tanzania. Geophysical Paper 6, 100.

Knopp S, Mgeni AF, Khamis IS, Steinmann P, Stothard JR, Rollinson D, Marti HP, Utzinger J, 2008. Diagnosis of soil-transmitted helminths in the era of preventive chemotherapy: effect of multiple stool sampling and use of different diagnostic techniques. PLoS Negl Trop Dis 2, (in press).

Koga K, Kasuya S, Khamboonruang C, Sukavat K, Nakamura Y, Tani S, Ieda M, Tomita K, Tomita S, Hattan N, et al., 1990. An evaluation of the agar plate method for the detection of *Strongyloides stercoralis* in northern Thailand. J Trop Med Hyg 93, 183-188.

Lengeler C, Utzinger J, Tanner M, 2002. Questionnaires for rapid screening of schistosomiasis in sub-Saharan Africa. Bull World Health Organ 80, 235-242.

Marti HP, Haji HJ, Savioli L, Chwaya HM, Mgeni AF, Ameir JS, Hatz C, 1996. A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of *Strongyloides stercoralis* and other soil-transmitted helminth infections in children. Am J Trop Med Hyg 55, 477-481.

MDG-Centre, 2007. An Assessment of Rainwater harvesting Potential in Zanzibar.

Mohammed KA, Haji HJ, Gabrielli A, Mubila L, Biswas G, Chitsulo L, Bradley MH, Engels D, Savioli L, Molyneux DH, 2008. Triple co-administration of ivermectin, albendazole and praziquantel in Zanzibar: a safety study. PLoS Negl Trop Dis 2, e171.

Mohammed KA, Molyneux DH, Albonico M, Rio F, 2006. Progress towards eliminating lymphatic filariasis in Zanzibar: a model programme. Trends Parasitol 22, 340-344.

Monkul MM, Ozden G, 2007. Compressional behavior of clayey sand and transition fines content. Eng Geol 89, 195-205.

Montresor A, Crompton DWT, Hall A, Bundy DAP, Savioli L, 1998. Guidelines for the evaluation of soil-transmitted helminthiasis and schistosomiasis at community level. A guide for managers of control programmes. World Health Organization (WHO), Geneva, Switzerland, pp. 1-45.

Renganathan E, Ercole E, Albonico M, De Gregorio G, Alawi KS, Kisumku UM, Savioli L, 1995. Evolution of operational research studies and development of a national control strategy against intestinal helminths in Pemba Island, 1988-92. Bull World Health Organ 73, 183-190.

Rudge JW, Stothard JR, Basáñez MG, Mgeni AF, Khamis IS, Khamis AN, Rollinson D, 2008. Micro-epidemiology of urinary schistosomiasis in Zanzibar: local risk factors associated with distribution of infections among schoolchildren and relevance for control. Acta Trop 105, 45-54.

Saathoff E, Olsen A, Kvalsvig JD, Appleton CC, Sharp B, Kleinschmidt I, 2005a. Ecological covariates of *Ascaris lumbricoides* infection in schoolchildren from rural KwaZulu-Natal, South Africa. Trop Med Int Health 10, 412-422.

Saathoff E, Olsen A, Sharp B, Kvalsvig JD, Appleton CC, Kleinschmidt I, 2005b. Ecologic covariates of hookworm infection and reinfection in rural Kwazulu-natal/south Africa: a geographic information system-based study. Am J Trop Med Hyg 72, 384-391.

Steinmann P, Zhou XN, Du ZW, Jiang JY, Wang LB, Wang XZ, Li LH, Marti H, Utzinger J, 2007. Occurrence of *Strongyloides stercoralis* in Yunnan province, China, and comparison of diagnostic methods. PLoS Negl Trop Dis 1, e75.

Stoltzfus RJ, Albonico M, Tielsch JM, Chwaya HM, Savioli L, 1997. School-based deworming program yields small improvement in growth of Zanzibari school children after one year. J Nutr 127, 2187-2193.

Stothard JR, Imison E, French MD, Sousa-Figueiredo JC, Khamis IS, Rollinson D, 2008. Soil-transmitted helminthiasis among mothers and their pre-school children on Unguja Island, Zanzibar with emphasis upon ascariasis. Parasitology (in press).

Stothard JR, Mgeni AF, Khamis S, Seto E, Ramsan M, Hubbard SJ, Kristensen TK, Rollinson D, 2002. New insights into the transmission biology of urinary schistosomiasis in Zanzibar. Trans R Soc Trop Med Hyg 96, 470-475.

Stothard JR, Rollinson D, 1997. Molecular characterization of *Bulinus globosus* and *B. nasutus* on Zanzibar, and an

investigation of their roles in the epidemiology of *Schistosoma haematobium*. Trans R Soc Trop Med Hyg 91, 353-357.

Vadlamudi RS, Chi DS, Krishnaswamy G, 2006. Intestinal strongyloidiasis and hyperinfection syndrome. Clin Mol Allergy 4, 8.